Laboratory Guidelines for the Detection and Diagnosis of COVID-19 Virus Infection

8 July 2020

Coronaviruses are a group of highly diverse RNA viruses in the *Coronaviridae* family that are divided in 4 genera: alpha, beta, gamma and delta, and cause disease varying from mild to severe in human and animals (1-3). There are endemic human coronavirus as alphacoronaviruses 229E and NL63 and betacoronaviruses OC43 and HKU1 that can cause influenza-like illness or pneumonia in humans (1, 3). However, two zoonotic coronaviruses have emerged causing severe disease in humans: Severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) (1-5).

In January 2020, the etiologic agent responsible for a cluster of severe pneumonia cases in Wuhan, China, was identified as being a novel betacoronavirus, distinct from SARS-CoV and MERS-CoV (6). On 11 February 2020, the International Committee on Taxonomy of Viruses (ICTV) announced that the virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (7) while, on the same day, WHO named the disease as coronavirus disease COVID-19 (8). For communication purposes we will refer the virus as "the virus responsible for COVID-19" or "the COVID-19 virus". Complete genomic sequences of the COVID-19 virus have been released and different molecular detection protocols developed (9). Given the current circulation of COVID-19 in the Americas region, the Pan American Health Organization / World Health Organization (PAHO/WHO) recommends to Member States to ensure timely identification of suspect cases, collection and shipping of samples to reference laboratories, and implementation of molecular detection protocols, according to the laboratory capacity.

On 19 March 2020, WHO updated its interim guidance on the Laboratory testing for coronavirus disease (COVID-19) in suspected human cases which includes information on specimen collection and shipment, laboratory testing, and reporting of cases and test results (9). WHO also updates COVID-19 suspect case definitions as needed (10).

Sample collection and proper shipment

Sample collection

Samples should be collected by trained personnel and considering all biosafety instructions including the use of personal protective equipment appropriate for standard, contact, and airborne precautions. In particular, personnel should use proper hand hygiene, gown, respirator (N95 or FFP2), eye (goggle) or facial (face shield) protection, and gloves (11).

Respiratory samples

The recommended samples are nasopharyngeal (NP) or oropharyngeal (OP) swabs, preferably combined (swabs should be placed and transported in the same tube with viral or universal transport medium) (9). If swabs are a limiting factor, a single swab can be used (prioritizing the NP swab). Samples from the lower respiratory tract, including sputum, bronchoalveolar lavage and tracheal aspirate are also useful; nevertheless, bronchoalveolar lavages and tracheal aspirates should only be collecting according to medical criteria and ensuring all the necessary biosafety measures (11).

If sampling of asymptomatic contacts is included in national guidelines, upper respiratory samples (NP and OP swabs) are preferred.

In general, flocked swabs made with synthetic materials (including nylon, Dacron or polyester) should be used; cotton swabs should be avoided. Protocols for the in-house production of viral transport media are available upon request to PAHO Regional Office. Additionally, sterile saline or nucleic acid preserving solution (*eg*, *DNA/RNA shield*) might be used if transport medium is not available (see below for sample transport considerations).

Sample shipment

Respiratory samples should be kept refrigerated (4-8 °C) and sent to the laboratory where they will be processed within the 24-72 hours of collection. If samples cannot be sent within this period, freezing at -70 °C (or less) is recommended until samples are shipped (ensuring the cold chain is maintained). If swabs were placed in sterile saline instead of viral transport medium, shipment should be expedited.

Shipment of suspected samples should comply with national regulations and use at a minimum a basic triple packaging system (12). Additionally, shipments to reference laboratories or collaborating centers outside of the country must ensure compliance with all international standards for Biological Substances, Category B (13).

Alternative samples

The COVID-19 virus as well as SARS-CoV and MERS-CoV, has been detected in other sample types, such as stools and blood (9). However, the viral dynamics in these samples has not been fully characterized. In fatal cases, samples of lung tissue or respiratory tract might also be useful for molecular detection, as long as the appropriate conditions are in place to perform the autopsy, particularly respiratory protection. Acute and convalescent blood samples might be useful as serological tests become available (see below).

Also, saliva has been proposed as an alternative sample especially because it can be easily collected from patients with no invasive or uncomfortable procedures, and minimizing healthcare worker potential exposure (14-16). Nevertheless, there are few publications supporting the use of saliva samples for COVID-19 detection; more validation data and larger datasets of results are still need. For these reasons, the implementation of this sample is not currently recommended.

Finally, pooled samples have been proposed as an alternative for reducing the number of tests needed for screening (17, 18). However, it is important to note that the sensitivity of the testing may decrease resulting in potential false-negative results. Additionally, although this strategy can be useful when COVID-19 prevalence in the population is low, once community transmission is established, this strategy might generate a burden since pools will likely be positive. Therefore, the use of sample pooling for the purpose of individual case diagnostic should be carefully evaluated.

Laboratory testing

Biosafety guidelines for the handling of suspected samples in the laboratory have been published elsewhere (13, 19).

Molecular methods

Routine confirmation of COVID-19 cases is based on detection of COVID-19 virus nucleic acid (RNA) using real time RT-PCR assays.

RNA extraction

RNA can be extracted from samples mentioned above using any standard extraction protocols or kits. In general, the sample lysis step in RNA extraction inactivates any live virus. Thus, lysed samples are generally considered non-infectious. The inactivation of COVID-19 virus through sample lysis has been verified for some commercial kits (20).

Sputum samples require liquification prior to molecular extraction (21), while tissue samples require lysis and homogenization.

Molecular detection protocols

WHO has made available several molecular diagnostic protocols (using RT-PCR) on the following link: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance

Please note that neither the names of vendors nor manufacturers included in the protocols are preferred/endorsed by WHO. Also, some of these protocols have not yet been validated through WHO process.

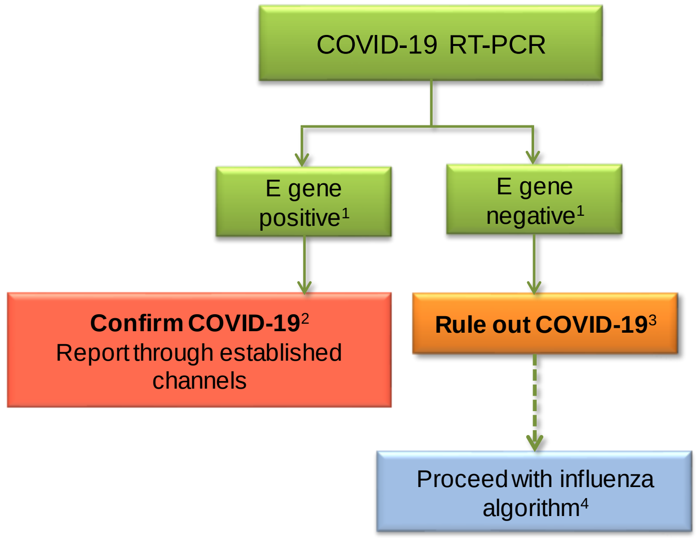
Through the effort of PAHO Member States, all national laboratories with the capacity to perform molecular tests, including National Influenza Centers (NIC), were trained in the use of the first protocol made available by WHO, developed by the Charité – Universitätsmedizin Berlin Institute of Virology, Berlin, German. The evaluation of the protocol has been published (22) and a work protocol is available on the following link: https://www.who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf

This protocol is based on the detection of two targets in the virus genome: the E gene and the RdRP gene (two probes, P1 and P2, were designed for the detection of the RdRP gene). The E assay is specific for all viruses of the *Sarbecovirus* subgenus (*ie*, SARS-CoV, COVID-19 virus, and related bat viruses), while the RdRP assay using the P2 probe only detects the COVID-19 virus. However, **the only Sarbecovirus that currently circulates in humans is the COVID-19 virus.** Thus, a positive result with the E assay confirms a case of COVID-19. Specific reagents (primers, probes, and positive controls) and work protocols for both the E and RdRP assays have been distributed by PAHO/WHO throughout the Region.

The detection of a single genetic target is sufficient for laboratory confirmation of cases. Although the initial recommendation was to detect two different genetic targets (*eg*, E gene detection followed by RdRP gene detection), a simpler algorithm will increase laboratory capacity while ensuring accuracy through the use of the highly specific Charité assays. As per standard procedures, laboratories must ensure that all assay quality control parameters (negative and positive controls, shape of the amplification curves) are optimal before releasing results. Either E or RdRP gene assays can be used for laboratory confirmation; nevertheless, the E gene assay has demonstrated slightly higher sensitivity, so **we recommend prioritizing the E gene as the selected target** (Figure 1).

Additional molecular assays are available and can be performed on open ("manual") or closed platforms (*ie*, with kits that only work on automated, proprietary platforms). These include assays that have been listed in the WHO Emergency Use Listing (23), independently evaluated by FIND (Foundation for Innovative New Diagnostics, a WHO Collaborating Center) (24), and/or approved for marketing by national regulatory authorities (in particular, those considered by WHO as SRA [Stringent Regulatory Authority] for its expedited pre-qualification of in-vitro diagnostic tests). Under the supervision of national health authorities and with the technical support of national public health laboratories and National Influenza Centers, these tests can be used in health care settings with the required capacity, or in decentralized laboratories.

Figure 1. Molecular detection algorithm



[1]When using the Charité reference protocol. If a different protocol is used, follow the indicated positivity criteria.
[2]As no other Sarbercovirus circulate globally, a positive result with the Charité E gene assay confirms the detection.
[3]Assuming the sample was collected properly, and all quality assurance processes were followed. Clinical and epidemiological information should also be considered before ruling out the case.
[4]Depending on surveillance protocols and available resources. Other respiratory viruses might also be tested.

Interpretation of the results[1]

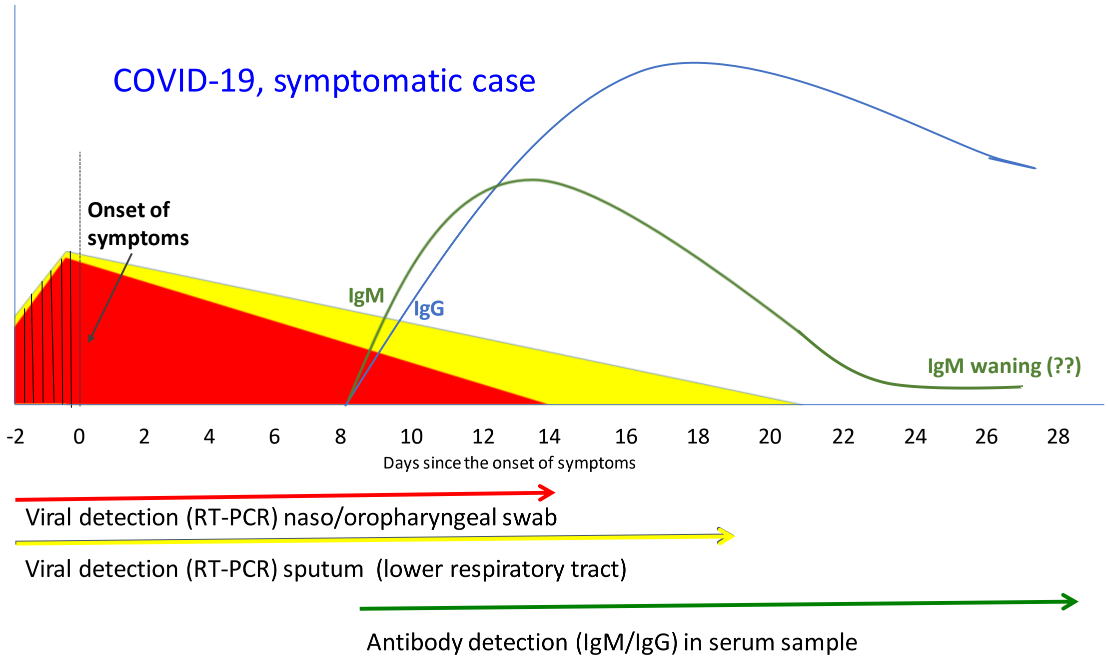
Although the dynamics of the infection including viral secretion in different fluids is still under study, to date it has been possible to establish that the virus can be detected from at least 48 hours before the onset of symptoms (pre-symptomatic cases) and up to 12-14 days (at least 6-7 days) after, in samples from the upper respiratory tract (NP/OP swabs) and up to 20 days (or more) in samples from the lower respiratory tract including sputum, tracheal aspirate, bronchioalveolar lavage, etc. (Figure 2).

In an individual identified as a contact of a confirmed case, the added value of conducting laboratory testing should be evaluated, keeping in mind that regardless of the result, the recommendation for the contact is 14 days of quarantine (from the day of last contact with the case). If a molecular test is performed, a negative result does not rule out previous contact, nor the possibility that the contact is in the incubation period. If a positive result is obtained, the case is either asymptomatic or pre-symptomatic, and must be isolated regardless.

In an asymptomatic individual, since there is no date that can be used as a reference, a negative molecular assay result can occur because the amount of virus is not sufficient to be detected, because the individual is in the post-infection period, or simply because the individual has never been infected. Thus, a negative result does not rule out a possible infection. If as part of an active surveillance (health workers, caregivers in nursing homes, etc.) a positive result is obtained by molecular detection, the result constitutes an asymptomatic case and the individual should be isolated.

[1] This section is based on PAHO document "Interpretation of laboratory results for COVID-19 diagnosis" available from: https://iris.paho.org/handle/10665.2/52138

Figure 2. Dynamics of COVID-19 infection (based on currently available data)



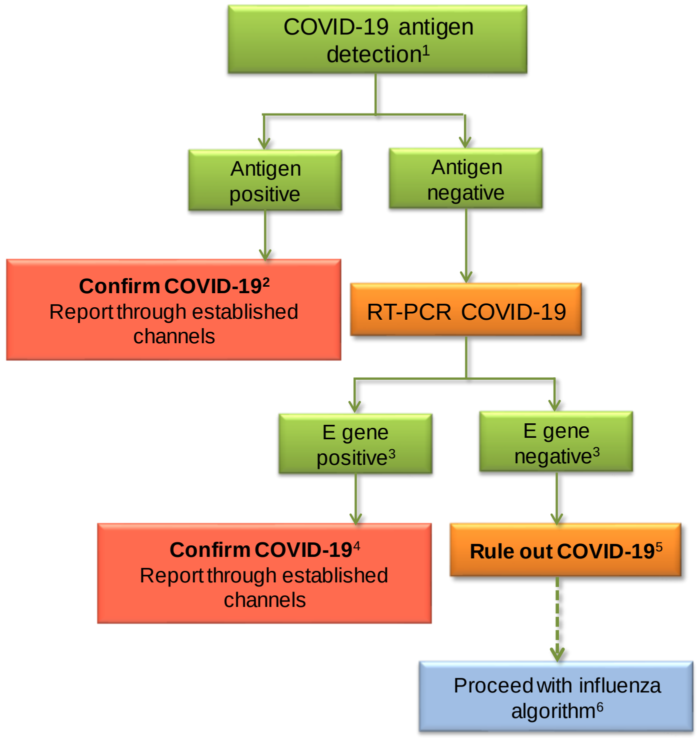
Molecular detection of COVID-19 virus using well-designed protocols is usually very specific; thus, a positive result confirms the detection of the virus. On the contrary, a negative result might not always mean the absence of COVID-19 virus infection (9). Several reasons might explain a negative result in a person infected with COVID-19 virus, mainly:

- Poor sample quality, handling, transportation and/or storage (to control for this, the qualitative detection of a human housekeeping gene [*eg*, RNase P (25)] can be performed).
- Poor/failed sample extraction, presence of PCR inhibitors in the extracted RNA (to control for this, an extraction control can be used, or the detection of a housekeeping gene undertaken as mentioned above).
- The sample was collected at a time where the patient was not shedding sufficient amounts of virus, for instance very early or very late during infection (this point is particularly relevant as the dynamics of the viral presence in different sample types has not been fully established).
- As with any molecular detection assay, virus mutations in the regions that are targeted by the assays might affect the sensitivity of the detection.

Antigen detection

During the first days after symptom onset (approximately 1 to 5), viral proteins (antigens) are generated and can be detected by different tests (*eg*, ELISA, immunofluorescence, or even rapid diagnostic tests [RDT]). However, the dynamics of production and secretion of these proteins has not been fully established. In general, antigen detection assays have acceptable specificity (depending on the assay), and can therefore be used as a confirmation criterion (in conjunction with the case definition, and the clinical and epidemiological history) and to make public health decisions (*eg*, isolation). However, these assays (in particular in the RDT format) often have lower sensitivity than molecular assays. Therefore, a negative result (at any stage of infection) **should not be used as a criterion to rule out a case**, and therefore additional testing with molecular assays is recommended (Figure 3).

Figure 3. Antigen detection-based algorithm



[1]ELISA or rapid tests with independent validation and regulatory approval.
[2]Assay specificity (including the potential cross-reactivity with other human coronaviruses) should be taken into account.
[3]When using the Charité reference protocol. If a different protocol is used, follow the indicated positivity criteria.
[4]As no other Sarbercovirus circulate globally, a positive result with the Charité E gene assay confirms the detection.
[5]Assuming the sample was collected properly, and all quality assurance processes were followed. Clinical and epidemiological information should also be considered before ruling out the case.
[6]Depending on surveillance protocols and available resources. Other respiratory viruses might also be tested.

Antigen detection assays should undergo independent evaluation to establish diagnostic performance and inform implementation modalities. Cost effectiveness should also be analyzed carefully. Given the likely loss of sensitivity, we recommend that these are only used for lower priority testing according to national guidelines and not for severe/hospitalized cases.

Serological methods

Serological assays detect antibodies (IgM, IgG or IgA) generated as part of the individual's immune response against the COVID-19 virus. In general, the highest proportion of antibodies are produced against the most abundant protein of the virus, the nucleocapsid (N). Therefore, assays that detect antibodies against this protein could be more sensitive. However, antibodies directed against the cellular receptor binding protein (protein S) are usually more specific. Therefore, using assays that detect IgG and/or IgM antibodies directed against the two antigens may perform better. In any case, these antibodies can cross react with SARS-CoV and even with other human coronaviruses (26).

Since the antibodies (IgM / IgG) against the virus are detectable only around day 7 from the onset of symptoms (in approximately 50% of cases), a negative serology result during the first 7 days of illness cannot be used as criteria to rule out a case (27). The sensitivity in the detection of total antibodies increases from the second week after the onset of symptoms; and by day 14 more than 90% of patients have already developed antibodies (detectable by ELISA). However, the detection of antibodies only indicates that there was previous contact with the virus, but it does not allow defining the moment in which the contact occurred. For example, a patient who has had previous contact with the virus (not necessarily ill) but who later becomes infected with another circulating pathogen that also generates respiratory symptoms (influenza or another pathogen), will be positive for COVID-19 antibodies leading to a wrong diagnosis. For this reason, the use of serology alone to confirm a case must be carefully evaluated.

On the other hand, it is important to note that the presence of antibodies does not necessarily indicate protection. The only way to infer the neutralization capacity of the antibodies will be through a plaque reduction neutralization test (PRNT). Even so, the duration of these antibodies over time and their protection capacity has not been fully established.

With all this, serological tests (both ELISA tests and rapid tests) are **not considered diagnostic tests** and their results should be carefully evaluated in light of the clinical information, the results of other tests and the epidemiological context. Thus, their implementation should be focused mainly on epidemiological research and seroprevalence studies.

Many commercial products are being marketed for the detection of antibodies (IgM and/or IgG) induced by COVID-19 virus infection, including RDTs. Any such test should be validated and its performance in terms of specificity and sensitivity assessed. Currently and at the request of WHO, evaluation and eventual validation processes are underway for some of these tests. Although preliminary validation data on ELISAs and RDTs have been generated, the results are based on limited datasets and not all have been conducted with well characterized panels of samples from COVID-19 patients.

Rapid diagnostic tests (RDTs) based on host antibody detection

So far there are no RDTs (immunochromatography, colloidal gold detection or other formats) that have been formally validated. In addition to all the limitations described above for serological tests, RDTs in general have lower sensitivity. Therefore, based on current data, **PAHO/WHO does not recommend the use of antibody-detecting rapid diagnostic tests for patient care or diagnosis of COVID-19** (28). Their usefulness in surveillance and epidemiological research is still to be established.

Influenza testing in the context of COVID-19

Influenza is a persistent threat and continued surveillance is needed for the detection of emergence of zoonotic and non-seasonal influenza viruses of pandemic potential (29). Therefore, **influenza detection must not be stopped, and laboratories should follow the influenza testing algorithm recommend by PAHO** under the routine influenza surveillance, in particular for unusual SARI cases.

Strengthening of laboratory capacity and networks

All national public health laboratories, including NICs, with molecular diagnostic capacity have implemented COVID-19 virus detection. Laboratories are urged to ensure the availability of human resources and generic supplies (*eg*, extraction kits and RT-PCR enzymes) for the detection of COVID-19 virus, and plan for a surge in laboratory testing.

Countries with no molecular diagnostic capacity to implement COVID-19 virus detection should send suspected clinical samples (strictly fitting the case definition) to a reference laboratory. The list of WHO reference laboratories providing confirmatory testing is available at:

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance

In the Americas, there are three WHO reference laboratories for COVID-19 virus:

- Laboratorio de Virus Respiratório e do Sarampo, Fiocruz, Rio de Janeiro, Brazil.
- Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE), Mexico City, Mexico.
- Respiratory Viruses Diagnostic Laboratory, US CDC, Atlanta, USA.

PAHO should be contacted before referring samples to WHO reference laboratories.

Genomic surveillance

Since the initial genomic characterization of the COVID-19 virus, the virus has diverged in different subclades (6). **Mutation is naturally expected in the virus evolution process.** In fact, some specific mutations define the viral subclades circulating. Although some of these mutations have been assessed for increased infectivity or virulence (30), at this moment **there is not sufficient evidence to show that some circulating COVID-19 viruses have increased virulence**.

Nevertheless, more genetic information about the circulating COVID-19 viruses in the Region is necessary to establish dispersion and evolution patterns. Thus, sequencing platforms may be used for COVID-19 virus genetic characterization in laboratories with Sanger or Next Generation sequencing capacity. These laboratories are encouraged to timely sequence positive samples and share genetic information through the Global Initiative on Sharing All Influenza Data Platform (GISAID) (6). PAHO is working on strengthening a COVID-19 genomic sequencing network in the Americas Region to make genomic data timely available through the GISAID platform. The COVID-19 Genomic Surveillance Regional Network is open to all countries in the Americas and relies on two Regional Sequencing Laboratories (Fiocruz, Brazil and Instituto de Salud Pública de Chile) for laboratories that need external sequencing.

Data reporting

According to the International Health Regulations (IHR), all COVID-19 confirmed cases should be notified within 24 hours through official IHR channels (10).

Additionally, all positive and negative results for COVID-19 must be reported in the FluNet database that is sent weekly to PAHO/WHO. Updated FluNet spreadsheets with the addition of a new column for COVID-19 reporting have been sent to the countries to replace the previous version. Additional information might be obtained through flu@paho.org.

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