

Corona Virus

PLAN RESPONSE FOR CLINICAL CHEMISTRY
LABORATORIES

05/18/2020

The Federal Pharmacy Council (CFF) makes this publication available with the objective of supporting pharmacists, employees and managers of clinical analysis laboratories in adopting actions aimed at ensuring the safety of patients, health workers and the population, and the provision of services, maintaining access to laboratory tests and health care (NHS, 2020; FIP, 2020). On March 11, 2020, the World Health Organization declared the disease caused by Coronavirus 2019 (COVID-19) a pandemic, an infectious disease with a high consequence (NHS, 2020). Between 80 and 85% of the cases are mild, not requiring hospitalization, and the suspected cases must remain in respiratory isolation at home. Among the cases that need hospitalization, about 15% will be out of the intensive care unit (ICU) and less than 5% need intensive support (AMB, 2020).

The population dissemination of coronavirus among people usually occurs after close contacts, and health professionals who provide care to patients are particularly vulnerable. In the outbreaks of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), health professionals represented a significant portion of the number of cases, having contributed to the amplification of epidemics. The virus is new and information about the disease and the pandemic is being dynamically consolidated. These guidelines are in accordance with the situation at the time of publication (26/03/2020). However, they are subject to updates. Therefore, the use of hyperlinks is of fundamental importance to the pharmacist to confirm that the information disclosed to the public is accurate and up to date. Collaborative efforts among health professionals to identify, isolate and contain COVID-19 are essential elements for an effective national response to coping with the disease.

Covid-19: an overview

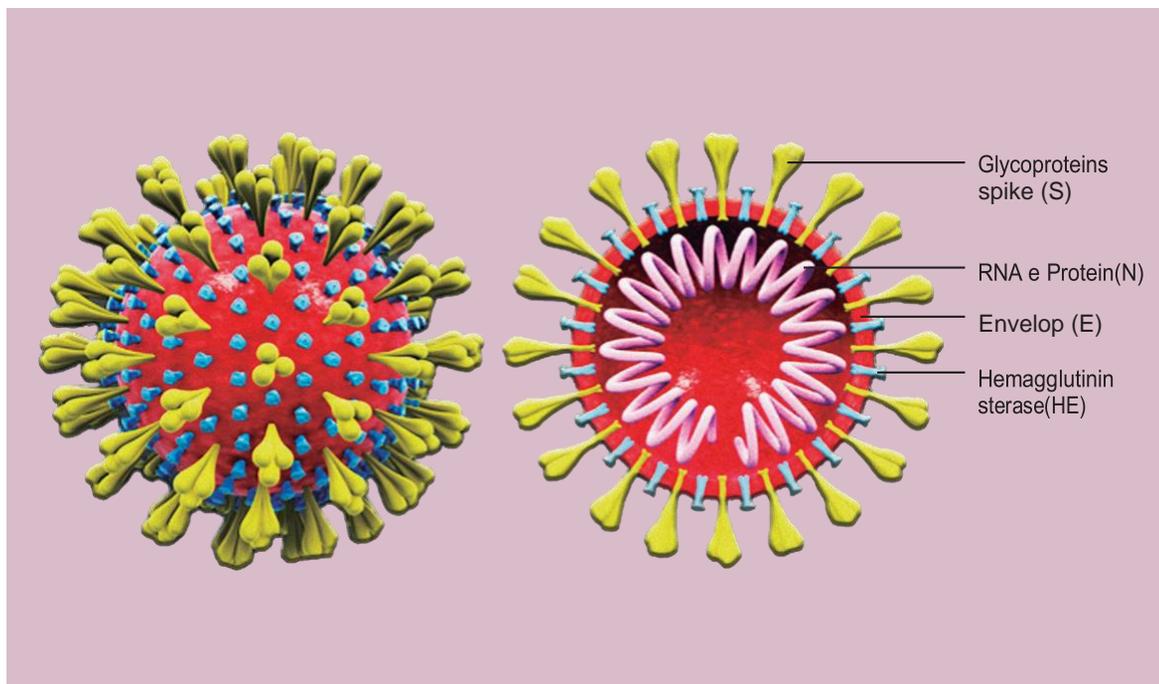
Coronaviruses (CoV) are a large family of viruses that cause diseases ranging from the common cold to more serious diseases, such as the Middle East Respiratory Syndrome (MERS-CoV) and the Severe Acute Respiratory Syndrome (SARS-CoV) (WHO, 2020). On December 31, 2019, an epidemic of lower respiratory tract infections of unknown etiology was reported to the World Health Organization (WHO) in the city of Wuhan, Hubei province, China (CASCELLA; RAJNIK; CUOMO; DULEBOHN et al., 2020; WANG; HORBY; HAYDEN; GAO, 2020). After investigations, on January 7, 2020, Chinese scientists were able to isolate a new coronavirus (CoV) in Wuhan patients, never before reported in humans. (WHO | Coronavirus disease (COVID-2019) R&D, 2020; CHAN; KOK; ZHU; CHU et al., 2020). Thus, on February 11, 2020, the Director General of the World Health Organization (WHO), named the disease caused by the new COVID-19 coronavirus, an acronym for “Coronavirus disease 2019” (CASCELLA; RAJNIK; CUOMO; DULEBOHN et al., 2020). Coronaviruses are zoonotic and have become the main emerging pathogens responsible for respiratory diseases. It is a large family of single-stranded RNA viruses (+ ssRNA) subdivided into two subfamilies: Orthocoronaviridae and Torovirinae (ASHOUR; ELKHATIB; RAHMAN; ELSHABRAWY, 2020; CASCELLA; RAJNIK; CUOMO; DULEBOHN et al.).

The subfamily Orthocoronaviridae, to which the new coronavirus belongs, named by the SARS-CoV-2 International Virus Taxonomy Committee (ICTV), is further subdivided into 4 genera: α , β , γ and δ (ASHOUR; ELKHATIB; RAHMAN; ELSHABRAWY, 2020; GUO;

CAO; HONG; TAN et al., 2020). α and β -CoV are capable of infecting mammals, including humans, while γ and δ -CoV, tend to infect birds (GUO; CAO; HONG; TAN et al., 2020).

In the past 20 years, two coronavirus epidemics have occurred, the Severe Acute Respiratory Syndrome (SARS) that started in China in 2002 causing about 8094 infections and 774 deaths, and the Middle East Respiratory Syndrome (MERS), responsible for a persistent epidemic in the Arabian Peninsula since 2012, with 862 deaths out of 2506 infected (ASHOUR; ELKHATIB; RAHMAN; ELSHABRAWY, 2020; CASCELLA; RAJNIK; CUOMO; DULEBOHN et al., 2020; CHAN; KOK; ZHU; CHU et al., 2020). Both were associated with severe complications of the lower respiratory tract and extrapulmonary manifestations such as diarrhea, lymphopenia, multiple organ dysfunction syndrome and mortality rates of $\pm 10\%$ and $\pm 35\%$, respectively (ASHOUR; ELKHATIB; RAHMAN; ELSHABRAWY, 2020). SARS-CoV-2 was isolated and sequenced from Wuhan patients who had respiratory symptoms and pneumonia in late 2019, and was characterized as a β -CoV, approximately 30 kb positive, non-segmented single-strand RNA envelope (Figure 1) (GUO; CAO; HONG; TAN et al., 2020). Phylogenetic analyzes showed that it shares 96% of its complete genome identity with a Bat CoV, BatCoV RaTG13, 91.02% with the Pangolin-CoV genome and 79% with SARS-CoV, suggesting inter-species transmission up to human infection and the existence of animal reservoirs for the new virus (ZHANG; WU; ZHANG, 2020).

Figure 1 – Schematic Representation from Coronavirus structure.



Source: adapted from <https://www.scienficanimations.com/wiki-images/>

COVID-19 CORONAVÍRUS

As far as is known, transmission occurs from person to person, through contact with droplets, aerosols and formulas containing viral particles. In addition, growing evidence points to the route of fecal-oral transmission (CHAN; WONG; TANG, 2020). SARS-CoV-2, like SARS-COV, binds to human type 2 angiotensin converting enzyme (ECA 2) receptors, which allows them to enter the host cell (ANDER-SEN; RAMBAUT; LIPKIN; HOLMES et al., 2020; TAI; HE; ZHANG; PU et al., 2020). The high affinity of SARS-CoV-2 with human ECA 2, may be related to the high transmissibility of the new CoV (ANDERSEN; RAMBAUT; LIPKIN; HOLMES et al., 2020; WAN; SHANG; GRAHAM; BARIC et al., 2020).

Since its identification, the number of SARS-CoV-2 infections has increased rapidly, reaching 185 countries to date, with more than 267,013 cases and 11,201 deaths (WHO | Coronavirus disease (COVID-2019) R&D, 2020). It is believed that symptomatic patients are primarily responsible for the spread of the virus, and that the incubation period is on average 5.1 days, and that 97.5% of patients will develop symptoms within 11.5 days of infection (CHAN; WONG; TANG, 2020; LAUER; GRANTZ; BI; JONES et al., 2020). However, a recent data raised the hypothesis of transmission by asymptomatic patients, because the peak viral load in symptomatic patients occurred 2 days after the onset of symptoms and proved to be similar to the viral load obtained from samples of asymptomatic patients (CHAN; WONG; TANG, 2020). In addition, a mathematical modeling study simulated the spatio-temporal dynamics of SARS-CoV-2 infections in 375 Chinese cities and demonstrated that 86% of infections were undocumented, and of these, 55% were as contagious as infections documented (LI; PEI; CHEN; SONG et al., 2020). However, there is still no consensus on this form of transmission, signaling the need to pay attention to the signs and symptoms of COVID-19, which include fever, cough, shortness of breath and breathing difficulties. In more severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death (WHO | Coronavirus disease (COVID-2019) R&D, 2020).

The great outbreak of COVID-19 led WHO to classify the disease as a pandemic on 03/11/2020 (WHO | Coronavirus disease (COVID-2019) R&D, 2020), leading to a great rush in the search for treatments and more effective and quick diagnostic methodologies. An article by Gautret et al., Brought the information that the use of the drug Chloroquine associated with Azithromycin was, in a small group of patients, effective in the treatment of the disease (GAUTRET; LAGIER; PAROLA; HOANG et al., 2020). However, results are still preliminary and are entering a testing phase in several pharmaceutical laboratories and hospitals around the world.

The concern with the rapid spread of the virus, and the lack of structure in hospitals to treat severe cases, in addition to the lack of beds in ICUs, led the most diverse state leaders in the affected countries to take extreme measures such as social isolation, closure of trade and borders and even a state decree of public calamity.

In view of this situation, this guide aims to outline a plan that helps clinical analysis laboratories in making decisions when facing COVID-19 and strengthens laboratory diagnosis and virological surveillance through standardized methods for biosafety, collection, packaging, transport and standards for biosafety, collection, packaging, transport and diagnostic methodologies.

Notification of suspected Coronavirus cases

Human infection caused by the New Coronavirus (COVID-19), represents a serious Public Health Emergency of International Importance (ESPII), according to Annex II of the International Health Regulations, thus being a public health event with immediate notification.

The notification must be carried out immediately through the fastest and most available means of communication, within 24 hours from the knowledge of the case, falling within the definition of a suspected case of a patient infected with the new coronavirus, as determined by the Ordinance of Consolidation No. 04, Annex V, Chapter I, Section I (<http://j.mp/portariadeconsolidacao4ms>).

The Ministry of Health makes available on its website all information on protocols, managements, referral hospitals and coronavirus bulletins through the electronic address: <https://coronavirus.saude.gov.br/>

The role of Clinical Analysis Laboratories

Clinical analysis laboratories are responsible for 95% of medical decisions procedures and, in the case of the corona virus, the laboratory is responsible for the etiological confirmation. This guidance document follows the approach recommended internationally for the Clinical Analysis Laboratories (ISO 15.189 / 2016) and ANVISA RDC302 / 2005 (www.pncq.org.br; www.dicq.org.br).

Every laboratory exam goes through 3 sequential and interdependent phases: pre-analytical, analytical and post-analytical phases.

1. Pre-Analytical Phase

1.1. Reception and Registration

To avoid crowding, you should:

- Demarcate space in the external area of the laboratory for the organization of the queue;
- Create a physical barrier to entry to the laboratory;
- The laboratory must restrict the entry of patients, guaranteeing the distance indicated by the Ministry of Health, which is 1 to 2 meters between all people present in the service space, including employees;
- Leave a 70 ° bottle of alcohol (liquid or gel) available at the entrance to the laboratory for use by patients;
- Provide and make patients with respiratory signs and/or symptoms wear a surgical mask (Figure 2);

Figure 2 – Use of disposable masks and aprons



- Mark chairs in the waiting room that may be used leaving a note on those that must not be occupied in order to respect social distancing (Figure 3).

Figure 3 – Guidance on the occupation of chairs in the waiting room



Source:
Pharmacist Waldirene Nicioli –
CRF-PR 13.735

To reduce contact with potentially contaminated materials:

- All employees' attire in attendance with PPE (personal protective equipment): glove, mask, goggles, caps and disposable apron (<http://portal.anvisa.gov.br>);
- Isolated flow for confirmed cases, probable cases, suspicious cases and their home contacts of those asymptomatic users;
- Limit collection, outside the hospital environment, to patients in home isolation in compliance with the determination of isolation of patients under investigation;
- Instructions for proper disposal and identification of specific trash for tissues and other disposables potentially contaminated by users during care;
- Intensify the cleaning and disinfection routine of the establishment (under construction);
- Provide a tray that allows disinfection so that patients' medical orders are placed, avoiding direct contact with the bench and between the employee's and patients' hands. In this case, disinfection must be carried out using an effective technique.

The use of Personal Protective Equipment (PPE) and its indication of use are summarized in Table 1.

Table 1 – Personal Protective Equipment (PPE) and its indication

Reception Screening	Health professionals	Preliminary screening with no direct contact	At least 1 meter of distance, with no PPE
	Patients with respiratory symptoms	Any	At least 1 meter of distance, with no PPE, with medical mask, if tolerated.
	Patients with no respiratory symptoms	Any	No PPE
Technical areas	Laboratory technician	Manipulation of respiratory samples	Medical mask, cap, gloves, goggles (IF there is risk of spill)
Administrative areas	All employees including health professionals	Administrative tasks with no contact to patients suffering from COVID-19	No requested PPE

1.2. Waste management

Plan the correct disposal and final destination of health products, PPE's and other materials used for the pharmaceutical services and procedures implemented. According to what is known so far, the new coronavirus (2019-nCoV) can be classified as a biological agent **class of risk 3**, following the Risk Classification of Biological Agents published in 2017 by the Ministry of Health (MS), being its transmission high-risk individual and moderate risk to the community. Therefore, **all residues from assistance to patients suspected or confirmed of infection with the new coronavirus must be classified in category A1**, according to Resolution RDC / Anvisa nº 222, of March 28, 2018.

The laboratory's waste management plan must be adequate and applied by all employees, supervised by the technician responsible and the laboratory manager. The disposal of all contaminating residues from personnel PPE tests, among others, must follow at least the general guidelines (MINISTRY OF HEALTH, 2020):

1. In washable material container, resistant to puncture, rupture, leakage and tipping, with lid provided with an opening system without manual contact, with rounded corners;
2. Pack the residues in a milky white bag, identified with the infecting substance symbol;
3. Replace the bags when they reach 2/3 of their capacity or at least once every 48 hours;
4. The collection and processing of contaminating waste must be done by a specialized company.

Additionally, in the circulation areas, there must be a trash bin available, which follows the recommendations above, for the disposal of infectious materials from patients, such as disposable tissues and others. These dumps should have guidance on other steps involved in disposal. The National Health System (NHS) recommends “Catch it”, “Bin it” and “Kill it”, as shown in Figure 4.

Figure 4 - Suggested poster for education on the correct disposal of contaminating waste from patients.



Grab it

Germs spread easily. Always have tissues or use your elbow to contain cough or sneezes.



Dispose it

Germs may live for many hours in tissues and clothes. Dispose them in appropriate bins.



Eliminate it

Hands may transfer germs to every surface they touch. Wash your hands as frequent as possible.

Source: Adapted from NHS (2019)

1.3. Sample collection

Collection will be carried out whenever there is a suspect patient (according to the definition of a suspected case) of COVID-19, following the biosafety rules recommended for biological materials.

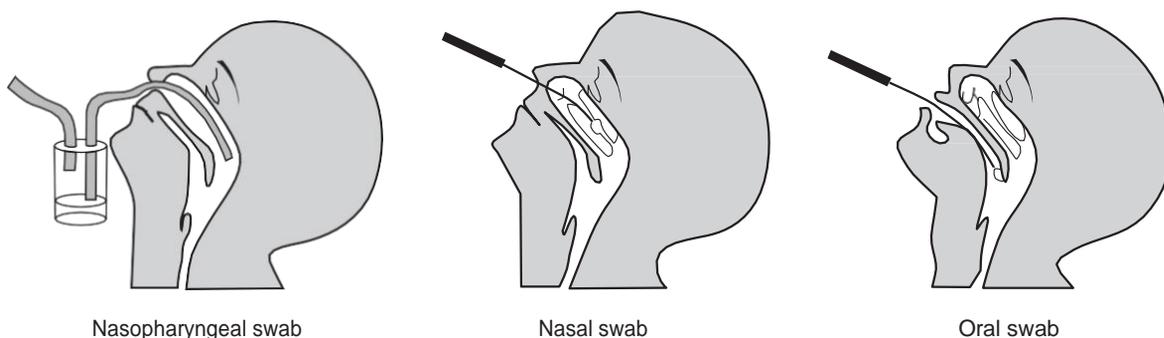
The collection will be performed, preferably, until the 3rd day of the onset of symptoms, and can be collected until the 7th day and being performed by a properly trained health professional using appropriate personal protective equipment (PPE): apron, goggles, cap, disposable gloves and mask (N95).

The collection of nasopharyngeal aspirate (ANF) or combined nasopharynx and oropharynx swabs (Rayon Swab, the same one used in suspected Influenza) is recommended, as shown in Figure 5.

The collection of a sample of lower respiratory secretion (sputum or tracheal lavage or bronchoalveolar lavage) must be restricted to the hospital environment.

The laboratory can standardize the collection with a swab in both nostrils and another in the oropharynx, both being placed in the same transport tube.

Figure 5 – Collection procedure for COVID-19 research.



Source: http://inrad.hc.fm.usp.br/wp-content/uploads/2017/11/SCIH_Vigilancia-influenza-2013.pdf

How to perform the combined swab collection (nasopharynx / oropharynx) - upper respiratory tract:

1. Carry out the introduction of the Rayon swab in the nasal cavity (about 5 cm), in the upward direction (as if in the direction of the eyes), following an angle between 30 and 45 ° in relation to the upper lip
2. Rub the swab with delicate circular movements, applying pressure against the side wall of the nose, always towards the ear;
3. Remove the swab from the patient's nose and immediately insert it into the means of transport;
4. Perform the collection in both nostrils (one swab in each nostril);
5. Pick the third swab in the posterior area of the pharynx and tonsils, avoiding touching the tongue;
6. Insert the three swabs in the same bottle containing the viral transport medium;
7. Perform identification of the sample in the transport tube with the patient's full name;

8. The collected samples must be kept refrigerated (4 to 8 ° C) up to 72 hours in a specific medium or 48 hours in sterile saline and must be sent to the laboratory in a thermal box with recyclable ice and accompanied by the notification.

For rapid testing, whole blood (from venipuncture or finger puncture), serum or plasma can be used.

How to perform the collection of whole blood samples by finger puncture:

1. Wash the patient's hand with soap and warm water or clean with an alcohol pad. After letting it dry;
2. Perform a massage (rubbing the patient's hand towards the tip of the middle or ring finger) without touching the puncture site;
3. Pierce the skin of the finger with a sterile lancet, but clean the first sign of blood;
4. Gently rub your hand from wrist to palm until a drop forms;
5. Bring the end of the capillary tube to the blood until it is filled with approximately 20µL;
6. Ping the whole blood sample to the test using the capillary tube.

In case of using serum or plasma, perform the separation as soon as possible to avoid hemolysis. Use only clear, non-hemolyzed samples. In this case, the test must be carried out immediately after the collection of the samples, not leaving them at room temperature for prolonged periods.

Tubes with EDTA K2, sodium heparin, sodium citrate and potassium oxalate as anticoagulant can be used for sample collection.

1.4. Storage

Serum and plasma samples can be stored at 2 to 8 ° C for up to 7 days. In the event of prolonged storage, serum / plasma samples should be kept below -20 ° C.

Before carrying out the tests, allow the refrigerated samples to reach room temperature; and frozen samples must be thoroughly thawed and mixed well before testing.

Observe and take care that the samples are not frozen and thawed repeatedly. If samples need to be transported, they must be packaged in accordance with local regulations covering the transport of etiological agents.

Whole blood collected by finger prick should be tested immediately. Do not freeze whole blood samples.

2. Analytical Phase

Laboratory methods for diagnosing COVID-19

2.1. Molecular testing

The laboratory diagnosis of COVID-19 available so far is considered the gold standard and is the quantitative reverse transcription polymerase chain reaction methodology in real time or qRT-PCR (from Real-Time Quantitative Reverse Transcription Polymerase Chain Reaction) performed with samples from the upper and lower respiratory tract.

Laboratories that intend to execute the qRT-PCR methodology must validate their tests with one of the reference laboratories linked to CGLAS- General Coordination of Public Health Laboratories.

2.2. Immunocytographic tests for COVID-19

2.2.1. Antigen Research

This test investigates the presence of SARS-CoV-2 antigens in samples collected from the nasopharynx using fluorescence as a method of reading the reaction. The manufacturer recommends that the sample should be tested immediately after collection, however, states that: “although not recommended, the sample can be stored at 2° to 8°C for up to 48 hours.” This test cannot be performed on samples that have been placed in a viral transport medium.

2.2.2. Search for anti-SARS-CoV-2 antibodies

The serological test will look for the presence of antibodies, which are specific proteins produced in response to infections. Antibodies can be found in the blood and other tissues of people who have tested positive for infection using the qRT-PCR method. The antibodies detected by this test indicate that a person had an immune response to SARS-CoV-2, developed from the infection. The results of antibody tests are important in detecting infections in people with few or no symptoms.

Some sets of reagents for serological tests were authorized by Anvisa on an emergency basis due to the seriousness of the situation and the need to expand the testing of the population, but the validation of these reagents by the laboratories is essential, since few studies were able to be published until the moment.

From the reagent sets that, until the edition of this document, had already been published, we can extract the following information:

1. Types of samples:
 - a) Serum: common to all tested reagent sets.
 - b) Plasma: common to all, however, only one manufacturer determines which anticoagulants can be used to obtain it.
 - c) Whole blood: common to all, however, with the same observation made above for the type of plasma sample.
2. Sample stability:
 - a) Serum or plasma: 2° to 8°C up to 7 days; storage below -20°C is quoted by one of the manufacturers, which however does not specify the maximum time.
 - b) Whole blood obtained by venipuncture: 2° to 8°C for up to 48 hours.
 - c) Whole blood obtained by capillary puncture: analysis must be immediate.
3. Reading time: the documents analyzed speak in 10 minutes for reading the result, but disagree about the maximum time for reading limit, which for some is up to 15 minutes and for others up to 20 minutes.
4. Specificity: the specificity cited for IgM type antibodies varies between 95% to 96% according to the manufacturer. For IgG type antibodies it ranges from 95% to 98%.
5. Sensitivity: for IgM antibodies everyone reports 85% and for IgG antibodies it ranges from 95% to 100%.
6. Cross reactions: the documents analyzed mention that they were tested with positive samples for anti-influenza A virus, anti-influenza B virus, anti-RSV, anti-adenovirus, anti-syphilis, anti-H. Pylori, anti-HIV, anti-HCV and HBsA, and that the results showed no cross-reactivity.

7. Limitations of the test: one of the manufacturers claims that the hematocrit level of the whole blood tested can affect the test result and states that the sample hematocrit value must be between 25% and 65% in order to obtain accurate results.
8. Interferents: one of the manufacturers states that the tests performed did not show any interference from the following substances up to the indicated concentrations:
 - a. Triglycerides up to 50 mg/dL
 - b. Hemoglobin up to 1000 mg/dL
 - c. Ascorbic acid up to 20 mg/dL
 - d. Bilirubin up to 60 mg/dL
 - e. Cholesterol up to 6 mmol/L (approximately 232 mg/dL)
9. None of the inserts state that positive and negative controls are provided with the reagents.
10. Precautions when performing tests:
 - a. Only trained professionals should perform in vitro diagnostic tests
 - b. Do not use the reagent set after expiration
 - c. Do not eat, drink or smoke in the area where samples and / or reagents are handled.
 - d. Do not use the test if the package is damaged
 - e. Every biological sample is potentially infectious. Handle in accordance with good laboratory practices. Observe established precautions against microbiological hazards throughout all procedures and follow standard procedures for proper sample disposal
 - f. Use PPE's like: lab coat, disposable gloves and eye protection during the analytical procedure
 - g. Make sure that the appropriate amount of sample was obtained at collection and will be used for testing. Too much or too little sample can give wrong results.
 - h. The test used must be discarded in accordance with local regulations
 - i. Humidity and temperature can adversely affect results.

3. Post-Analytical Phase

As in the pre-analytical and analytical phases, the employees of the clinical analysis laboratory must follow the biosafety protocols and adapt the processes to minimize contact with potentially infected patients.

The laboratory must prioritize the delivery of exams by digital means, organize and validate the laboratory processes, preparing it to serve its users with restrictions, train the entire team, supply and demand the use of personal protective equipment (LIPPI; PLEBANI, 2020; IWEN et al., 2020).

4. Other Recommendations and Guidelines

4.1. Vaccination

All laboratory collaborators must have the vaccination schedule up to date.

4.2. Sanitization of hands

Hand hygiene with water and liquid soap or 70 ° gel alcohol should be performed in five moments, as recommended by the WHO:

Moment 1: before contact with the patient;

Moment 2: before performing the procedure;

Moment 3: after risk of exposure to biological fluids;

Moment 4: after contact with the patient;

Moment 5: after contact with areas close to the patient, even if he has not touched the patient. Taking care directly or indirectly of the patient.

To perform the correct procedure, consult the WHO Guidelines on Hand Hygiene in Health Care, available at the link <https://bit.ly/2x7EOTa>. And watch the video with the demonstration of hand hygiene: <https://www.youtube.com/watch?v=2h8vc-voPNQ>

4.3. Cleaning the laboratory environment

The laboratory should implement a routine for cleaning and disinfecting the environments. Since SARS-CoV-2 can be transmitted through droplets and contact, all areas and objects that may have been contaminated with the virus must be disinfected.

- It is recommended to keep the environment ventilated, forcing air to circulate throughout the day. To do this, open the windows or turn on a mechanical fan for at least 30 minutes twice a day.
- In circulation areas, surfaces of objects such as telephones, computers, keyboards, mice, cash registers, scales, tables, chairs, handrails, counters, tables and knobs must be cleaned for disinfection with 70 ° liquid alcohol every 2 hours.
- Large surfaces such as floors, bathrooms, refrigerators, lockers, air conditioning equipment must be cleaned for disinfection with disinfectant containing active chlorine and / or hypochlorite solution 1% at least twice a day.
- Never sweep surfaces dry, as this favors the dispersion of microorganisms that are carried by the dust particles. Use wet sweeping that can be performed with mops or squeegee and floor cleaning cloths. To clean the floors, wet sweeping techniques, lather, rinse and dry must be followed.
- The cleaning products indicated for disinfection in the case of SARS-CoV-2 are: 70° alcohol, 1% hypochlorite solution and detergents containing active chlorine. An important observation is not to use chlorhexidine-based products for local antisepsis, as these are not effective against SARS-CoV-2. The cleaning team must be properly trained to handle these chemicals.
- Cleaning utensils: After cleaning, mop, brooms, floor cloths and wheels should be separated and cleaned in their own area. Rinse with water after each use, dip and sterilize with disinfectant solution containing chlorine for 30 minutes, rinse again with water and then dry to use again.

The basic principles for such action are described in Anvisa's Manual for Cleaning and Disinfecting Surfaces, available at <https://bit.ly/2IX7lgC>. Precautionary measures, as well as the use of PPE, must be appropriate for the activity to be performed and necessary for the procedure (<https://bit.ly/38XumdZ>);

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