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### RESEARCH ARTICLE

#### WHAT ROLE DOES THE BIOLOGY LABORATORY PLAY IN THE RESPONSE TO COVID19 PANDEMIC?

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#### Abstract

The new pandemic caused by SARS-Cov-2 has had a major impact on clinical microbiology since confirmation of infection is based on virological diagnosis. This publication has the aim to clarify the strategy of laboratories in the management of patients Covid 19. At the pre-analytical stage, the choice of the site of the sample at the level of the respiratory tract as well as the right time constitutes an essential step for a rapid and reliable virological diagnosis of COVID-19, while ensuring the optimal conditions of safety for laboratory staff. At the analytical stage, RT - PCR in real time remains the reference test for the diagnosis of the acute phase of Covid-19. Based on molecular biology methods, they make it possible to detect the presence of SARS-CoV-2 in the body of an individual and therefore to confirm a diagnosis of Covid-19. Serological tests meanwhile determine whether no one has been exposed to SARS-CoV-2, identifying the presence in the body of antibodies produced following infection. Asymptomatic individuals can thus also be identified. In some cases, for symptomatic patients, serological tests can be used in addition to RT-PCR tests to confirm a diagnosis or identify false negatives. Serological tests, however, have a crucial role in epidemiological surveillance in order to estimate the actual spread of the infection in the population. For the post - analytical stage, the test results must be carefully interpreted. Some data concerning the guidelines for diagnosing covid19 are subject to change, due to the emergence of several scientific publications and on the basis of new expert recommendations.

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#### Introduction:-

In December 2019, the appearance of several cases of unexplained severe pneumonitis [1] in Hubei province in China led to the identification, in January 2020, by the Chinese Center for Disease Control and Prevention of a new coronavirus [1]

In February 2020, the World Health Organization (WHO) assigned the name COVID-19 to designate the disease caused by this virus, initially called nCoV-2019, then SARS-CoV-2 by the international committee of taxonomy of viruses [2]. Parts of the SARS-CoV-2 genome sequence have been reported to be identical to those of two other strains of coronavirus, which are responsible for serious and life-threatening conditions: SARS-CoV-1 and

MERS- CoV identified respectively in 2003 and 2012 [3 - 5]. The origin of these two viruses was zoonotic: SARS-CoV-1 was probably transmitted to humans from civet, raccoon or ferret [6] and MERS- CoV from dromedary [7]. The natural host was in both cases the bat [8].

It is a Betacoronavirus probably transmitted to humans by the pangolin, on the Huanan seafood market, located in the city of Wuhan [9]. Person transmission resulted in the spread of the virus to different countries [10], according to a recent report, 29 May 2020 more than 5,991,102 cases of infection with SARS-CoV-2 and more than 366 875 deaths have been reported, it is the third global health threat linked to a coronavirus in less than two decades [11].

This new pandemic, caused by the new SARS-CoV-2 virus, poses a real challenge for biology laboratories since confirmation of infection is based on virological diagnosis; we wanted to discuss in this development the diagnostic strategies by specifying the role of the laboratory in the management of infection with SARS-CoV-2.

### **Epidemiological data**

The SARS-CoV-2 can affect all age brackets, the transmission of this infection can be through droplets generated when coughing or sneezing of symptomatic patients and asymptomatic or during the incubation period which is average of 3 to 7 days [12]. The infection is acquired either by direct inhalation of these droplets or by contact with infected surfaces where the virus can stay for days [13]. The virus is also present in stool and contamination of food and water can be responsible for subsequent transmission by aerosolization. The way of infection is also hypothetical [14]. According to current information, transplacental transmission from pregnant women to the fetus has not been described [15]. Studies have shown that contagiousness may be more important in the early days of symptoms that may persist even after symptoms [16-18], several cases of contamination during the incubation period or from patients asymptomatic have been reported [19]. This poses a serious challenge for the control and prevention of this disease, so screening on a large scale in the population to laboratories of biology, is the tool appropriate to stop the spread of the pandemic.

### **Tools for the virological diagnosis of SARS-CoV-2**

#### **Pre-analytical phase**

Given that viral load is low in liquid organic and viremia is transient, the sampling recommended is according to WHO for initial diagnosis of Covid - 19 are the samples upper respiratory tract by swabbing nasopharyngeal and lesions of lower respiratory tract by sputum, broncho-alveolar washing liquid or tracheobronchial aspiration in case of parenchymal involvement, to be preferred in case of infection progressing for more than 7 days since studies have shown that RNA remains positive in upper respiratory tract 7 to 10 days after the onset of symptoms and then gradually decreases while in samples of lower respiratory specimens, RNA remains present three weeks after the onset of the disease [20 - 21], so Although samples upper respiratory tract is negative, collection and analysis of lower respiratory tract samples is strongly recommended, especially in case of serious or progressive illness.

samples must be performed by experienced health professionals and informed personal protection (gloves, masks FFP2, goggles, gown, cap), with respect precautions rigorous: using swabs tip dacron / polyester for molecular biology, carefully protected deep or pharyngeal nasal swabs in a virological transport medium, transmission of samples to reference laboratories in triple packaging according to national or international regulations for the transport of infectious substances [22]. In the event of delay, the sample must be kept at + 4 ° C for 48 hours. The virological analysis request form and the patient identification sheet accompany each sample.

According to the recommendations of the WHO, CDC and ECDC, the virological diagnosis can only be carried out in specialized laboratories which meet very strict conditions of security and organization given the nature of the samples handled, in this case a laboratory security biological level 2 (LSB2). Only the culture of the virus which must be carried out in an LSB3.

### **Diagnostic Methods:-**

#### **RT-PCR in real time:**

The certainty diagnosis is based on the identification of the virus by RT-PCR carried out on respiratory samples. Several protocols have been used for the detection of viral RNA by real-time RT PCR [23 - 28]. These technologies differ in the viral gene target, the E gene (gene of the coat protein gene RdRP (gene RNA dependent RNA polymerase)) and N gene (gene of the nucleocapsid protein). The

analytical sensitivity of the reagents targeting the RdRP and E genes is higher (technical detection limit of 3.6 and 3.9 copies per reaction) than that of the N gene (8.3 copies per reaction).

Among the different protocols, some examine two genes using a two-stage interpretation algorithm [30-32]. In these protocols, the identification of a gene is used as a screening test, while that of the second gene is used as a confirmatory test. In contrast, results from other protocols, which examine three or more genes, are only considered positive when all of the genes are detected. If one of the genes is not detected in these protocols, the results are often interpreted as undetermined or negative. These guidelines were prepared on the basis of the guidelines provided by the WHO [25], which recommend PCR amplification of the viral E gene as a screening test and amplification of the RdRp region of the orf1b gene as a confirmation test. RT-PCR has a very good specificity which would be 100% (there would be zero false positives) and has the advantage of running large series at the same time but requires between 3 and 6 hours to obtain the result without counting the routing of the levy.

Currently, the ideal time to detect viral RNA is 1 to 7 days after the onset of symptoms. Beyond that, the nasopharyngeal swab is no longer optimal, as the High Authority for Health (HAS) indicates in a recent report. Other samples (saliva for example) can then be considered to establish a diagnosis.

However, this technique lacks sensitivity (false negatives). False negative results may be related to a low viral load, the quality of the sample and the stage of the disease (this is the case during the early contamination phase and then during the disappearance of symptoms), the presence of PCR inhibitors, mutation of the virus as well as the conditions of transport [25-28], this is why we should not hesitate to repeat the samples from the upper airways and also take deep samples. The sensitivity on samples other than respiratory (blood, urine, stool) is low (<50%) which makes its use in current practice unthinkable [29]

In order to shorten the duration of the virological test, other PCR techniques are available and allow to reduce the duration of the analysis, these are automated PCR in closed circuit (cartridge system) with a result obtained quickly, around an hour. It is a simple technique with good specificity and acceptable sensitivity, and easily achievable in LBS2 laboratories with a limited rate of requests.

In addition, the determination of the viral load (CV) by a quantitative or semi quantitative technique is mainly used for clinical research.

### **Serology:**

Members of the coronavirus family have four protein structures: peak (S), membrane (M), envelope (E) and nucleocapsid (N) proteins. Two of these proteins appear to be important antigenic sites for the development of serological tests to detect COVID-19. Serological methods have focused on the detection of serum antibodies against the S proteins of the tip of the coronavirus [38]. These proteins are responsible for binding and fusion receptors and determines the tropism and the transmission capacity to the host [39,40]. S proteins are determined by the S gene and are functionally divided into two subunits (S1 and S2). The S1 domain is responsible for binding to the receptor while the S2 domain is responsible for the fusion. SARS-CoV-2 binds to the human angiotensin 2 converting enzyme, which is found in human respiratory cells, kidney cells, and gastrointestinal cells [8-40-41].

The other protein that appears to be an important antigenic site for the development of serology is protein N, which is a structural component of the helical nucleocapsid. Protein N plays an important role in viral pathogenesis, replication and packaging of RNA. Antibodies to protein N are frequently detected in COVID-19 patients [41], suggesting that protein N MAY be one of the immune-dominant antigens in the early diagnosis of COVID-19[42].

Serological tests are not systematically used for the diagnosis of Covid19 because they do not allow to know if a person is contagious contrary to PCR and because they are not present in the early phase of the disease, since the IgM and IgG are not produced at the start of the infection, but a little later (from the 5th day and from the 10th day respectively of the start of the symptomatology for IgM and IgG) and we can thus move on to side of recently infected cases [33]. Serological tests facilitate diagnosis in patients with a strong clinical presumption of SARS-CoV 2, while RT-PCR tests are negative due to a false negative or in patients who presented late (more one week of

onset of symptoms) [ 34 ]. These tests are especially useful in epidemiological studies to assess the real extent of the pandemic by identifying asymptomatic forms, as well as estimating the case fatality rate [35].

Studies are underway to find out if these antibodies persist in the medium term ( 3 to 12 months) and in the long term (more than 1 year) and if they are really protective against subsequent infection. Assuming there is protective immunity, serological information can be used to guide deconfinement including return to work decisions, including for individuals who exercise in environments where they can potentially be re-exposed to SARS-CoV-2 [35]. These serological tests can be carried out on whole blood (by venipuncture or with the finger), serum or plasma. Serum and plasma samples can be stored at 2-8 ° C for up to 3 days. For long term storage, samples should be stored below -20 ° C. Whole blood drawn by venipuncture should be stored at 2-8 ° C and the test should be performed within 2 days. Do not freeze whole blood samples. Whole blood collected at the fingertip should be tested immediately.

#### **Rapid tests:**

According to the latest recommendations of the HAS [36] which are based on 16 studies, these tests constitute precious tools for carrying out epidemiological studies, RDTs (rapid diagnostic test) and TROD (rapid diagnostic orientation test) could supplement the diagnostic offer by automated serological tests, in the same indications and there also on medical prescription. Indeed, thanks to their greater speed of use and the little material required to carry them out, they would be accessible throughout the territory, without heavy technical platform.

Each corresponds to methods of implementation, but also to different purposes. The TDR for clinical laboratory tests, performed in the laboratory. The HAS recommends using it with the same populations as automated tests: in the catch-up diagnosis of symptomatic patients, in the event of a negative virological test but of symptoms suggestive of COVID-19, and with nursing staff or establishments of collective accommodation that has been in contact with the virus and for epidemiological investigations [37].

TRODs can be carried out in more places and by any health professional (doctors, midwives, nurses, pharmacists, **etc.** ) or even trained members of certain associations who could do them in a medical office, in a pharmacy, at home. ... The HAS recommends their use in a more restricted field than RDTs and automated tests: for nursing staff and collective accommodation and for symptomatic patients without signs of severity if they have difficulties accessing a laboratory of medical biology, but not in hospital.

TRODs are rather diagnostic orientation tests, not tests allowing to formally make the diagnosis of COVID-19. Therefore, they cannot replace medical laboratory biology examinations. It is necessary after a positive TROD to confirm the result by an ELISA or TDR serological test - reference tests.

L 'HAS considers it premature to recommend the use of self-tests for serological diagnosis Covid-19 to this day, because there are so far very little scientific data on the performance of self-tests for the diagnosis of COVID-19 in real life .

In addition to this uncertainty about the reliability of these tests, there is a difficulty in use: if the taking of the sample is simple (the patient performs it alone, at home, by pricking the fingertip), it is not the same for reading and interpreting the result. Without support, the patient takes the risk of drawing the wrong conclusions from this test.

#### **Conclusion:-**

The current COVID-19 pandemic, which has succeeded in winning the gamble of emergence with such magnitude and rapidity, has posed a real challenge for biology laboratories, given their essential role in the diagnosis of this new coronavirus, in the fight against the spread as well as in the adequate management of these infected patients. The first-line diagnostic tool is represented by RT-PCR which is to be distinguished from serological tests. Reliable serological tests can play a very important role in guiding public decision-making in the context of the Covid-19 pandemic and in advancing clinical research , but many questions remain about the immune response to the virus and the existence of certain and permanent protection following infection with SARS-CoV-2 is not yet guaranteed.

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