



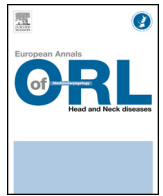
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Technical note

## Keys for analysis of diagnostic and serologic tests for CoV-2

O. Laccourreye<sup>a,\*</sup>, R. Cohen<sup>b</sup>, V. Couloigner<sup>c</sup>

<sup>a</sup> Service d'Otorhinolaryngologie, Université Paris-Centre, Hôpital Européen Georges-Pompidou, AP-HP, 20-40, rue Leblanc, 75015 Paris, France

<sup>b</sup> Service de Pédiatrie, Université Paris-Est, Centre Hospitalier Intercommunal, 40, avenue de Verdun, 94000 Créteil, France

<sup>c</sup> Service d'Otorhinolaryngologie, Université Paris-Centre, Hôpital Necker-Enfants malades, AP-HP, 149, rue de Sèvres, 75015 Paris, France



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### ABSTRACT

Based on a review of the medical literature, the authors document the key points regarding the tests available in France to screen for and diagnose of CoV-2 infestation.

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### 1. Introduction

To combat the SARS-CoV-2 (CoV-2) epidemic once France had gone into lockdown on May 7, 2020, the French Health Minister declared that all persons present in France showing symptoms suggestive of coronavirus disease (COVID-19) should consult their doctor and, if considered necessary, undergo screening (with full national health insurance cover as of May 11, 2020).

In the coming weeks and months, French ENT physicians will be prescribing tests in case of symptomatology typically revealing CoV-2 infection (fever, cough, respiratory disorder, taste and/or olfactory disorder), and will also need to interpret the results and explain them to the patient. The present technical note presents the key points of the tests, stressing test association and combined timely analysis, based on a recent study published in the JAMA [1].

### 2. CoV-2 identification tests

The first COVID-19 test is performed on swabs from the nasopharynx or sometimes tracheobronchial tract, oropharynx or sputum. It detects coronavirus ribonucleic acid (RNA) on polymerase chain reaction (PCR).

PCR shows almost 100% specificity but variable sensitivity, greatly depending on sample quality, ranging between 60% and 80% in early stages and decreasing over time to just 40–50% at 3–6 months of onset (Fig. 1), as viral load rapidly decreases with immune response [1]. As well as the problem of sensitivity, PCR, despite its cost advantages, has various drawbacks. Some of its reagents are expensive, and are running out with the exponential

growth of testing. The test also has to be performed in a laboratory, requiring sophisticated equipment, the availability of which is limited. Moreover, depending on the degree of automation, the test takes between 3 and 6 hours and results are often not available until 24 hours later or more.

To facilitate mass screening, various tests are under assessment, by the national reference centre for respiratory infection viruses in France. These rapid screening tests, using saliva, throat or nasal samples, detect either viral RNA (test performed by a clinician in less than 20 minutes) or viral protein on antigen techniques. Results are obtained within a matter of minutes, depending on the test, enabling mass implementation, but specificity and, above all, sensitivity remain to be determined. They also lack a signal amplification phase as strong as in PCR and detect the virus only at high levels of infestation, and are thus probably less sensitive than PCR in identifying an infected individual. In case of negative findings in a subject presenting suggestive symptoms, it is probably advisable to complete screening with PCR.

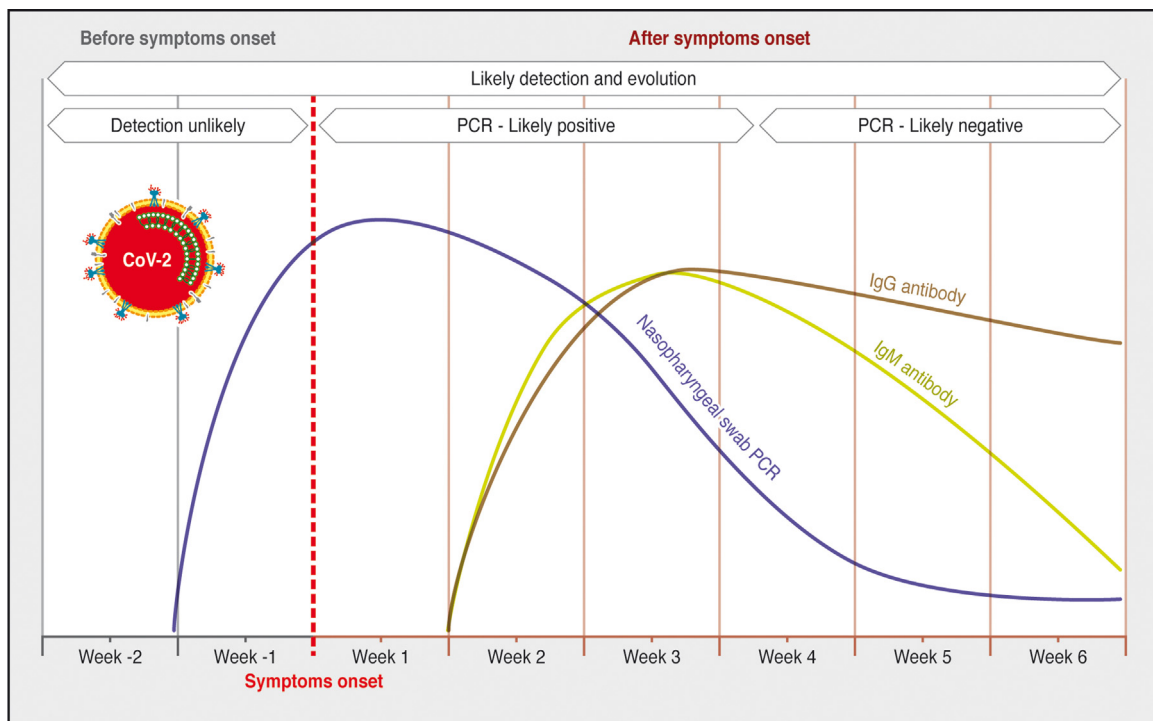
### 3. Serology tests

Compared to diagnostic tests, serology tests provide “historical” information on COVID-19, and can identify potentially protected subjects.

In response to CoV-2 infection, the immune system produces specific antibodies against viral proteins that can be detected in blood, with inter-individual variations in timing and in level. Antibody production begins at a mean 10–20 days after onset of infection (Fig. 1) [1]. The gold-standard test is ELISA (enzyme-linked immunosorbent assay). Performed in the laboratory on venous blood, this colorimetric reaction includes quantitative spectrometry, specifying IgG and IgM antibody levels. Positive findings indicate COVID-19, independently of symptoms. For care staff, this leads to an application for recognition of COVID-19 as an occu-

\* Corresponding author at: Service ORL, HEGP, 20-40, rue Leblanc, 75015 Paris, France.

E-mail address: [ollivier.laccourreye@aphp.fr](mailto:ollivier.laccourreye@aphp.fr) (O. Laccourreye).



**Fig. 1.** Probability of detection and progression of CoV-2 (based on Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA May 6, 2020 online).

pational disease. On April 16, 2020, the French Health Authority (<https://www.has-sante.fr/>) summarised the state of knowledge on CoV-2 serology dynamics. IgM production begins at day 5 following symptom onset, becoming detectable in some subjects at day 7 and in all cases during the second week. IgG production begins slightly later, but can often be more or less concomitant. IgM and/or IgG are thus detectable in symptomatic patients at week 2 following symptom onset. Level seems to be higher in more severe cases. Late production onset has also been reported, beyond 15 days after symptom onset and up to 30 days after infection, notably in asymptomatic or paucisymptomatic cases. IgM and IgG production kinetics remains unclear in asymptomatic or paucisymptomatic patients.

The national reference centre of Lyon found no decrease in antibody production 2 months after symptom onset (current maximum follow-up available in France).

Absence of antibodies indicates either absence of infection or infection too recent for antibodies to appear; certain populations (elderly, severely immune-depressed) might not develop antibodies at all, despite infection. And finally, there is a false-positive rate of less than 5%: positive serology does not rule out contagiousness or guarantee protection, especially in the light of uncertainties as to immunity duration.

Rapid IgM and IgG screening is also possible on the finger-prick test, using less than 20  $\mu$ l of blood, with visual read-out, but without quantification. Sensitivity and specificity are similar to the previous tests, especially after week 3.

#### 4. Conclusion

Combined and interpreted according to the clinical context (Fig. 1), diagnostic and serologic COVID-19 tests distinguish 3 groups of subjects. Non-infected individuals with neither virus nor immune response are liable to subsequent infection; they should adhere to social distancing or else wear a mask. Infected persons, positive for the virus, can spread infection and need to be isolated. Individuals who are no longer infected and show antibodies for the virus are presumed to be protected, although there is uncertainty as to the quality and above all to the duration of such protection; it is thus not at present clear whether such persons should be vaccinated or not.

#### Disclosure of interest

The authors declare that they have no competing interest.

#### Acknowledgments

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#### Reference

- [1] Sethuraman N, Jeremiah SS, Ryo A. Interpreting diagnostic tests for SARS-CoV-2. JAMA 2020, <http://dx.doi.org/10.1001/jama.2020.8259>.