HAS
HAUTE AUTORITÉ DE SANTÉ

Specifications setting out the performance assessment methods applicable to serological tests detecting anti-SARS-CoV-2 antibodies

Validated by the HAS Board on 16 April 2020

Key points

→ The only diagnostic test currently recommended for early diagnosis of COVID-19 is the RT-PCR molecular test used to detect the SARS-CoV-2 coronavirus genome.

→ Serological tests are not recommended in the context of early diagnosis of COVID-19 infection during the first week following the onset of symptoms.

→ Serological tests are unable to determine how contagious an individual is.

→ Serological tests are only able to determine whether an individual has produced antibodies in response to SARS-CoV-2 virus infection.

→ Antibody production kinetics against the virus remain poorly characterised to date primarily in asymptomatic subjects. The potential period of protection is also poorly elucidated.

→ It is critically important to be able to validate serological tests based on their initial analytical and clinical performances as of now, prior to their purchase and use in routine practice.

→ For this reason, the HAS has provided these specifications setting out the quality and requirement level criteria for all serological tests detecting specific antibodies targeted against SARS-CoV-2 with a view to facilitating their development and assessment.

→ The minimum threshold values estimated by the HAS are 98% for clinical specificity, and 90% or 95% according to test use for clinical sensitivity.

→ The HAS recommends obtaining the findings of the performance assessments conducted based on the information contained in these specifications prior to any purchase and use of serological tests.

→ The strategy of use of these tests will be specified in a future review.

Context

On 31 December 2019, WHO was notified of the outbreak of several cases of pneumonia of unknown origin in Wuhan City (China). The pathogen causing these cases of pneumonia has been identified – a novel coronavirus named SARS-CoV-2, the associated disease being referred to as COVID-19.

A number of diagnostic testing options for COVID-19 are available; these include:

→ **antigen tests** used to detect specific SARS-CoV-2 proteins. These tests can be conducted on nasopharyngeal specimens and lower respiratory tract specimens. Similar to RT-PCR tests, these tests enable early diagnosis of the disease from the acute phase. **However, in light of their poor performances particularly in cases of low viral load, these antigen tests are not currently recommended for clinical use in the COVID-19 context**, as outlined by the World Health Organization (WHO) in its position paper dated 8 April 2020;

→ **serological tests** used to detect specific antibodies (Ab) (immunoglobulins: Ig) produced by the body and targeted against SARS-CoV-2. These tests are conducted on blood samples and may be useful in identifying subjects who have developed immunity to SARS-CoV-2, whether they were previously symptomatic or not. Consequently, in some circumstances, serological tests may be able to identify subjects currently or previously infected with SARS-CoV-2 and ascertain the serological status of exposed individuals (e.g. healthcare professionals). Finally, these tests could also be useful in collecting epidemiological data in relation to COVID-19 (subjects actually infected, mortality rate, etc.). However, the appropriateness of the use of these tests in clinical practice is dependent on prior availability of physiopathological, technical and clinical knowledge enabling their assessment and validation;

→ the **RT-PCR molecular SARS-CoV-2 coronavirus genome detection test** which is currently **the only diagnostic test recommended for COVID-19**. This RT-PCR test enables diagnosis **during the acute phase** of COVID-19. It is conducted on deep nasopharyngeal swabs or lower respiratory tract specimens. **This procedure has been reimbursed since 7 March 2020** based on criteria defined by the HAS in its review dated 6 March 2020 and for the indications defined and updated by the health authorities. RT-PCR tests on saliva specimens have also been described, but their performances have not been sufficiently assessed to date to be recommended.

Initial physiopathological data on anti-SARS-CoV-2 antibody production

There are few data currently available on the immune response targeted against SARS-CoV-2. However, based on the small number of studies published up to 14 April 2020 and the position paper from the National Reference Centres (CNR) for "viral respiratory infections (including influenza)", consistent bodies of observations are available on a number of aspects of the adaptive humoral immune response, and more particularly on anti-SARS-CoV-2 antibody production kinetics.

As such, IgM isotype Ab production would appear to commence from the fifth day following the onset of symptoms, would be detectable in some subjects from the seventh day, and in all subjects during the second week after the onset of symptoms. IgG production occurs slightly out of step with that of IgM, but both productions can also be frequently quasi-concurrent. **IgM and/or IgG production is therefore detectable in symptomatic subjects from the second week following the onset of symptoms**. Antibody levels seem to be more elevated for the most severe cases. It should be noted that anti-SARS-CoV-2 IgA production has also been described. Nevertheless, cases with more delayed antibody productions, after the 15th day after the onset of symptoms, and up to 30 days post-infection, have also been reported, particularly in asymptomatic subjects or those with few symptoms. The latter observations have nonetheless yet to be confirmed. **IgM and/or IgG production kinetics remain poorly characterised to date primarily in asymptomatic subjects or those with few symptoms.**

As such, as expected, the adaptive humoral immune response targeted against the SARS-CoV-2 virus is not an immediate, but rather a delayed, response to the infection. **Therefore, serological tests are**

not recommended in the context of early diagnosis of COVID-19 infection during the first week following the onset of symptoms, in line with the WHO position paper dated 8 April 2020.

Other information from these studies: the long period of detectable IgM production at the end of infection. Indeed, IgM production remains detection for a large majority of subjects (80 to 97% depending on the studies), up to 7 weeks after the onset of symptoms. Consequently, over a window between 7 days and 7 weeks after the onset of symptoms, the isotype profile is therefore very predominantly IgM+ IgG+, without it being possible to discriminate between currently infected subjects and those at the end of infection. This has also been confirmed by the CNR (Lyon site), who pointed out that, to date, they had not observed any decline in antibody products two months after the onset of symptoms (maximum follow-up period currently available for the CNR). The kinetics of the appearance of the IgM- IgG+ antibody profile (in principle enabling the identification of subjects with past infection) are not known to date.

Serological tests are unable to determine whether an individual is contagious or not. Indeed, seroconversion is not accompanied by a reduction in the viral load. There is no established correlation between antibody production and the presence of infectious virus. Furthermore, neither the infecting dose of SARS-CoV-2, nor the dose initiating an antibody response are known to date. This particularly raises the question of associating serology and RT-PCR tests. **Serological tests are only able to determine whether an individual has produced antibodies in response to infection with the virus, in other words, whether the individual has triggered an immune response against the virus or not.** However, an immune response is not systematically synonymous with protective immunisation against reinfection with the same virus. For immunisation to be protective, it is particularly necessary that the body produces high titres of antibodies preventing the action of the virus (and particularly its entry into target cells). These are known as neutralising antibodies. Furthermore, these high neutralising antibody titres must be produced over a long period in order to be able to guarantee long-term protection. However, the target epitopes of the neutralising antibodies have not been identified to date. Furthermore, as recently pointed out by WHO, there is no evidence to support protective immunity against COVID-19 induced by antibodies produced against SARS-CoV-2. The neutralising antibody titre required to provide protection and the duration of neutralising antibody production are not known. The Scientific Council is nonetheless of the view that, on the basis of current scientific knowledge and in light of the lack of literature available to date in respect of SARS-CoV-2 virus reinfection and of ongoing research on the therapeutic use of sera obtained from recovered subjects, the presence of anti-SARS-CoV-2 antibodies indicates at this stage immune protection developed following recovery from symptomatic or asymptomatic/paucisymptomatic infection.

As regards the viral targets used in serological tests to detect IgM/IgG, two proteins are frequently used: S (spike) protein, a virus surface protein enabling interaction (*via* its RBD domain) and fusion with the target cell, and N protein (nucleocapsid protein, internal to the virus). While S protein (or its RBD domain) has been described as inducing an earlier IgM response or one better correlated with the presence of neutralising antibodies, the specific neutralising epitopes have yet to be characterised. These epitopes may also be dependent on the protein conformation, particularly as regards S protein. **Therefore, no robust data are available to date to support the use of a specific form of these proteins**.

Anti-SARS-CoV-2 antibody detection with serological tests

Serology enables qualitative or semi-quantitative (titration) measurement of the production of antibodies produced by the body against the virus. Serology can be performed using automatable tests (such as *enzyme-linked immunosorbent assay* (ELISA), for example), or unit tests (generally

immunochromatographic). Only ELISA tests can be qualitative or semi-quantitative, with unit tests being merely qualitative.

Regardless of the test, it belongs to the category of *In vitro* diagnostic medical devices (IVDs) and is therefore as such subject to European regulations and the CE marking requirement when placed on the market. However, in its guidelines dated 15 April 2020 on COVID-19 *in vitro* diagnostic tests and their performance, the European Commission states that Member States may exceptionally, in the interest of protection of health, authorise the placing on the market of tests that have not yet been awarded the CE mark.

Methods of use of serological tests

Automatable ELISA tests can only be conducted in a medical pathology laboratory (MPL), in view of the technical platform required. They are conducted on blood specimens, generally obtained by means of venepuncture. These tests are medical pathology tests (MPTs). Conducting such tests in an MPL also ensures traceability of results, on an individual and population level. For this type of test, in the COVID-19 context, the CE mark is awarded through manufacturer self-certification.

On the other hand, point of care tests trends to be conducted on capillary blood samples. They can in principle be conducted by different parties depending on the use of the test. As such, the same IVD may have three possible uses:

- **rapid diagnostic testing (RDT)** when used in an MPL. This test is a medical pathology test (MPT) and as such subject to the same requirements (particularly in respect of traceability) as automatable tests. The CE mark is awarded by manufacturer self-certification;
- **rapid diagnostic orientation testing (RDOT)** when conducted outside an MPL (private practice, dispensing pharmacies) by non-pathologist doctors/pharmacists, nurses. These tests are not MPTs and are conducted under the responsibility of the person performing the test, without outcome reporting. The CE mark is awarded by manufacturer self-certification. The performance of RDOTs is subject to the publication of a ministerial decree;
- **self-testing** where carried out directly by the subject, without outcome reporting. Self-tests are not MPTs and are sold in dispensing pharmacies after obtaining the CE mark awarded by a Notified Body.

Interpretation of point of care serological test results

The interpretation of point of care test results may prove to be problematic and give rise to a large number of false-positives or false-negatives in the COVID-19 context. Indeed, many point of care test results are liable to be at the limit of detection and hence difficult to interpret. Moreover, interpreting IgG/IgM profiles is difficult for the lay user.

Assessment principles for diagnostic tests (including serologicali tests)

As a general rule, the development and assessment of a diagnostic test involve three successive phases:

- **the analytical validity** of a diagnostic test consists of its ability *in vitro* to perform the measurement of interest accurately and reliably. In other words: does the test correctly measure what it is intended to measure? This validation includes the study of the analytical sensitivity and analytical specificity, reproducibility (within- and between-observer agreement), robustness (repeatability), limits of detection and quantification, linearity, and quality control compliance;

- **the clinical validity** of a diagnostic test consists of its ability to predict, accurately and reliably, the clinical phenotype of interest (presence or absence of disease): is there a correlation, and if so which, between the test results and the phenotype of interest? The clinical validity includes the clinical sensitivity and specificity, as well as the positive and negative predictive values of the test, parameters which can be covered under the term "diagnostic performances" of the test;

- **the clinical utility** of a diagnostic test consists of its ability to improve the clinical outcome of patients in measurable clinical events, and to provide added value in terms of treatment decision, and consequently therapeutic strategy, optimisation. It is used to define the role of the test in the diagnostic strategy.

In light of the evolving and recent nature of the COVID-19 pandemic and consequently the very short follow-up period (a few weeks), we are not, at this stage, in possession of the requisite epidemiological, physiopathological and clinical data to conduct a full assessment of the diagnostic performances (conducted on prospective cohorts of patients of unknown clinical status at the time of inclusion) and the clinical utility (framework of use) of serological tests detecting anti-SARS-CoV-2 antibodies.

However, it is possible and desirable to assess, as of now, the analytical validity and the initial diagnostic performance data in respect of serological tests detecting anti-SARS-CoV-2 antibodies, in order to be able to ensure that they are reliable and to minimise the risks of false-positive and false-negative results.

Indeed, given the health emergency context associated with the COVID-19 pandemic and the urgent need for reliable tests, **it is critically important to be able to validate serological tests at least on the basis of these initial analytical and clinical aspects as of now prior to their purchase and use in routine practice**: the consequences of a diagnostic error (false positives or false negatives) are liable to have adverse impacts on individual and collective levels.

> **For this reason, the HAS has provided these specifications setting out the quality and requirement level criteria for all serological tests detecting specific antibodies targeted against SARS-CoV-2.**
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> **Therefore, this document is aimed at industrial firms and academic teams seeking to develop a reliable serological test detecting specific antibodies targeted against SARS-CoV-2, as well as the structures required to assess or validate these serological tests.**

Specifications aimed at facilitating assessment of the analytical validity of serology tests detecting antibodies targeted against the SARS-CoV-2 virus

In order to ensure that they are reliable and to minimise the risks of false-positive and false-negative results, the serological tests to be used to detect antibodies targeted against SARS-CoV-2 must meet the following criteria:

- **the tests used must be CE-marked.** However, in its guidelines dated 15 April 2020 on COVID-19 *in vitro* diagnostic tests and their performance, the European Commission states that Member States may exceptionally, in the interest of protection of health, authorise the placing on the market of tests that have not yet been awarded the CE mark. These guidelines also note that **the technical documentation of the test must systematically contain all of the data used to establish the analytical and clinical data in respect of the test, as well as the methods used to obtain the data;**

– **the European Commission has also recommended carrying out additional validation of clinical performances. To this end, the HAS recommends that serological tests be previously assessed by the National Reference Centre for viral respiratory infections (including influenza) prior to any purchase/use. To facilitate this additional assessment, the HAS recommends that the technical documentation of the test be forwarded by the manufacturer to the CNR.**

Based on the numerous inventories carried out, the vast majority of anti-SARS-CoV-2 serological tests are point of care tests. The HAS reiterates the need to also avail of automatable tests to enable the processing of large quantities of samples in parallel, and therefore encourages the development of automatable tests.

➔ **Tests concerned**
  - Any serological test capable of detecting antibodies targeted against SARS-CoV-2 virus antigens (see below with regard to antigens). This may be an automatable or unit, qualitative or semi-quantitative test.
➔ **Serological test format to use**
  - Applicable to all serological test formats: ELISA, immunochromatographic, etc.
➔ **Viral antigens to use**
  - The viral antigens recommended for serological tests **are the S protein** (spike protein), **its RBD domain**, or **the N protein** (nucleocapsid protein). As stated above, there is no evidence to date in favour of one specific form of these viral proteins over the other.
➔ **Antibody isotypes to detect**
  - The recommended seroloicaly tests must **preferentially enable the specific IgM and IgG of the viral antigens to be detected separately in the same test.** IgA detection is optional on the basis of current knowledge. This IgM/IgG configuration makes it possible to cover a more extensive antibody production period (earlier with IgM and later with IgG). Furthermore, as stated above, each isotype combination is liable to provide complementary information regarding infection status.
  - At the present time, and until proven otherwise, it is not envisaged to reject tests detecting IgM and IgM indiscriminately or tests only specific for IgG or IgM. However, the performance of these tests may be restricted to more limited indications than the recommended tests.
  - Precise classification of each isotype of IgG (IgG1, IgG2a, IgG2b, IgG3, IgG4) or IgA (IgA1, IgA2) is not necessary in clinical practice.
➔ **Serological test validity data to be collected and documented**
  - NB: some analytical variables are only determined for semi-quantitative tests.
  - The following analytical validity data must be collected and published:
  - **the precision** of the test expresses the agreement between the results of a series of different measurements made on multiple samples of the same origin containing the target detected by the test. The precision is assessed in three phases:
    - **the repeatability** (within-test precision, with measurement of the coefficient of variation (Cv) on at least 30 tests),
    - **the intermediate precision** (or within-laboratory reproducibility, also with measurement of the coefficient of variation carried out on the quality control series),

- **the reproducibility** (between-observer precision) which expresses the results between different laboratories;

- **the exactness** of a test expresses the agreement between the value of the result of the test under development and the data considered to be true;

- **the accuracy** is the closeness of the agreement between the mean value obtained from a broad series of test results and an accepted reference value;

- **the analytical sensitivity (or limit of detection)** denotes the smallest quantity of test substance in a sample capable of being detected. It can be measured by limit serum dilution up to the dilution for which antibodies are no longer detected, on at least 30 serums. For qualitative tests, this value corresponds to the positive threshold value (see below);

- **the positive threshold value:** conservatively, the positive threshold value is determined with sera diluted to 1:10. It corresponds to the value of the mean + 3 Standard Deviations of the signal measurements observed on at least 30 sera from "healthy" subjects;

- **the analytical specificity** denotes the ability of the test not to exhibit cross-reactions with other test substances, in the case of the COVID context with other antibodies targeted against viruses related to SARS-CoV2, viruses causing common respiratory infections, or other compounds known to produce non-specific cross-reactions (rheumatoid factor in particular). The analytical specificity of the serology test is established by testing sera known to contain Ab targeted against viruses responsible for respiratory infections (other coronaviruses, of which beta-coronaviruses OC43 and HKU1 and alpha-coronaviruses NL63 and 229), influenza virus (a reaction with the latter indicating a major problem in respect of analytical specificity of the test), rheumatoid factor or subjects presenting with other infections (malaria, dengue, etc.). The expected analytical specificity is 100%. In any case, the manufacturer must specify the methodology adopted to estimate the analytical specificity of the test (number of sera tested, classification of sera used particularly in terms of test substances (antibodies targeted against other respiratory viruses, rheumatoid factor)) and, if applicable, the reasons for which the analytical specificity is below 100%;

- **the clinical sensitivity** is assessed by the ability to detect Ab (IgM and/or IgG) targeted against the SARS-CoV-2 virus, on sera from subjects previously known to have been infected with COVID-19, i.e. for whom SARS-CoV-2 has been strictly confirmed with a positive RT-PCR test in compliance with the HAS requirements set out in the review dated 6 March 2020. Insofar as the clinical sensitivity of serology tests can vary according to the test sampling period (e.g. first or second week after the onset of symptoms), the serum panel used to validate the clinical sensitivity should be explicitly documented (total number of sera included in the panel, number of sera for each 5-day period after the onset of symptoms, relative proportion of sera obtained from symptomatic/asymptomatic patients in the panel). **In theory, 100% clinical sensitivity is expected in order to minimise the number of false negatives.** Therefore, the sensitivity of the serology tests should tend towards this value. **However, on the basis of current knowledge, the minimum acceptable threshold value for clinical sensitivity is estimated at 90% or 95% according to test use. These values will be reviewed periodically according to experience acquired in the assessment of serology tests and adapted according to the purpose of the test and therefore its indication.** Nevertheless, in any case, the manufacturer must specify the clinical sensitivity value of the test as well as the methodology adopted to estimate this clinical sensitivity value (calculation methods, type of comparator);

- **the clinical specificity** consists of the likelihood of obtaining a negative test in the absence of disease, i.e. ensuring that the test does not detect Ab (IgM and/or IgG) targeted

against SARS-CoV-2 virus, in sera from healthy donors (e.g. pre-epidemic donors). In order to minimise the number of false positives and on the basis of current knowledge, **the minimum acceptable threshold value for clinical specificity is estimated at 98% regardless of the serological tests.** These values will be reviewed periodically according to experience acquired in the assessment of serolog**ical** tests and **adapted** according to the purpose of the test and therefore its indication. Nevertheless, in any case, the manufacturer must specify the clinical specificity value of the test as well as the methodology adopted to estimate this value (calculation methods, type of comparator).

It is reminded that, in the absence of robust data on the prevalence of COVID-19 infection, the determination of positive and negative predictive values (PPV and NPV) is not appropriate at this time.

Finally, these specifications will be updated based on the arrival of new scientific data and experience acquired when assessing serology tests in the future, particularly at CNR level, and during the use of the tests.

The HAS recommends obtaining the findings of the performance assessments conducted based on the information contained in these specifications prior to any purchase and use of serology tests.

The strategy of use of these tests will be specified in a future review.

Future prospects

This initial HAS paper relating to the qualification of serology tests is part of an overarching approach to the strategy of use of these tests:

- full characterisation of antibody production, the protective role of these antibodies and the window period for all subject categories;
- appropriateness and public health impact of self-testing, when point of care test performance data become available;
- precise definition of the role of serological tests in the COVID-19 care strategy, both in terms of the definition of indications (diagnosis, follow-up, epidemiology) and coordination among the different types of tests (RT-PCR/serology and automated/point of care serology) in each of these contexts and potential use when lockdown measures have been lifted.

These questions will therefore be addressed by the HAS in further papers in the pipeline, in coordination with all professional stakeholders (public and private), patients, institutional stakeholders, etc. involved in the definition of COVID-19 care on national territory. Subject to the availability of the requisite scientific data, a first version of these second component could be produced by the end of April 2020, with a possible update in early May, again based on the rapidly evolving scientific knowledge.

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Drafting method and warning

These recommendations are based on the publications referenced above as well as on the hearings with the National Reference Centre for "viral respiratory infections (including influenza)" on 1 April 2020 (Paris site) and 9 April 2020 (Lyon site) as stakeholders.

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List of participants

Haute Autorité de santé (French National Authority for Health): Nassim Brahmi

Haute Autorité de santé (French National Authority for Health): Denis-Jean David

Haute Autorité de santé (French National Authority for Health): Cédric Carbonneil

This document has been drafted on the basis of available knowledge on the date of its publication. It is liable to evolve on the basis of new data.

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