Indications for SARS-CoV-2 serological tests
Update October 2022

RAG 17/10/2022

Validated by the RMG on 20/10/2022

CONTEXT AND QUESTION

Serological tests are currently reimbursed for the following indications:

1- Hospitalized patients who meet the case definition of a possible case AND have a CT-thorax suggestive of COVID-19 but a negative PCR. Serology has to be performed at least 7 days after the onset of symptoms.

2- Outpatients or inpatients with a clinical presentation suggestive of COVID-19 for a prolonged period of time, but with a negative PCR test, or who could not be tested within 7 days of symptom onset. Serology should be performed at least 14 days after symptom onset.

3- Patients with an atypical clinical presentation as part of differential diagnosis. Serology should be performed at least 14 days after symptom onset.

4- Health care personnel and personnel working in hospitals/departments and other communities with a high risk of exposure to COVID-19 (COVID- units or nursing homes), to investigate their serological status.

The RIZIV/INAMI requested the RAG to revise the above mentioned indications and review the relevance of including two additional indications, that were recommended respectively by the RAG and by the KCE, but that are currently not reimbursed:

1- Patients with a PCR result showing low viral loads could perform a serological test in order to distinguish a recent infection from an old infection (see recommendation from the RAG October 2020);

2- To initiate prophylactic treatment against COVID-19 in patients belonging to one of the severely immunocompromised group. A serological test (anti-S-test) is part of standard operating procedures when prophylactic treatment with tixagevimab/cilgavimab (Evusheld™) is administered (see recommendation of the Task Force therapeutics from February 2022 NL/FR, and the associated SOP). Currently, a serological test is reimbursed in this context using code 551655 from RIZIV-INAMI article 24, “determination of antibodies to viruses, different from those for which a specific code is foreseen”. However in practice, the code is not always accepted by health insurance companies.

RECOMMENDATIONS

- Clear guidance and communication is needed to both physicians (especially general practitioners) and the general population on the current bad practices regarding the prescription of serology tests.
  These are NOT indicated/useful for:
    - follow-up of post-vaccination or post-infection immunity in immunocompetent persons;
    - differential diagnosis for patients with mild clinical presentation.
- Tests should be reimbursed for the following indications:
    - as part of a differential diagnosis in exceptional situations at hospital level (not in first line/general practice), such as for immunocompromised persons or suspected MIS-C, with a negative PCR;
    - before administration of prophylactic treatment by Evusheld™ for immunocompromised patients, as recommended by the TF therapeutics. However, regular revisions (eg of the threshold set for non-responders to vaccination) and updates of the advice of the TF are recommended. Given that the indication might thus evolve over time (e.g. in a context of a new variant), it should not be included as such in a KB/AR, but it should rather be a more generic recommendation, leading for example to the KCE website.

ELEMENTS OF DISCUSSION

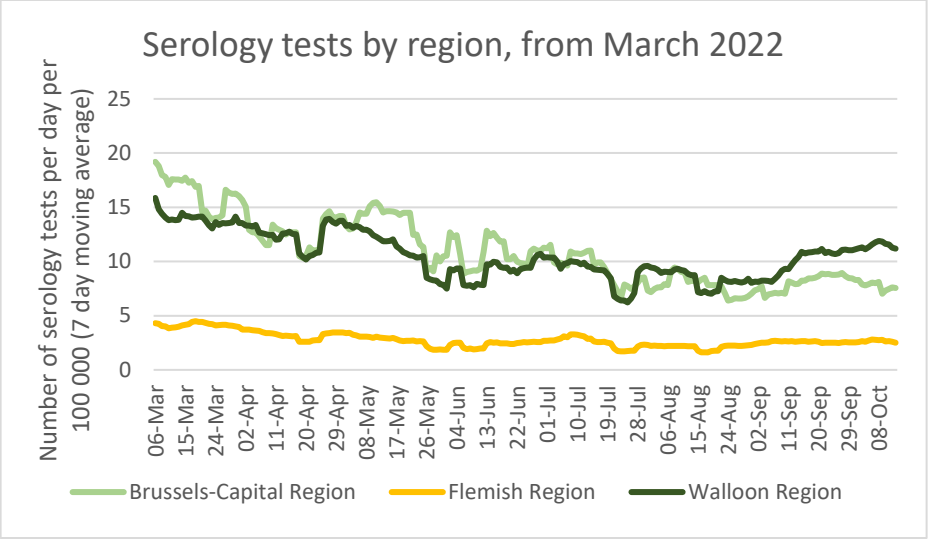
- Overall, there is an important overuse/misuse of serology tests, because of lack of knowledge among the population as well as physicians. After more than two years and a half of circulation of SARS-CoV-2 and vaccination with high coverage, almost every person has been exposed and/or vaccinated. Also, a positive serology test is not linked to a protective immune status. Therefore, a serology test is not relevant to follow-up post-vaccination or post-infection immunity in immunocompetent persons, as is often done now. Indication 4 (investigation of the serological status of health care personnel) should therefore no longer be kept as an indication for serological test.
- There is an important difference in the use of serology tests in 2022 between Flanders, compared to Brussels and Wallonia. Some factors that could play a role here are different practices/habits in different regions and different vaccination coverage, especially in health care staff in hospitals and nursing homes (where tests were reimbursed for investigation of the immune status). More in depth analyses on the indications of serology tests and prescribers is needed to better understand this differences, and identify bad practices (Sciensano is analysis available data, but these are limited).
- Although the use of serology tests became progressively less relevant for clinical indications (such as persons with a suggestive CT thorax but negative PCR result) because of the high exposure to the virus or the vaccination of the population, it remains useful as part of a differential diagnoses in certain clinical situations, such as in immunosuppressed persons, or for MIS-C in children.

- The RAG recommendation on the use of a serological test in order to distinguish a recent infection from an old infection in asymptomatic persons with a low viral load was made in October 2020 and is outdated. In the current epidemiological context, where most persons have been infected, a positive serology test will not allow to distinguish a recent infection. This indication should therefore not be withheld.
- According to the TF therapeutics, Evusheld™ should only be considered for patients with a documented non-response to COVID-19 vaccination. This is measured based on an antibody test that shows an anti-S antibody concentration or titer below 260 BAU/ml. This threshold is based on a definition of a non-responder to vaccinations by the French Haute Autorité de Santé (HAS). However, this cut-off was set based on a study published in November 2021, on correlates of protections after vaccination with Astra Zeneca, where a vaccine efficacy of 80% against symptomatic infections was achieved with 264 BAU/ml, in a context of the Alpha variant circulation (B.1.1.7) (1). It can be questioned if the results from this study can still be extrapolated to the current epidemiological context, with different variants circulating and where other vaccines are used. In addition, in the current context of emerging new variants, the efficacy of antiviral treatment might also be limited. As disclaimed by the TF, regular updates of the advice are therefore recommended, and the indication for reimbursement should also be flexible.
- Making a distinction between anti-S (as indication of vaccination) and anti-N antibodies (as indication of previous infection) is possible in some laboratories, but not all. The sensitivity is often higher for anti-S, but is essay-dependant. In practice, differentiation is only relevant for therapeutic indications (see above, pre-treatment with Evusheld™) or in a context of research/seroprevalence studies.
- A distinction between IgM and IgG antibodies is also not useful, in a context of (repeated) possible reinfections, with different kinetics in antibody development. These essays should therefore not be used in routine.

BACKGROUND INFORMATION

Belgian data

- Number of serological tests performed in BE. The figure below shows the number of serological tests performed per 100,000 persons and per day, by region. There is an important difference, especially for Flanders compared to Wallonia and Brussels.



- The number of patients who would be eligible for treatment with Evusheld™ in Belgium has been estimated by the TF Therapeutics at approximately 15,500 patients (low or non-responders and belonging to one of the subgroups at very high risk of severe COVID-19). The number of persons that would need serology testing to verify their eligibility for prophylactic treatment is estimated at 50,000 to 60,000 (Source: RIZIV/INAMI).

International recommendations

The most recent advice from the ECDC regarding the use of antibody tests is from February 2022; it was published in the context of considering antibody tests to issue or prolong digital COVID-19 certificates, which was not recommended (2). However, the ECDC highlighted the value of antibody tests for the following:

- Seroprevalence studies, including estimation of the proportion of individuals who have evidence of natural or-vaccine induced immunity (using different assay targets).
- Assessing whether a vaccination series was successful in inducing antibody responses in individuals with a compromised immune system.
- Research purposes, for instance to analyse correlates of protection.

Likewise, in the Netherlands, serology tests are primarily used for research and screening at the population level, by selected laboratories.

In France, serology tests are used for initial diagnosis of symptomatic patients with a clinical or CT picture suggestive of COVID-19 and a negative RT-PCR test (or no PCR test performed).

The CDC recommends antibody testing to support the diagnosis of COVID-19 illness or complications of COVID-19, as well as for sero-surveys.

Literature

Baseline information on the immunity to SARS-CoV-2, the development of the antibody response and serology assays is available in the ***FactSheet*** published on the Sciensano website (last update of these sections July 2021).

In most individuals, antibodies are generated after infection with SARS-CoV-2 (IgM and IgG). Antibody levels peak four to five weeks after infection and decrease in subsequent months (3,4). The presence of antibodies is not necessarily linked to protection, but so far, neutralizing antibodies have provided the best indication of protection from SARS-CoV-2 symptomatic infection (5).

Several different antibody tests have been developed using different epitopes as targets, such as the spike protein (S) or the nucleocapsid (N). These tests can also detect various antibody types such as IgM and IgG. In a population where vaccines based on the spike protein are used, antibody tests can identify the proportion of vaccinated (anti-spike antibodies only) and infected individuals (presence of anti-nucleocapsid and spike antibodies) (6).

In a study from Brlic et al, the humoral response to nucleocapsid and spike proteins was followed in vaccinated healthcare workers and critically ill patients. A sustained anti-spike antibody response was observed for more than 6 months, but the infection-induced anti-nucleocapsid response was waning significantly in a 6-month period (7). This is in line with several publications suggesting that anti-N antibodies are not detectable in the majority of patients who recovered from COVID-19 6 months after the onset of symptoms (8,9).

It has to be noted however that different assays used to detect anti S- or anti-N antibodies show variable performance; and this performance also vary with time after infection or exposure. The performance of serological tests is usually evaluated at 14-21 days post-infection, but Torres Ortiz et al showed that some assays, targeting anti N-antibodies, failed to detect them as time passes since infection (200 days follow-up period). Other assays, including those targeting the anti-S antibodies maintained high sensitivities over time (10).

The following persons gave input for this advice:
Emmanuel André (KU Leuven); Steven Callens (UZ Gent); Géraldine De Muylder (Sciensano); Achille Djiena (AVIQ); Naima Hammami (Zorg en Gezondheid); Frank Hulstaert (KCE); Vicky Jespers (KCE); Benoit Kabamba-Mukadi (UCLouvain); Tinne Lernout (Sciensano); Karel Maelegheer (AZ Sint Lucas); Reinout Naesens (Ziekenhuisnetwerk Antwerpen); Elizaveta Padalko (UZGent); Giulietta Stefani (Sciensano); Anne Tilmanne (CHU Tivoli); Steven Van Gucht (Sciensano); Guido Vanham (UAntwerpen); Marc Van Ranst (KU Leuven); Pieter Vermeersch (UZ Leuven).

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