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INDICATIONS FOR REIMBURSEMENT OF SEROLOGY BY THE INAMI/RIZIV, APPROVED BY RMG ON 08/05/2020

This proposition is done based on knowledge that is currently still weak. The RAG will continue to gather new evidences and will consequently adapt the recommendations.

Indications	Description	Financial source
DIAGNOSTIC FRAMEWORK	For hospitalized patients with a suggestive clinical picture and in case of divergence between PCR and CT Scan - by a paired sera **OR** - serum from 14 days after the onset of symptoms	INAMI/RIZIV
	For ambulatory patients with a suggestive and prolonged clinical picture but a negative PCR or who would not have benefited from PCR within 7 days after the onset of symptoms - by a paired sera **OR** - serum from 14 days after the onset of symptoms	INAMI/RIZIV
	For differential diagnosis of atypical clinical presentation.	INAMI/RIZIV
	For diagnostic confirmation in recognition for occupational diseases	Occupational medicine
HEALTHCARE WORKERS / CAREGIVERS	Epidemiological studies aiming to describe the exposure of personnel in contact with covid-19 patients, to make comparisons between services	To be defined: Occupational medicine, health authorities, EU project, …
HEALTHCARE WORKERS / CAREGIVERS OUTSIDE THE HOSPITAL SYSTEM	During home care it can be more difficult (e.g. a home nurse alone giving care to a patient) to apply preventive and protection measures. Health authorities may consider to screen those ones having an increased risk of exposure because performing acts involving proximity to the patient.	Regional health authorities
OTHER PROFESSIONAL CATEGORIES	Under no circumstances a positive serology may be used by the employer to decide on a subsequent shift in activity since it is not known whether the antibodies are protective. Serology could be performed in some professional groups which were not confined (police, store staff, ...) in the context of an epidemiological study measuring the prevalence in some specific groups.	To be defined: Occupational medicine, health authorities, EU project, …
MANAGEMENT OF CLUSTERS	Testing strategy will be developed in consultation with the infectious disease prevention and control services of the health authorities: - Symptomatic cases°[1] - Other cases if necessary	INAMI/RIZIV Regional health authorities
EPIDEMIOLOGICAL FRAMEWORK	Serological tests can be used to conduct epidemiological studies which are essential for the management of the crisis situation	To be defined: Health authorities, EU project, …

The Microbiology Working Group of the Commission for Clinical Biology Possibility is proposing that testing for non-indicated testing/outside case definitions should be possible at a reasonable price (not on RIZIV/INAMI budget) but in order to prohibit commercial drive for internet tests in these particular cases.

[1] First by PCR and by serology according to the indications for serology mentioned in Serology framework

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SEROLOGY COVID-19

RAG, second opinion, 05/05/2020

At the request of Minister De Block's office, an opinion is sought on the relevance of
- defining the immune status of health care staff in order to direct staff to high-risk units
- retain serum from patients who have had or will have respiratory infections for future testing

1. Summary

Use serological tests to determine the immune status of health care workers in order to direct staff to high-risk units	This indication is not recommended on an individual basis as there is not yet precise information on the level of antibodies required for protection, nor the persistence of these antibodies. Serological tests among health care workers can be carried out in studies, see point 5.4. Fedris is interested in such studies.
Using serological tests to define immune status in other occupational categories	This indication is not recommended on an individual basis for the same arguments as mentioned above in addition to low prevalence which induces low positive predictive value even with good test sensitivity. Serological testing among staff in certain professions that could not be confined may reveal a public health interest, see point 5.4. Fedris is interested in such studies.
Retain serum from patients who have had, or will have, respiratory infections for future testing	Such an objective is covered by ongoing and future seroprevalence studies, which will also need to be repeated.
On the basis of current knowledge, the place of serology is	1. Limited to a few diagnostic indications (see point 5.1) 2. Useful in support of local risk management and grouped cases 3. Essential for conducting prevalence studies

2. Introduction

In the context of COVID-19 crisis management, indications for the use of a diagnostic test may allow to
- To diagnose a patient with symptoms based on the principle that the test must have an added value for the patient's health.
- Defining a person's immune status
- To describe the susceptibility of the population and to improve knowledge while facing a new pathology with a public health perspective.

Indications for the use of the tests must keep the principles of
- medical care: to allow a good therapeutic management
- the characteristics of diagnostic tests in microbiology: sensitivity, specificity, prevalence, etc.

The recommendations contained in this opinion are based on the best current state of knowledge but will need to be reviewed in the light of new findings, the evolution of the epidemic and the quality of available tests.

Serological tests are eligible for use in the control of the COVID-19 epidemic as a complement to molecular tests, but their use must take into account a series of limitations which are presented in the following chapter.

3. Knowledge immune reponse

Neither the infecting dose of SARS-CoV-2 nor the dose initiating an antibody response is currently known.

IgM and/or IgG production is detectable in the majority of symptomatic patients between 7 and 11 days after the onset of symptoms. IgM production may occur earlier, around day 5, but is frequently almost concomitant with IgG production.

Antibody levels appear to be higher in more severe cases but their kinetic seems to be delayed in such cases .

IgM and/or IgG production kinetics are poorly characterized in asymptomatic or paucisymptomatic patients. Some studies are mentioning that some individuals with a confirmed diagnosis by RT-PCR may have weak, delayed or no antibody responses while a publication on a series of 285 hospitalized patients with COVID-19 highlights that all subjects were IgG seropositive after 19 days.

The kinetics of appearance of the IgM and IgG antibody profile is not yet known. Depending on the studies, IgM production remains detectable in 80 to 97% of patients up to 7 weeks after the onset of symptoms. The concomitant presence of IgM and IgG for 7 weeks does not allow discrimination between patients during, at the end of or after infection.

Serological tests do not make it possible to decide whether a person is contagious or not because seroconversion is not accompanied by a simultaneous drop in viral load. There is no established correlation between the production of antibodies and the presence of the infectious virus while results of animal studies show however a critical role of neutralizing antibodies on viral excretion.

The immune response is not always synonymous with protective immunization against new virus infection. This requires the production of sufficient levels of neutralizing antibodies over a long period of time. Limited data suggest that neutralizing antibody appear early following SARS-CoV-2 infection in humans and in a majority of patients but the neutralizing antibody titer required for protection and the duration of neutralizing antibody production are unknown. Previous experience with SARS-CoV indicate that total IgG response and neutralizing activity may persist at least 3 years in the majority of infected subjects (Cao NEJM 2007)

The presence of anti-SARS-CoV-2 antibodies signifies an immune response developed after recovery from symptomatic or asymptomatic/paucisymptomatic infection. The impact of SARS-CoV-2 specific antibodies on SARS-CoV-2 susceptibility and COVID-19 severity after reexposure remain to be determined.

4. Place of serological tests

On the basis of current knowledge, serology does not make it possible to define whether a person :

- is infected with CoV-2-SARS within the first week of symptom onset,
- has developed an asymptomatic/paucisymptomatic (sometimes undetectable threshold) form,
- is protected against reinfection and if so, for how long,
- is no longer contagious,
- is in the course of infection or post-infection.

Serology is used to determine whether a person whether or not it has triggered an immune response to the virus.

Serological tests are therefore not recommended for the early diagnosis of COVID-19 infection in the first week after the onset of symptoms.

5. Indications of serological tests

5.1. DIAGNOSTIC FRAMEWORK

According to the opinion of the RAG of 20/04, the place of serology for diagnostic purposes concerns :

- For hospitalized patients with a suggestive clinical picture and in case of divergence between PCR and CT Scan by a paired sera or serum from 14 days after the onset of symptoms.
- For ambulatory patients with a suggestive and prolonged clinical picture but a negative PCR or who would not have benefited from PCR within 7 days after the onset of symptoms.
- For differential diagnosis of atypical clinical presentation.
- Serological testing has its place in the context of occupational medicine and recognition of occupational diseases (but should not be charged to the clinical biology budget).

5.2. HEALTHCARE WORKERS / CAREGIVERS

Healthcare workers/caregivers are at the forefront of the response to COVID-19 and as such, have a risk of exposure to suspect cases but are also in contact with vulnerable individuals. The intensity of the crisis also exposes them to a situational risk related to long working hours, psychological distress, fatigue, burnout, ...
Protecting the healthcare workers /caregivers from these two risks is based above all on the following elements:

- Putting in place the specific prevention and protection measures necessary to maximize safety at work (e.g. personal protective equipment, hygiene, incident reporting, self-assessment, ...)
- Detecting any suspicious cases

Testing of health care workers is indicated in the following situations:

- Any health care professional/caregiver at the onset of symptoms (extended case definition), by PCR
- Identification of failures in the application of protective measures and grouped cases (local risk management), by PCR and/or serology
- Description of the risk of exposure of health professionals (Public health monitoring, studies in a local risk management approach), by PCR and/or serology

In order to take into account a certain reality such as screening among healthcare staff already organized in some hospitals, the RMG had validated that a screening strategy could be organized among healthcare professionals '*according to a strategy to be detailed in consultation with the ad hoc platform'*. This work was carried out under the coordination of DG Healthcare: "*Testing strategy for general and psychiatric hospitals*". In this document, systematic screening, based on serology, is not retained in the monitoring of staff, whether asymptomatic or symptomatic, since a serological result does not indicate, on the basis of current knowledge, that the person is protected against the virus.
Serology, on the other hand, has its full place in the context of a study to estimate the exposure of health care personnel in order to assess the effectiveness of prevention and protection measures.

In COVID units or home care of COVID patients

- Healthcare professionals/caregivers are tested by PCR at the onset of symptoms (extended case definition)
- No routine PCR testing as health care professionals/caregivers are expected to be equipped with personal protection when caring for patients

- Serology can be used in epidemiological studies aiming to describe the exposure of personnel in contact with covid-19 patients (see section 5.4).

In non-COVID units or home care of individuals

- Healthcare professionals/caregivers are tested by PCR at the onset of symptoms (extended case definition)
- Serology can be used in epidemiological studies aiming to describe the exposure of personnel in contact with any patient in different departments (see point 5.4).

In the case of clusters, a testing strategy will be developed in consultation with the infectious disease prevention and control services of the health authorities. This is mainly carried out by a PCR test and is aimed at managing the event.

Outside the hospital system, prevention and protection measures are also the essential element to protect healthcare professionals / caregivers. However, it may be more difficult (e.g. a home care nurse alone to do the patient's care) to apply them. Health authorities that have decided to test collectivities because they have an increased risk of exposure to the virus and of clusters may consider to test in a similar approach categories of people with an increased risk of exposure when performing acts involving proximity to the patient (e.g.: nurse, home care workers).

5.3. OTHER PROFESSIONAL CATEGORIES

During the confinement, several socio-professional groups were not able to be confined, given the requirements of their professional activities: police, store staff, ... while they were in regular contact with the general public. In the context of an epidemiological study, measuring the prevalence in these groups would make possible to define the level of immunity and compare it to that of the general population. Such a study could be coupled with the collection of information on the possible presentation of symptoms, co-morbidity or risk factors. Under no circumstances could a positive serology be used by the employer to decide on a subsequent shift in activity since it is not known whether the antibodies are protective.
Furthermore, it should be kept in mind that with a prevalence <5% in the general population, the positive predictive value of a serological test with good sensitivity is limited (+/- 70% if sensitivity > 90%). There would therefore be 30% false positives.

The prevalence in groups not exposed during the containment period must be even lower, so a serological study in these groups would have a very high number of false positives and is not recommended.

5.4. EPIDEMIOLOGICAL FRAMEWORK

Serological tests can be used to conduct epidemiological studies, the results of which will help in crisis management by describing herd immunity, both at the general population level and in certain risk groups.
These studies should be repeated at regular intervals to detect a change in herd immunity.
Sciensano will describe the different initiatives underway, planned or future and submit a surveillance plan that will cover for example the following aspects:

1. Level and duration of immunity in the general population
2. Level and duration of immunity in specific groups, according to demographic characteristics, ...
3. Level and duration of immunity among persons of different clinical severity.
4. Existence of Immunity in Asymptomatic Patients
5. Probability of protection against reinfection
6. Evolution of viral load and the appearance of antibodies

These studies may be carried out by ELISA or rapid tests. Rapid capillary blood or saliva tests would be very useful for studies or surveillance in the general population, especially in primary care settings. The latter two tests have yet to be validated.
A list of ongoing, planned or proposed studies by different groups of researchers should be finalized by 08/05/2020.

6. Types of serological tests

More and more serological tests are available on the market, both commercial and in house.

Rapid tests and routine tests like ELISA are available.

Belgium has had some of these tests validated and there are large differences in quality between the tests. The FAMHP has also been informed of a number of frauds and this also includes a test marked with an IVD-EC. The tests used will have to be validated and carried out in a medical laboratory.

Definitions:

Automated tests (ELISA) = qualitative or semi-quantitative test (titration) of the production of antibodies, only in a medical laboratory, on blood samples taken by venous blood sampling.

Snel-test (usually immunochromatographic)= qualitative test, possibly performed outside a medical laboratory (e.g. general practice), on blood samples taken by capillary puncture. Interpretation of snel-test results can be difficult if at the limit of detection. A positive result should be confirmed by an ELISA test. To date, these tests have only been validated on serum.

Contributions from
Prof. Dr Pierre Gillet, CHU Liège
Dr Nicolas Dauby, Centre Hospitalier Universitaire Saint-Pierre
Dr Olivier Vandenberg, Centre Hospitalier Universitaire Saint-Pierre
Dr Bénédicte Delaere, Cliniques universitaires Saint-Luc, Mont-Godinne
Dr Olivier Denis, Cliniques universitaires Saint-Luc, Mont-Godinne
Dr Leïla Belkhir, Cliniques universitaires Saint-Luc

Microbiology Working Group of the Commission for Clinical Biology :
We are glad to support the proposal and are able and willing to perform serological testing in the clinical laboratories.

- Serology for healthcare workers should be on non-Clinical Biology budget;

- Possibility for non-indicated testing/testing outside case definitions at a reasonable price should be possible: not on RIZIV/INAMI budget of course but in order to prohibit commercial drive for internet tests in these particular cases.

7. References

1. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology 2020; :200642.
2. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 2020; :200463.
3. Cassaniti, I., et al. (2020). "Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department." J Med Virol.
4. Dong, X., et al. (2020). "Eleven faces of coronavirus disease 2019." Allergy.
5. Du, Z., et al. (2020). "Detection of antibodies against SARS-CoV-2 in patients with COVID-19." J Med Virol.
6. Fan Wu et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered 2 patient cohort and their implications. https://doi.org/10.1101/2020.03.30.20047365
7. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis Published Online First: 21 March 2020. doi:10.1093/cid/ciaa310
8. Haveri, A., et al. (2020). "Serological and molecular findings during SARS-CoV-2 infection : the first case study in Finland, January to February 2020." Euro Surveill 25(11).
9. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci Published Online First: 4 March 2020. doi:10.1007/s11427-020-1661-4
10. Huang, C., et al. (2020). "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." Lancet 395(10223): 497-506.
11. Inui S, Fujikawa A, Jitsu M, Kunishima N, Watanabe S, Suzuki Y, et al. Chest CT Findings in Cases from the Cruise Ship “Diamond Princess” with Coronavirus Disease 2019 (COVID-19). Radiology: Cardiothoracic Imaging 2020; 2:e200110.
12. Jiang, S., et al. (2020). "Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses." Trends Immunol.
13. Jin, Y., et al. (2020). "Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019." Int J Infect Dis.
14. Lee, N. Y., et al. (2020). "A case of COVID-19 and pneumonia returning from Macau in Taiwan : Clinical course and anti-SARS-CoV-2 IgG dynamic." J Microbiol Immunol Infect.
15. Lei Liu et al. A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. https://doi.org/10.1101/2020.03.06.20031856
16. Li, Z., et al. (2020). "Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis." J Med Virol.
17. Liu, W., et al. (2020). "Evaluation of Nucleocapsid and Spike Protein-based ELISAs for detecting antibodies against SARS-CoV-2." J Clin Microbiol.
18. Ningshao Xia, Guiqiang Wang, Wenfeng Gong. Serological test is an efficient supplement for detecting RNA to confirm SARS-CoV-2 infection. doi: 10.20944/preprints202003.0184.v2
19. Okba, N. M. A., et al. (2020). "Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease 2019 Patients." Emerg Infect Dis 26(7).
20. Pan, Y., et al. (2020). "Serological immunochromatographic approach in diagnosis with SARSCoV-2 infected COVID-19 patients." J Infect.
21. Patel R, Babady E, Theel ES, Storch GA, Pinsky BA, St. George K, Smith TC, Bertuzzi S. 2020. Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: Value of diagnostic testing for SARS–CoV-2/COVID-19. mBio 11:e00722-20. https://doi.org/10.1128/mBio.00722-20.
22. Quan-xin Long, Hai-jun Deng, Juan Chen, Jie-li Hu, Bei-zhong Liu et al. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. https://www.medrxiv.org/content/10.1101/2020.03.18.20038018v1.full.pdf

23. Revel M-P, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, et al. COVID-19 patients and the Radiology department – advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). 2020; :11.
24. Roman Wölfel, Victor M. Corman, Wolfgang Guggemos, Michael Seilmaier, Sabine Zange ert al. Virological assessment of hospitalized patients with COVID-2019. Nature, https://doi.org/10.1038/s41586-020-2196-x
25. To, K. K., et al. (2020). "Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2 : an observational cohort study." Lancet Infect Dis.
26. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology 2020; :200843.
27. Wang, Q., et al. (2020). "A method to prevent SARS-CoV-2 IgM false positives in gold immunochromatography and enzyme-linked immunosorbent assays." J Clin Microbiol.
28. World Health Organisation. Advice on the use of point-of-care immunodiagnostic tests for COVID-19 ; 2020. https://www.who.int/docs/default-source/coronaviruse/sb-2020-1-poc-immunodiagnostics-2020-04-08.pdf?sfvrsn=5b6820_2
29. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical 2019-nCoV Pneumonia: Relationship to Negative RT-PCR Testing. Radiology 2020; :200343.
30. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. medRxiv 2020; :2020.03.02.20030189.
31. Zheng, C., et al. (2020). "Risk-adapted Treatment Strategy For COVID-19 Patients." Int J Infect Dis.
32. Zhong, L., et al. (2020). "Detection of serum IgM and IgG for COVID-19 diagnosis." Sci China Life Sci.
33. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020; :S0140673620305663.
34. Antibody responses to SARS-CoV-2 in patients with COVID-19. Quan-Xin Long, Bai-Zhong Liu, Ai-Long Huang. Nature Medicine (2020). https://doi.org/10.1038/s41591-020-0897-1