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Recommendation of the Swiss Society of Microbiology for usage of SARS-CoV-2 specific antigen tests.

Updated version 3.0.
What has changed compared to the last version?

We adapted the recommendation of the controls used in the validation protocol. The Roche and Abbott assay are not "gold standards" in diagnostics, but internal "reference standards" in the validation process. The negative control group for specificity was further adapted with more details.

This document provides guidance on validation and usage of SARS-CoV-2 specific antigen tests. It summarizes expert opinions from members of the Coordination Commission of Clinical Microbiology (CCCM) of the Swiss Society of Microbiology. The members declare no conflict of interest with any diagnostic company producing or selling rapid antigen tests. All members have approved this version of the document.

The current epidemiological situation in Switzerland is worrisome with very high case numbers. Molecular diagnostics is challenged by increasingly limited test capacities and lack of reagents. In addition, the turn-around times in laboratories with robotic based molecular diagnostics is ranging from multiple hours to >24h. New available and validated rapid antigen test may close some of these challenges and diversify the tests arsenal.

Summary:

SARS-CoV-2 antigen tests provide rapid turn-around times from sample collection to result availability. In these very special circumstances, the CCCM agrees with the guidelines of the FOPH on the use of these antigen tests. These antigenic tests, even if not perfect, will make possible to increase testing capacity and will partially solve the current shortage of RT-PCR reagents.

Among the different antigen tests on the market, the Roche and Abbott antigen tests exhibited acceptable specificity and sensitivity in two recent clinical studies done in Geneva and Lausanne, with a specificity > 99% and a sensitivity of about 85%. Such performance is acceptable at least for precise indications such as those proposed by FOPH (see below). Now, it is mandatory to also be able to assess additional antigen tests and to compare the analytical performance of the different tests.

Indications for use of antigen tests may also include various additional indications, for example in an outbreak with pre-test probability of more than 20%, as described below in the document.

The Coordination Commission of Clinical Microbiology (CCCM) of the Swiss Society of Microbiology (SSM) make a call for evaluation of these antigen tests and propose minimal validation criteria that should be used in pre-defined scenarios.

Detailed recommendations

1. Which patient should be evaluated with the rapid antigen tests?

SARS-CoV-2 specific antigen test should in principle follow the published guidelines from the Federal Office of Public Health (FOPH), i.e.:

(i) for patients with symptoms of a respiratory infection with less than 4 days duration.
(ii) for patients managed in an outpatient setting with general less severe symptoms and in no need for hospitalization or intensive care medicine.
(iii) not for patients working in the health care system.
(iv) not for patient in close contact with vulnerable people e.g. nursing at home.
(v) not for patients belonging to a specific high-risk population (see FOPH website)

The reason the FOPH proposed a four days' post-symptom onset is, that the viral load is higher early after symptoms onset. However, it may be acceptable to also use the antigen testing in more patients when the objective of testing is mainly an epidemiological assessment. For instance, when an elderly home-care is suspected to get contaminated, antigen tests may also be used to conduct a first survey on many residents and healthcare workers, in order to rapidly identify the persons positive with highest risk of transmission. However, the CCCM considers that cohorting in such elderly care centers should not be done based on antigen results given the relatively high rate of false negative results estimated to 15%.

Possible additional indications during major outbreak setting

When there is a very high number of hospitalized subjects in a given hospital and when positivity rate of tests is above 20%, then in such outbreak setting, the antigen rapid test may be useful for early cohorting of symptomatic infected patients and may significant decrease the time to triage a patient. If the antigen test is positive, the patient may be cohorted with other COVID patients given the specificity above 98%, but a RT-PCR has to be done rapidly (< 24h), given rare false positive results. Conversely, whenever a result is negative in such symptomatic subjects, a rapid RT-PCR tests has to be conducted as fast as possible, given the low sensitivity of antigen tests (80 to 90%). This strategy would help to use different PCR tests in a more targeted fashion and reduce the amount of rapid RT-PCRs. This recommendation can be adapted based on currently ongoing studies in the field to use antigen test in triaging.

In case of shortage of human resources among the healthcare workers, it is acceptable to do the antigen test. However, we can only rely on positive tests results, negative results with antigen tests have to be confirmed two days later by a RT-PCR, before the exposed health- care employee may go back to work in the hospital.

2. How to conduct a rapid antigen test?

Only antigen tests fulfilling CCCM and FOPH minimal acceptance criteria should be used in above mentioned test scenarios.

Non-laboratory test sites should perform the internal quality control of the assay and document the result. In addition, we recommend that these sites ideally participate in external quality controls to monitor the diagnostic process. This external quality control will likely be proposed soon by MQ and CSCQ. On a voluntary basis, pharmacies may control the testing with one of the SSM laboratories for initial quality controls.

The current available antigen tests are validated only for nasopharyngeal sample material. No other sample material should be used at this stage.

As previously demonstrated with PCR, a critical element in any type of diagnostic assay is the pre-analytical quality. Especially in naso-pharyngeal swabs obtained by less experienced personnel the quality of the collected sample may greatly vary and impact the overall test performance. It is therefore recommended that only trained personnel use antigen tests. Training includes the proper performance of the naso-pharyngeal swab with the collection of a good quality sample for subsequent testing. The CCCM section of the Swiss Society of Microbiology website provides instruction material (LINK: to document) and links to videos how to best perform a nasopharyngeal swab. The antigen test should be strictly performed according to the manufacturer instructions.

3. How to safely handle samples?

Sample collections should be standardized and follow published instructions from CCCM to improve pre-analytical quality (see SSM website). Only specific trained personnel should collect samples and perform the antigen tests.

Testing personnel should wear personal protective equipment. Institutions should provide a dedicated and separated area for testing, which is regularly cleaned.

Safety of health care and laboratory personnel is of utmost importance. Sampling an infected patient is a potential source of infection. However, sampling is safe when correctly executed and following some basic rules - also in non-hospital settings such as private practices or pharmacies. The test facility should provide a dedicated and separated testing area, where samples can be collected, properly labelled, and the analytical step is performed. This “sample collection and testing zone” should be regularly cleaned with viral-inactivating disinfecting agents. In addition, the personnel conducting the sampling should have basic knowledge on biosafety and medical waste disposal. Personnel has to follow strict hygiene with disinfecting hands after each patient visit. Finally, the testing personnel has to wear personal protective equipment includes gloves, gown, a mask, and googles, which is regularly renewed. The safety precautions protect both, the personnel and the patient, that is tested.

4. How should antigen results be reported?

The training of testing personnel should include knowledge on the post-analytical process. This includes communication of medical results to the patient e.g. a positive test result with respective consequences, but also to public health authorities. For such communication scenarios a fact sheet “what to do with a positive result?” should be

developed as there will be repeated questions. Collection and reporting of positive and negative cases, and clinical and epidemiological information is required by law. The FOPH website provides further information how to transfer the antigen test results (see Link below).

5. What is the antigen test performance of tests currently available in Switzerland?

Currently multiple companies offer a series of non-validated and non-approved antigen test assays. The CCCM aims to provide guidance for assay validations and acceptance criteria for performance.

Recently, the CRIVE has evaluated two rapid antigen tests from SD Biosensor/Roche (Standard Q COVID-19 Rapid Antigen Test) and Abbott (Panbio Covid-19 Ag Rapid Test).

The validation data is shared on the CRIVE website and shows an 85-89% sensitivity and 99- 100% specificity in a clinical study setting. The CRIVE test setup compared the clinical test performance between the antigen test with the PCR on different samples. The performance of both assays tested is seen as comparable. With currently increasing pre-test probabilities, the positive predictive value will further increase and the negative predictive values will decline. With a pre-test probability of 50% the negative predictive value remains above 90% for these two tests. Due to the changing epidemiology, also test performance in clinical application will be variable.

Additional validated antigen tests will face the same changing test performance based on changing prevalence. Therefore, the epidemiological situation has to be continuously monitored and considered while testing and interpreting results. Recommendations on any SARS-CoV-2 specific test, including antigen tests, could therefore be adapted on a regular basis.

6. What antigen test performance do we need?

CCCM consider that the antigen tests should exhibit more or equal than 85% sensitivity and 98% specificity, as compared to RT-PCR.

Variability in antigen tests performance (sensitivity and specificity) may further guide which test to use in specific scenarios. Therefore, the CCCM recommendation will also include which test to use in which scenario. As example, in a nursing home all residents are tested (similar to a mass screening) then slightly lower sensitivities could be accepted due to the likelihood that a positive member within an institution will provide sufficient evidence to initiate infection control measures.

The CCCM encourages that further antigen tests are validated against the reference standard (RT-PCR) during the next weeks.

7. How should an antigen test be validated?

The performance of the assays is largely unclear and due to lack of knowledge of the specific tests, the CCCM has developed a step-by-step evaluation protocol (Standard operating procedure) to validate SARS-CoV-2 antigen tests in a standardized way (see document on our website). The CCCM will regularly summarize and publish these test results on an internal website. An official white list of approved tests will appear on the FOPH website.

Briefly validations should include a sufficient large cohort of patients (of at least 300 individuals) with a broad range of viral loads (low, medium, and high) and also negative control ideally with other respiratory viruses. For assessment of sensitivity, only fresh samples will be used. Evaluation of specificity especially with potential cross-reaction to other respiratory

viruses is more difficult, as these viruses are currently not frequent – here a mixture of fresh and frozen samples with specific viruses is recommended to evaluate the specificity.

Two types of validation scenarios are suggested addressing different advantages and disadvantages.

Clinical validations are more complex in its study design, but allow direct comparison of antigen test performance with PCR testing. In such a scenario the patient receives two nasopharyngeal swab – one swab is used directly for PCR testing and the other swab is used directly for the antigen test. Obviously, such a validation is a clinical diagnostic trail and requires specific patient consent and evaluation by an ethical committee. This test setup does not allow to directly compare the test performance of antigen tests between each other as each swab can only be used once for an antigen test. Thus, CCCM would recommend rather a technical validation (see below) with a comparison of tests that have already been clinically validated in Geneva and Lausanne (Roche & Abbott) as a reference standard.

Technical validations are less complex and allow to compare different antigen test versus each other. In such a setup the nasopharyngeal left-over material from the PCR assay is used for different antigen tests in parallel. At least 100 PCR positive and 200 PCR negative samples should be tested. In a first step, as the viral input is known a technical sensitivity can be determined and directly compared between different assays. As the sample is diluted a direct comparison between clinical performance of antigen test and PCR (clinical sensitivity) is not possible. In a second step, for high positive PCR samples (at least 5) a 2-fold serial dilution should be done to determine the limit of detection of each antigen test.

Thus, practically, sensitivity and specificity have to be assessed at least on 100 positive samples and 200 negative samples. Two hundred may seem a high number, but given the impact of false positive results, it is very important to precisely define at least once the specificity and be able to differentiate tests with 99% versus 99.5% specificity. In addition, for an antigen test to receive the validation approval requires some additional criteria: the test should either be clinically validated as well as proposed by FIND or exhibit a non-inferiority with the SD Biosensor/Roche (Standard Q COVID-19 Rapid Antigen Test) and Abbott (Panbio Covid-19 Ag Rapid Test) antigen tests, hereafter coined “reference antigen tests “ (for which clinical validation is already available). Non-inferiority is obtained if there is an overall congruence of 95% or more between the new antigen test and the

reference antigen test. Moreover, when considering the reference tests, the new test should exhibit at least 99% specificity and at least 95% sensitivity on the same 300 samples (100 positive and 200 negative). In addition, a limit of detection will be assessed by a 2-fold dilution of 5 samples with about 320'000 SARS-CoV-2 copies/ml. At least 4 of the 5 diluted samples should be positive with the antigen test investigated with similar detection limits in comparison to the reference standard. Within the 200 negative samples, each antigen tests will be tested for specificity on 50 frozen samples including diverse respiratory viruses, including 12 samples taken from subjects with seasonal coronavirus.

Verification. Antigen tests are IVDs (in vitro diagnostics), and are set into market after the known guidelines and expectations of medical product regulations. Usually a laboratory can evaluate those tests and they must perform a verification of a select test before implementing it into it is routine. This what authorize laboratories are competent for. This competence is regulated via the new Art 24 of the COVID 19 Ordinance 3. The CCCM recommends that each laboratory uses a shorter technical verification as pointed out that includes 15 samples with at least 5 positive samples. This is necessary after the validation for laboratories using this assay.

Quality control. It is strongly recommended that institutions using the rapid antigen tests use an internal positive control at least 1x per day using a control from the manufacturer. This control should be documented and in case of problem the manufacturer should be contacted. In addition, an external quality assessment should be performed at least 1x per 3 months' period to regularly control and compare the test performance. Such a ring trial could be organized by the Quality control organisation in Switzerland. Additional controls should include one random RT-PCR verification of 1 test about every 100 tests.

Disclaimer. These recommendations are developed based on the current epidemiological situation in Switzerland in November 2020 and may be adapted in case of changing epidemiology. The FOPH provides the mandate for SARS-CoV-2 antigen test validation and comparison to the SSM.

1. **Links:**

- Website FOPH recommendation for testing: https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien- pandemien/aktuelle-ausbrueche-epidemien/novel-cov/testen.html

- Website FOPH high risk population: https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien- pandemien/aktuelle-ausbrueche-epidemien/novel-cov/krankheit-symptome- behandlung-ursprung/besonders-gefaehrdete-menschen.html

- Website SSM instruction material for safe swabbing
  https://www.swissmicrobiology.ch/sars-cov-2-antigen-tests

- Links for instruction videos “how to perform a naso-pharyngeal swab?”:
  - Short Video: https://vimeo.com/402580767/31df31e432
  - Detailed Video: https://www.youtube.com/watch?v=syXd7kgLSN8

- Website from FOPH on how to report a antigen test result:
  https://www.bag.admin.ch/bag/de/home/krankheiten/infektionskrankheiten- bekaempfen/meldesysteme-infektionskrankheiten/meldepflichtige- ik/meldeformulare.html

- Website CRIVE antigen test validation Roche and Abbott:
  https://www.hug.ch/laboratoire-virologie/centre-national-reference-pour-infections- virales

- Website WHO recommendation:
  https://www.who.int/publications/i/item/antigen- detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

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