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

The current epidemiological situation in Switzerland is worrisome with continuous high case numbers. Molecular diagnostics remains the gold standard for diagnostics of patients who need hospitalization and are in need for precise diagnostics. However, turn-around times in laboratories with robotic-based molecular diagnostics are ranging from hours to more than 24 hours. Rapid PCR tests can provide much faster results, and can provide results were needed more urgently. New available and validated rapid antigen tests 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 Coordination Commission of Clinical Microbiology (CCCM) agrees with the guidelines of the Federal Office of Public Health (FOPH) on the use of these antigen tests. These antigenic tests, even if not perfect, will make possible to increase testing capacity. Among the different antigen tests on the market, the Standard Q COVID-19 Rapid Antigen Test from SD Biosensor/Roche and the Panbio Covid-19 Ag Rapid Test from Abbott exhibited acceptable specificity and sensitivity in two recent clinical validation studies done in Geneva and Lausanne, with a specificity >99% and a sensitivity of about 85% in symptomatic patients with a recent infection. Such performance are 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 CCCM of the SSM makes 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 hospitalisation or intensive care medicine.

(iii) not for patients working in the healthcare 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-day 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 homecare 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 the 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% among symptomatic subjects with acute onset COVID-19 symptoms. The sensitivity will drop quite significantly for patients with more than 7 days symptoms and among infected asymptomatic individuals, that present a median viral load about 10 to 100-fold lower than symptomatic subjects.

Possible additional indications during major outbreak setting

When there is a very high number of hospitalised subjects in a given hospital and when positivity rate of tests is above 20%, then in such an outbreak setting, the antigen rapid test may be useful for early cohorting of symptomatic infected patients and may significantly 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 99%, 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 test has to be conducted as fast as possible, given the variable sensitivity of antigen tests (ranging from 40 to 90%, strongly depending on the patient cohort). 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 due to increasing rates of COVID-19 infections in healthcare workers, it might be acceptable to do the antigen test to detect potential contagious healthcare workers in a team. However, we can only rely on positive tests results, negative results with antigen tests have to be
confirmed by a RT-PCR, before the exposed healthcare 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. 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 nasopharyngeal 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 nasopharyngeal swab with the collection of a good quality sample for subsequent testing. The CCCM section of the Swiss Society of Microbiology website provides instructional material (see Link below) and links to videos on 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 standardised and follow published instructions from CCCM to improve pre-analytical quality (see SSM website). Only specifically 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 healthcare 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 which includes gloves, a gown, a mask, and goggles and 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 on 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, two University centers (Geneva and Lausanne) have evaluated two rapid antigen tests from SD Biosensor/Roche (Standard Q COVID-19 Rapid Antigen Test) and Abbott (Panbio Covid-19 Ag Rapid Test) in a clinical setting. Both studies showed an 85–89 % sensitivity and a 99–100 % specificity in a clinical study setting. The CRIVE test set-up 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 SAR-CoV-2 specific test, including antigen tests, could therefore be adapted on a regular basis.

6. What antigen test performance do we need? CCCM considers that the antigen tests should exhibit more than or equal to 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 are 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 standardised way (see document on our website). The CCCM will regularly sum-
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parison of antigen test performance

their study design, but allow direct com-

i.e from a swab put in the transport me-

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 con-

sent and evaluation by an ethical com-

mittee. This test set-up 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. A clinical study, in which
the antigen test is done from a wet swab, i.e from a swab put in the transport me-
dium may also be considered and will
then have the advantage to compare dif-
fferent samples types (saliva & nasopha-
ryngeal swabs for instance and allow on

the wet swab to perform several antigen
tests and the RT-PCR starting from the
same sample. Due to the complexity of
clinical validation studies, the CCCM fa-
vours a technical validation (see below)
with a comparison of tests that have al-
ready been clinically validated in Ge-

nea and Lausanne (SD Biosensor/
Roche (Standard Q COVID-19 Rapid
Antigen Test) and Abbott (Panibo Co-

vid-19 Ag Rapid Test)) as a reference
standard.

Technical validations are less complex
and allow to compare different antigen
test versus each other. In such a set-up
the nasopharyngeal left-over material
from the PCR assay is used for different
antigen tests in parallel. At least 100
PCR positive and 200-300 PCR negative
samples should be tested. In a first step,
as the viral input is known, a technical
sensitivity can be determined and di-
rectly compared between different ass-
says. As the sample is diluted, a direct
comparison between clinical perfor-
mance of antigen test and PCR (clinical
sensitivity) is not possible.

Thus, practically, sensitivity and spec-
ificity have to be assessed at least on 100
positive samples and a minimum of 200
negative samples. Two hundred may
seem a high number, but given the im-
 pact of false positive results, it is very
important to precisely define at least once
the specificity and be able to differenti-
ate 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 technical performance as described
below. In the technical validation, the
assays should show a sensitivity of 95%,
90%, and 80% for 10e7, 10e6, and 10e5
copies/mL, respectively. These perfor-
mances were reached by previously
mentioned antigen assays. Moreover,
when considering the reference tests
(RT-PCRs), the new test should exhibit
at least 99% specificity. Within the nega-
tive samples, each antigen tests should
be tested for specificity on 50 samples
including diverse respiratory viruses, in-
cluding seasonal coronavirus. Verifica-
tion. Antigen tests are IVDs (in vitro
diagnostics), and are set into mar-
ket after the known guidelines and ex-
pectations of medical product regula-
tions. Usually, a laboratory can evaluate
those tests and they must perform a ver-
fication of a select test before imple-
menting it into it is routine. This is what
authorised 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 veri-
fication as pointed out that includes
about 15 samples with ideally 5 positive
samples. This is necessary after the vali-
dation for laboratories using this assay.

Quality control. It is strongly recom-
mended that institutions using the rapid
antigen tests use an internal positive
control at least once per day using a
control from the manufacturer. This
control should be documented and in
case of problems, the manufacturer
should be contacted. In addition, an ex-
ternal quality assessment should be per-
formed at least once every three months
to regularly control and compare the
test performance. Such a ring trial could
be organized by the quality control or-
ganisation in Switzerland.

Disclaimer. These recommendations are
developed based on the current epide-
miological 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 com-
parison to the SSM.

Members of CCMC of the Swiss Society of
Microbiology (in bold the members who
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have endorsed the present recommendation)

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References and links
Online on www.sulm.ch/d/pipette ->
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