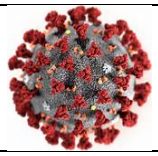
National COVID-19 Science Task Force (NCS-TF)



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The role of serological testing in the COVID-19 response in Switzerland

Summary of request/problem

The Krisenstab has asked the NCS-TF to look into the role of serological testing in the COVID-19 response. Several initiatives in Switzerland have sprung up to examine the seroprevalence of SARS-Cov-2 in the population. The Swiss School of Public Health (SSPH+) is planning a nationwide serological testing programme called "Corona Immunitas", using a large random sample of residents [1]. A separate initiative, "Corona Immunity", targets testing of individuals [2]. The action plans to launch rapid serological tests at home from May 2020, with support from business, politics, medicine and health insurance companies [2].

Executive summary

Serological studies, performed on blood samples, have the potential to provide information about the true number of people who have had a SARS-CoV-2 infection. The data allow robust estimates of infection mortality and morbidity in the general population and in subgroups at increased risk of exposure. At the individual level, serological tests are proposed as a means to identify individuals who have developed immunity to SARS-Cov-2 and can return to work with low risk ("immunity passport"). This policy brief reviews the potentials and limitations of serology in Switzerland and outlines the priorities for future research.

The use of rapid to detect SARS-CoV-2 antibodies at the individual level is currently not indicated:

- Prevalence of infection is low
- The available tests have not been fully validated
- There will be with many false positives if specificity is below 100%
- Neutralising effect of antibodies not established.

The issue of "immunity passports" is problematic from a medical and ethical point of view. A recent study in Geneva established that the seroprevalence at the population level is low (around 5%), despite the high incidence of COVID-19 in Geneva compared to other cantons. The focus for research at the population level should, therefore, be on subpopulations at higher risk of infection. Test accuracy studies of different test types are another priority. Immunological studies of cellular and humoral immune response to SARS-CoV-2, to establish putative immune correlates of protection and the correlations between disease severity and antibody response, and to examine the duration of immunity are another important priority.

Unresolved issues

This policy brief will be updated as soon as better data on test accuracy, the development of immunity and the seroprevalence in subpopulations becomes available.

1. Introduction

As Switzerland shows encouraging signs that confinement measures, implemented four weeks ago, have limited the damaging effects of COVID-19, planning a de-confinement strategy is moving centre stage. This endeavour requires support by proper testing, contact tracing, and quarantining capacities. This policy brief responds to a request from the government to comment on the availability and potential uses of serological testing.

Figure 1 shows a typical course of SARS-CoV-2 infection, emphasizing the place of virus detection and serological tests. The panel on the left shows viral loads in patients with active SARS-CoV-2 infection (from Tan et al. [3]), which peaks early after symptom onset. The average time to reach undetectable levels is about 14 days (blue arrow). The panel on the right shows the IgM and IgG antibody responses (from the UK National COVID Testing Scientific Advisory Panel [4]). The IgM response peaks 7 to 10 days after infection, the IgG response after about 3 weeks after infection.

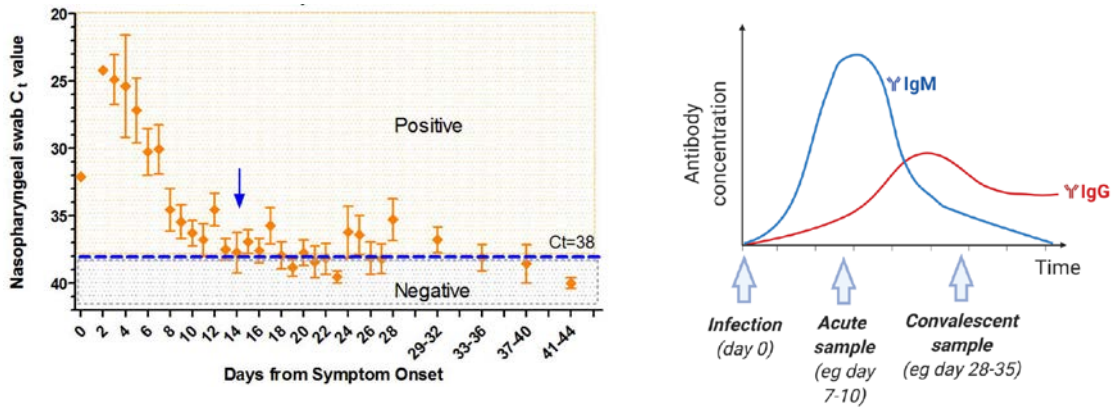

Figure 1. The course of SARS-CoV-2 infection with viral load (left panel) and IgM and IgG antibody response (right panel). From [3] [4].

Of note, up to 40% of patients may be asymptomatic [5]. Furthermore, the higher the viral load, the earlier and higher the antibody response, and the higher the risk of prolonged viral excretion.

The virus detection test identifies *active* cases, based on the presence of the virus in nasal or throat swabs. It allows for the appropriate medical management of COVID-19 patients by confirming SARS-CoV-2 as the cause of their symptoms. Virus detection is a cornerstone of approaches aimed at curbing the propagation of the epidemics, but only as part of a strategy that includes intensive contact tracing and containment measures.

The virus detection test has limitations. First, the time window of positivity is narrow, which carries a risk of false-negative results, especially early in the course of infection. Second, it is technically demanding, both in reagents and equipment. Third, fulfilling needs with sufficient numbers of tests, notably during a transition towards de-confinement, is challenging for most countries, including Switzerland, due to shortages in supplies and consumables.

Serological tests identify individuals who *have been* infected by demonstrating the presence of virus-specific antibodies in their blood. Once these antibodies reach detectable levels, by analogy with other viral diseases, the test is predicted to remain positive for weeks, months and even years. However, a serological test is not suitable for the diagnosis of acute infection because of the delay in development of antibodies.

In general, serological testing is technically straightforward, but the development of highly specific and sensitive assays requires a significant effort. Intensive efforts to develop such tests are currently in progress for SARS-CoV-2. The different types of serological tests, the typical time to results, and what they can and cannot tell us are summarized in Table 2.

Table 2 – Types of serological tests (from [6]).

Type of test	Time to results	What it tells us	What it cannot tell us
Rapid diagnostic test (RDT)	10-30 minutes	The presence or absence (qualitative) of antibodies against the virus present in patient serum.	The quantifiable amount of antibodies in the patient serum, or if these antibodies are able to protect against future infection
Enzyme linked immunosorbent assay (ELISA)	1-5 hours	The presence or absence (quantitative) of antibodies against the virus present in patient serum.	If the antibodies are able to protect against future infection.
Neutralization assay	3-5 days	The presence of active antibodies in patient serum that are able to inhibit virus growth ex vivo, in a cell culture system. Indicates if the patient is protected against future infection.	It may miss antibodies to viral proteins that are not involved in replication.

RDT – most rapid diagnostic tests are lateral flow immunoassays, which use a finger-prick blood sample and look and work like pregnancy tests. These tests can be done at home and are also known as point-of-care tests.

ELISA – these tests require a larger blood sample, taken by trained personnel, which needs to be sent to a laboratory for testing.

Neutralizatizon assays – these tests can only be done in the laboratory and are often used as confirmatory tests.

2. Uses of serological tests

The serological test to detect past SARS-CoV-2 infection has the potential to fulfil the following goals:

1. Obtain accurate assessments of the prevalence of infection in a population and in subpopulations thereof;
2. Contribute to more accurate estimation of infection mortality and morbidity;
3. Monitor progression of epidemics and assess the impact of measures retrospectively;
4. Anticipate priority groups for vaccination when vaccines become available;

5. Identify who is protected by naturally acquired immunity and will no longer transmit virus. Identify potential donors for antibody-based therapy.
6. Plan “precision de-confinement” (if robust clinical studies allow prediction of the risk of severe disease in various population subgroups).

Of the seven potential goals of serological testing listed above, the first is the most relelvant for Switzerland at this stage of the epidemic. Cross-sectional, ‘snapshot’ studies, in progress in a couple of cantons, will give an overall estimate of seroprevalence within the next few days.

3. Accuracy of serological tests

Data on the accuracy of the available serological tests are compiled by FINDDx [7] and the Johns Hopkins Center for Health Security [6]. Estimates of test performance are highly variable, ranging from 63.9% to 100% for sensitivity and 18.4% to 100% for specificity when compared with detection of virus by RT-PCR. The studies are small, resulting in wide confidence intervals around sensitivity and specificity (Figure 2). Most studies are diagnostic case-control studies, which are known to be prone to biases that overestimate accuracy [8,9]. An evaluation of nine rapid lateral flow immunoassays, compared with both ELISA and RT-PCR, found that none of the rapid tests was adequate for individual-use applications [10]. Other tests have been approved for research use only, and cannot be used as a public health diagnostic tool or for at-home diagnosis.

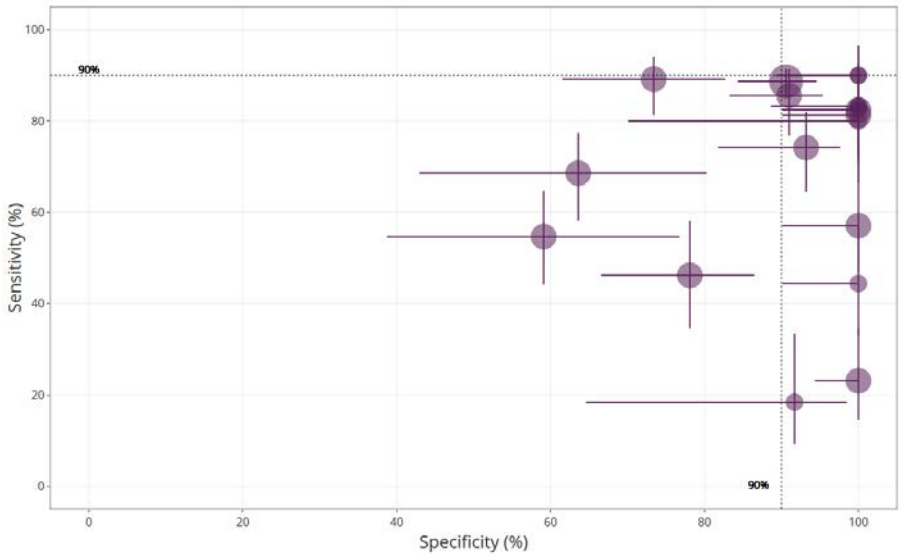

Figure 2 – Sensitivity and specificity of serological tests for SARS-Cov-2 infection, with 95% confidence intervals (from [7])

4. Serological testing for SARS-CoV-2 antibodies in Switzerland

Several certified Swiss labs, including HUG, UniZH, and IFIK Bern are evaluating commercially available tests.

- Euroimmun, an ELISA-based assay (semi high-throughput) shows promise with a second-generation test that detects IgG but not IgA. How much can be supplied is uncertain.
- DiaSorin, an Italian company, has set up a proprietary liquid-based assay (170 tests/hr on machines reportedly significantly available in Switzerland). Discussions are ongoing about evaluation at HUG.
- Roche, a test will be available within a month or so and evaluated at HUG before distribution. It will run on the Elecsys analyser platforms (300 tests/hr), widely available in Switzerland. They think they will be able to produce >10 million tests/wk by June or so.
- VivaDiag point-of-care assay (purchased in high volume by Swiss Red Cross). Ethical approval from Canton of Bern granted for evaluation at IFIK and HUG.
- Several other small biotech companies, some in Switzerland, have tests in the pipeline, using a variety of technologies (microarrays, plates, liquid etc.)

Serological assays developed by G. Pantaleo's team at Swiss Vaccine Research Institute in Lausanne, by A. Trkola and A. Aguzzi's teams at UniZH, by Federica Sallusto in Bellinzona, partly thanks to viral antigens produced by EPFL protein production core facility.

5. Methodological considerations at the population and individual level

An important distinction needs to be made between surveys at the **population level** (uses 1-4 above) and a subgroup of a population, and testing at the **individual level** (uses 5-7).

Several factors complicate efforts to determine seroprevalence of, and immunity to, SARS-CoV-2 at the **population level** [11]. First, serological tests have imperfect sensitivity and specificity. Second, the study population is unlikely to be an entirely representative random sample, which may distort estimates of seroprevalence. Third, estimates from seroprevalence studies cannot predict immunity to future infection, regardless of the quality of the test, because the relationship between seropositivity and immunity is still unknown [11] [3]. Another important issue is the delay in the antibody response detected by serological tests; serological data reflect the cumulative incidence of SARS-CoV-2 infections one week to three weeks earlier [3], which means the serological data are not suitable for real-time monitoring of the epidemic.

Larremore and colleagues at Harvard University have compared estimates from different sampling methods using a framework that integrates uncertainty from test characteristics, sample size, and heterogeneity in seroprevalence across tested subpopulations. They concluded that sampling schemes informed by demographics and contact networks are more efficient than population-based random surveys [11]. Specifically, sampling informed by an appropriate model and demographics can decrease uncertainty in the estimate of seroprevalence. The group has developed a prevalence calculator, which produces the posterior distribution of true prevalence in the population, given the test results in a population sample, using a test with known sensitivity and specificity (https://larremorelab.github.io/covid-serology).

At the **individual level**, two issues are essential: if the prevalence is low and the test is not 100% specific, there will be a large number of false positives. Table 1 shows this for the

Cellex rapid diagnostic test, which is licensed in the USA. The sensitivity is 93.8% and the specificity 95.6% [6]. The table shows that, with the Cellex test and a true seroprevalence of 5% in the population, almost 50% of samples with positive test results would be false positives.

Table 1 – False positive rate in function of prevalence for Cellex rapid diagnostic test for SARS-CoV-2 infection

Prevalence	% false positive
5%	47%
10%	30%
20%	16%
50%	4.5%

The other important issue at the individual level is the question of **immunity**. At this early stage of the epidemic with a new virus, the characteristics of a protective immune response to infection and the role of different antibodies are not known. Of note, the mechanism of protection might not be the same as the mechanism of recovery from infection [12]. Further research is urgently needed to examine these mechanisms, to establish putative correlates of protection, and to investigate the duration of immunity (see section 7).

6. An immunity passport?

There is debate about the so-called "immunity passport", which would certify that a person is immune to SARS-Cov-2 infection [13]. Such passports could, for example, be used for key workers in health care or other service industries. In the absence of a reliable test system with 100% specificity and high sensitivity, and a good understanding of the nature and duration of immunity, such a passport should not be considered. Furthermore, there are important ethical and legal issues. These issues are addressed in detail in a separate policy brief [14], and summarized in the box below.

- Different duties and privileges for the immune and non-immune would:
  - create inequalities based on health
  - turn non-immunity (or immunity) into a disadvantage
  - encourage differential treatment in work and public life, increase stigmatization and marginalization
  - make it impossible to keep immunity status confidential
- »Immunity passports » could harm persons:
  - The « immune » may not be immune, and could take excessive risks
  - The « non-immune » may seek contagion if immunity carries social advantages
- Distribution of testing would need to respect principles outlined in the pandemic plan
- Mandatory tests would require a legal basis; « serological passports » would also require a legal basis (including access to it, consequences, appeal).
- As long as scientific uncertainty in identifying immunity and its duration persists, such passports should not be used as they restrict human rights, create societal dangers, and cannot be justified by a legitimate public interest.

7. Priorities for future research

Studies in different populations

All surveys should be done using a serological test that has been validated in the target population

- Presumed highly-exposed population groups, such as health workers, residents and staff in old people's homes and long-term care facilities. Consider sampling strategies, such as model and demographics informed sampling [11].
    - The aim is to determine attack rates and proportion of asymptomatic SARS-CoV-2 infections.
- Post-outbreak surveys, for example, in asylum seekers or old people's homes.
    - The aim is to determine attack rates and proportion of asymptomatic SARS-CoV-2 infections.
- Longitudinal studies in highly-exposed groups, e.g. healthcare workers.
    - The aim is to examine duration or boosting of immunity in antibody-positive and susceptibility in antibody-negative.
- National representative cross-sectional survey in the general Swiss population. Based on the low initial seroprevalence estimates in Geneva in April 2020, such surveys are unlikely to contribute important further information. They are not an efficient use of resources at this time.
- Future population-based surveys, including children, might be needed if there are large waves of resurgent infection.
    - The aim is to determine changes in population-level immunity and priority populations for vaccination, when available.
- Studies of convalescent individuals.
    - The aim is to identify potential donors for studies of antibody-based therapy.

Laboratory studies

- Test accuracy studies of different test types (see section 5), including in different types of population. Study designs should follow best practice in diagnostic research [8,9].
- Immunological studies of cellular and humoral immune response to SARS-CoV-2.
    - The aim is to establish putative immune correlates of protection using neutralization assays; to examine correlations between disease severity and antibody response, and to examine the duration of immunity.

8. Conclusions

The use of rapid tests for antibodies to SARS-CoV-2 at the individual level is currently not indicated

- Prevalence of infection low
- Tests are not well validated, with many false positives if specificity below 100%
- The protective effect of antibodies against future infection is not established.

The issue of "immunity passports" is problematic from a medical and ethical point of view.

Serosurveys tests are useful at the population level to measure the likely level of infection.

A recent study in Geneva has established that, as expected, the seroprevalence in the general population is low (around 5%), despite the high incidence of COVID-19 in Geneva compared to other cantons.

The focus for research at the population level now should be on subpopulations at higher risk of infection.

9. References

[1] Swiss School of Public Health. Corona Immunitas. SSPH+ n.d. https://www.corona-immunitas.ch/program (accessed April 20, 2020).

[2] www.20min.ch www 20minuten ch 20 Minuten, 20 Min. Massentests für zu Hause sollen Lockdown beenden. 20 Minuten n.d. https://www.20min.ch/schweiz/news/story/Massentests-fuer-zuhause-sollen-Lockdown-oeffnen-21562836 (accessed April 20, 2020).

[3] Tan W, Lu Y, Zhang J, Wang J, Dan Y, Tan Z, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. MedRxiv 2020:2020.03.24.20042382. https://doi.org/10.1101/2020.03.24.20042382.

[4] Evaluation of antibody testing for SARS-Cov-2 using ELISA and lateral flow immunoassays | medRxiv n.d. https://www.medrxiv.org/content/10.1101/2020.04.15.20066407v1 (accessed April 22, 2020).

[5] Low N. The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis. University of Bern; 2020.

[6] Global Progress on COVID-19 Serology-Based Testing. Johns Hopkins Center for Health Security n.d. https://www.centerforhealthsecurity.org/resources/COVID-19/serology/Serology-based-tests-for-COVID-19.html (accessed April 19, 2020).

[7] SARS-CoV-2 diagnostics: performance data - FIND n.d. https://www.finddx.org/covid-19/dx-data/ (accessed April 19, 2020).

[8] Whiting P, Rutjes AWS, Reitsma JB, Glas AS, Bossuyt PMM, Kleijnen J. Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med 2004;140:189–202. https://doi.org/10.1016/j.jclinepi.2013.05.014.

[9] Whiting P, Rutjes A. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529.

[10] Adams ER, Anand R, Andersson MI, Auckland K, Baillie JK, Barnes E, et al. Evaluation of antibody testing for SARS-Cov-2 using ELISA and lateral flow immunoassays. MedRxiv 2020:2020.04.15.20066407. https://doi.org/10.1101/2020.04.15.20066407.

[11] Larremore DB, Fosdick BK, Bubar KM, Zhang S, Kissler SM, Metcalf CJE, et al. Estimating SARS-CoV-2 seroprevalence and epidemiological parameters with uncertainty from serological surveys n.d.:45.

[12] Plotkin SA. Correlates of Protection Induced by Vaccination. Clin Vaccine Immunol 2010;17:1055–65. https://doi.org/10.1128/CVI.00131-10.

[13] Proctor K, Sample I, Oltermann P. “Immunity passports” could speed up return to work after Covid-19. The Guardian 2020.

[14] Hurst S, for the ELSI Expert Group. Ethical, legal, and social issues associated with “serological passports.” Bern: Swiss National COVID-19 Science Task Force; 2020.