Summary on SARS-CoV-2 serology for the COVID19 Certificate

The following document summarizes the expert opinion and recommendations of the Coordination Commission of Clinical Microbiology (CCCM) of the Swiss Society of Microbiology (version 1.0, as of 12th of November 2021) on the measurements and determination of SARS-CoV-2 serology to qualify for the COVID19 certificate. The document will regularly be adapted based on the current state of evidence.

General aspect. The SARS-CoV-2 serology testing can only be done in Swissmedic authorized microbiological diagnostic laboratories for this indication. CE/IVD assays based on ELISA or automated immunoassays have to be used to measure antibodies only in serum or plasma. No immune-chromatography tests (ICT) are allowed or any other sample type can be used to generate the COVID19 certificate.

Detection of SARS-CoV-2 specific IgG antibodies is not a guarantee to be protected from infection or severe disease caused by SARS-CoV-2.

Antigen target. We recommend using SARS-CoV-2 Spike (S)-protein as the primary target for serology testing for the above mentioned context.

Positive serology against SARS-CoV-2 does not necessarily correlate with the presence of neutralizing antibodies. However, antibodies against the SARS-CoV-2 S-protein, and in particular against the Receptor Binding Domain (RBD) correlate well with neutralization [1-4]. Currently no commercial high-throughput assays to measure antibody neutralizations are available. Anti-S antibodies also tend to be detectable for a longer time-period in serum/plasma samples in comparison to anti-N antibodies [5, 6]. Therefore, anti-S antibodies seem to be more sensitive to detect previous exposure to SARS-CoV-2 (either by infection or vaccination).

Type of antibodies. We recommend using only IgG or total Ig for serology testing for the above mentioned context.

Serology tests that only include IgM or IgA should not qualify as these may be unspecific or cross-reactive [7, 8], or indicate an early phase of the infection [9], where neutralizing antibodies are still insufficient. In case of a positive IgA or IgM follow-up testing after three to four weeks seroconversion could be documented using IgG or total Ig.

Semi-quantitative serology. We recommend using commercial CE/IVD serology assays for the above mentioned context.

In Switzerland, most laboratories will or already use serology assays that will measure a value of a detected signal. This value is interpreted along a manufacturer threshold to indicate test positivity (above the threshold) or negativity (below the threshold). Values from such assays are not directly comparable between and within each other. Quantitative serology assay requires a standard curve with reference material, which is rarely done, not widely commercially available and not needed here to simply determine positivity [10].

Threshold of positive serology. We recommend using the manufacturers cut-off for positivity and add 3-times the standard deviation (SD) of technical replicates using the assay's internal control, in order to generate an equivocal zone.

Semi-quantitative serologies are subject to a coefficient of variation analysis by the manufacturer, in order to define a positivity cut-off offering sufficient specificity. We recommend that each laboratory performs a verification of the particular serology assay in use. This verification should include at least 20 technical replicates of the assay's internal control. The measured values will be used to determine the SD. A value ≥ 3-times the SD from this data is added to the manufacturer's cut-off for positivity to add an equivocal buffer zone. Measurements above this threshold would qualify to get the COVID19 certificate. This is an application of the first rule of Westgard (3s). The result should be given as either "positive" or "negative" without any value on the report used to generate the certificate. Values in the equivocal zone should be considered negative.

Specificity. We recommend that only tests with a specificity of more than 98% will be considered [11], which corresponds to the tests implemented in the vast majority of the Swissmedic authorized microbiological diagnostic laboratories.

The specificity of serological tests is crucial. To generate a certificate, a high positive predictive value is needed. Thus, only serology assays with a specificity of more than 98% on a sample size of at least 200 samples will be considered [10-12].

Measurement of cellular immunity. The measurement of SARS-CoV-2 specific T-cell responses [13, 14] using e.g., interferon gamma release assay has only recently become available. The correlation with neutralizing antibodies and protection against severe clinical courses remains to be explored. There is currently no sufficient evidence to recommend the broad establishment of these tests.

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