COVID-19
LITERATURE REPOSITORY

What is the role of antibody testing in COVID-19?

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Discussion

Acute symptomatic COVID-19 is usually diagnosed by detecting viral RNA in respiratory specimens using reverse transcription (RT)-PCR-based assays. Serology is generally not indicated since the sensitivity of antibody tests is too low in the first weeks after symptom onset. However, antibody tests are useful to indicate past-infection (e.g. in someone with potential post-infectious phenomena such as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; PIMS-TS) at a time when the virus is no longer excreted and RT-PCR tests are negative. SARS-CoV-2 (the virus that causes COVID-19)-specific immunoglobulin (Ig)M, IgA and IgG start to appear in the blood after the first week from infection, and are generally detectable after 2-3 weeks(1-3). Serology tests do not have a role in prognostication, as current evidence does not suggest a clear correlation between antibody levels and severity of disease or likelihood of clinical improvement(2, 4, 5).

There has been a rapid growth in the number of available SARS-CoV-2 serological tests which differ between one another in the antigens used for antibody detection (whole spike protein, spike subdomain (S1), spike receptor-binding domain [RBD] or nucleoprotein [Np]), the type of antibodies identified (IgG, IgM, IgA), and the laboratory method. The virus neutralisation test, which measures “functional” antibodies that prevent susceptible cells from infection with the virus, is considered the gold standard. However, these assays need to be performed in high-containment laboratories using infectious virus and are not widely available. Alternatively, enzyme-linked immunosorbent assays (ELISAs), chemiluminescent immunoassays (CLIAs) and lateral flow assays (LFAs) detect binding to a given antigen, but do not measure antibody function. In comparison to standard ELISAs, CLIA testing is considered to be more sensitive and LFAs are far less sensitive. LFAs are sometimes marketed as point-of-care tests to complement COVID-19 diagnosis, however, their poor sensitivity and weak agreement with the results of RT-PCR tests for SARS-CoV-2 infection likely limits their use in any setting(6).

IgM and IgA seem to appear around the same time as IgG, but rapidly decline (within 3-4 weeks(7, 8)), which is

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useful to assess the timing of infection. Confirmatory diagnosis of COVID-19 using serology requires acute (at presentation) and convalescent (after three or more weeks) serum, showing seroconversion, or a fourfold rise in anti-SARS-CoV-2 antibodies. However, it should be noted that a small number of people do not to develop measurable antibodies despite proof of infection by RT-PCR(5); while early seroconversion (as early as 3–5 days post infection), and plateau of IgG and IgM(2), may prevent a four-fold rise being detected.

A Cochrane review(9) found 38 studies (including commercial tests and in-house assays) that stratified results by time since symptom onset; the combination of IgG/IgM had a pooled sensitivity of 30% in the first week from symptom onset, 72% in the second week and 91% in the third week. Based on fewer studies and smaller sample sizes, the pooled sensitivity of IgG/IgM tests was 96.0% in the fourth week. Specificities reported for all target antibodies among 35 studies exceeded 98%.

Given that a large proportion (up to 80%(10)) of infected individuals are either asymptomatic or have mild symptoms and may not present for testing, PCR-based assays are less helpful in quantifying the actual number of SARS-CoV-2 infections in the population. Antibody tests are essential to sero-epidemiological studies, but should be interpreted with some caveats. Based on published data of the sensitivities and specificities of antibody tests, sero-epidemiological surveys conducted in a relatively high-prevalence setting (e.g. 20% infection rate), 17 individuals would be missed per 1000 people tested using antibody tests and 10 would be falsely assumed to be positive. At a lower prevalence of 5%, which is more likely in most national surveys, only 4 individuals would be missed per 1000 tested, but 12 would be falsely positive, i.e. approximately 21% of all positive tests would be false. In addition, most currently available serology tests have only been evaluated in hospitalised patients, so it is unclear whether the tests are able to detect lower antibody levels likely seen with mild or asymptomatic infection(9). Furthermore, these calculations are based on the 'best-case scenario' assuming testing is always performed at least 3 weeks after symptom onset. Performance will be more problematic in large-scale sero-epidemiological surveys, with the majority of infections being mild or asymptomatic, and with no information available on the timing from "infection". Nonetheless, undertaking serial serosurveys to investigate trends over time may be useful, since these trends are less subject to test performance limitations compared to single point seropositivity rates.

Conclusions

1. Antibody testing has very limited value in the acute diagnosis of COVID-19.
2. Antibody testing may assist retrospective diagnosis of COVID-19 in patients who present later with complications or post-infectious sequelae.
3. Sensitivities and specificities of the available serological assays should be carefully considered, also in the context of the background prevalence of infection.
4. The value of antibody tests for sero-epidemiological surveys requires further evaluation.

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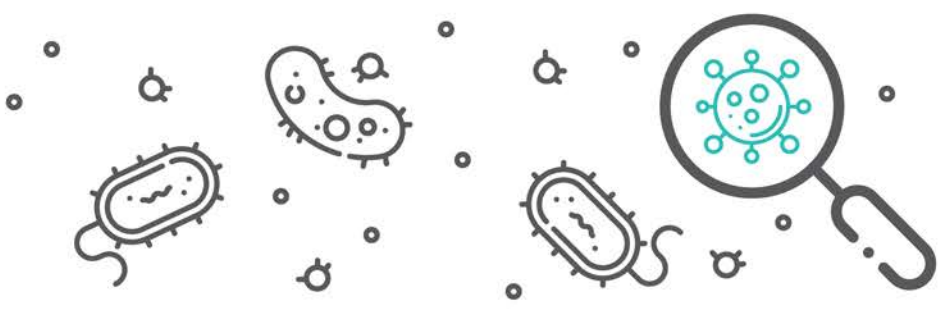

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