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Testing for antibodies to SARS-CoV-2

Not as simple as ABC

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The UK government has adopted testing for antibody responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins as a strategy for estimating the proportion of the population that has been infected, to better understand the spread of the virus.[1] The UK Rapid Test Consortium's "AbC-19™ Rapid Test" (AbC-19) detects the presence of IgG antibody against the trimeric SARS-CoV-2 spike protein in a finger prick device resembling a pregnancy test, allowing for rapid and scalable deployment in the community. Despite ongoing concerns,[2] the UK Government has committed to purchasing 1 million AbC-19 devices.[3]

In the linked study commissioned by the UK government's Department of Health and Social Care (doi:10.1136/bmj.m4262),[4] Mulchandani and colleagues evaluate the accuracy of the AbC-19 assay and find that it may be considerably lower than previously suggested by an as yet unpublished study reported by Robertson and colleagues.[4 5]

Using blood samples from people with a previous positive polymerase chain reaction (PCR) test for SARS-CoV-2 to represent "known positives," and pre-pandemic blood samples to represent "known negatives," Mulchandani and colleagues estimated that the AbC-19 assay has a sensitivity of 92.5% (95% confidence interval 88.8% to 95.1%) and a specificity of 97.9% (97.2% to 98.4%).[4] They calculate that in a population with a 10% prevalence of previous SARS-CoV-2 infection, only 83.0% (78.3% to 86.8%) of positive results would be correct, and 17% would be incorrect.[4] This contrasts with the findings of Robertson and colleagues, who reported a sensitivity of 97.7% (95.7% to 99.3%) and a specificity of 100% (95% confidence interval reported as 100% to 100%).[5]

The discrepancy between the two studies is explained by critical differences in ascertaining known positives and known negatives. Robertson and colleagues chose as known positives people who had already tested positive for antibodies to SARS-CoV-2 proteins in three other assays and chose as known negatives people who tested negative in the same three assays.[5] Such a relatively extreme choice of reference standards likely overestimated the accuracy of the AbC assay, owing to a well known phenomenon called spectrum bias.[6 7]

Mulchandani and colleagues acknowledge that their choice of known positives (PCR positive cases) may also have overestimated the accuracy of the AbC-19 test, because it tends to be the most severe cases of coronavirus 2019 (covid-19) that undergo PCR testing, and these patients generate stronger antibody responses.[4 8] In an alternative analysis—using as known positives unselected key workers with no PCR confirmation of infection but a positive antibody test with the Roche Elecsys anti-nucleoprotein assay—they estimated an even lower sensitivity (84.7%, 80.6% to 88.1%) of the AbC-19 assay.[5]

Finally, interpretation of the AbC-19 device was limited in Mulchandani and colleagues' study by the weak strength of some signals, leading to discordance between three trained laboratory staff for 3.9% of assays.[4] Such uncertainty would likely increase if the test was used in a community setting.

These findings add to mounting evidence that SARS-CoV-2 seroprevalence studies are limited in their ability to correctly identify people who have and have not been infected.[9] The risk of false positives is particularly concerning. If antibody responses are used as an indicator of immunity, for example, test results may influence both individual and government decisions about permissible risk of exposure, and false positives may therefore do considerable societal harm.[10]

Although neutralising antibody responses to SARS-CoV-2 infection may persist for months after infection,[11 12] they can vary considerably between individuals,[13] and the prevalence of detectable antibodies in populations decreases over time.[14] Further work is urgently needed to clarify the relation between circulating antibody concentrations and immunity to SARS-Cov-2. As antibody tests are increasingly available in community pharmacies,[15] a clear message must be communicated to the public that positive results from these assays do not provide evidence of immunity.

The study by Mulchandani and colleagues identifies notable limitations of the UK government's antibody test of choice and provides good evidence that its specificity in a "real life" setting is highly unlikely to be 100%. Apart from limited surveillance to estimate the proportion of a population that has been infected,[9] widespread use of this assay in any other role could risk considerable harm.

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