Are antibody tests underestimating the spread of COVID-19?

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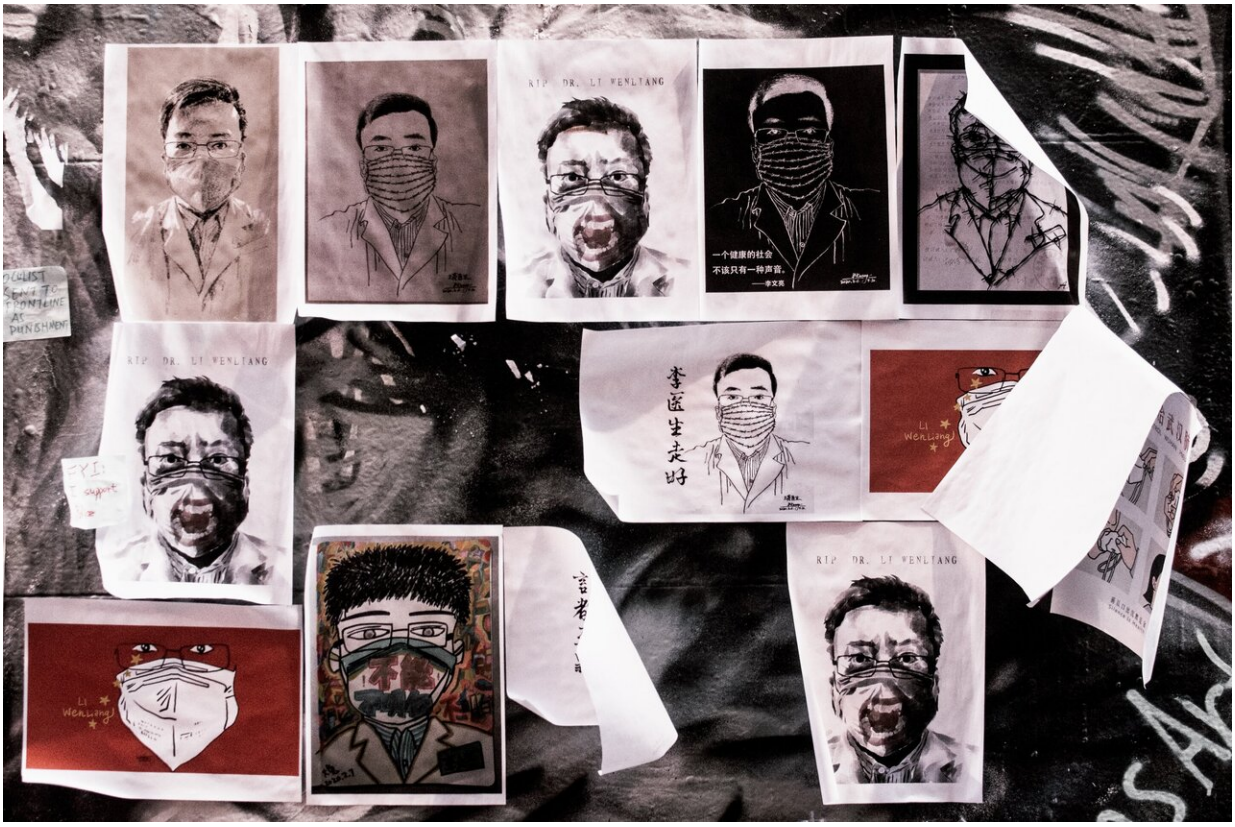

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Dr. Dipender Gill from St George's, along with researchers from the Medical Research Council Biostatistics Unit (part of the University of Cambridge) and University Hospital Wales in Cardiff, have published an

editorial piece in the *British Medical Journal* today titled "Are we underestimating seroprevalence of SARS-CoV-2?"

In this article, the researchers provide reasons why surveys of how far the novel coronavirus (SARS-CoV-2) has spread based on antibody testing may underestimate the number of people previously infected by the virus.

Seroprevalence surveys estimate the proportion of the population that have previously been infected with a virus by measuring the presence of antibodies produced to fight off the virus. This is important for calculating severity measures such as the hospitalization rate and fatality rate, as well as to understand the impact of public health policies, such as social distancing and mask wearing. They also inform our progress towards herd immunity, and the likelihood of a "second wave" of infections.

Large-scale UK seroprevalence surveys have generally provided low estimates of virus spread, suggesting that 15% of those in London and only 4% of those in the South West and South East of England have been exposed to the virus.

However, there are several reasons why these surveys may not capture all those who have developed an immune response to the virus.

Seroprevalence surveys typically only measure IgG and sometimes IgM antibodies, which represent the dominant antibody classes in the bloodstream. They do not typically measure IgA antibodies, which represent the main antibody class in mucous secretions, including saliva and the protective fluid around the eyes, respiratory tract, and digestive tract.

As the main site of viral entry into the body is the respiratory tract,

failure to measure IgA antibodies may result in false negative tests. A previous survey in Luxembourg found IgG antibodies in 1.9% of individuals, whereas IgA antibodies were found in 11.0%, over five times as many. Another survey of local residents in Ischgl, Austria used a combination of IgG and IgA antibody testing. Positive antibody tests were obtained for 42.4% of residents in Ischgl, far higher than other population-based surveys of infection hotspots. Additionally, most large seroprevalence surveys have been based on blood samples only. In a survey of UK healthcare workers, 15% of those tested for IgG, IgA and IgM antibodies provided a positive saliva test but a negative blood test.

A further reason for underestimation is that antibody tests were calibrated in hospitalized patients, meaning that the threshold for detecting a positive case may be too high to accurately capture cases with mild symptoms. There is also evidence that antibodies to part of the viral coating (the "spike-protein") may be more easily detectable; however, several tests currently only measure antibodies to the virus core (the "nucleocapsid").

Another issue is timing: both early testing (after infection but before immune response has developed) and late testing (after immune response has diminished with time) may result in false negative tests.

Stephen Burgess, group leader at the Medical Research Council Biostatistics Unit, University of Cambridge, said: "Accurate estimates of immune response to infection are critically important to judge whether the potential danger of future infections is outweighed by the harm incurred by measures taken to reduce the risk of these infections."

Mark Ponsford, a clinical immunologist at the University Hospital of Wales, said: "The immune response to the virus is more complex than a simple 'yes ' or 'no' to the presence of a single antibody type in the blood. It's important that future surveys take this into account, and that we

begin to standardize our approach to testing. This will help us to improve accuracy and allow more valid comparisons of the results from different surveys."

Dr. Dipender Gill from the Institute of Medical and Biomedical Education and Institute for Infection and Immunity at St George's said: "Current seroprevalence surveys may be dramatically under-estimating the proportion of people that have been infected by the virus. Further work is required to determine the optimal survey strategy and appropriately revise these figures."

More information: Stephen Burgess et al. Are we underestimating seroprevalence of SARS-CoV-2?, *British Medical Journal* (2020). DOI: 10.1136/bmj.m3364

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