



Serosurveys underestimate building of herd immunity

Antibody prevalence data derived from serosurveys must be interpreted with caution and correction factors

The theory behind population based serological surveys (seroprevalence surveys or serosurveys) to detect the prevalence of antibodies against COVID19 is robust. Their purpose is to measure the proportion of a population already infected, as evidenced by antibody positivity. When applied on a national scale, a random sample of the entire population is tested. Then, the data are extrapolated to the whole population.



‘Random’, according to the dictionary, means something without a deliberate order. In biostatistics, it means each individual has an equal probability of getting selected. Statisticians stratify the population and select a random sample from all strata so that the prevalence figure obtained is representative of the whole population. The result of random sample serosurveys can be confidently extrapolated to obtain national level prevalence of antibodies.

WHAT ANTIBODY TESTS SAY

Unfortunately there are problems with the antibody tests. Antibodies are the footprints of the host’s response to virus infection. Their presence in the blood serum confirms past infection. However, test results for antibodies throw up surprises. Antibody prevalence data derived from serosurveys must be interpreted with caution and correction factors.

The virus carries several antigens, both on the surface and internally. The body responds to all of them. Four antigens selected to detect antibodies are spike protein (S1, S2), receptor-binding Domain (RBD) and nucleocapsid (N).

An antibody against each antigen has its own time of appearance, duration in blood and rate of decay over time. Moreover, detection of antibodies does not correlate well with the protective virus neutralizing function of immunity. Testing for virus neutralizing antibodies is not an option, since handling the virus is risky for lab personnel. It is prohibited in clinical labs and restricted to selected research labs.

Recent publications in The Journal of the American Medical Association and The New England Journal of Medicine say that in people with asymptomatic or mildly symptomatic infections, these antibody levels decline over time, reaching 50% of the initial levels by about 36 days and become undetectable by 60 days after proven infection. Such asymptomatic and mildly symptomatic cases constitute more than 80% of those infected with the virus. In a study on exposure-prone healthcare workers in Tennessee, nearly half the subjects with S2 antibodies became negative in two months. If both S2 and RBD antibodies are detected, the results correlate better with the neutralising function. Also, one or the other may persist longer. However, available test kits use only one antigen.

An Institute for MPPSC Examination

The Indian Council of Medical Research conducted two serosurveys: May 11- June 4 and August 17- September 22. The first survey measured S1 antibody and the second survey used another antigen, rendering inter survey Comparison problematic.

The latent period between infection and the appearance of a detectable antibody is about four weeks. Therefore, the results of the first serosurvey pertain predominantly to the antibody status of subjects from April 13 to May 7. Those who got infected after May 7 would have been eclipsed in the study. So the result is an underestimate of the true value. The seroprevalence was 0.73% and that was extrapolated to about 30%-35% of the population having antibodies when India saw the epidemic peak in mid September. Since infections were very few before April 13, the results of the first serosurvey were reasonably time appropriate and the extrapolation close to the true

situation. A study by the Department of Science and Technology concluded that at the peak time, the proportion of the population with antibodies was 28%, close to the published estimate of 30%-35%.

The second serosurvey gave 7.1% prevalence for those immune between July 20 and August 25. For the sake of simplifying calculations, we assign August 4, the midpoint of this time interval to represent the second survey results. Subjects who were antibody positive by August 4 would have contracted the infection a month earlier by July 4. The result is not Time appropriate as at least 50% of those infected two months earlier by June 4 (representing the midpoint between April 20 and June 25) would have become antibody negative. This was the time when infections were rapidly rising. In short, the result is a gross underestimate of the true level of those with antibodies. Taking 50% as the correction factor, prevalence was 14.2% on August 4.

From August 4 to September 16, (the day of the peak) new cases increased from 51,282 to 97,859 by a factor of 1.9. So, the estimated proportion of the population infected at the peak could have been $14.2 \times 1.9 = 27\%$.

CAUTIOUS INTERPRETATION

Evidently, serosurvey results have to be cautiously interpreted to arrive at the true level of prevalence of antibodies. If taken at face value, serosurvey results grossly underestimate true prevalence, except in the very early phase of the epidemic when infected people two months earlier were very few.

Misinterpreting serosurvey results has serious consequences for understanding the epidemic profile. What is in store for India? Several countries have second or even third waves of infection. Will India face such waves? If the peak coincided with 27%-35% prevalence, the epidemic is likely to evolve as endemic after another 30% are infected in the post peak phase of the epidemic. The predicted herd immunity level needed to end the epidemic was 60%, for a normal epidemic curve with peak at its halfway mark. For a

normal epidemic curve, the cumulative number of people infected before the peak will be equal to the number who will be infected after the peak because the curve is bell shaped. That means we did not manage to flatten the curve and further waves are unlikely. However, the speed with which people will get infected in various localities depends on human behaviour. Pre peak there was fear and people practised social distancing and wore masks. Post peak, many have no fear and are more relaxed about good practices to prevent infection. Major festivals are approaching. Unless care is taken, they may enhance transmission frequency, giving rise to local outbreaks and infection waves, but they are unlikely to disturb the downward slope of the national epidemic curve because half of the herd immunity level required to end the epidemic was already reached by mid September.

Governments must continuously exhort citizens not to let their guard down, not only for the safety of those who celebrate, but also, more importantly, their family members, particularly senior citizens. People can celebrate festivals but governments must enforce strict norms regarding crowding, especially inside buildings.

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