The BMJ
pdoshi@bmj.com
Cite this as: *BMJ* 2020;370:m3563
http://dx.doi.org/10.1136/bmj.m3563
Published: 17 September 2020

COVID-19

Do many people have pre-existing immunity to covid-19?

It seems a truth universally acknowledged that the human population had no pre-existing immunity to SARS-CoV-2, but is that actually the case? Peter Doshi reports

Peter Doshi *associate editor*

Even in local areas that have experienced some of the greatest rises in excess deaths during the covid-19 pandemic, serological surveys since the peak indicate that at most only around a fifth of people have antibodies to SARS-CoV-2: 23% in New York, 18% in London, 11% in Madrid. Among the general population the numbers are substantially lower, with many national surveys reporting in single digits.

With public health responses around the world predicated on the assumption that the virus entered the human population with no pre-existing immunity before the pandemic, serosurvey data are leading many to conclude that the virus has, as Mike Ryan, WHO's head of emergencies, put it, "a long way to burn."

In a study of donor blood specimens obtained in the US between 2015 and 2018, 50% displayed various forms of T cell reactivity to SARS-CoV-2. A similar study that used specimens from the Netherlands reported T cell reactivity in two of 10 people who had not been exposed to the virus.

In Germany reactive T cells were detected in a third of SARS-CoV-2 seronegative healthy donors (23 of 68). In Singapore a team analysed specimens taken from people with no contact or personal history of SARS or covid-19; 12 of 26 specimens taken before July 2019 showed reactivity to SARS-CoV-2, as did seven of 11 from people who were seronegative against the virus. Reactivity was also discovered in the UK and Sweden.

Though these studies are small and do not yet provide precise estimates of pre-existing immunological responses to SARS-CoV-2, they are hard to dismiss, coming from different laboratories in different continents and with several being published in *Cell* and *Science*. Researchers are also confident that they have made solid inroads into ascertaining the origins of the immune responses.

"Our hypothesis, of course, was that it's so called common cold coronaviruses, because they're closely related," said Daniela Weiskopf, senior author of a paper in *Science* that confirmed this hypothesis. "We have really shown that this is a true immune memory and it is derived in part from common cold viruses."

Taken together, this growing body of research may force pandemic planners to revisit some of their foundational assumptions about how to measure population susceptibility and monitor the extent of epidemic spread.

Population immunity: underestimated?

Seroprevalence surveys measuring antibodies have been the preferred method for gauging the proportion of people in a given population who have been infected by SARS-CoV-2 (and have some degree of immunity to it).

The fact that only a minority of people, even in the hardest hit areas, display antibodies against SARS-CoV-2 has led most planners to assume the pandemic is far from over. In New York City, where just over a fifth of people surveyed had antibodies, the health department concluded that "as this remains below herd immunity thresholds, monitoring, testing, and contact tracing remain essential public health strategies." Whatever that threshold number is, "we're nowhere near close to it," said WHO's Ryan in late July.

But memory T cells are known for their ability to affect the clinical severity and susceptibility to future infection, and the T cell studies documenting pre-existing reactivity to SARS-CoV-2 in 20-50% of people suggest that antibodies are not the full story.

"Maybe we were a little naive to take measurements such as serology testing to look at how many people were infected with the virus," the Karolinska Institute immunologist Marcus Buggert told *The BMJ*. "Maybe there is more immunity out there."

The research offers a powerful reminder that very little in immunology is cut and dried. Physiological responses may have fewer sharp distinctions than in the popular imagination: exposure does not necessarily lead to infection, infection does not necessarily lead to disease, and disease does not necessarily produce detectable antibodies. And within the body, the roles of various immune system components are complex and interconnected. B cells produce antibodies, but B cells are regulated by T cells, and while T cells and antibodies both respond to viruses in the body, T cells do so on infected cells, whereas antibodies help prevent cells from being infected.

Unexpected twist of the curve

Buggert's home country has been at the forefront of the herd immunity debate, with Sweden's light touch strategy against the virus resulting in much scrutiny and scepticism. The epidemic in Sweden does seem to be declining, Buggert says. Something must have happened, he says, particularly considering that social distancing was "always poorly followed, and it has only become worse."

Understanding this "something" is a core question for Sunetra Gupta, an Oxford University epidemiologist who developed a way to calculate herd immunity thresholds that incorporates a variable for pre-existing innate resistance and cross protection. Her group argues that herd immunity thresholds "may be greatly reduced if a fraction of the population is unable to transmit the virus."

"The conventional wisdom is that lockdown occurred as the epidemic curve was rising," Gupta explains, "So once you remove lockdown that curve should continue to rise." But that is not happening in places like New York, London, and Stockholm. The question is why.

Possible answers are many, Gupta says. One is that social distancing is in place, and people are keeping the spread down. Another possibility is that a lot of people are immune because of T cell responses or something else. "Whatever it is, if there is a significant fraction of the population that is not permissive to the infection, then that all makes sense, given how infectious SARS-CoV-2 is."

Buggert's study in Sweden seems to support this position. Investigating close family members of patients with confirmed covid-19, he found T cell responses in those who were seronegative or asymptomatic. While around 60% of family members produced antibodies, 90% had T cell responses. (Other studies have reported similar results.) "So many people got infected and didn't create antibodies," concludes Buggert.

Deeper discussion

T cell studies have received scant media attention, in contrast to research on antibodies, which seem to dominate the news (probably, says Buggert, because they are easier, faster, and cheaper to study than T cells). Two recent studies reported that naturally acquired antibodies to SARS-CoV-2 begin to wane after just 2-3 months, fuelling speculation in the lay press about repeat infections.

But T cell studies allow for a substantially different, more optimistic, interpretation. In the Singapore study, for example, SARS-CoV-1 reactive T cells were found in SARS patients 17 years after infection. "Our findings also raise the possibility that long lasting T cells generated after infection with related viruses may be able to protect against, or modify the pathology caused by, infection with SARS-CoV-2," the investigators wrote.

T cell studies may also help shed light on other mysteries of covid-19, such as why children have been surprisingly spared the brunt of the pandemic, why it affects people differently, and the high rate of asymptomatic infections in children and young adults.

The immunologists I spoke to agreed that T cells could be a key factor that explains why places like New York, London, and Stockholm seem to have experienced a wave of infections and no subsequent resurgence. This would be because protective levels of immunity, not measurable through serology alone but instead the result of a combination of pre-existing and newly formed immune responses, could now exist in the population, preventing an epidemic rise in new infections.

But they were all quick to note that this is speculation. Formally, the clinical implications of the pre-existing T cell reactivity remain an open question. "People say you don't have proof, and they're right," says Buggert, adding that the historical blood donor specimens in his study were all anonymised, precluding longitudinal follow-up.

There is the notion that perhaps T cell responses are detrimental and predispose to more severe disease. "I don't see that as a likely possibility," says Alessandro Sette, an immunologist from La Jolla Institute for Immunology in California, while emphasising that we need to acknowledge the possibility. "It's also possible that this absolutely makes no difference. The cross reactivity is too small or weak to affect the virus. The other outcome is that this does make a difference, that it makes you respond better."

Weiskopf adds, "Right now, I think everything is a possibility; we just don't know. The reason we're optimistic is we have seen with other viruses where [the T cell response] actually helps you." One example is swine flu, where research has shown that people with pre-existing reactive T cells had clinically milder disease.

Weiskopf and Sette say that compelling evidence could come through a properly designed prospective study that followed a cohort of people who were enrolled before exposure to SARS-CoV-2, comparing the clinical course of those with and without pre-existing T cell responses.

Understanding the protective value of pre-existing SARS-CoV-2 T cell reactivity is "identical to the situation on vaccines," says Antonio Bertoletti, professor of infectious disease at Duke-NUS Medical School in Singapore. "Through vaccination we aim to stimulate antibodies and T cell production, and we hope that such induction of immunity will protect ... but we need a phase III clinical study to really demonstrate the effect."

"At the start of the pandemic, a key mantra was that we needed the game changer of antibody data to understand who had been infected and how many were protected," two immunologists from Imperial College London wrote in a mid-July commentary in *Science Immunology*. "As we have learned more about this challenging infection, it is time to admit that we really need the T cell data too."