Covid-19: Do many people have pre-existing immunity?

Box 2

Calculating the herd immunity threshold

In theory, outbreaks of contagious disease follow a certain trajectory. In a population that lacks immunity new infections grow rapidly. At some point an inflection in this growth should occur, and the incidence will begin to fall.

The 1970s gave rise to a theory that defined this inflection point as the herd immunity threshold (HIT) and offered a straightforward formula for estimating its size: $HIT=1–1/R_0$ (where R_0 is the disease's basic reproduction number, or the average number of secondary cases generated by an infectious individual among susceptible people). This simple calculation has guided—and continues to guide—many vaccination campaigns, often used to define target levels of vaccination.20

The formula rests on two assumptions: that, in a given population, immunity is distributed evenly and members mix at random. While vaccines may be deliverable in a near random fashion, from the earliest days questions were raised about the random mixing assumption. Apart from certain small closed populations such as "orphanages, boarding schools, or companies of military

recruits," Fox and colleagues wrote in 1971,21 truly random mixing is the exception, not the rule. "We could hardly assume even a small town to be a single homogeneously mixing unit. Each individual is normally in close contact with only a small number of individuals, perhaps of the order of 10-50."

Nearly 50 years later, Gabriela Gomes, an infectious disease modeller at the University of Strathclyde, is reviving concerns that the theory's basic assumptions do not hold. Not only do people not mix randomly, infections (and subsequent immunity) do not happen randomly either, her team says. "More susceptible and more connected individuals have a higher propensity to be infected and thus are likely to become immune earlier. Due to this selective immunization by natural infection, heterogeneous populations require less infections to cross their herd immunity threshold," they wrote.22 While most experts have taken the R_0 for SARS-CoV-2 (generally estimated to be between 2 and 3) and concluded that at least 50% of people need to be immune before herd immunity is reached, Gomes and colleagues calculate the threshold at 10% to 20%.2223

Ulrich Keil, professor emeritus of epidemiology from the University of Münster in Germany, says the notion of randomly distributed immunity is a "very naive assumption" that ignores the large disparities in health in populations and "also ignores completely that social conditions might be more important than the virus itself."

He added, “Tuberculosis here is the best example. We all know that the immune system is very much dependent on the living conditions of a person, and this depends very much on education and social conditions.”

Another group led by Sunetra Gupta at the University of Oxford has arrived at similar conclusions of lower herd immunity thresholds by considering the issue of pre-existing immunity in the population. When a population has people with pre-existing immunity, as the T cell studies may be indicating is the case, the herd immunity threshold based on an R_0 of 2.5 can be reduced from 60% of a population getting infected right down to 10%, depending on the quantity and distribution of pre-existing immunity among people, Gupta’s group calculated.24

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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 antibodies 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.282930

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,”8 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,” Sette said, while emphasising that we still 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 added, “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 (box 1).121314

Weiskopf and Sette maintain that compelling evidence could come through a properly designed prospective study that follows 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,” said 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."

German investigators came to the same conclusion, arguing that their T cell findings represented a "decisive rationale to initiate worldwide prospective studies" mapping pre-existing reactivity to clinical outcomes.31 Other groups have called for the same thing.6

"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."32

Theoretically, the placebo arm of a covid-19 vaccine trial could provide a straightforward way to carry out such a study, by comparing the clinical outcomes of people with versus those without pre-existing T cell reactivity to SARS-CoV-2. A review by *The BMJ* of all primary and secondary outcome measures being studied in the two large ongoing, placebo controlled phase III trials, however, suggests that no such analysis is being done.3334

Could pre-existing immunity be more protective than future vaccines? Without studying the question, we won't know.