T-cells Are the Superstars in Fighting COVID-19. But Why are some People So Poor at Making Them?

By Eshani M King, Evidence Based Research in Immunology and Health

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Thank you to Eshani M King for allowing Children's Health Defense to run her letter in response to Dr. Peter Doshi's article *— Covid-19: Do many people have pre-existing immunity? — that was featured in The BMJ last week.*

Dear Editor,

Thank you to Dr. Doshi for raising the profile of T-cells. Incidentally, German researchers found that a staggering *81% of individuals* had pre-existing T-cells that cross-react with SARS-CoV-2 epitopes. This fits with modelling in May by Imperial College's Professor Friston, a world authority in mathematical modelling of complex dynamic biological systems, *indicating* that around 80% and 50% of the German and UK populations, respectively, are resistant to COVID-19.

Antibodies can only latch onto and help destroy pathogens outside cells and may also occasionally, paradoxically, enhance a pathogen's ability to infect cell instead by antibody dependent "enhancement" or ADE. It is only the T-cell that can cleverly sense and destroy pathogens inside infected cells using "sensors" which detect foreign protein fragments.

In the late 60's, the Lancet described a case of a child with agammaglobulinemia, a condition in which absence of B cells prevent them from producing antibodies, who overcame a measles infection quite normally and did not become re-infected thereafter. We now know that, although this condition can compromise immunity, in that particular case the rest of the immune functions, including T-cells, must have been perfectly up to the job of clearing infection and establishing immune memory without help from antibodies. The importance of T-cells in fighting SARS-CoV-1 and establishing immune memory has also been well documented and discussed in a number of *pre-COVID papers* from 2017 and earlier.

Then, early in April, it was *reported* that two patients with agammaglobulinemia overcame COVID-19 infections without requiring ventilation, prompting the Italian authors to write: "This observation suggests that T-cell response is probably important for immune protection against the virus, while B-cell response might be unessential."

All this should have shifted the focus of efforts towards T-cells at an early stage — the real question is why mainstream media and others continued to focus efforts and narrative on antibodies. Is it because vaccines are good at provoking antibody responses but not so great at generating T-cells? Some of the vaccines presently under trial do elicit some T-cells but it seems that neither the quantity nor variety are hugely impressive.

Does this matter? Apparently so: Research establishments including Yale *found* that in mild or asymptomatic cases, *many T-cells are produced*. These were highly varied, responding not just to parts of the Spike, S protein or Receptor Binding Domain *but to many other parts of the virus*. Notably, in these mild cases there were few or no detectable antibodies. Conversely, the severely ill produced few T-cells with less variety but had plenty of antibodies. What is also of interest is that *men produced fewer T-cells than women*, and unlike women, their T-cell response reduced with age.

So why are some people unable to mount a good protective T-cell response? The key to this question might be a *10-year-old Danish study* led by Carsten Geisler, head of the Department of International Health, Immunology and Microbiology at the University of Copenhagen. Geisler noted that "When a T cell is exposed to a foreign pathogen, it extends a signalling device or 'antenna' known as a vitamin D receptor, with which it searches for vitamin D," and if there is an inadequate vitamin D level, "they won't even begin to mobilize." In other words, adequate vitamin D is critically important for the activation of T-cells from their inactive naïve state. The question of whether T-cells might also need a continuing supply of vitamin D to *prevent the T-cell exhaustion* and apoptosis observed in some serious COVID-19 cases deserves further research.

High levels of vitamin D are also *critical for first line immune defences* including physical mucosal defences, human antiviral production, modulating cytokines, reducing blood clotting and a whole host of other important immune system functions. The obese, diabetics and people of BAME origin are far more deficient in vitamin D and men have lower levels than women.

Another intriguing clue is that Japan has the highest proportion of elderly on the planet but despite lack of lockdowns, little mask wearing and high population densities in cities, it escaped with few COVID deaths. Could this, at least in part, be because of *extraordinarily high vitamin D levels* of over 30 ng/ml in 95% of the active elderly? By comparison, UK average levels are *below 20ng/ml*. Vitamin D is made in the skin from the action of UV sunlight, food usually being a poor source, but the Japanese diet includes unusually high levels. Sunny countries near the equator (e.g. Nigeria, Singapore, Sri Lanka) also have very low COVID related deaths.

The *results of the first vitamin D intervention* double blind RCT for COVID was published on 29 August by researchers in Córdoba, Spain. This very well conducted study produced spectacular outcomes for the vitamin D group (n=50), virtually eliminating the need for ICU (reducing it by 96%) and eliminating deaths (8% in the n=26 control group). Although this was a small trial, the ICU results are so dramatic that they are statistically highly significant.

Substantially more vitamin D is required for optimal immune function than for bone health. It seems Dr Fauci is not ignorant of this, having apparently confirmed on TV and by email that he takes 6,000 IU daily! (see Dr John Campbell on YouTube Vitamin D and pandemic science, 16 September 2020). Meanwhile the US's health body continues to recommend only 600-800 IU and the UK's, only 400 IU.

It is high time for joined up solid scientific rationale to overthrow mainstream narratives based on an alternative "science" controlled by industry interests/politics. Beda M Stadler, the former Director of the Institute for Immunology at the University of Bern, a biologist and Professor Emeritus, certainly appears to think so (see Ivor Cummins Ep91 Emeritus Professor of Immunology...Reveals Crucial Viral Immunity Reality on YouTube, 28 July 2020).

In the same way that prior infections protect us against future infections by means of cross-reacting T-cells, overcoming COVID-19 naturally offers potential for greater protection against future coronaviruses. Vaccines have their place but so do our amazingly complex, sophisticated, highly effective immune systems which have evolved over millennia to protect us from a world teeming with trillions of pathogens.

L'article de Peter Doshi cité en introduction :

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

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It seemed 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*** *explores the emerging research on immunological responses*

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.*123* 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,[4] 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."

Yet a stream of studies that have documented SARS-CoV-2 reactive T cells in people without exposure to the virus are raising questions about just how new the pandemic virus really is, with many implications.

Not so novel coronavirus?

At least six studies have reported T cell reactivity against SARS-CoV-2 in 20% to 50% of people with no known exposure to the virus.[5,6,7,8,9,10]

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.[5,11] 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.[7]

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.[8] Reactivity was also discovered in the UK and Sweden.[6,9,10]

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, with several being published in *Cell* and *Nature*. Alessandro Sette, an immunologist from La Jolla Institute for Immunology in California and an author of several of the studies (*box 1*), told *The BMJ*, "At this point there are a number of studies that are seeing this reactivity in different continents, different labs. As a scientist you know that is a hallmark of something that has a very strong footing."

Box 1

Swine flu déjà vu

In late 2009, months after the World Health Organization declared the H1N1 "swine flu" virus to be a global pandemic, Alessandro Sette was part of a team working to explain why the so called "novel" virus did not seem to be causing more severe infections than seasonal flu.[12]

Their answer was pre-existing immunological responses in the adult population: B cells and, in particular, T cells, which "are known to blunt disease severity."[12] Other studies came to the same conclusion: people with pre-existing reactive T cells had less severe H1N1 disease.[13,14] In addition, a study carried out during the 2009 outbreak by the US Centers for Disease Control and Prevention reported that 33% of people over 60 years old had cross reactive antibodies to the 2009 H1N1 virus, leading the CDC to conclude that "some degree of pre-existing immunity" to the new H1N1 strains existed, especially among adults over age 60.[15]

The data forced a change in views at WHO and CDC, from an assumption before 2009 that most people "will have no immunity to the pandemic virus"[16] to one that acknowledged that "the vulnerability of a population to a pandemic virus is related in part to the level of pre-existing immunity to the virus."[17] But by 2020 it seems that lesson had been forgotten.

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.[18] "We have really shown that this is a true immune memory and it is derived in part from common cold viruses." Separately, researchers in Singapore came to similar conclusions about the role of common cold coronaviruses but noted that some of the T cell reactivity may also come from other unknown coronaviruses, even of animal origin.[8]

Taken together, this growing body of research documenting pre-existing immunological responses to SARS-CoV-2 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), with estimates of herd immunity thresholds providing a sense of where we are in this pandemic. Whether we overcome it through naturally derived immunity or vaccination, the sense is that it won't be over until we reach a level of herd immunity.

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."[19] "Whatever that number is, we're nowhere near close to it," said WHO's Ryan in late July, referring to the herd immunity threshold (*box 2*).

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%.[22,23]

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*

But memory T cells are known for their ability to affect the clinical severity and susceptibility to future infection,*25* 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.

An 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.*26* The epidemic in Sweden does seem to be declining, Buggert said in August. "We have much fewer cases right now. We have around 50 people hospitalised with covid-19 in a city of two million people." At the peak of the epidemic there were thousands of cases. Something must have happened, said Buggert, particularly considering that social distancing was "always poorly followed, and it's 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.*24* 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 explained. "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.

"If it were the case that in London the disease hadn't disseminated too widely, and only 15% have experienced the virus [as serology tests indicate] . . . under those circumstances, if you lift lockdown, you should see an immediate and commensurate increase in cases, as we have observed in many other settings," Gupta told *The BMJ*, "But that hasn't happened. That is just a fact. The question is why."

Possible answers are many, she 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," Gupta added, "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.*10* While around 60% of family members produced antibodies, 90% had T cell responses. (Other studies have reported similar results.*27*) "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 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.*28 29 30*

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*).*12 13 14*

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.[33][34]

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

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Footnotes

Competing interests: I am a colleague of Ulrich Keil, quoted in this article. A generic statement of competing interests may be found at *https://www.bmj.com/about-bmj/editorial-staff/peter-doshi*

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