Herd immunity to COVID-19 and pre-existing immune responses

I showed in my May 10th article Why herd immunity to COVID-19 is reached much earlier than thought that inhomogeneity within a population in the susceptibility and in the social-connectivity related infectivity of individuals would reduce, in my view probably very substantially, the herd immunity threshold (HIT), beyond which an epidemic goes into retreat. I opined, based on my modelling, that the HIT probably lay somewhere between 7% and 24%, and that evidence from Stockholm County suggested it was around 17% there, and had been reached.

I then showed in a July 27th update article[1] that mounting evidence supported my reasoning.

It is pleasing to report that the evidence for heterogeneity of susceptibility across the population, arising from variability in both social connectivity and biological susceptibility, has continued to increase. Not least, there have been a number of further papers reporting pre-existing cross-reactive T-cells in a substantial proportion of people, which as I discussed in my July 27th article is likely be a key reason for heterogeneity in biological susceptibility. Mainstream journals are now starting to acknowledge that these factors are significant, with the implication that the herd immunity threshold (HIT) can be expected to be substantially lower than that often quoted by scientists close to governments. Unfortunately, in the UK at least, there is little sign as yet that those scientific advisors are prepared to recognise these facts.[2] [3]

Here I will focus excerpt on statements in a recent, quite hard hitting, feature article in the British Medical Journal by one of its associate editors.[4]

The article points out serological studies have generally indicated that no more than around a fifth of people now have antibodies to SARS-CoV-2, saying:

> 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."

As the article says, this has led most planners to assume that 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 number is, we're nowhere near close to it," said WHO's Ryan in late July, referring to the herd immunity threshold

However, the article notes:

> 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.

It also points out that the WHO and the CDC has been repeating mistakes that they made and recognised in the past, suggesting a lack of scientific competence (unless explainable by a prioritising of other objectives over scientific ones).

> 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. 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." Other studies came to the same conclusion: people with pre-existing reactive T cells had less severe H1N1 disease. 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. 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" 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." But by 2020 it seems that lesson had been forgotten.

Regarding pre-existing T-cell mediated immunological responses to SARS-CoV-2, the article quotes Alessandro Sette, an immunologist from La Jolla Institute for Immunology in California and an author of several of the studies:

> 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." It also notes that a paper in *Science* confirmed its authors' hypothesis that, because they're closely related, the origin of these immune responses would be 'common cold' coronaviruses.

As the article says, the T-cell evidence suggests that antibodies are not the full story, in relation to which it gives this quotation:

> "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."

and comments that studies by Buggert and others have shown that many people who have been exposed to SARS-CoV-2 generate T-cell responses but no antibodies.

The article makes the telling point that:

> Taken together, this growing body of research documenting pre-existing immunological responses to SARS-CoV-2may force pandemic planners to revisit some of their foundational assumptions about how to measure population susceptibility and monitor the extent of epidemic spread.

The article also discusses the fact that the classical formula HIT = $1 - 1/R_0$ (where R_0 is the disease's basic reproduction number) assumes that immunity (the complement of biological susceptibility) is distributed evenly and members mix at random, saying:

> While vaccines may be deliverable in a near random fashion, from the earliest days questions were raised about the random mixing assumption. Fox and colleagues wrote in 1971 [that] truly random mixing is the exception, not the rule.

The author quotes Gabriella Gomes, noting that she and her colleagues wrote:

> 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.

and points out that

> While most experts have taken the R0 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%.

The article further notes that Sunetra Gupta's group 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.

The author also quotes Ulrich Keil, professor emeritus of epidemiology from the University of Münster in Germany, as saying

> the notion of randomly distributed immunity is a "very naive assumption"

that ignores the large disparities in health and social conditions in populations.

As so often, the case of Sweden is brought up, in this quotation:

> 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 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."

Social distancing will reduce the R_0 level of an epidemic and thus, while it continues, with reduce the HIT. The fact that social distancing in Sweden has become relatively minor therefore means that the epidemic's recent behaviour there should provide a better guide to the HIT in the absence of social distancing than its behaviour in many other countries. Supporting Marcus Buggert's comments, that in Stockholm (a densely populated region where R_0 will be higher than average) the epidemic is almost extinct and social distancing is now minor, are these recent comments from a hospital doctor[5] in Stockholm:

> In the hospital where I work, there isn't a single person currently being treated for covid.
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> I haven't seen a single covid patient in the Emergency Room in over two and a half months.
>
> My personal experience is that people followed the voluntary restrictions pretty well at the beginning, but that they have become increasingly lax as time has gone on.
>
> When I sit in the tube on the way to and from work, it is packed with people. Maybe one in a hundred people is choosing to wear a face mask in public. In Stockholm, life is largely back to normal. If you look at the front pages of the tabloids, on many days there isn't a single mention of covid anywhere.
>
> Covid is over in Sweden. We have herd immunity.

In Sweden, the epidemic gradually spread throughout the country from its original centre in Stockholm, with different regions seeing differently timed surges in cases, almost all of which have now tailed off despite national seroprevalence estimates of only 5-6%.[6] However, it looks as if in countries such as the UK lockdowns may have impeded the epidemic's spread from its original centre to regional metropolitan centres, where the epidemic is growing now that young people in particular no longer fear COVID-19 much. Nevertheless, serious illness and deaths remain rare in the UK; in recent weeks only 1% of death certificates have any mention of COVID-19[7].

Returning to the T-cell immunity issue, the BMJ article further comments:

> 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.

Although noting that these epidemiologists added the qualification that this hypothesis is currently unproven, the article quotes Daniela Weiskopf (the senior author of the Science paper mentioned earlier) as commenting:

> 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."

As the paper says, one example is swine flu, where research has shown that people with pre-existing reactive T cells had clinically milder disease.

In conclusion, it is encouraging to see an article like this in an medical establishment journal like BMJ. I can only hope that epidemiologists, other scientists and modellers advising governments will now finally take seriously the issues that it raises.

Nicholas Lewis 22 September 2020

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[1] Lewis, N: Why herd immunity to COVID-19 is reached much earlier than thought - update; with further update added on July 31st.

[2] For example: The academy of Medical Sciences 14 July 2020 report "Preparing for a challenging winter 2020/21" appears to rely on modelling by Professor Ferguson and colleagues from Imperial College, whose models make little allowance for population heterogeneity of susceptibility https://www.gov.uk/government/publications/covid-19-preparing-for-a-challenging-winter-202021-7-july-2020

[3] https://www.bbc.co.uk/news/uk-54234084

[4] Peter Doshi: "COVID-19: Do many people have pre-existing immunity?" BMJ 2020;370:m3563 https://dx.doi.org/10.1136/bmj.m3563

[5] https://sebastianrushworth.com/2020/09/19/covid-19-does-sweden-have-herd-immunity/

[6] https://www.folkhalsomyndigheten.se/contentassets/376f9021a4c84da08de18ac597284f0c/pavisning-antikroppar-genomgangen-covid-19-blodgivare-delrapport-2.pdf The latest published estimate is 5% for week 22; it may have grown since then but based on disease incidence seems likely to have remained under 10%.

[7] https://www.ons.gov.uk/file?uri=%2fpeoplepopulationandcommunity%2fbirthsdeathsandmarriages%2fdeaths%2fdatasets%2fweeklyprovisionalfiguresondeathsregisteredinenglandandwales%2f2020/publishedweek372020.xlsx