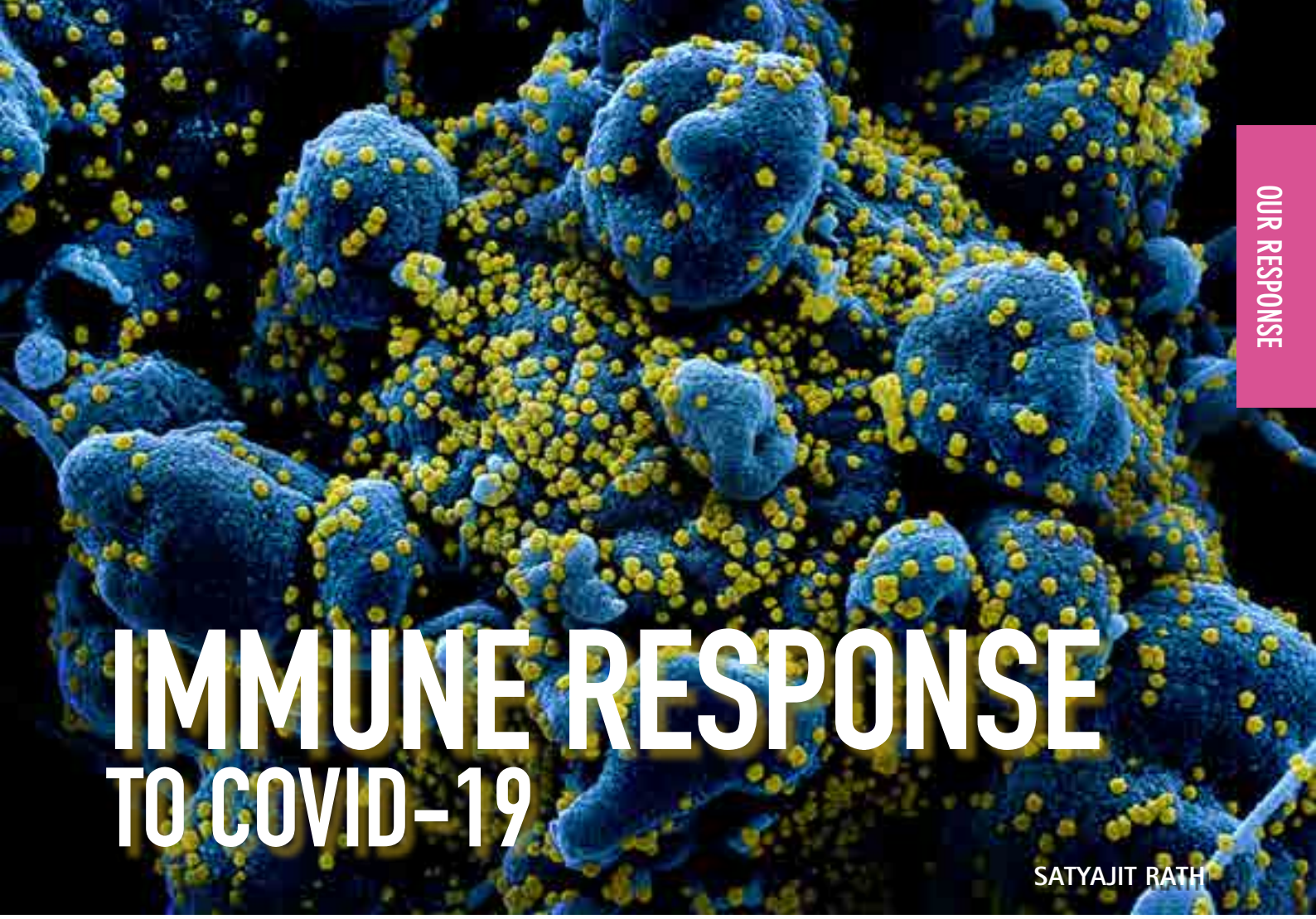

IMMUNE RESPONSE TO COVID-19

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How does our body respond to infection? Can it limit infection by a virus? How is inflammation different from an adaptive response? What factors can weaken our immune response? What do 'cytokine storms' have to do with COVID-19? How do we develop herd immunity?

Our body responds to any infection — viral, bacterial, fungal, whatever — in ways that tend to restrict its spread. In other words, these responses tend to 'quarantine' the infection in 'containment zones'. This category of responses is what we refer to as **inflammation**. In addition, the human body also has responses that are directly **antiviral**.

Antiviral responses

It is useful to think about interactions between the human body and the viruses infecting it in ways that are more nuanced than a 'fight'. Many a time, the body simply tolerates viruses. At other times, viruses simply 'ride along' with cells of the body rather than damaging them. At yet other times, the body's response does not really 'fight' the virus infection.

That said, the body has three major direct ways of limiting a virus infection. In one antiviral response, the body sends signals to its own cells to make life difficult for any virus entering them. Examples of such signals include interferon-alpha and interferon-beta that are being tried as treatments for COVID-19. Another response is for the body to produce proteins, called **antibodies**, that stick to the exact part of the virus surface through which the virus sticks to body cells. Such antibody-coated viruses cannot get into cells to infect them. This is what treatments like plasma therapy or monoclonal antibody therapy hope to achieve. It is also what we hope to generate with the SARS-CoV-2 vaccines that are in the pipeline. A third way the body limits virus infection is through 'killer' cells. Killer cells can identify and kill recently infected body cells before the production of new virus copies in them can be completed.

Antiviral responses involving antibodies and killer cells are called **adaptive responses**. They 'look' at the virus that has come in, then 'search' and 'find' antibody-producing and killer cells in their own repertoires that can match bits on the surface of the virus or a virus infected cell. This part of the body's repertoire of cells is then expanded and brought into operation, either as antibodies or as killer cells. The expanded repertoire remains in the body even after the virus is dealt with.

Adaptive responses

Everyone has inflammatory and interferon responses to viral infection. These responses come into operation immediately (within minutes to hours) after infection. Adaptive antiviral responses are perhaps more effective, but take a little time to kick in. Especially if we have no previous exposure to anything that looks like the virus (the virus itself, a very very similar virus, or a mimic vaccine). This is because it takes time (usually only a couple of days, but sometimes a little more than that) to expand the body's initial repertoire of matching antibody-producing or killer cells. On the other hand, if the virus enters a body that already has an expanded adaptive repertoire capable of recognising the virus, then adaptive responses also kick in quickly (within minutes to hours). This is why we are better protected against reinfection by the same virus (or by vaccination). Keep in mind that we **are** protected by these immune responses even when we meet an infection for the first time. It is just that having an expanded adaptive repertoire gives quicker and better protection. However, these expanded adaptive repertoires can be lost over time. If this happens, then we become as susceptible to that particular infection as we would be if we had never met the virus before (or had not been vaccinated against it).

Here is what we do **not** know. We do not know how to predict which particular bits of the virus the body will make the most antibodies against. A paradoxical disadvantage of having a large adaptive repertoire is that there will be matches with most parts of the virus particle. In other words, the adaptive response will make antibodies against the virus surface and its interior. Only those antibodies that stick to the specific patches on the virus surface through which the virus sticks to body cells will provide protection (see **Fig. 1**). This means that we can never be sure if we will make lots of useful antibodies or not. Similarly, we do not know how to predict how long the expanded adaptive repertoire against any given infection will last in the body. This means that for every new pathogen we meet, and for every new vaccine we want to make, we have to learn these two things afresh, through trial and error. This is why we are, and should be, so uncertain about SARS-CoV-2 and COVID-19; we are still learning new things about them. This is also why 'designing' and 'making' vaccines against SARS-CoV-2 is uncertain and time-consuming, why there are over a hundred different efforts going on the world over, and why most of them stand equal chances of success (or failure).

Recent findings suggest that antibody responses against SARS-CoV-2 may be modest, and may last for only a few weeks or months, especially in people without any symptoms or with only mild symptoms. We should keep this possibility in mind when we think about how we, as a society, are going to respond to the disease over the long term (until there are reasonably effective vaccines available to everyone!).

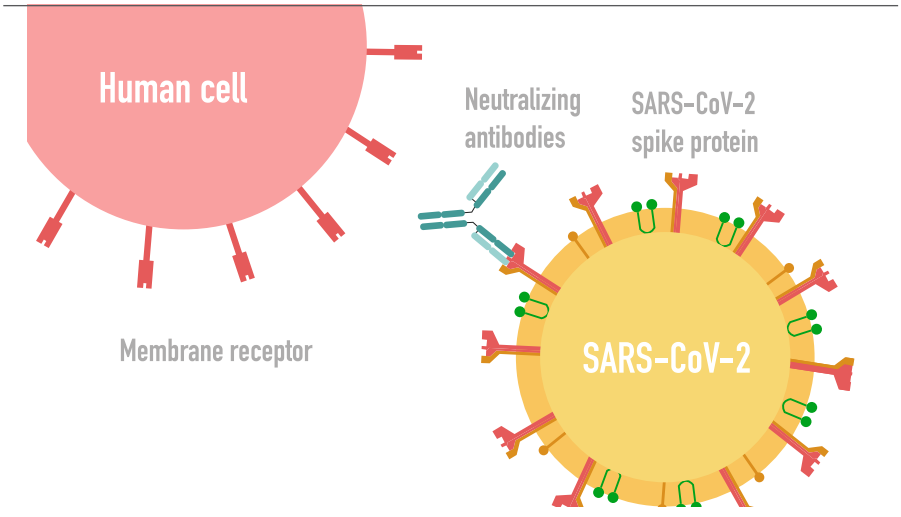

Fig. 1. Antibodies offer protection when they stick to the exact part of the virus surface through which the virus sticks to body cells.

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Factors affecting our immune response

Most of us have fairly good immune responses. If we did not, we would have had lots of other infections since childhood, and would most likely have been in and out of hospitals! In fact, this is what happens in the case of people who have been undergoing chemotherapy for cancer. As a side-effect of this therapy, their immune responses are poor enough to make them more likely to have severe COVID-19 illness. A little differently, any ongoing inflammation can affect containment and antiviral responses enough to increase our chances of developing severe COVID-19 illness. This is what happens in the case of the elderly, those with obesity, type 2 diabetes, heart disease or hypertension, as well as those with chronic kidney, liver, or lung diseases.

Cytokine storms

The inflammatory immune response tends to provide containment of any incoming pathogen to the site where it is first encountered by the body. The body uses locally made chemical signals, called **cytokines**, to create 'micro-containment' zones. Of course, the cytokines leak a bit beyond, but in such small amounts that they will have no effect outside these zones.

This can backfire when we are exposed to very high doses of the virus. This is common in caregivers, nurses, doctors, and other healthcare workers with prolonged exposure to infected people (or those who spend hours in a crowded and closed room with air-conditioning). In such cases, the virus enters our body through many different points in the airways. This can also backfire if our early immune responses are somewhat off-kilter and slow to get off and running. This is seen in people undergoing chemotherapy for cancer, or with ongoing inflammation in the body. In such cases, even a small dose of the virus will expand and spread to a number of locations in the body by the time the immune response is activated. In both cases, all the immune response can, and will, try to do is achieve micro-containment at all locations. The trouble is that cytokines will leak out from each of these 'wannabe' micro-containment zones. All the leaking chemicals add up to a lot, and begin to have effects outside the localised zones, all over the body. The result is that the entire body attempts to become a huge containment zone, like an entire country shut down for months in a policed 'lockdown'. This accumulation of cytokines all over the body is referred to as a **cytokine storm**, and results in severe illness.

Herd immunity

Let us think about how a virus spreads (or is 'transmitted') in a community. Let's say one person is exposed to the virus (in some remote jungle, let us assume!) and is infected. Till they deal with the virus, new virus copies will get made in their body. If the virus is lucky (!), these copies will be thrown out of the body somehow (usually via bodily fluids). On making appropriate contact with other people, these copies can establish infection. So, by the time the first person to be infected eliminates the virus from their body, the next round of people will be making and transmitting copies of it.

A crucial factor for the 'success' of the virus is the number of people who get successfully infected from one infected person. If this number (called 'R') is less than one, then each cycle of spread will be smaller than the one before it, and the infection will simply die down. The greater than one this number is, the more rapid the spread of the infection in the community. However, this number also depends on the immunity of people exposed to an infected person. People who have met the virus earlier, and have expanded their adaptive repertoire in response are **adaptive immune**. Such people do not get infected. If most of the people an infected person comes into contact with are adaptive immune, then it reduces the efficiency with which the virus spreads. This will also happen

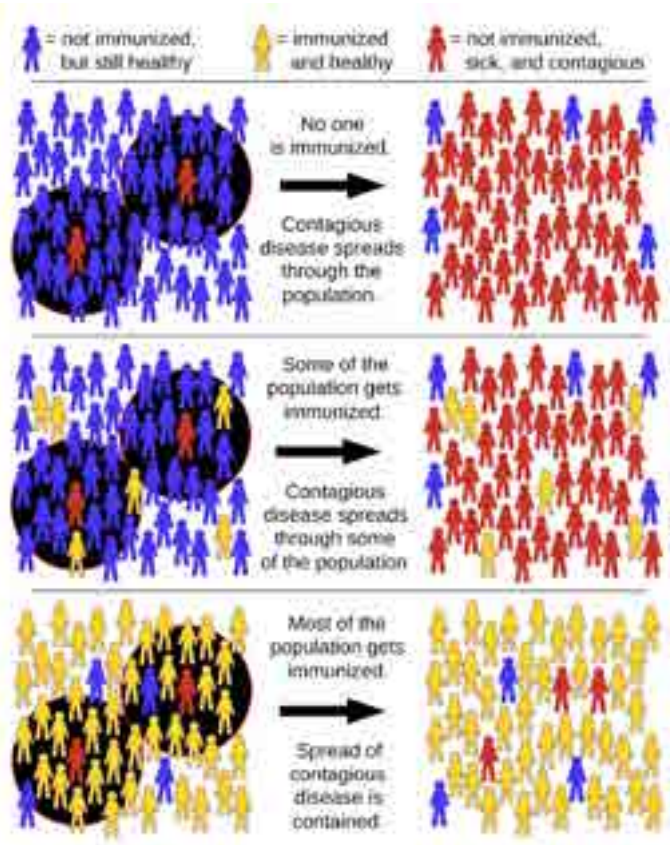

Fig. 2. Herd immunity is a natural consequence of a critical proportion of people in a community becoming adaptive immune to a pathogen. To start with, no one is immune to novel pathogens like SARS-CoV-2. The infection spreads rapidly through the community. Over time, two categories of people become adaptive immune to it — those who recover from the infection, and those who receive a vaccine against it. Research suggests that protection from the adaptive immune response in COVID-19 infected people may last for only a few weeks or months. As of now, there is no proven vaccine against the virus. If enough people in a community become adaptive immune to the pathogen, it reduces the chances of those who are less immune to it from coming into contact with an infected person. This reduces the spread of infection. Estimates suggest that this is likely to happen with SARS-CoV-2 when 50-80% of the population becomes adaptive immune to it.

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if a large proportion of people become adaptive immune because they are exposed to a reasonably effective vaccine (rather than actually getting infected). So, if a large enough proportion of people in a community are adaptive immune to the virus, it is likely that the spread of the virus will essentially come to a halt (see **Fig. 2**). This situation is called **herd immunity**. But, perhaps, we should call it 'community immunity', which is both rhyming and accurate?

Parting thoughts

As we can see, most infections will, in all likelihood, reach the point of herd immunity sooner or later. So herd immunity is just a natural outcome, not a policy strategy that either Sweden or Mister Boris Johnson designed (and, of course, relying on it as a 'strategy' is quite silly in both cases).

What proportion of people must be adaptive immune to SARS-CoV-2 for this point of herd immunity to be reached? We don't know for sure — the percentage varies based on a number of factors specific to individual infections and microbes. However, numbers between 50-80% have been brought up. As of now, the highest recorded proportion of people with adaptive immunity to SARS-CoV-2 is about 20%. Clearly, SARS-CoV-2 herd immunity has not developed in any part of the world yet.

It will be evident that for a stable situation of herd immunity to come about, virus infection must result in a good protective adaptive immune response, **and** this response (antibodies, for example) must not disappear quickly. For SARS-CoV-2 virus, while the first condition appears to be fulfilled in a fair proportion of infected people, there seems to be some uncertainty about how long antibodies last. So it is possible that herd immunity for SARS-CoV-2 will be somewhat unstable. To stabilise the situation, it is likely that we will depend (more than we had originally thought) on the vaccines that will begin to come out next year.

Key takeaways

- The human body uses inflammation and antiviral responses to protect us from a virus infection.
- Inflammation restricts spread of infection by using cytokines to quarantine it in containment zones.
- Antiviral responses limit infection in three major ways — signalling cells to make virus entry difficult, producing antibodies that prevent the virus from attaching to cells, and recruiting killer cells to identify and kill infected cells.
- Since antiviral responses involving antibodies and killer cells are 'adaptive', they may take time to kick in.
- Antibody responses against SARS-CoV-2 may be modest, and may last for only a few weeks to months.
- People undergoing chemotherapy for cancer, and with ongoing inflammation are more prone to severe COVID-19 illness.
- Two factors — exposure to high doses of virus, and compromised immunity — can lead to cytokine storms that result in severe illness.
- Herd immunity is the natural consequence of a large number of people becoming adaptive immune because of prior exposure to the virus, or effective vaccination.

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