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The hope of immunity

Promising evidence suggests that we can develop at least some immunity to the coronavirus – but how strong is it and how long will it last? Graham Lawton reports

WHEN the novel pneumonia circulating in China was confirmed to be caused by a coronavirus, an already troubling situation suddenly got that bit worse. As a rule, coronaviruses don’t produce a very strong “immune memory”: the long-lasting response that allows our bodies to thwart a subsequent attack, and which makes vaccines possible. When reports emerged from Japan and China of people who had been given the all-clear catching the virus again, immunologists’ worst fears seemed to be confirmed.

But seven months later, hopes are rising. There is no longer any serious doubt that our bodies can form an immune memory to the SARS-CoV-2 virus – although we still don’t know how effective that memory will be. “That is the main outstanding question for covid-19,” says Nicolas Vabret at the Icahn School of Medicine at Mount Sinai in New York. “It’s absolutely the right question to be asking now because so many things depend on it,” says Paul Klenerman at the University of Oxford. That includes the prospect of developing vaccines, therapies and herd immunity (see box, right), but also decisions on whether to issue immunity passports to people who have recovered from the virus, and how and when to ease lockdown measures.

Immune memory can be an incredibly powerful and durable force. Immunologists like to tell the story of a measles epidemic on the Faroe Islands in 1846. When Danish doctor Peter Panum went to investigate, he discovered that the disease was raging, but also that 98 older people were immune to it. They turned out to be the survivors of the islands’ previous outbreak in 1781. A single encounter with the measles virus had endowed them with lifelong protection.

Other viruses, however, don’t generate such a strong immune response, which can make them difficult to vaccinate against. Respiratory syncytial virus, for example, has thus far resisted all efforts to develop a vaccine. Other viruses elicit a moderate immune response and weak, brief memory. Vaccines for these viruses are possible, but often require regular boosters to maintain immunity.

Lines of defence

Until SARS-CoV-2 came along, immunologists would have placed coronaviruses at the recalcitrant end of the spectrum. There are four coronaviruses in general human circulation, all of which cause common colds. They do raise an immune response, but don’t leave behind much of an immune memory. Within a year or so of clearing out such a cold virus, we are vulnerable to reinfection. Protection against the SARS and MERS coronaviruses is somewhat better, lasting a few years, says Vabret. “Is SARS-CoV-2 going to look like MERS and SARS, with a few years of protection, or is it going to be like the others?”

There are two components to immune memory. The first is the antibody response, which is mediated by immune cells called B-cells. A healthy immune system maintains a huge repertoire of B-cells, each capable of producing a different antibody, which recognises and binds to particular molecules on the surface of pathogens called antigens.

When the immune system encounters a novel pathogen, any B-cells that happen to produce the right ones proliferate wildly, pumping out antibodies that neutralise the threat. Once the immune response gains the upper hand, a type of antibody called immunoglobulin G (IgG) becomes detectable in the blood.

After the pathogen is cleared, IgG continues to circulate in the bloodstream for weeks, months or even years, provided by long-lived B-cells in bone marrow. If these antibodies are potent enough, they are known as neutralising antibodies and provide an impenetrable shield to reinfection known as sterilising immunity.

Although antibody tests for coronavirus can indicate whether you have had the infection, a positive result doesn’t necessarily mean you are immune or will be for a long time. The other branch of immune memory also starts to sprout around the time that the pathogen is defeated. Some B-cells mature into memory B-cells, which take
There are now promising signs that the coronavirus elicits both forms of immune memory. “I think it’s very likely that we will have effective immunity,” says Ashley St John at Duke-NUS Medical School in Singapore.

**Antibody response**

As for antibodies, we now know that IgG tends to appear in the bloodstream about five days after a person develops coronavirus symptoms. In a recent study of 624 people with mostly mild or moderate covid-19, a team from the Icahn School of Medicine found that all but three of them had the antibodies in their blood (medRxiv, doi.org/d1f5). Another study looked at 177 recovered patients who had been more seriously ill and found that more than 90 per cent had the antibodies, and still had high levels of them two months later (medRxiv, doi.org/d2nb).

This probably also means that memory B-cells are forming. “Antibody responses are usually a very good proxy for B-cell responses,” says St John.

As for T-cells, Klenerman and his colleagues have reported that all of a group of 42 people recovering from covid-19 generated “broad and strong” memory T-cell responses (bioRxiv, doi.org/ggzw9n). “I think there’s a reasonable chance that people will develop some level of immune protection through antibody and T-cell responses,” he says.

But there are worries. One is that people who are infected but have no or only mild symptoms don’t generate a strong enough response to lay down immune memories. Another is that even a strong immune response may dwindle quickly.

According to Klenerman, the strength of immune memory usually depends on the magnitude of the initial response. “The bigger the peak, the longer it will generally last, because everything is going to decay once the antigen has gone away.” This suggests that people who get mild or asymptomatic infections may remain vulnerable, he says.

One recent study in China seems to confirm that these are issues. It found that people who were infected but asymptomatic had lower levels of IgG than symptomatic patients. In addition, their levels dropped quite quickly once they were virus-free, with 40 per cent back to normal after two months. The same study found that about 60 per cent of symptomatic patients also had declining IgG levels after two to three months (Nature Medicine, doi.org/gg26dx). “This is in line with some concerns that natural immunity to coronaviruses can be quite short-lived,” says Danny Altmann at Imperial College London.

The concentration of antibodies in the bloodstream doesn’t necessarily equate to how protected a person is, says St John. “You can have a lot of poor-quality antibodies, and that doesn’t help very much. Whereas if you have a few really good, high-quality antibodies, even if it’s a little bit lower concentration, those can be even more protective.”

On that front, there is also good news. A team at the Scripps Research Institute in California has isolated antibodies from the blood of recovered covid-19 patients and tested their potency. Of more than 1,800 different antibodies, they found three super-potent neutralising antibodies (Science, doi.org/dznz). If people with mild or asymptomatic cases are making these or similar antibodies, even in small quantities, they may well be protected, says St John.

Another hope is that people with mild infections might develop a newly discovered form of immune memory. When infections are confined

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**Herd immunity**

Despite evidence that people can develop at least some immunity to the coronavirus, the prospect of developing herd immunity without a vaccine remains slim.

Roughly two-thirds of a population would have to catch and recover from covid-19 to reach the herd immunity threshold, according to Haley Randolph and Luis Barreiro at the University of Chicago (Immunity, doi.org/ggwthm).

That would lead to some 30 million deaths from the virus worldwide, including 6 million in China, a million in the US and 250,000 in the UK. On top of that, healthcare systems would probably be overwhelmed, resulting in additional deaths.

“Building up SARS-CoV-2 herd immunity through natural infection is theoretically possible,” say Randolph and Barreiro. “However, there is no straightforward, ethical path to reach this goal, as the societal consequences of achieving it are devastating.”
to the airways, they don’t generate circulating antibodies, but they may still lead to the formation of memory cells. Immunologists have recently discovered that memory B and memory T-cells can both take up residence in mucosal membranes in the nose and lungs and can block a virus from re-entering the body. There is some evidence of this from a study of Swiss healthcare workers who were exposed to the virus but didn’t fall ill (bioRxiv, doi.org/d2nd). Many had no antibodies circulating in their blood, but they did have antibodies in nasal swabs and tears.

Original sin

Yet more good news comes from the discovery that people who have never been infected with SARS-CoV-2 can nevertheless have memory cells that respond to it. Immunologists say these must be memories from previous infections with common cold viruses, even though the received wisdom is that these don’t elicit a strong immune memory.

“There’s some data for T-cells that some of the immune responses are cross-reactive,” says Klenerman. “In other words, you’ve already got memory to something that’s a bit like SARS-CoV-2 and the memory is boosted when you see it.”

For example, a team led by Daniela Weiskopf at the La Jolla Institute for Immunology in California and Katharina Schmitz at Erasmus University Medical Center in the Netherlands analysed the T-cell responses of 10 people who had been hospitalised with severe covid-19. In keeping with other recent studies, they found that all 10 had helper T-cells that respond to the coronavirus, and eight had killer T-cells (Science Immunology, doi.org/d2nf). But they also found T-cells that respond to SARS-CoV-2 in two out of 10 people who had never been infected with the virus. This, they conclude, is “indicative of cross-reactivity due to past infection with common cold coronaviruses”.

“That will provide some level of protection, potentially,” says Klenerman. “It’s a hidden piece of the puzzle that needs working out, on both the T and B-cell side.” Cross-reactivity is also a positive sign that we will develop some level of long-term immune response to SARS-CoV-2, says Vabret, although whether it will be strong enough to prevent infection isn’t yet known.

It may also, paradoxically, make the disease worse, he says. In some other viral diseases, cross-reactive immunity can cause immune interference or what immunologists call “original antigenic sin”. This is where the immune system falls back on its immune memory and fails to mount a new response despite never having seen that actual pathogen before. This is one potential reason why the disease is worse in older people, he says, because they have been exposed to many cold viruses over their lives and their bodies may be more likely to fall back on a previous response. Again, more research is needed to fully understand this.

As for those initial reports of people being reinfected by the coronavirus, they now appear to have been false positives.

“There is no confirmed example of reinfection,” says Vabret. Animal experiments point in the same direction. Early on in the pandemic, a team in China discovered that macaques can catch covid-19 but can’t be reinfected 28 days after they recover (bioRxiv, doi.org/ggn8r8). That small study has since been replicated with more macaques and over five weeks (Science, doi.org/dwck). Intriguingly, the macaques seem to have been protected by functional immunity rather than sterilising immunity. “There’s virtually complete resistance to disease and few clinical symptoms,” says Altmann. “This seems a useful and clear answer. Of course, the big caveat is that this tells us about immunity at five weeks, whereas the answer we really want to know is about immunity at one or two years.”

That remains the great unknown. The earliest survivors of covid-19 are only seven months into recovery, so knowing how long immunity will last is educated guesswork at best. “We have effective immunity,” says St John. “The question is, for how long? That is something that we will have to continue to monitor.”

“We will have some long-term immunity,” says Vabret. “Will this immune response be sufficient to prevent reinfections? We don’t know.”

Even if our immune memory of the coronavirus is short-lived, it is still a boon because we can improve on it. Functional immunity opens the door to vaccines to induce and strengthen immunity. “The kind of immunity you get from a vaccine is not necessarily going to be the same as natural immunity,” says Klenerman. “Vaccines are designed to generate really high levels of immune response. Hopefully we can do even better.”