



Belfast

chrisbaraniuk@gmail.com

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## BRIEFING

## How long does covid-19 immunity last?

Many questions remain about both natural and vaccine induced immunity to SARS-CoV-2. **Chris Baraniuk** reviews what we know so far

Chris Baraniuk *freelance journalist*

## How long does covid-19 immunity last?

This is difficult to say definitively. When the body's immune system responds to an infection, it isn't always clear how long any immunity that develops will persist. Covid-19 is a very new disease, and scientists are still working out precisely how the body fends off the virus.

There is reason to think that immunity could last for several months or a couple of years, at least, given what we know about other viruses and what we have seen so far in terms of antibodies in patients with covid-19 and in people who have been vaccinated. But getting to a ballpark figure, yet alone putting an exact number on it, is difficult, and the results of immunological studies of covid-19 vary. One reason for this is confounding factors that scientists do not yet fully understand—in some studies, for example, the longevity of antibodies targeting the spike of SARS-CoV-2 is shorter than one might expect.<sup>1</sup> We lack clear data to understand whether this is a problem for covid-19.

Immunity is also determined by other factors besides antibodies, such as T and B cell memory, which some studies estimate could last for years.<sup>2</sup> And immunity is induced differently by natural infection versus vaccination, so one can't just combine studies to arrive at a definitive figure.

## How long do antibodies against covid-19 stay in the body?

Data indicate that neutralising antibodies last for several months in patients with covid-19 but gently fall in number over time. One study, published in the journal *Immunity*, of 5882 people who had recovered from covid-19 infection, found that antibodies were still present in their blood five to seven months after illness.<sup>3</sup> This was true for mild and severe cases, though people with severe disease ended up with more antibodies overall.

All of the vaccines approved so far produce strong antibody responses. The study group for the Moderna vaccine reported in April that participants in an ongoing clinical trial had high levels of antibodies six months after their second dose.<sup>4</sup> A study in the *Lancet* found that the Oxford-AstraZeneca vaccine induced high antibodies with “minimal waning” for three months after a single dose.<sup>5</sup>

Neutralising antibodies are expected to decline in number over time, says Timothée Bruel, a researcher at the Pasteur Institute, given what we know about the immune response to other infections. In April,

Bruel and colleagues published a paper in *Cell Reports Medicine* that looked at antibody levels and functions in people who had experienced symptomatic or asymptomatic covid-19.<sup>6</sup> Both types of participant possessed polyfunctional antibodies, which can neutralise the virus or assist in killing infected cells, among other things.

This broad response, says Bruel, might contribute to longer lasting protection overall, even if neutralising capabilities wane. A modelling study published in *Nature Medicine* examined the decay of neutralising antibodies for seven covid-19 vaccines. The authors argued that “even without immune boosting, a significant proportion of individuals may maintain long-term protection from severe infection by an antigenically similar strain, even though they may become susceptible to mild infection.”

More research is needed, however, to determine exactly how the body fights off SARS-CoV-2 and for how long polyfunctional antibodies might play a defensive role after infection or vaccination.

## What about T and B cell responses?

T and B cells have a central role in fighting off infections and, crucially, in establishing long term immunity. Some T and B cells act as memory cells, persisting for years or decades, primed and ready to reignite a broader immune response should their target pathogen arrive in the body again. It's these cells that make truly long term immunity possible.

A study published in February in *Science* assessed the proliferation of antibodies as well as T and B cells in 188 people who had had covid-19.<sup>7</sup> Although antibody titres fell, memory T and B cells were present up to eight months after infection. Another study in a comparably sized cohort reported similar results in a preprint posted to MedRxiv on 27 April.<sup>8</sup>

Monica Gandhi, an infectious disease doctor and professor of medicine at the University of California San Francisco, says we have evidence that T and B cells can confer lifelong protection against certain diseases similar to covid-19. A well known *Nature* paper from 2008 found that 32 people born in 1915 or earlier still retained some level of immunity against the 1918 flu strain, 90 years hence.<sup>9</sup> “That is really profound,” she says.

A paper published in July 2020 in *Nature* found that 23 patients who had recovered from severe acute respiratory syndrome still possessed CD4 and CD8 T cells, 17 years after infection with SARS-CoV-1 in the 2003 epidemic.<sup>10</sup> What's more, some of those cells

showed cross reactivity against SARS-CoV-2, despite the participants reporting no history of having covid-19.

But again, these are early studies and we still lack definitive conclusions about the role of T and B cells in covid-19 immunity. There's a conundrum, for example, in knowing that T cells help B cells to rapidly make high affinity antibodies on re-exposure. How much does it matter that serum antibodies have a short life and wane rapidly, if the cells making them are established and ready to go?

### How does natural immunity compare with vaccine induced immunity?

Various studies have shown that an immune response involving memory T and B cells emerges after covid-19 infection.<sup>11</sup> But people's immune systems tend to respond in very different ways to natural infection,<sup>12</sup> notes Eleanor Riley, professor of immunology and infectious disease at the University of Edinburgh. "The immune response after vaccination is much more homogenous," she says, adding that most people generally have a really good response after vaccination. Data from the clinical trials of the leading vaccine candidates have found T and B cell reactivity.<sup>13</sup>

### Does vaccination make a difference to those who have already had covid-19?

There is some evidence that vaccination can sharpen immunity in people who have previously been infected with SARS-CoV-2 and recovered. A letter published in the *Lancet* in March discussed an experiment in which 51 healthcare workers in London were given a single dose of the Pfizer vaccine. Half of the healthcare workers had previously recovered from covid-19 and it was they who experienced the greatest boost in antibodies—more than 140-fold from peak pre-vaccine levels—against the virus's spike protein.<sup>14</sup>

### Is there any difference in vaccine induced immunity between the first and second doses?

It's difficult to get a sense of the entire immune response after one dose of vaccine versus two, but multiple studies have investigated antibody levels at different stages of dosing. One preprint study from researchers at University College London involving more than 50 000 participants found that 96.4% were antibody positive one month after their first dose of either the Pfizer or AstraZeneca vaccines, and 99.1% were antibody positive between seven and 14 days after their second dose.<sup>15</sup> Median antibody levels changed slightly up to two weeks after the second dose, at which point they rocketed.

Another study, also a preprint by researchers in the UK, evaluated the difference in peak antibody levels among 172 people over 80 who received the Pfizer vaccine.<sup>16</sup> Those who had no previous record of covid-19 infection had 3.5 times more antibodies at their peak if they received their second dose 12 weeks later rather than three weeks later. However, median T cell levels were 3.6 times lower in those who had the longer dosage interval (the authors note that the relatively low T cell responses in both cohorts in the study may be because of their age). This again shows how early we are in our understanding of the virus and immunity to it.

### How does immunity affect reinfection?

Detected cases of reinfection are rare.<sup>17</sup> Riley thinks that, even if people become infected after vaccination or an initial natural infection, they will probably experience only a mild illness at worst. (Note, however, that this does not necessarily mean they cannot transmit the virus even if they have mild or no symptoms.)

### Will covid-19 vaccine boosters be necessary?

Albert Bourla, the chief executive of Pfizer, has said that a booster dose will "likely" be required within 12 months of the second dose.<sup>18</sup> There are understandable reasons for this. Riley points out that older people, for example, might have weaker immune responses, so they could be threatened by a rise in virus transmission during the winter. Boosters might also be necessary to heighten immunity against emerging variants of SARS-CoV-2, she adds.

Gandhi argues that SARS-CoV-2 is known to mutate relatively slowly, and early studies have found there is still good cross reactivity against new versions of the virus.<sup>19</sup> She thinks it is unlikely that the immunity induced by the original vaccines won't be enough to tackle new variants.

An article published in *Science* in March 2021 reviewed the evidence so far and concluded that the currently available vaccines give sufficient protection against extant and foreseeable variants.<sup>20</sup> "Ultimately, the best defence against emergence of further variants of concern is a rapid, global, vaccination campaign—in concert with other public health measures to block transmission," the authors concluded. "A virus that cannot transmit and infect others has no chance to mutate."

Gandhi agrees: "Clamping down [on] this pandemic when we know we have the tools to do so worldwide is our first priority, as opposed to thinking about boosters that may not be needed for rich countries."

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