Newcastle upon Tyne
stokel@gmail.com
Cite this as: *BMJ* 2023;380:p19
http://dx.doi.org/10.1136/bmj.p19
Published: 30 January 2023

COVID-19

What do we know about the adaptive immune response to covid-19?

As our understanding of covid-19 has grown, so has our knowledge of how the adaptive immune system responds to create longer term immunity to it. **Chris Stokel-Walker** asks what we know and what we don't

Chris Stokel-Walker,

What is adaptive immunity?

The immune system is often described as two parts working together: the innate (general, nonspecific) immune system and the adaptive (specialised) immune system.[1]

The innate immune system forms the body's baseline defence. It generally responds in the same way to most germs and foreign substances (which is why it is sometimes referred to as nonspecific). It acts quickly but has only limited power to stop germs from spreading.

The adaptive immune system is more specialised. It targets the type of germ that is causing the infection, but needs first to identify the germ. The first time it encounters a pathogen it is slower to respond than the innate system, but the next time it is more accurate and extremely rapid.

The main components of the adaptive immune system are B and T lymphocytes (B and T cells) found in the tissue between the body's cells, and antibodies in the blood and other bodily fluids. B cells trigger antibody-based immunity, while T cells trigger cell-based immunity.[2]

Critically, the adaptive arm interacts significantly with the innate aspects optimally to carry out the immune system's functions. For example, non-neutralising antibodies from the adaptive system mark pathogens for destruction, enabling cells of innate immunity to destroy them. Especially in the context of variant evolution—a moving target—and waning immunity, this coordinated attack is essential.

How long does adaptive immunity to SARS-CoV-2 last?

It's unclear exactly how long B and T cells against SARS-CoV-2 last in the body—a consequence of the relative newness of covid-19 and the science surrounding it. "In terms of the length of memory, I don't think anybody really knows," says Stan Jordan at the Cedars-Sinai Medical Centre in Los Angeles.

A 2021 paper by Jordan and colleagues[3 4] looked at adaptive immunity to the alpha and delta variants. They found that nearly 90% of patients showed positive T cell immunity to one or more of five proteins associated with SARS-CoV-2.[4] That would suggest that immunity will be long lasting, because T cells contribute to long term adaptive immunity.

Another 2021 study, by a group looking at bone marrow plasma cells, had found that B cell memory against SARS-CoV-2 lasted at least 11 months.[5] "If you have covid or get a vaccine, you're going to have long term memory B cell responses that can be potentially reactivated with re-exposure," says Jordan.

More than how long adaptive immunity lasts, what matters is how adaptive immunity may help prevent severe covid-19 disease.

Paul Hunter, professor of medicine at the University of East Anglia, says that, generally, immunity to initial respiratory infections (affecting the mucosal part of the immune system found in body cavities (peritoneum and pleura) and the skin) is short lived. Secretory IgA antibodies against covid-19 have been shown to have a relatively short half life, for instance.[6] But immunity against severe disease tends to be much longer lived—and this tends to be triggered by vaccination or infection.

He says this is because prevention of severe disease isn't down to neutralising antibodies (broadly speaking, types of antibodies that block a virus from being infectious or pathogenic) but non-neutralising antibodies (which don't block infectivity but mark the virus for destruction) and T cells, both of which are part of the adaptive immune system. "It's a much more complex, but much longer lasting protection," says Hunter.

What effect do covid-19 vaccines have on adaptive immunity?

Rita Carsetti, an immunologist at the Bambino Gesú Children's Hospital in Rome, says vaccination directly stimulates adaptive immunity.

T cells in the bodies of those who have had a covid vaccination tend to focus on the elements of the SARS-CoV-2 virus that haven't mutated. This could help us in the long run: recent research suggests that a new wave of experimental vaccines specifically designed to trigger a strong T cell response could help enhance response to variants. Tested successfully in mice so far, there are hopes for this as the future of covid-19 vaccination.[7]

How do new variants affect adaptive immunity?

Science's understanding of this is still at a comparatively primitive stage. It's possible that if the immune system has been stimulated by an individual strain of SARS-CoV-2, that it created adaptive immunity for other variants. A lot of attention has been paid to mutations in the spike protein that help

the virus to infect cells and evade the immune system better, but other parts of the virus stay unchanged meaning immunity triggered by earlier variants can still protect to some degree.

Adaptive immunity does appear to be present across some variants. Carsetti points out that, until the most recent vaccination booster drives in the UK, US, and elsewhere, most people have had jabs that are not primed to tackle the omicron variant—yet the general population's immunity from first generation vaccines has held up and most new infections have been mild, with far fewer hospital admissions and deaths than in the early pandemic when there were no vaccines.[8]

Carsetti says that blood serum, taken from patients before the omicron variant appeared, show cross-reactive antibodies, including T cells and memory B cells, that work against the mutations in the spike protein commonly found in the original omicron variants.[9]

That said, there is plenty of evidence that despite some recognition from the adaptive immunity, infection is often still possible. We are still dealing with a moving target and we do not know how prior adaptive immunity will interact with future emerging variants. We also don't know the full scope of chronic impacts, including persistent infection, as outlined in a recent *Nature* paper.[10] There is much we still don't understand.

How does the adaptive immune response to covid-19 compare with influenza and other coronaviruses?

"They're quite similar," says Carsetti. SARS-CoV-2 is a new virus that stimulated immune systems too much in the early days of the pandemic, as our bodies struggled to understand what they were encountering. "But then it stimulated the adaptive immune system, as do all other viruses," says Carsetti. "Now we've built an adaptive immune system that is able to see the virus and also the variants."

That offers a modicum of hope for the future: a 2008 paper looking at the B cells of those who lived through the 1918 influenza pandemic found longstanding adaptive immunity, 90 years on.[11]

Commissioned, externally peer reviewed

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

1 The innate and adaptive immune systems. Institute for Quality and Efficiency in Health Care. 30 July 2020. www.ncbi.nlm.nih.gov/books/NBK279396.

2 Çölkesen F, Kepenek Kurt E, Vatansev H, etal. Memory B cells and serum immunoglobulins are associated with disease severity and mortality in patients with covid-19. *Postgrad Med J* 2022;98:-71. doi: 10.1136/postgradmedj-2021-140540 pmid: 35046114

3 Jordan SC. Innate and adaptive immune responses to SARS-CoV-2 in humans: relevance to acquired immunity and vaccine responses. *Clin Exp Immunol* 2021;204:-20. doi: 10.1111/cei.13582 pmid: 33534923

4 Jordan SC, Shin BH, Gadsden TM, etal. T cell immune responses to SARS-CoV-2 and variants of concern (alpha and delta) in infected and vaccinated individuals. *Cell Mol Immunol* 2021;18:-6. doi: 10.1038/s41423-021-00767-9 pmid: 34531555

5 Turner JS, Kim W, Kalaidina E, etal. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. *Nature* 2021;595:-5. doi: 10.1038/s41586-021-03647-4 pmid: 34030176

6 Quinti I, Mortari EP, Fernandez Salinas A, Milito C, Carsetti R. IgA antibodies and IgA deficiency in SARS-CoV-2 infection. *Front Cell Infect Microbiol* 2021;11:655896. doi: 10.3389/fcimb.2021.655896 pmid: 33889552

7 Kingstad-Bakke B, Lee W, Chandrasekar SS, etal. Vaccine-induced systemic and mucosal T cell immunity to SARS-CoV-2 viral variants. *Proc Natl Acad Sci U S A* 2022;119:e2118312119. doi: 10.1073/pnas.2118312119 pmid: 35561224

8 Looi M-K, Mahase E. Has covid-19 become milder?*BMJ* 2022;379:. doi: 10.1136/bmj.o2516 pmid: 36302516

9 Gobeil SM-C, Henderson R, Stalls V, etal. Structural diversity of the SARS-CoV-2 omicron spike. *Mol Cell* 2022;82:-2068.e6. doi: 10.1016/j.molcel.2022.03.028 pmid: 35447081

10 Stein SR, Ramelli SC, Grazioli A, etalNIH COVID-19 Autopsy Consortium. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. *Nature* 2022;612:-63. doi: 10.1038/s41586-022-05542-y pmid: 36517603

11 Yu X, Tsibane T, McGraw PA, etal. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. *Nature* 2008;455:-6. doi: 10.1038/nature07231 pmid: 18716625