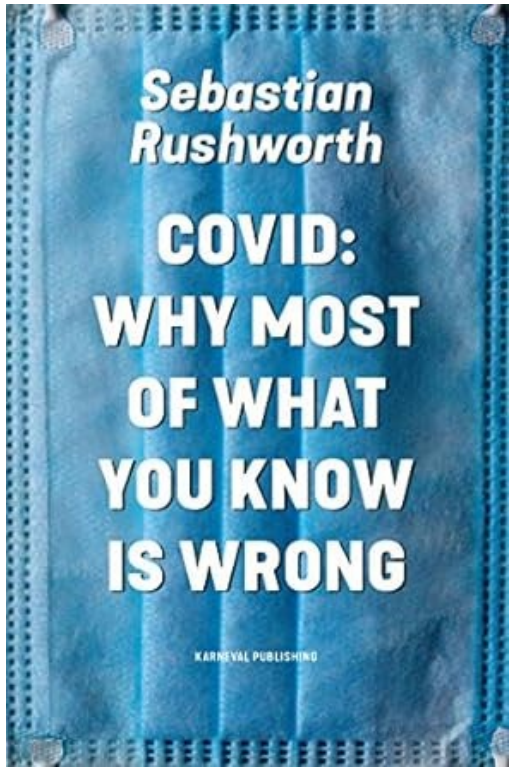
Part 2
Immune memory to SARS-CoV-2

Don’t forget you can download all my slides, including the study references, at https://hert.org.uk/resourcetype/covid-19/

Immune memory is not a continuation of the original acute response

- Some people make the mistake of thinking that immunological memory is merely the continuation of the immediate adaptive immune reaction to the virus.
- It is in fact **a very important and separate element of the immune system.**
- **After the original infection has resolved, B and T cells that are specific for the virus are maintained in a dormant state but can quickly be reactivated if the virus is encountered again.**
- So there is none of the adaptive immune system delay seen in the original infections.
- There is a lot of confusion around antibodies. **Antibodies from the original infection may still be present after 6-12 months but this is NOT immune memory. The memory B cells will produce fresh antibodies as needed.**
- The immune system is confronted with new proteins all the time and our survival does not depend on it having seen them before. The immune system learns from all foreign material and remembers the experience.

A frontline opinion on antibodies and duration of immunity: Dr Sebastian Rushworth



https://sebastianrushworth.com/2021/04/24/covid-prior-infection-vs-vaccination/
Sebastian Rushworth 'Covid: Why most of what you know is wrong. On Amazon.

- **'Antibodies are a "surrogate" marker. We think they might tell us something useful, but we can't really be sure.'**
- 'It's kind of like looking at the share of a population that have high blood pressure instead of looking at the proportion that are having strokes.'
- 'We really don't know whether the presence of antibodies after infection means that someone is immune, or whether the absence of antibodies means that someone has lost their immunity.'
- '…we still don't really know whether antibodies play a meaningful role in fighting covid or not.'
- **'Antibodies appear to be a good marker for prior infection, but that doesn't mean that they have a causal role in preventing a re-infection.'**

Lessons from SARS-CoV-1 and other pandemics

- A Nature paper from 2008 found that some **people born in 1915 retained some memory B cells against the 1918 flu strain, as demonstrated when their blood was tested 90 years later.** (Yu X, et al. Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors. Nature. 2008 Sep 25;455(7212):532-6)
- A Nature paper from 2020 found that some **patients who had recovered from SARS-CoV-1 in 2003, still possessed memory T cells, 17 years after infection, despite undetectable antibodies.** (Le Bert N, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020 Aug;584(7821):457-462)
- 10–20% of the plasma cells (the B cells that produce antibodies) in an acute immune reaction become memory plasma cells (Manz RA, et al. Lifetime of plasma cells in the bone marrow. Nature. 1997 Jul 10;388(6638):133-4; Crotty S, et al. SAP is required for generating long-term humoral immunity. Nature. 2003 Jan 16;421(6920):282-7).
- Once plasma cells have become memory B cells, they can be maintained for decades in bone marrow, where they continue secreting antibodies for long-lasting protection (Chang HD, Radbruch A. Maintenance of quiescent immune memory in the bone marrow. European Journal of Immunology. 2021 Jul;51(7):1592-601).

SARS-CoV-2 memory B cell (MBC) duration

- **A meta-analysis of 54 studies** from 18 countries, comprising around 12 million subjects **followed up at 6-8 months showed that 80.6% retained memory B cells**.
- **A longer study found memory B cells after 15 months,** regardless of disease severity.
- **Most studies found that SARS-CoV-2-specific memory B cells increased up to at least 6 months.**
- Analyses of **B cell responses up to 12 months after infection show stable neutralising antibody production** with memory B cells against both the nucleocapsid and spike proteins in most recovered COVID-19 patients.
- Upon reinfection, long-lived MBCs generate a new wave of short-lived and long-lived antibody-producing plasma cells while preserving the pool of MBCs.

Duration of immunity: memory T cells

- **Many T cell studies, including a meta-analysis, showing that memory T cells specific to SARS-CoV-2 are long-lasting.**
- Memory T cells remained active for **at least 2 years after COVID-19.**
- **Memory T cell duration was independent of original disease severity** and showed no difference in T cell half-lives.
- **In children, SARS-CoV-2-specific memory T cells are quickly and robustly activated following exposure to the SARS-CoV-2 antigen.**
- T cell memory is also effective against COVID variants, with reactivity of spike-specific CD4+ T cells to variants well preserved at 12 months.

Immune memory: summary

- Immune memory is not a continuation of the original acute response; it is a very important and separate element of the immune system.
- Immune memory comprises memory B cells and memory T cells, which are maintained for many years in a dormant state but can quickly be reactivated if the virus or its variants are encountered again.
- If antibodies are required, the memory B cells will manufacture them. Antibodies from the original infection may be present some months after the infection is resolved but this should not be confused with immune memory.
- Memory B and T cells to SARS-CoV-2 show every sign of being long-lasting.

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