Part 1
Pre-existing immunity to COVID-19

But first, some information about the immune system (additional slides on HERT website)

- The **innate immune system,** which **acts immediately**:
  - Carries out immune surveillance for pathogens using pattern recognition receptors (PRRs).
  - Eliminates pathogens using circulating macrophages, inflammatory cytokines and natural killer (NK) cells.
  - Activates the adaptive immune system if necessary.
  - However, the innate immune system is not very effective against viruses. This is when we need….
- The **adaptive immune system,** which provides a tailored and specific response to each pathogen **after several days** once the microbe has been identified. **3 different elements to the adaptive immune system:**
  - B lymphocytes (B cells), which make;
  - Antibodies: classes IgG, IgA, IgM, IgE; neutralising and non-neutralising (binding) antibodies
  - T lymphocytes (T cells)
- The adaptive immune system also generates an **immunological memory** in the form of memory cells for every pathogen encountered by the immune system.

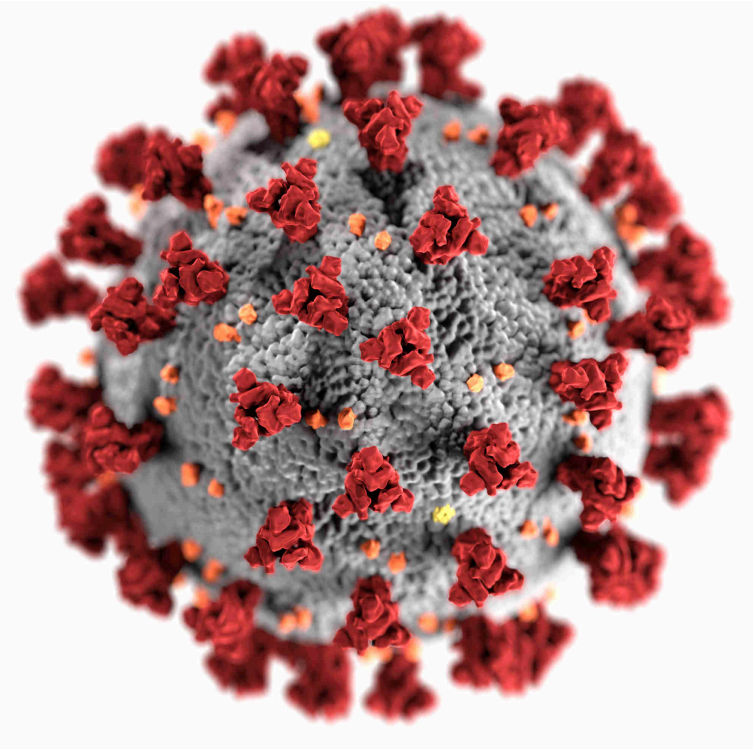
Understanding difference between the innate and adaptive immune systems

Innate immune system: a bobby on the beat

Adaptive immune system: specialist detectives assigned to drug squad, vice, etc

And some information about the structure of coronaviruses

- Coronaviruses are spherical, enveloped respiratory viruses with positive sense single strand linear RNA.
- The term coronavirus is based on the crown-shaped spike proteins that are wrapped around the surface of these viruses.
- Coronaviruses contain four immunogenic proteins composed of spike (S), nucleocapsid (N), envelope (E) and membrane (M) proteins.
- The spike protein (S) allows the virus to infect cells; mutations in this protein help the virus escape from existing neutralising antibodies.
- The nucleocapsid is distinct from the spike protein as it contains the viral RNA, whereas the spike protein contains the receptor-binding domain (RBD), which facilitates the entry of coronaviruses into host cells.
- The RBD and nucleocapsid (N) proteins act as antigens that elicit B cell-mediated antibody responses.
- Coronaviruses mainly target epithelial cells, particularly in the respiratory tract.



The human coronavirus family

- Coronaviruses can be categorized into four subtypes: alpha- beta-, delta- and gamma-.
- **There are 7 human coronaviruses:**
  - **4 are common cold viruses:** alpha-coronaviruses NL63 and 229E and beta-coronaviruses OC43 and HKU1. **These are endemic in the human population and cause c20% of upper respiratory tract infections in adults.**
  - **Severe Acute Respiratory Syndrome (SARS, now becoming known as SARS-CoV-1)**
  - **Middle East Respiratory Virus (MERS)**
  - **SARS-CoV-2: the cause of COVID-19**
- Common cold viruses comprise not only coronaviruses but also rhinoviruses, adenoviruses and enteroviruses; some of these may also provide some protection from SARS-CoV-2.
- **Both SARS-CoV-1 and SARS-CoV-2 use the receptor for the angiotensin-converting enzyme (ACE) 2,** present in lungs, blood vessels, gut and other organs, to gain entry to the body. Given the many studies of SARS-CoV-1, it is surprising that it took so long for it to be recognised that the ACE2 receptor was the target in COVID-19.

SARS-CoV-2 shares 65-82% of its genetic identity with other human coronaviruses

S·No	Viral strains	Genus	Percent identity
1	HCoV-229E	α	65.04
2	HCoV-NL63	α	65.11
3	HCoV-HKU1	β	67.59
4	HCoV-OC43	β	68.93
5	MERS-CoV	β	69.58
6	SARS-CoV-1	β	82.45

- Furthermore, the fusion subunit of these common cold coronaviruses has high identity to the equivalent sequence of SARS-CoV-2.

(Kaur N, et al. Genetic comparison among various coronavirus strains for the identification of potential vaccine targets of SARS-CoV2. Infect Genet Evol. 2021 Apr;89:104490; Zhu Z, et al. From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. Respir Res. 2020 Aug 27;21(1):224)

The official line on COVID-19

(https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020)

- **At his media briefing on 3 March 2020, the WHO Director General said:**
- "This virus is not SARS, it's not MERS, and it's not influenza. It is a unique virus with unique characteristics."
- "While many people globally have built up immunity to seasonal flu strains, **COVID-19 is a new virus to which no one has immunity."**
- We don't even talk about containment for seasonal flu – it's just not possible. But it is possible for COVID-19.
- **Let's see how true his statements were.**

Cross-reactivity of coronaviruses

- **Cross-reactivity:** the ability of immune memory cells to react to more than one viral strain or variant.
- **SARS-CoV-1 was cross-reactive with other coronaviruses** and it is the job of T cell receptors to recognise foreign peptides which are similar to those encountered before.
- **After SARS-CoV-1, even the WHO acknowledged that "the vulnerability of a population to a pandemic virus is related in part to the level of pre-existing immunity to the virus."** (Wkly Epidemiol Rec, 2009;84(22):197-202).
- **No sign of the WHO having remembered this!**
- **Although most of us have not been exposed to SARS-CoV-1 or MERS, we have all been exposed to common cold coronaviruses. More than 90% of the human population has antibodies to at least three of the common cold coronaviruses.**
- Several immunogenic SARS-CoV-2 CTL epitopes are identical to those contained in low-pathogenicity coronaviruses circulating in the population. Thus, we suggest that some level of CTL immunity against COVID-19 may be present in some individuals prior to SARS-CoV-2 infection.
- Research on other viruses (e.g. influenza A) has shown that, generally speaking, cross-reactive immune responses may protect against coronavirus infection or infection severity. There is also crossreactivity to non-coronaviruses, such as the herpes viruses.

(Petrova G, Ferrante A, Gorski J. Cross-reactivity of T cells and its role in the immune system. Crit Rev Immunol. 2012;32(4):349-72; Sette A, et al. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. Nat Rev Immunol2020;20:457-8; Gorse GJ, Clin. Vaccine Immunol. 2010; 17, 1875–1880; Gao A, et al. Predicting the Immunogenicity of T cell epitopes: From HIV to SARS-CoV-2. bioRxiv [Preprint]. 2020 May 15:2020.05.14.095885 - Still a preprint)

Do we have any cross-reactivity and pre-existing immunity for SARS-CoV-2?

- **Yes, pre-existing memory B cells and antibodies show cross-reactivity to SARS-CoV-2: many studies** (all on this slide PDF on the HERT website)
- B cells: Cross-reactive memory B cells are found but may have limited viral neutralisation properties, although they may contribute to the memory B cell pool. One study (Galson *et al*) observed 'there was also evidence of a proportion of the response arising from memory recall, which may be due to recall of B cells activated in response to previously circulating human coronaviruses". Compared with adults, children had higher frequencies of cross-reactive memory B cells.
- Antibodies: Most studies show cross-reactive antibodies from other human coronaviruses but are divided on whether the antibodies are neutralising and also whether they are even protective. One study showed that developing antibodies to a common cold coronavirus in the recent past could decrease the risk of contracting COVID-19 by 80%-90% but another showed that pre-existing immunity to seasonal coronaviruses may increase susceptibility to SARS-CoV-2 and worse outcome.

Do we have any cross-reactivity and pre-existing immunity for SARS-CoV-2?

- **Yes, pre-existing memory T cells show cross-reactivity to SARS-CoV-2: many studies**
- Generally, these memory T cells were derived from common cold coronaviruses but **long-lasting memory T cells from those who had previously recovered from SARS-CoV-1, 17 years earlier were also cross-reactive to SARS-CoV-2.** (Le Bert N, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature2020;584:457-62).
- Pre-existing T cell immunity induced by circulating human alpha- and betacoronaviruses is present in young adults but largely absent in older adult subjects and their effect declines with age. In children, spike-specific T cell responses were detected in many seronegative children, indicating pre-existing cross-reactive responses to seasonal coronaviruses.
- Many studies have found that cross-reactive T cell responses could be directed against the membrane, spike or nucleocapsid proteins of SARS-CoV-2 in a high proportion of individuals (up to 81% or 90%).
- Cross-reactive CD4+ T cells that recognise SARS-CoV-2 are more commonly detected in peripheral blood of unexposed individuals compared with CD8+ T cells and have been reported in c40-60% of SARS-CoV-2-unexposed individuals. Nevertheless, both cross-reactive memory CD4+ T cells and CD8+ T cells could be found at similar frequencies in the tonsils of unexposed individuals.
- Cross-reactive CD8+ T cells could be observed in convalescent subjects who were seronegative. In one study, CD8+ T cells specific for the nucleocapsid epitope cross-reacted with seasonal betacoronaviruses but not alphacoronaviruses.

Cross-reactive memory T cells can reduce COVID severity

- **Pre-existing T-cell immunity does not seem to reduce the incidence of SARS-CoV-2 infection but it may prevent severe disease,** contributing to asymptomatic or mild disease and rapid viral clearance.

- In a large international study, there was a **significant inverse correlation between the levels of cross-reactive T cells against SARS-CoV-2 and mortality rates**; CD4+ T cell cross-reactivity has not been reported in severe COVID patients.

Age is a factor in cross-reactivity

- **People aged >65 years, who suffer disproportionately with COVID-19, had lower overall cross-reactivity compared with children**, suggesting that pre-existing immunity to the betacoronaviruses, which are more similar to SARS-CoV-2, may confer more protection than the alphacoronaviruses.
- The magnitude of pre-existing SARS-CoV-2 spike protein cross-reactive IgG antibodies was higher in children versus adults, had more functional responses against SARS-CoV-2 receptor binding domain (RBD) and the S1 sub-unit of the spike protein and proved able to neutralise SARS-CoV-2 infection *in vitro.*
- Children aged <5 years were found to have the highest prevalence of infection with the OC43, the betacoronavirus that is most closely related to SARS-CoV-2, suggesting a high degree of cross-reactivity in this age group.

What proportion of the population had pre-existing immunity?

- A US study detected **SARS-CoV-2-reactive CD4+ T cells in 40% – 60% of unexposed individuals,** suggesting cross-reactive T cell recognition between circulating common cold coronaviruses and SARS-CoV-2." (Grifoni A, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. Cell2020;181:1489-1501.e15)
- And a review article by Peter Doshi (a BMJ Editor) found **at least six studies reporting T cell reactivity against SARS-CoV-2 in up to 50% of people** with no known exposure to the virus (Doshi P. Covid-19: Do many people have pre-existing immunity? BMJ, 2020;370:m3563).
- **In other words, about half the population would probably only develop mild or asymptomatic COVID due to cross-reactivity.**
- As Marc Giradot blogged: 'If one believes in vaccines, one has to believe in acquired immunity from past viral coronavirus infections.' 'Coronavirus infections had already acted as universal vaccines'. (https://covidmythbuster.substack.com/p/most-already-had-robust-immunity?r=4jnik)

Pre-existing immunity summary

- March 2020, WHO Director General: “COVID-19 is a new virus to which no one has immunity.”
- SARS-CoV-2 is 1 of 7 coronaviruses and a considerable proportion of its genetic identity is shared with the other 6 (up to 82%).
- We have all been exposed to the 5 common cold viruses. More than 90% of the human population has antibodies to at least three of the common cold coronaviruses. Cross-reactive T cell memory was still present after 17 years in those who had recovered from SARS-CoV-1 in 2003.
- Many studies show the pre-existing T-cell immunity to SARS-CoV-2. It may not reduce the incidence of SARS-CoV-2 infection but may prevent severe disease and death.
- Around 50% of the population appear to have T cells cross-reactive to SARS-CoV-2.

Studies detecting cross-reactive antibodies 1/2

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Studies detecting cross-reactive antibodies 2/2

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Studies detecting cross-reactive T cells 1/2

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