Immune responses that confer protection against severe disease and variants, short- and long-term protection

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Adaptive immune responses to SARS-CoV-2

• Neutralizing antibody responses in serum (produced by plasmablasts and long lived plasma cells)
• Binding antibody responses in serum (produced by plasmablasts and long lived plasma cells)
• Memory B cells
• T-cell mediated cellular immunity
• Mucosal immunity
What do vaccines do?

**Infection-induced immunity**

- Spike protein (S)
- Envelope protein (E)
- Matrix protein (M)
- Nucleoprotein (N) and viral RNA

+ all other nonstructural proteins

likely some intra-host sequence diversity

potentially longer presence of antigen

- systemic immunity
- mucosal immunity

**Vaccine-induced immunity**

- one consensus spike

*except inactivated vaccines

- systemic immunity
What do vaccines do?

All currently licensed COVID-19 vaccines

Krammer, Nature, 2020
Protection from infection

• Mechanistically, this can really only be achieved by neutralizing antibodies

• Antibodies need to be present on mucosal surfaces of the upper and lower respiratory tract

• For SARS-CoV-2 vaccination this is IgG which ends up on mucosal surfaces
  • Good protection of the lower respiratory tract
  • Little in the URT, and levels may decline rapidly

• After natural infection locally produced sIgA may be the main mechanism of protection in the upper respiratory tract

• Virus dose and viral fusogenicity may be factors here as well
Protection from disease

• The virus infects cells but replication is significantly reduced

• Potential contributing factors
  • Neutralizing antibodies at suboptimal levels
  • Non-neutralizing antibodies via effector functions
  • T-cells
  • Memory B cells which differentiate into plasmablasts and quickly increase (neutralizing) antibody levels

• The effect of T-cells and memory B cells likely depends strongly on incubation time – which is already very short for the recent Delta and Omicron variants
Protection from **severe disease**

• The virus infects cells, spreads, causes symptoms but replication is significantly slowed/attenuated, especially in the lower respiratory tract

• Potential contributing factors:
  • Neutralizing antibodies at suboptimal levels, but high enough IgG titers to protect the lower respiratory tract
  • Non-neutralizing antibodies via effector functions
  • T-cells
  • Memory B cells which differentiate into plasmablasts and quickly increase (neutralizing) antibody levels

• T-cells and memory B cells have significantly more time to respond since disease progression takes time
Longevity of immune responses

- Serum antibody levels peak, wane and stabilize

Plasmablast derived (periphery)  Long lived plasma cell derived (bone marrow)

Mucosal IgG correlates with serum IgG, sIgA does not
Longevity of immune responses

• T-cell and memory B-cell responses are long lived

Goel et al., Science, 2021
Variants make everything more complicated

- Antigenic changes mediate escape from (neutralizing) antibody response
- To a lesser degree, antigenic changes also impact on binding antibody and T-cell responses
- Variants may also indirectly ‘escape’
  - High viral loads/more robust virus replication may increase how much virus is shed and that may increase infectious dose for exposed individuals
  - Higher fusogenicity may facilitate escape from antibodies due to faster cell entry
  - Shorter incubation time means less time for an anamnestic response to prevent (severe) disease