Adaptive immunity and SARS-CoV-2

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Outline

- Adaptive cellular and humoral immunity
- Correlates and contributors to immunity
- Immune durability
- Age-related immunosenescence
- Variant circulation might affect immunity
- Conclusions
Adaptive cellular and humoral immunity
Adaptive immunity includes cellular and humoral responses

https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/
Antibodies decay with a known half-life

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Approximate half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM</td>
<td>5-6</td>
</tr>
<tr>
<td>IgA</td>
<td>5-6</td>
</tr>
<tr>
<td>IgG1</td>
<td>21</td>
</tr>
<tr>
<td>IgG2</td>
<td>21</td>
</tr>
<tr>
<td>IgG3</td>
<td>7</td>
</tr>
<tr>
<td>IgG4</td>
<td>21</td>
</tr>
</tbody>
</table>
Memory T and B cells are generated, which can initiate anamnestic responses after re-exposure.
Immunity – correlates and contributors
Immunity is a gradient

Levels of immunity

- Sterilizing
- Asymptomatic
- Mild symptomatic URI
- Symptomatic URI
- Symptomatic LRI
- Hospitalization / Death

Contributors

- Antibody levels
- Antibody isotypes
- Antibody functionality (neutralizing / epitopes / affinity)
- Antibody location
- Number and specificity T cells
- T cell ratios

URI – upper respiratory tract infection
LRI – lower respiratory tract infection
Transfer of IgG with high neutralization titer is sufficient to protect against SARS-CoV-2 challenge of rhesus macaques

Lower respiratory tract

https://doi.org/10.1038/s41586-020-03041-6
Anti-spike antibodies are correlates of risk

- **Khourey et al.** normalized neutralizing antibody titers after vaccination with different vaccine products to mean convalescent titers. Used these normalized values to compare vaccine efficacy (VE) estimates. Used the normalized values to estimate the level of neutralizing antibodies required for 50% protection against infection.

- **Goldblatt et al.** assayed binding and neutralization in participants who had received BNT162b, mRNA1272, AZD1222, or Ad26Cov2.S and used a population-based method to estimate a protective threshold (60 BAU/ml anti-spike IgG).

- **Feng et al.** calculated the levels binding and neutralizing antibodies required for 50, 60, 70, 80, and 90% VE from symptomatic infection after vaccination with AZD1222.
Correlates analysis of mRNA-1273 indicates 68% of VE mediated through serum neutralizing antibodies

- Day 29 and Day 57 correlates analysis examining inhibitory concentrations 50% (IC50) with neutralization assays
- VE was estimated to be 45 – 60% for vaccine recipients without detectable binding or neutralizing antibodies
- Increased to >98% VE in recipients with highest neutralization titers
- Analysis estimated 68% of VE against symptomatic infection was mediated through Day 29 neutralization titers

Gilbert et al. medRxiv
Correlates studies focus on humoral arm of adaptive immunity, but that is not the only contributor.
In previously infected macaques with low levels of antibodies, CD8+ T cells contribute to protection.

Upper respiratory tract

\[ \log_{10}(\text{sgRNA copies per swab}) \]

- Sham \((n = 5)\)
- Anti-CD8\(\alpha\) \((n = 5)\)
- Anti-CD8\(\beta\) \((n = 3)\)

McMahan et al. Nature
What happens during infections in vaccinated people?

- Sterilizing
- Asymptomatic
- Symptomatic URI
- Symptomatic LRI
- Hospitalization / Death

- Antibody levels
- Antibody isotypes
- Antibody functionality (neutralization / epitopes / affinity)
- Antibody location
- Number and specificity T cells
- T cell ratios
Culturable virus recovered from unvaccinated and vaccinated infected health care workers
Immune durability
Anti-spikes antibodies decay after BNT162b2 vaccination

Naber et al. The Lancet Regional Health - Europe

Maeda et al. medRxiv
mRNA vaccine recipients maintain spike-specific memory B cells at 6 months

Goel et al. bioRxiv

Ciabattini et al. medRxiv
BNT162b2 mRNA vaccine recipients generate spike-specific early memory CD8+ T cells

Oberhardt et al. Nature
Durability

- Serum antibodies decrease over time

- Memory B cells are maintained out to 6 months post-vaccination

- Early memory CD8+ T cells are detected >80 days after vaccination with BNT162b2
Immunosenescence
Pool of naïve T cells diminished with age
Adaptive immunity includes cellular and humoral responses

https://www.virology.ws/2020/11/05/t-cell-responses-to-coronavirus-infection-are-complicated/
Adults ≥80 years have reduced neutralization titers compared to younger adults after BNT162b2 vaccination.
Adults ≥ 80 years had less mature antibodies and fewer functional T cells after BNT162b2 vaccination.
Variants
Decay of neutralizing antibodies could be confounded by circulation of variants of concern

- Some variants have amino acid changes near the spike receptor binding domain that could result in reduction in neutralization titers.
- Neutralization loss ranges from nil (alpha) to about 7-fold (beta). Delta is approximately 1.5-2-fold reduction.

Liu et al. Nature
Antibody decay plus reduction in neutralization titers yield lower titers at six months after mRNA-1273 boost

Pegu et al. Science
Reduced titers in older adults can also be further confounded by variant circulation.

Collier et al. Nature

Pegu et al. Science
T cell activity maintained against variant spikes after BNT162b2 vaccination

Richardson et al medRxiv
Summary
Conclusions 1 of 3

- There are degrees of protection from different outcomes based on a person’s level of immunity.

- Multiple components of the immune system are required to prevent infection and illness; these components are complex and dynamic.

- When a vaccinated person becomes infected, they may shed culturable virus, and therefore may be infectious.
Conclusions 2 of 3

- Antibodies decrease over time in all age groups; cellular memory is maintained after waning.

- Neutralizing antibodies likely confer a majority of, but not all, immunity.

- Cellular responses likely contribute to protection against severe disease through anamnestic response even after antibodies wane.
Conclusions 3 of 3

- Older adults
  - Start with lower neutralization titers than younger adults.
  - Because they start at lower titers, they may be faster to fall below the lower limit of detection.
  - May have less robust cellular memory generation because of immunosenescence and therefore may be more dependent on humoral immunity.
  - Reduced neutralization of variant viruses may confound antibody waning in all age groups.
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.