Immune responses to SARS-CoV-2 infections

Natalie J. Thornburg, PhD
Respiratory virus immunology team lead
ACIP SARS-CoV-2 working group

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Outline

1. What do we know about immunity to coronaviruses in general?
2. What do we know, so far about SARS-CoV-2 immunity?
3. How do we test for immune responses?
4. Updates on severity of disease vs. antibody response and antibody kinetics
5. Conclusions
Coronaviruses

- Common coronaviruses
  229E
  NL63
  OC43
  HKU1

- Uncommon coronaviruses
  SARS-1
  MERS
What do we know about protective immune responses in common CoV infections?

- In common CoV infections, protection is transient. Waning serum antibody contributes to susceptibility to reinfection.

- 229E Human challenge model (Callow et al, Epidemiol Infect., 1990)
  - 15 volunteers were inoculated with HCoV-229E.
  - 10 with lower antibody titers became infected; 8 developed colds.
  - On re-challenge a year later, 9 became re-infected (virus shedding) but none developed a cold

- Household respiratory virus infection study (Kiyuka et al, JID, 2018)
  - 2.5% NL63+
  - Most household subjects had one infection in 6 month study
  - Repeat infections with NL-63, OC43, and 229E detected in 21, 5.7, and 4.0% respectively; >90 days apart
  - A minority of repeat infections exhibiting higher viral titers on second infection (41% NL-63, 31% OC43, and 1% 229E)
- Does SARS-CoV-2 immunity resemble common coronavirus immunity?
• Knowns

- Most COVID-19 patients mount IgG and IgM responses to the virus
- Many COVID-19 patients mount neutralizing antibody responses
- Magnitude of antibody response correlates to disease severity
Unknons

- Are COVID-19 patients susceptible to reinfection?
- Are antibodies a correlate of immunity?
- If so, what quality (Isotype, antigenic region, neutralizing)?
- Is there a threshold of protection?
- How long will serum antibodies last?
Assays to detect antibodies that bind SARS-CoV-2

- **Antigens**
  - Spike – **Target for neutralizing antibodies**
    - RBD
    - S1
    - Ectodomain (S2P)
  - Nucleocapsid – **Abundant during viral replication**

- **Secondary antibodies**
  - Pan Ig, IgG, IgM, IgA
Spike is highly glycosylated trimeric, class I fusion protein – metastable prefusion conformation

Wrapp et. Al, Science 13 Mar 2020
Three different forms of spikes used in most ELISAs: antibodies to all three might contribute to neutralization

- N terminal domain
- One protomer of ectodomain or S2P
- S2
Residue 614 is located at the S1 / S2 interface

Nucleocapsid protein ELISA

PROS
• Easy to produce large quantities of protein
• Abundantly expressed during early infection
• Used to identify immunity from natural infection vs. vaccine-induced immunity

CON
• Unlikely a target for neutralizing antibodies
ELISA and CMIA assays with FDA EUA authorization

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Isotype</th>
<th>Antigen</th>
<th>% Positive Agreement (n)</th>
<th>Negative Agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euroimmune</td>
<td>IgG</td>
<td>S1</td>
<td>42.3-48.2; NCI panel 90 (597; 110)</td>
<td>98.6-100 (1756)</td>
</tr>
<tr>
<td>Roche Diagnostics</td>
<td>pan Ig</td>
<td>N</td>
<td>77 (209)</td>
<td>99.81 (5252)</td>
</tr>
<tr>
<td>Bio-Rad</td>
<td>pan Ig</td>
<td>N</td>
<td>92.2 (51)</td>
<td>99.60 (687)</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>IgG</td>
<td>N</td>
<td>95 (122)</td>
<td>95 (1070)</td>
</tr>
<tr>
<td>DiaSorin, Inc</td>
<td>IgG</td>
<td>S1/S2</td>
<td>72.5 (135)</td>
<td>99.3 (1090)</td>
</tr>
<tr>
<td>Ortho Clinical</td>
<td>IgG</td>
<td>S</td>
<td>87.5 (48)</td>
<td>100 (470)</td>
</tr>
<tr>
<td>Ortho Clinical</td>
<td>IgM, IgG</td>
<td>S</td>
<td>83 (36)</td>
<td>100 (400)</td>
</tr>
<tr>
<td>InBios</td>
<td>IgG</td>
<td>S</td>
<td>97.8 (44)</td>
<td>99.0 (95)</td>
</tr>
<tr>
<td>Siemens</td>
<td>Pan Ig</td>
<td>S</td>
<td>100 (47)</td>
<td>99.8 (1586)</td>
</tr>
<tr>
<td>Vibrant</td>
<td>S and N</td>
<td></td>
<td>98.1 (53)</td>
<td>98.6 (501)</td>
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Current as of 6/19/2020
Several different types of virus inhibition assays – with differing sensitivities, time to results, throughput, and need for containment lab

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<thead>
<tr>
<th>Assay</th>
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<tbody>
<tr>
<td>Plaque reduction neutralization titer</td>
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<tr>
<td>Clinical isolate microneutralization</td>
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<tr>
<td>Infectious clone reporter microneutralization</td>
</tr>
<tr>
<td>Focus reduction assay</td>
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<tr>
<td>Psuedovirus</td>
</tr>
</tbody>
</table>
More severe patients exhibit more robust and faster antibody responses

To et al. The Lancet. 20: 565-574
A majority of hospitalized COVID-19 patients develop neutralizing antibody responses

Suthar et al. Cell Reports Medicine. 2020 Jun 8
Thirty percent of patients with mild infection have low neutralizing antibody titers at hospital discharge

https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2.full.pdf+html
Older patients had higher neutralizing antibody titers

https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2.full.pdf+html
Most of what we know about SARS-CoV-2 immunology are from hospitalized patients. What about milder infections?
41% of antibody-positive USS TR sailors did not have detectable neutralization titers (IC100)

Payne et al. MMWR. 69: 714-721
Serum antibodies drop between acute phase and 8-weeks post discharge
Conclusions

- Most SARS-CoV-2 patients mount serum antibody responses
- Even mild cases of SARS-CoV-2 can result in development of antibodies
- Magnitude of antibody response roughly correlates with severity (consistent with other coronavirus infections)
- A portion of individuals with antibody responses may not develop serum neutralizing antibody responses
- By 8 weeks after discharge, a portion of patients have dropped below 50% inhibition neutralization threshold