Immune responses to SARS-CoV-2 infections

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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

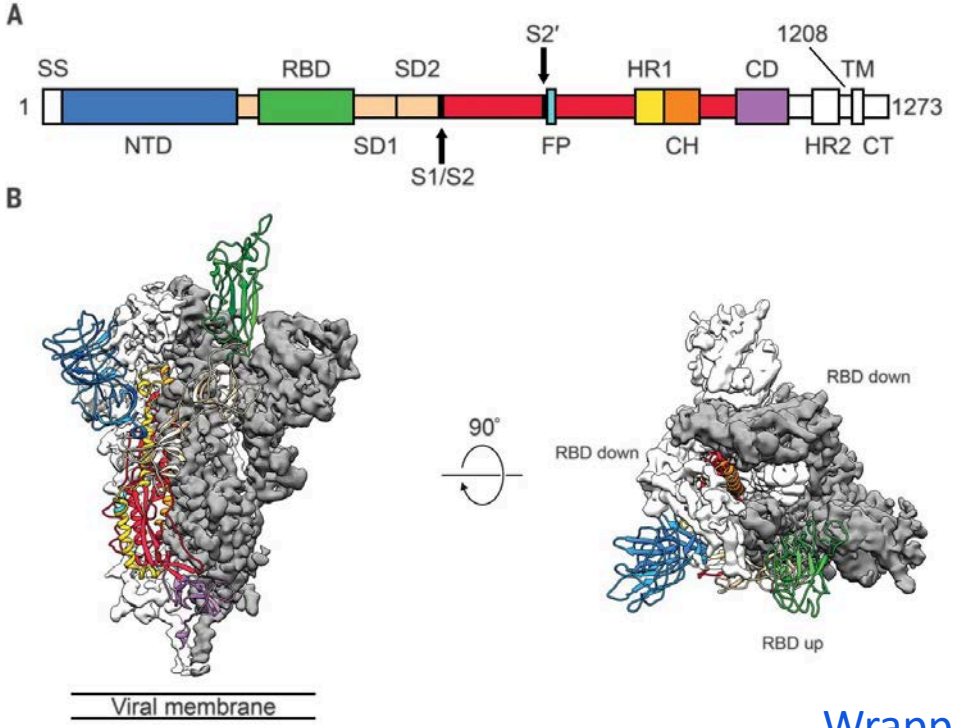
- Unknowns
  - Are COVID-19 patients susceptible to reinfection?
  - Are antibodies a correlate of immunity?
  - If so, what quality (Isotype, antigenic region, neutralizing)?
  - Is there a threshold of protection?
  - How long will serum antibodies last?

Assays to detect antibodies that bind SARS-CoV-2

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

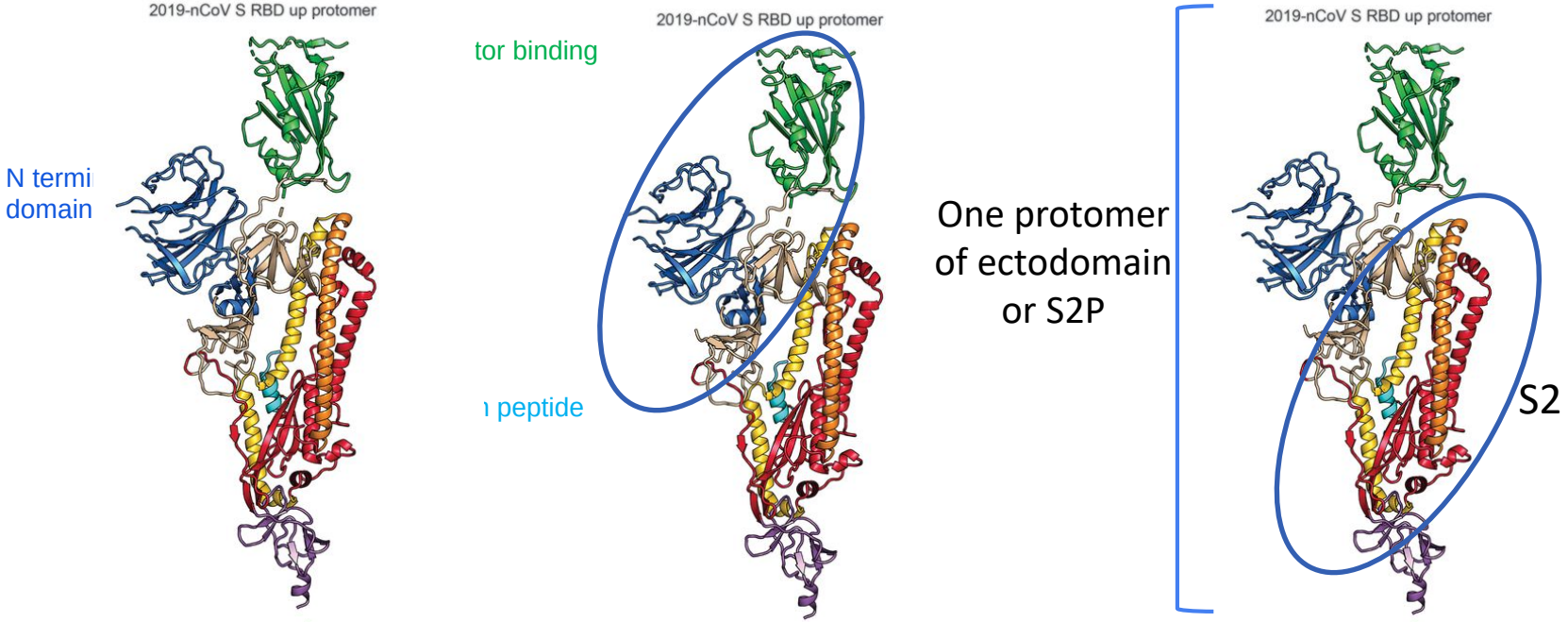
- Secondary antibodies
  - Pan Ig, IgG, IgM, IgA

Spike is highly glycosylated trimeric, class I fusion protein – metastable prefusion conformation



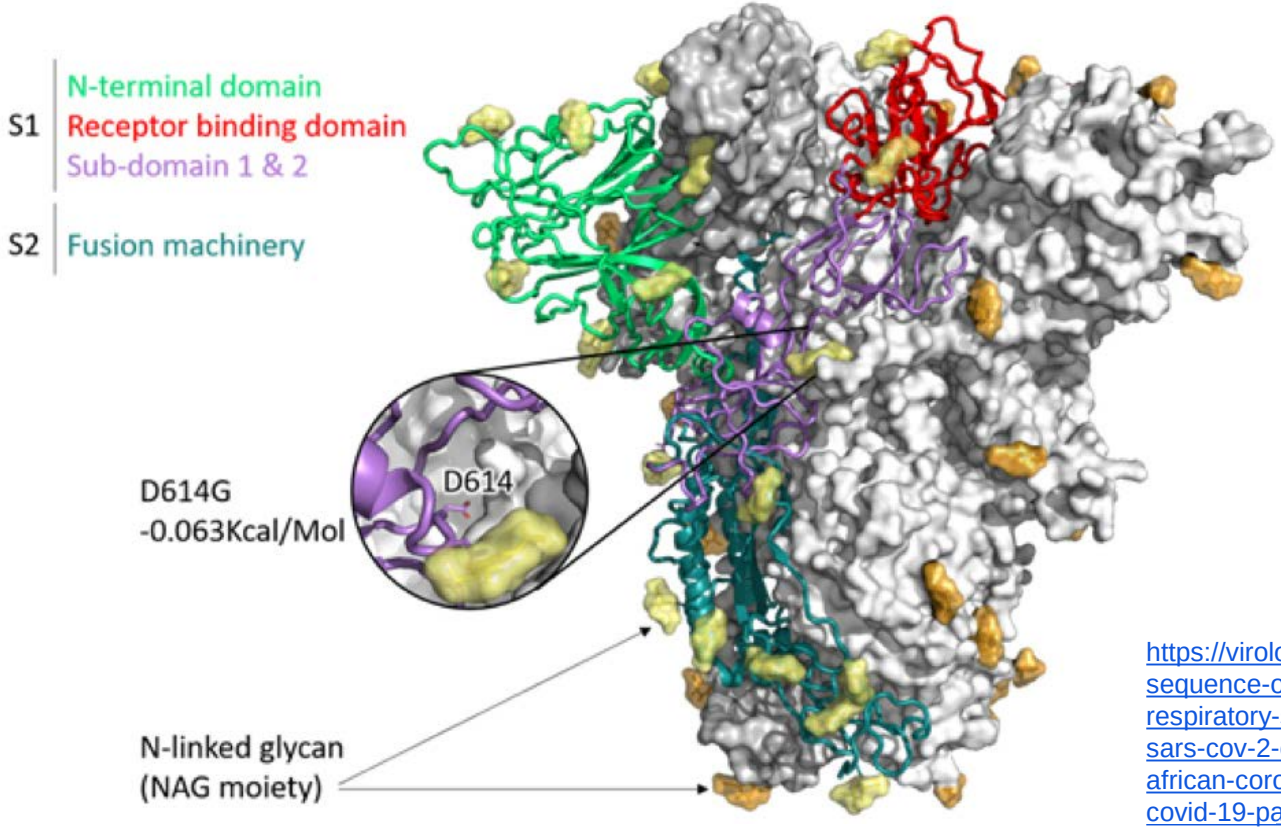
Wrapp et. Al, Science 13 Mar 2020

Three different forms of spikes used in most ELISAs: antibodies to all three might contribute to neutralization



Wrapp et. Al, Science 13 Mar 2020

Residue 614 is located at the S1 / S2 interface

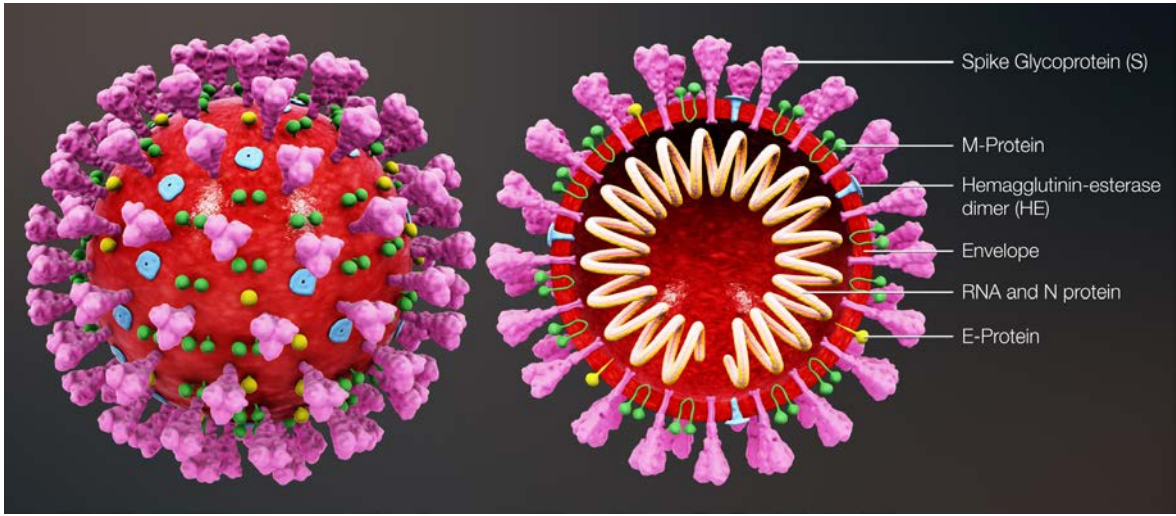


https://virological.org/t/whole-genome-sequence-of-the-severe-acute-respiratory-syndrome-coronavirus-2-sars-cov-2-obtained-from-a-south-african-coronavirus-disease-2019-covid-19-patient/452

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

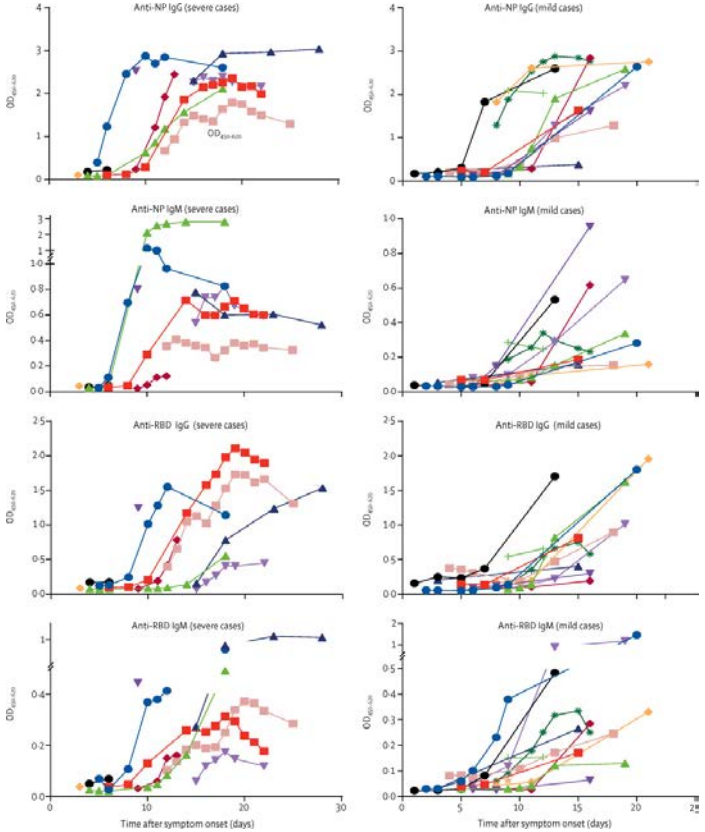
Manufacturer	Isotype	Antigen	% Positive Agreement (n)	Negative Agreement (%)
Euroimmune	IgG	S1	42.3-48.2; NCI panel 90 (597; 110)	98.6-100 (1756)
Roche Diagnostics	pan Ig	N	77 (209)	99.81 (5252)
Bio-Rad	pan Ig	N	92.2 (51)	99.60 (687)
Abbott Laboratories	IgG	N	95 (122)	95 (1070)
DiaSorin, Inc	IgG	S1/S2	72.5 (135)	99.3 (1090)
Ortho Clinical	IgG	S	87.5 (48)	100 (470)
Ortho Clinical	IgM, IgG	S	83 (36)	100 (400)
InBios	IgG	S	97.8(44)	99.0 (95)
Siemens	Pan Ig	S	100(47)	99.8 (1586)
Vibrant		S and N	98.1 (53)	98.6 (501)

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

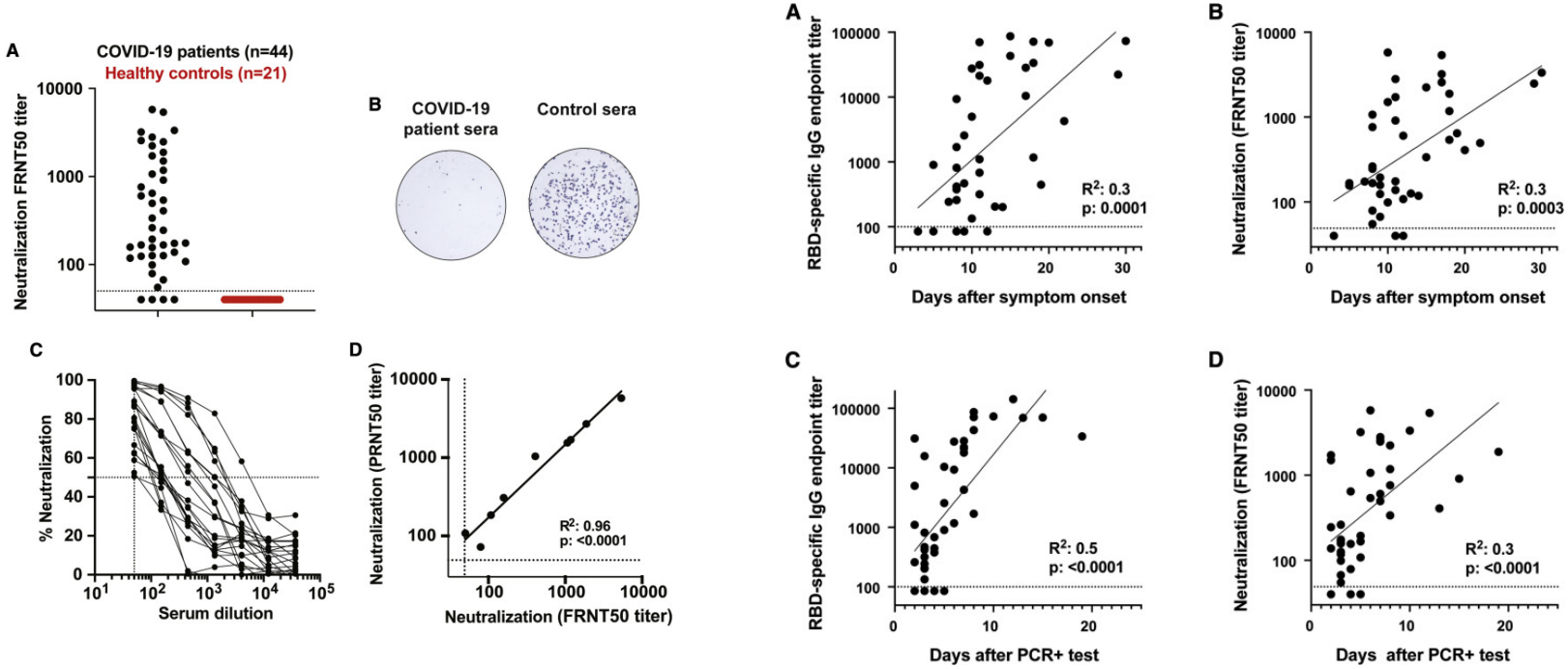
Assay
Plaque reduction neutralization titer
Clinical isolate microneutralization
Infectious clone reporter microneutralization
Focus reduction assay
Psuedovirus

More severe patients exhibit more robust and faster antibody responses



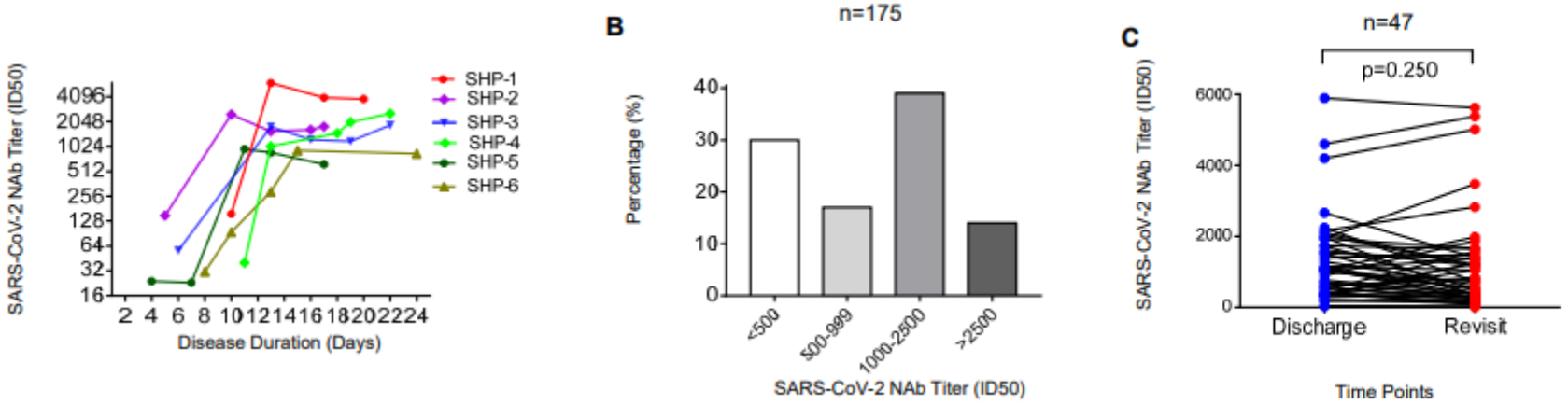
To et al. The Lancet. 20: 565-574

A majority of hospitalized COVID-19 patients develop neutralizing antibody responses



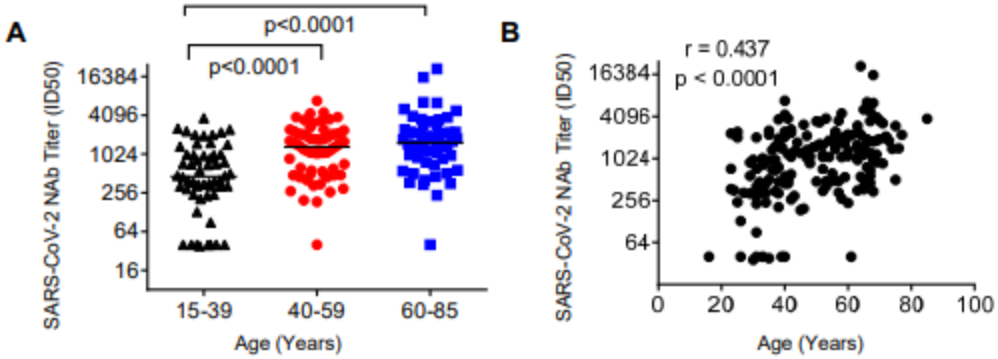
Suthar et al. Cell Reports Medicine. 2020 Jun 8

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

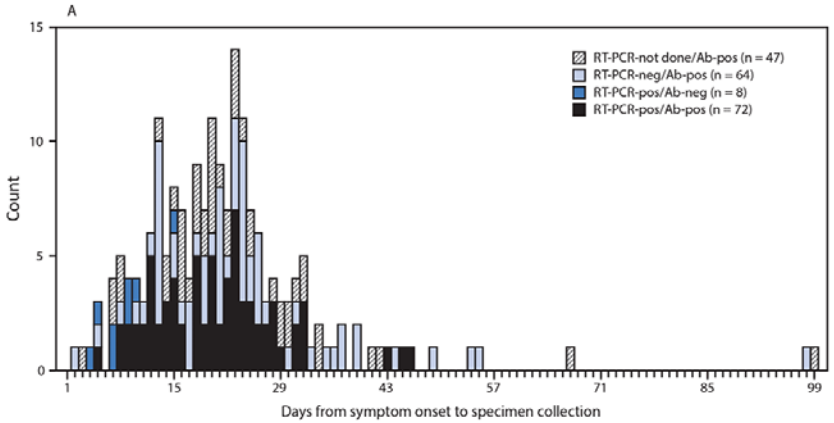
Older patients had higher neutralizing antibody titers

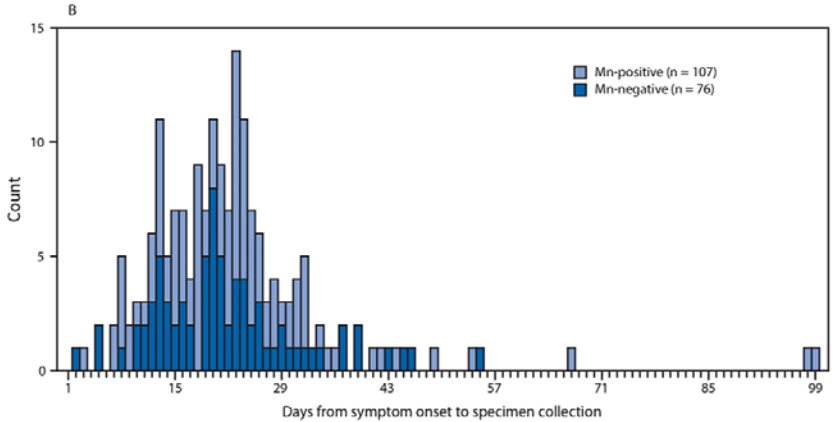


https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2.full.pdf+html

- Most of what we know about SARS-CoV-2 immunology are from hospitalized patients. What about milder infections?

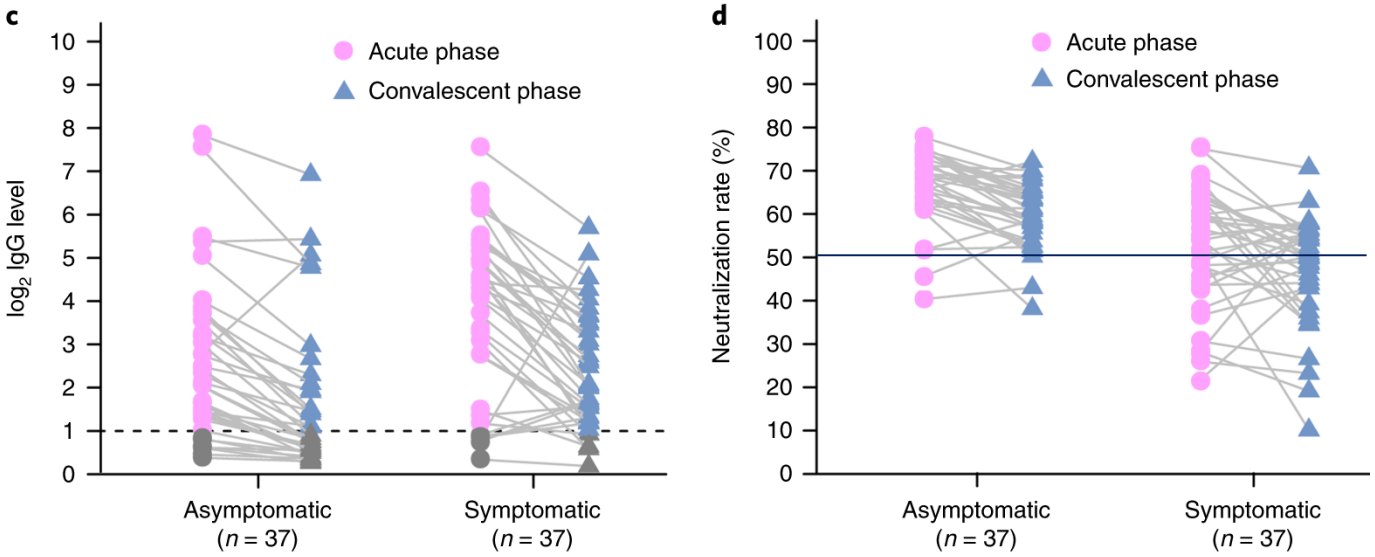
41% of antibody-positive USS TR sailors did not have detectable neutralization titers (IC100)





Payne et al. MMWR. 69: 714-721

Serum antibodies drop between acute phase and 8-weeks post discharge



Long et al. Nature Medicine. 18 JUN 2020

Conclusions

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

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov