

# Antibody Response in COVID-19 – Serology, Neutralizing Antibodies and Vaccine Breakthrough

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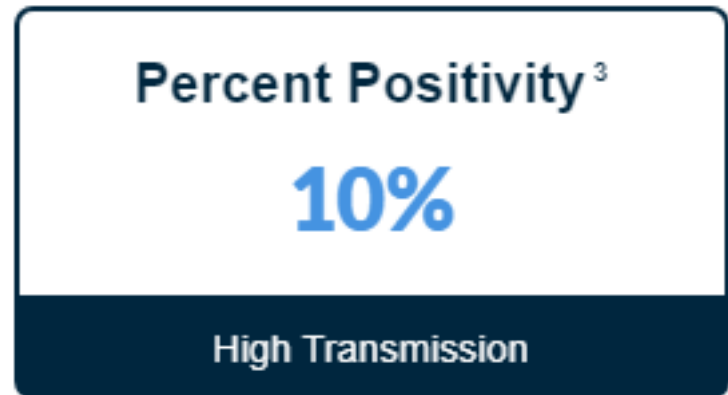
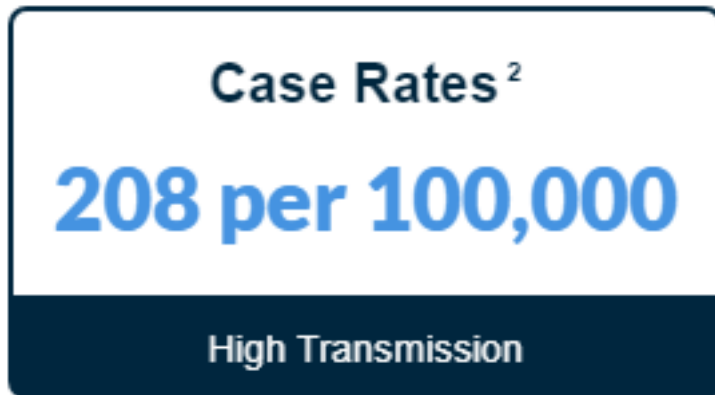
**MAYO  
CLINIC**



# Disclosures

- **I, Dr. Erin Kaleta, have no relevant financial relationships with ineligible companies to disclose.**

# Where are we now?

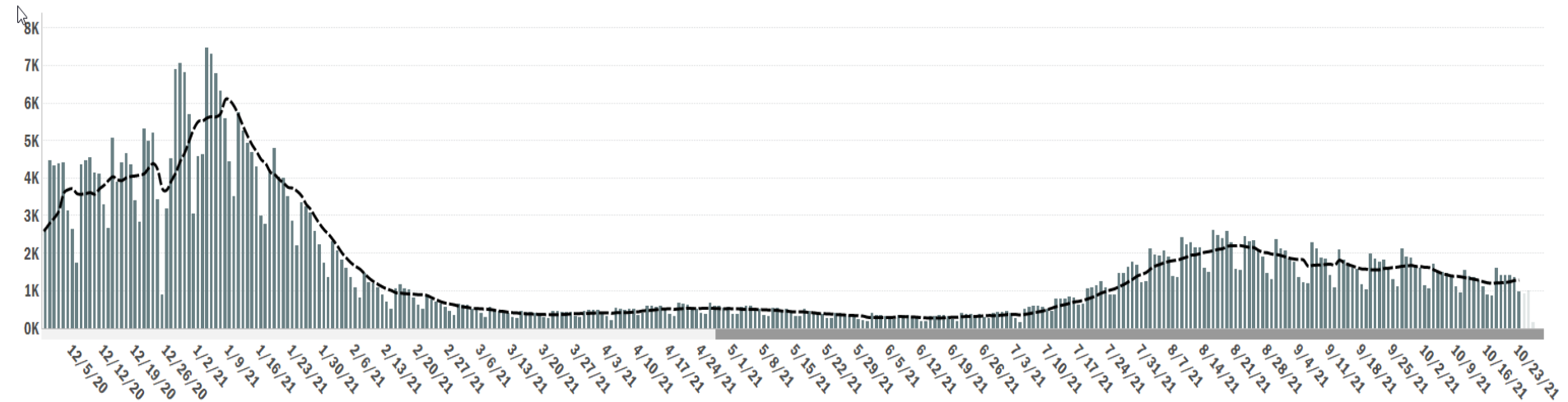


Maricopa County – Current as of 10/28/21 from week 10/17-10/23.

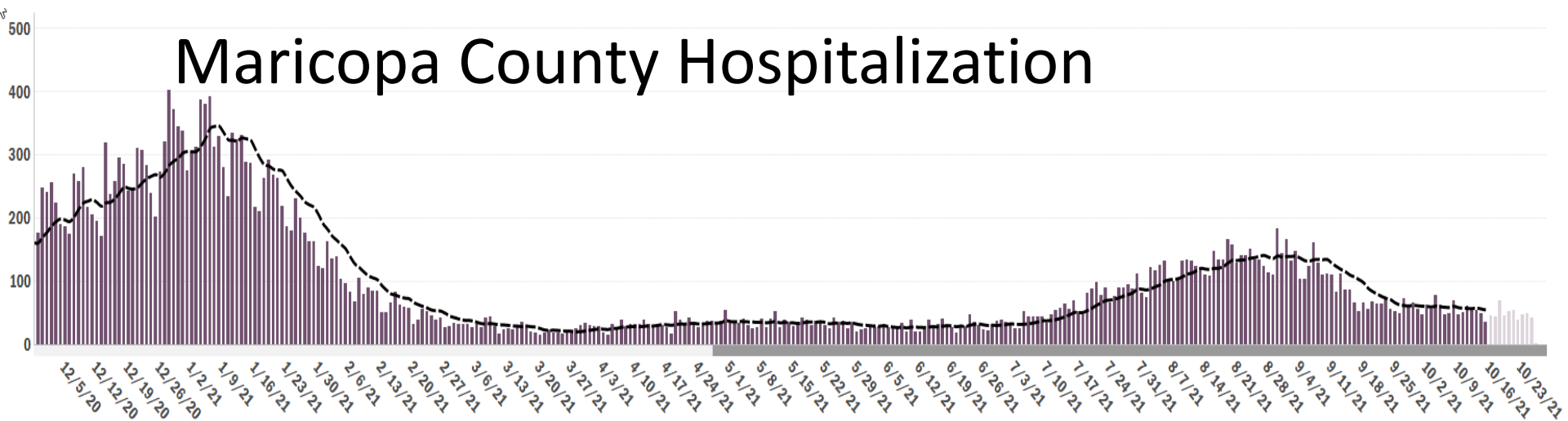
# Where are we now?

<https://www.maricopa.gov/5460/Coronavirus-Disease-2019>

- Maricopa County Epidemic Curve



## Maricopa County Hospitalization

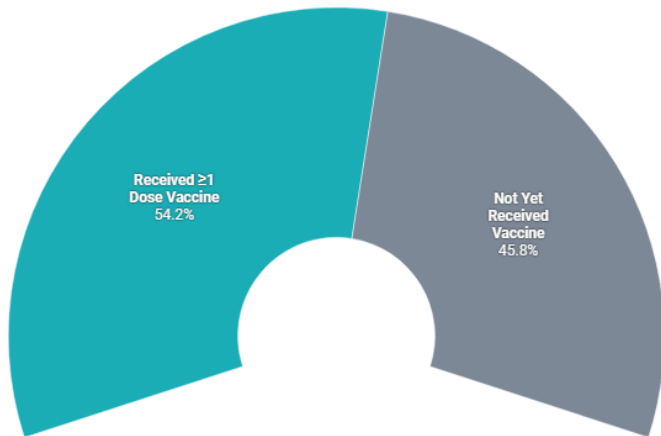


# Where are we now?

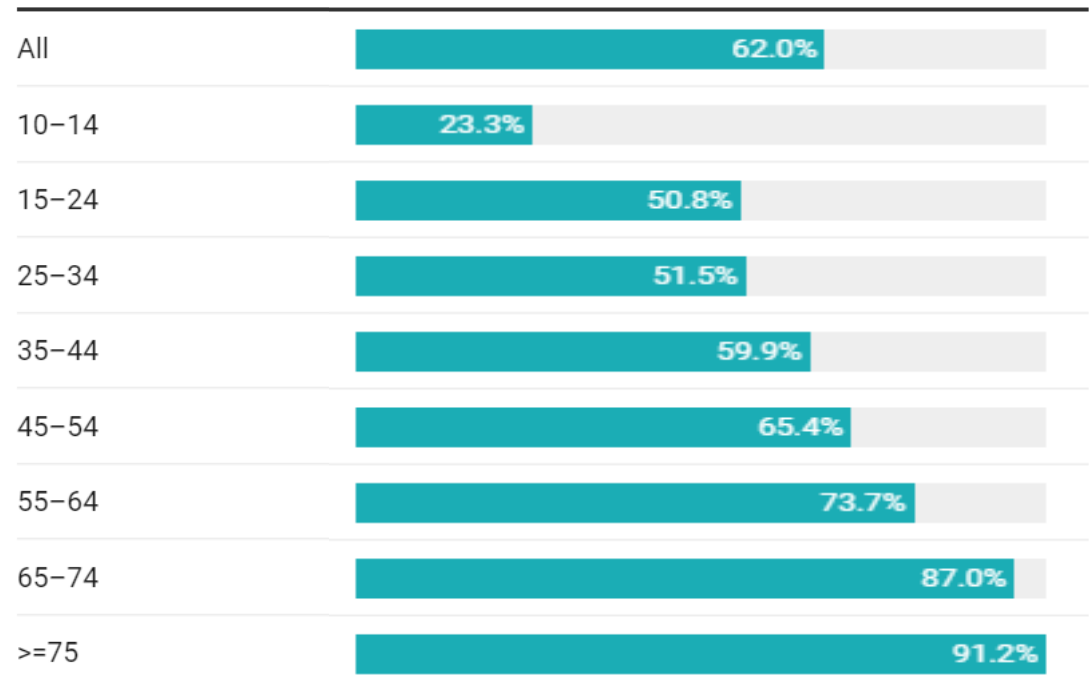
- Vaccine Statistics:

- Total doses administered: 4,775,993

- Full series completed: 2,183,743



Percent of Maricopa Residents in Each Age Group\*

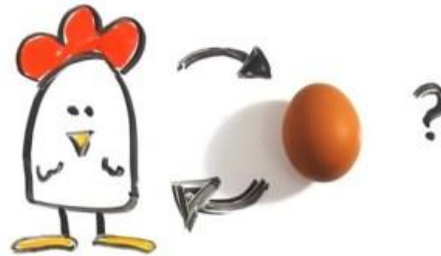


# Types of Testing

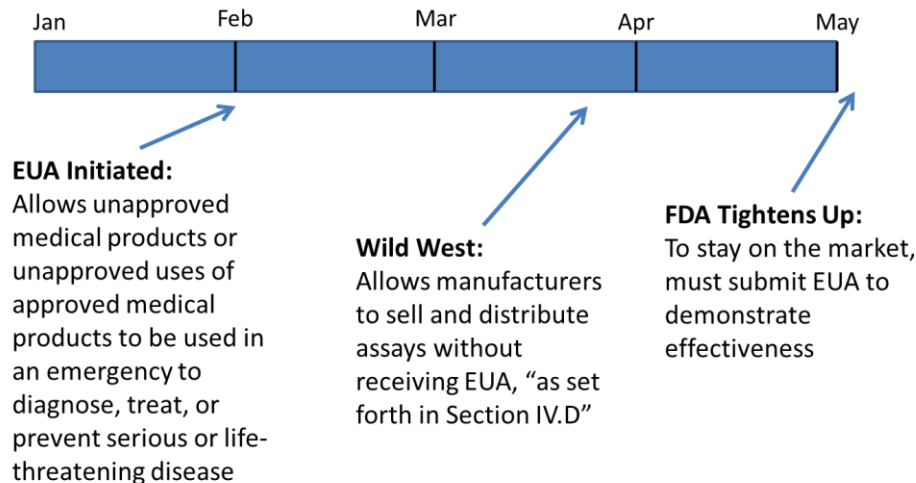
- Molecular Tests
  - Rapid or 1-3 days
  - Best in acute period of infection
- Antigen Tests
  - Rapid, often lateral flow assays, 15-30 min
  - Sacrifices accuracy
- Serology Tests
  - Takes 1-3 weeks for antibody response
  - Best for identifying previous infection

# Hurdles to Sars-CoV-2 Testing

- Regulatory requirements for EUA testing



- Regulatory issues exacerbated for Serology

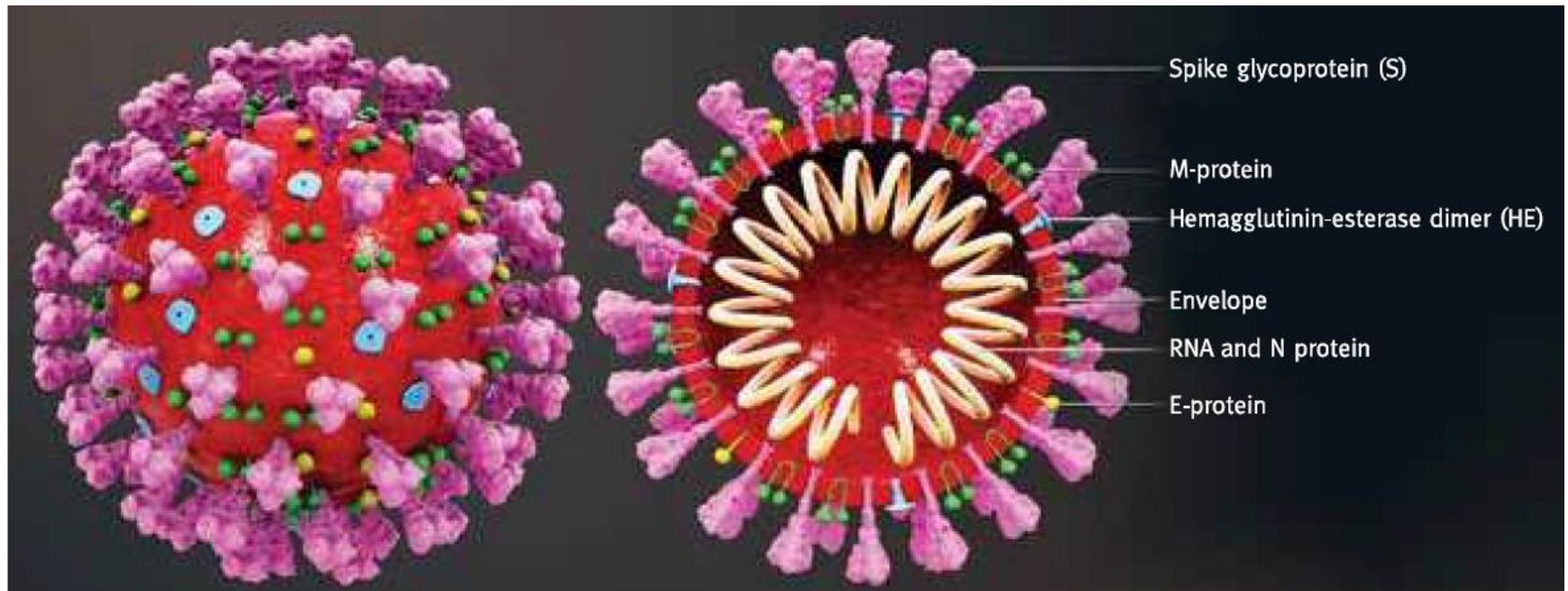


# IDSA Guidelines – Clinical Utility of Serology Testing

- **Supplementing PCR for late-presenting cases**
  - Particularly 3-4wks post-symptom onset
  - Identifying prior exposure
- **Identifying convalescent plasma donors and potential for assessing vaccine response**
- **Tracking SARS CoV 2 exposure in the community**



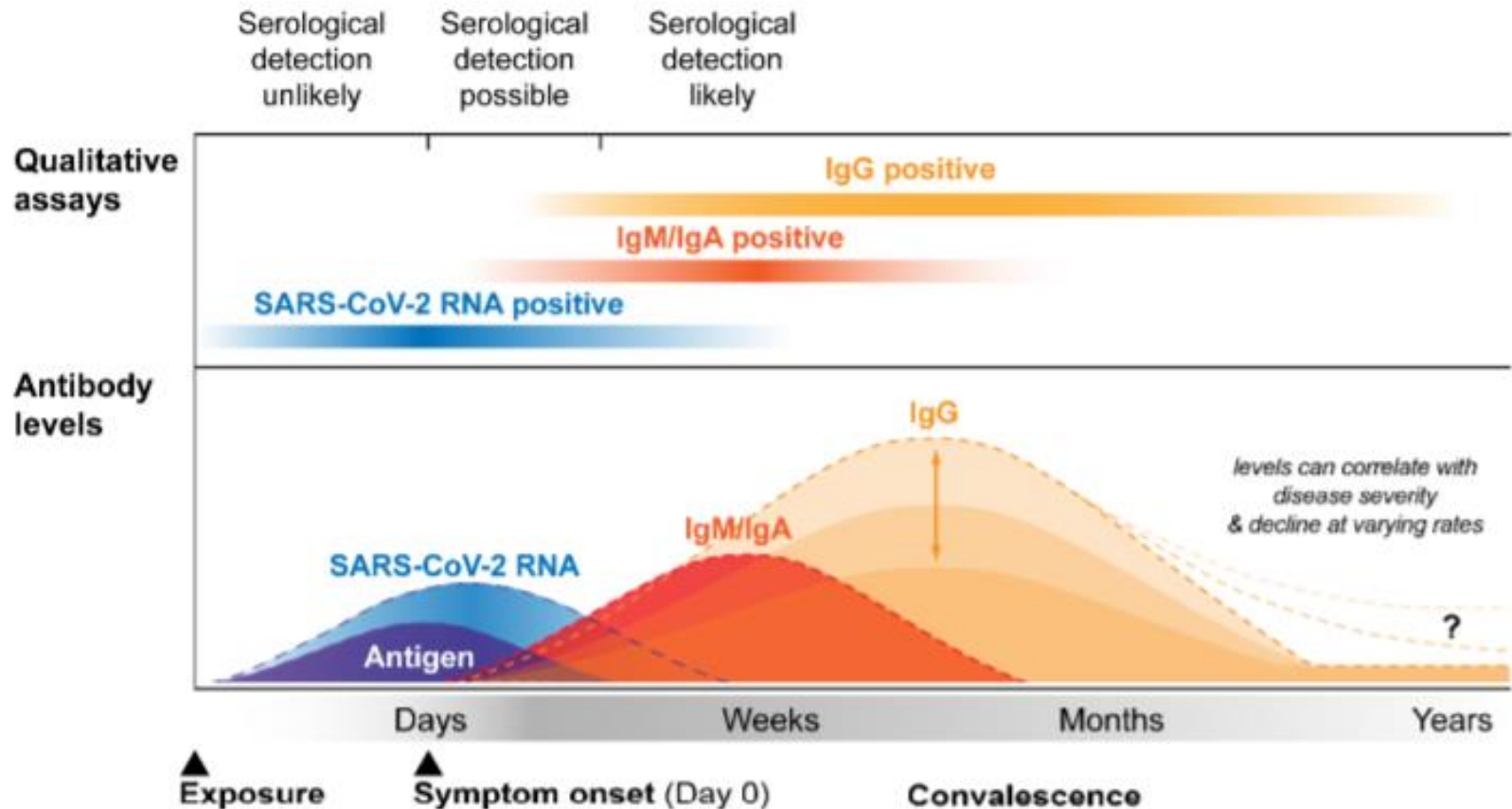
# Sars-CoV-2 Antigens of Interest



**Spike Protein: S1 + S2:** Trimeric glycoprotein Essential for recognizing host ACE2 receptors (S1/RDB) and facilitate entry into host cells (S2)

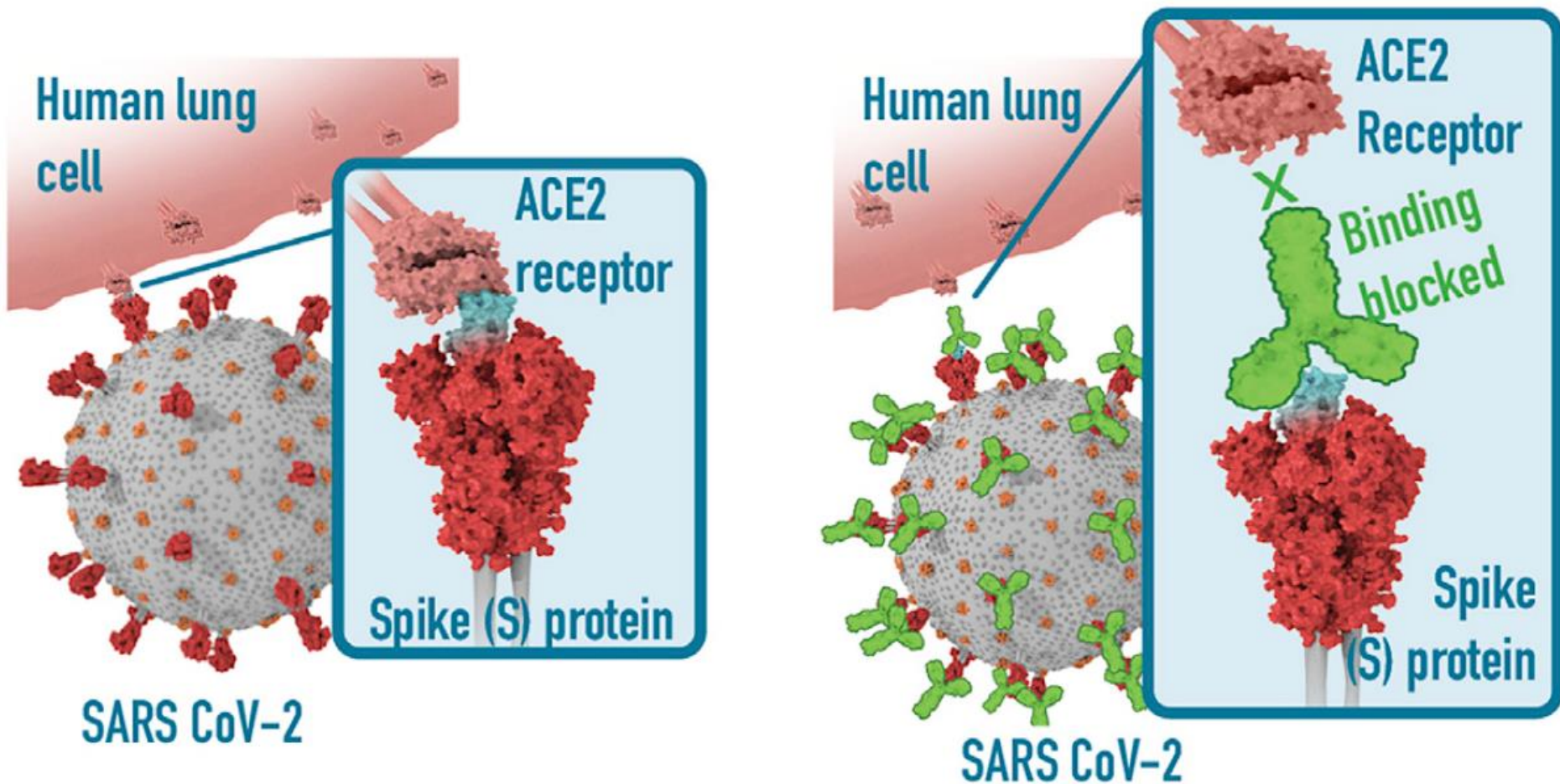
**N Protein: Nucleocapsid:** Binds to viral RNA; non-glycosylated and more highly conserved than Spike Protein

# Sars-CoV-2 Antibody Kinetics



Zhang YV, Wiencek J, Meng QH, Theel ES, Babic N, Sepiashvili L, Pecora N, Slev P, Cameron A, Konforte D. *AACC Practical Recommendations for Implementing and Interpreting SARS-CoV-2 EUA and LDT Serological Assays.*

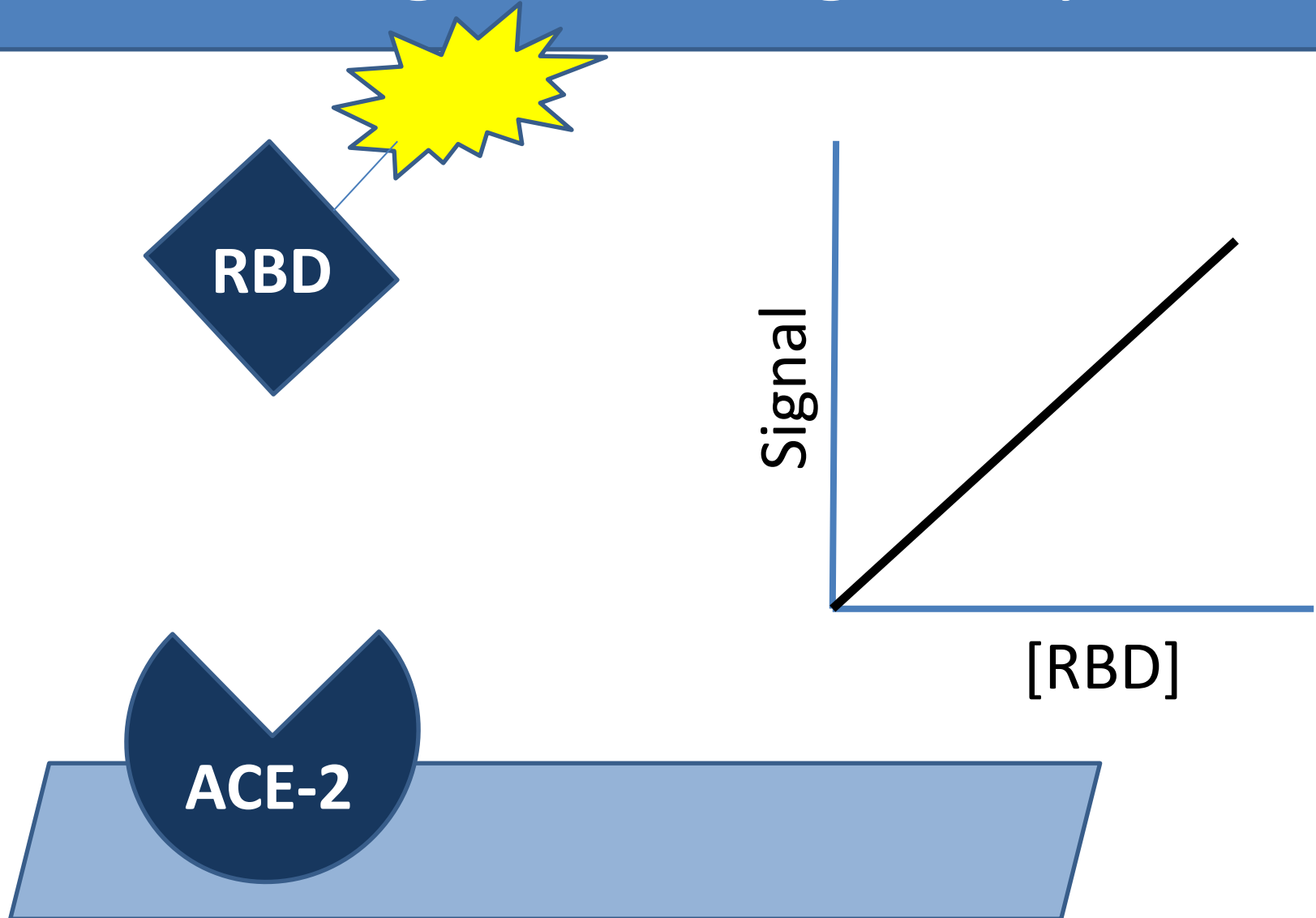
# Antibodies, but do they Neutralize?



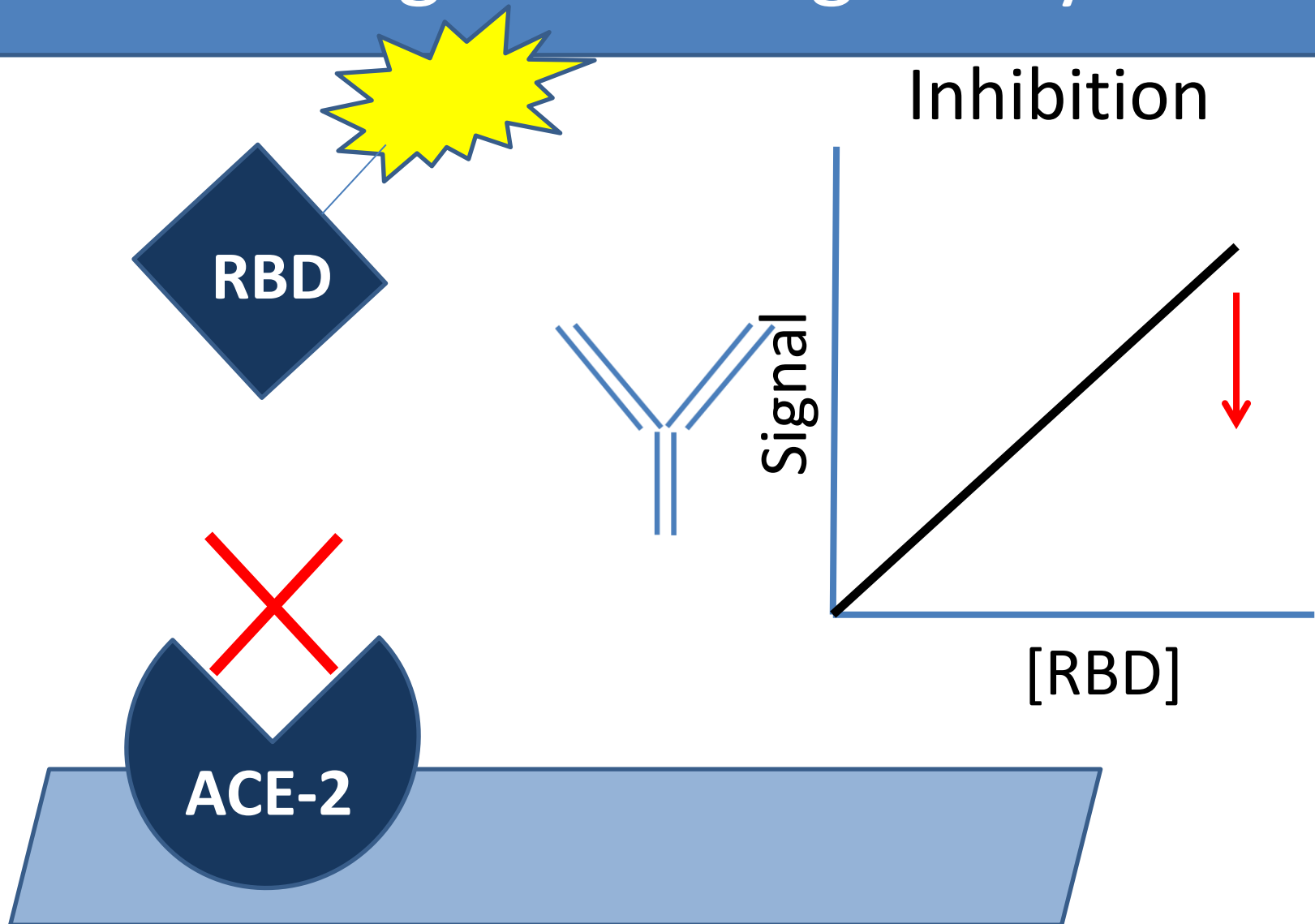
# ACE2/RBD Surrogate Neutralizing Ab Tests

- **Types of Neutralizing Antibody tests**
  - Virus Neutralizing Tests/PRNT
    - Live cells, BSL-3
  - Pseudotype-based Virus Neutralizing Tests
    - Live cells, BSL-2
  - Surrogate Virus Neutralizing Tests
    - Mimics the virus/host interaction
    - Uses purified ACE2 and S1-RBD
    - No live virus
    - ELISA format for high-throughput applications

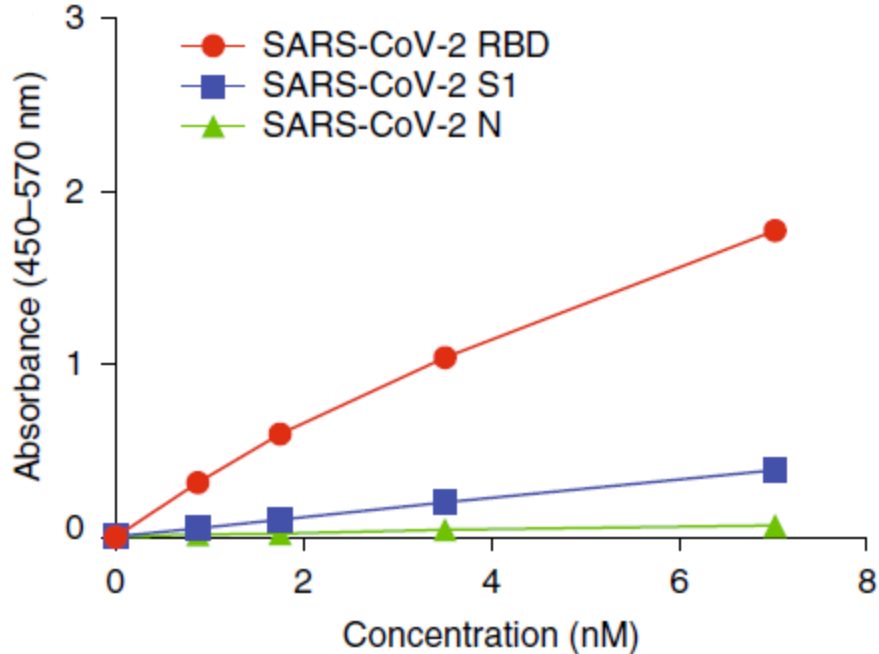
# Blocking of Binding Assays



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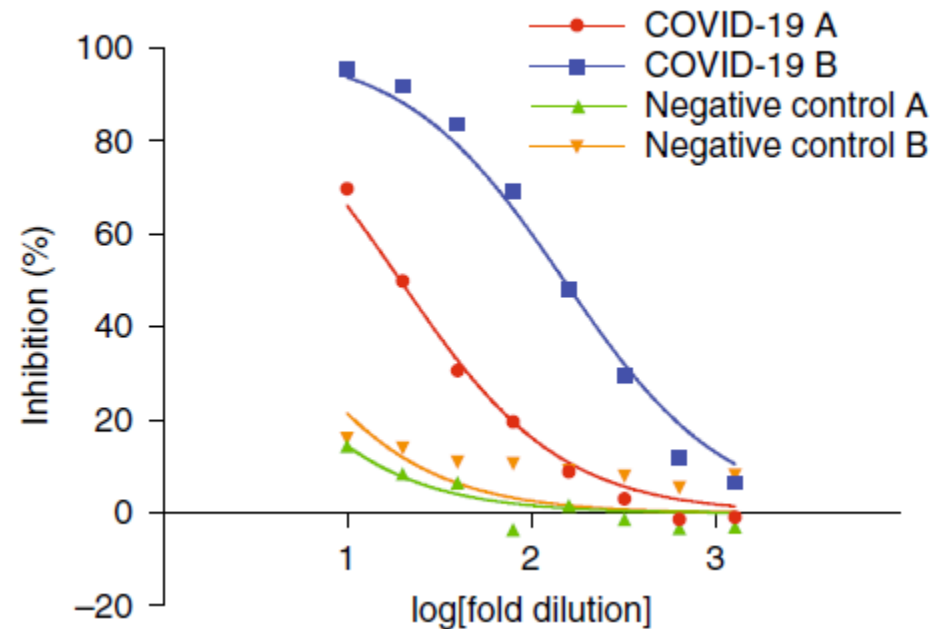
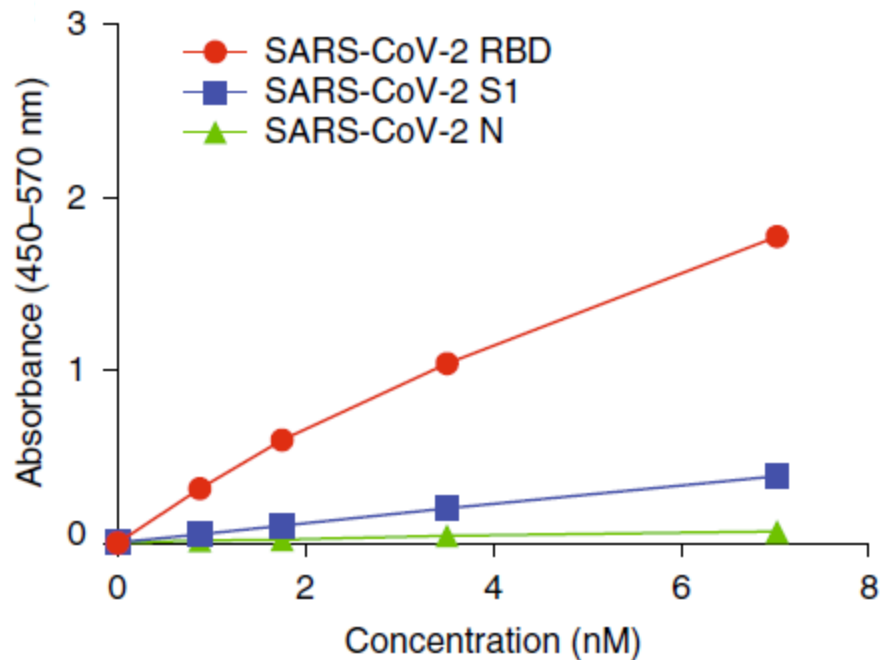


# Surrogate Neutralizing Antibody Assay



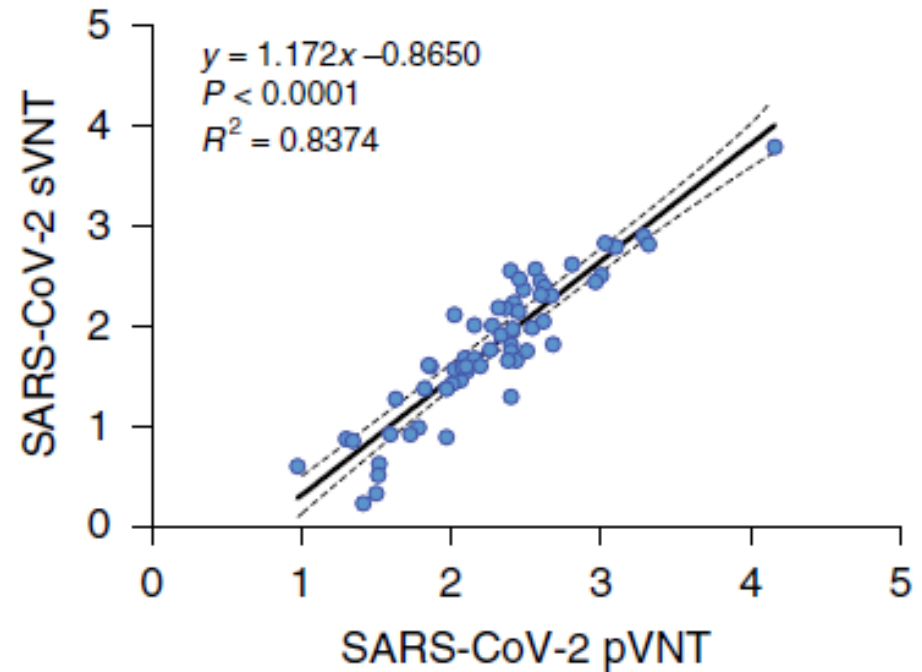
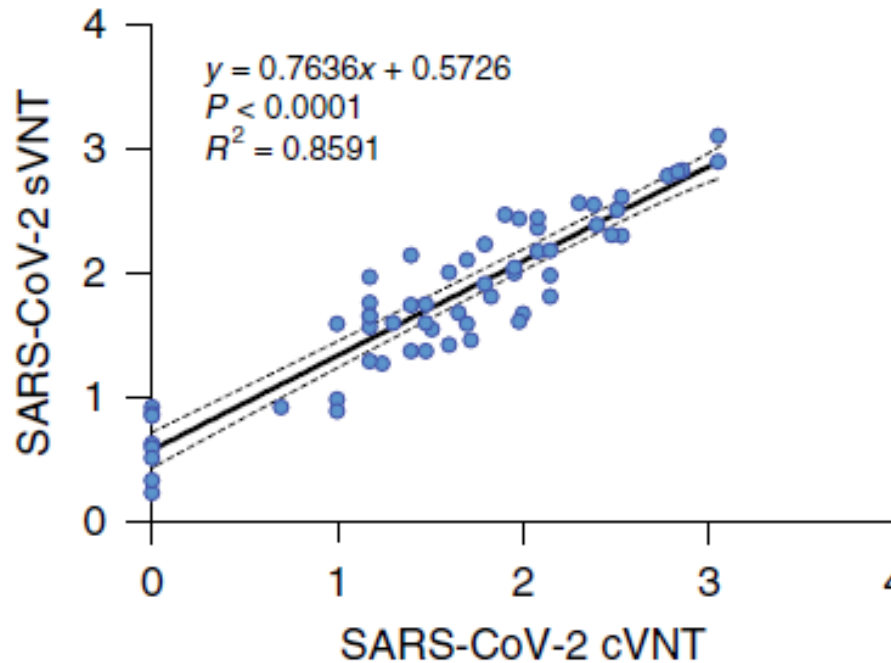


# Surrogate Neutralizing Antibody Assay

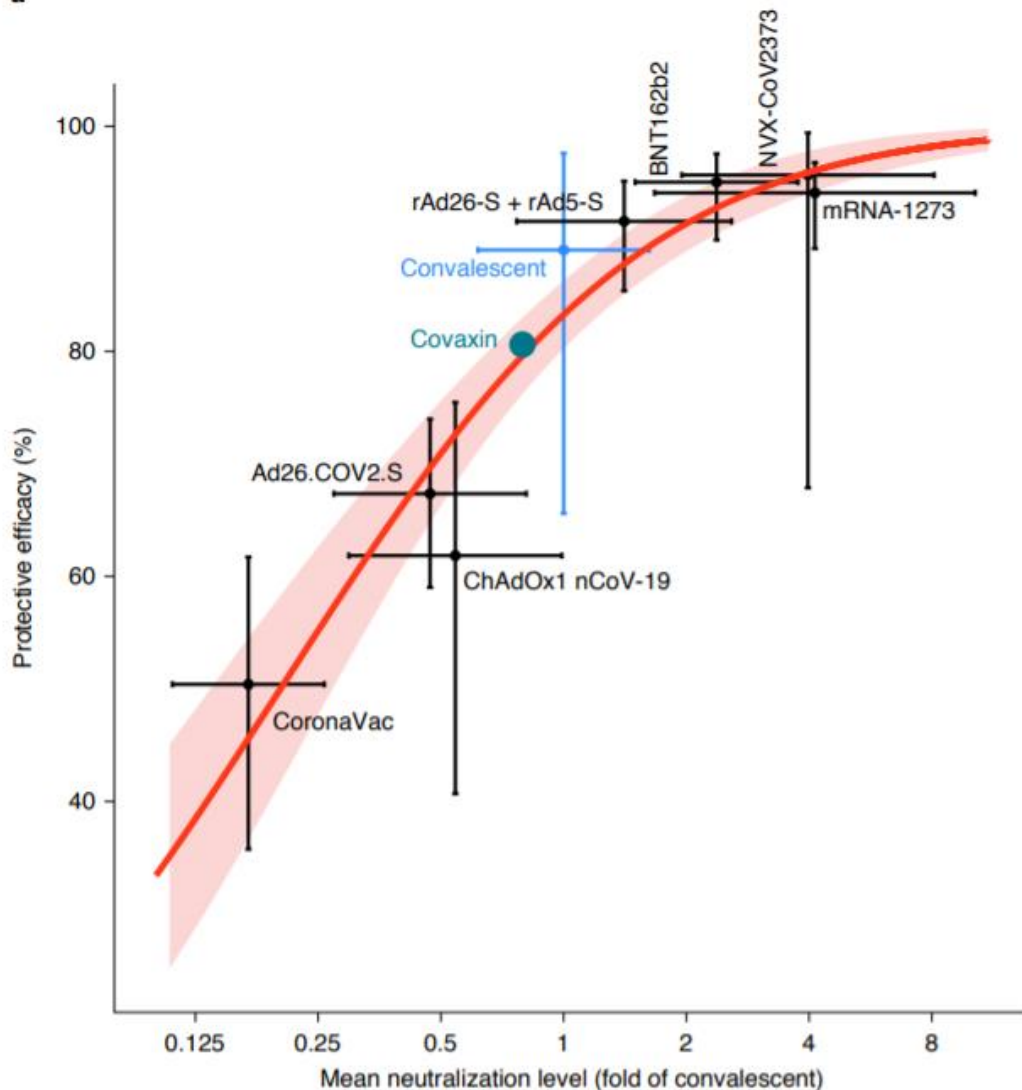




# Surrogate Neutralizing Antibody Assay



# What Titer is Needed?



Khoury DS, Cromer D, Reynaldi A, et al. 2021. *Nature Medicine*, 27, 1205-1211.

Modelling data from vaccine trials can predict a titer necessary for protective immunity

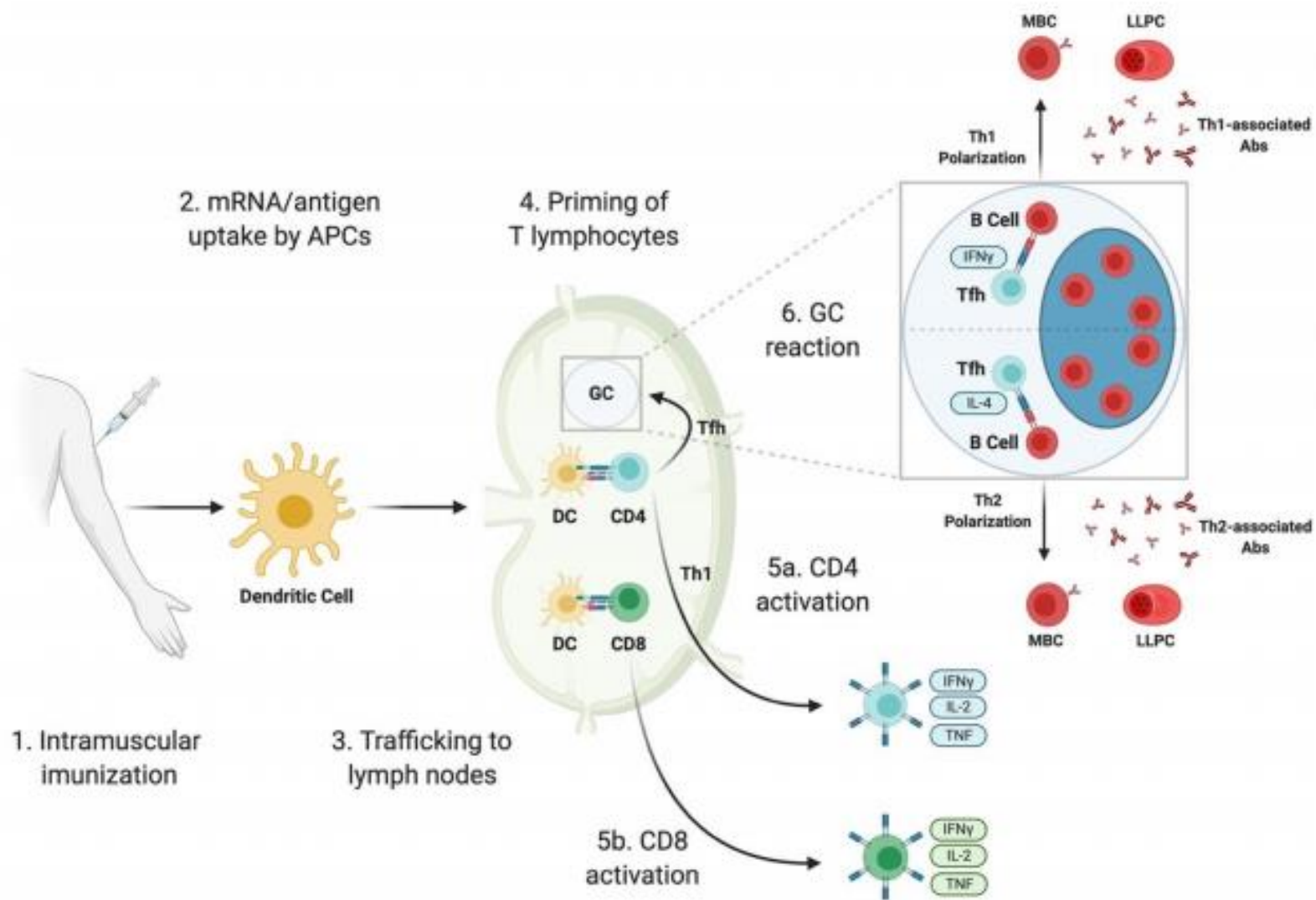
Normalizes vaccine trials against convalescent plasma to account for non-standardized assays

Estimates that a titer of 20% convalescent plasma is required for protection (1:160 PRNT)

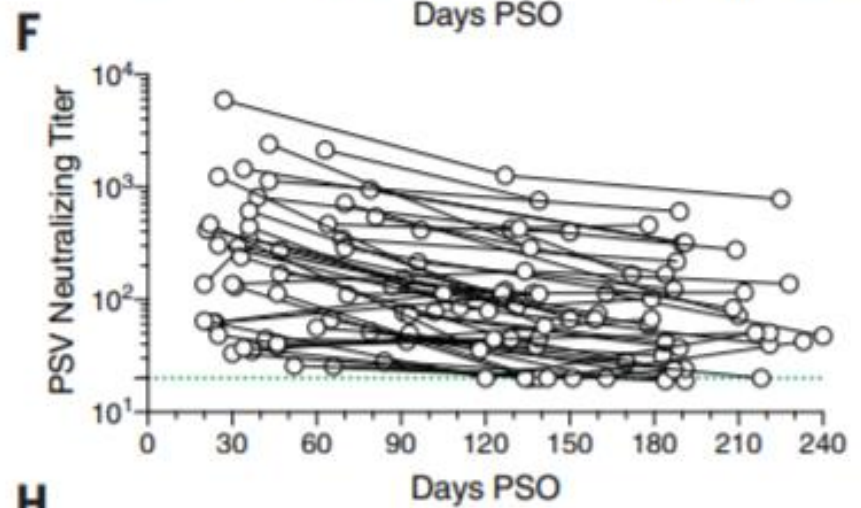
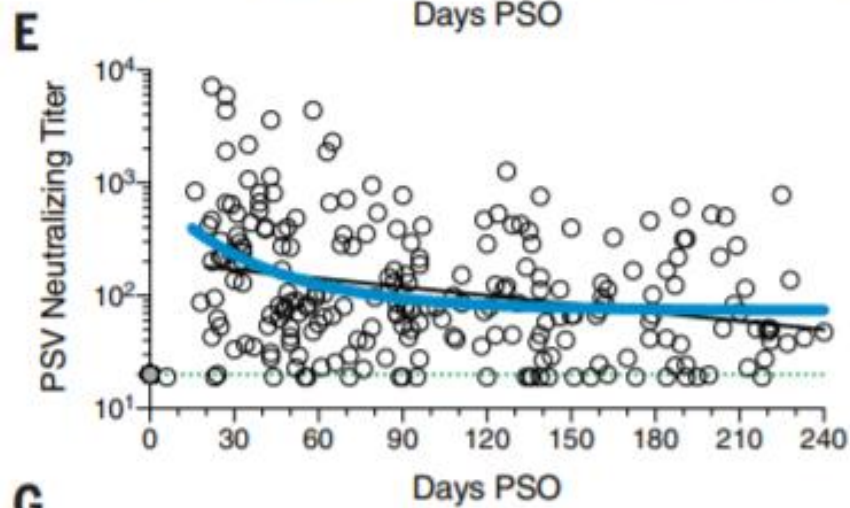
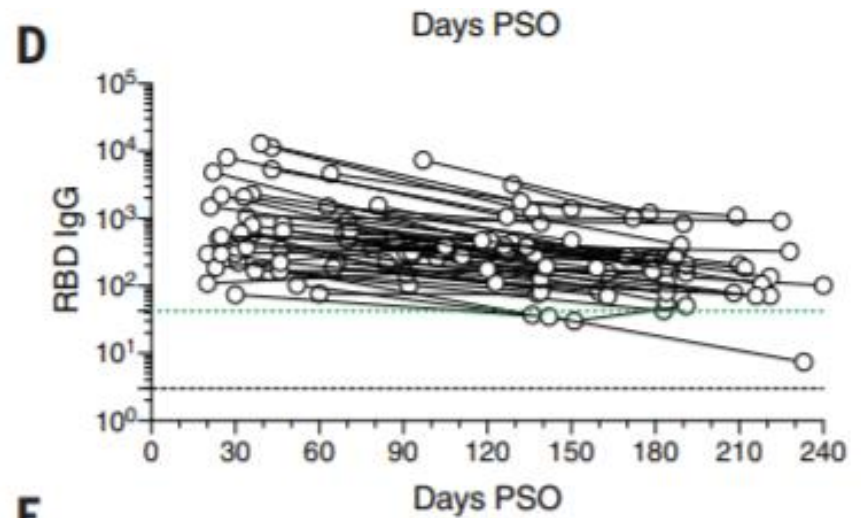
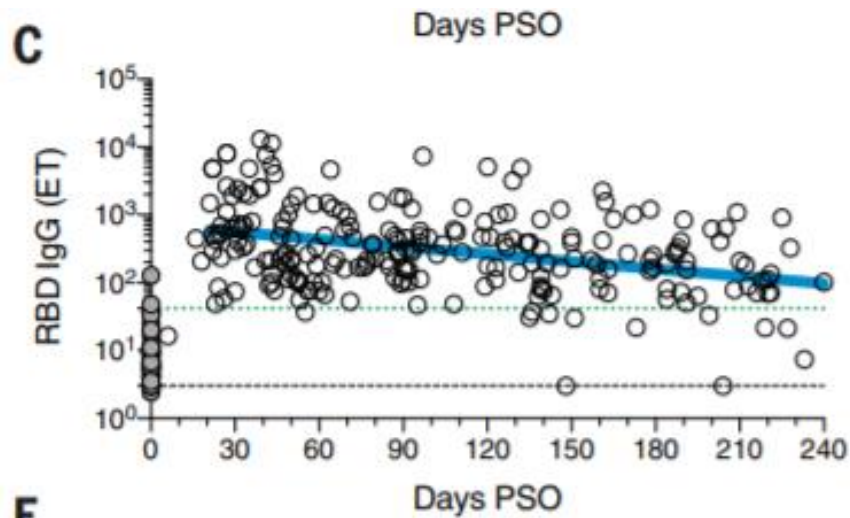
# How Long Does Immunity Last?

- Depends on many factors
  - Neutralizing antibodies = “Sterilizing” immunity
  - Cell Mediated immunity
    - T-cells
    - B-cells
  - Dose of exposure
    - Initial dose
    - Duration of illness
    - Severity of illness

# Immunity with mRNA Vaccines



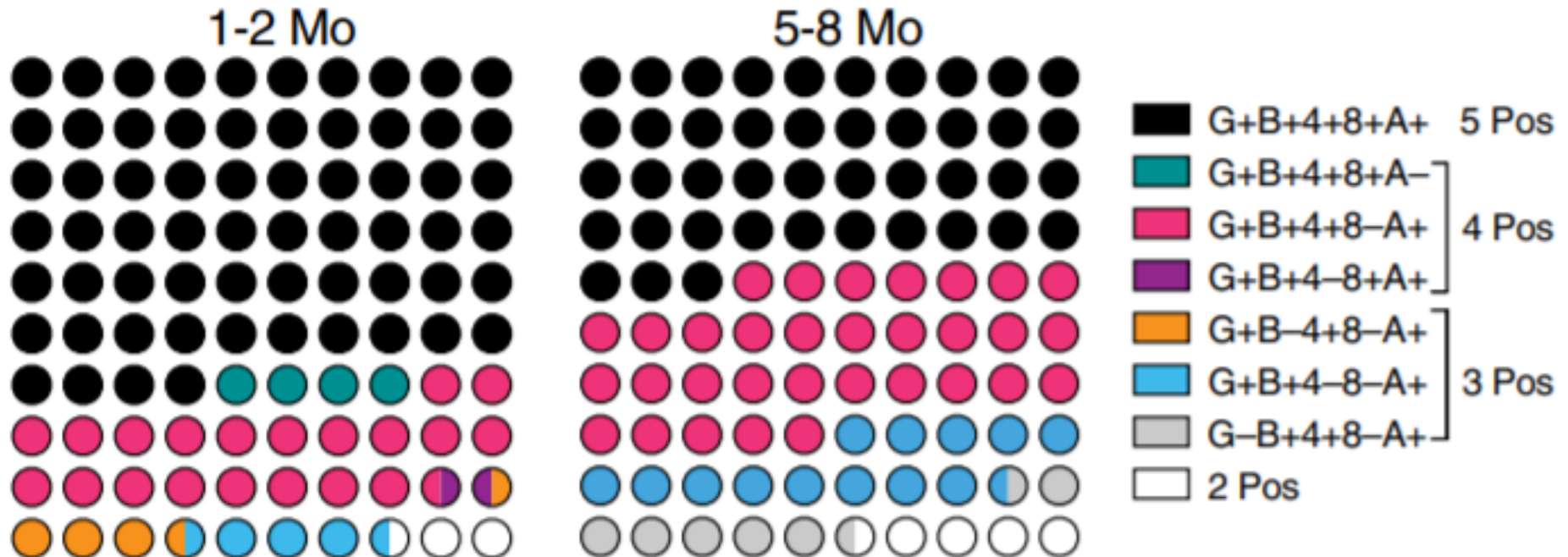
# How Long Does Immunity Last?



# How Long Does Immunity Last?

- Memory B-cells
  - Increased over 120 days and remained high at  $\geq 6m$  post infection
  - Produced and maintained in all subjects with no apparent half-life
- CD8<sup>+</sup> T Cells
  - 50% recovered patients positive at  $\geq 6m$  post infection
  - Decline estimated  $t_{1/2} = 125 - 190$  days or greater
- CD4<sup>+</sup> T Cells
  - 92% positive at  $\geq 6m$  post infection
  - Declined  $t_{1/2} = 94$  days

# How Long Does Immunity Last?



- Immunity memory has interpatient variability
- 95% of individuals were positive for at least 3/5 markers 5-8m Post Symptom Onset

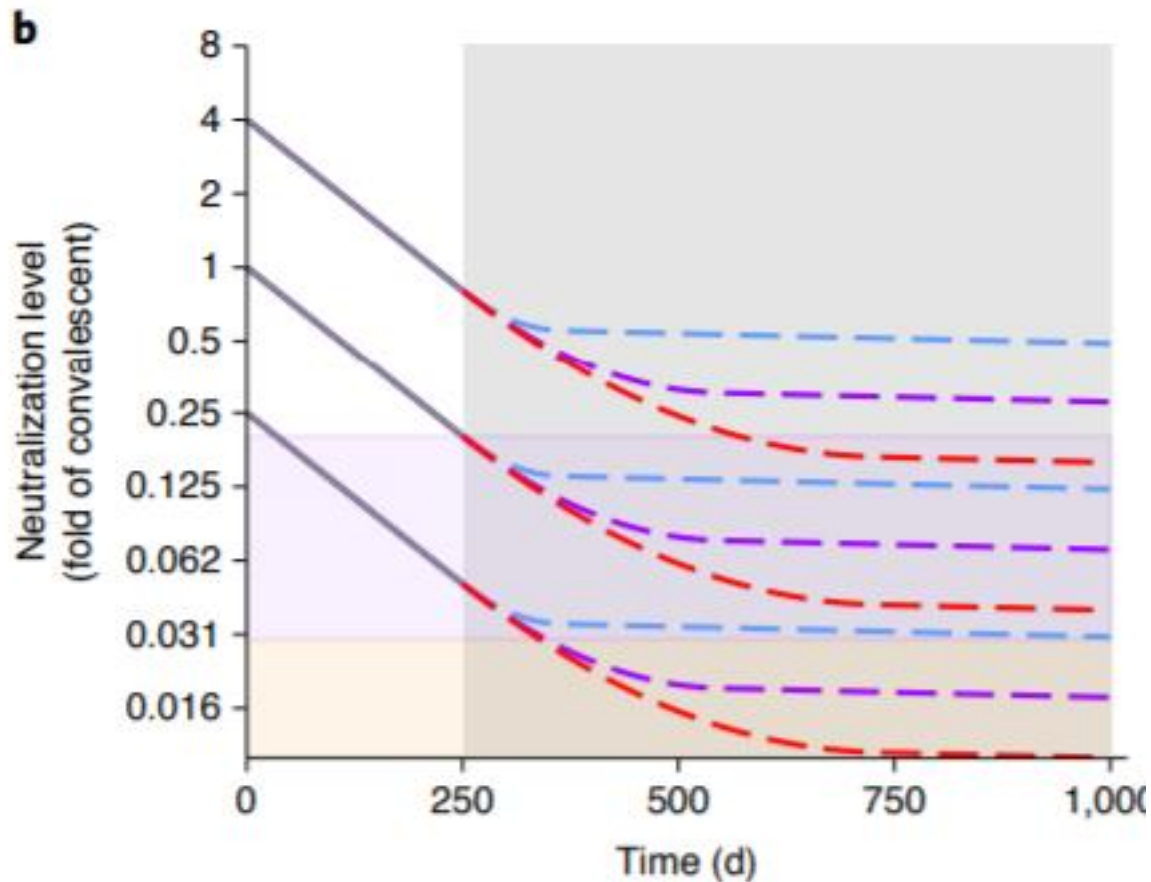


# How Long Does Immunity Last?

- Many factors contribute:
  - As circulating sterilizing immunity wanes, memory-based immunity predominates
  - Memory can take 3-5 days to ramp up, during which virus can replicate
  - Transmission events can become more likely



# How Long vs. Titters Needed



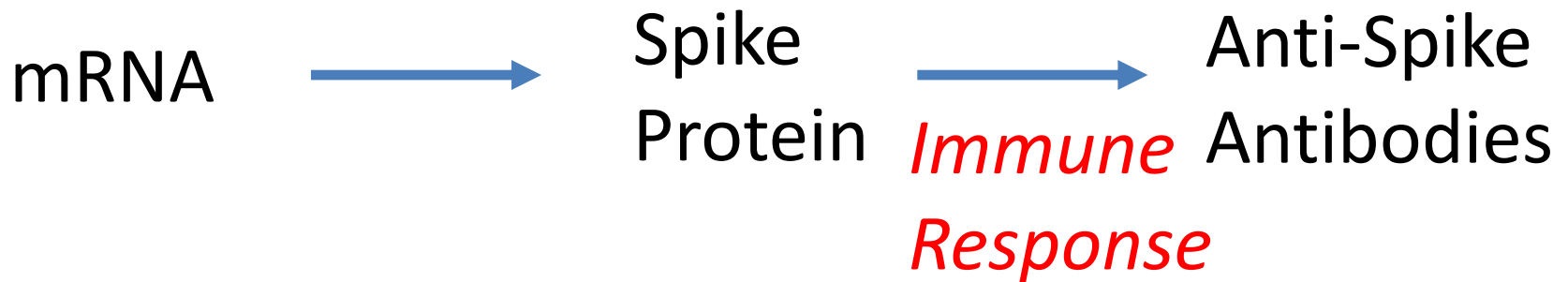
Various vaccines have a different starting neutralization level

Studies show decay is predicted to be linear up to 8 months

Durable plateau titer will vary dependent on initial titer

# Natural Infection vs. Vaccine Immunity

- **mRNA Vaccines**
  - **Pfizer BNT162b2**
  - **Moderna mRNA-1273**



# Natural Infection vs. Vaccine Immunity

## Antibody Results

	Nucleocapsid Ab	Spike Ab	Neutralizing Ab
Natural Infection	+	+	+
Vaccine-Induced	-	+	+

# Natural Infection vs. Vaccine Immunity

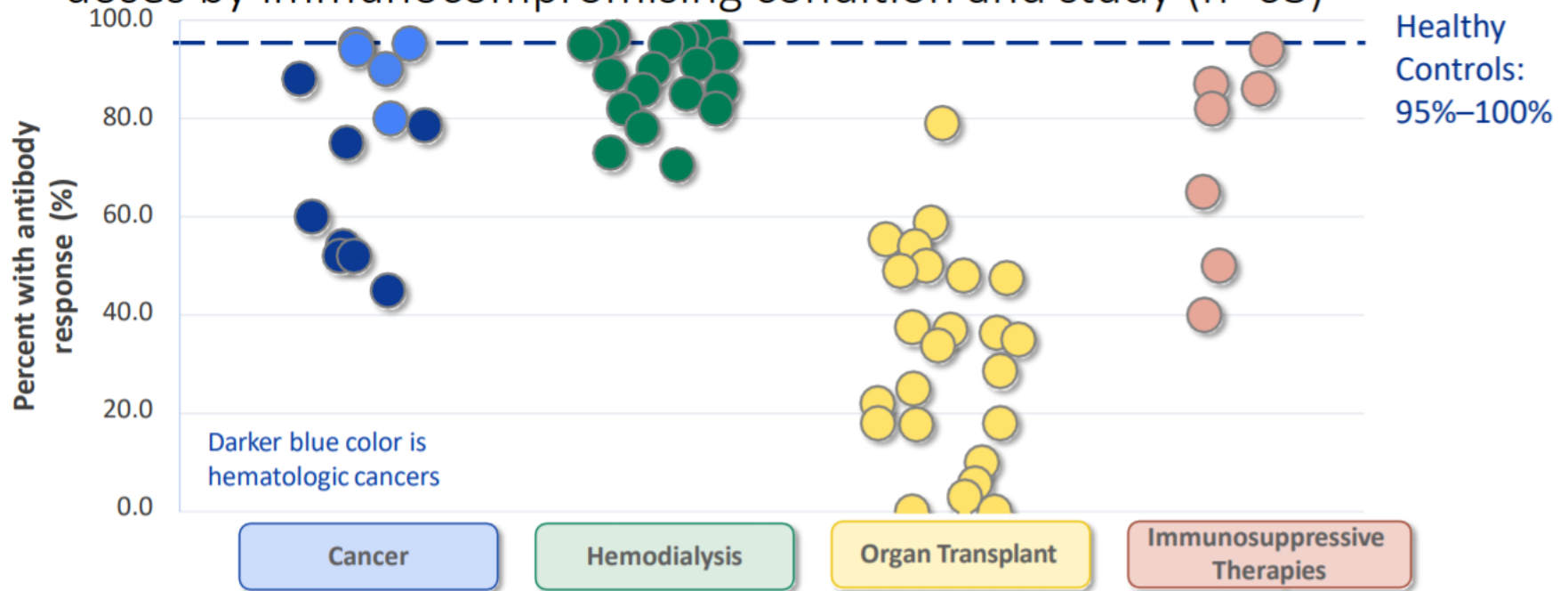
- **Are serology assays useful for measuring vaccine response??**
  - *Most* individuals seroconvert: 91-100%
  - Limited correlation to protective immunity
- What about immunocompromised patients?
  - Unknown value of positive result in U/mL
  - Negative results could be informative

# Approved for Use in Immunocompromised Patients

- Who is immunocompromised?
  - HIV+ participants show equivalent antibody production
  - Kidney Tx patients: 25%
  - Solid organ Tx patients: 54%
  - Autoimmune Disease: 80%
  - Hematologic cancers: 55% or 66%
- Doesn't tell the whole story – Cell mediated immunity is higher.

# Approved for Use in Immunocompromised Patients

Percent of subjects with antibody response after two mRNA vaccine doses by immunocompromising condition and study (n=63)

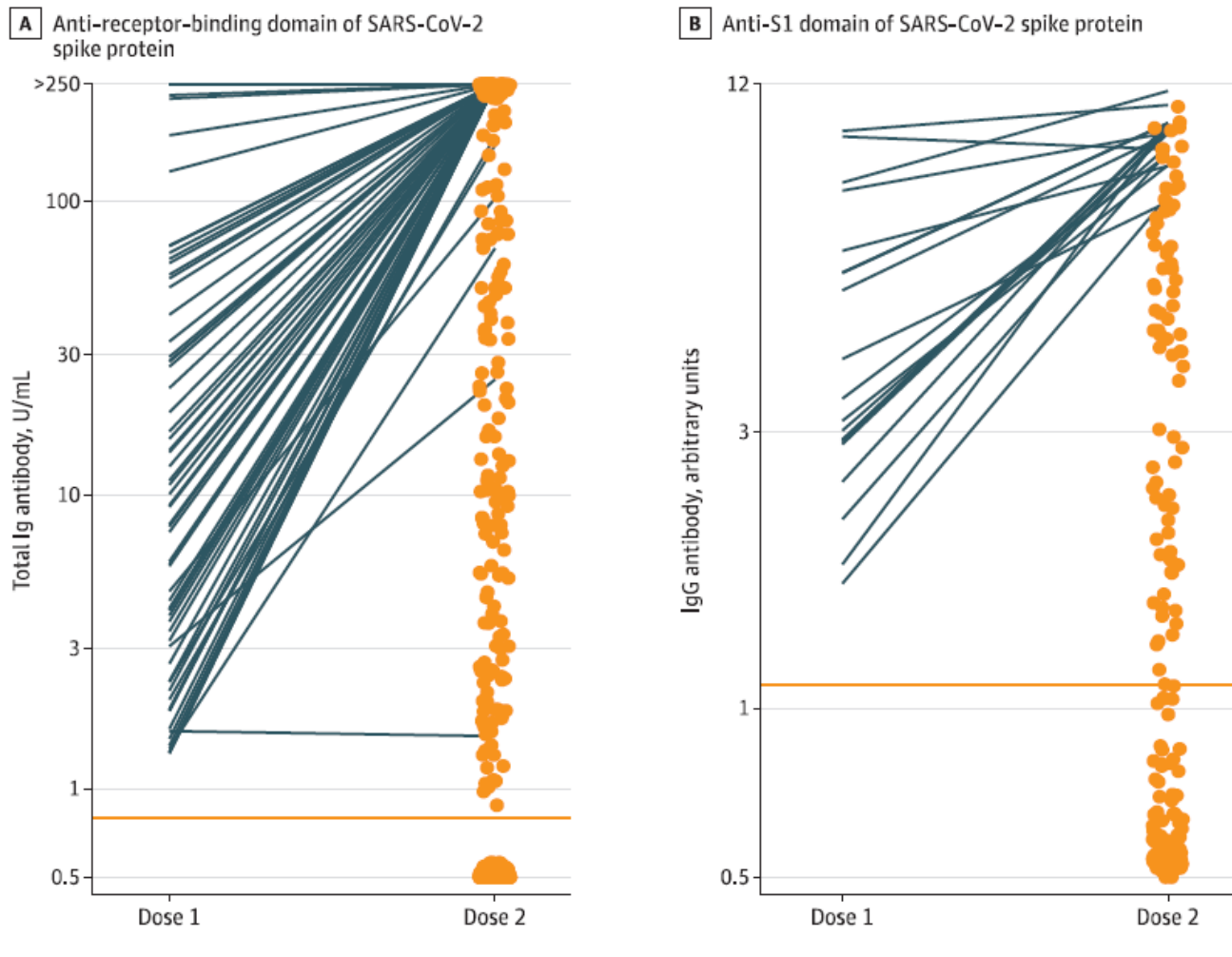


- Studies that compared response after 1st and 2nd dose demonstrated poor response to dose 1
- Antibody measurement and threshold levels vary by study protocol

Adapted from ACIP Data and Clinical Considerations for Additional Doses in Immunocompromised People  
Sara Oliver ACIP July 22, 2021

# Antibody Levels in Solid Organ Transplant Patients

Figure. Antibody Levels of Study Participants After 2-Dose Series of SARS-CoV-2 mRNA Vaccine



# Vaccine Breakthrough

- Defined as:
  - Detection of SARS-CoV-2 RNA or antigen
  - $\geq 14$  days after vaccine series completed



# Vaccine Breakthrough Cases

- Through 5/1/2021:
  - 10,262 vaccine breakthrough cases
  - 27% asymptomatic infections
  - 10% hospitalized
    - 29% of these were hospitalized for unrelated reasons
  - 2% death
    - 18% of these died from unrelated causes
- After 5/1/2021:
  - CDC only monitoring *hospitalized* breakthrough

# Vaccine Breakthrough Cases

- Since 5/1/2021

<b>Hospitalized or Fatal Vaccine Breakthrough cases reported to CDC</b>		<b>8,054</b>
Female	3,856	(48%)
≥ 65 years	5,928	(74%)
Asymptomatic	1,400	(17%)
Hospitalizations*	7,608	(94%)
Deaths**	1,587	(20%)

\* 1,883 (25%) of hospitalized cases were not related to COVID-19

\*\* 341 (21%) of fatal cases were not related to COVID-19

# Vaccine Breakthrough Cases

- If breakthrough is happening, why bother vaccinating?

# Vaccine Breakthrough Cases

- HEROES RECOVER study
  - 3975 Frontline Workers
    - Phoenix/Tucson AZ, Miami FL, Duluth MN, Portland OR, Temple TX, Salt Lake City UT
    - 67.5% fully vaccinated, 80% at least 1 dose
  - Monitored by weekly molecular testing
    - 5% COVID+ (204 participants)
    - 5 fully vaccinated, 11 partially vaccinated
    - 156 unvaccinated

# Vaccine Breakthrough Cases

**Table 3.** Viral RNA Load, Duration of Viral RNA Detection, Frequency of Febrile Symptoms, and Duration of Illness in Vaccinated and Unvaccinated Participants with SARS-CoV-2 Infection.\*

Variable	Unvaccinated	Partially or Fully Vaccinated	Difference (95% CI)
Viral RNA load			
No. assessed	155	16	—
Mean — log <sub>10</sub> copies/ml†	3.8±1.7	2.3±1.7	40.2 (16.3–57.3)‡
Duration of viral RNA detection			
No. assessed	155	16	—
Mean — days	8.9±10.2	2.7±3.0	6.2 (4.0–8.4)
Detection of viral RNA for >1 week — no./total no. (%)	113/156 (72.4)	4/16 (25.0)	0.34 (0.15–0.81)§
Febrile symptoms — no./total no. (%)¶	94/149 (63.1)	4/16 (25.0)	0.42 (0.18–0.98)
Total days of symptoms			
No. assessed	148	16	—
Mean — days	16.7±15.7	10.3±10.3	6.4 (0.4–12.3)
Days spent sick in bed			
No. assessed	147	15	—
Mean — days	3.8±5.9	1.5±2.1	2.3 (0.8–3.7)

# Point of Care Testing Options

- POCT Rapid Antigen Tests
  - Immunoassay for viral protein
  - Less sensitive
  - May detect active virus vs. PCR
  - Best in symptomatic individuals
  - Confirmatory testing with molecular method recommended



# Point of Care Testing Options

- Many options ranging from Direct-to-Consumer mail in kits to in home rapid PCR

3



# Wrapping Up

- Sars-CoV-2 diagnostics have come a long way in a short period of time
- Serology is best utilized for identifying previous exposures
  - Not ready for mainstream immunity testing
- Breakthrough infections are happening and were expected
- Our greatest tool is **VACCINATION!**



# Thank you!

