



# Third Doses for COVID Vaccines?

by Stanley A. Plotkin

# Why are Correlates of Immunity Important?

1. Basic immunology
2. Enables correct choice of vaccine antigen
3. To permit consistency of potency
4. To determine susceptibility of an individual or a population
5. If efficacy trial not feasible or ethical, immunological data enable licensure of vaccine
6. Enables bridging from first-generation vaccine to second generation

# mCoP – Mechanistic Correlate of Protection

An immune response  
that is responsible for protection

# nCoP – non-mechanistic Correlate of Protection

Formerly called:

**Surrogate**: An immune response that substitutes for the true immunologic correlate of protection, which may be unknown or not easily measurable

# Principle 1

**Must Define Protection**

**Against what?**

**Infection?** (*Local or Disseminated*)

**Disease?** (*Mild or severe*)

# Principle 2

**The Mechanism of  
Protection against  
infection vaccination is  
*not* necessarily the same  
Mechanism as recovery  
from infection**

# Principle 3

**A large challenge dose can  
overcome immunity**

# Potential Protective Adaptive Immune Mechanisms Induced by Vaccination

## Serum Antibody

Neutralizing

Non-neutralizing (ADCC, etc.)

Functionality (opsonophagocytosis)

Avidity

## Mucosal Antibody

IgA locally produced

IgG diffused from serum

## CD4+ T cells

B cell help

T cell help

Th17)

Cytokines

Lysis

Tregs

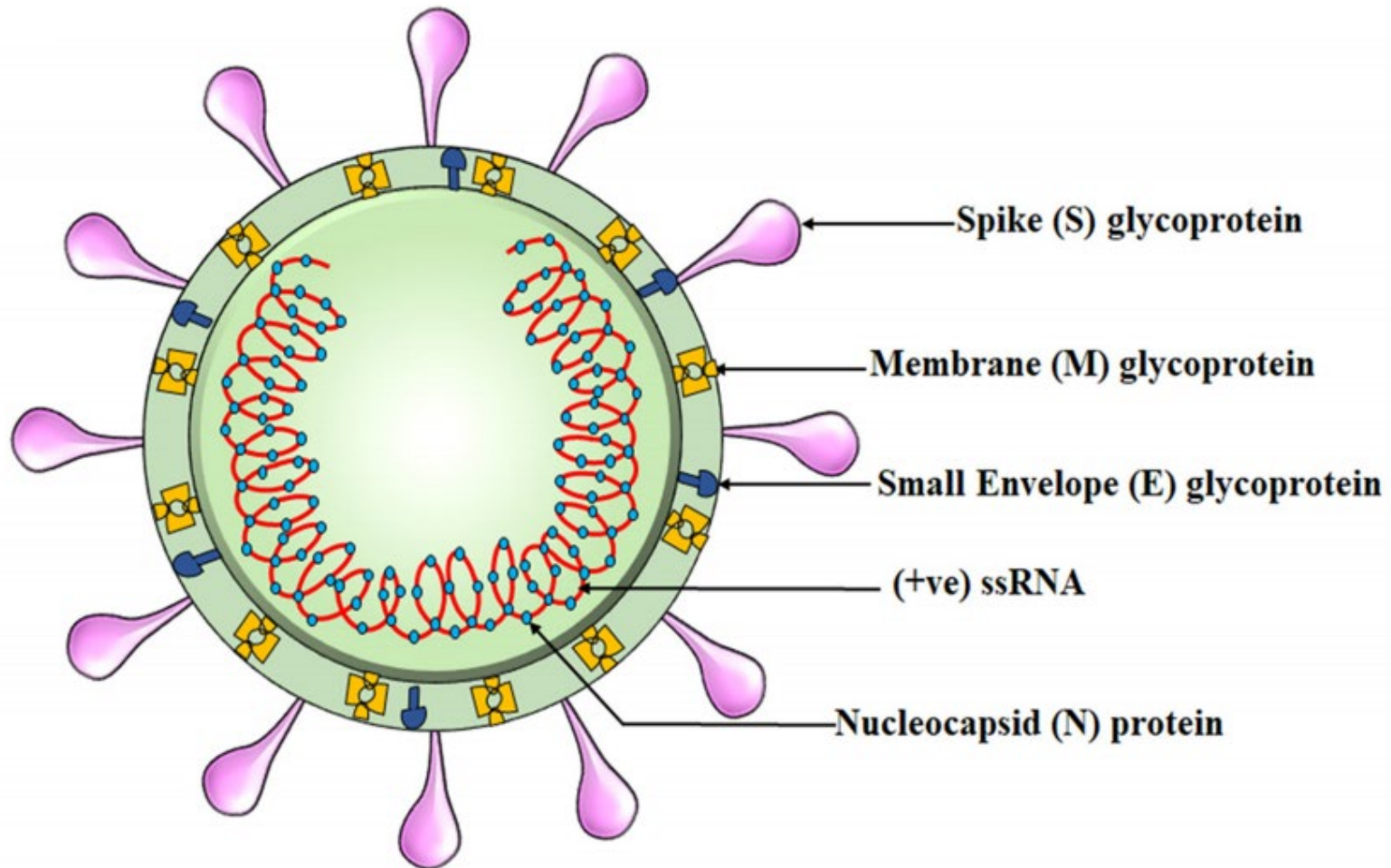
## CD8+ T cells

Lysis

Avidity



# SARS-2 VIRUS: Cause of COVID-19



# Vaccine Platforms Against SARS-2

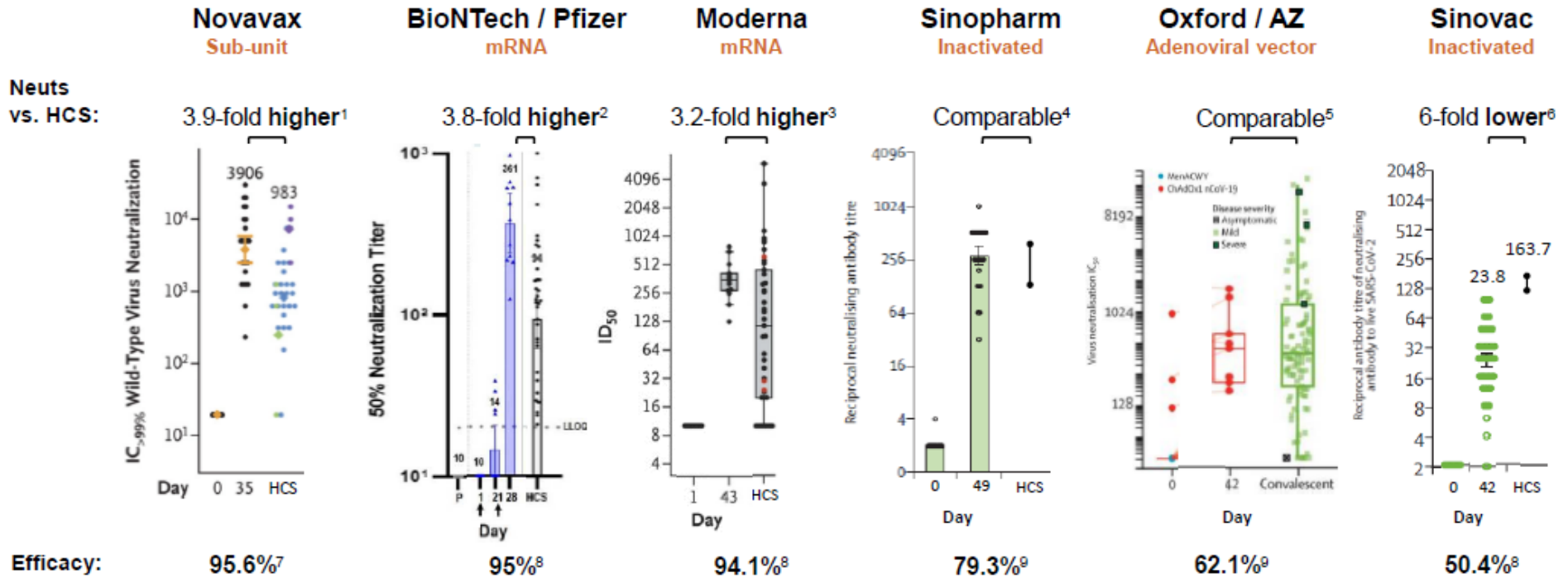
Technology	Candidates
Protein subunit	Clover Biopharmaceuticals Sanofi Pasteur and GSK Novavax Biological E U. Queensland
DNA	Inovio Pharmaceuticals
RNA	Imperial College London Curevac Moderna/NIAID Pfizer

# Vaccine Platforms Against SARS-2

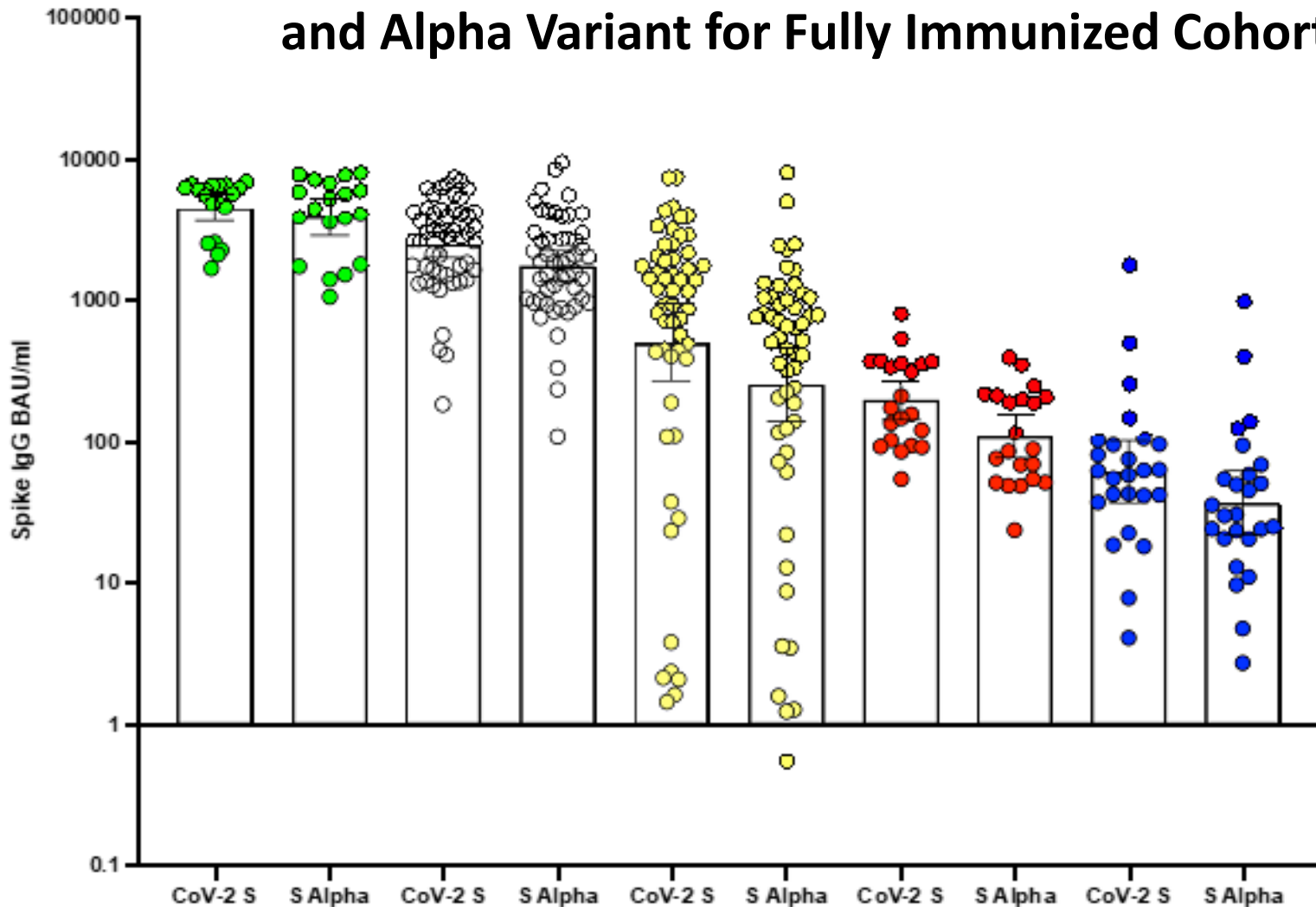
<b>Technology</b>	<b>Candidates</b>
<b>Inactivated</b>	<b>Sinovac</b>
<b>Live</b>	<b>Codagenix/Serum Institute of India</b>
<b>Vectors</b>	<b>Janssen (Ad 26) CanSino Biologics (Ad 5) University of Oxford (Ch Ad)</b>
<b>Measles vector</b>	<b>Institut Pasteur/Themis</b>
<b>VSV Vector</b>	<b>IAVI</b>

# Elevated neutralization titers in Ph I/II correlate with efficacy against ancestral SARS-CoV-2 strains

Note: Figures have been cropped / re-labeled as needed to enable comparison; Convalescent sera variably sourced from severe, moderate, mild disease and asymptomatic cases

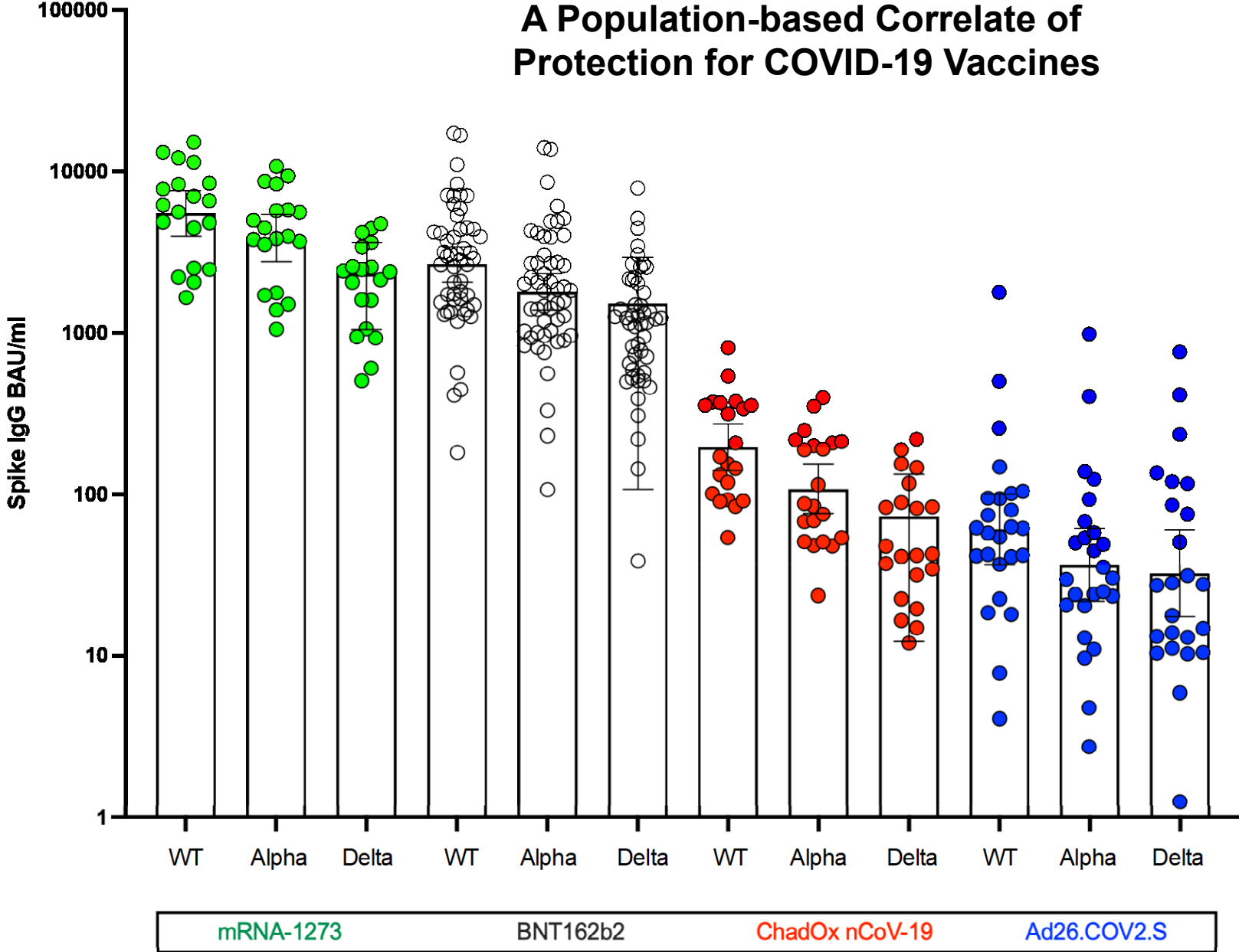


# Spike and RBD IgG Antibody to Original Virus and Alpha Variant for Fully Immunized Cohorts

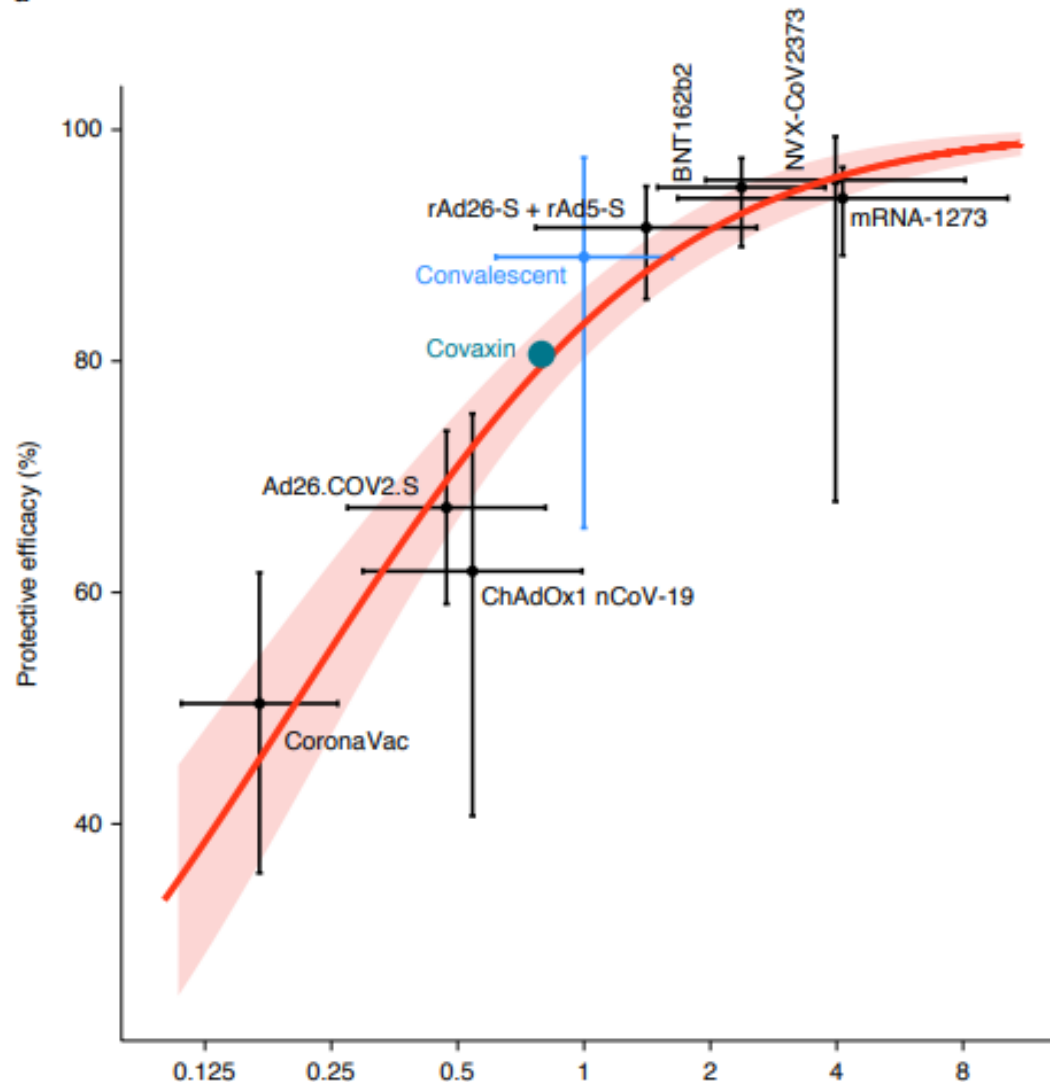


mRNA-1273    BNT162b2    NVX-COV2373    ChadOx nCoV-19    Ad26.COV2.S

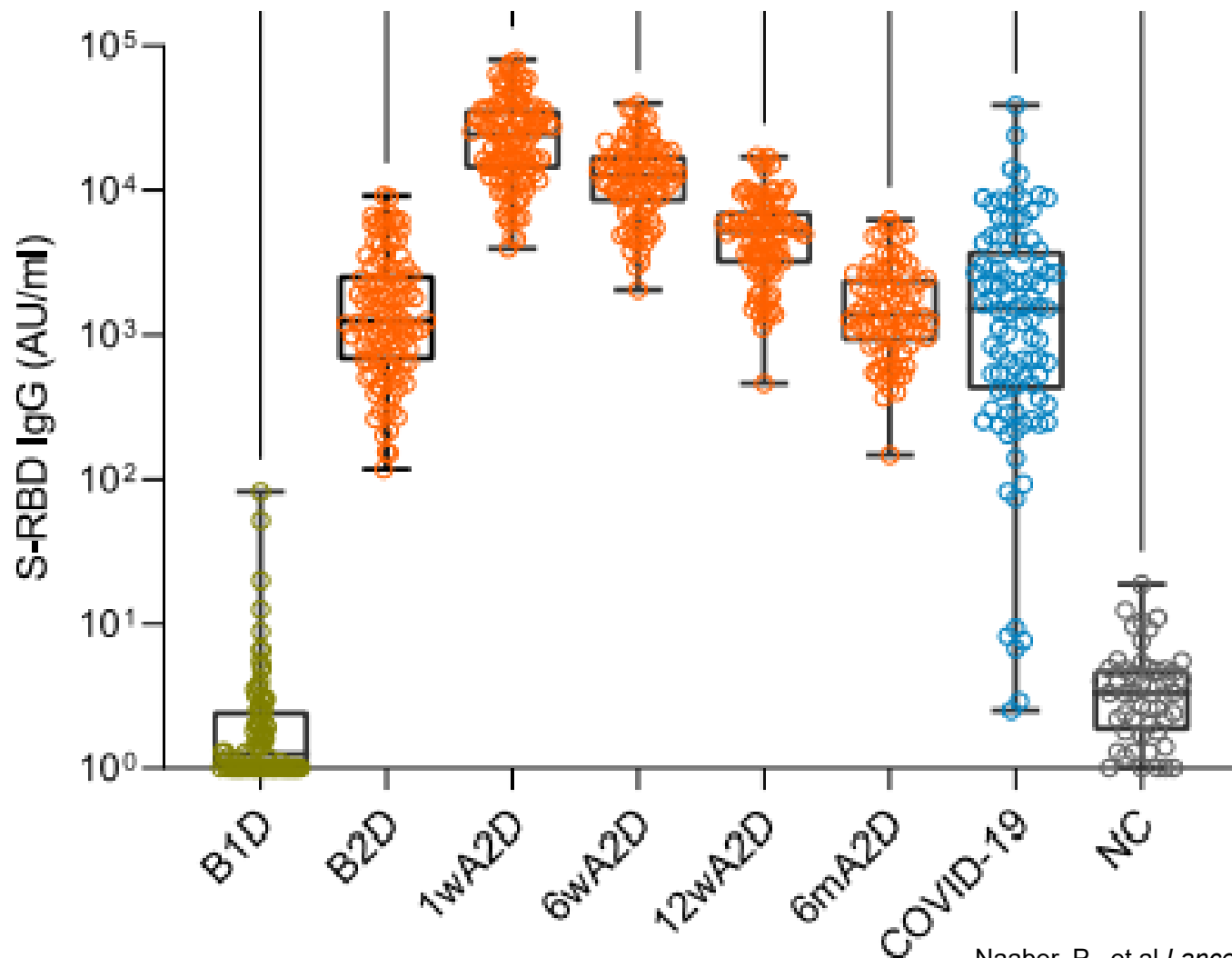
# A Population-based Correlate of Protection for COVID-19 Vaccines



# Mean neutralization level (fold of convalescent)

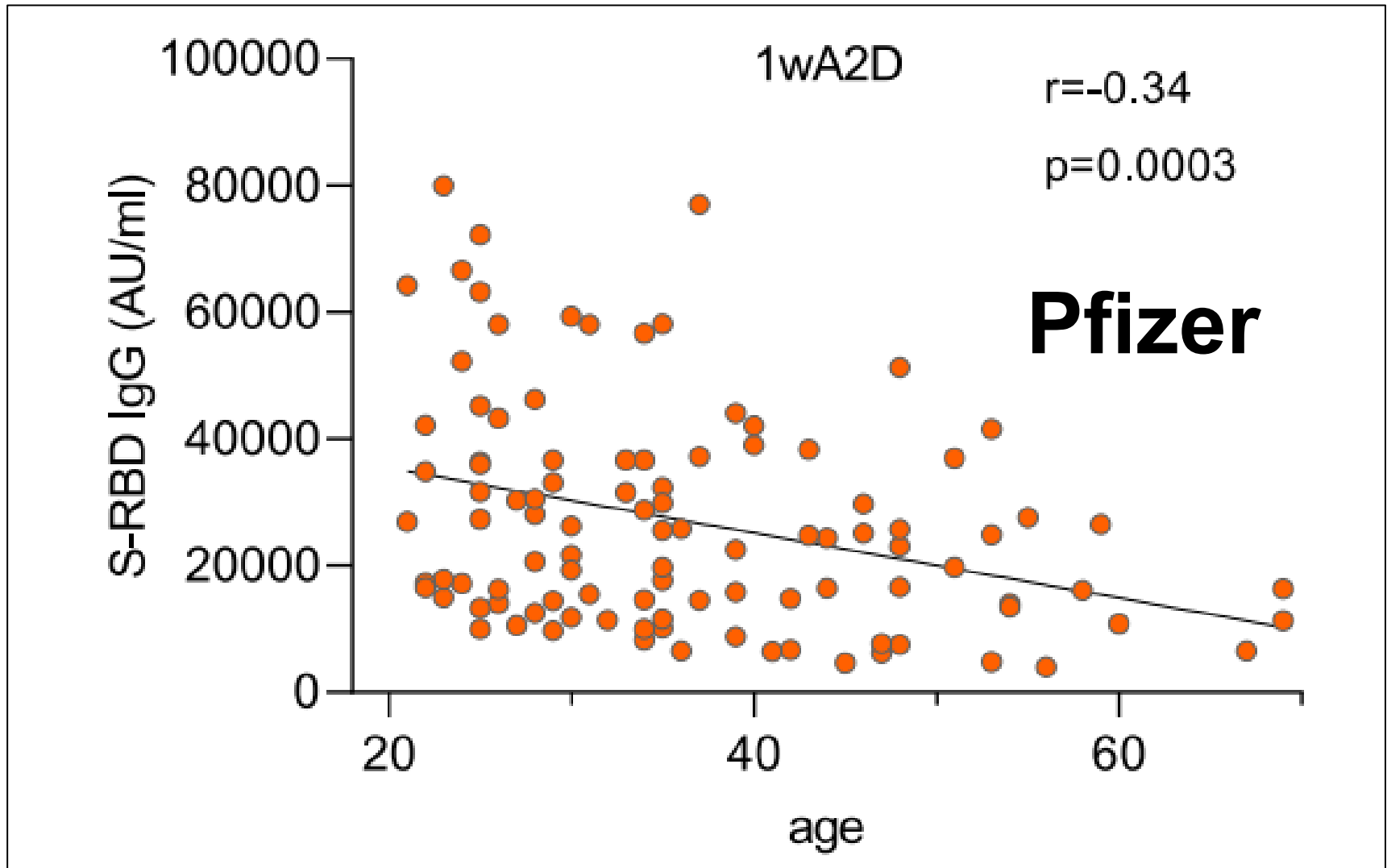


# Antibody responses in individuals vaccinated with Pfizer-BioNTech vaccine

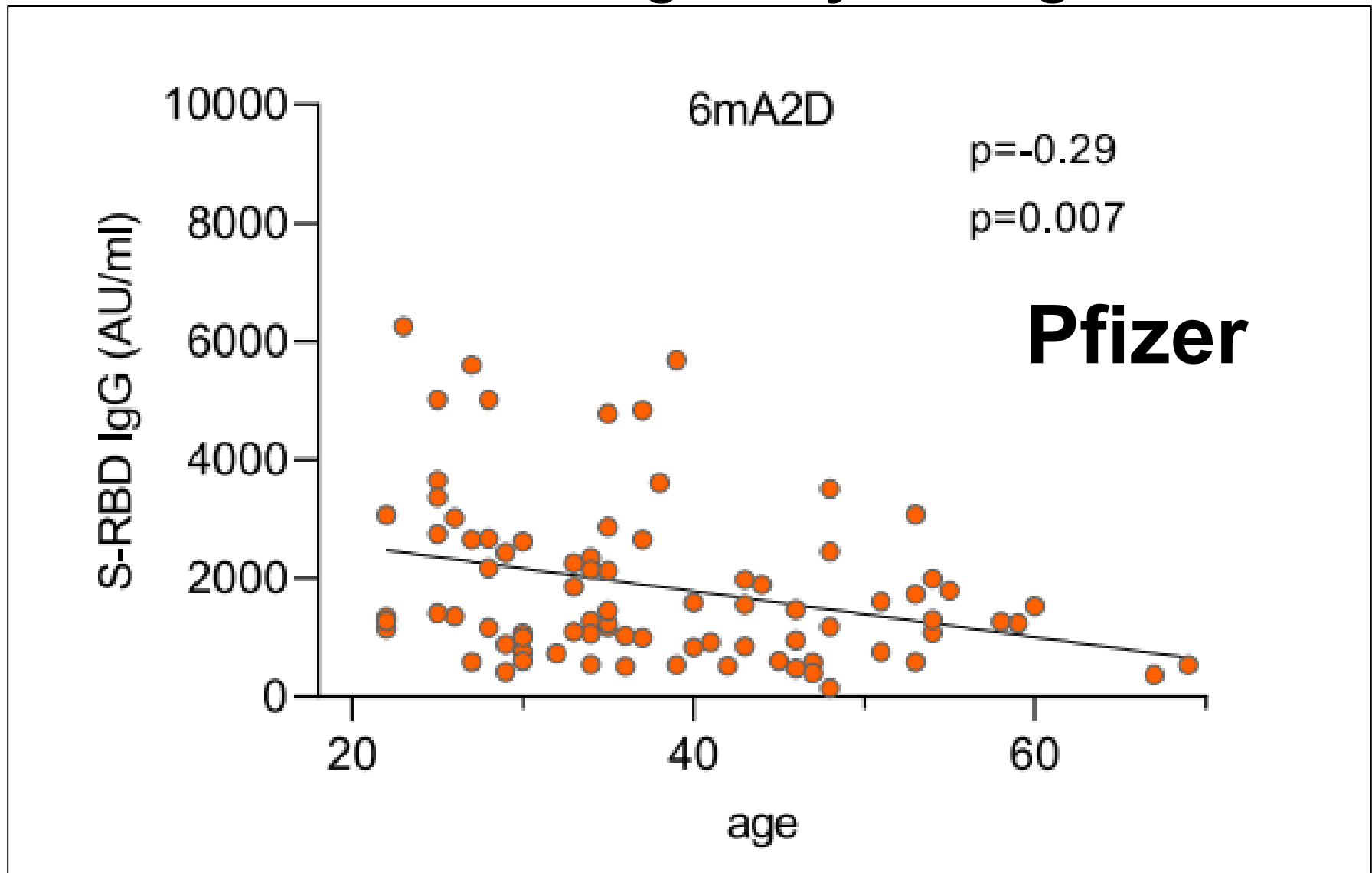




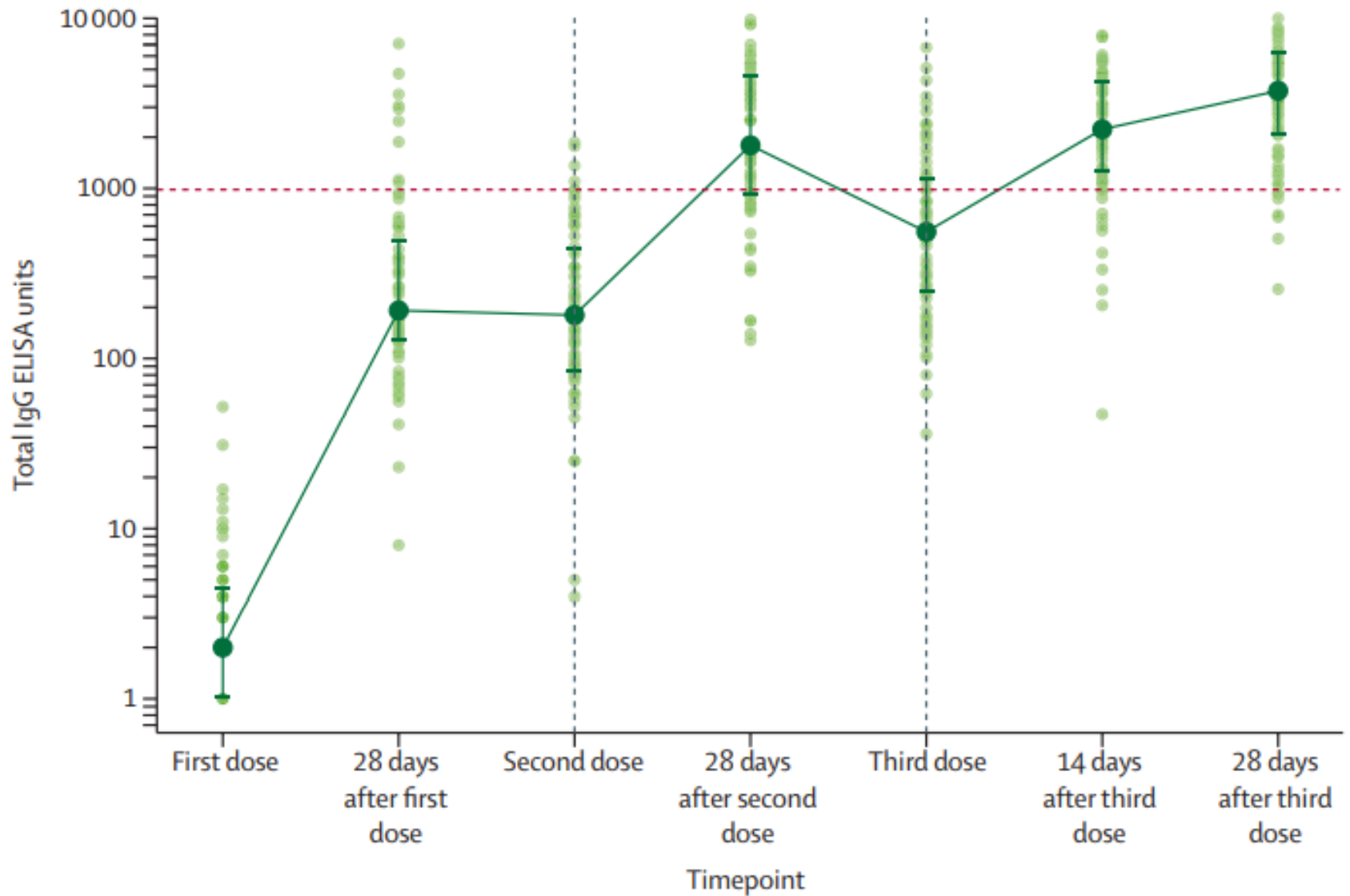
# Post-vaccination antibody responses correlate negatively with age



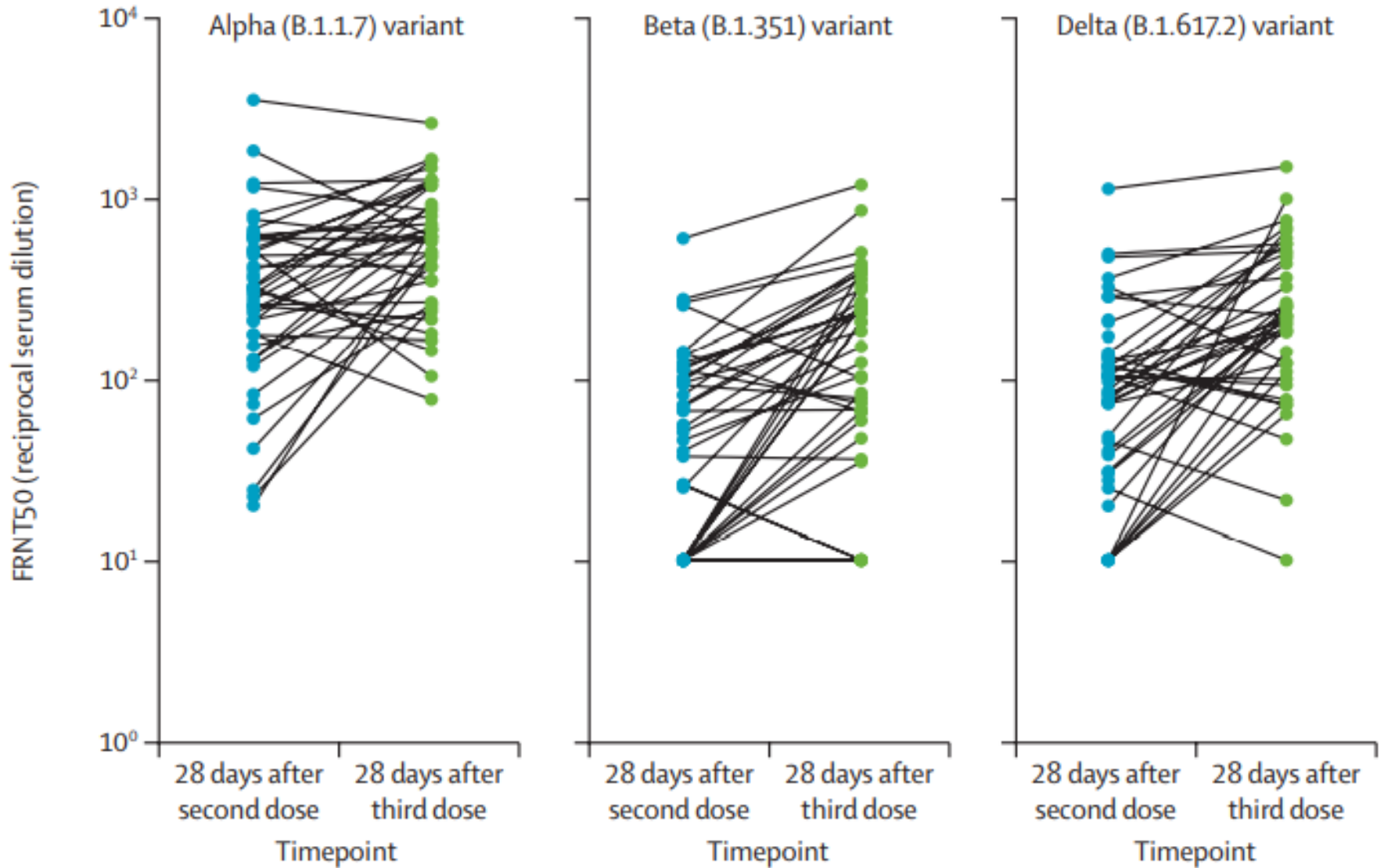
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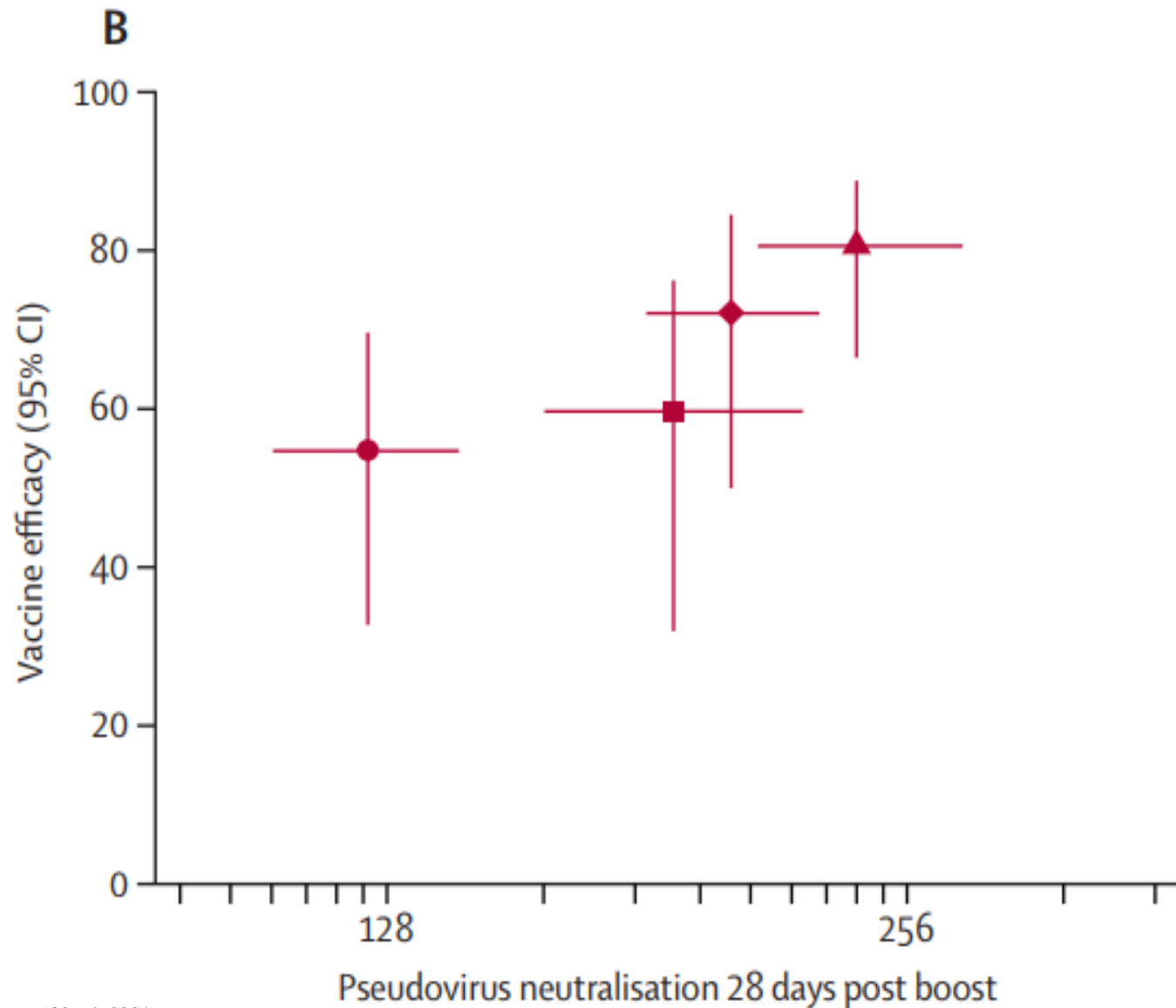
# Antibody responses in participants who received a third dose of ChAdOx1 nCoV-19



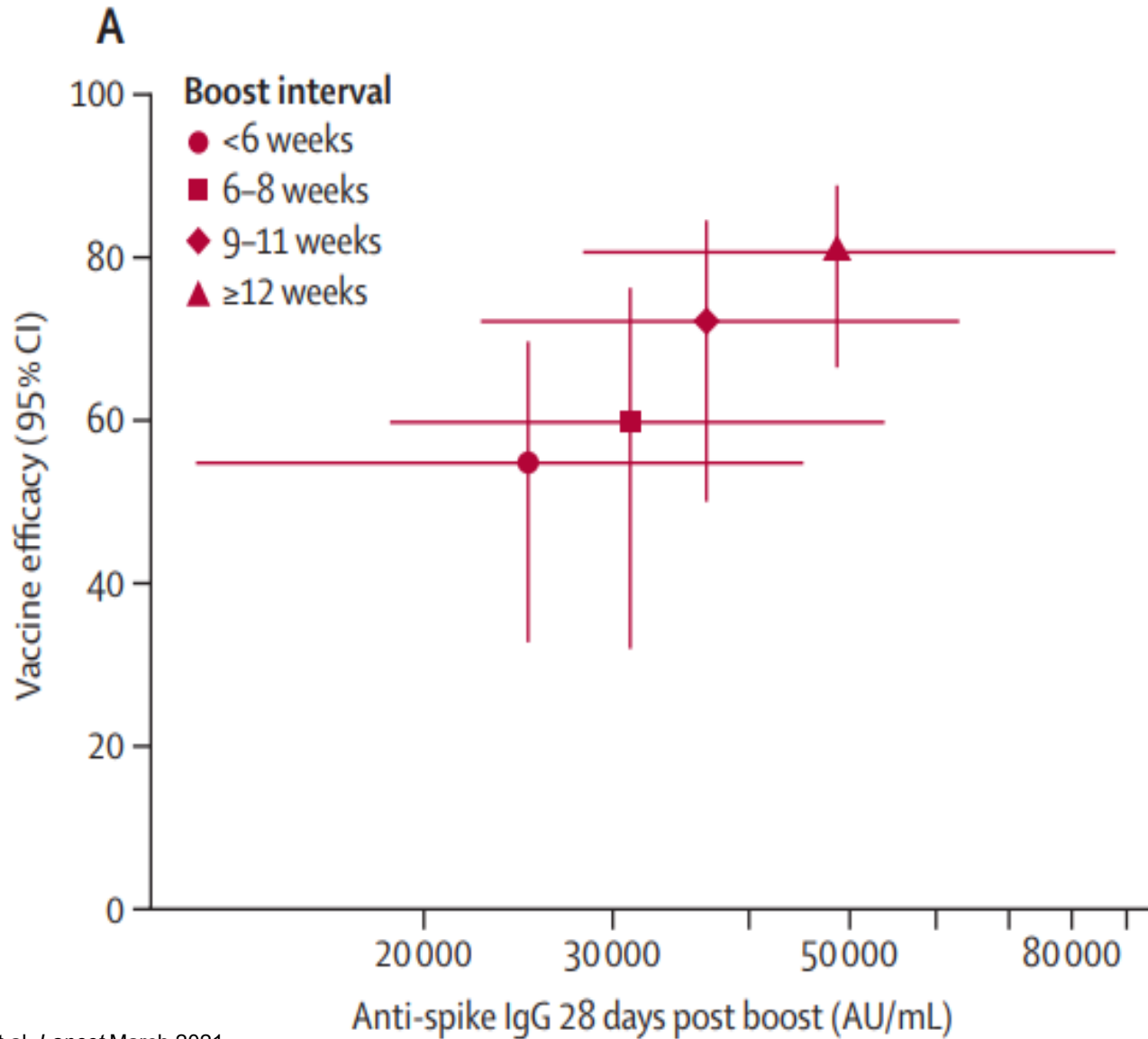
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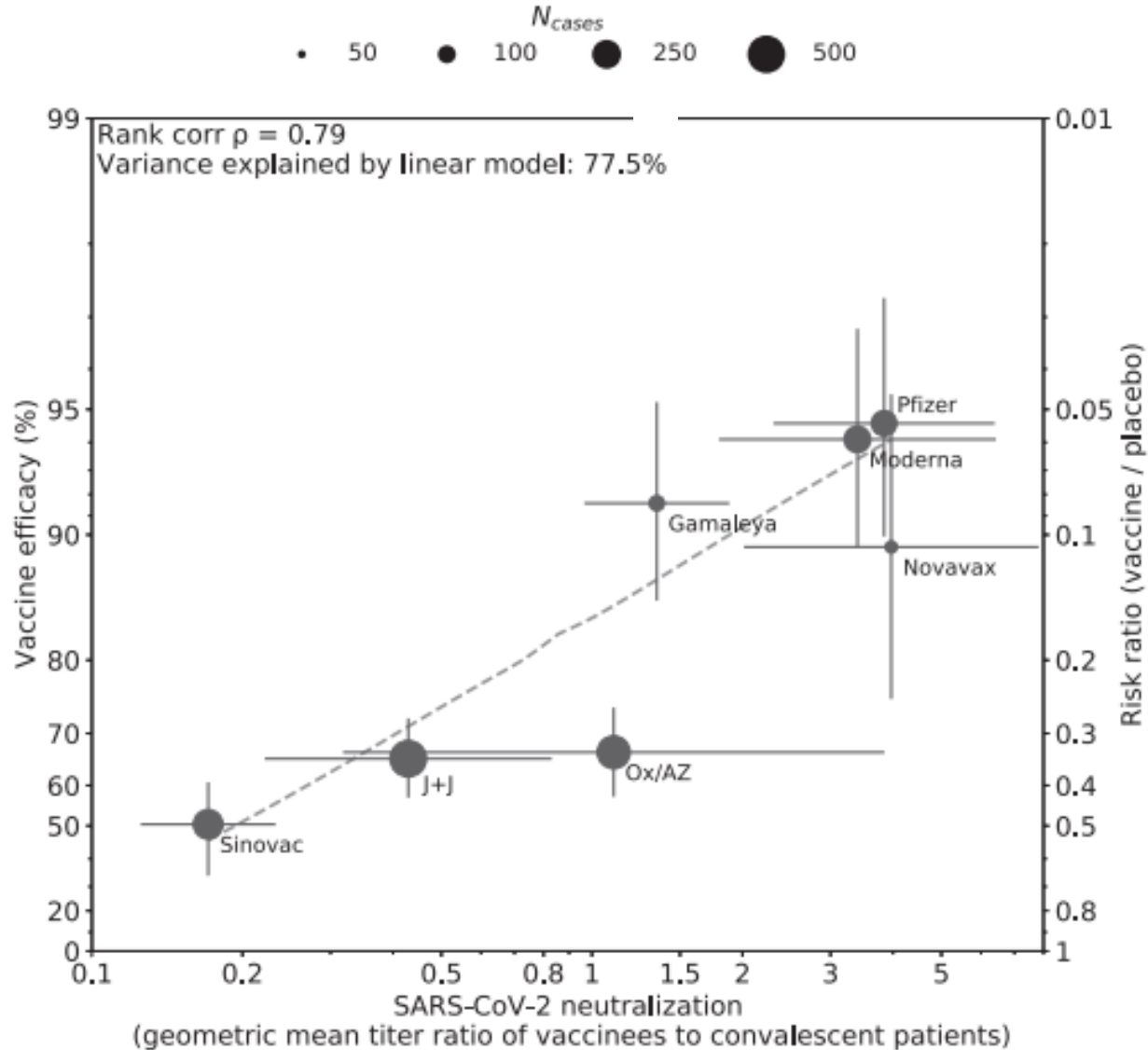
# Relationship between and neutralising antibody 28 days after second dose, and vaccine efficacy against primary symptomatic COVID-19



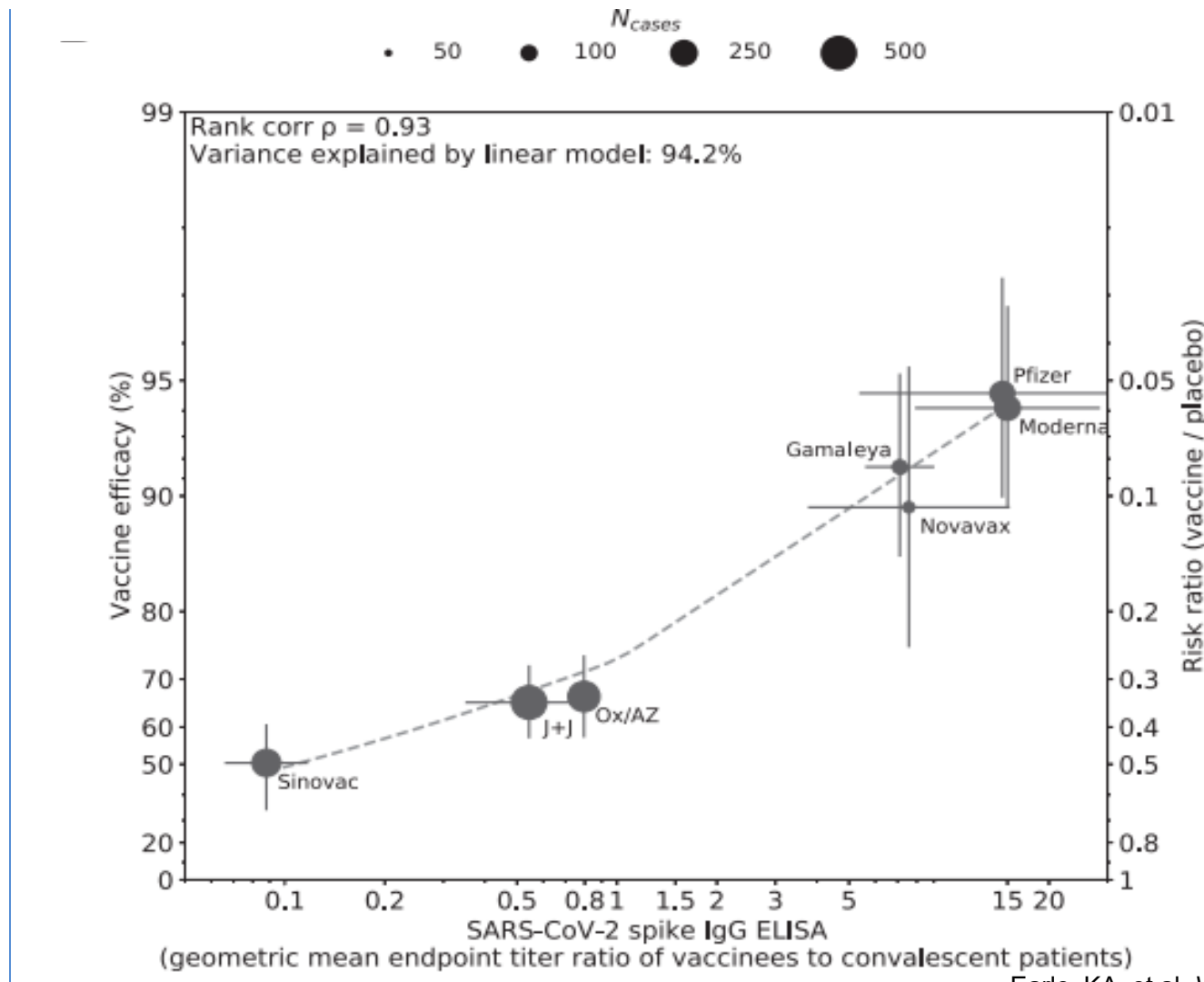
# Relationship between binding antibody 28 days after second dose, and vaccine efficacy against primary symptomatic COVID-19



# Correlation between antibody responses and efficacy rate

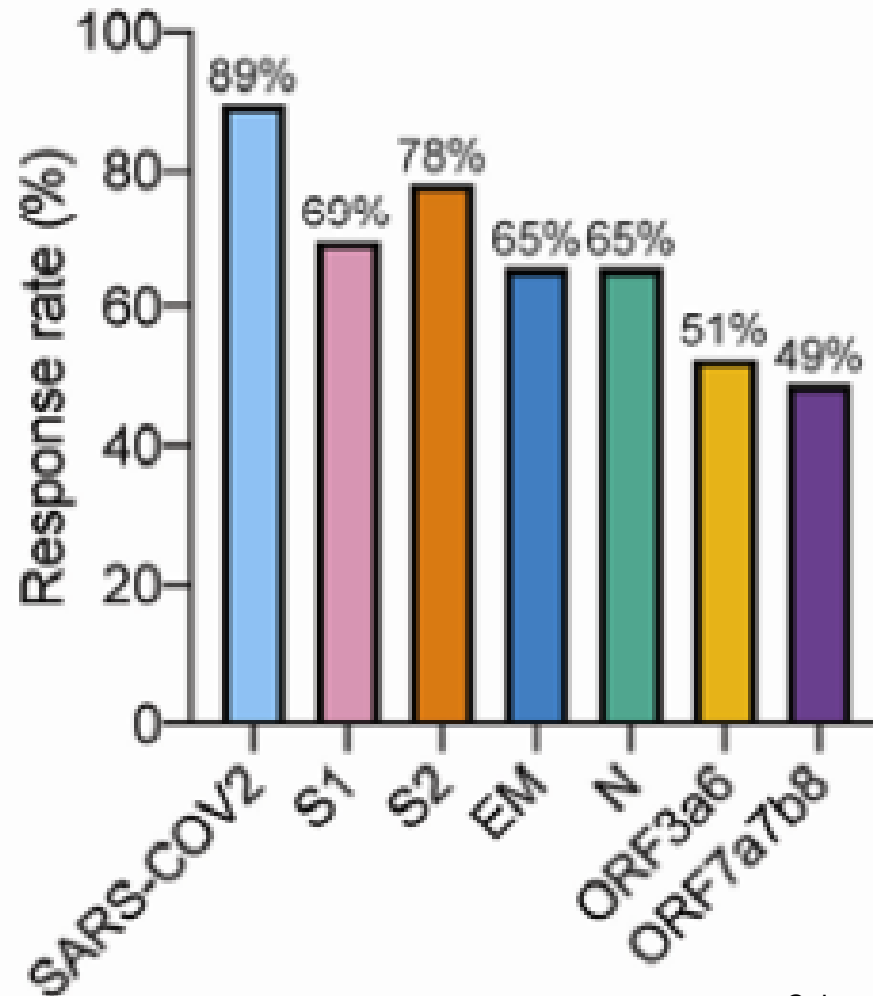


# Correlation between antibody responses and efficacy rate

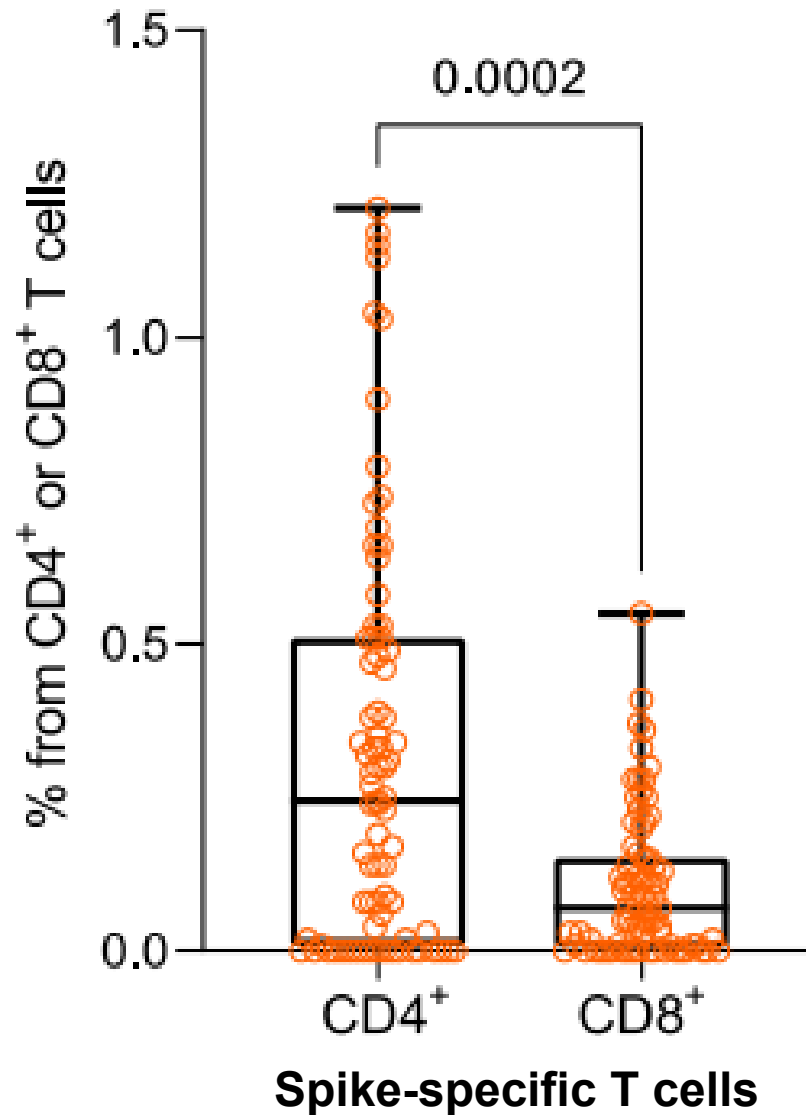




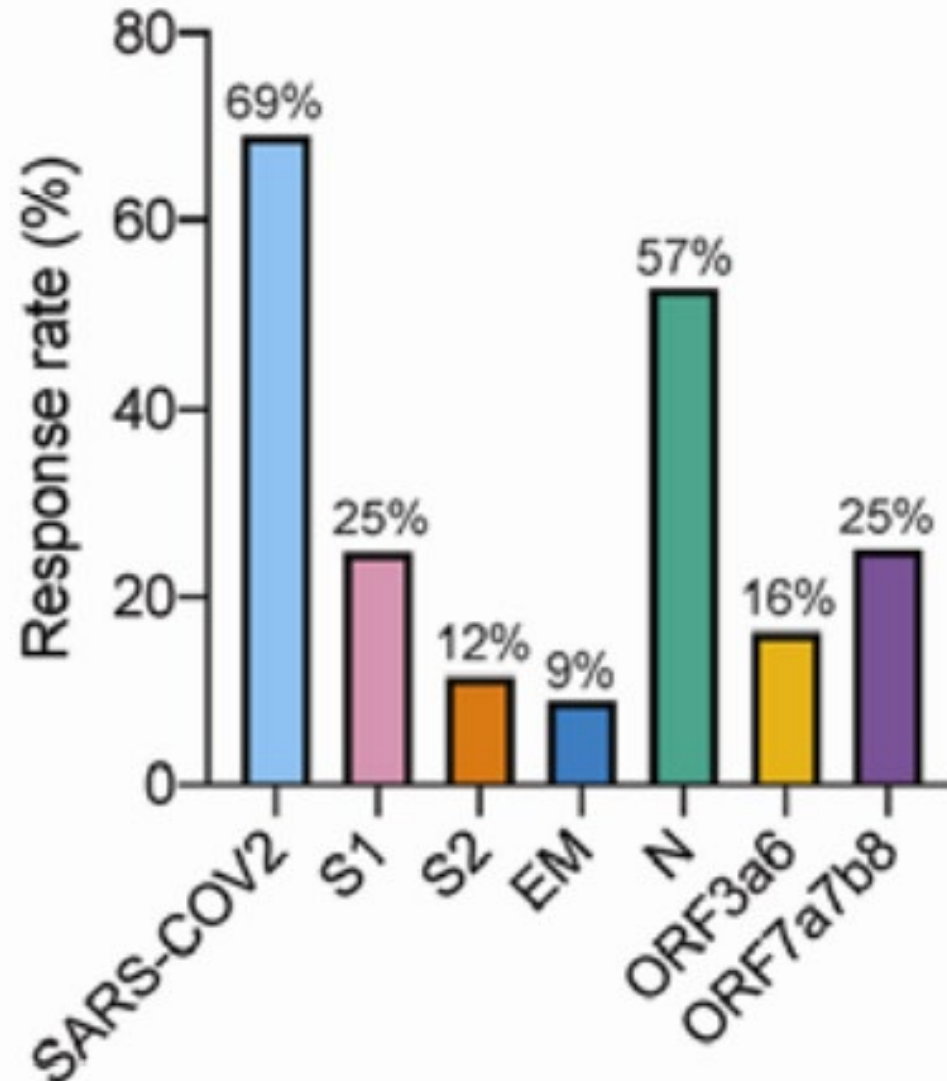
# CD4+ T cell responses to SARS-CoV-2 antigens.



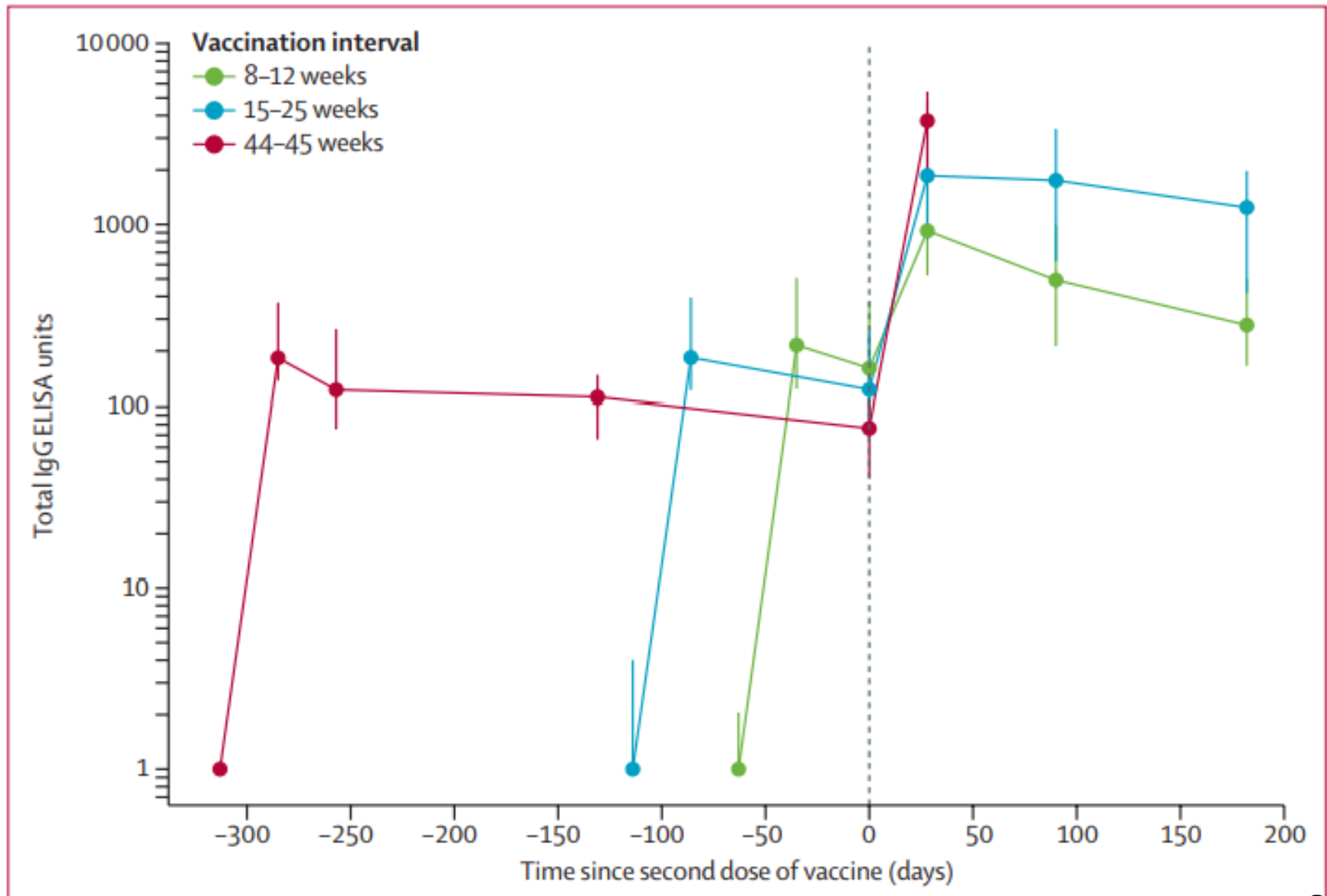
# Spike-specific T cell responses in vaccinated individuals 12 weeks after the second dose



# CD8+ T cell responses to SARS-COV-2 antigens.



# Antibody response by interval between first and second vaccination



# Known Unknowns (1)

Importance of T cell responses

Is RBD sufficient for antibody responses?

Duration of antibody responses

Induction of mucosal responses

# Known Unknowns (2)

Will the elderly respond to vaccine?

Will vector immunity become a problem?

Will decline in immunity lead to frequent infections?

Will Covid-19 become endemic?

Will SARS-2 continue to mutate?