

# SARS-CoV-2 Surveillance and Variant Analysis

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Co-lead, Laboratory and Testing Task Force

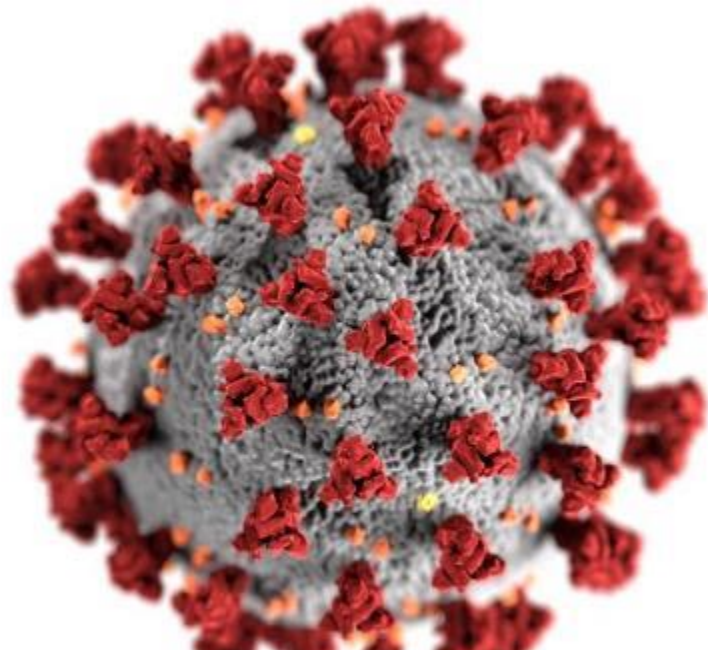
CDC COVID-19 Emergency Response

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Director, WHO Collaborating Center for Surveillance,  
Epidemiology and Control of Influenza

Influenza Division, NCIRD, CDC

NAIIS, 21 April 2022



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.



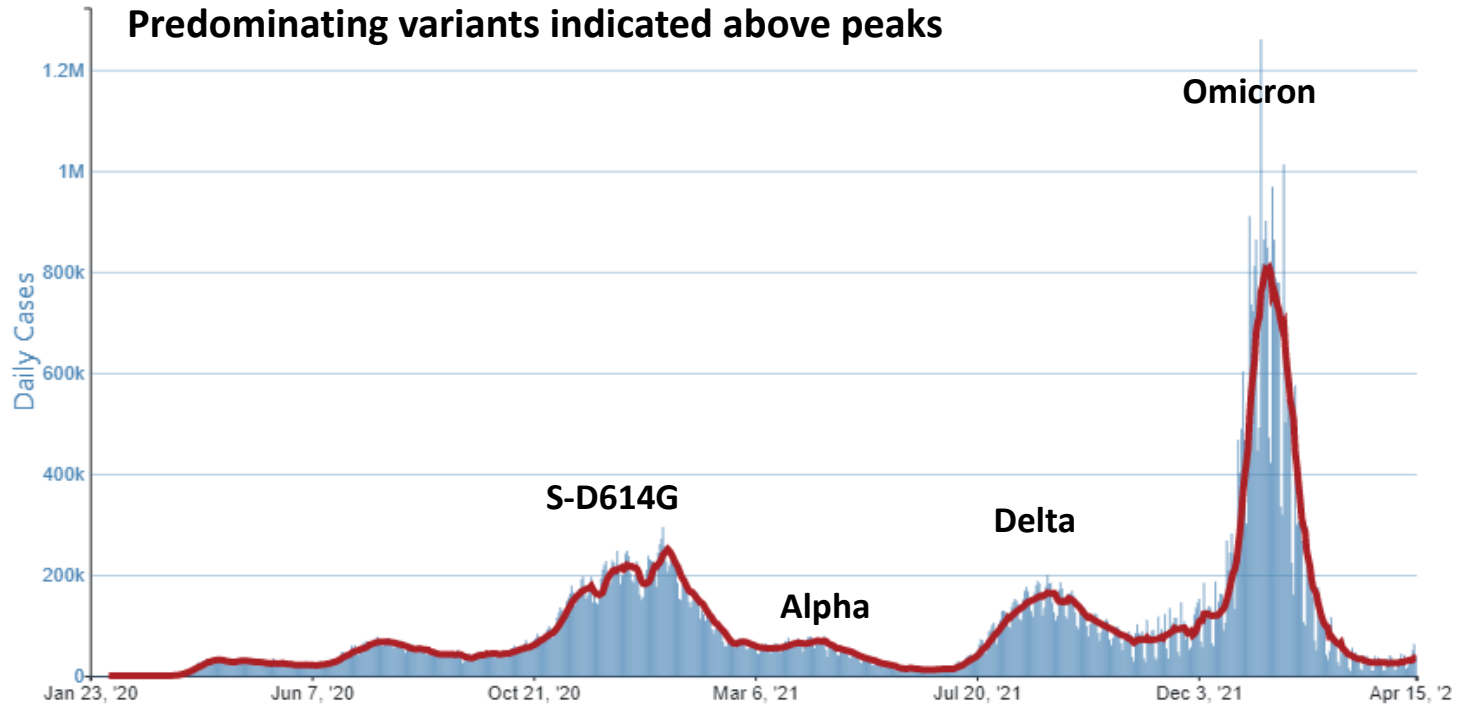
[cdc.gov/coronavirus](https://cdc.gov/coronavirus)

# CDC SARS-CoV-2 Surveillance

- **Goals:**
  - Identify and track variants circulating nationally and globally
  - Conduct risk assessment through genomics and virological characterization under appropriate biosafety
  - Reporting data internally and externally
  - Use the data to inform SARS-CoV-2 Interagency Group (SIG) recommendations to leadership for decision making
- **Surveillance systems in use (genotypic and phenotypic)**
  - Contract sequencing established to expand our data and data publicly available
  - NS3 and enhanced surveillance generates sequence data and provides representative specimens needed for characterization (key for genotype to phenotype analysis)
  - Continual analysis of viral genomic sequence (GISAID/GenBank)
- **Solution to a limitation**
  - Occasionally, variants are identified by sequence analysis, but there are no specimens available in the U.S. and it may take a long time to obtain representatives
  - Our solution is to engineer recombinant SARS-CoV-2 variants by reverse genetics



# Daily Trends in Number of COVID-19 Cases, United States



CDC COVID Data Tracker. [https://covid.cdc.gov/covid-data-tracker/#trends\\_dailycases](https://covid.cdc.gov/covid-data-tracker/#trends_dailycases) Accessed April 17, 2022



# National SARS-CoV-2 Genomic Surveillance

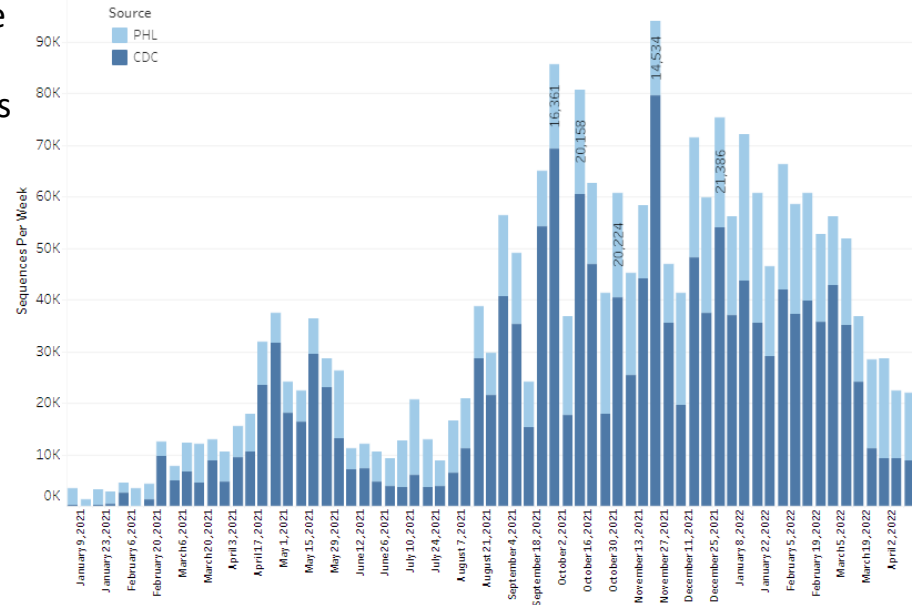
Three primary data sources (tens of thousands sequences weekly)

- Leading the National SARS-CoV-2 Strain Surveillance (NS3) system
- Partnering with commercial sequencing laboratories
  - Most have close ties to diagnostic laboratories
- Supporting state, territorial, local, and tribal health departments

## Additional data sources

- Partnering with universities
- Leading the SARS-CoV-2 Sequencing for Public Health Emergencies Response, Epidemiology, and Surveillance (SPHERES) Consortium
- Have established a tagging system to identify specimens that would be considered to meet surveillance criteria.

## SARS-CoV-2 Sequences Published

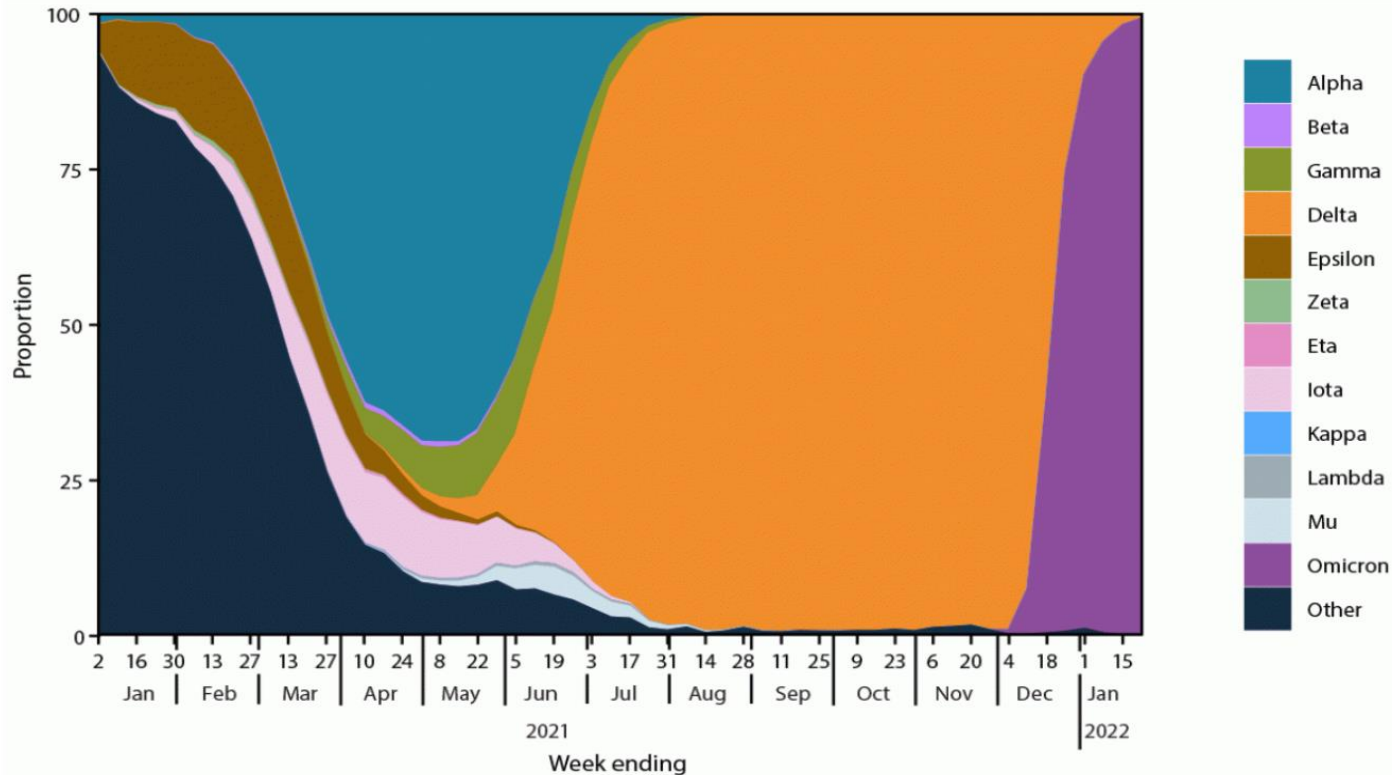


<https://www.cdc.gov/coronavirus/2019-ncov/variants/cdc-role-surveillance.html>

<https://covid.cdc.gov/covid-data-tracker/#published-sars-cov-2-sequences>

# Changing Landscape of Circulating Variants

FIGURE 1. National weekly proportion estimates\* of SARS-CoV-2 variants† — United States, January 2, 2021–January 22, 2022



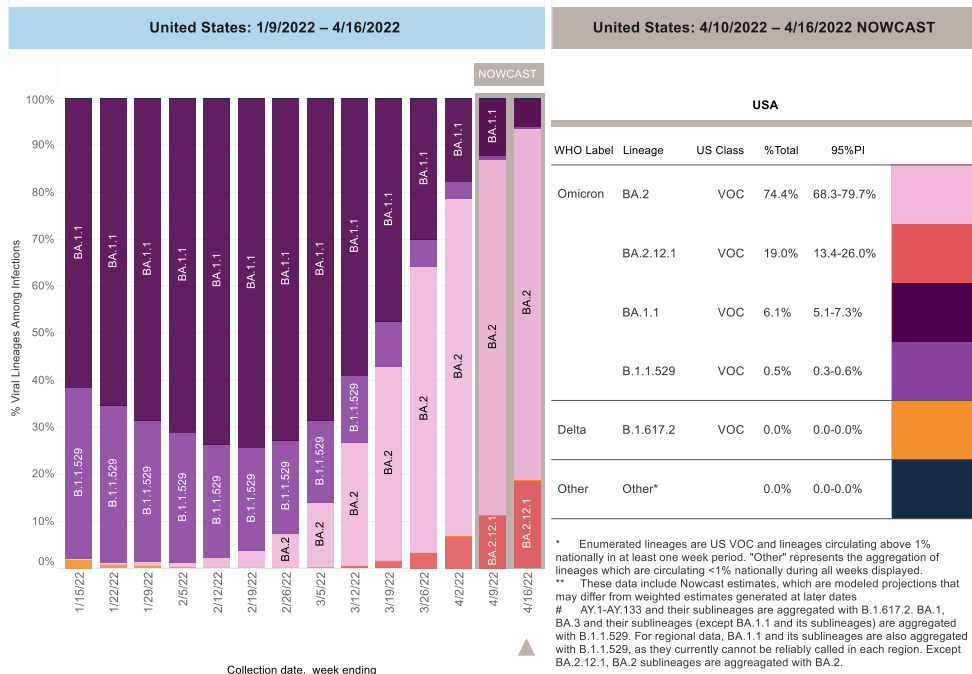
Lambrou et al. Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants — United States, June 2021–January 2022 <https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a4.htm>



# Estimates of SARS-CoV-2 Lineages Are Publicly Disseminated (CDC COVID Data Tracker)

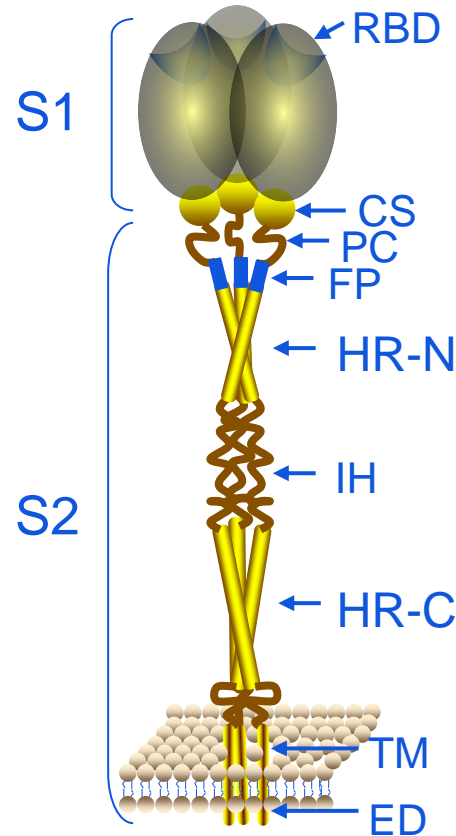
## Nowcast estimates (as of 04/16/2022)

- A tool to compensate for the time needed for next generation sequencing
  - Most data available 2-3 weeks after swab is collected
- A multinomial logistic regression model
  - Shows predicted proportion and 95% prediction interval
- Omicron is estimated at 100%
  - BA.2 (except BA.2.12.1) -> 75% (68-80% PI)
  - BA.2.12.1 -> 19% (13-26% PI)
  - BA.1.1 -> 6% (5-7% PI)

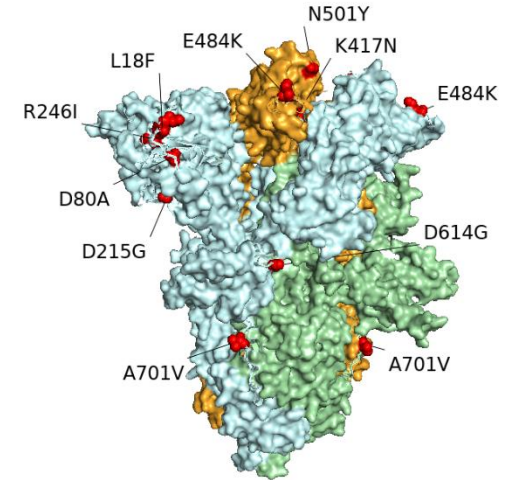


# Coronavirus Spike (S)

- “Corona” appearance
- Receptor binding (S1, RBD)
  - Host range
  - Transmission
  - Pathogenesis
- Membrane fusion (S2)
  - Induced by infection and/or vaccination



**B.1.351 Variant Spike**  
Substitutions from (Wuhan-Hu-1) Shown in Red



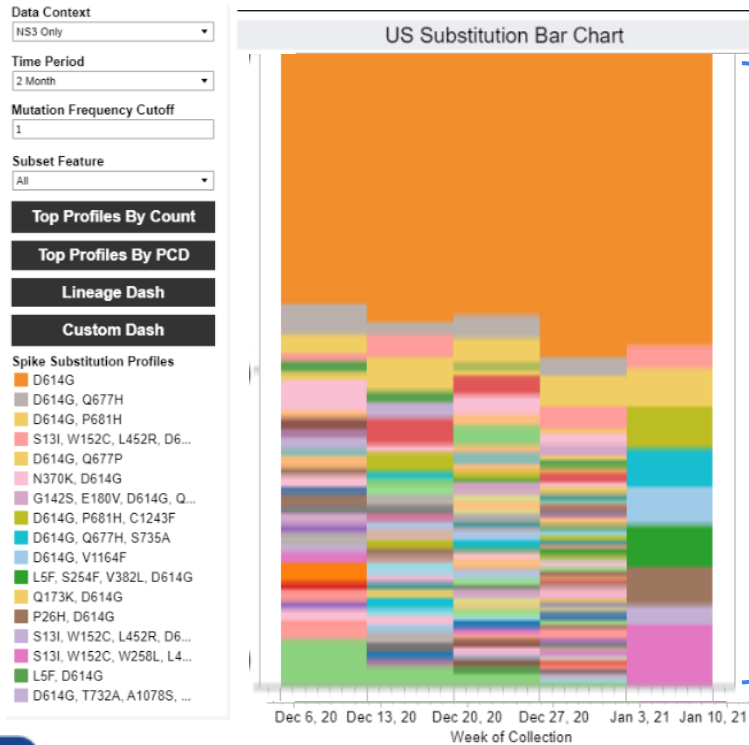
**Homomer (trimer)**

SWISS-MODEL to  
PDB: 7DK3

Coronavirus binding and entry  
DE Wentworth, KV Holmes - 2007



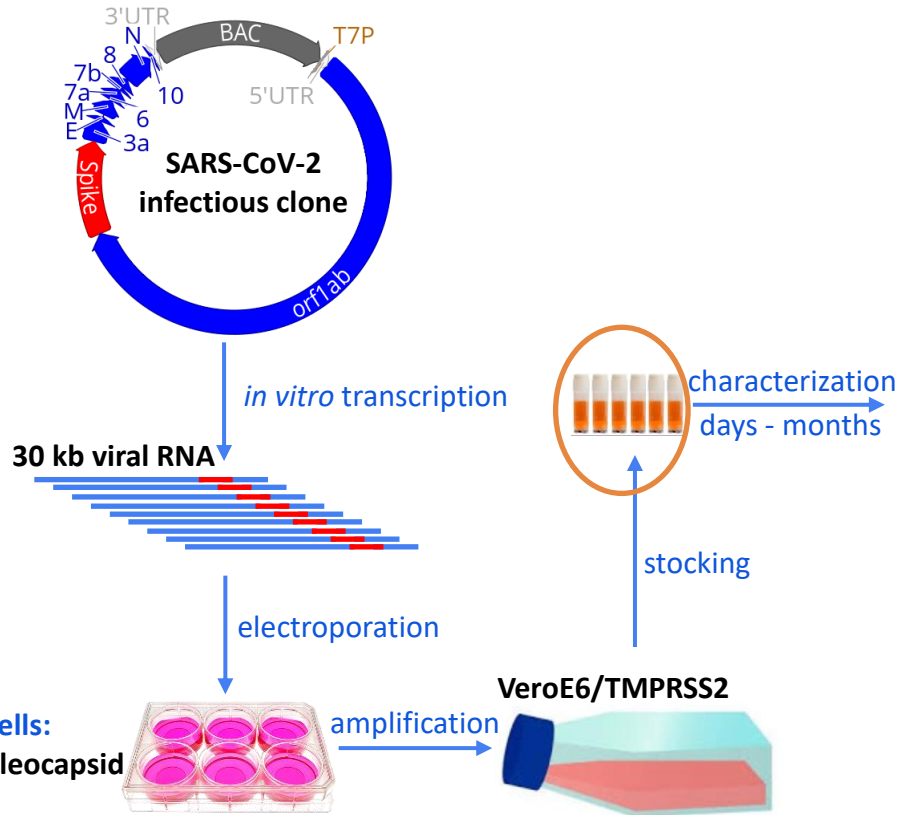
# Virus Characterization: Genotype to Phenotype Analysis (via NS3)



- Representative viruses selected
- Virus isolation and propagation
  - Sequencing of stock viruses
  - Titration of stock viruses
- Antigenic characterization
  - Virus neutralization assays
  - Comparative reactivity with antisera (community infected, vaccinated)
- Subsets used for additional phenotypic analysis
  - In vitro replication (various cell types)
  - In vivo studies
    - Transmission/pathogenesis
    - Immune protection



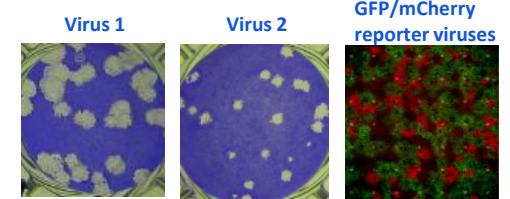
# Specific Variants Obtained from Swabs or by Developing Recombinant SARS-CoV-2 Viruses



CDC made cells:  
VeroE6/Nucleocapsid



## Plaque assay (WT & reporter viruses)

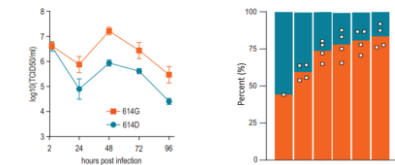


## Antigenicity (e.g. PRNT, FRNT)



Inhibition of SARS-CoV-2 by a DSR developed mAb

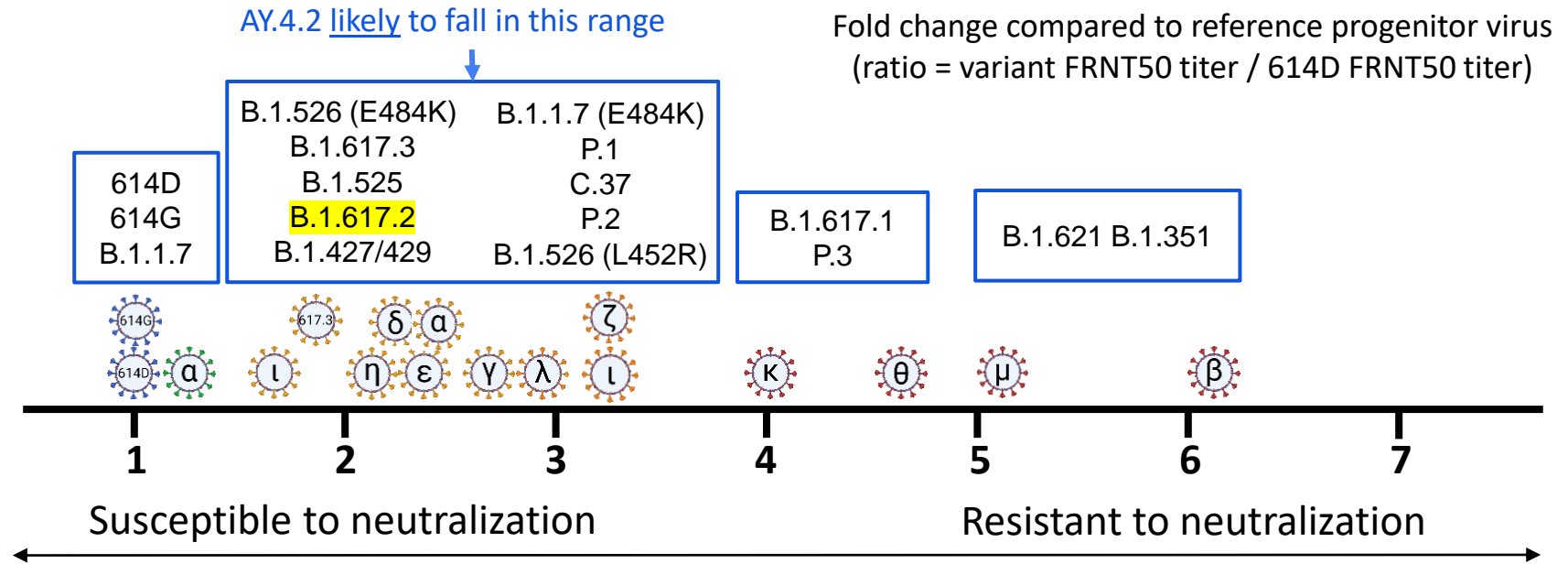
## Replication fitness ?



## Pathogenicity & transmissibility ?



# Antigenic Ranking of rSARS-CoV-2 Variants Generated by Reverse Genetics Prior to Omicron

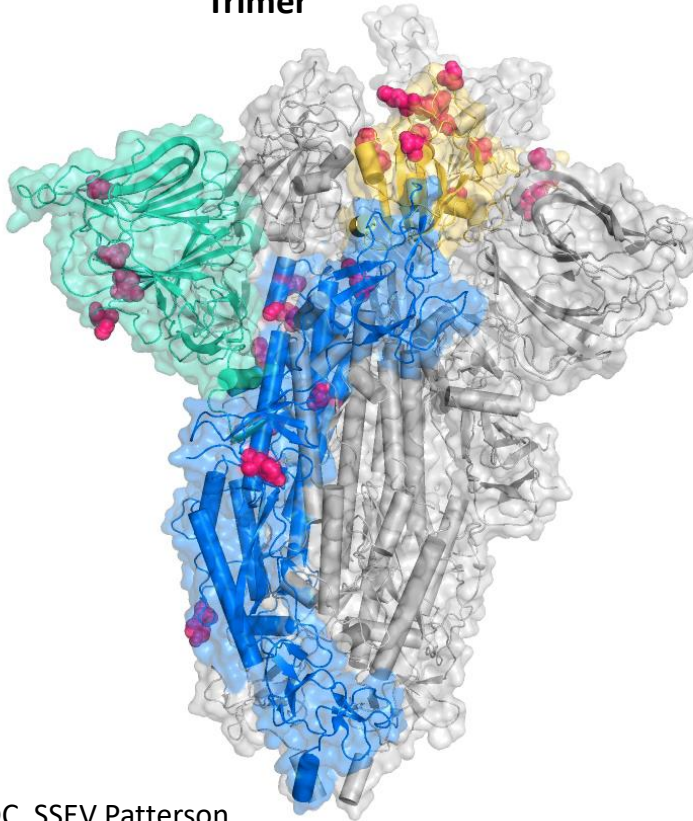


Graph is only for comparing variants to 614D reference virus (set as 1-fold). If comparing between two variants, don't be misled by the linear scale of the axis, e.g., the FRNT50 ratio of B.1.351/B.1.621 is only 1.2-fold, very small difference



# In silico Analysis to Infer Impact Genetic Changes (e.g., Omicron spike)

Trimer



*Preliminary  
Analysis  
12/02/2021*

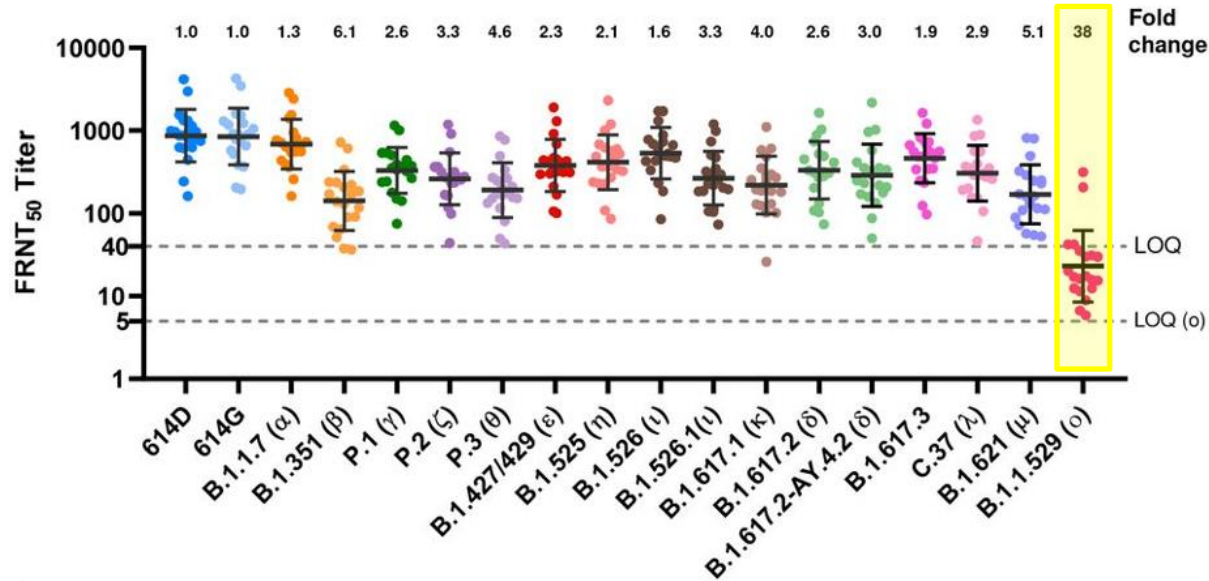
*N679 and P681  
Not visible*

CDC, SSEV Patterson

Has substitutions, insertion, and deletions

- S mutations likely to increase transmission:
  - Increase binding to hACE2 (e.g., N501Y)
  - Fusion
    - S1/S2 cleavage site changes (H655Y, N679K, P681H)
- Changes in multiple epitopes (RBD and NTD), anticipate reduced neutralization by:
  - Therapeutic antibodies
  - Polyclonal antibodies induced by natural infection or vaccination (e.g., E484, G446, K417, and Q493)
- Insertion and deletions in S gene
  - Del 69/70 may lead to target failure in some rt-RTPCR assays
  - In/Del in NTD likely reduce neutralization

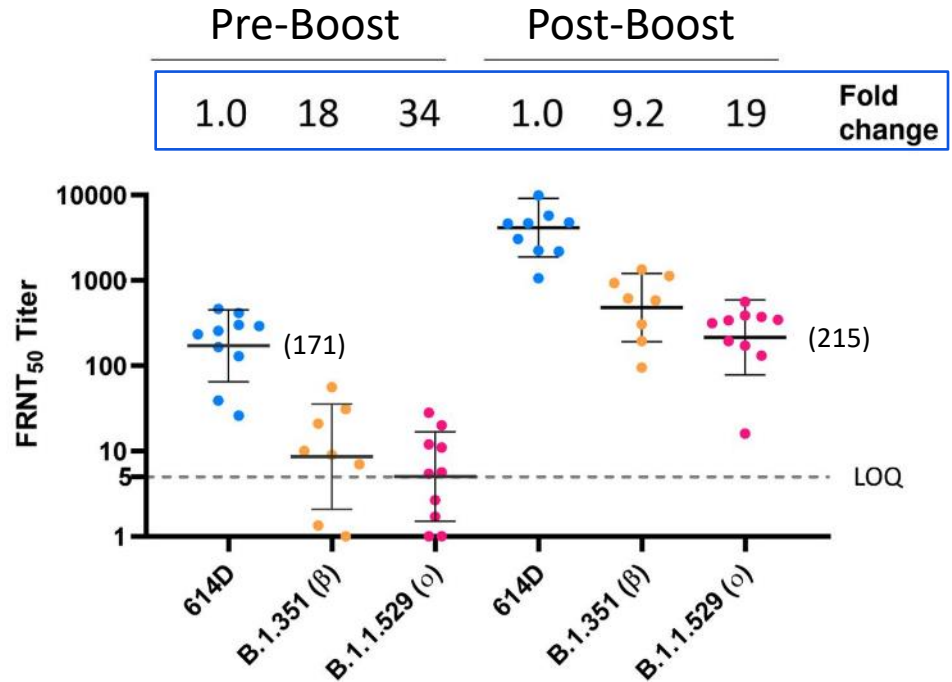
# Comparison of Neutralization Profile of Human Post Vaccination Sera (mRNA vaccines)



- Omicron recombinant reporter virus shows significant escape from neutralization (38-fold) using Focus Reduction Neutralization Test (FRNT)
  - Much lower than Beta (6-fold), the variant of concern (VOC) that previously had the greatest antigenic difference from the vaccine antigen

# Comparing Neutralization Profiles of Sera Collected pre- and post-boost (mRNA vaccines)

- Omicron (BA.1.1.529)
  - Pre-boost
    - Geometric mean titer (GMT) is very low (GMT=5) and 34-fold reduced compared to 614D (GMT=171)
  - Post-boost
    - GMT increases to 215 and is similar to 614D pre-boost (171)
    - 19-fold reduction compared to G614D post-boost (GMT=4,152)



\*Post-boost sera were collected 2-to-6 weeks post boost vaccination (5 Moderna and 5 Pfizer). The average fold changes of natural isolates relative to reference virus 614D (set as 1-fold)



# Acknowledgements: SSEV Team Members

## SSEV Management

- **David Wentworth**
- **John Barnes**
- Juliana DaSilva
- Nicole Paterson
- Richard Stanton
- Jenifer Perkins

## NS3- NGS

- **Justin Lee**
- Mili Sheth
- Mark Burroughs
- Sarah Nobles
- Jasmine Padilla
- Morgan Davis
- Lex Burgin
- Meghan Bentz
- Joe Madden
- Malania Wilson
- Matthew Keller
- Lisa Keong
- David Owuor

## Bioinformatics

- **Rebecca Kondor**
- **Clint Paden**
- Jason Caravas
- Peter Cook
- Nicholas Kovacs
- Brian Mann
- Normal Hassell
- Dakota Howard
- Tymeckia Kendell
- Thomas Stark
- Yamundow Camara
- Ben Rambo-Martin
- Kristine Lacek

## Molecular Virology

- **Bin Zhou**
- Li Wang
- Gaston Bonenfant
- Jaber Hossain
- Masato Hatta
- Nannan Jiang
- Xudong, Lin
- Brenda Calderon
- Sarah Osman
- Gloria Larson
- Esther Morantz
- Dan Cui
- Yasuko Hatta
- Ginger Atteberry
- Yu-Jin Jung
- Michael Currier
- Cindy Adolphus

## Phenotypic

### Characterization

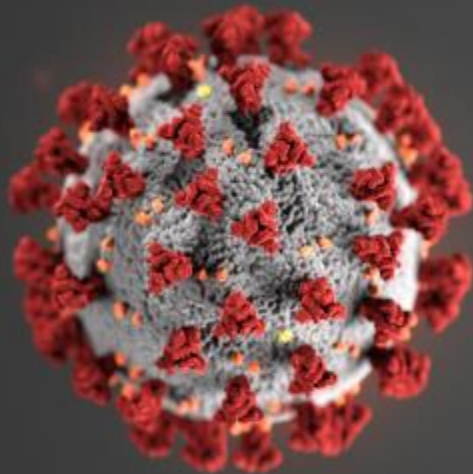
- **Todd Davis**
- Joyce Jones
- Han Di
- Natosha Zanders
- Elizabeth Pusch

### Ferret Studies

- **Taronna Maines**
- Joanna Pulit-Penalzoa
- Jessica Belser
- Xiangjie Sun
- Claudia Pappas
- Nicole Brock
- Hui Zeng
- Troy Kieran
- Poulami Thakur

## Virus Culture and Neutralization

- **Natalie Thornburg**
- Lydia Atherton
- Jennifer Harcourt
- Mohammad Ata Ur Rasheed
- Azaibi Tamin
- Christine Warnes



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

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