Novel Coronavirus (COVID-19): An Update

Presentation to the 20th Meeting of the Clinical Center Research Hospital Board National Institutes of Health

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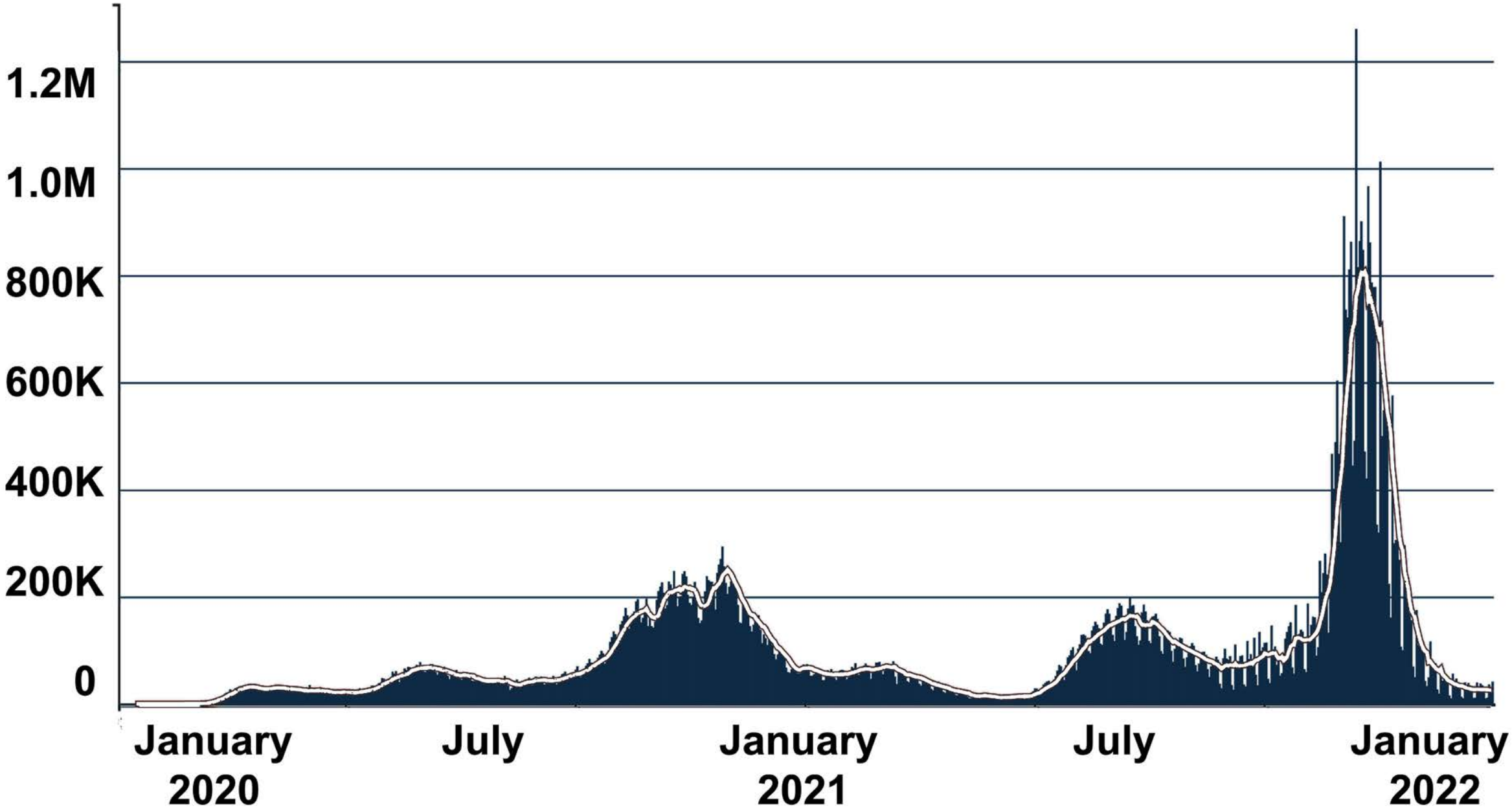
Clinical Director
Deputy Director for Clinical Research and Special Projects
NIAID, NIH
April 1, 2022

US COVID-19 Cases as of March 30 2022



Outline of the Presentation:

- Updates from the prior presentation on:
  - Organizational structure
  - Pathogenesis
  - Diagnostics
  - Therapeutics and Treatment Guidelines
  - Prevention
  - Post-acute Sequelae of COVID-19 (PASC)

Andy Slavitt was the House Senior Advisor on the COVID-19 response

Jeff Zients Will be Leaving the White House Coronavirus Response Coordinator Position Later this Month

Dr. Ashish Jha Will Take Over as White House Coronavirus Response Coordinator

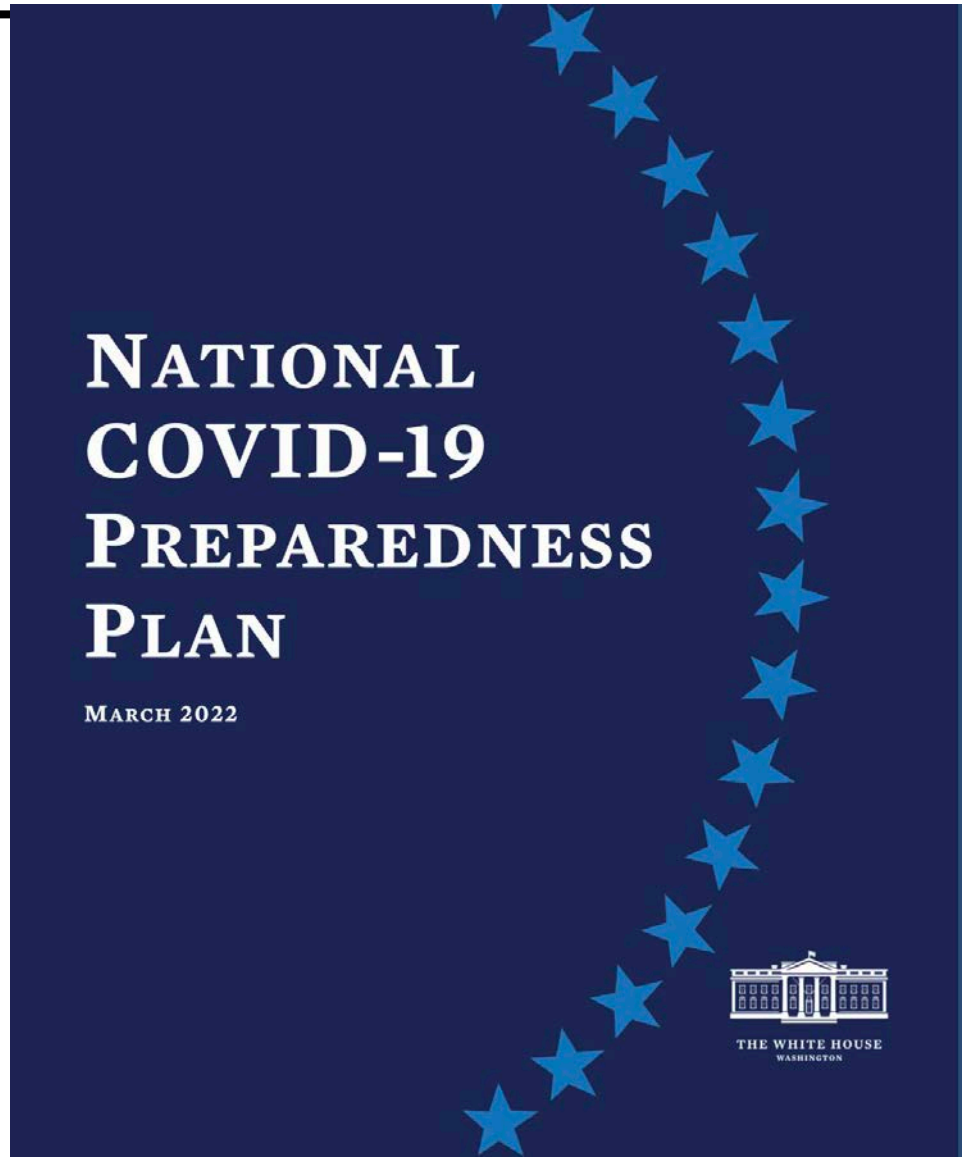
- Currently the Dean of Brown University's School of Public Health
- Appointment scheduled to begin April 5, 2022
- In announcing the appointment, President Biden noted: "Dr. Jha is one of the leading public health experts in America, and a well-known figure to many Americans from his wise and calming public presence. "

Transition of Operation Warp Speed (OWS) to HHS Coordination Operations and Response Element (H-CORE)

- On December 31, 2021, the Memorandum of Understanding between HHS and DOD expired.
- On January 1, 2022, HHS completed the transition of OWS work to the recently established HHS Coordination Operations and Response Element, or HCORE.
  - Comes out of the office of the Assistant Secretary for Preparedness and Response (ASPR, Dawn O'Connell)
  - Led by Jason Roos, Ph.D. as Chief Operating Officer
- David Kessler remains the HHS Chief Science Officer for COVID-19

National COVID-19 Preparedness Plan

- Released March 2, 2022
- Four main elements
  - Protect against and treat COVID.
  - Prepare for any new variants.
  - Prevent economic and educational shutdowns.
  - Continue to lead the effort to vaccinate the world and save lives
- Funding included in pending COVID-19 supplement



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Different Stages of COVID-19 Illness

COVID-19+ Disease Progression →

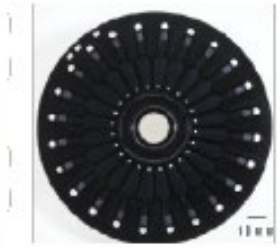
No Symptoms → Outpatient, Mild Symptoms → Inpatient, No Oxygen → Inpatient, Low-flow Oxygen → Inpatient, High-flow Oxygen → Mechanical Ventilation

Anti-viral Strategies

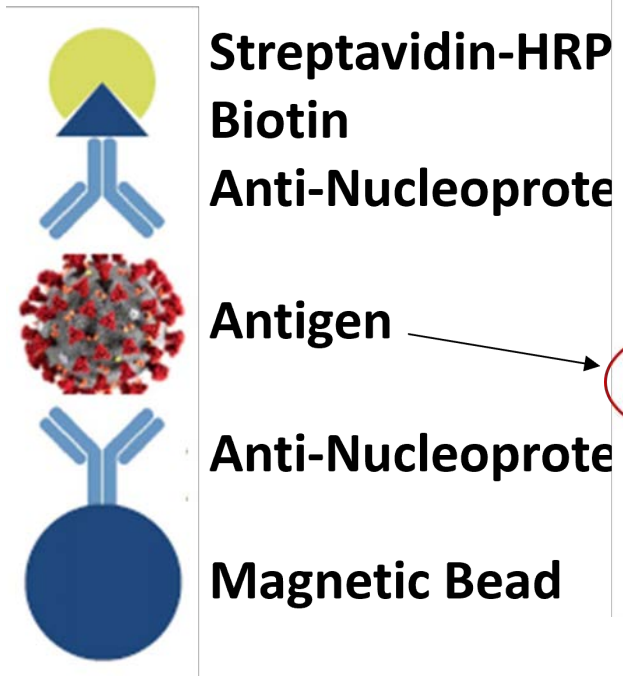
Immunomodulatory Strategies

Anti-coagulation Strategies

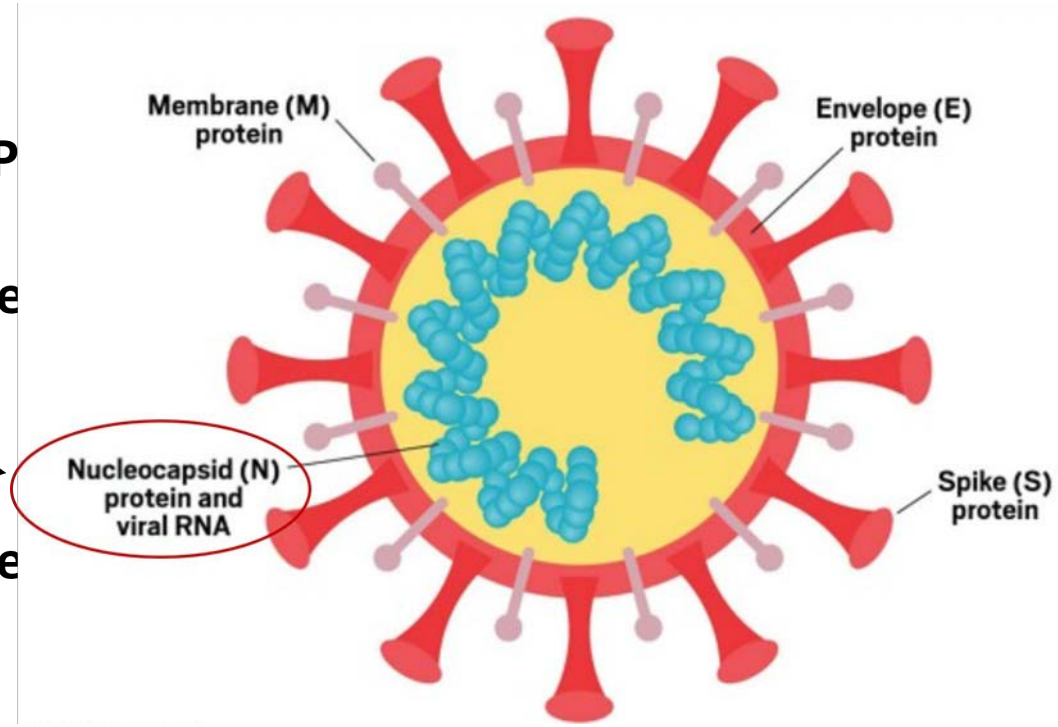
Quanterix Technology: Sensitive and Specific SARS-CoV-2 Nucleoprotein Antigen Detection



Simoa Disc

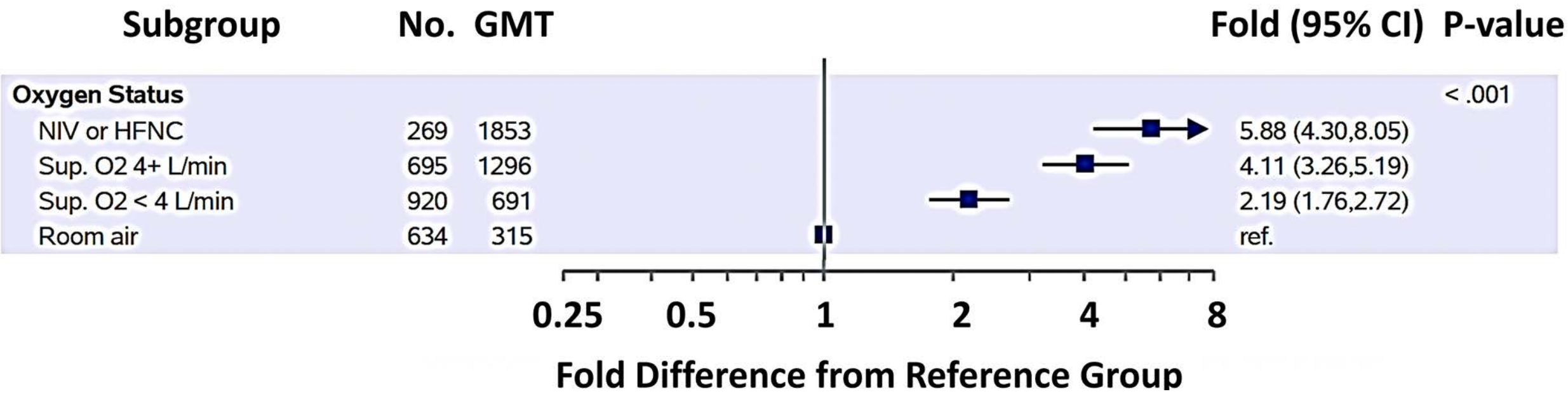


Sandwich Immunoassay



Shan et al., medRxiv 2020.08.14.20175356

Levels of SARS CoV-2 Antigen are Highest in the Most Severely Ill Patients



Angela Roberts on behalf of the ACTIV-3 Team

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Anti-viral Strategies

?Anti-viral strategies

Immunomodulatory Strategies

Anti-coagulation Strategies

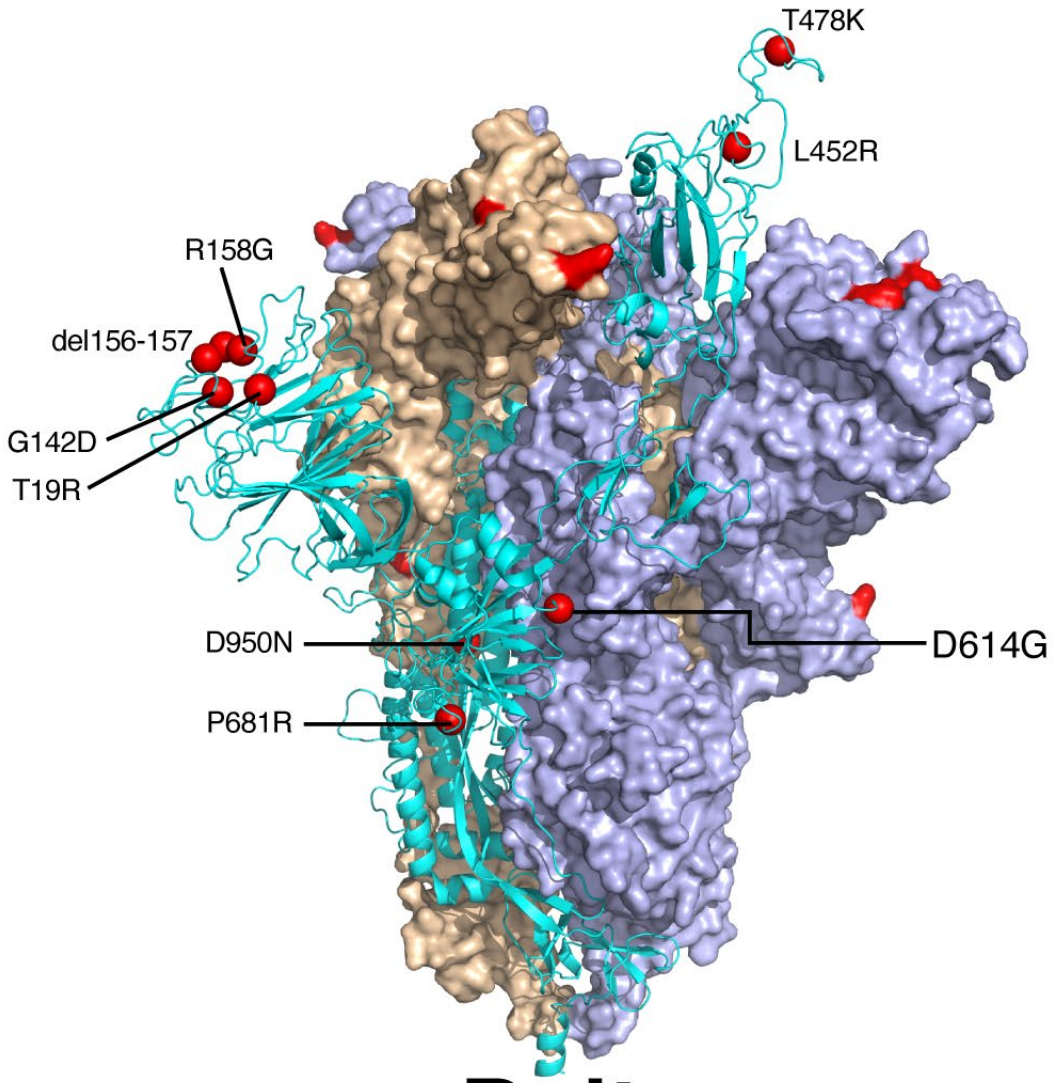
WHO SARS-CoV-2 Variants of Concern (VOCs)

WHO Name	PANGO lineage*	Earliest documented samples
Alpha	B.2.2.7	9/2020
Beta	B.2.351	5/2020
Gamma	P.1	11/2020
Delta	B.1.617.2	10/2020
Omicron	B.1.1.529	11/2021

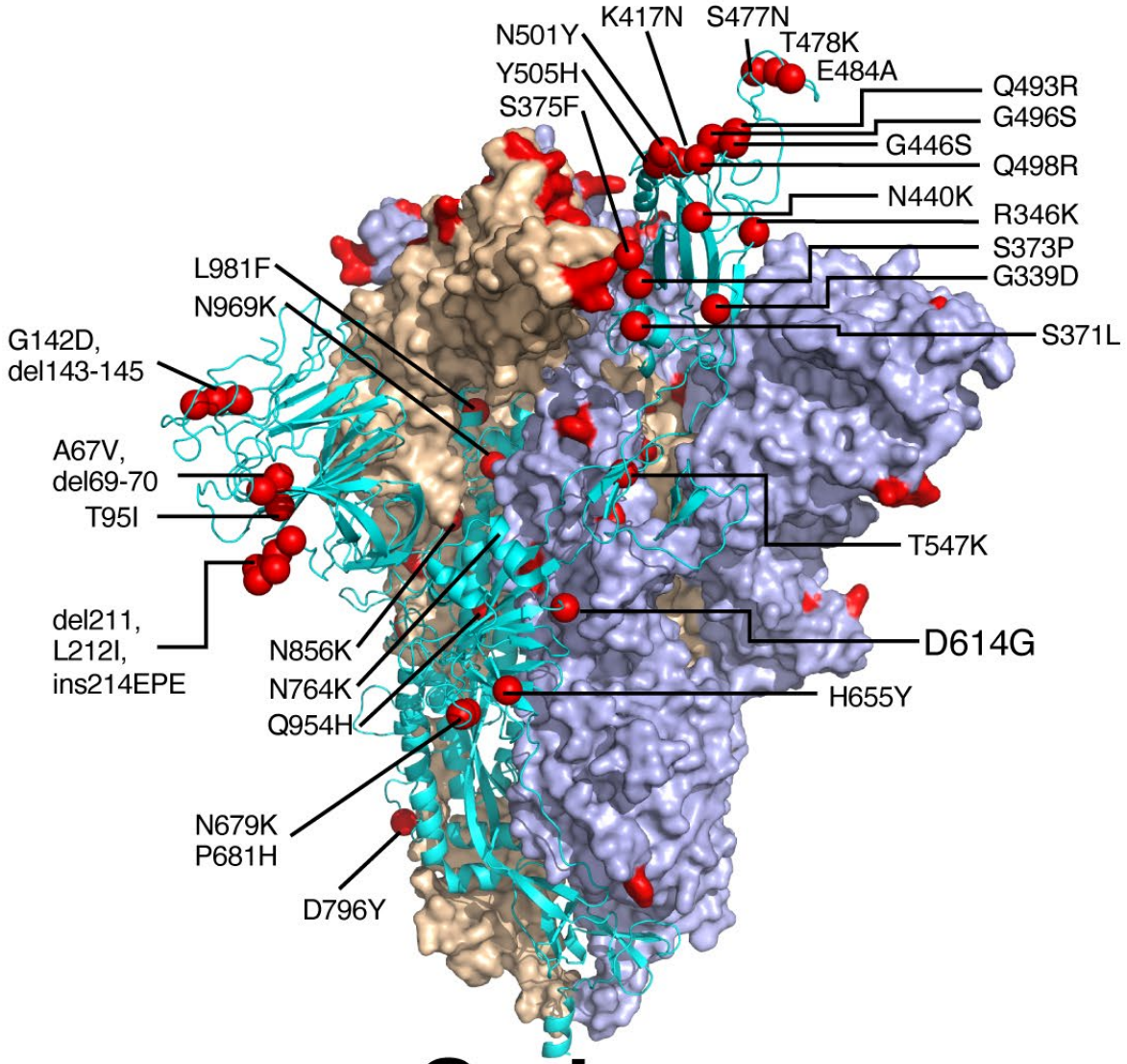
*VOCs also include descendent lineages

Source: WHO

SARS-CoV-2 Variants of Concern (VOCs)



Delta

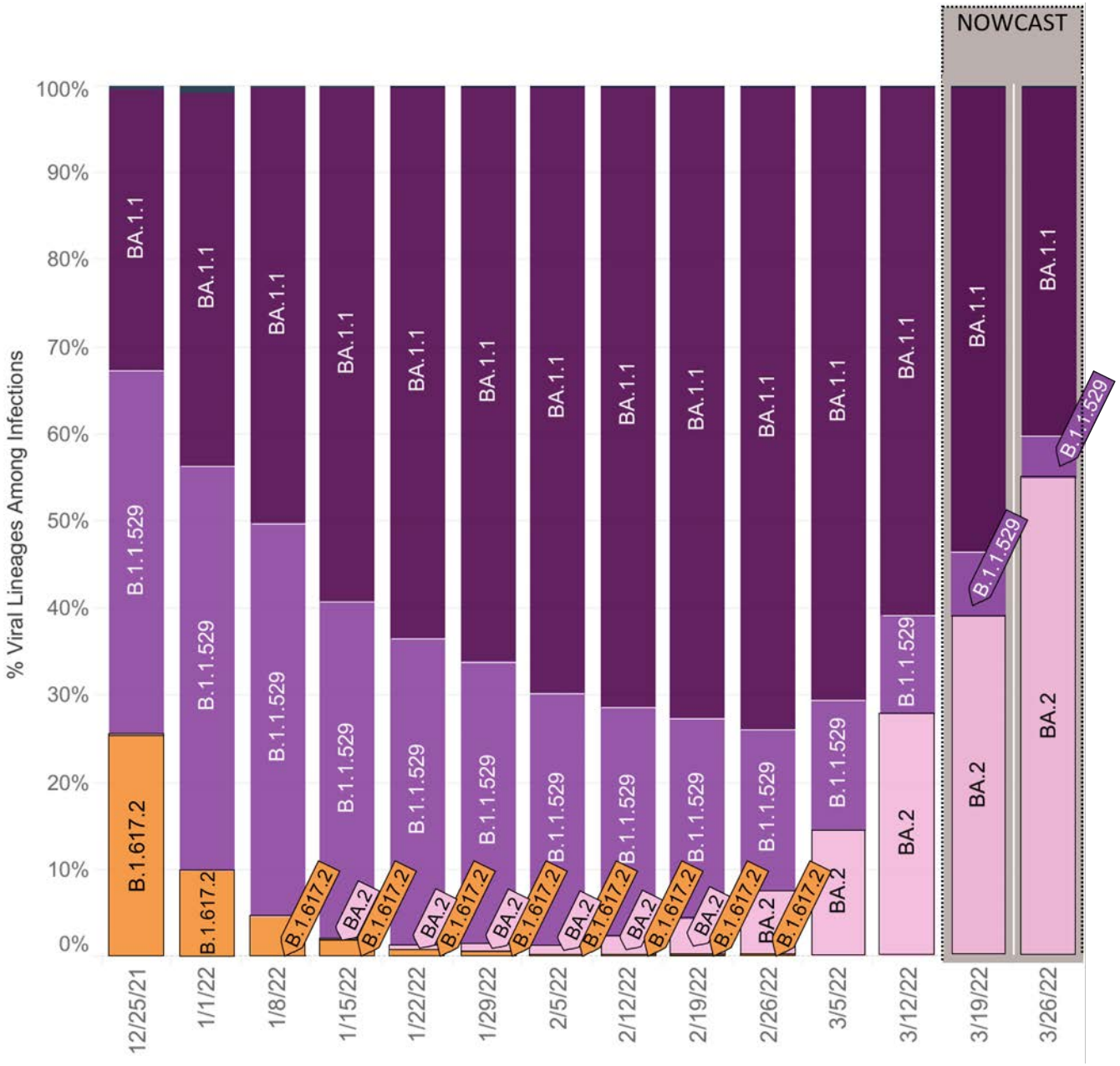


Omicron

Source: Tongqing Zhou, Ph.D. NIAID Vaccine Research Center

CDC Variant Reporting Actual Data and Nowcast as of March 26, 2022

United States: 12/19/2021-3/26/2022



United States: 3/20/2022-3/26/2022 NOWCAST USA

WHO label	Lineage #	US Class	% Total	95%PI
Omicron	BA.2	VOC	54.9%	50.8-59.1%
	BA.1.1	VOC	40.4%	36.4-44.5%
	B.1.1.529	VOC	4.7%	3.9-5.7%
Delta	B.1.617.2	VOC	0.0%	0.0-0.0%
Other	Other*	Blank	0.0%	0.0-0.0%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

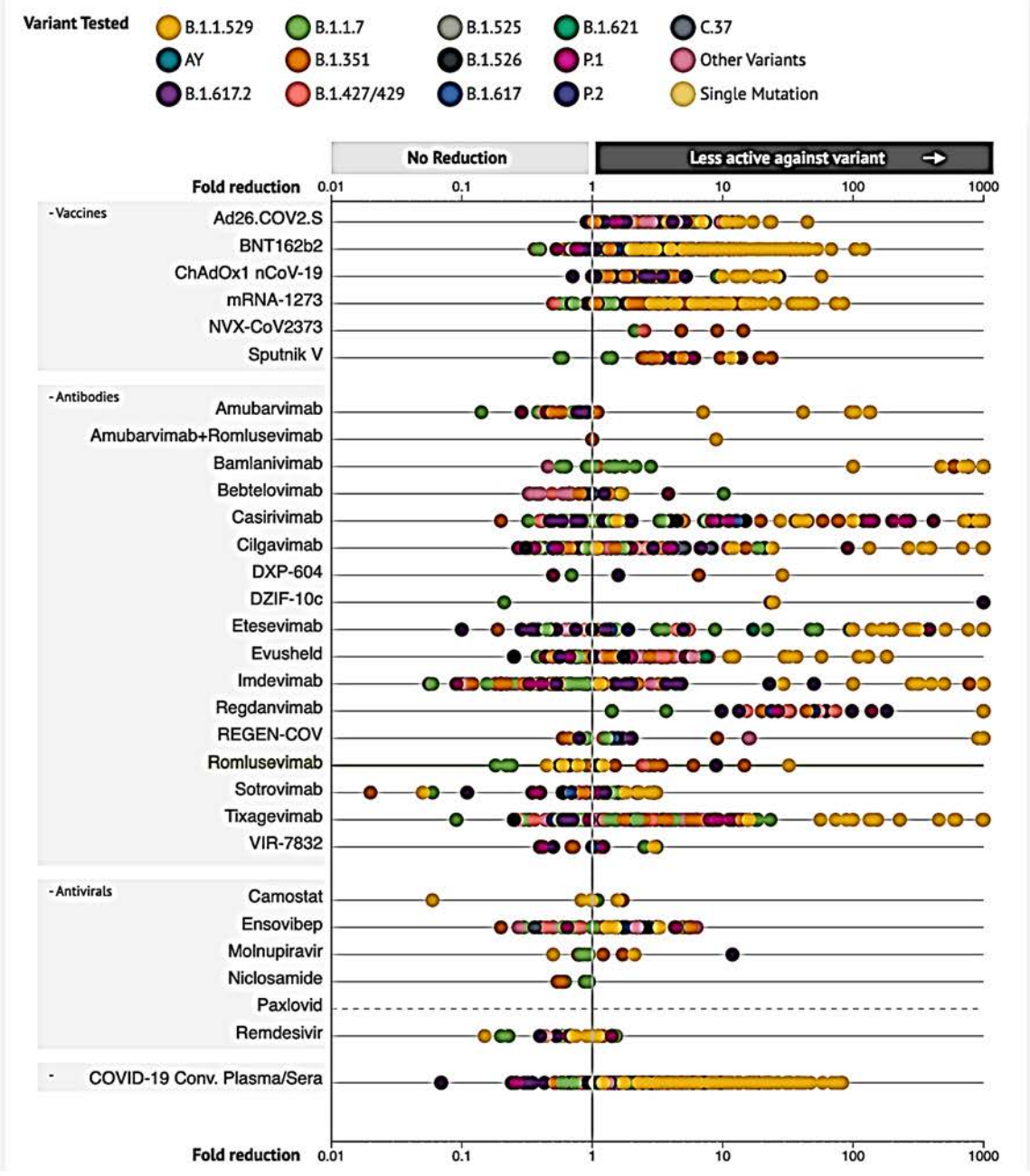
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates.

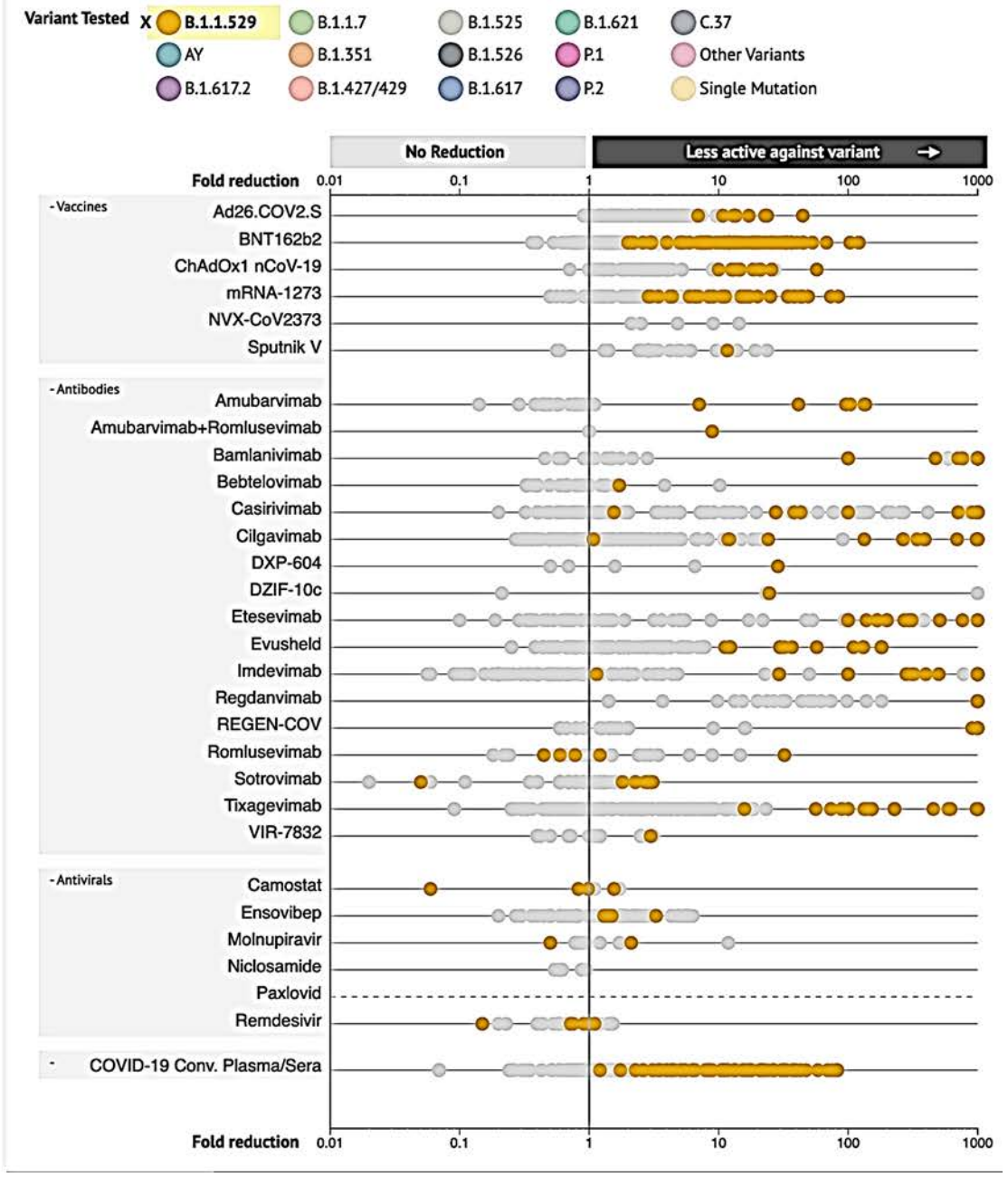
\# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2 BA.1 and BA.3 are aggregated with B.1.1.529. For regional data, BA.1.1 is also aggregated with B.1.1.529, as it currently cannot be reliably called in each region.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Impact of Variants on Countermeasures

https://opendata.ncats.nih.gov/variant/activity





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RT-PCR and Rapid Antigen Tests are the Main Tools for Diagnosis

- RT-PCR
  - Most sensitive
  - Can remain positive for a prolonged period of time
  - Can help identify variants via S-gene drop-out
- Antigen
  - Less sensitive
  - Typically represents a higher viral load
  - Adapted to home use (15 minute test)
- Both are available under Emergency Use Authorization; will need FDA approval before the end of the Public Health Emergency

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The NIH Therapeutics Research Agenda is Largely Carried Out via the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) PPP

- ACTIV -1, -3, -4a and -5: Host-directed therapies and anti-virals in hospitalized patients
- ACTIV – 2: Anti-viral therapies in ambulatory patients
- ACTIV – 6: Re-purposed drugs in ambulatory patients

The Landscape of Treatment for COVID-19

- As of March 22, 2022
  - A search of clinicaltrials.gov for COVID-19 treatment studies yielded 4,651 hits
  - A PubMed search for articles on COVID-19 treatment yielded 5,384 hits
  - A Google search for COVID-19 treatment yielded about 4,270,000,000 results
- It is extremely difficult for anyone to remain current with all this (rapidly changing) information

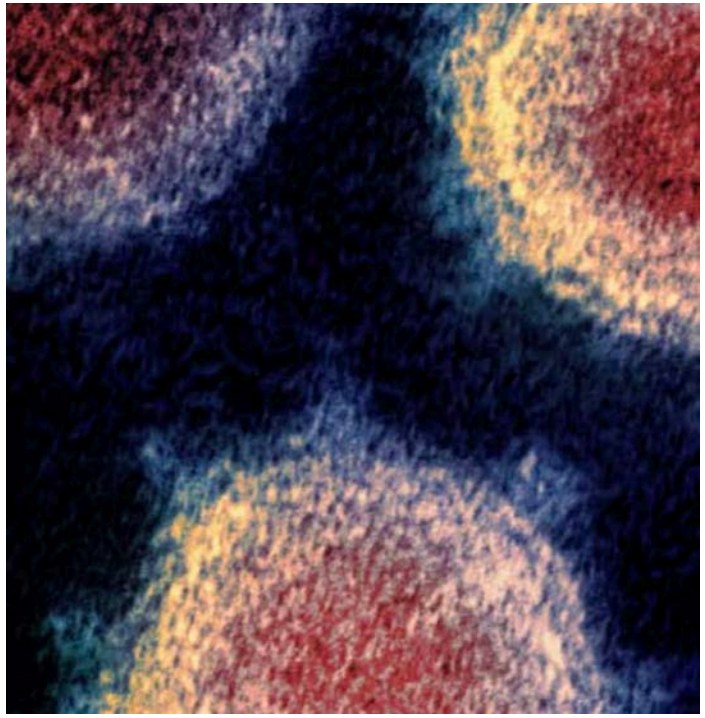
National Institutes of Health
Turning Discovery Into Health

Tuesday, April 21, 2020

News Release

Expert U.S. Panel Develops NIH Treatment Guidelines for COVID-19

- COVID19TREATMENTGUIDELINES.NIH.GOV
- March 20, 2020 – request from HHS
- March 24 – initial meeting of 37 members; 6 US government agencies; 8 societies
- April 7 – first release ready
- April 21 2021 – final approval and first release
- Mar 2022 - 48 updates; 34,500,000 page views



Ratings by the NIH Guidelines Panel

- Strength of the Recommendation
  - A = strong
  - B = moderate
  - C = weak
- Strength of the Evidence
  - I = data from robust, randomized controlled trials
  - II = data from other trials or observational studies
    - IIa = other randomized trials; subgroup data
    - IIb = observational studies
  - III = expert opinion

NIH Guidelines Panel Recommendations for Non-Hospitalized Patients

March 2022

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Does Not Require Hospitalization or Supplemental Oxygen	All patients should be offered symptomatic management **(AIII).** For patients who are at high risk of progressing to severe COVID-19 (treatments are listed in order of preference based on efficacy and convenience of use): • **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)** • **Sotrovimab (AIIa)** • **Remdesivir(BIIa)** • **Molnupiravir (CIIa)** The Panel **recommends against** the use of **dexamethasone**[0] or **other systemic corticosteroids** in the absence of another indication **(AIII).**
Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa), dexamethasone (AIIa)**,or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen ***For those who are stable enough for discharge but who still require oxygen***	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged From ED Despite New or Increasing Need for Supplemental Oxygen ***When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured***	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII).** Since remdesivir is recommended for patients with similar oxygen needs who are hospitalized, clinicians may consider using it in this setting. Given that remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Therapy for Ambulatory Patients with Mild to Moderate Disease at High Risk of Disease Progression

- Oral agents under EUA
  - Paxlovid (5 days) AIIa
  - Molnupiravir (5 days) CIIa
- Single infusion monoclonal antibody therapy under EUA / BA2
  - Bamlanivimab + etesevimab (Lilly)
  - Casirivimab + imdevimab (Regeneron)
  - Sotrovimab (Vir/GSK)
  - Bebtelovimab – next update
- FDA-approved Intravenous agent
  - Remdesivir (3 days) BIIa
- Do not use corticosteroids unless the patient requires oxygen

NIH Guidelines Panel Recommendations for Hospitalized Patients

March 2022

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	Recommendations for Anticoagulation Therapy
Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII).** There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients who are at high risk of disease progression, remdesivir may be appropriate.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir (BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug (e.g., **baricitinib** or **tocilizumab) (CIIa).**	For nonpregnant patients with D-dimer levels >ULN who are not at increased bleeding risk: • **Therapeutic dose** of heparin **(CIIa)** For other patients: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir (BIIb)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib (BIIa)** or **IV tocilizumab (BIIa)** to 1 of the options above.	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)**
Hospitalized and Requires MV or ECMO	**Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, **IV sarilumab** can be used **(BIIa).**	For patients without evidence of VTE: • **Prophylactic dose** of heparin, unless contraindicated **(AI)** If patient is started on therapeutic heparin before transfer to the ICU, switch to a **prophylactic dose** of heparin, unless there is a non-COVID-19 indication **(BIII).**

Therapy for Hospitalized Patients

- Not requiring supplemental oxygen
  - Avoid dexamethasone/corticosteroids - AIIa/AIII
- Requiring supplemental oxygen
  - Remdesivir - BIIa
  - Dexamethasone – AI
  - Baricitinib - BIIa
  - IL-6 inhibitors (tocilizumab, sarilumab) – BIIa
  - Combinations of the above

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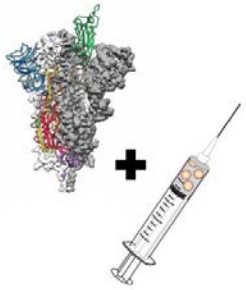
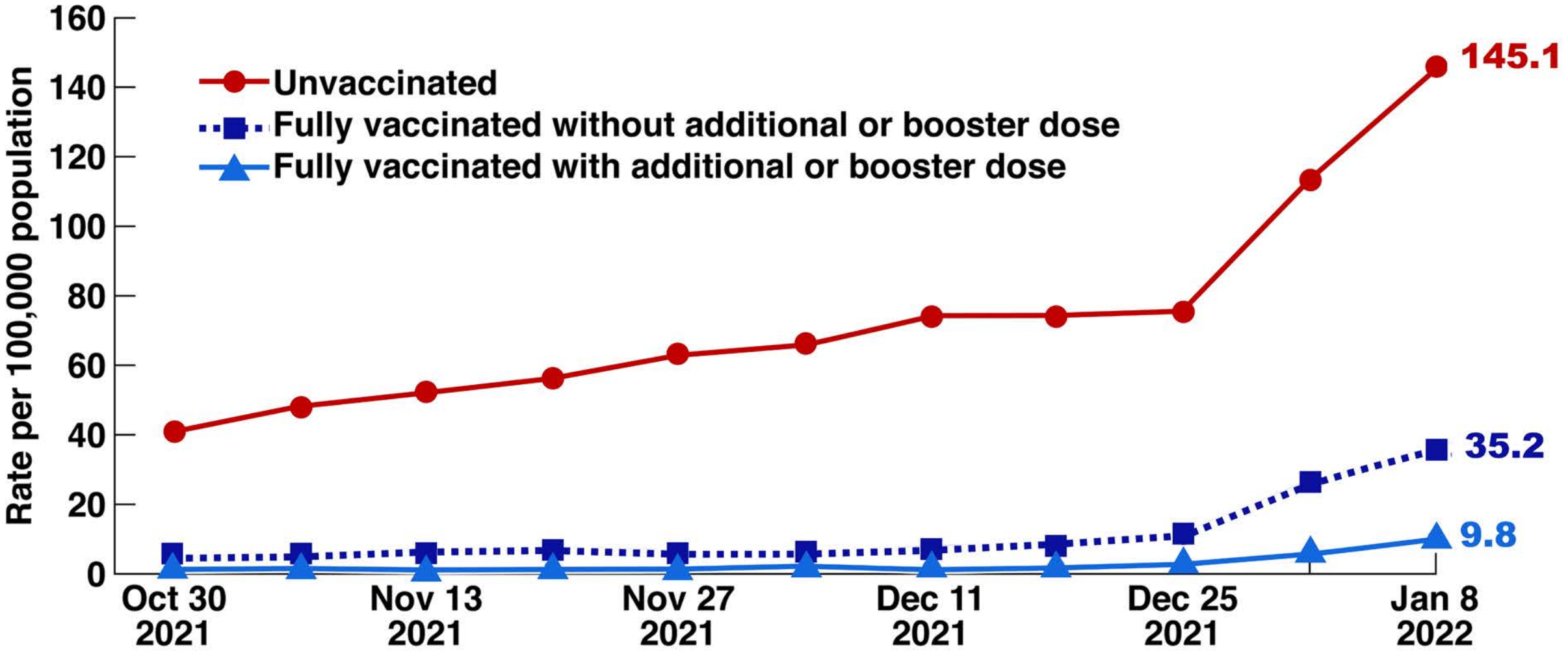
COVID-19 Vaccines in U.S. Government Development Portfolio

Platform	Immunogen		Developer	Status
Nucleic Acid (mRNA)	S2P		moderna	BLA (Age 18+)
	S2P		BIONTECH Pfizer	BLA (Age 16+); EU (Age 5-15)
Adenovirus Vector	S2P		Johnson & Johnson	EUA (Age 18+)
	Wild-type spike		AstraZeneca	EUA/BLA TBD
Recombinant Protein and Adjuvant	S2P		gsk SANOFI	EUA request 2/2022
	S2P		NOVAVAX Creating Tomorrow's Vaccines Today	EUA request 1/2022

10 Vaccines Approved for Use by WHO

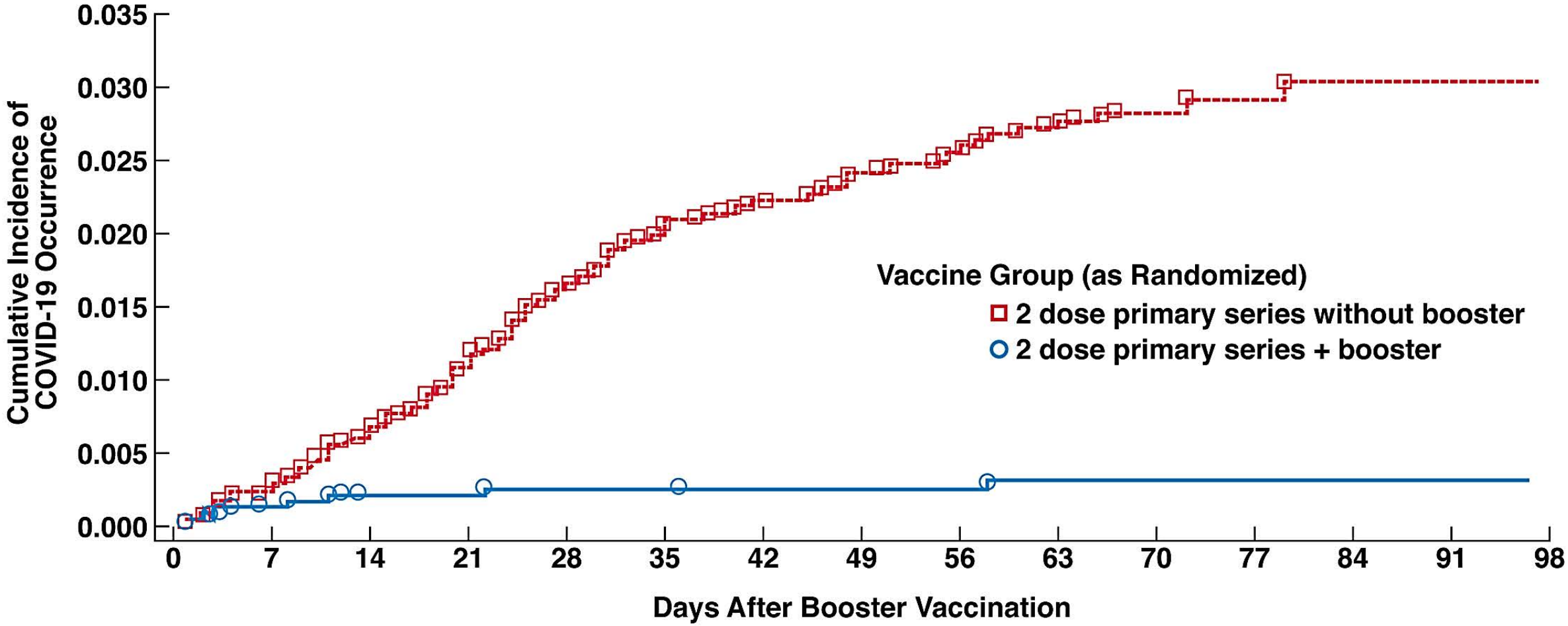
Novavax	NVX-CoV2373	Protein Subunit
Serum Institute of India	COVOVAX	Protein Subunit
Moderna	mRNA-1273	RNA
Pfizer/BioNTech	BNT162b2	RNA
Jannsen (Johnson & Johnson)	Ad26.COV2.S	Non-replicating Viral Vector
Oxford/AstraZeneca	AZD1222	Non-replicating Viral Vector
Serum Institute of India	Covishield	Non-replicating Viral Vector
Bharat Biotech	Covaxin	Inactivated
Sinopharm (Beijing)	BBIBP-CorV	Inactivated
Sinovac	CoronaVac	Inactivated

Age-Adjusted Rates of COVID-19-Associated Hospitalizations by Vaccination Status in Adults Ages ≥18 Years, October 2021–January 2022



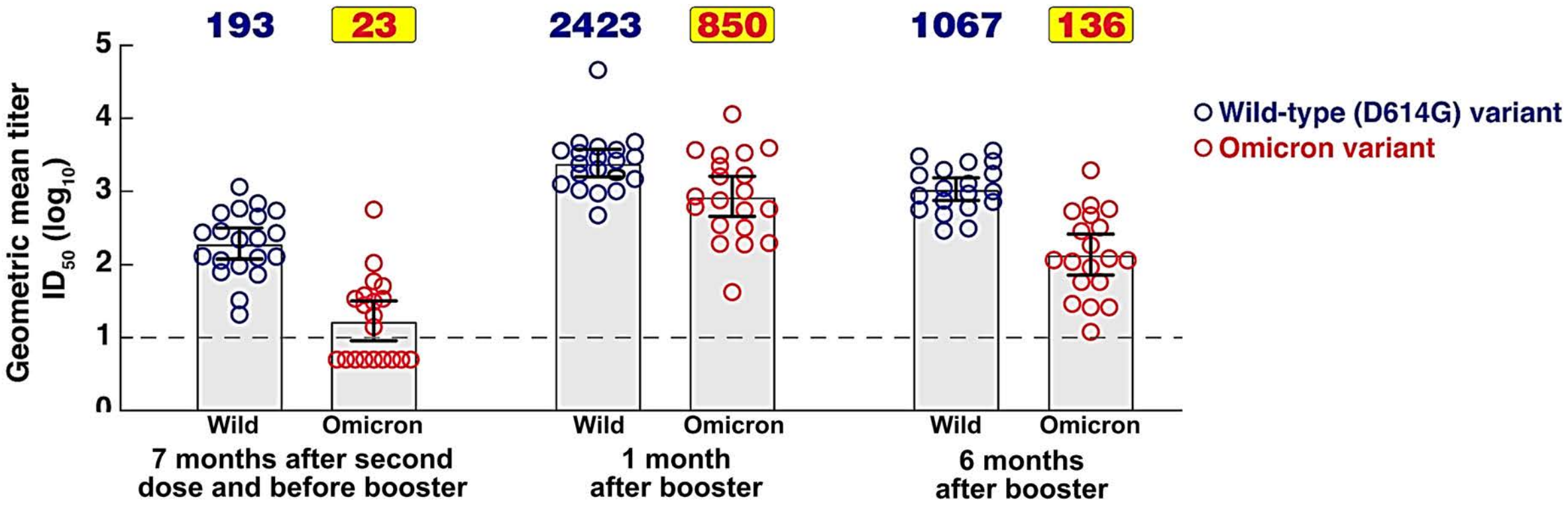
Source: CDC

Pfizer Study: Cumulative Incidence Curve for First COVID-19 Occurrence After Booster Vaccination



ED Moreira Jr et al. N Engl J Med 2022. DOI: 10.1056/NEJMoa2200674

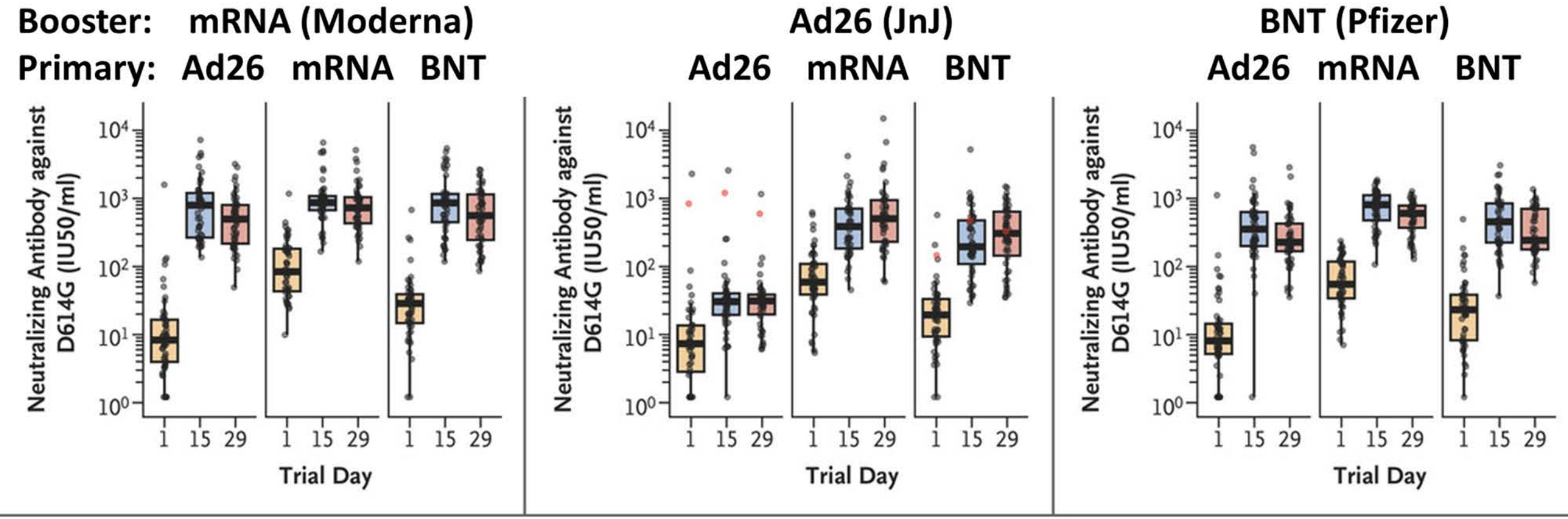
Third Dose of mRNA-1273 (Moderna Vaccine) Improved Antibody Response to Omicron Variant



Pseudovirus neutralization assay antibody titers in serum samples from mRNA-1273 recipients

Source: RE Pajon et al. *NEJM*, 1/26/2022.

Boosting is Seen with Either Homologous or Heterologous Vaccines



RL Atmar et al. N Engl J Med 2022;386:1046-1057

COVID-19 Vaccines: Knowledge and Knowledge Gaps

- **What we know**
  - In adults (≥18 years)
    - Safe
    - Effective
    - Additional protection from 3rd dose
  - In children
    - Safe and effective in ages 5–17 years

- **What we do not know**
  - Correlates of protection
  - Duration of protection
    - From infection
    - From Symptoms
    - From Hospitalization
    - From Death
  - Optimum regimen for children <5 years

March 29: FDA Authorizes Fourth RNA Dose (Second Booster) For Additional Individuals

- Individuals 50 years of age and older at least 4 months after receipt of a first booster dose and
  - For Pfizer: individuals 12 and older with immunocompromise
  - For Moderna: individuals 18 and older with immunocompromise
- Supporting evidence
  - Safety in 700,000 persons with Pfizer and 120 with Moderna
  - Increased antibody levels following a second booster

March 29: FDA Authorizes Fourth RNA Dose (Second Booster) For Additional Individuals

- Supporting evidence (con't.)
  - In a non-randomized cohort of 563,465 individuals ages 60-100 followed for 40 days who received the Pfizer vaccine (Abel R. et al. doi.org/10.21203/rs.3.rs-1478439/v1)
    - There were 232 deaths in those who did not receive a fourth dose (n at risk ranging from 12,817 to 328,022)
    - There were 92 deaths in those who did receive a fourth dose (n at risk ranging from 550,648 to 233,847)
    - The adjusted HR for death was 0.22 (0.17-0.28)

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Post-acute Sequelae SARS-CoV-2 Infection (PASC)

- Being studied through the Researching COVID to Enhance Recovery (RECOVER) initiative
  - Co-led by NHLBI and NINDS (https://recovercovid.org/)
  - Seeks to understand, prevent, and treat PASC, including Long COVID
- Also being studied through 3 protocols at the NIH Clinical Center (NIAID, NINDS, CC)

A Longitudinal Study of COVID-19 Sequelae and Immunity (M. Sneller, PI)

- Studies 3 cohorts of adults
  - Individuals with a history of COVID and persistent symptoms
  - Individuals with a history of COVID and no persistent symptoms
  - Individuals without a history of COVID who have been a close contact of a COVID survivor

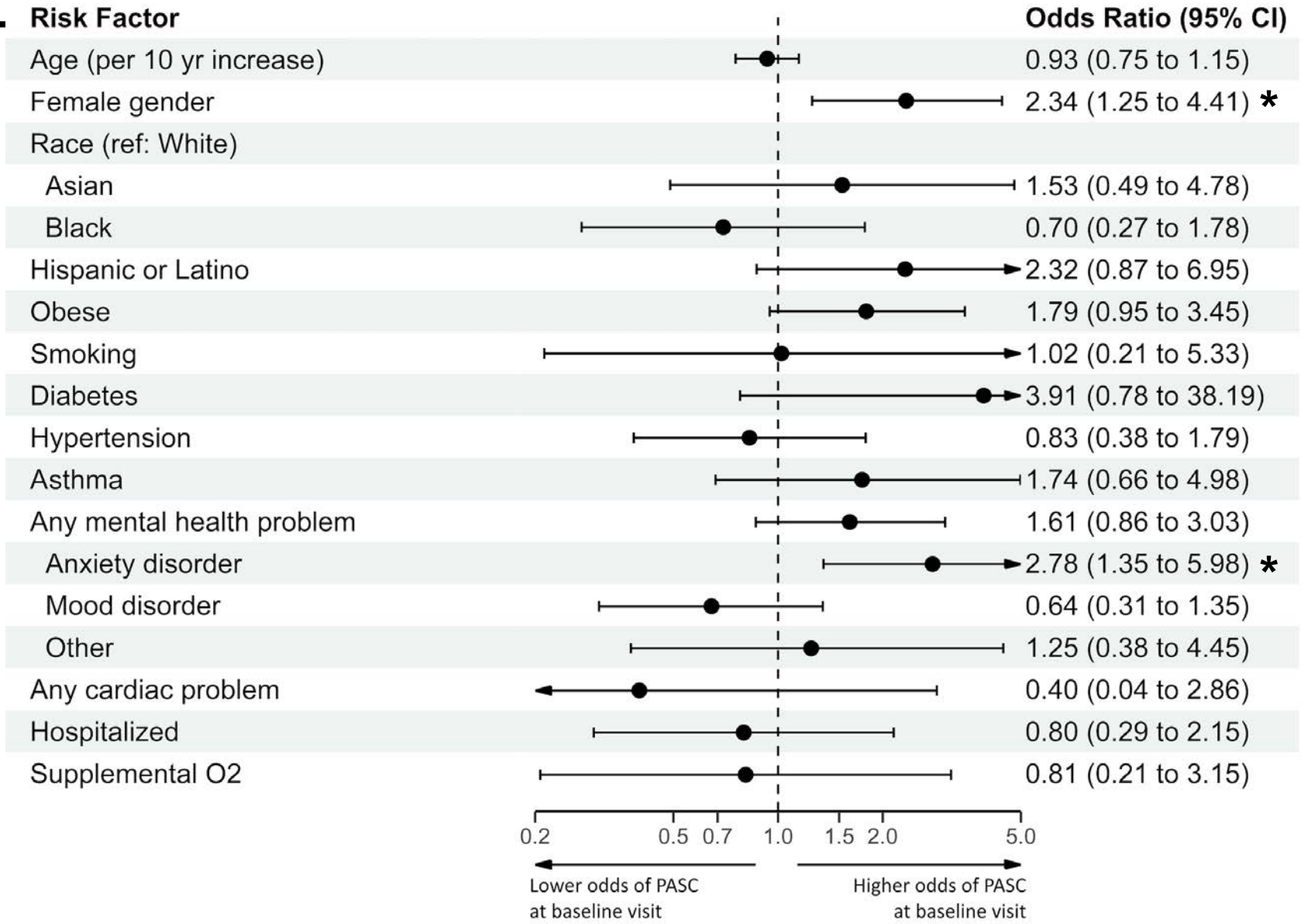
A Longitudinal Study of COVID-19 Sequelae and Immunity (M. Sneller, PI)

- Data Collection includes
  - Individual history and physical
  - Routine labs
  - Markers of inflammation and coagulation
  - SARS-CoV-2 immunology and virology
  - Mental Health Evaluation
  - ECG and Echocardiogram
  - PFT and 6 minute walk test

Selected Symptoms and Physical Findings Controls vs. Total COVID-19 Cohort

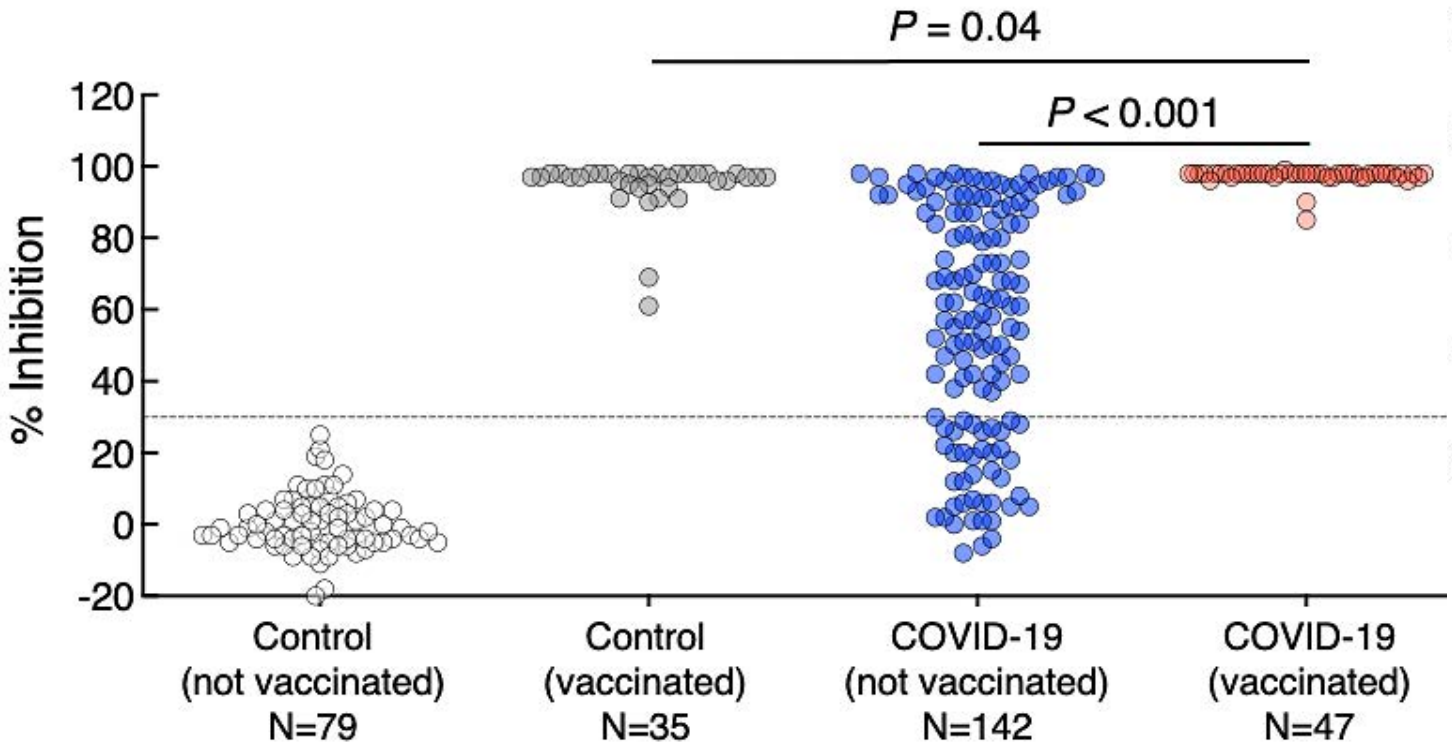
Selected symptoms - no. (%)	Controls (n=120)	Total COVID-19 Cohort (n=189)	Odds Ratio or Mean Difference (95% CI)	p-value
Fatigue	0 (0)	50 (26)	Inf (10.9, Inf)	<0.001
Dyspnea	0 (0)	35 (19)	Inf (6.79, Inf)	<0.001
Anosmia/Parosmia	0 (0)	26 (14)	Inf (4.69, Inf)	<0.001
Concentration impairment	1 (1)	23 (12)	16.4 (2.59, 682.72)	<0.001
Headache	0 (0)	22 (12)	Inf (3.82, Inf)	<0.001
Memory impairment	1 (1)	18 (10)	12.46 (1.92, 524.99)	0.001
Insomnia	0 (0)	17 (9)	Inf (2.8, Inf)	<0.001
Chest Pain/Discomfort	0 (0)	16 (8)	Inf (2.6, Inf)	<0.001
Anxiety	4 (3)	11 (6)	1.79 (0.51, 7.89)	0.42
Myalgia	1 (1)	11 (6)	7.32 (1.04, 318.71)	0.033
Tinnitus	1 (1)	11 (6)	7.32 (1.04, 318.71)	0.033
Palpitations	0 (0)	10 (S)	Inf (1.47, Inf)	0.008
Neurologic	2 (2)	2 (1)	0.63 (0.45, 8.83)	0.643
Lung	0 (0)	0 (0)	NA	NA
Musculoskeletal	1 (1)	16 (8)	10.95 (1.66, 464.39)	0.003
Heart	2 (2)	7 (4)	2.26 (0.42, 22.70)	0.491
Lymphatic	0 (0)	1 (1)		

Risk Factors for PACS

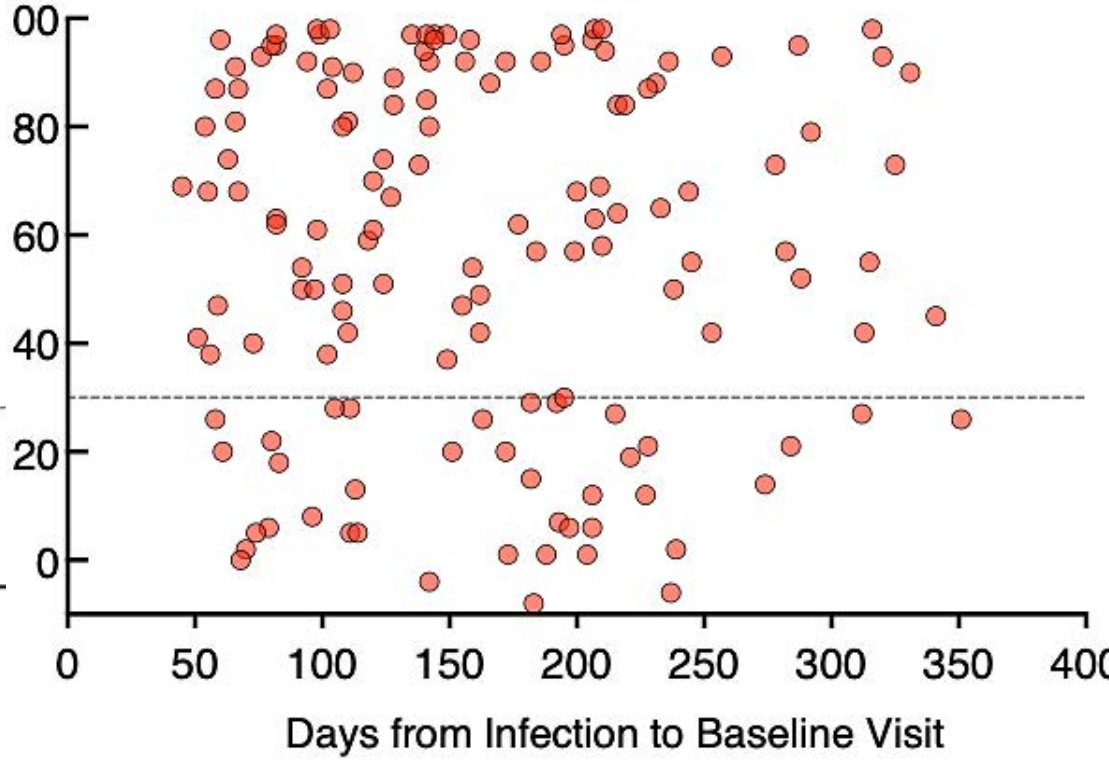


Antibody Responses Following COVID-19 Infection with or without Vaccination

Percent inhibition of ACE2 binding as a surrogate for neutralizing antibodies



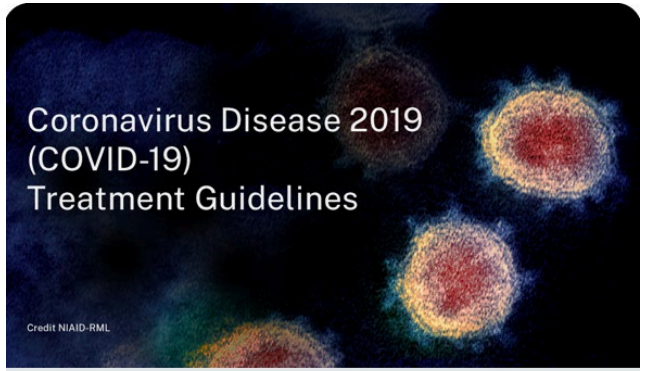
Antibody levels as a function of time post-infection



Summary of NIAID Intramural PACS Study (March 2022)

- Participants in the COVID-19 group reported more symptoms than those in the control group
  - Among them were fatigue, dyspnea, parosmia, headache concentration and memory impairment, insomnia, chest discomfort and anxiety
- Abnormal findings on physical exam or lab evaluations were uncommon and were not associated with PASC

Websites



Information on COVID-19 Treatment, Prevention and Research
covid19treatmentguidelines.nih.gov

NIH Treatment Guidelines

https://www.covid19treatmentguidelines.nih.gov/

odp-covid19-ui
ncats.nih.gov

Countermeasures vs. Variants

https://opendata.ncats.nih.gov/variant/activity