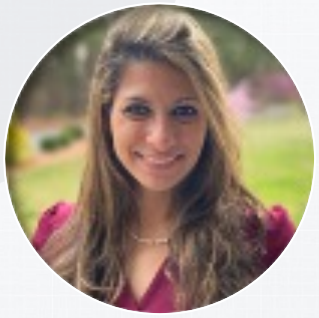
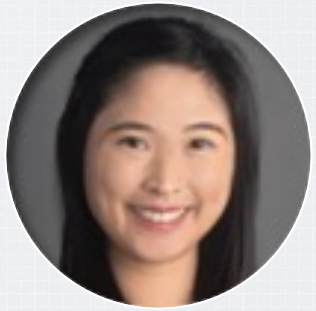
COVID Vaccines & Transplantation:
Where Are We now?

TODAY'S PANELISTS



Macey Levan
JD, PhD
Associate Professor of Surgery & Population Health
NYU Grossman School of Medicine

William Werbel
MD, PhD
Associate Professor of Medicine
Johns Hopkins School of Medicine



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Post-Doctoral Research Fellow
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MD
General Surgery Resident; Post-Doctoral Research Fellow
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The Alliance | *Leadership & Engaged Learning in Organ Donation & Transplantation*

Wednesday, November 30, 2022, 2:00pm – 3:00pm ET

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- Group leaders, please share the follow-up email with all group participants who attended the webinar.

Deanna Fenton

Senior Manager, Program Development and Operations

THE Alliance

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Meet Our Moderator

Julie Anderson MSN, MPH, RN, CCTC

Assistant Director of Transplant Quality

MUSC Medical University

Meet Our Panelists

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COVID-19 Vaccination for Solid Organ Transplant Recipients: Science and Frontiers

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Wednesday, November 30th, 2022

The Alliance Webinar

Disclosures & Funding

Dr. Chang and Dr. Alejo have no financial disclosures

Dr. Werbel has the following disclosures:

- Infectious Diseases Society of America
  - CDC/IDSA COVID-19 Real-Time Learning Network (section editor)
- AstraZeneca (speaking fees)
- Novavax (advisory board)

Dr. Levan has the following disclosures:

- Patients Like Me/Takeda (consulting)

Grants/funding

- National Institute of Allergy and Infectious Diseases
- National Institute of Diabetes and Digestive and Kidney Diseases
- NIH Center for AIDS Research
- ASTS Jonathan P. Fryer Resident Scientist Scholarship
- Ben-Dov and Trokhan Patterson families

Notes

- We speak in generalities about SOTRs, though there is major variability in this group
- Largely defer to CDC and medical societies for COVID-19 recommendations
- Please do not disseminate slides that are “Under Review”

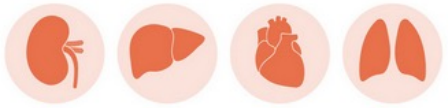
Objectives

- Summary of COVID-19 vaccine responses among solid organ transplant recipients (SOTRs) -> focus on antibody
- Describe COVID-19 outcomes in the Omicron era among transplant recipients
- Discuss the impact of new variants on monoclonal antibody and vaccine-associated immunoprotection

SOTRs historically have poor COVID-19 outcomes

5083 excess deaths during first 13-months of the pandemic

All SOTR groups had excess death in the COVID-era



41% 27% 19% 15%

increases over expected

Demographics of excess deaths:

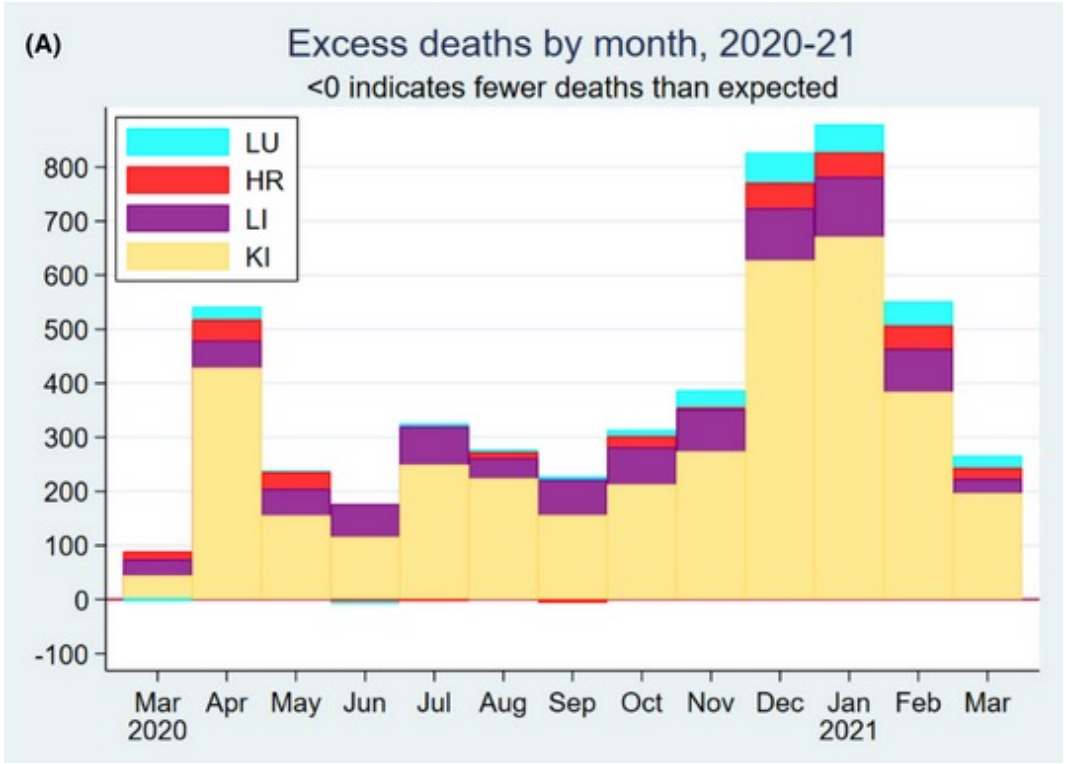
93% Age ≥ 50yo

56% Black or Hispanic

65% ≥5yrs postTx

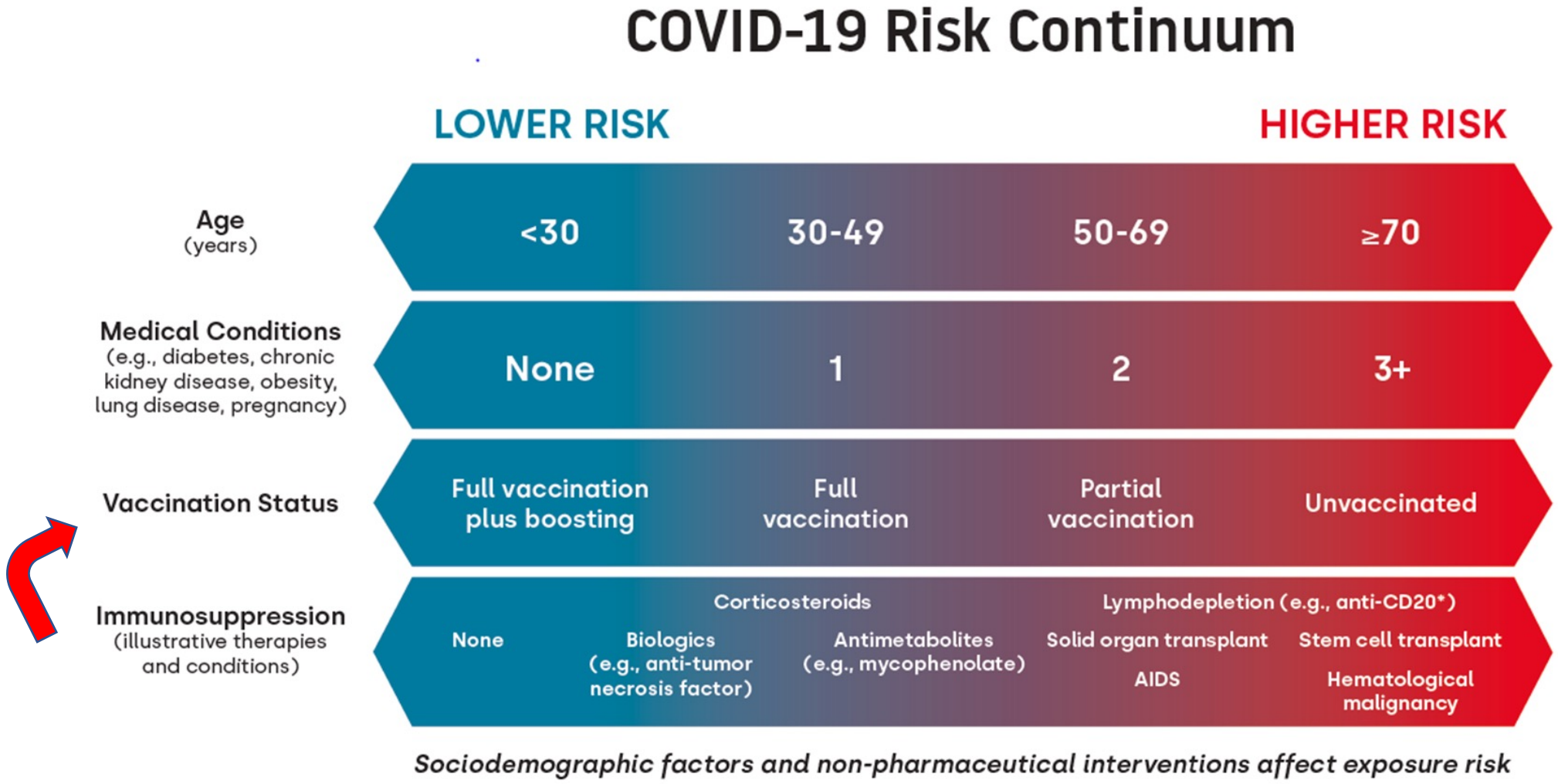
AJT

10.1111/ajt.17036



Massie *Am J Transplant* 2022

Understanding COVID-19 Risk



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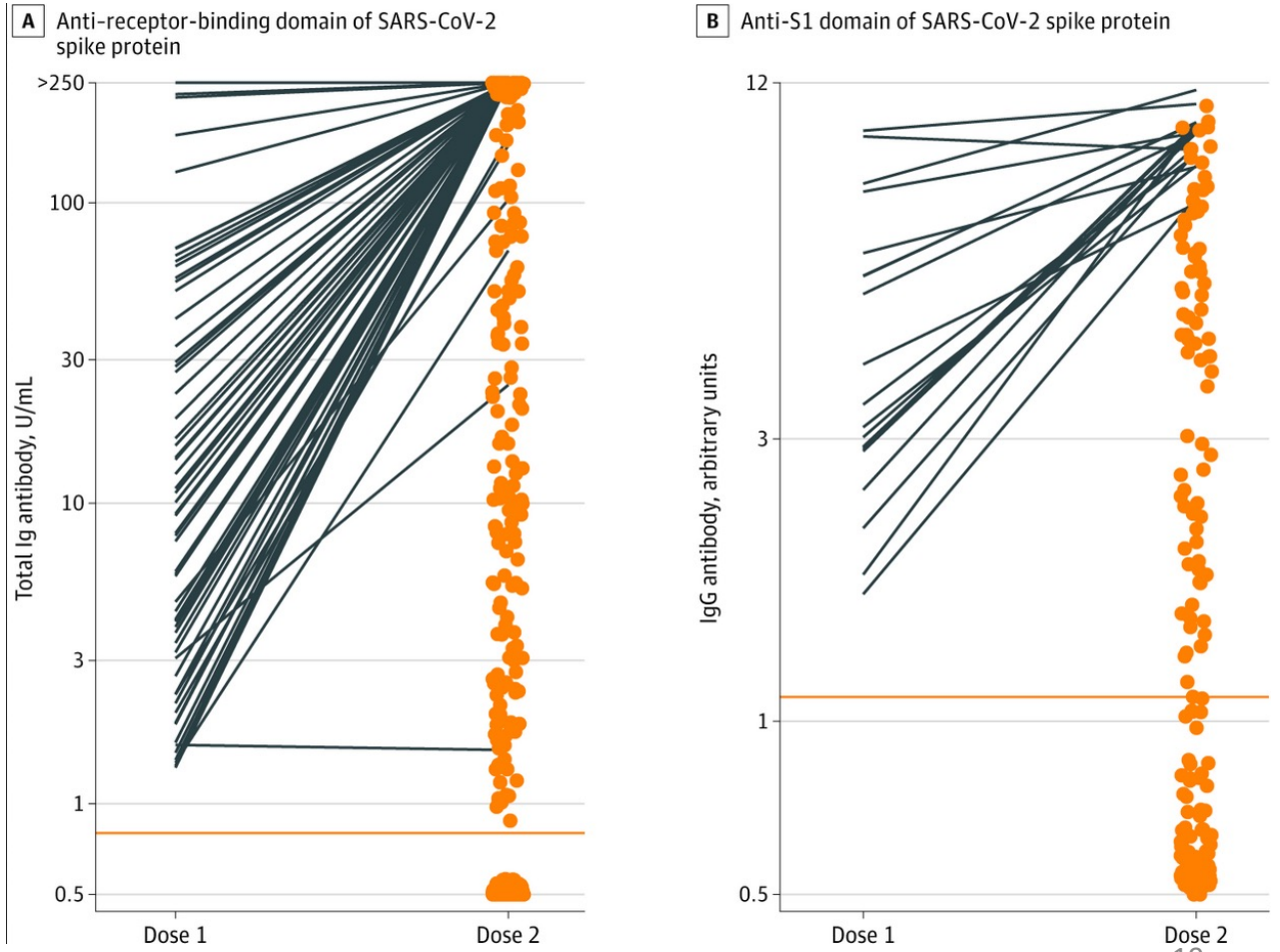
Original illustration by Dr. William Werbel. Adapted for the COVID-19 Real-Time Learning Network. Brought to you by CDC and IDSA

Impaired antibody response to two-dose mRNA vaccines

- **BNT162b2 (Pfizer)** or **mRNA-1273 (Moderna)**

- 17% seropositive post-D1
- 54% seropositive post-D2

(versus 100% in general population, to higher levels)



Boyarsky *JAMA* 2021

Impaired antibody response to one-dose adenovirus vaccine

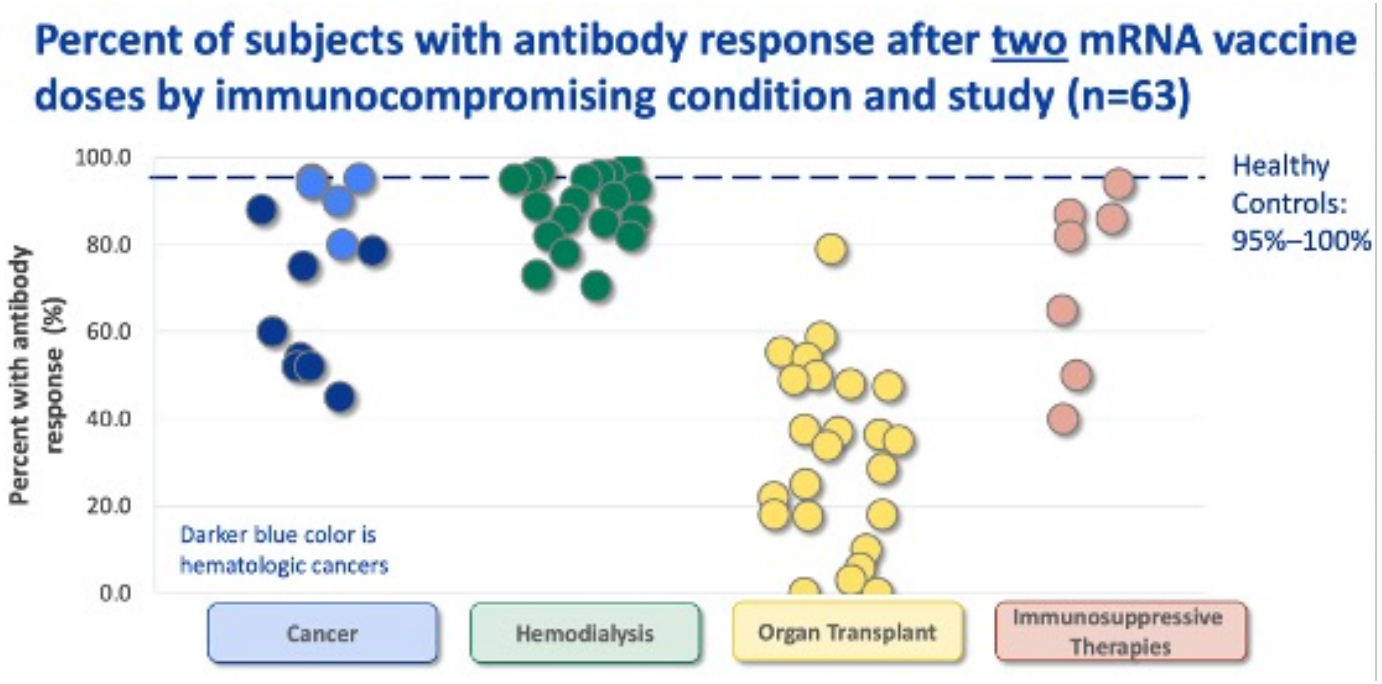
- **Ad26.COV2.S (Johnson & Johnson)**

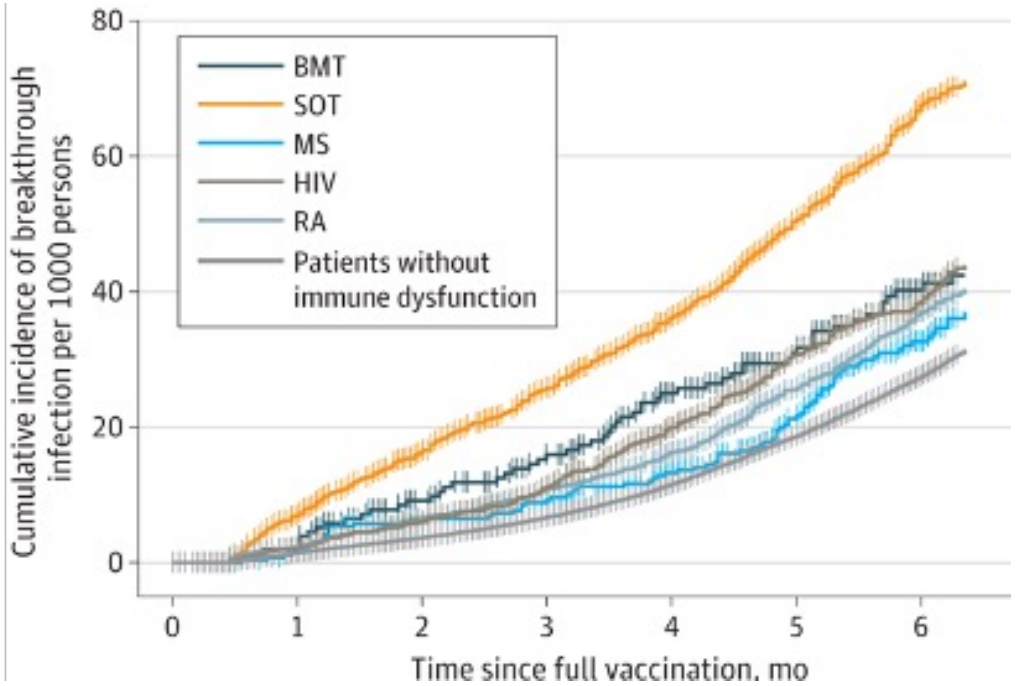
- 17% seropositive post-D1
- Compared to mRNA vaccine, 83% lower odds of a developing an antibody response (adjusted for antimetabolite [ie, MMF] use and time since transplant)

Boyarsky *Transplantation* 2021

Poor antibody responses correlate with higher rates of vaccine breakthrough

82x higher risk of breakthrough
485x higher risk of death
(*after 2 mRNA doses*)





Oliver, ACIP, 2021, Tenforde et al., CID, 2021, Chavarot et al., AJT, 2021
Sun et al., JAMA IM, 2021, Qin et al., Transplantation, 2021

Factors associated with poor response to COVID vaccination:

- Shorter time between transplant surgery and vaccine
- Older age
- Immunosuppressant medication (anti-metabolite [MMF], belatacept)
- Non-liver transplant recipient (kidney, heart, lung, multi-organ)
- Vaccine Type/Count

Factors associated with poor response to COVID vaccination:

Change immunosuppression

Additional vaccine doses

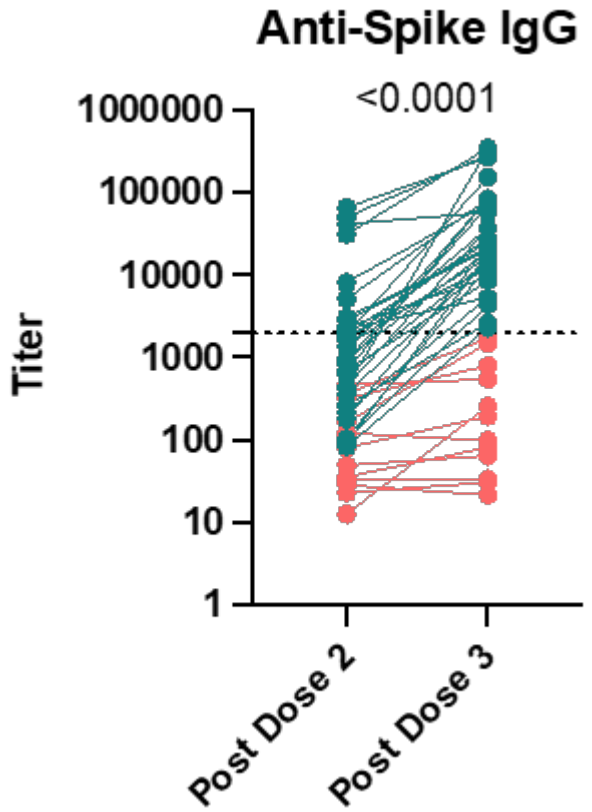
- More mRNA?
- Switch platforms?
- Update vaccine strain?

Anti-metabolites & Belatacept

- Anti-metabolites and Belatacept are associated with lower antibody and cellular responses

Outcomes	Control	Belatacept	p value
(+), %	77	36	
≥250 U/mL, %	62	16	0.003
% ACE2 inhibition, wildtype, median(IQR)	13 (9-24)	5 (3-7)	0.008
% ACE2 inhibition, Delta, median(IQR)	12 (3-16)	5 (3-8)	0.11

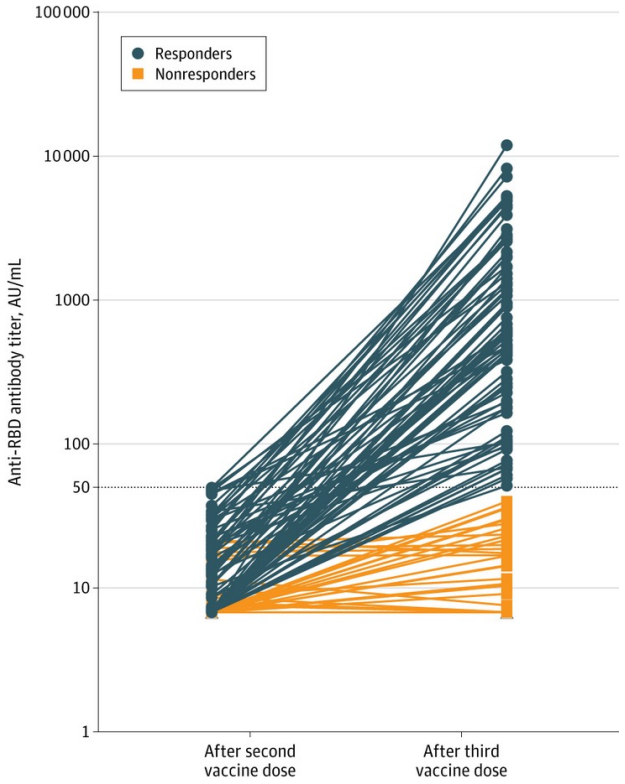
No MMF vs MMF

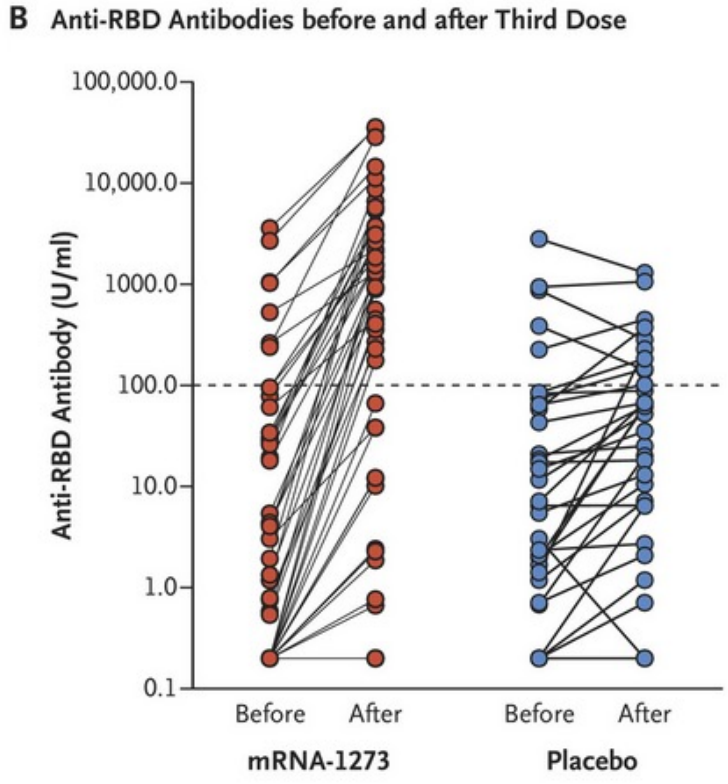


Mitchell *Transplantation* 2022; AH Karaba

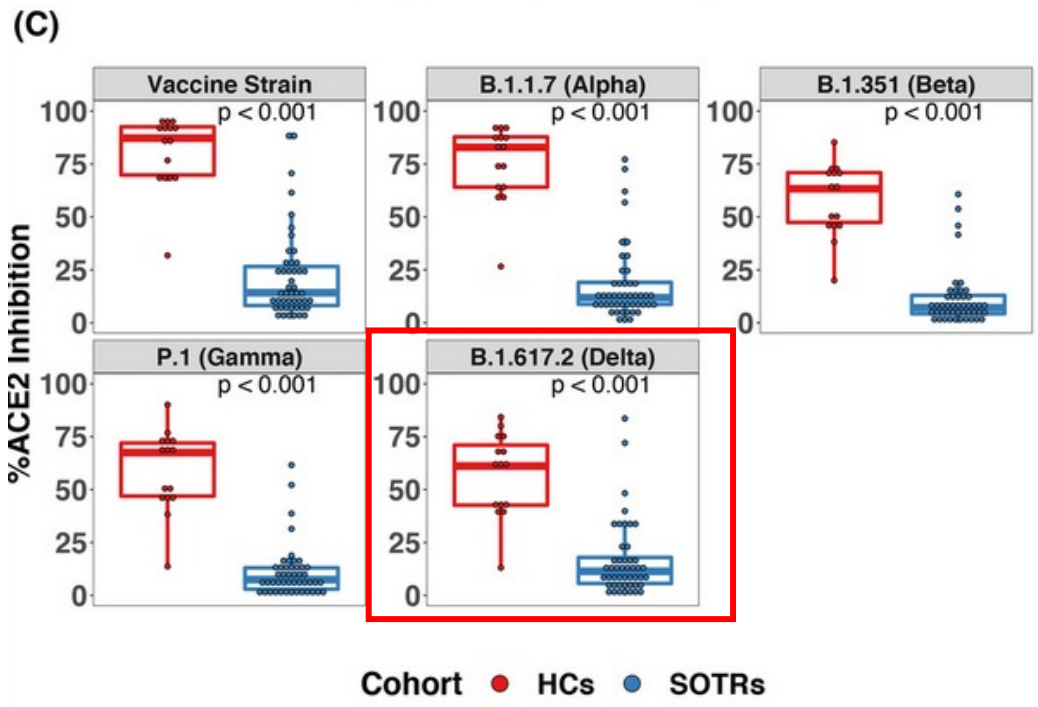
Improved antibody response to a third dose, but highly variable

Binding antibody
Measure of antibody level





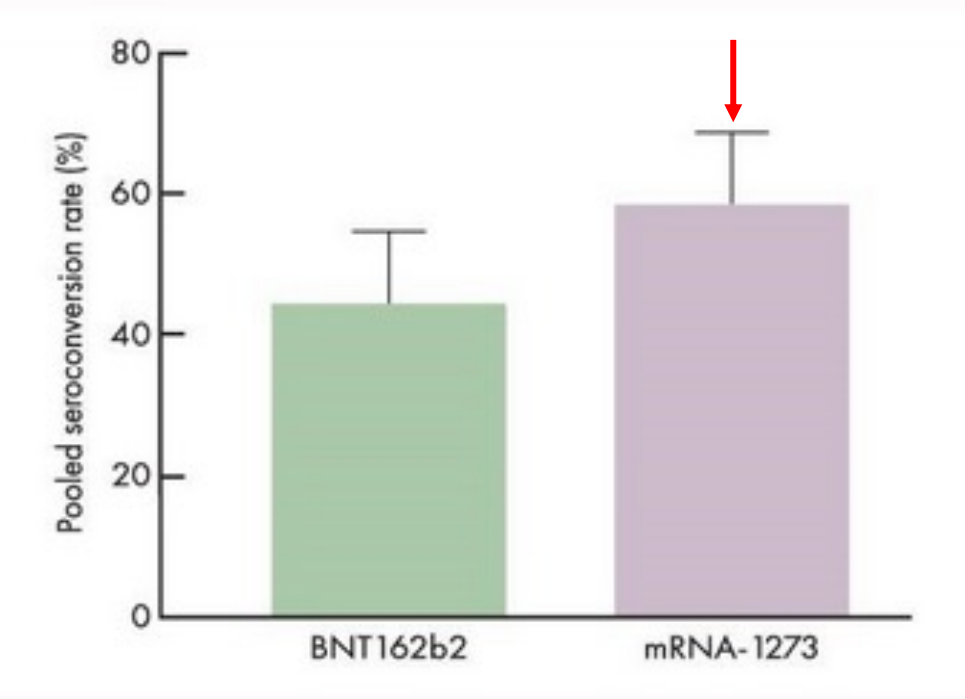
Neutralizing antibody
Measure of antibody *function*



Werbel *Annals Internal Med* 2021; Benotmane *JAMA* 2021; Hall *NEJM* 2021; Karaba *Am J Transplant* 2022

Two-Doses: BNT162b2 vs mRNA-1273

- BNT162b2 had an 80% lower seroconversion rate compared to mRNA-1273
  - More pronounced with greater immunosuppression



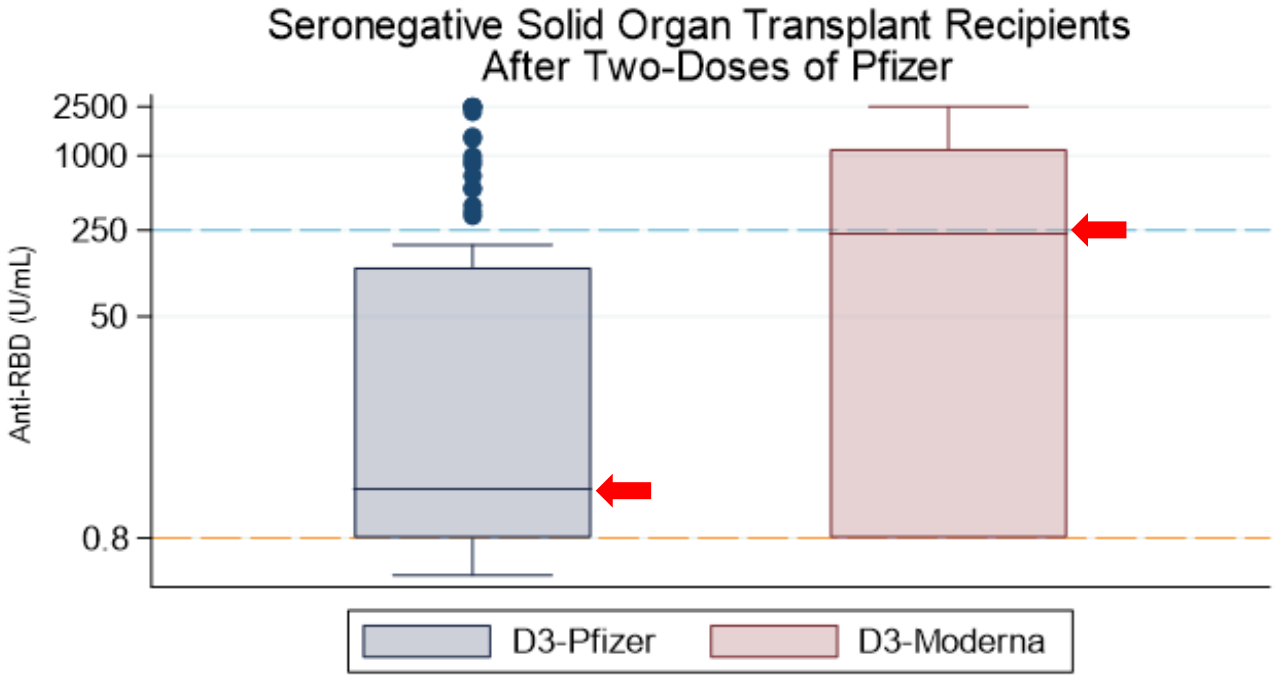
Anti-RBD Titer (U/mL)	IRR	p-value
SOTR‡ not on MMF (n=260)		
≥ 50	$_{1.16}$ **1.38** $_{1.64}$	**<0.001**
≥ 100	$_{1.22}$ **1.47** $_{1.77}$	**<0.001**
≥ 250	$_{1.24}$ **1.56** $_{1.96}$	**<0.001**
SOTR‡ on MMF (n=437)		
≥ 50	$_{1.11}$ **1.69** $_{2.58}$	**0.02**
≥ 100	$_{1.42}$ **2.40** $_{4.07}$	**<0.01**
≥ 250	$_{1.28}$ **2.62** $_{5.37}$	**0.01**

Verleye *Nephrol Dial Transplant* 2022; Mitchell *JAMA* Netw Open 2021

Third Dose Among Antibody Negative SOTRs: BNT162b2 vs mRNA-1273

- mRNA-1273 associated with induce higher antibody levels than BNT162b2, even among SOTRs who failed to make antibodies after 2 doses of BNT162b2

Anti-RBD	D3-Pfizer	D3-Moderna	p value
(+)	43 (52%)	8 (57%)	0.78
≥250 U/mL	16 (19%)	7 (50%)	0.02



Chang *Transplantation* 2022

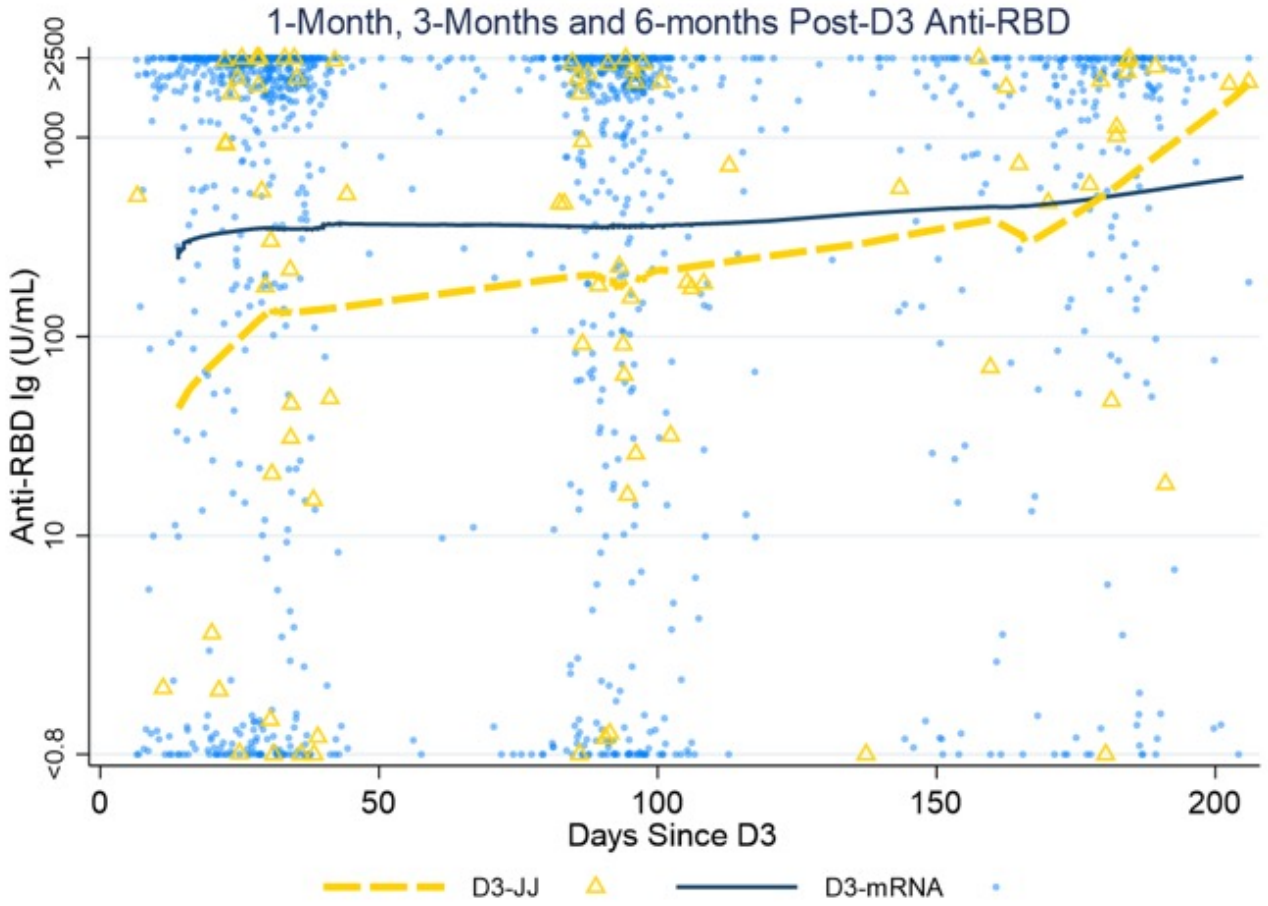
Third Dose Among Antibody Negative SOTRs: mRNA vs Adenovirus

SOTRs who received J&J after 2 mRNA vaccines were...

1.4x More likely to make antibodies

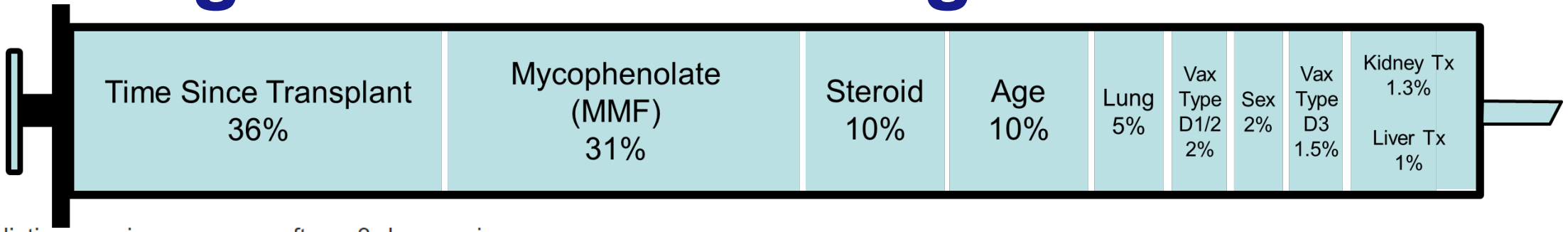
2.6x More likely to make high levels of antibodies (>250 U/mL)

… than SOTRs who received a third mRNA vaccine (BNT162b2 or mRNA-1273) at 6 months



Chiang, Alejo *Am J Transplant* 2022

Predicting Vaccine Response using Machine Learning



Predicting vaccine response after a 3-dose series

Enter patient characteristics and click **Submit** to predict the probability of a positive antibody response after a 3-dose series of SARS-CoV-2 vaccines.

Age (y)

0yrs | 50yrs | 100yrs

0 10 20 30 40 50 60 70 80 90 100

Race

- (•) White
- ( ) Non-White

Sex

- (•) Male
- ( ) Female

Doses 1 & 2 Vaccine Product

- (•) Moderna
- ( ) Pfizer-BioNTech

Dose 3 Vaccine Product

- (•) Moderna
- ( ) Pfizer-BioNTech
- ( ) J&J

Years since transplant

5

Organ Transplanted

- (•) Kidney
- ( ) Liver
- ( ) Pancreas
- ( ) Lung
- ( ) Heart
- ( ) Intestine
- ( ) Kidney-Liver
- ( ) Kidney-Pancreas

Immunosuppressive agents (Select all that apply)

- [x] Corticosteroids
- [x] Tacrolimus
- [x] Mycophenolates
- [ ] Everolimus
- [ ] Sirolimus
- [ ] Azathioprine

Submit

Result: 67.3%

(Predicted probability of a positive antibody response after a 3-dose SARS-CoV-2 vaccination.)

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Reference: Alejo *et al*, A Machine Learning Model for Predicting Antibody Response After Three Doses of Vaccine Against SARS-CoV-2 In Solid Organ Transplant Recipients. *Under Review*.

www.transplantmodels.com/covidvaccine_d3/

Alejo, Bae *Under Review*

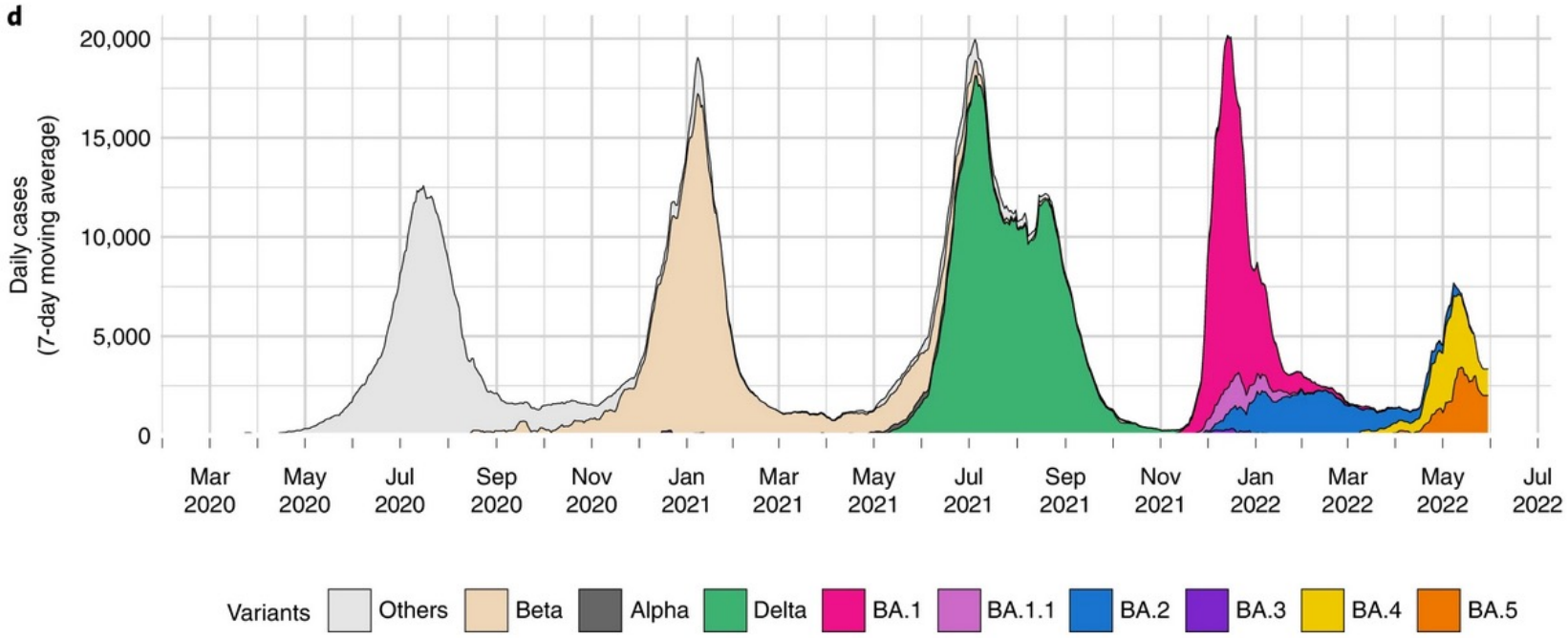
Impact of the Omicron Variant

Omicron Infections - General Public

Non-SOTR: 3 doses, compared to unvaccinated, had an estimated effectiveness of

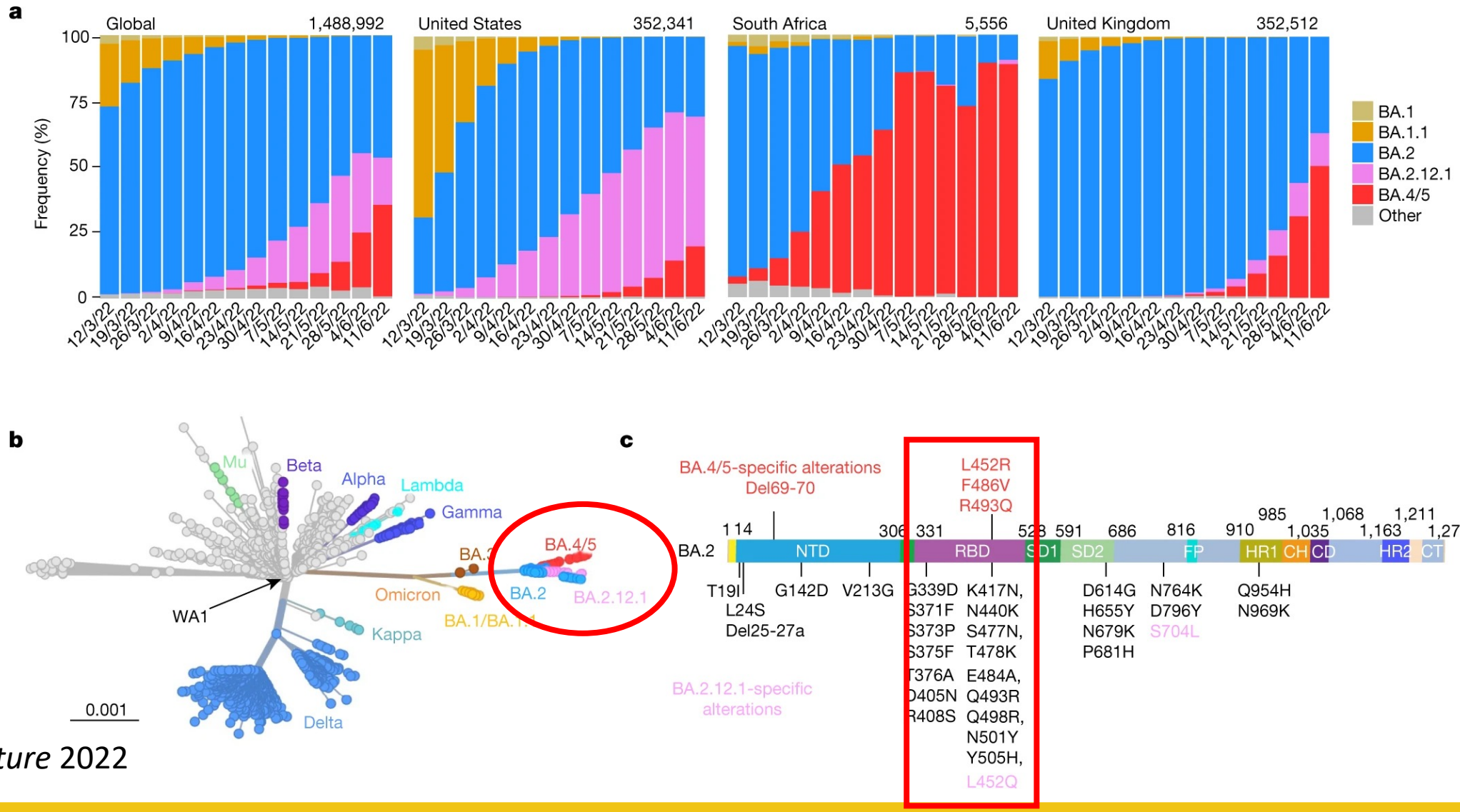
94% (95% CI: 93-94) for Delta

67% (95% CI: 65-69) for Omicron



Tegally *Nature Medicine* 2022
Accorsi *JAMA* 2022

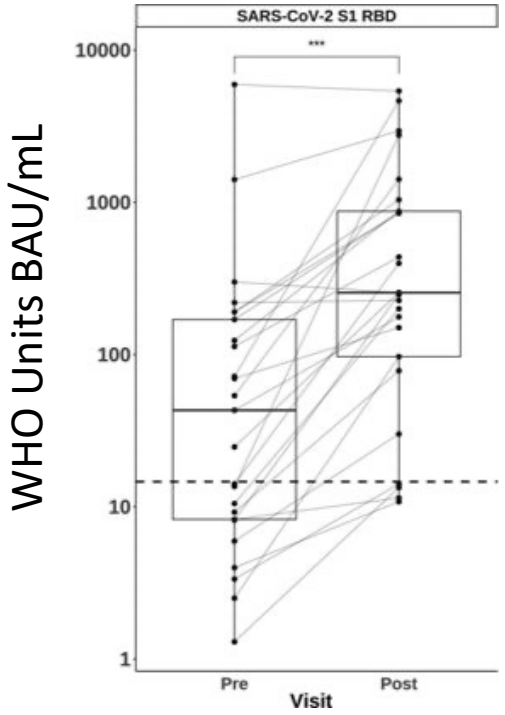
Omicron Sublineage Evolution

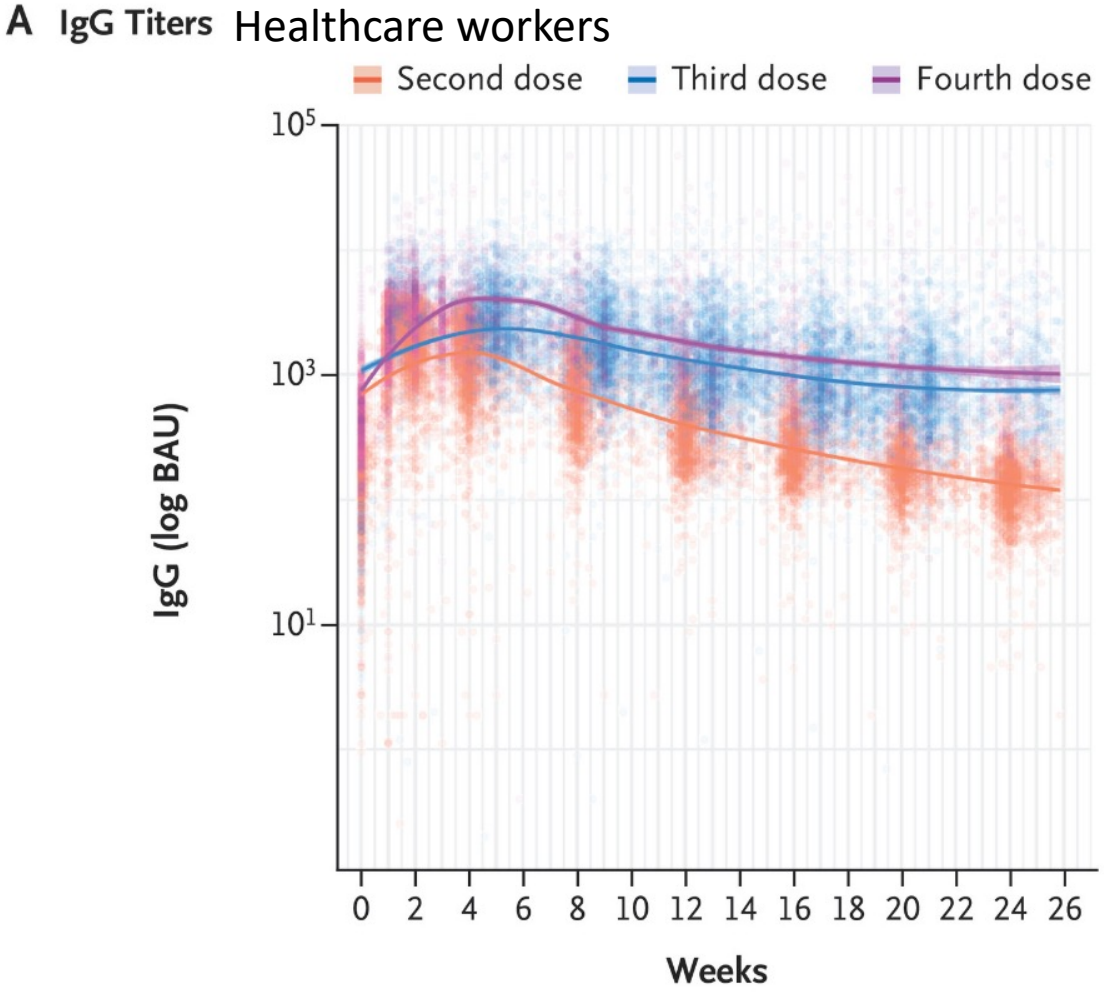


Wang *Nature* 2022

Vaccine-Induced Antibody Effectiveness against Omicron

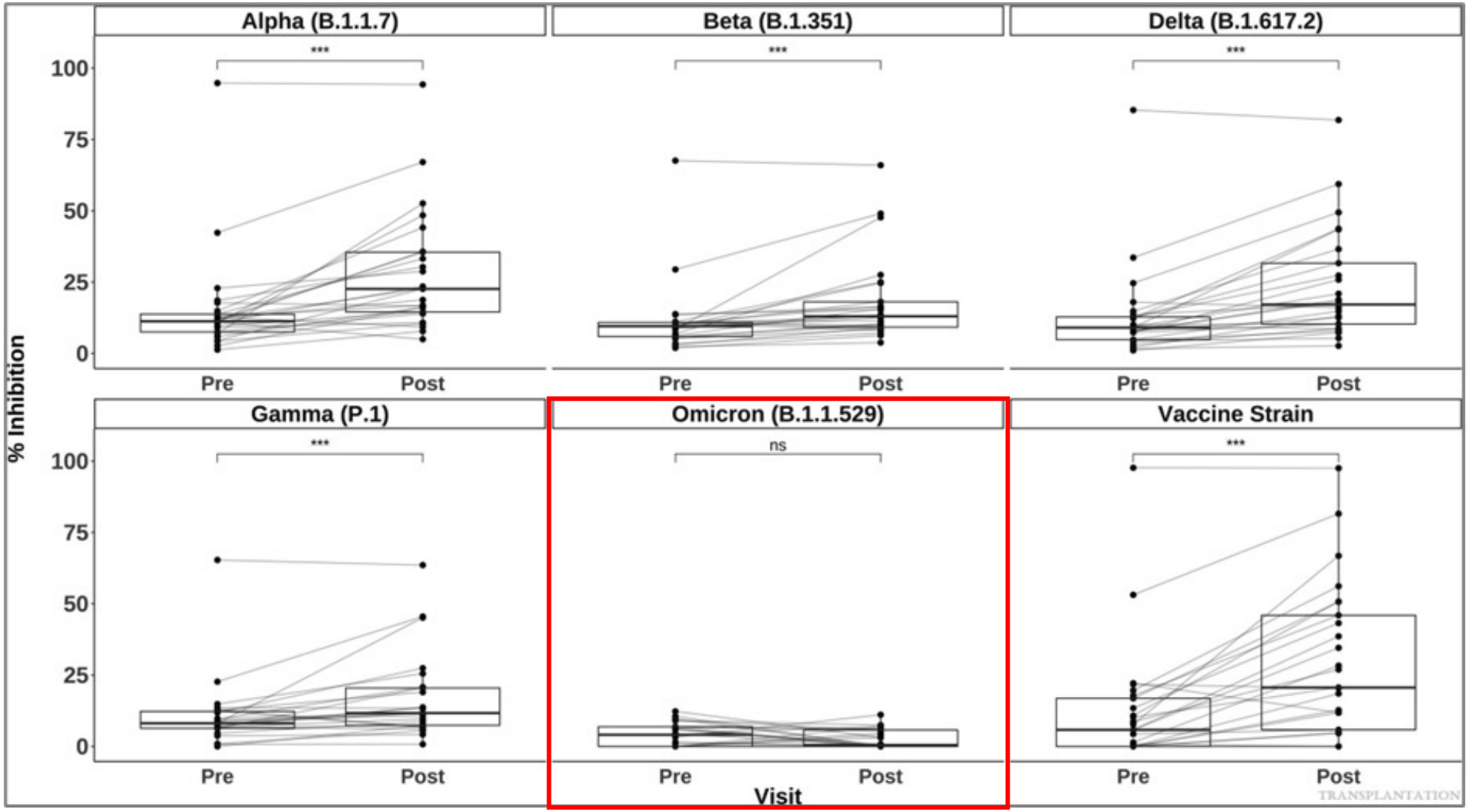
4 doses increased binding antibody, even over 6 months post-D4





Karaba *Transplantation* 2022; Canetti *NEJM* 2022

Few SOTRs mount antibody neutralization of Omicron (BA.1) after even 4 vaccine doses



Karaba *Transplantation* 2022; Canetti *NEJM* 2022

Omicron Infections in 3x-Vaccinated SOTRs

- Surveyed 1500 SOTRs after the Omicron Wave: 13% reported a positive or suspected COVID-19 infection
- Median (IQR) time from most recent vaccine to breakthrough infection was 5 (4-5) months

	No Omicron Infection Pre-wave Antibody Titer	**Confirmed or suspected Omicron** Pre-infection Antibody Titer	**p-value**
Anti-RBD, median (IQR)	2158 (95 – >2500) U/mL	380 (19 – >2500) U/mL	0.031
Anti-S, median (IQR)	8.5 (4.8 – 8.9) AU	4.0 (0.4 – 8.9) AU	0.19

98% of SOTRs with titers above 250 U/mL or 4 AU reported NO infection.

50% of SOTRs with titers below 250 U/mL or 4 AU reported a CONFIRMED OR SUSPECTED infection.

Alejo *Transplantation* 2022

Omicron Infections in 3x-Vaccinated SOTRs

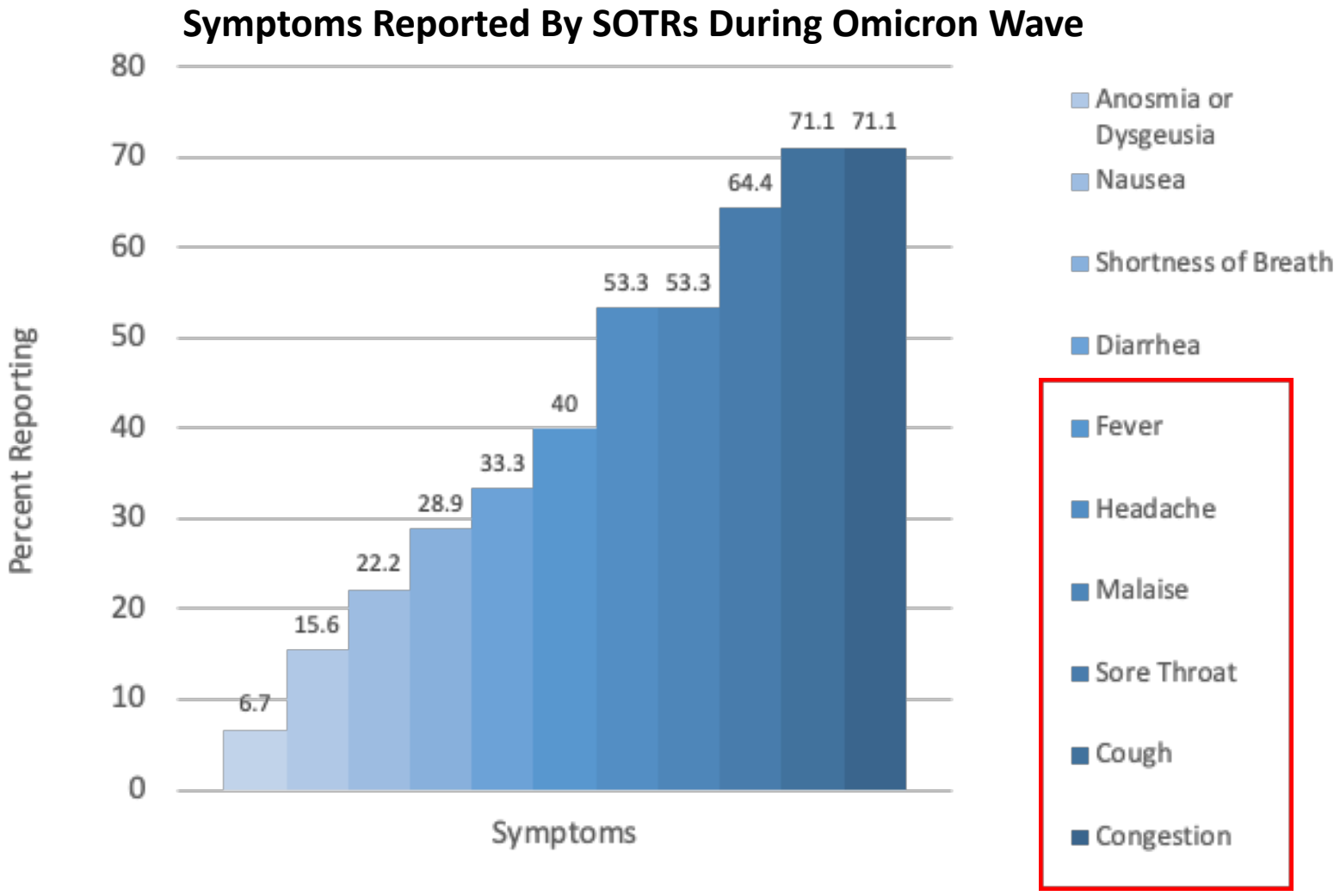
Symptom Duration

7 (4-10) days

Symptom Severity

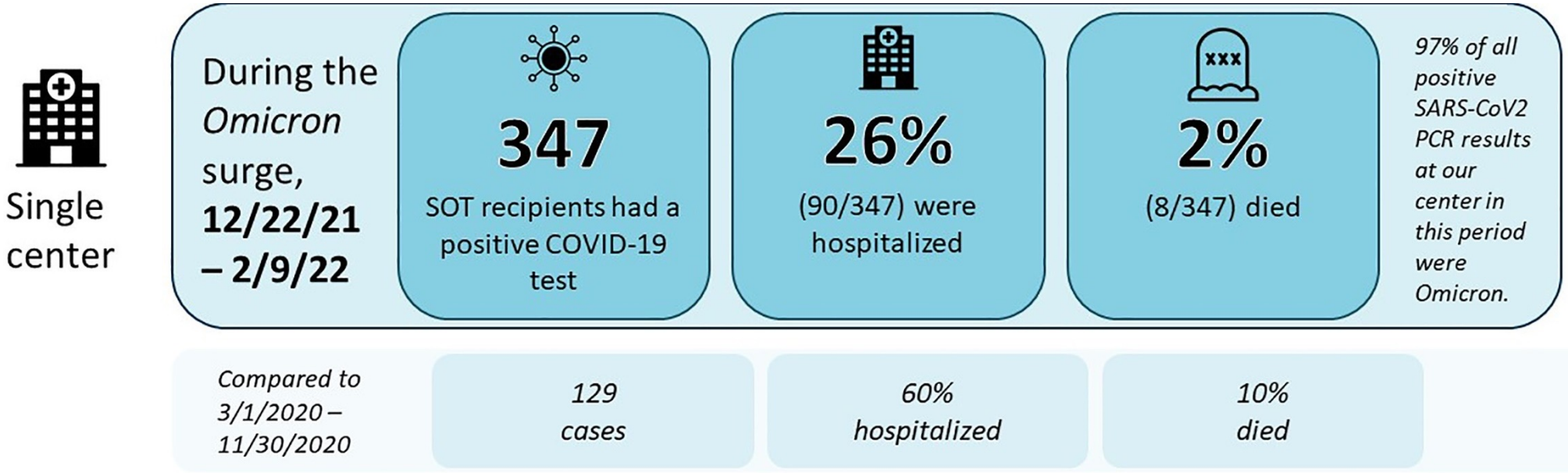
No symptoms...5%
Mild 52%
Moderate 35%

Severe (Hospitalized) 6%



Alejo *Transplantation* 2022

Omicron Infections in SOTRs – Hopkins Experience



Omicron variant COVID-19 caseloads were **high** among transplant recipients, but disease severity & mortality were **low**, compared to earlier in the pandemic.

Cochran et al. *Transplantation*. March 2022

@TransplantJrnl

Transplantation

Impact of vaccination plus, importantly, active monoclonal antibody therapies and antivirals

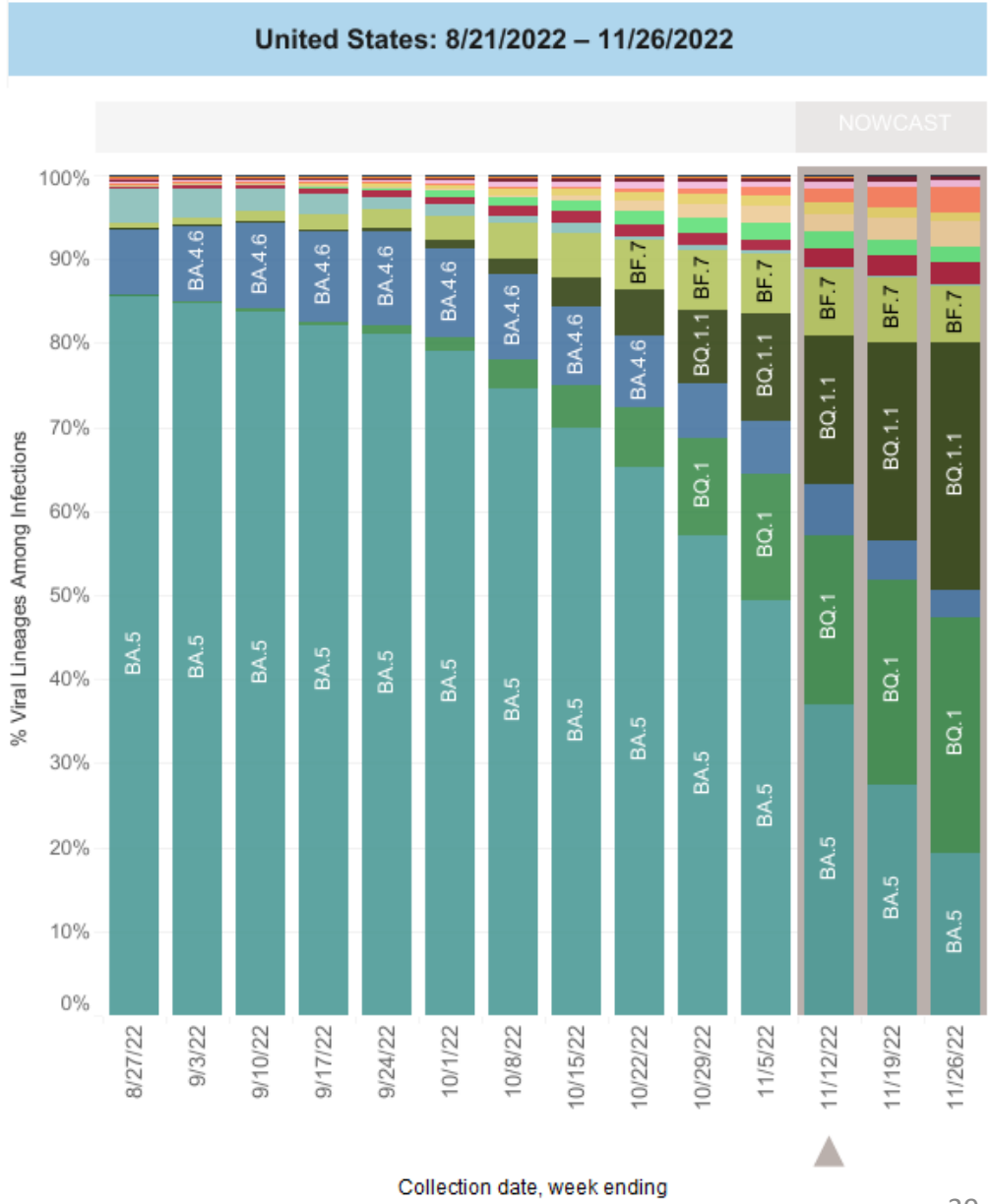
Summary: Omicron outcomes in SOTRs

- Omicron variant show major evasion of neutralizing antibody
- Results in decreased vaccine effectiveness, increased breakthrough
- Variant-active therapies have helped reduce serious disease

New Variants

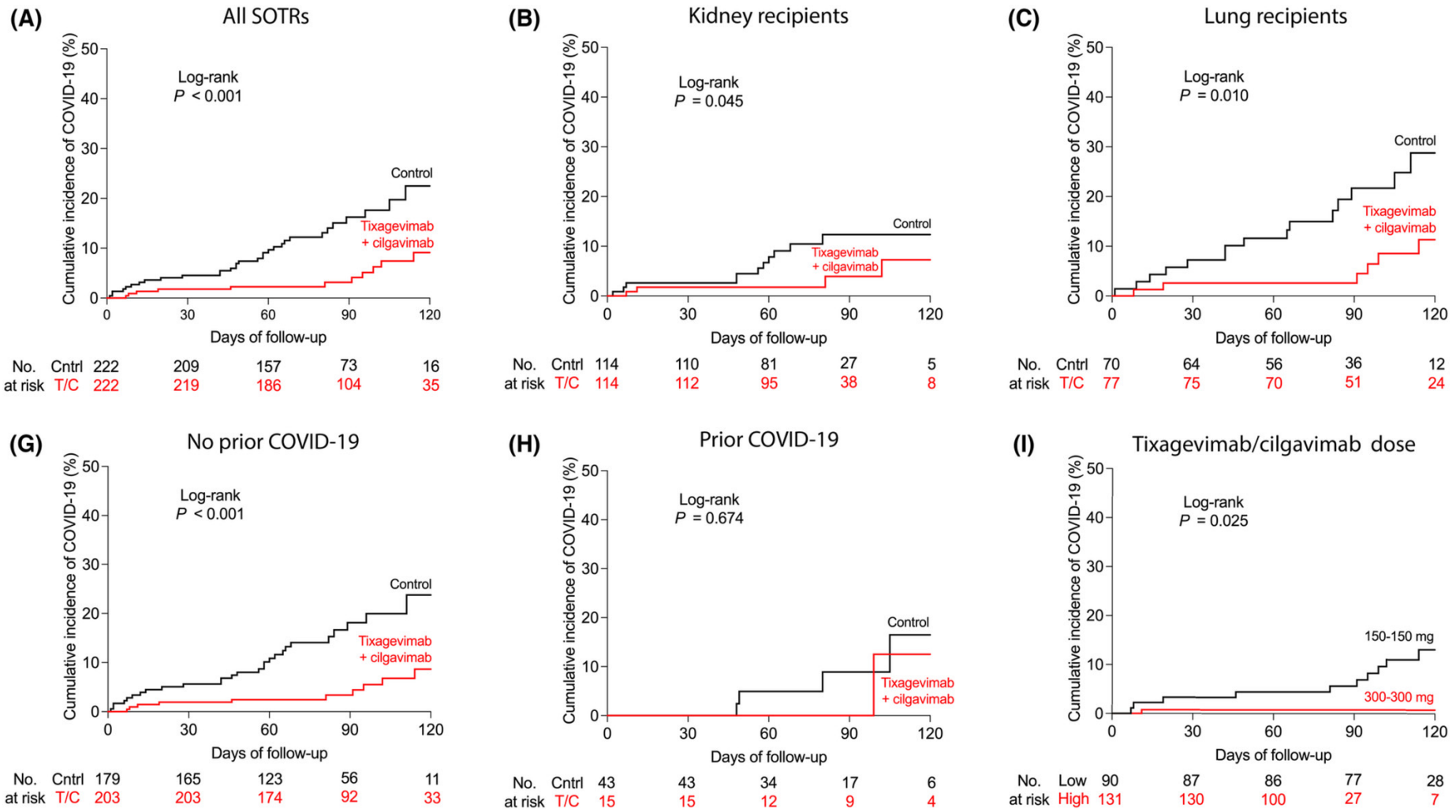
- Many sublineages have emerged this fall

- Convergent evolution among these variants show key mutations in spike protein → immune evasion



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

Tixagevimab/Cilgavimab (EVUSHELD™) Prophylaxis Reduced COVID-19 in SOTRs (Early Omicron Waves)



Al Jurdi *Am J Transpt* 2022

Activity of Select Monoclonal Antibodies Versus Omicron

Neutralization color coding is based upon synthesized available data regarding change in in vitro neutralization relative to that of an ancestral variant: green <10-fold reduction, yellow 10-100-fold reduction, orange >100-fold reduction.

Change in neutralizing activity adapted from NIH COVID-19 Treatment Guidelines.

Lineage	Tixagevimab and cilgavimab (Evusheld®) in vitro neutralization	Bebtelovimab in vitro neutralization
BA.5†		
BQ.1*		
BA.4		
BA.4.6		
BA.2† BA.2.12.1		
BA.1 BA.1.1		

In vitro activity may not correlate to real-world effectiveness and is only one component of clinical decision-making.

†Sublineages exhibiting additional mutations such as at spike positions 346, 444, 460, and/or 486 (e.g., BA.2.75.2, BN.1 [a BA.2 sublineage], or BF.7 [a BA.5 sublineage]) may show further in vitro immune evasion of tixagevimab and cilgavimab.

*This asterisk denotes that the category encompasses other members of the sublineage including BQ.1.1.

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COVID-19 Real-Time Learning Network
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Summary: New variants and other prevention/treatments

- The new variants evade immune response from mAb

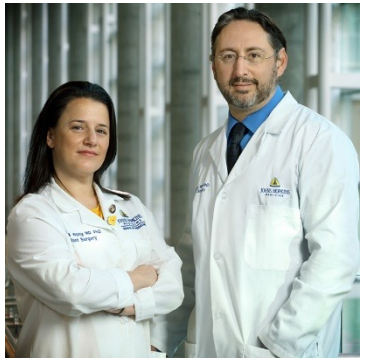
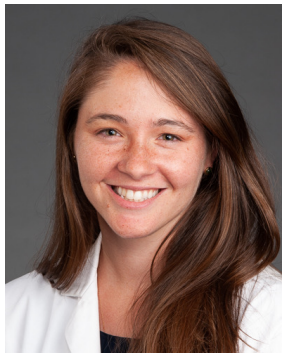
- Immune evasion limits the prevention and treatment options that are available to SOTRs

Future directions

- New vaccines
- Immunosuppressant modulation
- Next generation monoclonal antibodies

Johns Hopkins National COVID-19 Observational Study

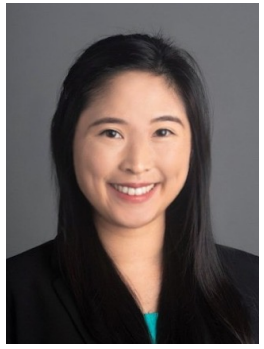
>70 peer-reviewed articles directly from the cohort data since March 2021!











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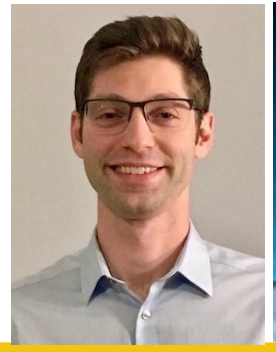
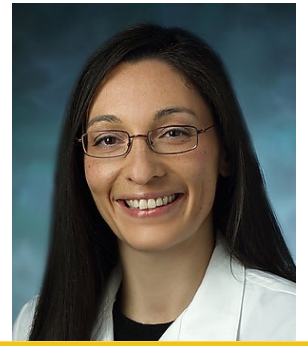
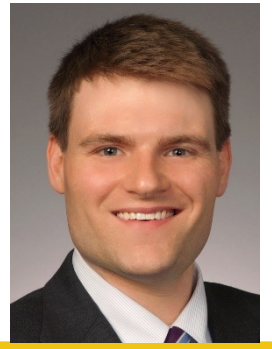


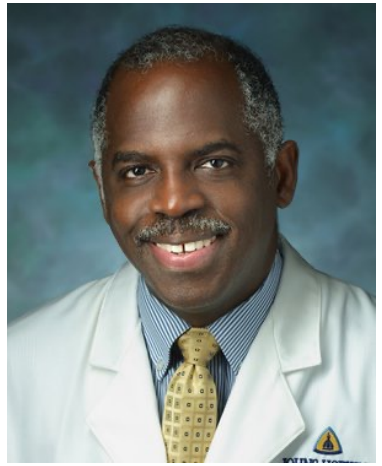

Basic and Translational Scientists











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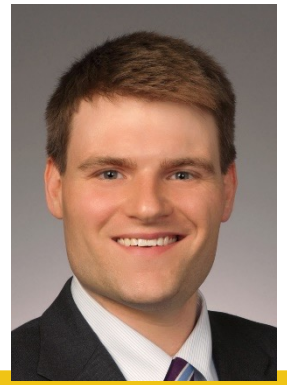
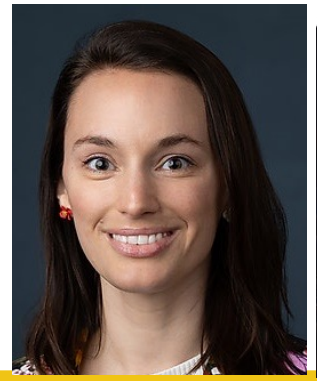


Tao Liang
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Mags Chahoud
Maggie Rodriguez
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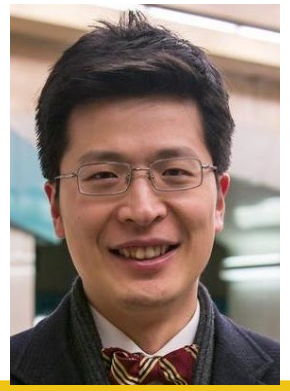
C-STAR

A Special Thanks to Our Panelists

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Q&A
QUESTIONS & ANSWERS