

COVID-19 Vaccination in Immunocompromised Patients

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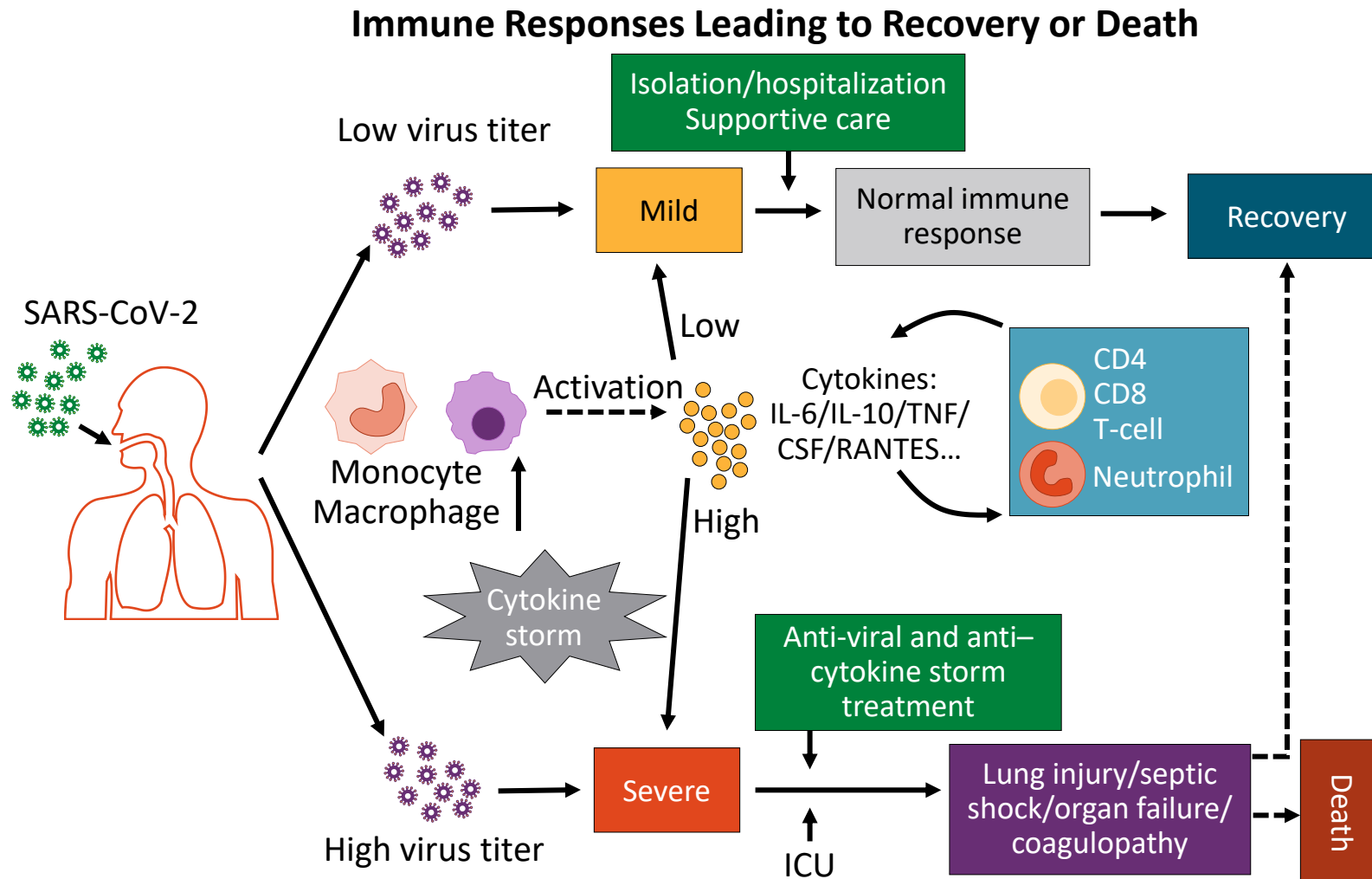
- Princeton University – BSE
- Icahn School of Medicine at Mount Sinai – MD, MPH
- Medicine Residency at Boston Medical Center
- Infectious Diseases Fellowship at MGH/BWH
- Transplant Infectious Diseases Fellowship at BWH
- Associate Clinical Director of Solid Organ Transplant Infectious Diseases
 - Clinical focus: transplant and oncology infectious diseases and cardiac device infections
 - Research focus: Clinical investigator, clinical trials



CDC: COVID-19 and Immunocompromised Patients

- *“Many conditions and treatments can cause a person to be immunocompromised or have a weakened immune system”*
 - Solid organ transplantation
 - Recent hematopoietic stem cell transplant
 - Active or recent treatment for solid tumor or hematologic malignancies
 - Severe primary immunodeficiency
 - HIV with a low CD4+ cell count or not on treatment
 - Prolonged use of corticosteroids, or use of other immune weakening medications (alkylating agents, antimetabolites, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory)
- Having a weakened immune system may increase the risk of severe illness from COVID-19

Immune Response to SARS-CoV-2



Adequate immune responses

- Timely innate/adaptive responses
- Quick type 1 IFN response
- Activation of efficient antiviral response (clearance by macrophages)
- Activation of Th1 cells and B-cells for production of neutralizing antibodies

Inadequate immune responses

- Delayed/limited type 1 IFN
- Endothelial cell death
- Epithelial/endothelial leakage
- Overactivation/exhaustion T-cells and NK cells
- Accumulation of activated macrophages → cytokine storm

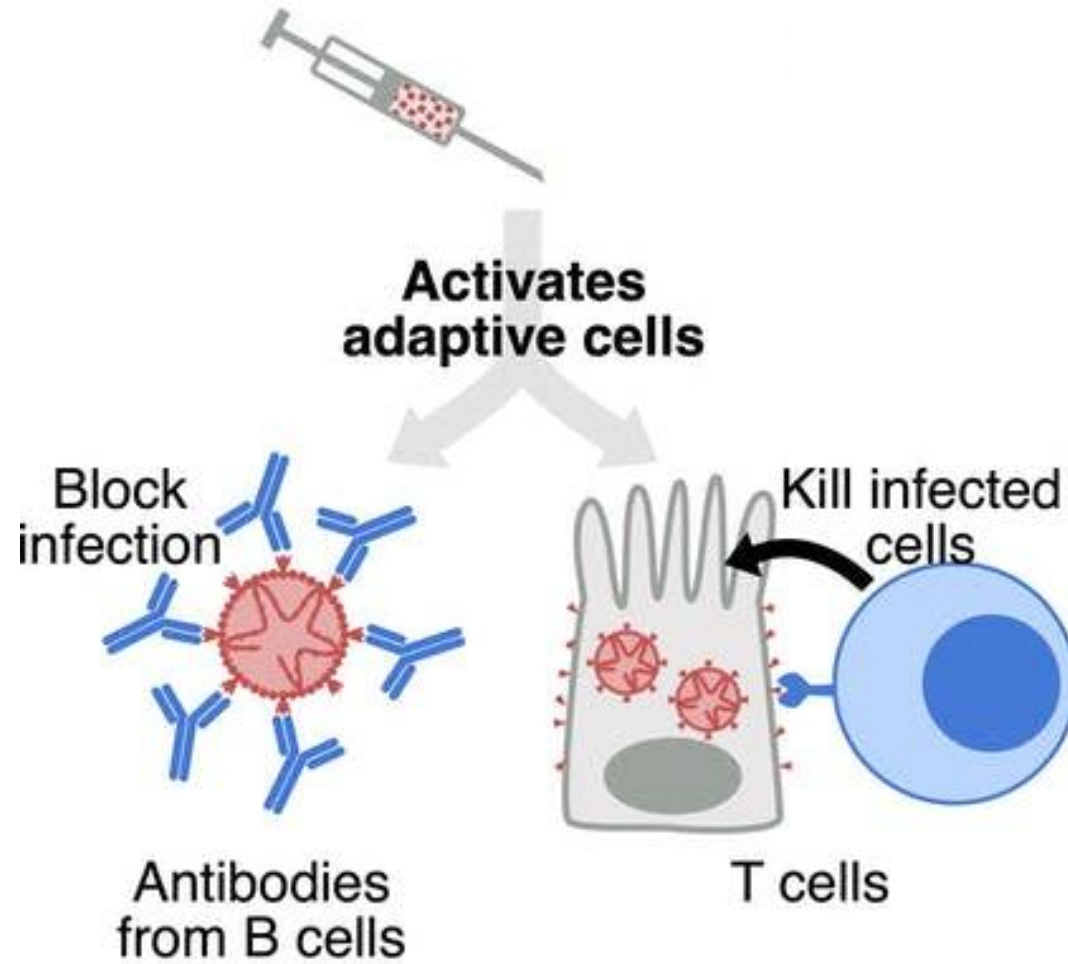
Immune-Related Risk Factors for Susceptibility to Severe COVID

- Older persons have impaired B-cell and T-cell immune responses vs younger persons
 - Impaired B-cell response: reduced ability to mount a neutralizing antibody response
 - Impaired T-cell response: we are learning more about the role of T-cell response in control of ongoing SARS-CoV-2
- Younger persons with impaired or dysregulated B-cell and T-cell immune responses may also be at risk

SARS-CoV-2 Impact on Immunocompromised Individuals

- Immunocompromised individuals comprise ~2.7% (~7 million) of U.S. adults
- More likely to get severely ill from COVID-19
- Higher risk for:
 - Prolonged SARS-CoV-2 infection and viral shedding
 - Viral evolution during infection and treatment (hospitalized patients)
- More likely to transmit SARS-CoV-2 to household contacts
- Lower antibody/neutralization titers to SARS-CoV-2 variants compared to immunocompetent individuals
- More likely to have vaccine breakthrough infections

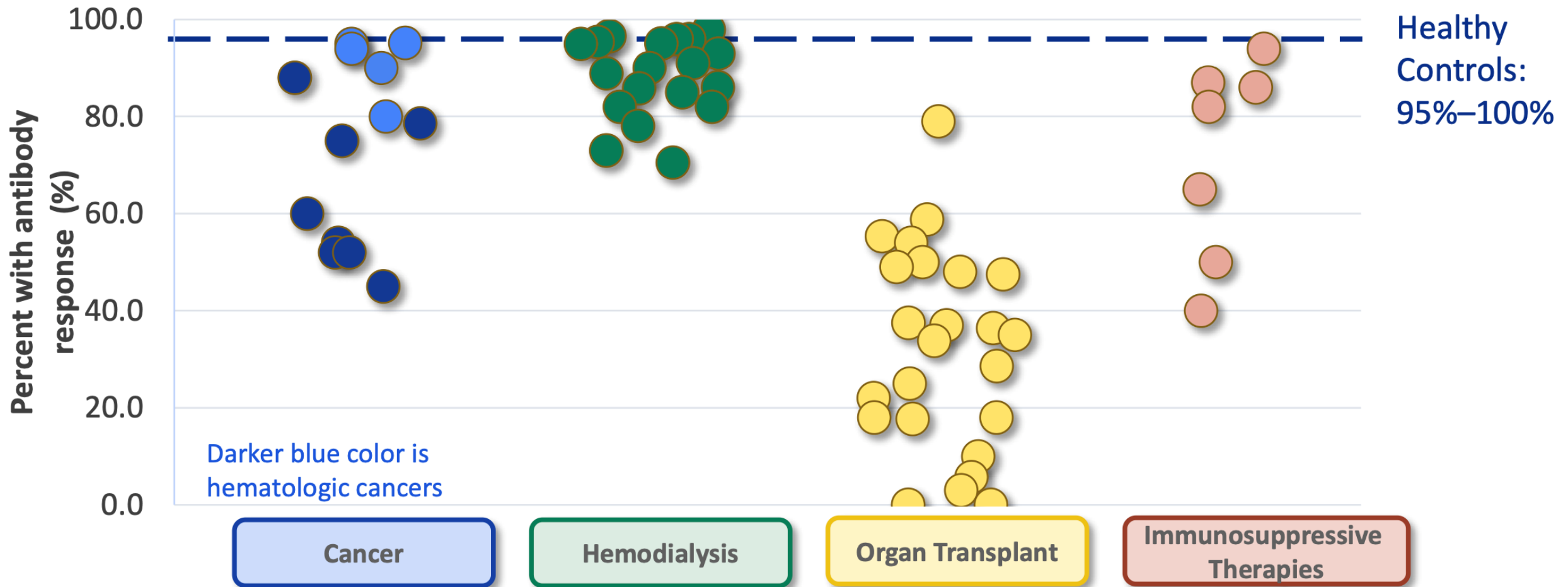
Vaccination and Immunity



Vaccine Breakthrough Infections

- Lower vaccine effectiveness among immunocompromised individuals
 - 59-72% vaccine efficacy among immunocompromised vs. 90-94% among immunocompetent after 2nd dose of mRNA vaccine
- Immunocompromised individuals – *solid organ transplant recipients* – mount a less robust humoral response post-COVID vaccination compared to immunocompetent individuals

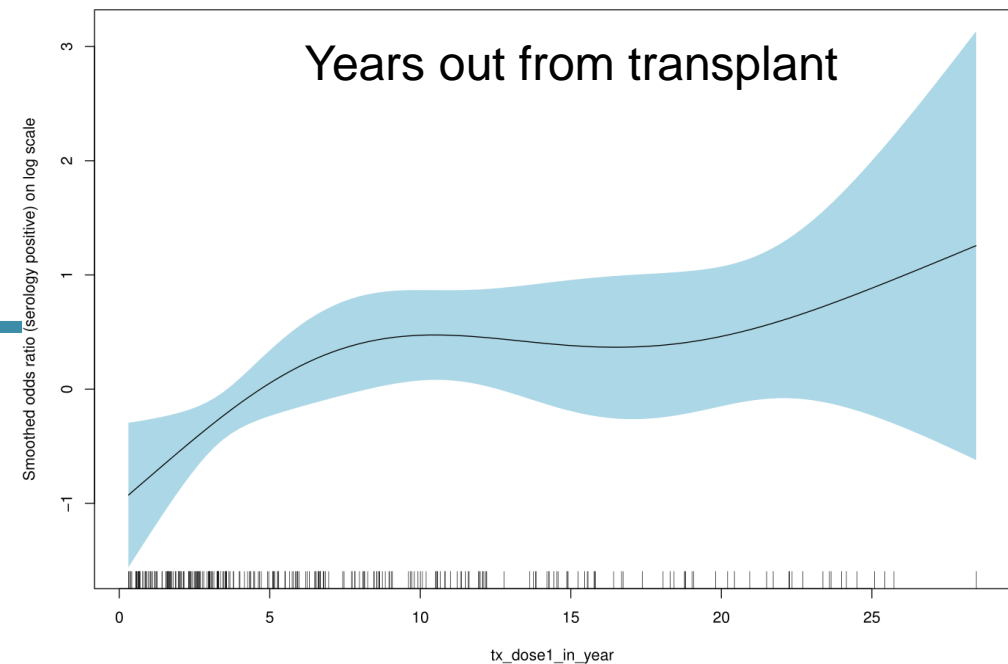
Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)



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

Factors that most contributed to having a positive antibody?

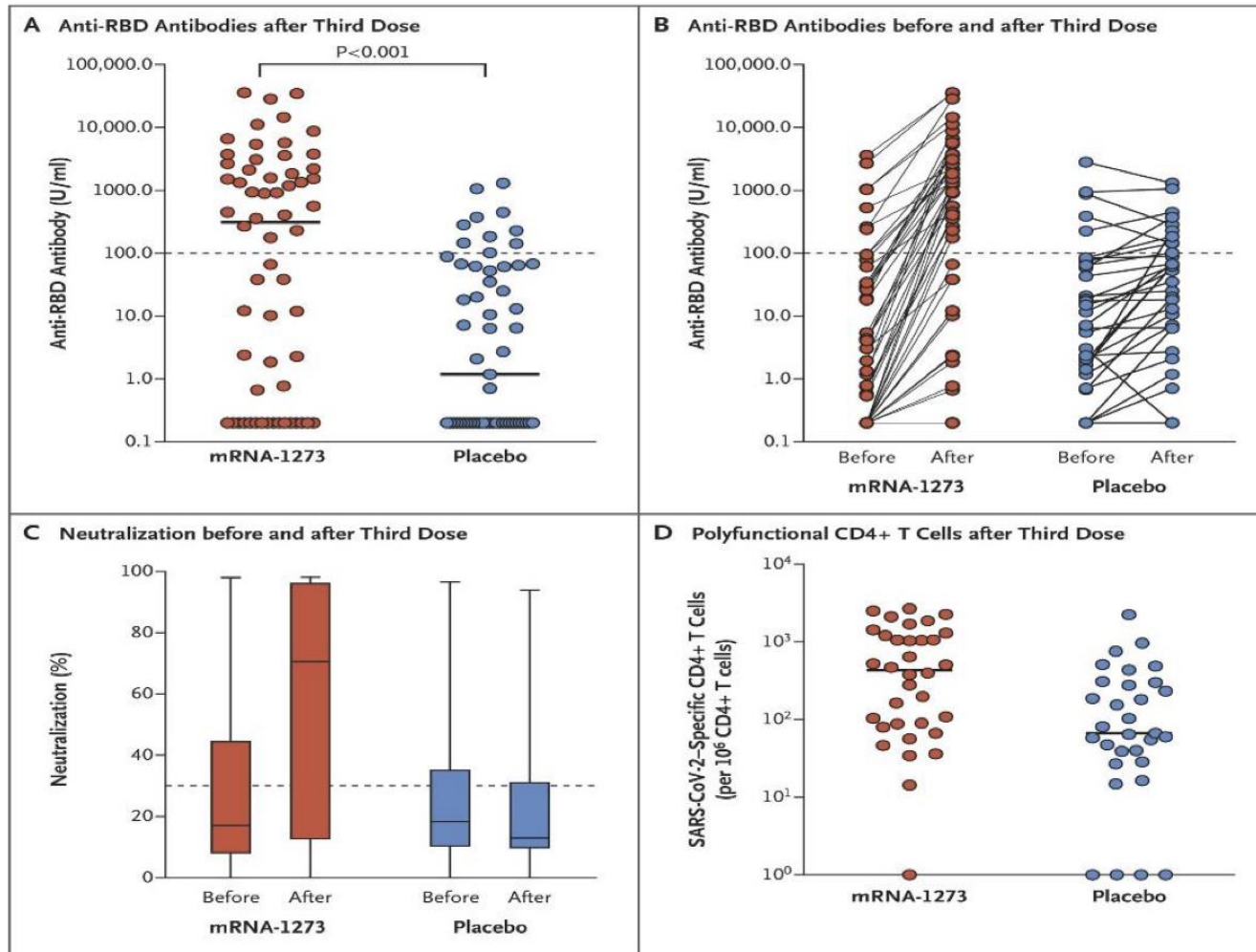
- **Abdominal organ transplant** (kidney or liver) rather than a thoracic organ transplant (lung or heart)
- **>10 years out from transplant**
- ***Not*** being on **mycophenolate**



Vaccine Breakthrough Infections

- Lower vaccine effectiveness among immunocompromised individuals
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 - Immunocompromised individuals – *solid organ transplant recipients* – mount a less robust humoral response post-COVID vaccination compared to immunocompetent individuals
 - Prior studies demonstrated an increased immune response post-3rd COVID vaccine dose when given 1-month post-2nd dose in transplant recipients
-

Randomized Trial of a 3rd Dose of Moderna Vaccine in Transplant Recipients (n=120)



RBD antibody (≥ 100 U/ml) 1
month post dose 3:

33 of 60 patients
(55%) vaccine group

vs.

10 of 57 patients
(18%) placebo group

COVID-19 Vaccination in Transplant Patients

- Many questions remain
 - What is the optimal timing of additional vaccine doses in immunocompromised individuals?
 - Does a mix-and-match strategy for mRNA COVID vaccines impact response?
 - What is the correlate for immune protection and does measuring SARS-CoV-2 spike Ab impact clinical care?
 - Objective of the BWH transplant COVID-19 vaccine study:
 - *Does a 3rd mRNA vaccine dose administered 6-months post-2nd dose enhance humoral immune response in transplant recipients?*
-

Single-center Prospective Cohort Study

Inclusion Criteria

- Heart, lung, kidney or dual organ txp recipient
- Had not received COVID vaccine prior to txp
- Did not have COVID-19 prior to receipt of 3rd vaccine dose

mRNA-1273 [**Moderna**]
BNT162b2 [**Pfizer-BioNTech**]

236 SOT
patients

Jan 2021

6 months

Feb 2022

- COVID-19 Infection?
- Survival

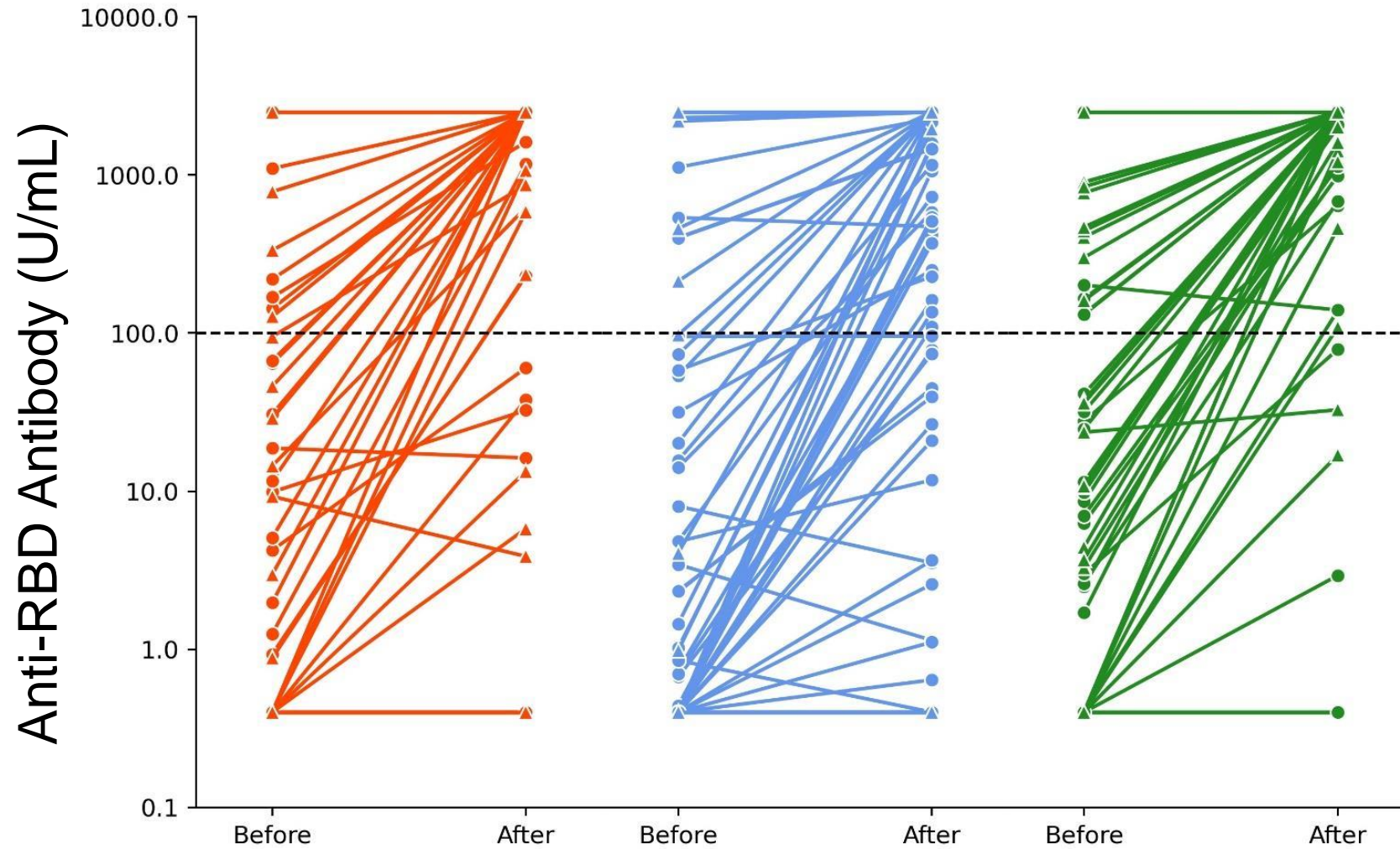
Roche Elecsys anti-SARS-CoV2
spike enzyme immunoassay

Proportion with a Positive Ab Post-3rd Vaccine Dose



	Positive Antibody Post-3 rd Dose	Negative Antibody Post-3 rd Dose
Total 236	132 (56%)	104 (44%)

Anti-RBD Antibodies Before and After 3rd Vaccine Dose



- <10 years post-transplant
- ▲ ≥10 years post-transplant

Heart
n = 48

Lung
n = 72

Kidney
n = 51

Multivariate Analysis



Characteristic	Adjusted Odds Ratio (95% CI)	Adjusted p-value
Age, >60 years old (<i>ref</i> = <60 yo)	0.38 (0.20 to 0.71)	0.0023
Years out from transplant (<i>ref</i> = 1 year)		
2 years	5.19 (1.42 to 18.99)	0.0129
3-5 years	5.83 (1.62 to 20.93)	0.0069
6-10 years	4.59 (1.25 to 16.86)	0.0216
11-15 years	10.96 (2.59 to 46.36)	0.0011
>= 16 years	16.61 (3.78 to 72.93)	0.0002
Organ type (<i>ref</i> = kidney)		
Lung	0.17 (0.07 to 0.39)	<0.0001
Heart	0.25 (0.11 to 0.59)	0.0013
Mycophenolate	0.29 (0.15 to 0.56)	0.0002

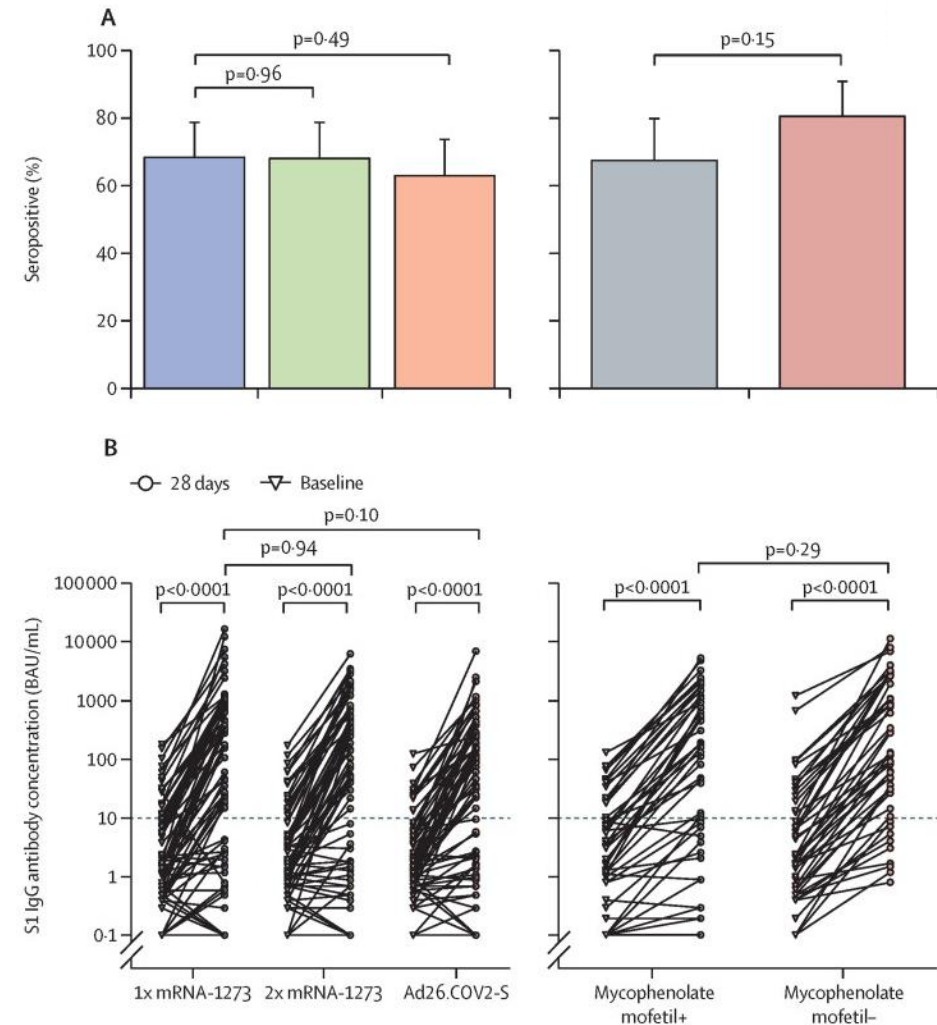
Outcomes	Positive Antibody (<i>n</i> = 132)	Negative Serology (<i>n</i> = 104)
COVID+ post-3 rd dose	30 (23%)	22 (21%)
Months between post-3 rd dose and COVID+	3.7 (3.0 – 4.3)	4.2 (1.3 – 4.6)
Hospitalized	6 (20%)	8 (36%)
Mortality	4 (3%)	4 (4%)

- Despite extended interval of 6 months, the proportion of non-responders (44%) was similar to other studies when the 3rd dose was given 1-month post-2nd vaccine dose
- Significant factors to having a positive spike antibody post-3rd vaccine dose
 - Age less than 60 years old
 - Having an abdominal organ transplant (kidney) rather than a thoracic organ transplant (heart > lung)
 - Being >10 years out from transplant
 - Not being on mycophenolate
- A similar proportion of individuals had COVID-19 infection post-3rd vaccine dose, irrespective of positive vs negative antibody result
 - Median time to COVID-19 infection was 4 months post-3rd vaccine dose

What additional strategies are there for those immunocompromised individuals who do not mount a robust humoral response to vaccination?

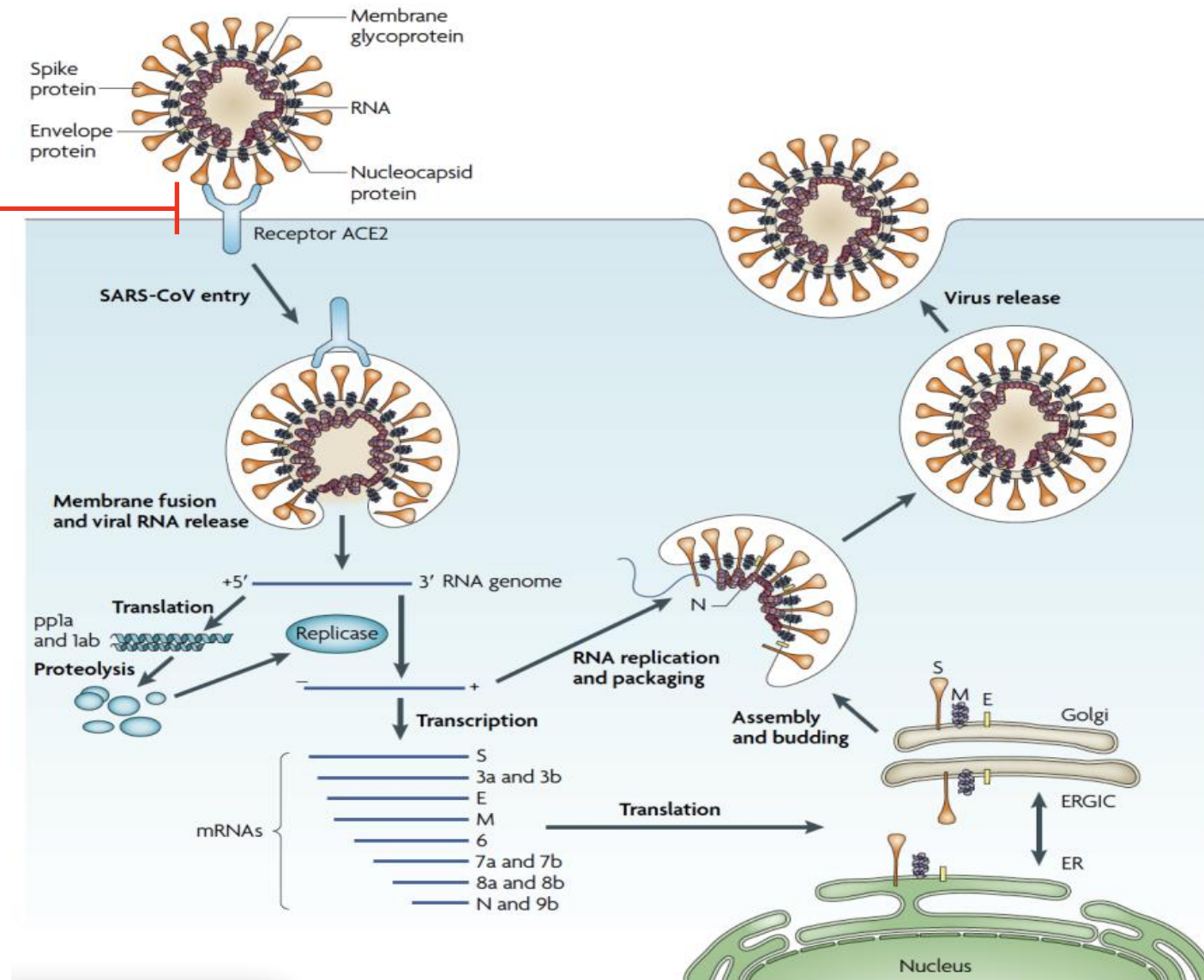
Strategies to increase the immunogenicity of COVID-19 vaccines in kidney transplant recipients

- RCT to compare 3 strategies with a control single dose mRNA-1273 vaccination in kidney transplant recipients (KTRs):
 - double vaccine dose, heterologous vaccination, and temporary discontinuation of mycophenolate mofetil or mycophenolic acid
- Repeated vaccination increases SARS-CoV-2-specific antibodies in KTRs, without further enhancement by use of a higher dose, a heterologous vaccine, or 2 weeks discontinuation of mycophenolate mofetil or mycophenolic acid



SARS-CoV-2 Viral Life Cycle

Neutralizing
Antibodies



Monoclonal Antibodies Bind to Spike Protein

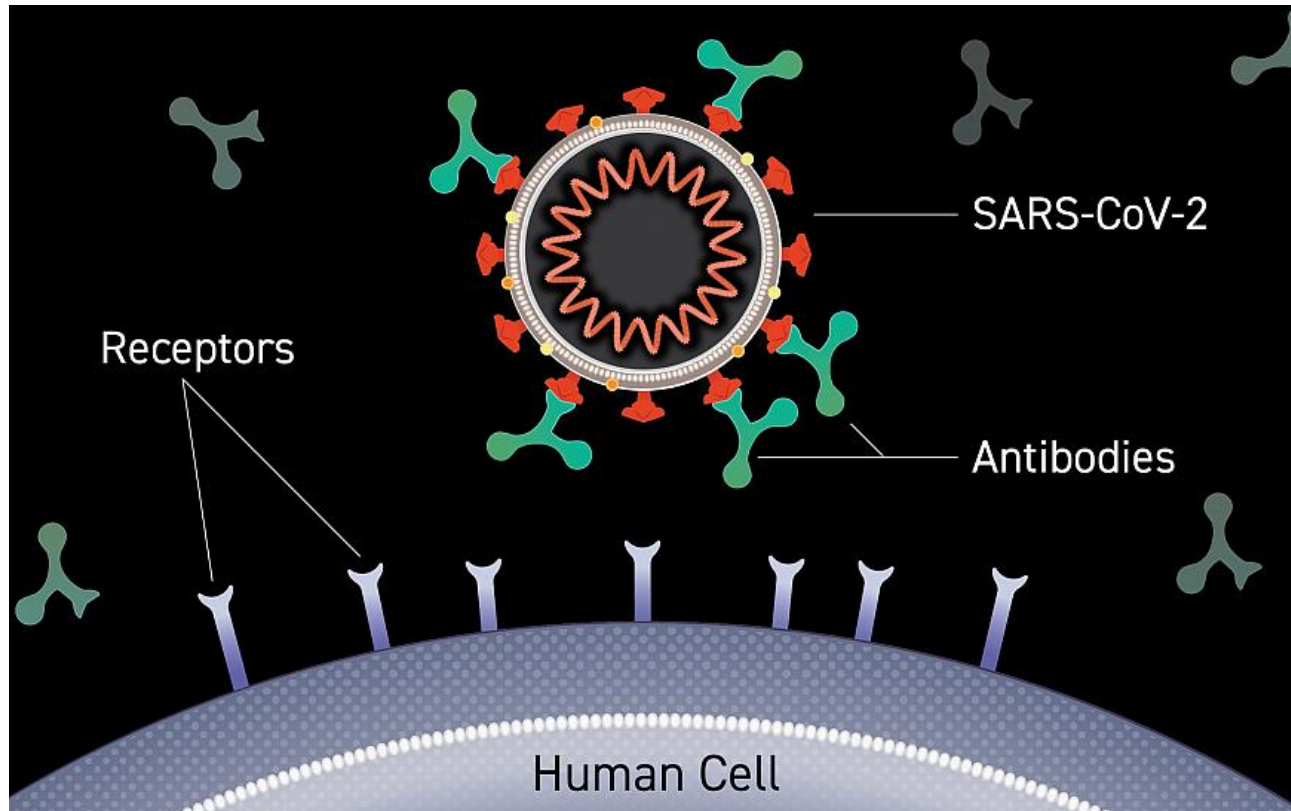


Image credit: <https://www.nih.gov/>

Monoclonal antibodies

Bamlanivimab + Etesevimab

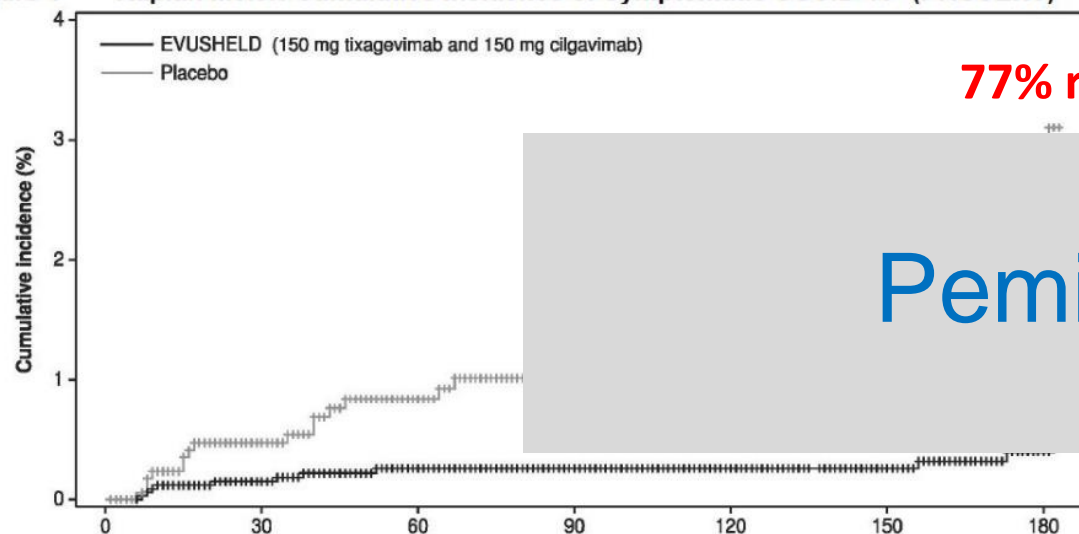
Casirivimab + Imdevimab

Sotrovimab

Bebtelovimab

Tixagevimab/cilgavimab – COVID-19 Pre-exposure Prophylaxis

Figure 1 Kaplan Meier: Cumulative Incidence of Symptomatic COVID-19* (PROVENT)



Levin. IDWeek 2021. Abstr LB5.

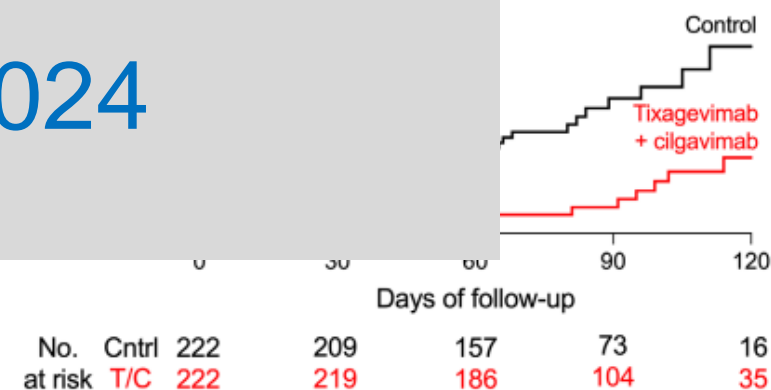
(A)

All SOTRs

COVID-19 (%)

Log-rank
 $P < 0.001$

Pemivibart 2024



Question #1

I am an adult in 2024 who underwent a stem cell transplant 6 months ago and have had one or more doses of a COVID-19 vaccine in the past. What is the current recommendation?

- A. Get a first dose of the updated 2023-2024 COVID mRNA vaccine
 - B. Get a second dose 3 weeks after the last dose
 - C. Get a third dose at least 8 weeks after the last dose
 - D. Get one dose only of the updated 2023-2024 COVID vaccine
 - E. It depends
 - F. A, B, C
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Question #2

Vaccinated immunocompromised individuals no longer have an increased risk of hospitalization and death from COVID-19 compared to non-immunocompromised individuals.

- A. True
 - B. False
-

Question #2

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A. True

B. False

TABLE 3. Association of vaccination status* with intensive care unit admission and in-hospital death among patients hospitalized for COVID-19, by immunocompromise status—COVID-NET, 10 states, † March 1, 2021–February 28, 2022

Vaccination status*	No. (weighted %) [§]											
	Immunocompromised†						Not immunocompromised**					
	ICU admission			Death			ICU admission			Death		
	Yes	No	aOR (95% CI)	Yes	No	aOR (95% CI)	Yes	No	aOR (95% CI)	Yes	No	aOR (95% CI)
Vaccinated	85 (25.0)	269 (75.0)	1.01 (0.64–1.58)	55 (16.5)	298 (83.5)	1.34 (0.71–2.51)	257 (18.7)	1,044 (81.3)	0.85 (0.60–1.12)	113 (9.5)	1,188 (90.5)	0.58 (0.39–0.86) ^{††}
Unvaccinated	129 (25.5)	351 (74.5)	Ref	66 (12.9)	413 (87.1)	Ref	1,121 (21.6)	3,771 (78.4)	Ref	488 (10.1)	4,409 (89.9)	Ref

Thank you!

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References

1. Al Jurdi A, Morena L, Cote M, Bethea E, Azzi J, Riella LV. Tixagevimab/cilgavimab pre-exposure prophylaxis is associated with lower breakthrough infection risk in vaccinated solid organ transplant recipients during the omicron wave. *Am J Transplant*. 2022 Jun 21. doi: 10.1111/ajt.17128. Epub ahead of print. PMID: 35727916.
2. Kim L, Garg S, O'Halloran A, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)–associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis* 2021;72:e206–14. <https://doi.org/10.1093/cid/ciaa1012> PMID:32674114
3. Garg S, Patel K, Pham H, et al. Clinical trends among U.S. adults hospitalized with COVID-19, March to December 2020: a cross-sectional study. *Ann Intern Med* 2021;174:1409–19. <https://doi.org/10.7326/M21-1991> PMID:34370517
4. Tenforde MW, Patel MM, Gaglani M, et al.; IVY Network. Effectiveness of a third dose of Pfizer-BioNTech and Moderna vaccines in preventing COVID-19 hospitalization among immunocompetent and immunocompromised adults—United States, August–December 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:118–24. <https://doi.org/10.15585/mmwr.mm7104a2> PMID:35085218
5. Tenforde MW, Self WH, Gaglani M, et al.; IVY Network. Effectiveness of mRNA vaccination in preventing COVID-19–associated invasive mechanical ventilation and death—United States, March 2021–January 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:459–65. <https://doi.org/10.15585/mmwr.mm7112e1> PMID:35324878
6. Harpaz R, Dahl RM, Dooling KL. Prevalence of immunosuppression among US adults, 2013. *JAMA* 2016;316:2547–8. <https://doi.org/10.1001/jama.2016.16477> PMID:27792809
7. Chow N, Fleming-Dutra K, Gierke R, et al.; CDC COVID-19 Response Team. Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019—United States, February 12–March 28, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:382–6. <https://doi.org/10.15585/mmwr.mm6913e2> PMID:32240123
8. Andrejko KL, Pry JM, Myers JF, et al.; California COVID-19 Case-Control Study Team. Effectiveness of face mask or respirator use in indoor public settings for prevention of SARS-CoV-2 infection—California, February–December 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:212–6. <https://doi.org/10.15585/mmwr.mm7106e1> PMID:35143470
9. Sami S, Horter L, Valencia D, et al. Investigation of SARS-CoV-2 transmission associated with a large indoor convention—New York City, November–December 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:243–8. <https://doi.org/10.15585/mmwr.mm7107a4> PMID:35176005
10. Wiltz JL, Feehan AK, Molinari NM, et al. Racial and ethnic disparities in receipt of medications for treatment of COVID-19—United States, March 2020–August 2021. *MMWR Morb Mortal Wkly Rep* 2022;71:96–102. <https://doi.org/10.15585/mmwr.mm7103e1> PMID:35051133
11. Fu J, Reid SA, French B, et al.; COVID-19 and Cancer Consortium (CCC19). Racial disparities in COVID-19 outcomes among black and white patients with cancer. *JAMA Netw Open* 2022;5:e224304. <https://doi.org/10.1001/jamanetworkopen.2022.4304> PMID:35344045
12. Singson JR, Kirley PD, Pham H, et al. Factors Associated with Severe Outcomes Among Immunocompromised Adults Hospitalized for COVID-19 — COVID-NET, 10 States, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:878–884. DOI: <http://dx.doi.org/10.15585/mmwr.mm7127a3>

