EPIDEMIOLOGY
RESEARCH GROUP IN
ORGAN TRANSPLANTATION

JOHNS HOPKINS
MEDICINE

The Impact of COVID-19 on Donation and Transplantation

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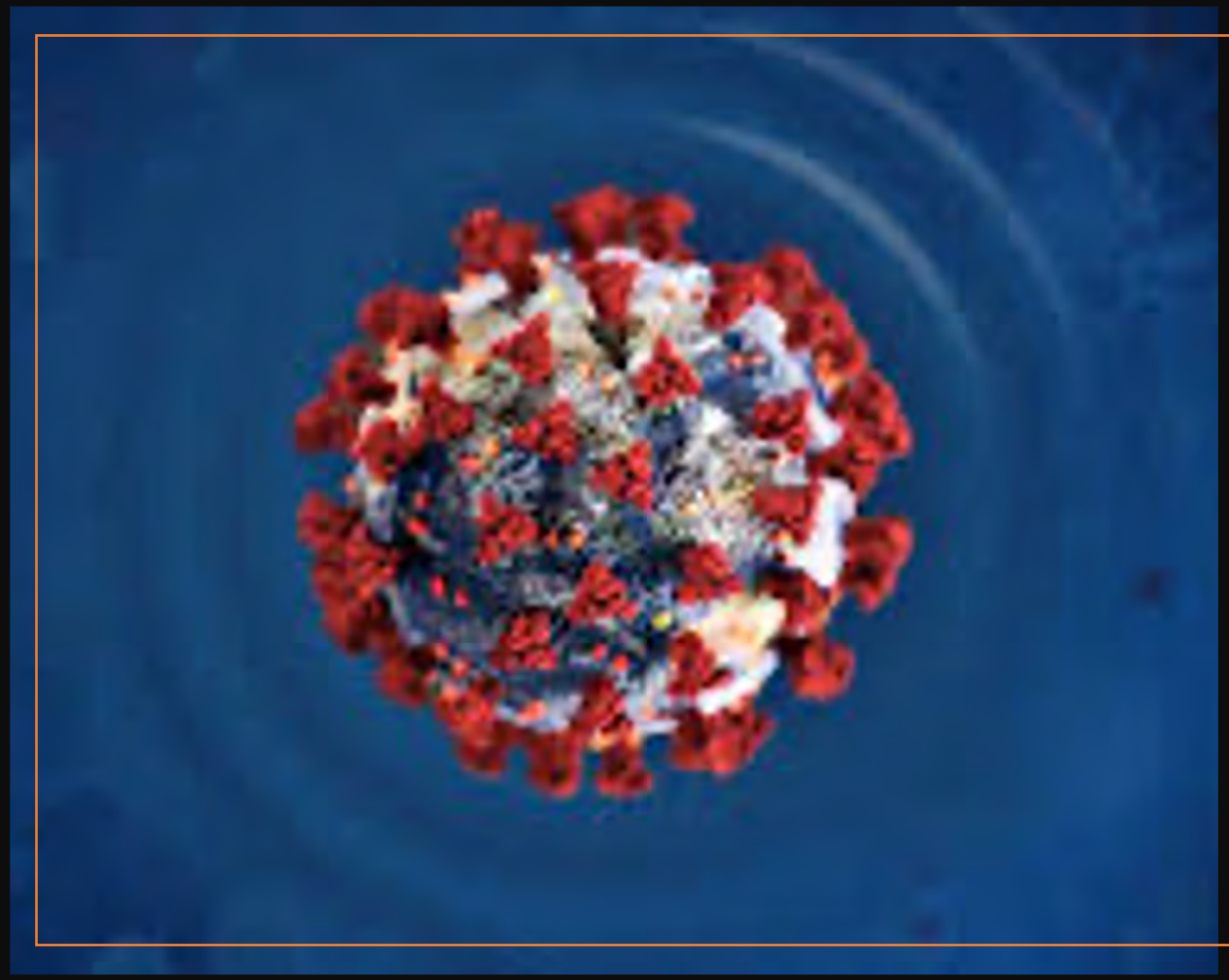
Disclosures

We thank Dr. Facui and the NIAID for funding the Covid Protection After Transplantation study (PI: Segev).

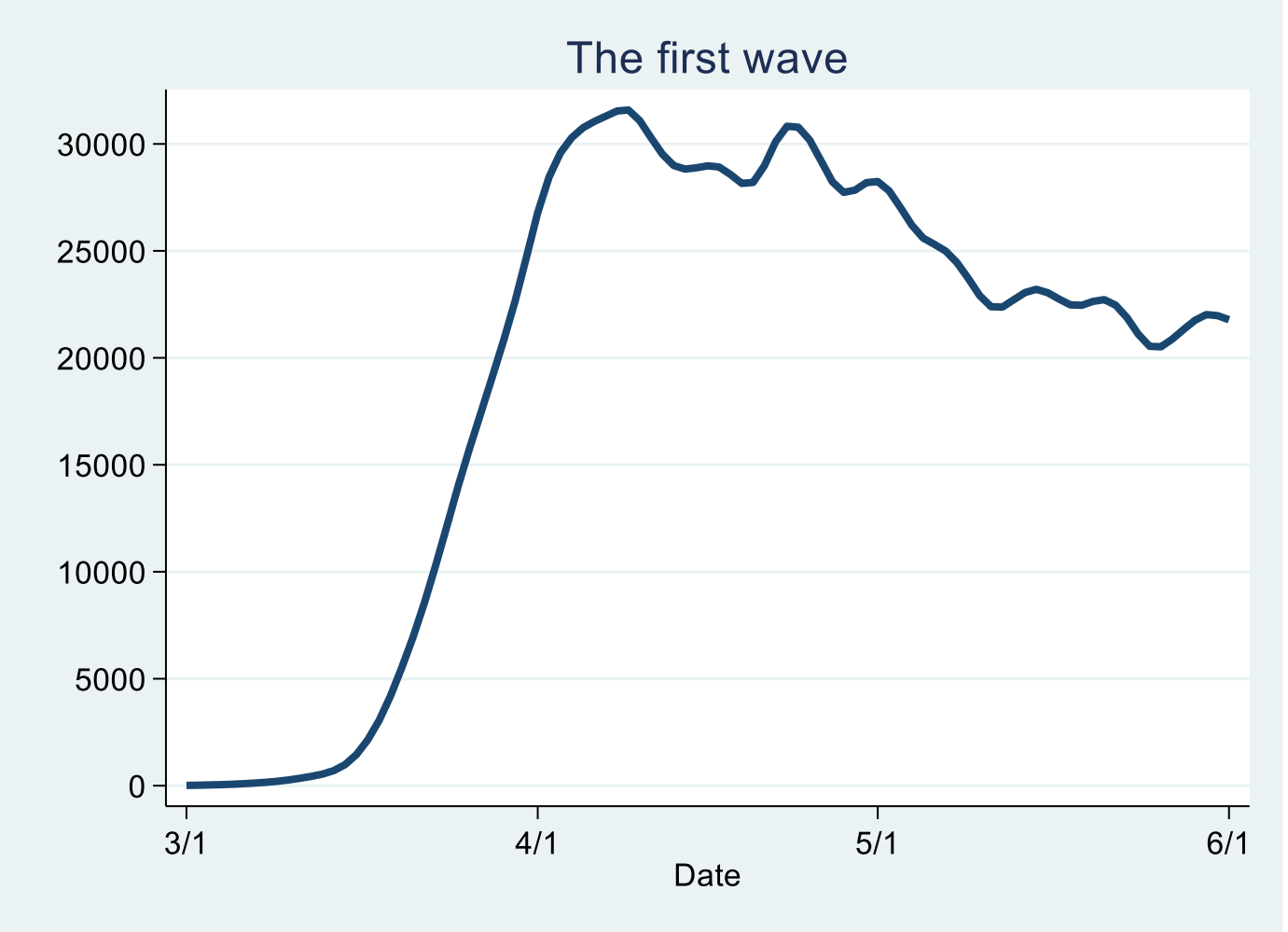
Dr. Levan is a member of the Alliance for Donation and Transplantation Innovation Leadership Council



The Impact of COVID-19 on Deceased Donation

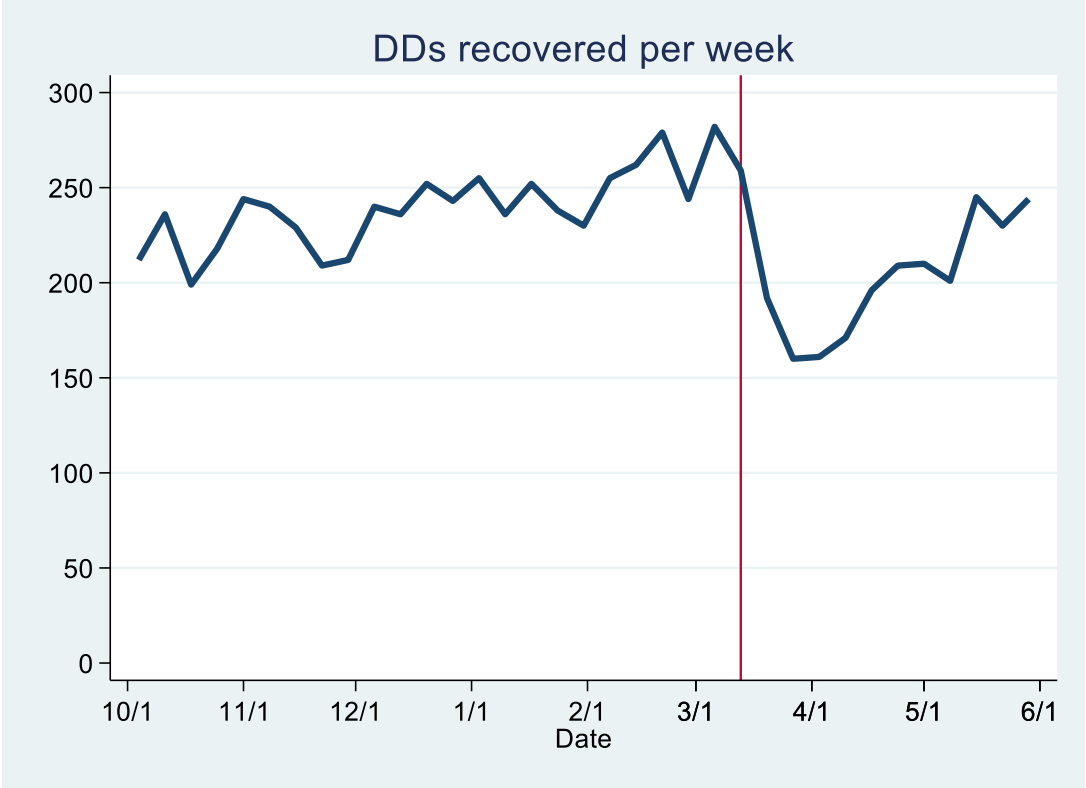
The First Wave:

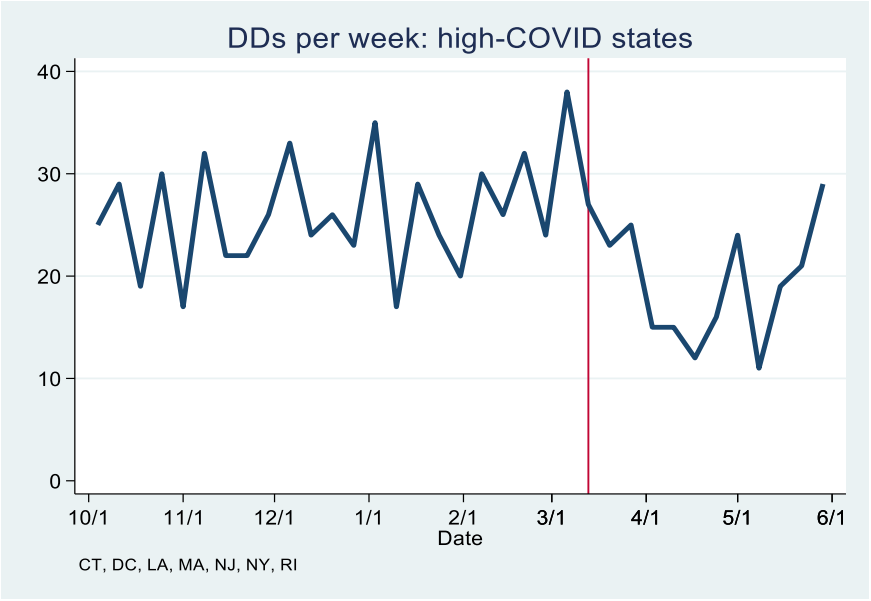
March 1, 2020
June 1, 2020



State of Emergency Delcared

When the state of emergency was declared on Friday March 13, there was a decrease in deceased donors. This trended up again to pre-pandemic levels around June 1.




DDs per week: high-COVID states
40
30
20
10
0
10/1
11/1
12/1
1/1
2/1
3/1
4/1
5/1
6/1
Date
CT, DC, LA, MA, NJ, NY, RI

Composition of the 1st Wave

Median age dropped from 44 to 40

	Pre-Wave 1	Wave 1	P
Median (IQR) age	44 (33-56)	40 (29-53)	**<0.01**
% DCD	25.4%	22.2%	**<0.01**
% DM	14.4%	11.9%	**<0.01**
% IRD	27.5%	29.2%	0.06

Composition of the 1st Wave

The proportion of DCD donors dropped from 25 to 22%

	Pre-Wave 1	Wave 1	P
Median (IQR) age	44 (33-56)	40 (29-53)	**<0.01**
% DCD	25.4%	22.2%	**<0.01**
% DM	14.4%	11.9%	**<0.01**
% IRD	27.5%	29.2%	0.06

Composition of the 1st Wave

The proportion of diabetic donors dropped from 14-12%

	Pre-Wave 1	Wave 1	P
Median (IQR) age	44 (33-56)	40 (29-53)	**<0.01**
% DCD	25.4%	22.2%	**<0.01**
% DM	14.4%	11.9%	**<0.01**
% IRD	27.5%	29.2%	0.06

Composition of the 1st Wave

- The proportion of increased risk donor organs stayed the same.

With the 1st wave, OVERALL donor selection became more conservative.

	Pre-Wave 1	Wave 1	P
Median (IQR) age	44 (33-56)	40 (29-53)	**<0.01**
% DCD	25.4%	22.2%	**<0.01**
% DM	14.4%	11.9%	**<0.01**
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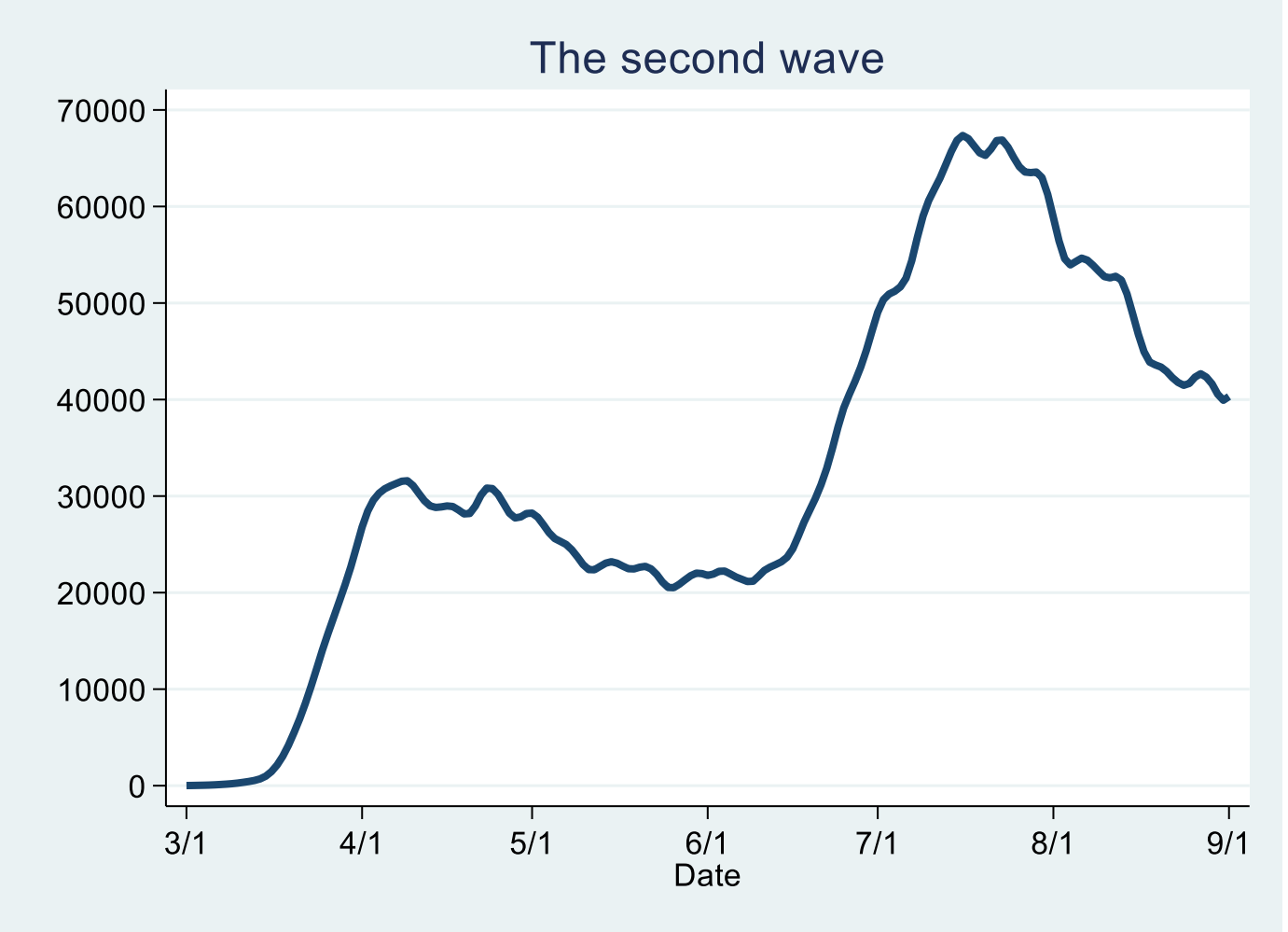
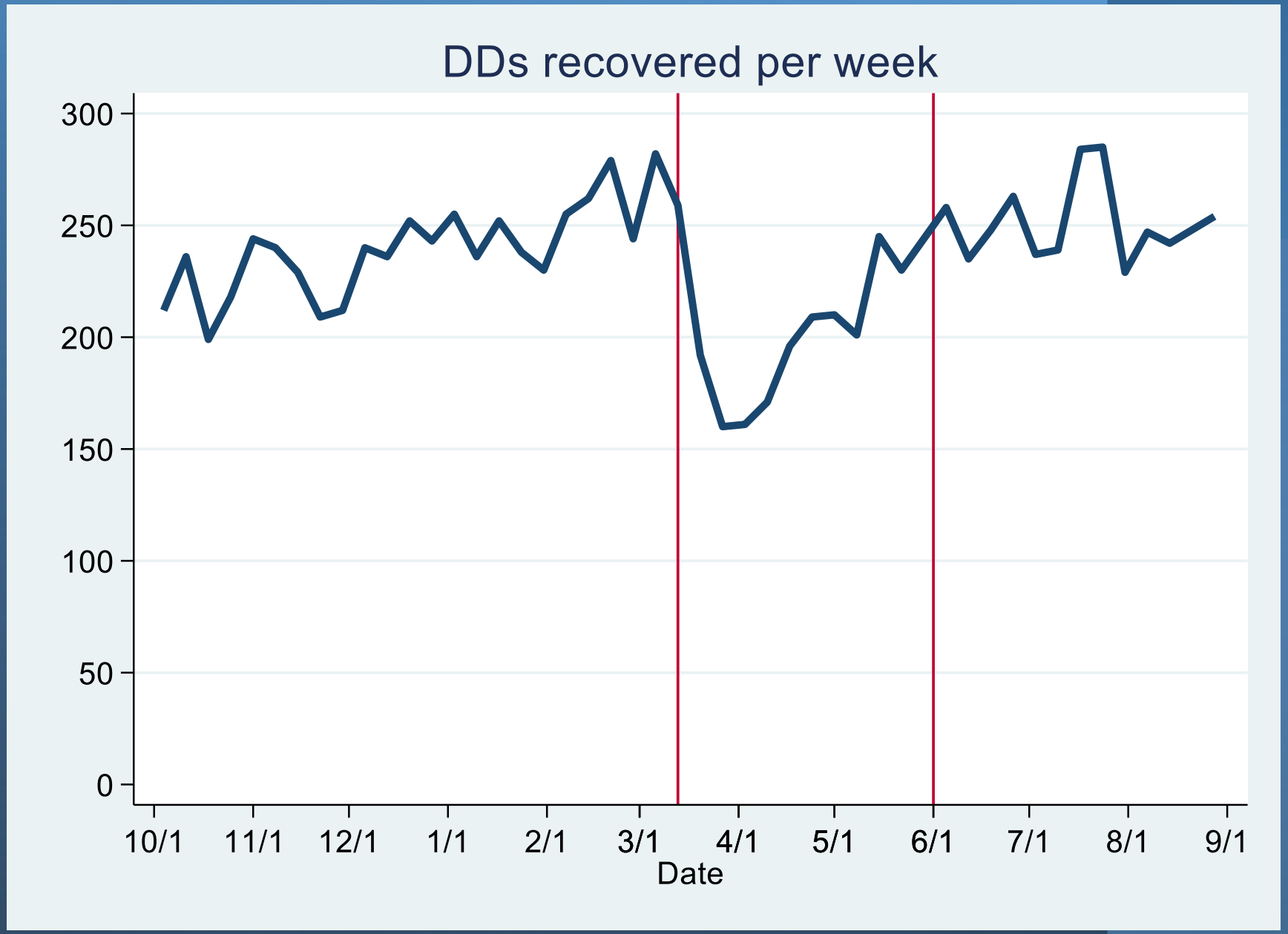
The 2nd Wave:

March 1, 2020
June 1, 2020




DDs recovered per week
300
250
200
150
100
50
0
10/1
11/1
12/1
1/1
2/1
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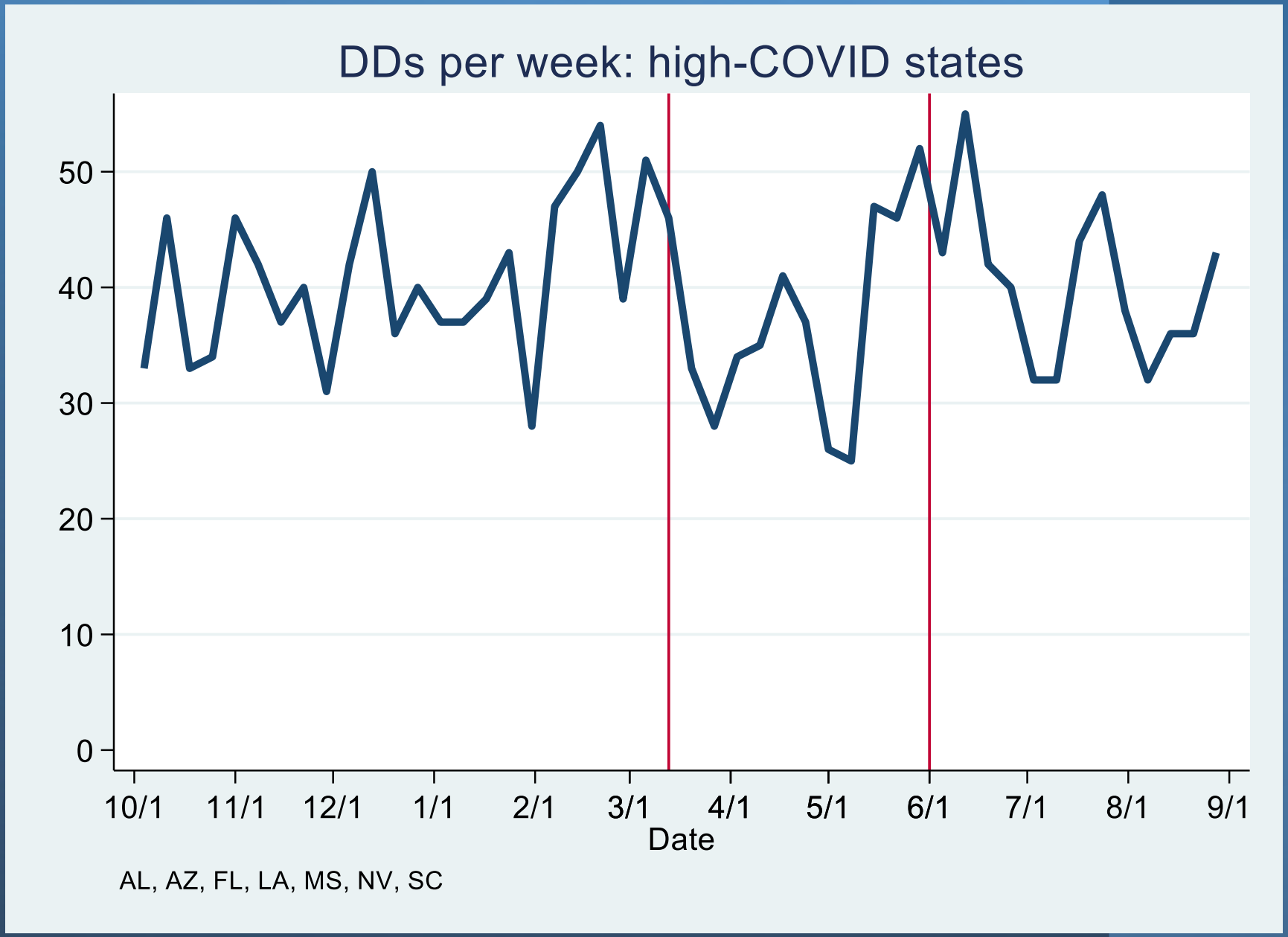
4/1
5/1
6/1
7/1
8/1
9/1
Date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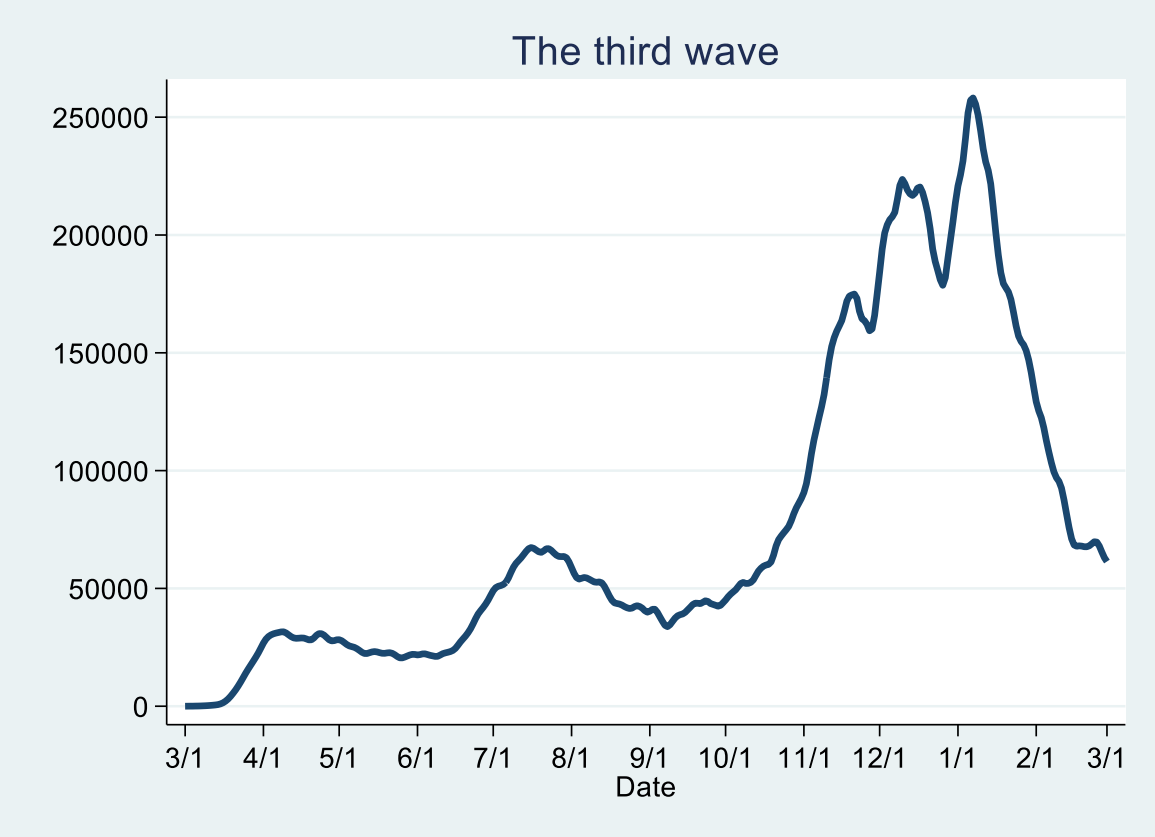
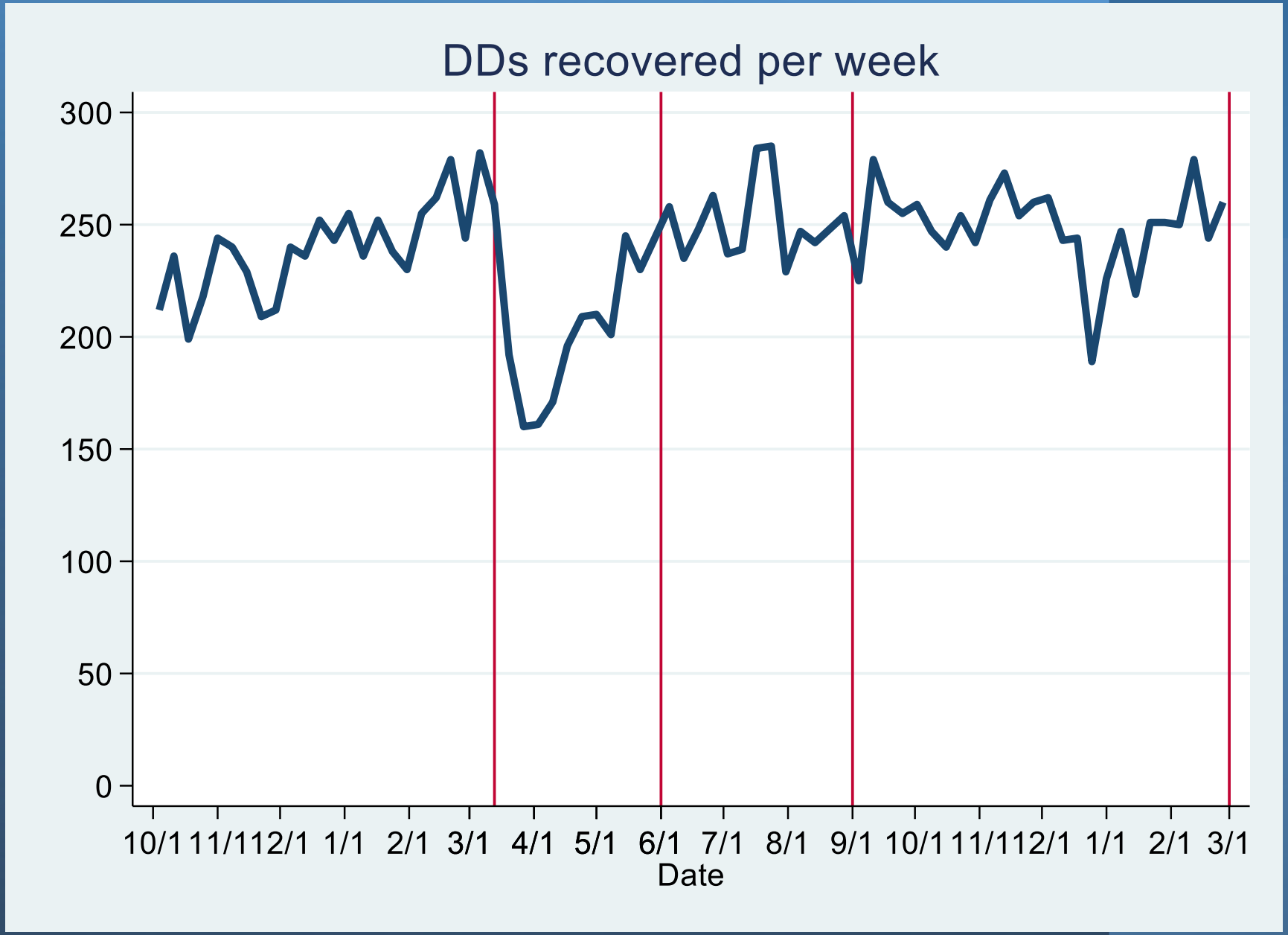
1/1
2/1
3/1
4/1
5/1
6/1
7/1
8/1
9/1
Date
AL, AZ, FL, LA, MS, NV, SC

Conclusion of the 2nd Wave

- **No change in donor recovery.**
- **Even in high COVID-19 states during the 2nd wave.**

The Third Wave: Sept 1. 2020- March 1, 2021

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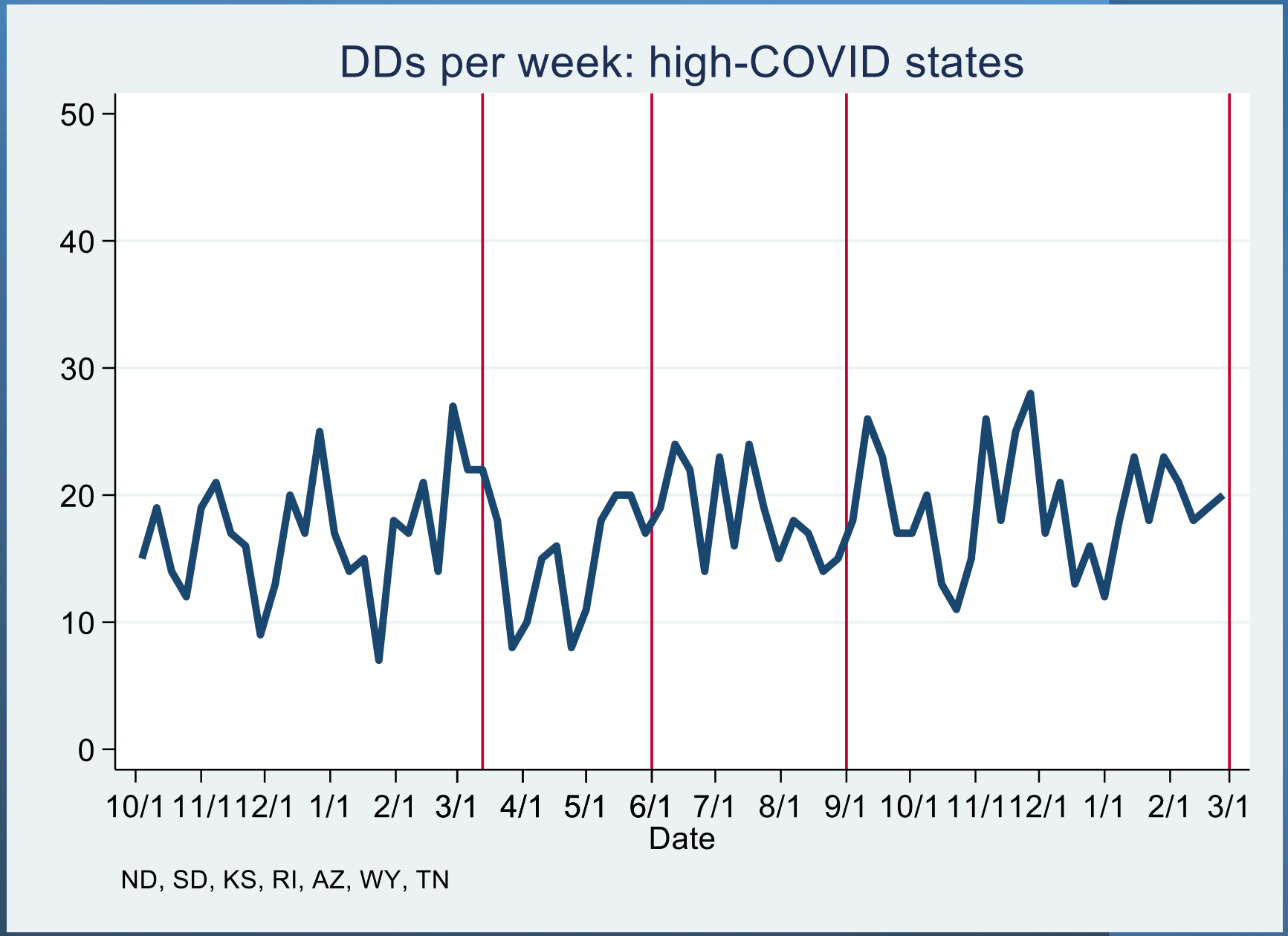
11/1
12/1
1/1
2/1
3/1
Date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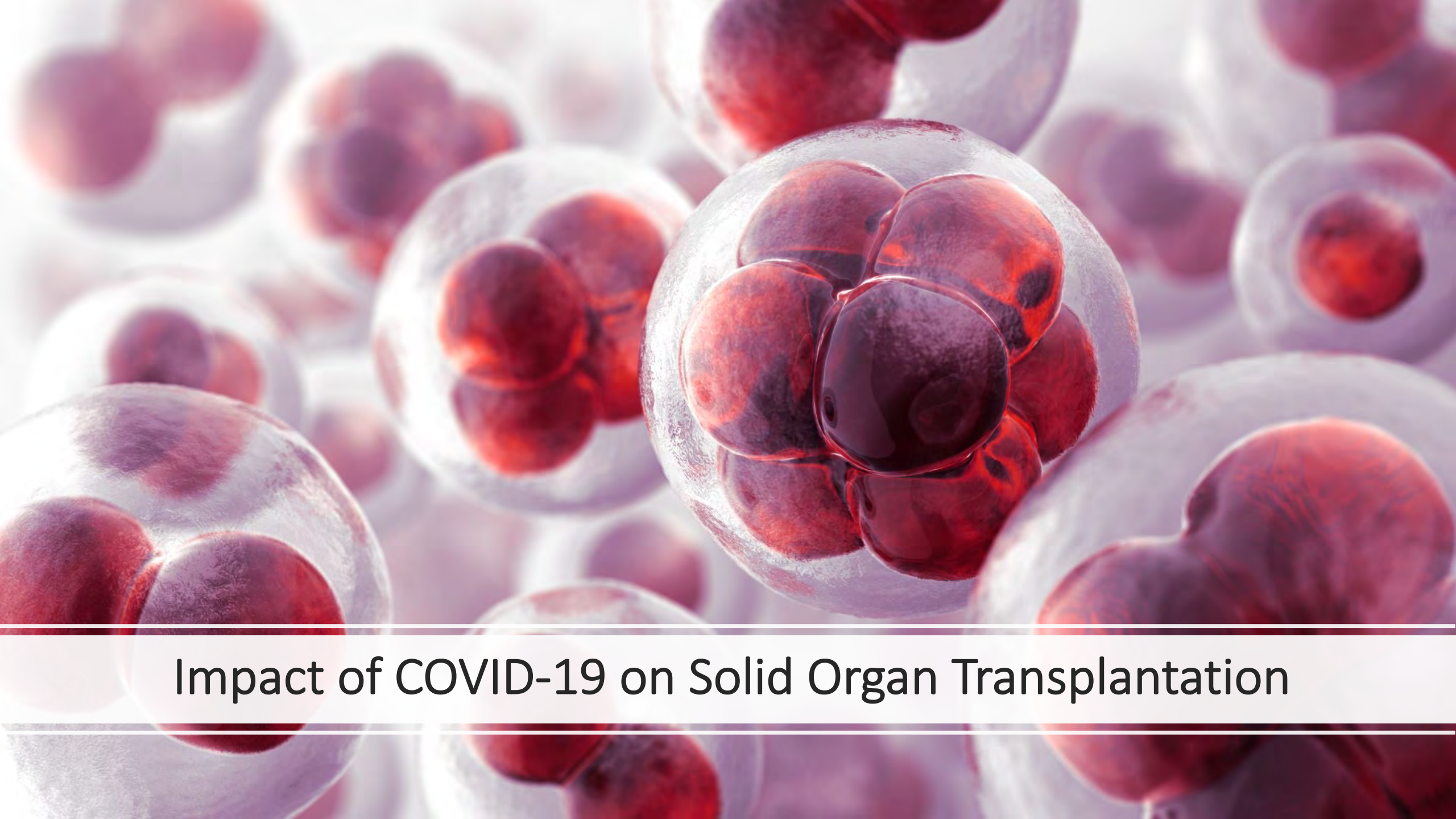
5/1
6/1
7/1
8/1
9/1
10/1
11/1
12/1
1/1
2/1
3/1
Date
ND, SD, KS, RI, AZ, WY, TN

Conclusion from 3nd Wave

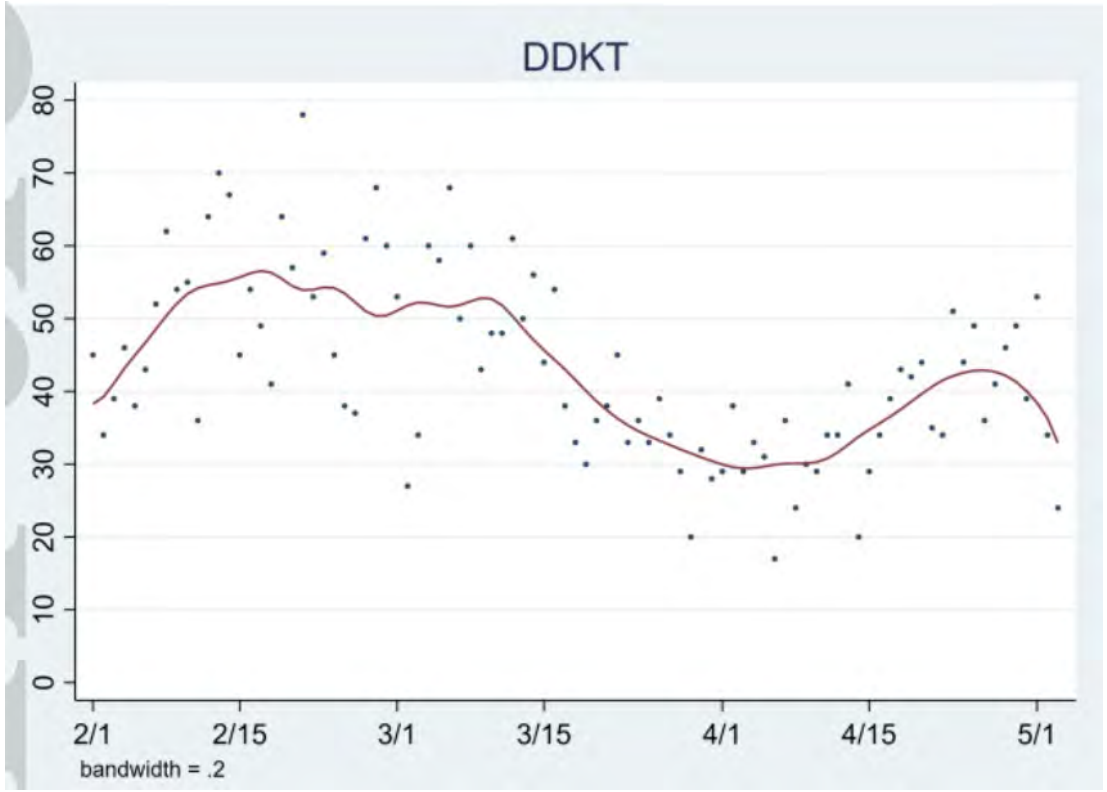
No change in donor recovery even in high COVID-19 states during the 3rd wave.

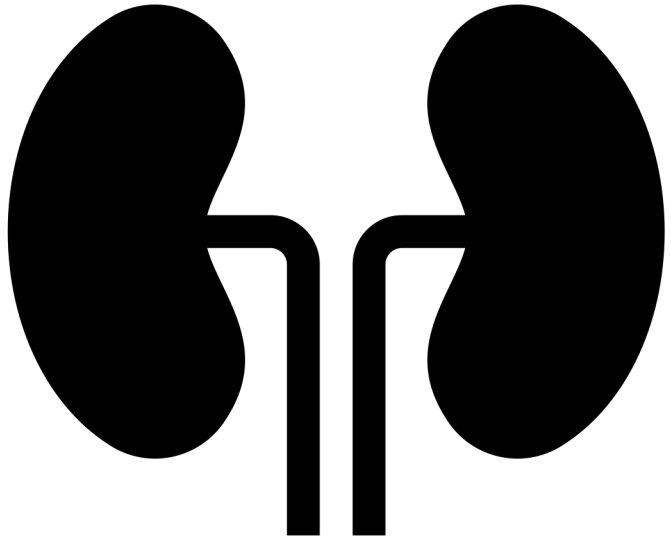


Impact of COVID-19 on Solid Organ Transplantation

Kidney: Wave 1 (Boyarsky/Massie 2020 AJT)

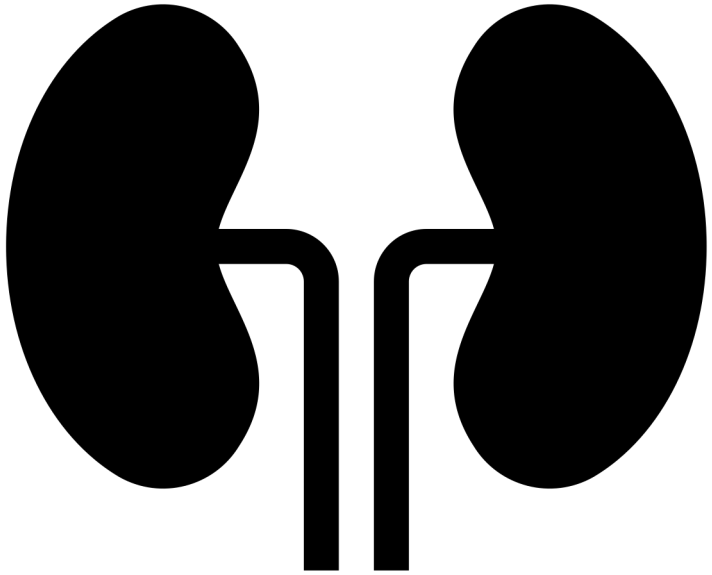
- DDKT declines during first wave
- Concentrated in high-COVID states (41% decline vs pre-COVID)

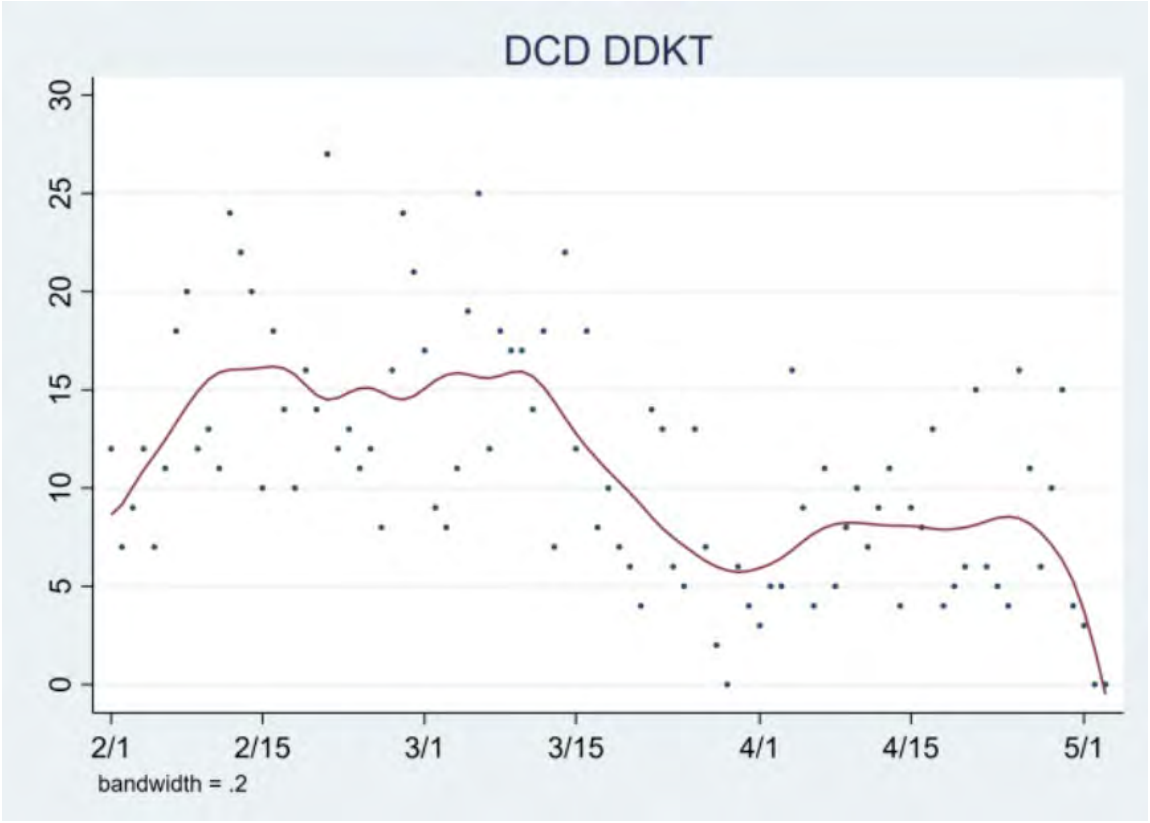




Kidney: Wave 1 (Boyarsky/Massie 2020 AJT)

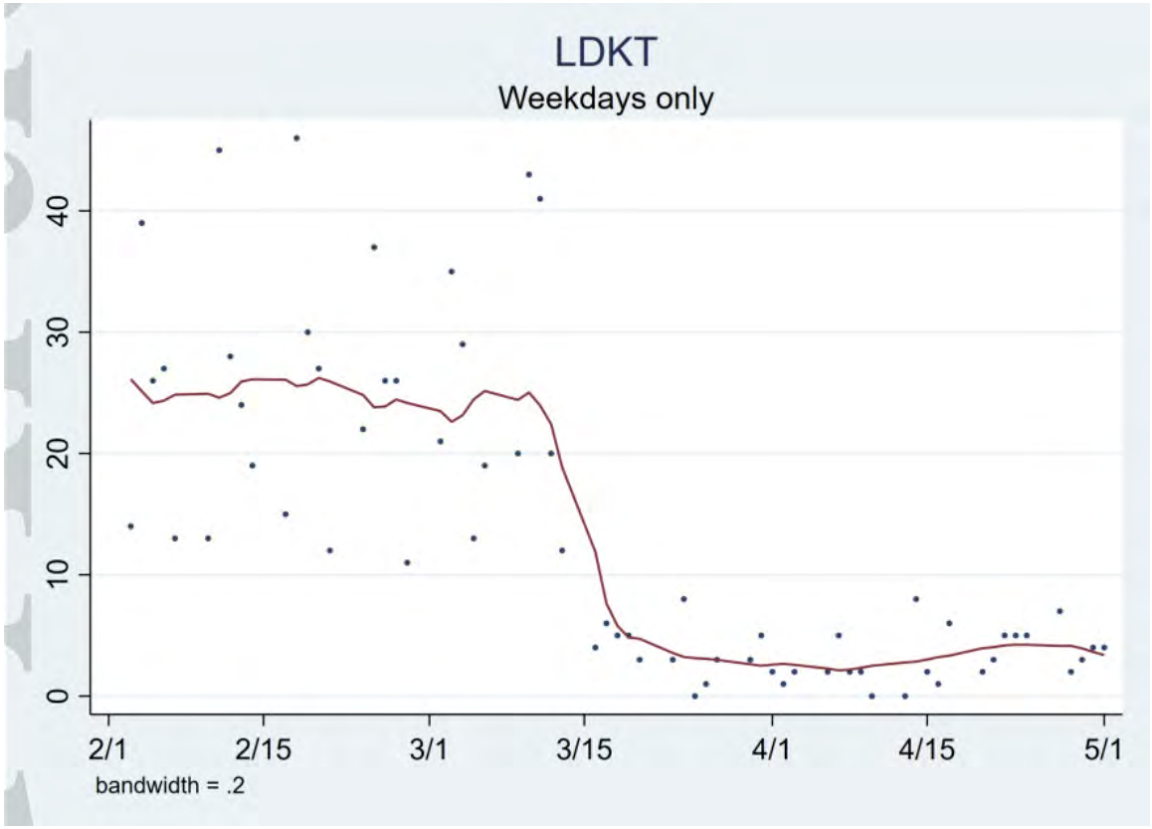
Steeper decline in DCD donations





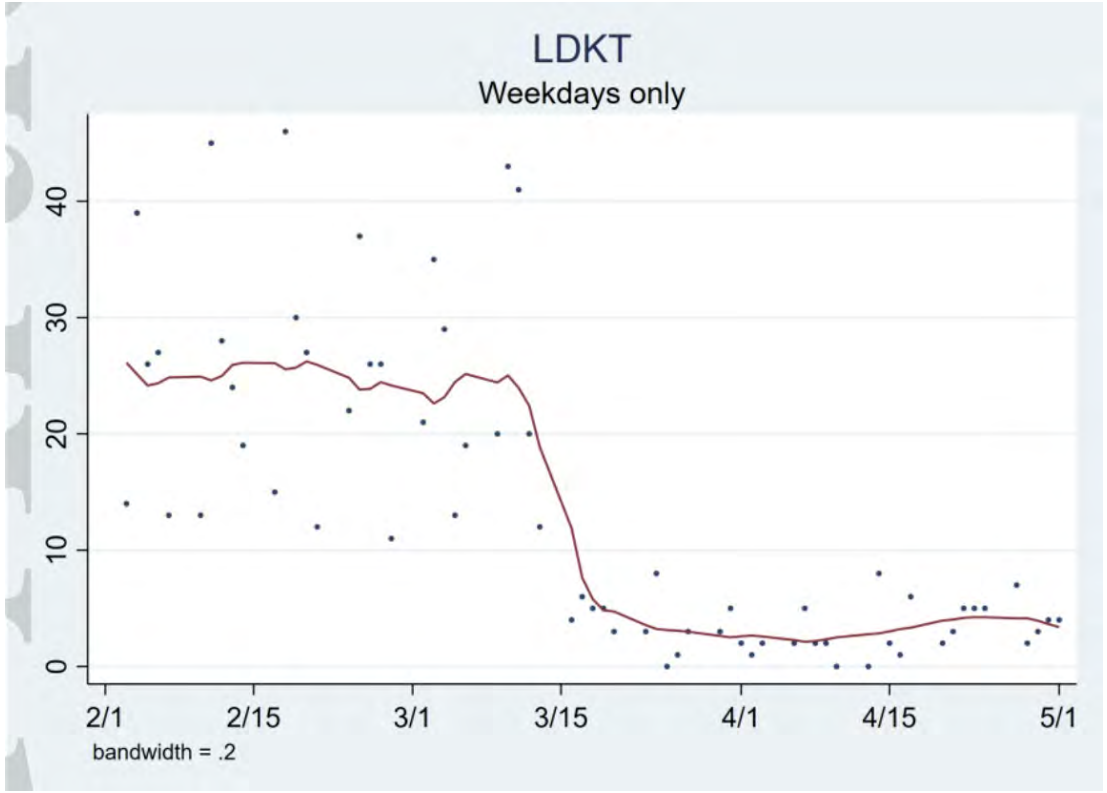
Kidney: Wave 1 (Boyarsky/Massie 2020 AJT)

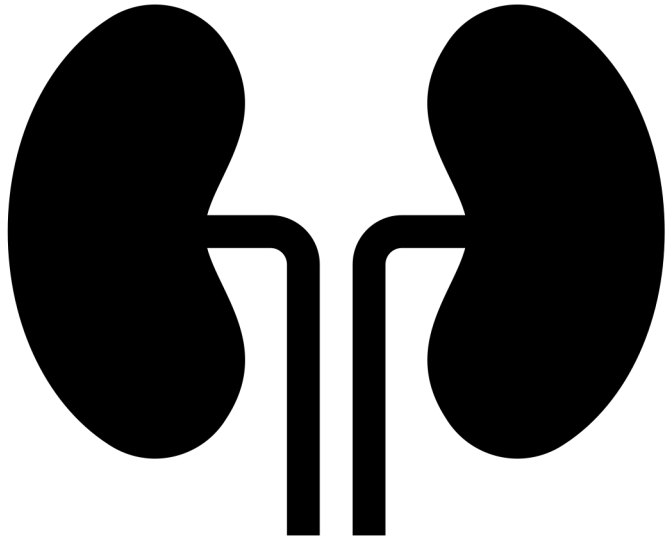
Near total halt in live donor kidney transplants



Kidney: Wave 1 (Boyarsky/Massie 2020 AJT)

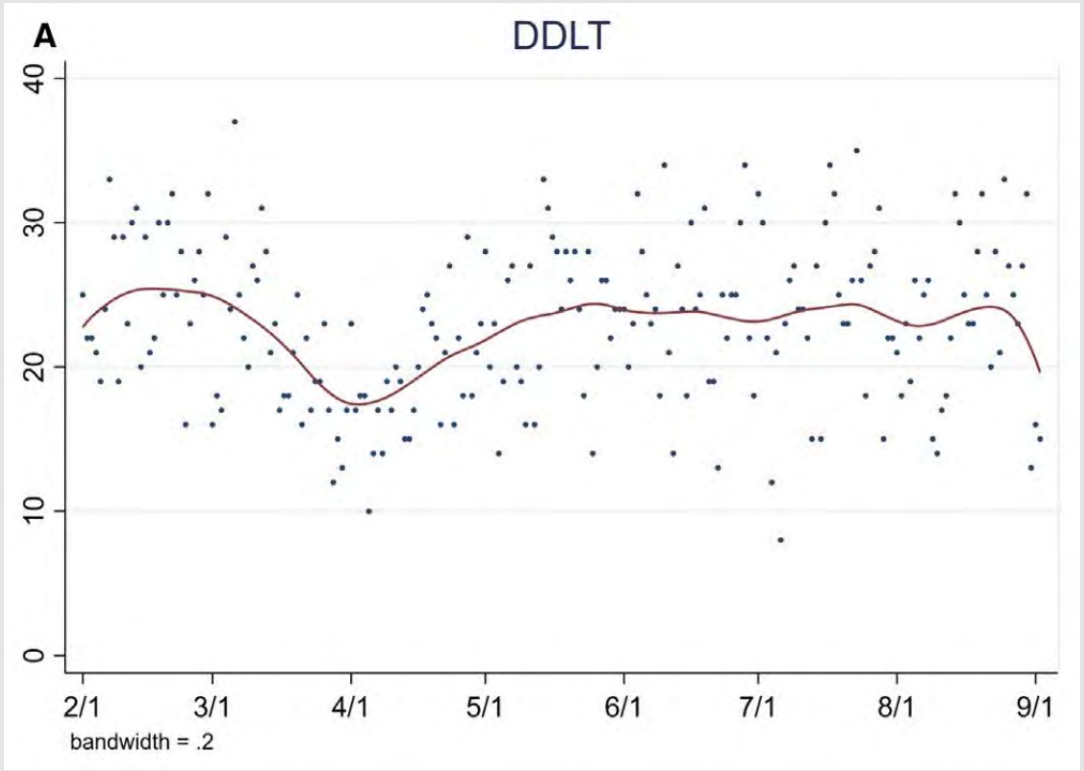
- Deceased donor kidney transplant back to pre-pandemic levels by May 2020
- Living kidney donor transplants back to pre-pandemic levels by June 2020





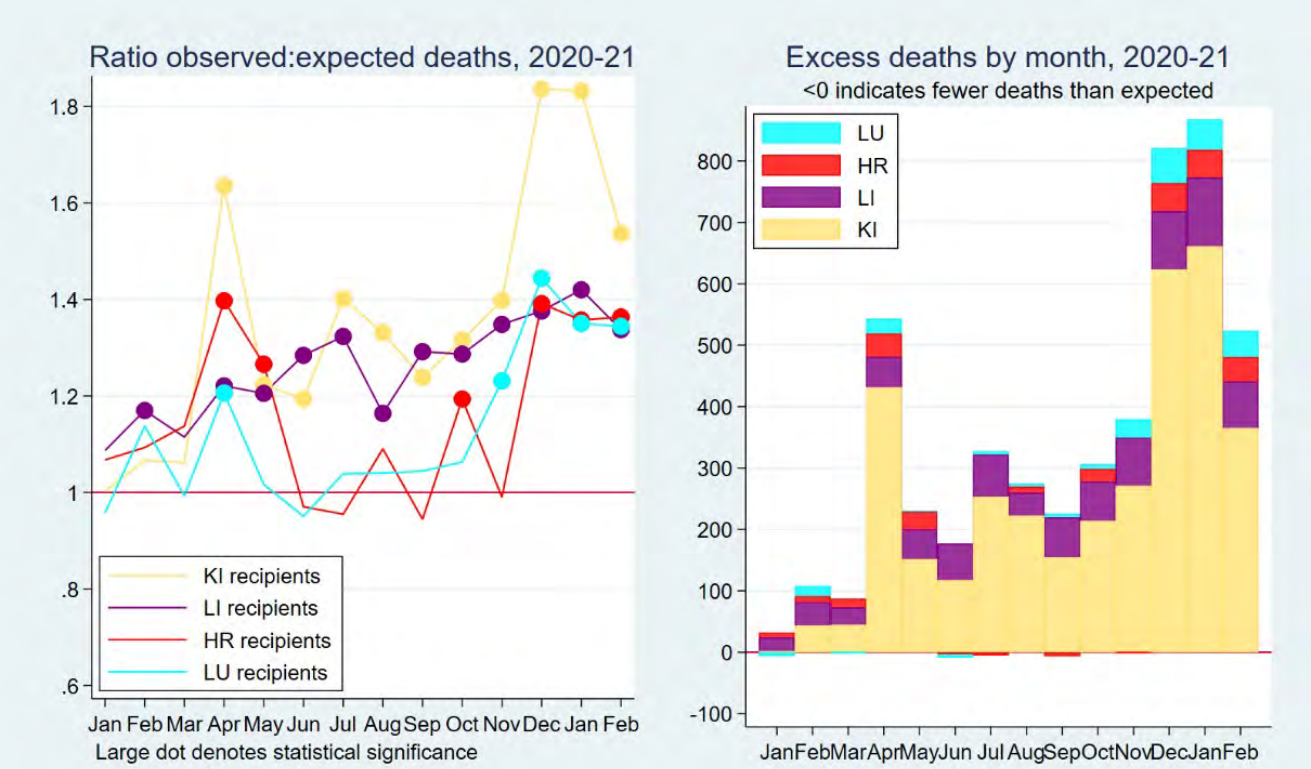
Liver: Wave 1
(Strauss/Massie 2020 AJT)

Liver: Wave 1 (Strauss/Massie 2020 AJT)

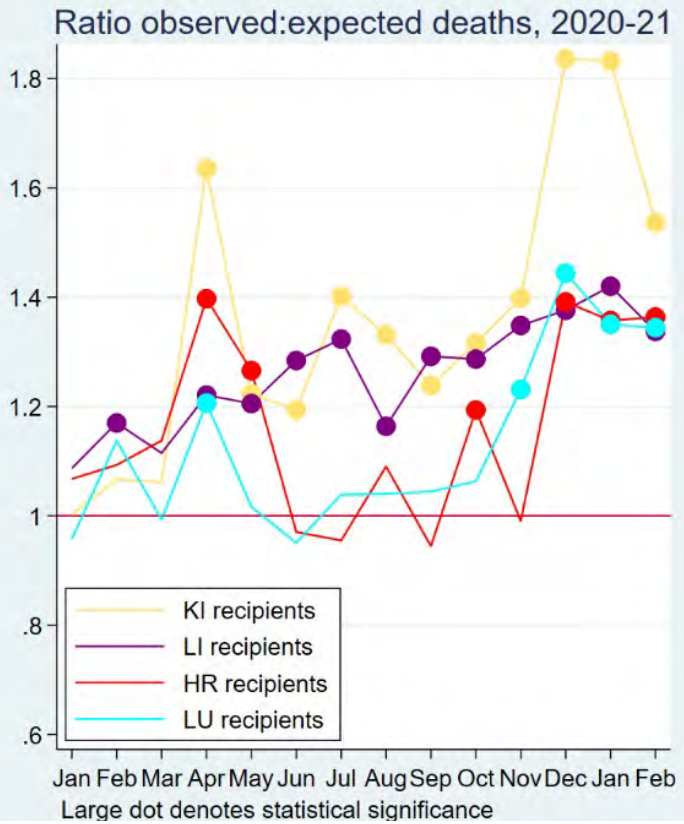


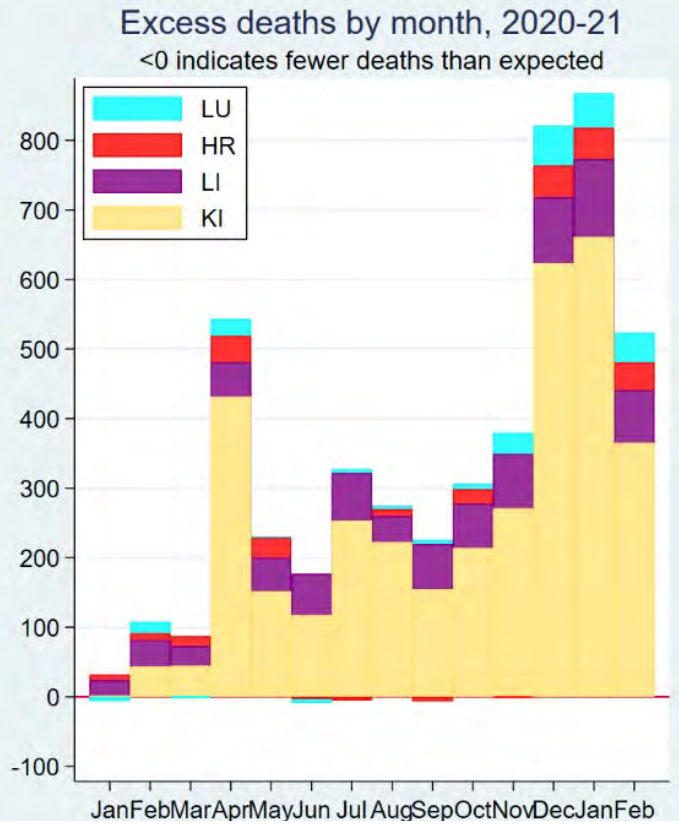
- However, only a mild and transient decrease in DDLT

COVID-19 Associated Excess Deaths



- Substantially higher mortality among transplant recipients than expected based on pre-COVID mortality rates, in all organs
- Highest mortality kidney patients





COVID-19 Associated Excess Deaths-With Cause of Death Data

- Total recorded COVID-19 deaths: **1243 that were attributed to COVID**
- Total excess deaths 3/2020-2/2021: **4740** (34% above expected)
- **More transplant patients die from COVID than are are recorded.**

COVID-19 Associated Excess Deaths

Excess deaths greatest for patients age 50 and above

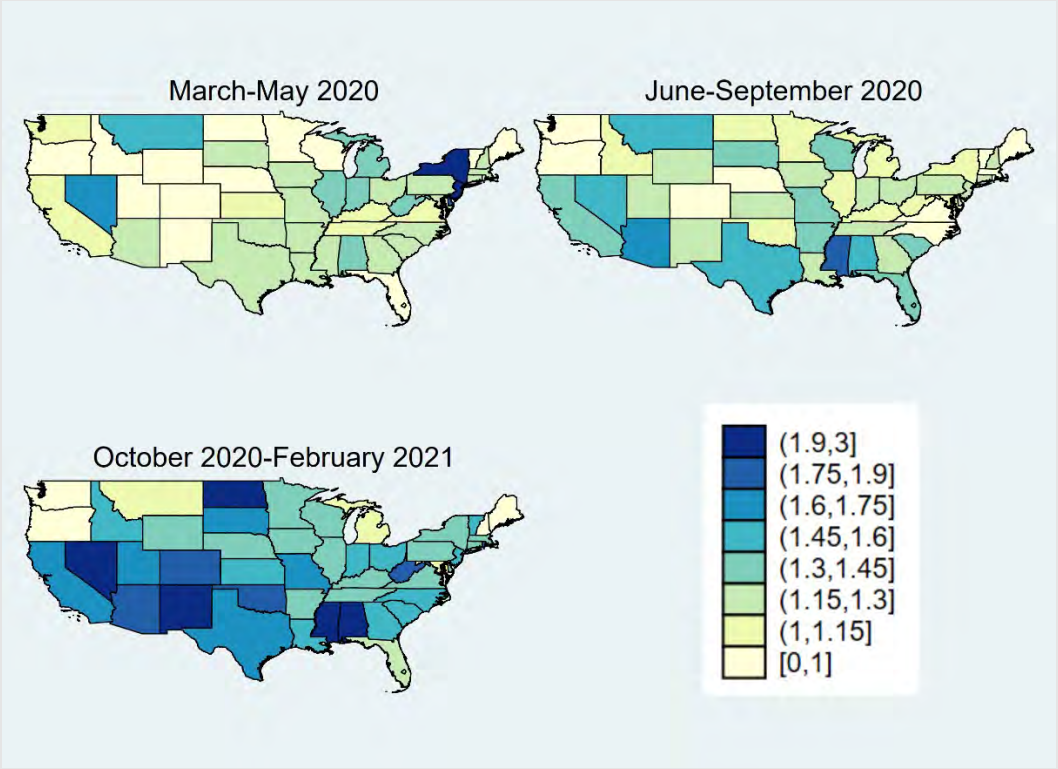
Subgroup	Observed	Expected	Excess	O/E ratio
Kidney	11734	8223.8	3510.2	**1.43**
Liver	3554	2772.2	781.8	**1.28**
Heart	1551	1325.4	225.6	**1.17**
Lung	1757	1535.4	221.6	**1.14**
Age				
0-11	110	112.7	-2.7	0.98
12-17	76	66.4	9.6	1.14
18-29	329	331.0	-2.0	0.99
30-39	529	482.7	46.3	**1.10**
40-49	1202	942.5	259.5	**1.28**
50-59	3175	2313.3	861.7	**1.37**
60-69	6823	4843.2	1979.8	**1.41**
70+	6352	4764.9	1587.1	**1.33**

COVID-19 Associated Excess Deaths by Race/Ethnicity

- Excess deaths greatest for Hispanic transplant recipients
- Least for White transplant recipients

Subgroup	Observed	Expected	Excess	O/E ratio
Race/Ethnicity				
Asian	760	547.2	212.8	**1.39**
Black	4282	2974.6	1307.4	**1.44**
Hispanic	2936	1589.7	1346.3	**1.85**
White	10262	8507.8	1754.2	**1.21**
Other	356	237.5	118.5	**1.50**

COVID-19 Associated Excess Deaths-Geography



- Geographic/temporal pattern of excess deaths matches COVID-19 incidence.
- Blue = as a lot of excess deaths. If it is yellow, it has a less excess deaths.

COVID-19 Vaccination in Transplant Recipients

Response to mRNA First Dose

RESEARCH LETTER

Immunogenicity of a Single Dose of SARS-CoV-2 Messenger RNA Vaccine in Solid Organ Transplant Recipients

Immunocompromised individuals have been excluded from studies of SARS-CoV-2 messenger RNA (mRNA) vaccines. In such patients, the immune response to vaccination may be blunted. To better understand the immunogenicity of mRNA vaccines in immunocompromised individuals, we quantified the humoral response to the first dose in solid organ transplant recipients.

Methods | Transplant recipients across the US were recruited though social media to participate in this prospective cohort, and those who underwent SARS-CoV-2 vaccination between December 16, 2020, and February 5, 2021, were included. The study was approved by the Johns Hopkins University institutional review board and participants provided informed consent electronically. Participants underwent either at-home blood sampling with the TAPII blood collection device (Seventh Sense Biosystems) or standard venipuncture.

The TAPII samples were tested using an enzyme immunoassay (EUROIMMUN) that tests for antibodies to the S1 domain of the SARS-CoV-2 spike protein.[1] The venipuncture

since transplant was 6.2 years (IQR, 2.7-12.7 years). The maintenance immunosuppression regimen included tacrolimus (83%), corticosteroids (54%), mycophenolate (66%), azathioprine (9%), sirolimus (4%), and everolimus (2%). At a median of 20 days (IQR, 17-24 days) after the first dose of vaccine, antibody (anti-S1 or anti-receptor-binding domain) was detectable in 76 of 436 participants (17%; 95% CI, 14%-21%).

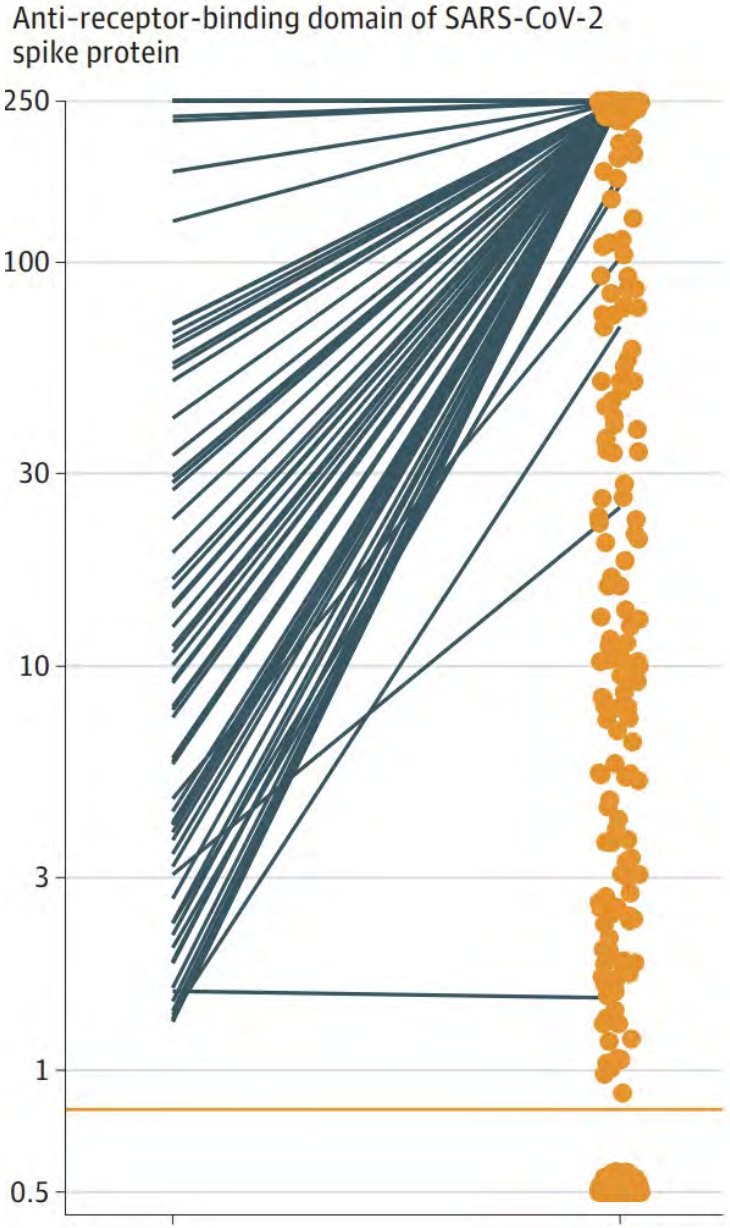
Transplant recipients receiving anti-metabolite maintenance immunosuppression therapy were less likely to develop an antibody response than those not receiving such immunosuppression therapy (37% vs 63%, respectively; adjusted incidence rate ratio [IRR], 0.22 [95% CI, 0.15-0.34]; $P < .001$) (Table). Older transplant recipients were less likely to develop an antibody response (adjusted IRR, 0.83 [95% CI, 0.73-0.93] per 10 years; $P = .002$). Those who received mRNA-1273 were more likely to develop an antibody response than those receiving BNT162b2 (69% vs 31%, respectively; adjusted IRR, 2.15 [95% CI, 1.29-3.57]; $P = .003$). This association was similar in a sensitivity analysis limited to those tested 14 to 21 days after vaccination (n = 245; adjusted IRR, 2.29 [95% CI, 1.32-3.94]; $P = .003$).

Discussion | In this study of immunogenicity of the first dose of the mRNA SARS-CoV-2 vaccine among solid organ transplant recipients, the majority of participants did not mount appre-

Boyarsky/Garonzik-Wang 2021 JAMA

- Anti-spike antibody detectable in 76/436 participants (17%)
- Lower rate if patient on MMF (9% vs 41%)
- Higher rate for Moderna (25%) than Pfizer (10%)

Response to mRNA 2nd Dose



- Positive response in 357/658 participants (54%)
- Response rate remains lower for patients on MMF
- Patients who had a weak response to D1 tended to have a strong response to D2

Boyarsky/Garonzik-Wang 2021 JAMA

Response to 3rd Dose

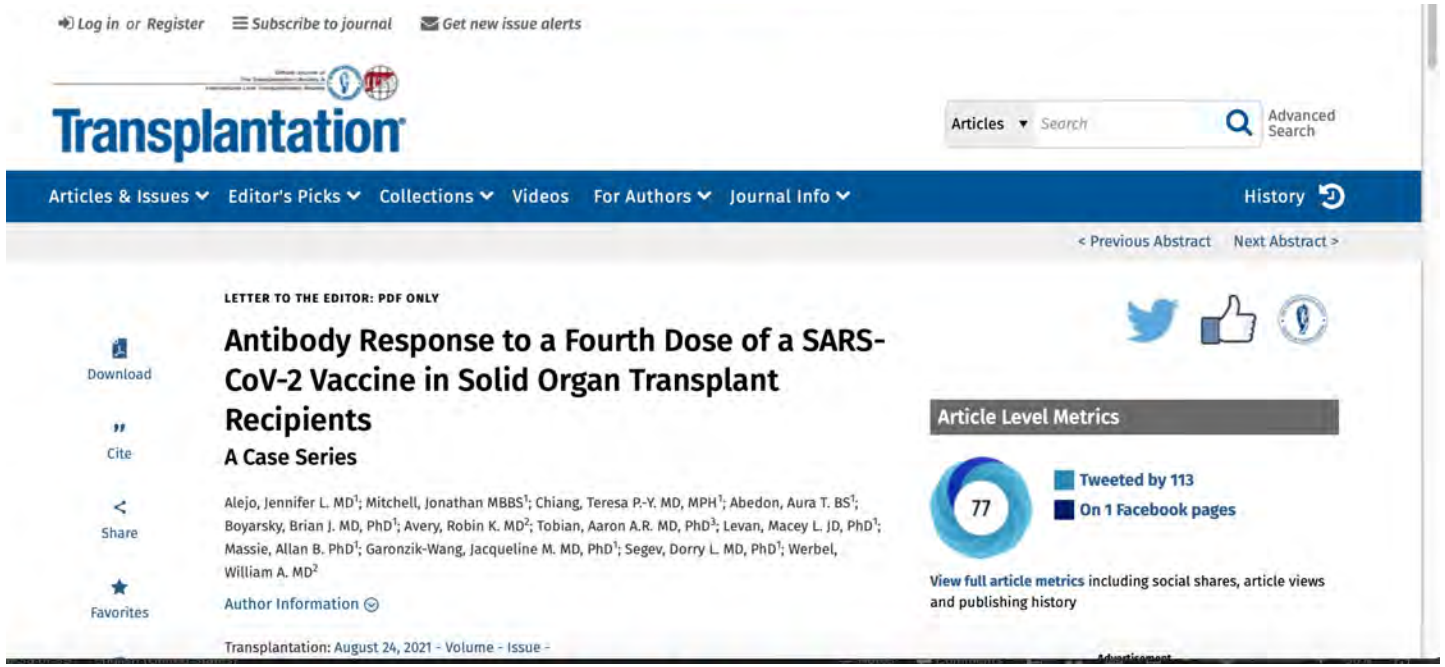
Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

Background: The antibody response after 2 doses of an mRNA vaccine against SARS-CoV-2 is excellent in the general population (1), but the response is different in recipients of solid organ transplants. For example, we have found markedly attenuated antibody responses in transplant recipients after 2 doses of an mRNA vaccine against SARS-CoV-2 (2). In addition, reports of COVID-19 breakthrough infections in vaccinated transplant recipients (3) have prompted interest in administering additional doses of vaccine.

Werbel/Segev 2021 Annals

- 30 patients with poor response to two mRNA doses (24 neg, 6 low positive) received a third dose (15 mRNA, 15 Jannsen)
- The six low-positive all had a high-positive response to D3
- Of the 24 negative, six (25%) had a high-positive response; 2 (8%) had a low-positive response

Response to 4th dose



Alejo/Werbel 2021 Transplantation

- 18 patients (10 hi-positive, 2 lo-positive, 6-negative pre-D4)
- 5/8 patients went from neg/low pos to hi-positive post-D4
- Most previously hi-positive patients showed further boosting post-D4

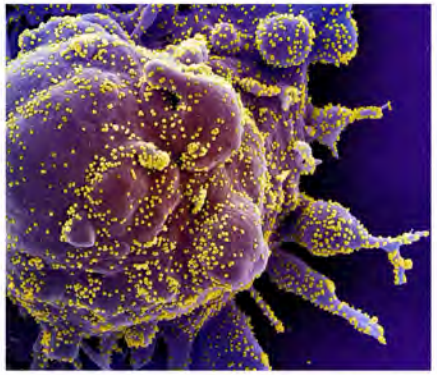
NIH launches study of third COVID-19 vaccine dose in kidney transplant recipients

Trial will assess antibody response in people who did not respond to two-dose regimen.

What

A pilot study has begun to assess the antibody response to a third dose of an authorized COVID-19 mRNA vaccine in kidney transplant recipients who did not respond to two doses of the Moderna or Pfizer-BioNTech COVID-19 vaccine. The Phase 2 trial is sponsored and funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

The lifelong immunosuppressive therapy that organ transplant recipients must take to prevent organ rejection blunts their immune response to both pathogens and vaccines. Research has shown that many organ transplant recipients do not develop antibodies against SARS-CoV-2, the virus that causes COVID-19, after receiving an authorized COVID-19 vaccine regimen. The purpose of the new study is to determine whether a third dose of one of the mRNA COVID-19 vaccines could overcome this problem for at least some kidney transplant recipients. This is particularly important because this population has a high prevalence of conditions that are risk factors for severe COVID-19, such as cardiovascular disease and diabetes.



Colorized scanning electron micrograph of a cell (purple) heavily infected with SARS-COV-2 virus particles (yellow), isolated from a patient sample. Image captured at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. *NIAID*

Planned Covid Protection After Transplant (CPAT) clinical trials

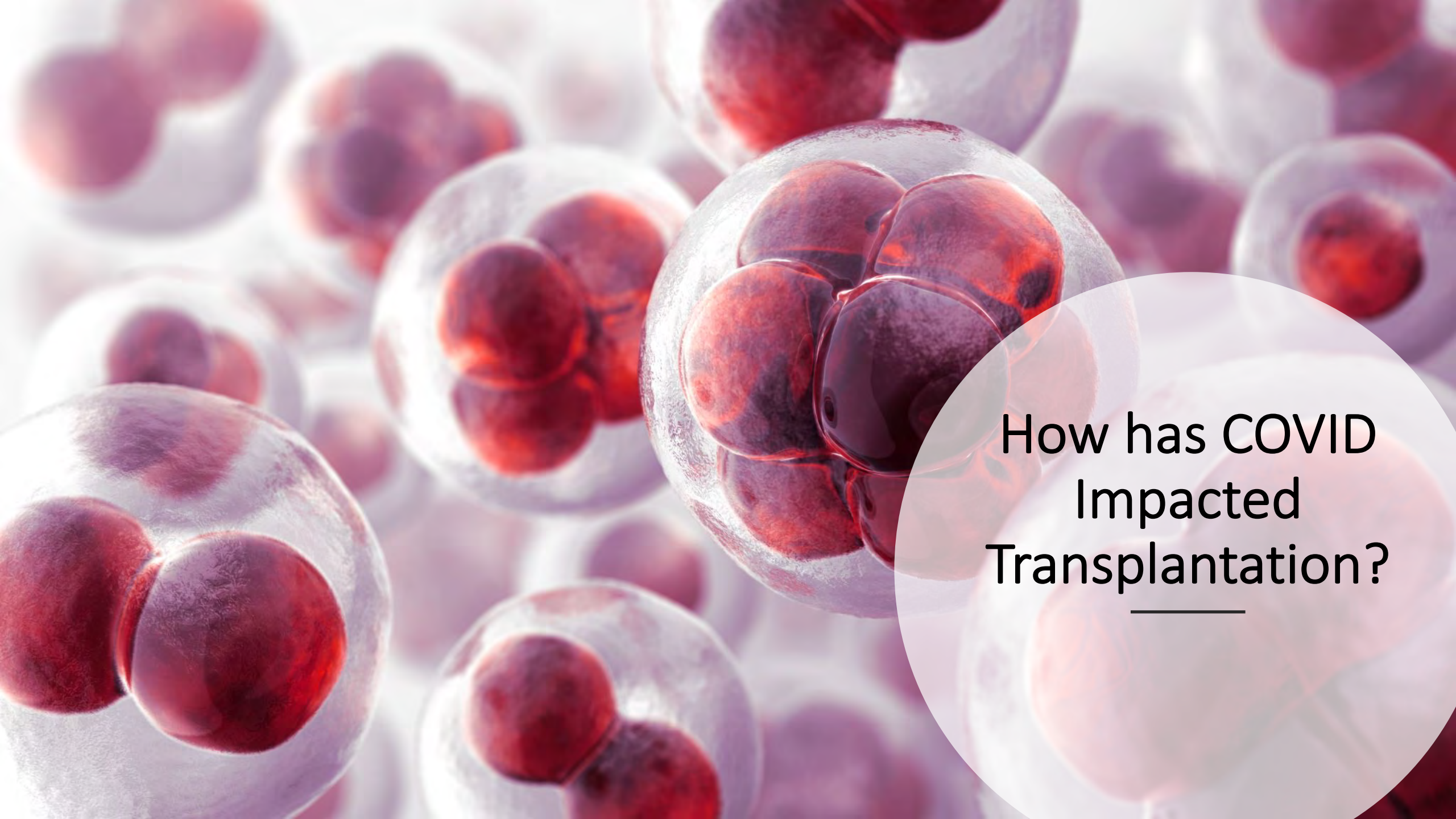
Immunomodulation:

- 400 KT recipients with no/minimal response to prior mRNA vaccination randomized to SOC or immunomodulation. All participants than receive an additional booster
- Primary efficacy outcome: post-dose antibody titer
- Primary safety outcomes: dnDSA, rejection, graft loss, mortality

Planned Covid Protection After Transplant (CPAT) clinical trials

Homologous/heterologous:

- 400 SOTRs with no/minimal response to prior mRNA vaccination randomized to additional booster with mRNA (homologous) or Jannsen (heterologous)
- Primary efficacy outcome: post-dose antibody titer



How has COVID Impacted Transplantation?

Conclusions

- The first wave of COVID-19 led to a sharp, but ultimately transient, drop in deceased donor recovery and kidney transplantation. There was relatively little disruption to liver transplantation
- Subsequent waves have had no negative effect on donor recovery and transplantation
- In the first year of COVID, before availability of a vaccine, there were over 4700 excess deaths among transplant recipients
- Transplant recipients have varying response to COVID-19 vaccination, but generally worse than the general population
- Boosters can boost immunity in transplant recipients

Conclusions

- The first wave of COVID was an unprecedented crisis for transplantation in the US, but the transplant system adapted successfully
- Lessons learned from the COVID crisis can be applied to future disruptions in health care
- Solid organ transplant recipients remain at very high risk of COVID complications and death, even after vaccination
- Innovative vaccine strategies are urgently needed to protect our patients

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