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COVID-19 Vaccination and Dialysis Patients: An Evolving Story



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Public Health Ontario Microbiology Rounds

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Disclosures

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**COVID-19
IMMUNITY
TASK FORCE**

**GROUPE DE TRAVAIL
SUR L'IMMUNITÉ
FACE À LA COVID-19**

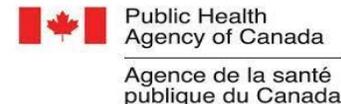


**DIVISION OF NEPHROLOGY
DEPARTMENT OF MEDICINE**

Determining the Safety and Effectiveness of COVID-19 Vaccination in the CKD Population

- **Study Objectives:**

1. Humoral and Cellular Immunity
2. Epidemiologic Studies
3. Vaccine Safety



Objectives

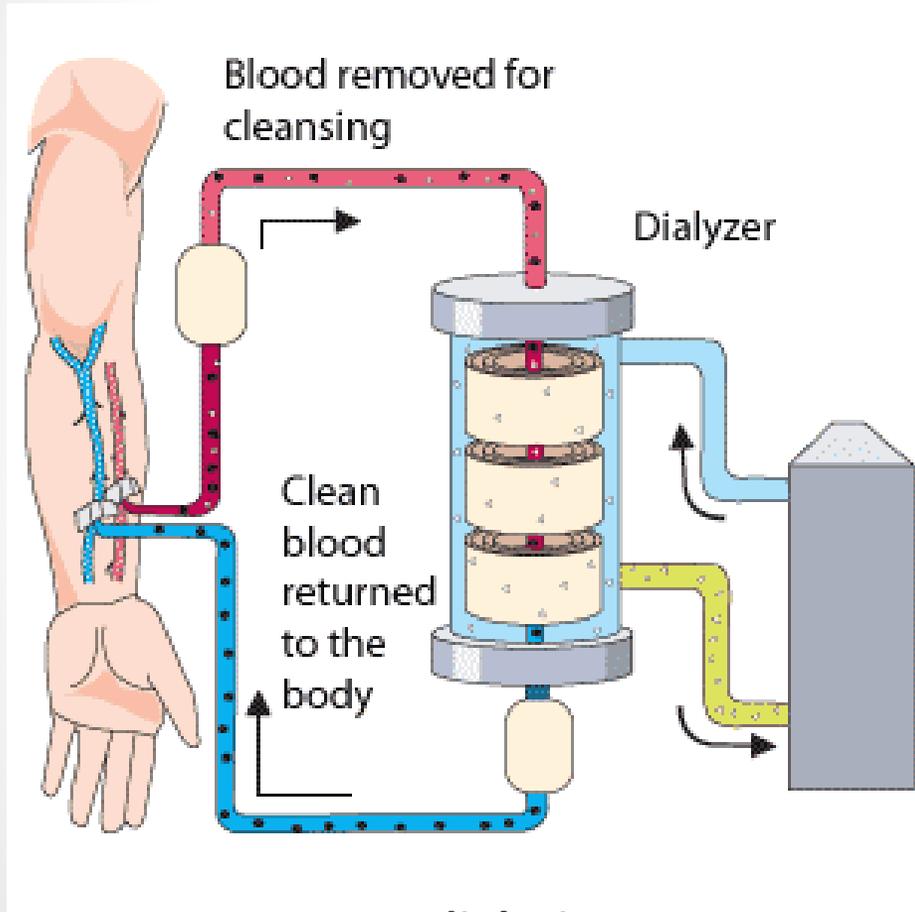
1. Describe the impact of COVID-19 on the dialysis population
2. Understand how antibody response is assessed post-vaccination
3. Describe vaccine effectiveness in the dialysis population
4. Discuss booster doses in the dialysis population

Chronic Kidney Disease is a Major Problem in Canada

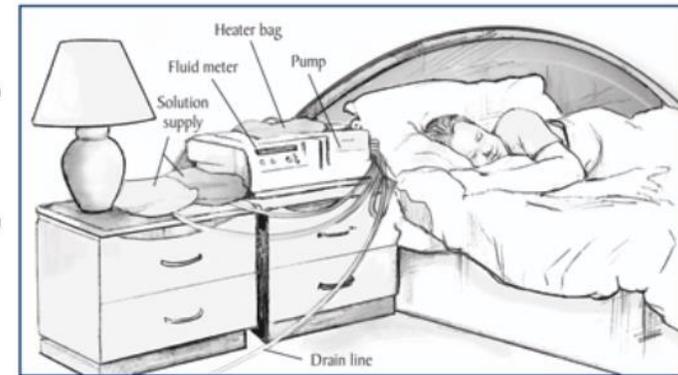
Stage of CKD	STAGE 1	STAGE 2	STAGE 3A	STAGE 3B	STAGE 4	STAGE 5
eGFR	90 or greater	Between 60 and 89	Between 45 and 59	Between 30 and 44	Between 15 and 29	Less than 15
Level of kidney damage	 Mild kidney damage	 Mild kidney damage	 Mild to moderate kidney damage	 Mild to moderate kidney damage	 Moderate to severe kidney damage	 End-stage kidney disease. Kidneys are close to failure or have completely failed. You will need to start dialysis or have a kidney transplant.

- Top Causes of CKD:
 - Diabetes Mellitus
 - Hypertension
 - Glomerulonephritis
- 23,000 patients on Chronic Dialysis (2019)

Types of Dialysis



Hemodialysis



Peritoneal Dialysis

Risk of Infection is Higher in HD

- Ontario Data 1.5% of the HD population contracted SARS-CoV-2 infection in the first 5 months of 2020 – a rate 5x the Ontario Population
- 264 in HD compared to 27 Ontario population per 100,000

Taji et al. CMAJ Feb 2021

Risk Factor	OR (95% CI)
In-centre vs Home Dialysis	2.54 (1.59-4.05)
LTC Resident	7.67 (5.30-11.11)
GTA Resident	3.27 (2.21-4.80)
Non-Caucasian especially Black	3.05 (1.95-4.77)
Lower Income Quintile	1.83 (1.15-2.89)

Outbreaks in dialysis units expose difficult juggling act for hospitals

CARLY WEEKS > HEALTH REPORTER
PUBLISHED MAY 6, 2020

TRENDING

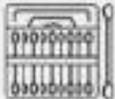
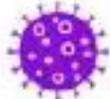
- “We’re telling people to stay at home, but dialysis patients can’t stay at home”

Dr. Matthew Muller, IPAC, St. Michael’s Hospital

- Mandatory treatment at least 3x/week
- Transportation issues
- Multiple health care providers

Dialysis Outbreaks do Occur

COVID - 19 Outbreak in an Urban Hemodialysis Unit

Setting & Participants	Interventions	Results
 Toronto, Canada	 Universal screening for SARS-CoV-2 using nasopharyngeal swabs for all patients and staff	4.6% 11 of 237 PATIENTS SARS-CoV-2 positive
 COVID-19 Outbreak	 Droplet and contact precautions for all patients	12% 11 of 93 STAFF SARS-CoV-2 positive
 237 Hemodialysis Patients 93 Hemodialysis Staff	 Infected staff quarantined at home	SARS-CoV-2-Positive Patients & Staff 55% 12 of 22 asymptomatic at testing 32% 7 of 22 asymptomatic at follow up

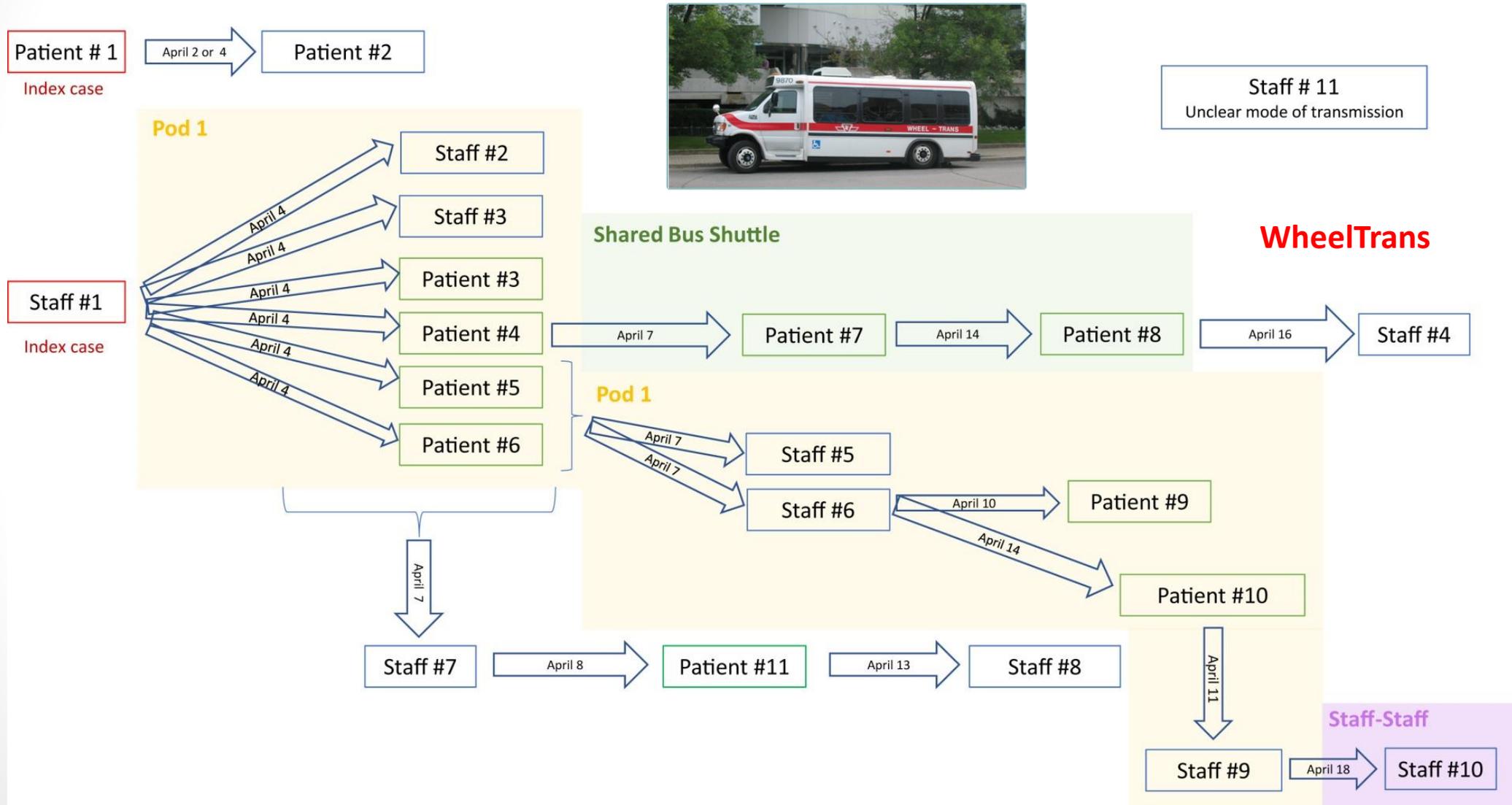
CONCLUSION: Universal screening for SARS-CoV-2 with nasopharyngeal swabs detected asymptomatic cases and was essential in containing a COVID-19 outbreak.

Kevin Yau, Matthew P. Muller, Molly Lin, et al (2020)

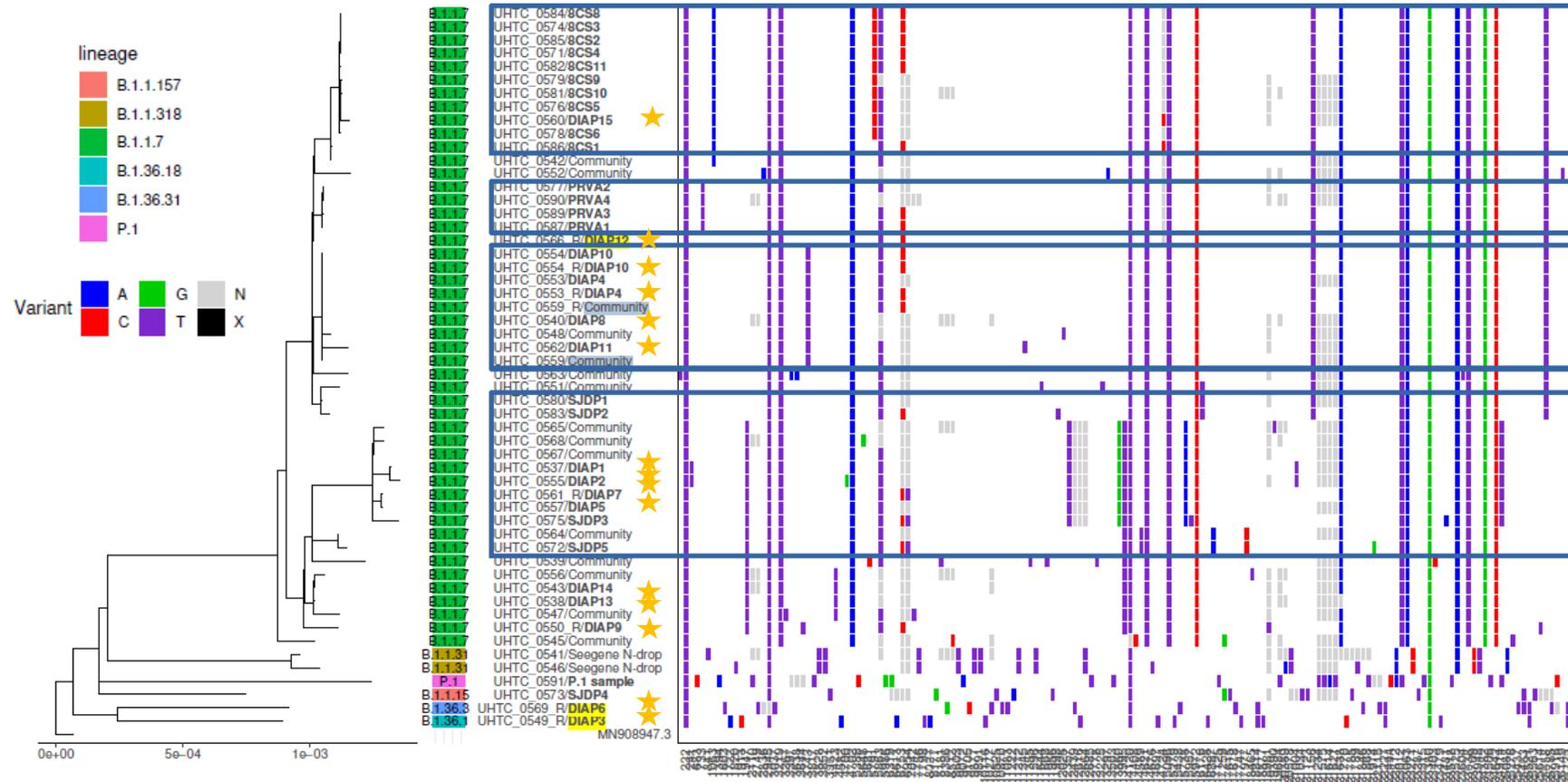
@AJKDonline | DOI: 10.1053/j.ajkd.2020.07.001

AJKD
AMERICAN JOURNAL OF KIDNEY DISEASES

Hypothesized Transmission



Next Generation Sequencing of COVID-19 Cases



★ Dialysis Patient

Courtesy of Naureen Siddiqui

Containment was Complex

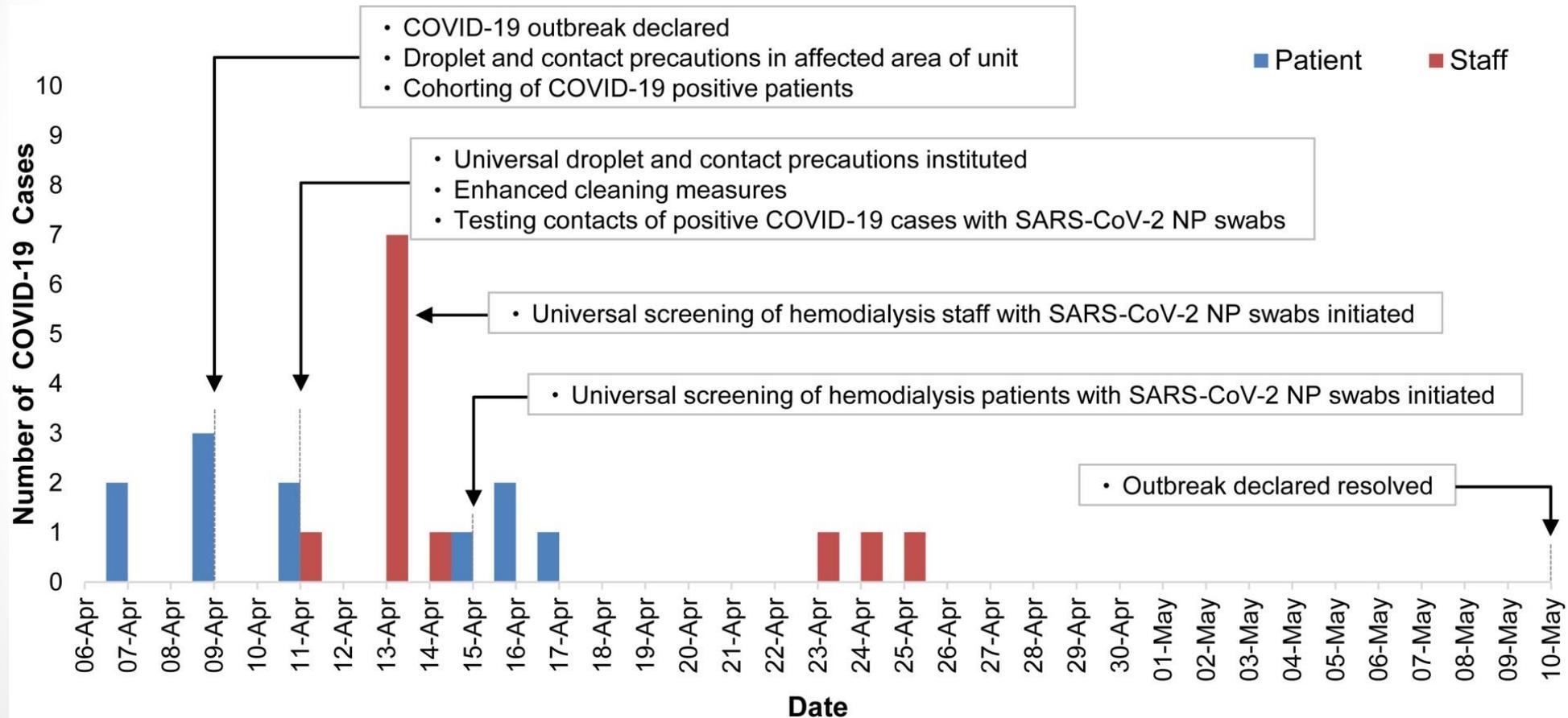


Figure 1. Epidemic curve of the coronavirus disease 2019 (COVID-19) outbreak in the St. Michael's Hospital hemodialysis unit. Abbreviations: NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Polling Question

- What was the mortality from COVID-19 in dialysis patients in Ontario in 2020?
1. 5-7.5%
 2. 10-15%
 3. 25-30%
 4. 40-45%

Morbidity and Mortality are Higher in HD

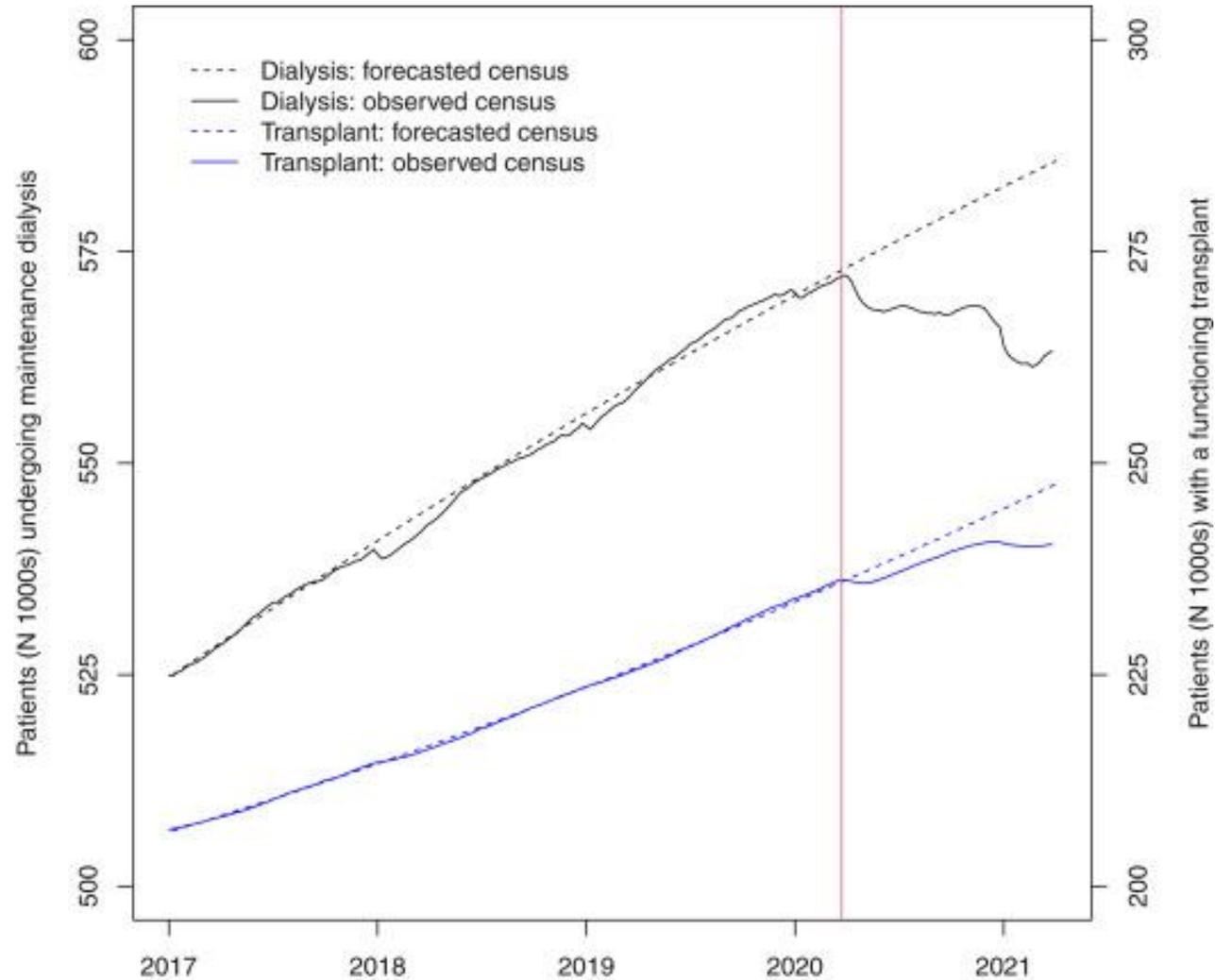
RESEARCH ■ VULNERABLE POPULATIONS

COVID-19 in patients undergoing long-term dialysis in Ontario

Leena Taji MPH, Doneal Thomas MSc, Matthew J. Oliver MD, Jane Ip BSc, Yiwen Tang MSc, Angie Yeung BSc MBA, Rebecca Cooper BA LLB, Andrew A. House MD, Phil McFarlane MD, Peter G. Blake MSc MB

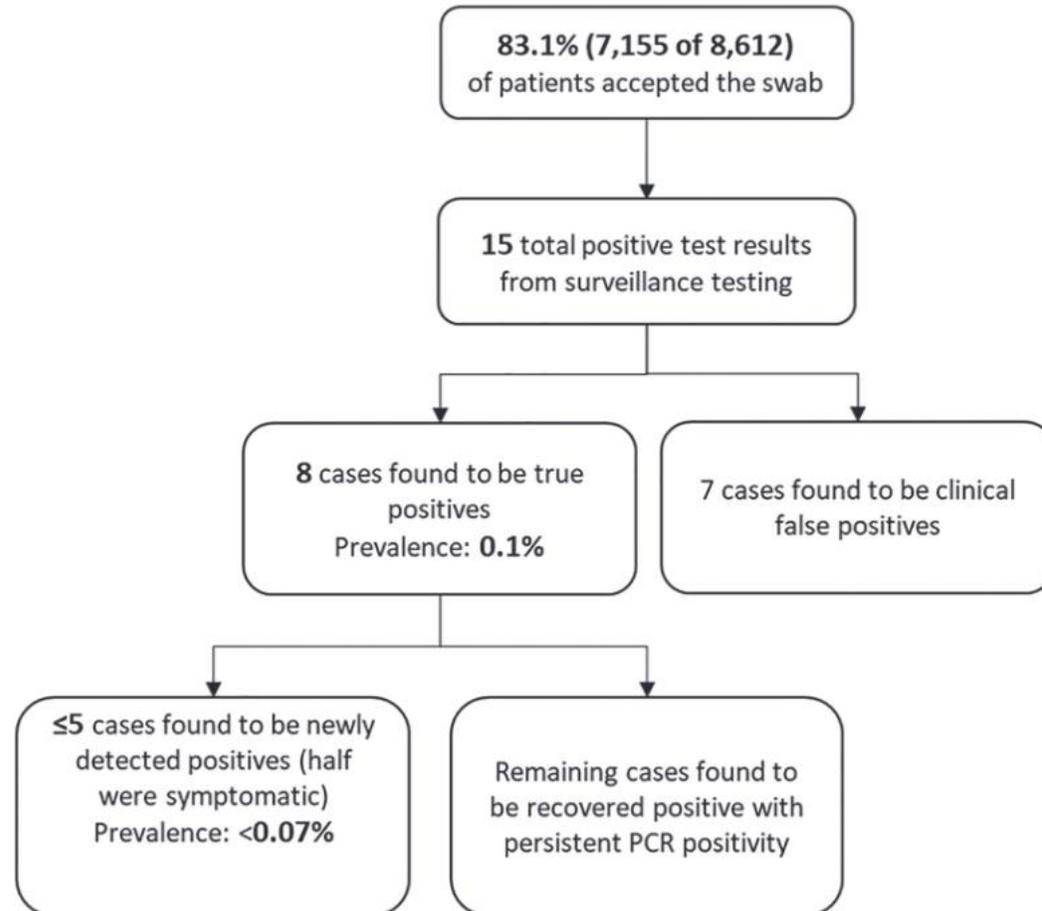
- **62% required hospitalization**
- **Case Fatality Rate of 28.3%**

Decline in the U.S. Dialysis Population

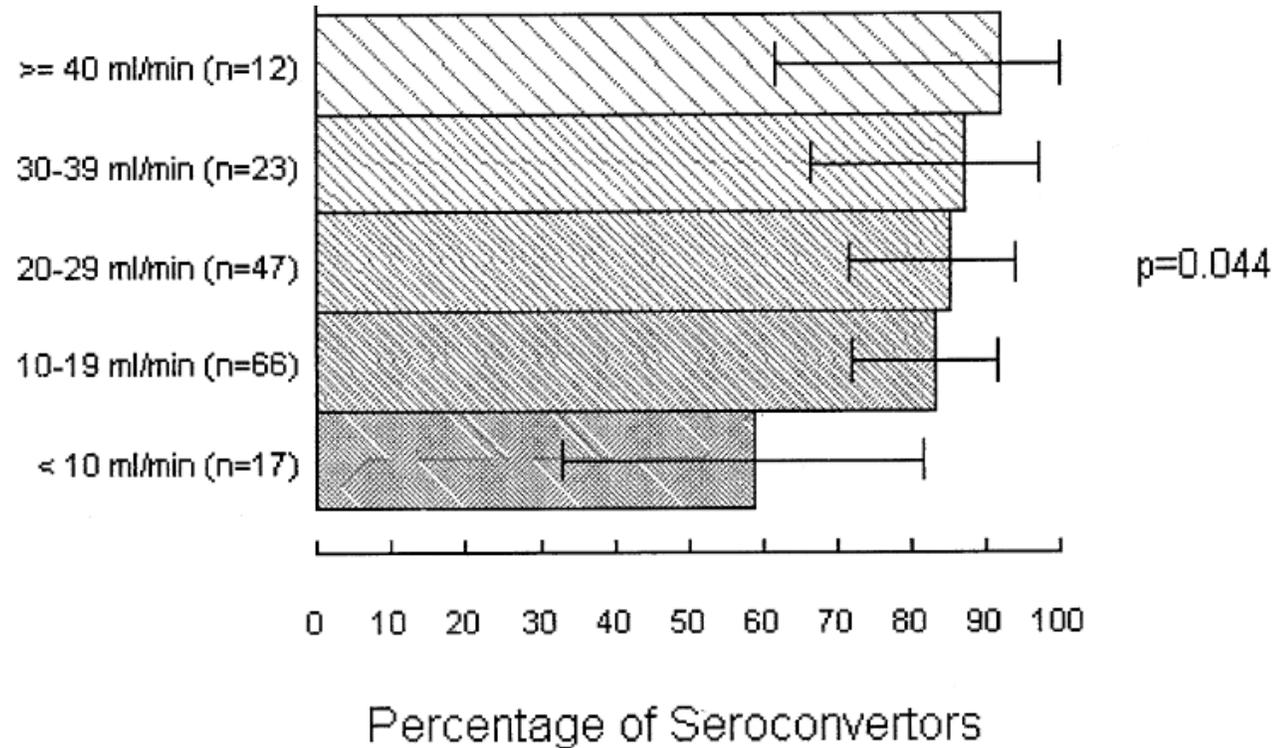


Asymptomatic COVID-19 was uncommon in HD Patients

March and June 2020



CKD Patients Have Poor Response to Hepatitis B Vaccination



mRNA-1273 (Moderna) - Spikevax

- 30,420 participants
 - No CKD/Dialysis

Risk factor for severe Covid-19 — no. of participants (%)

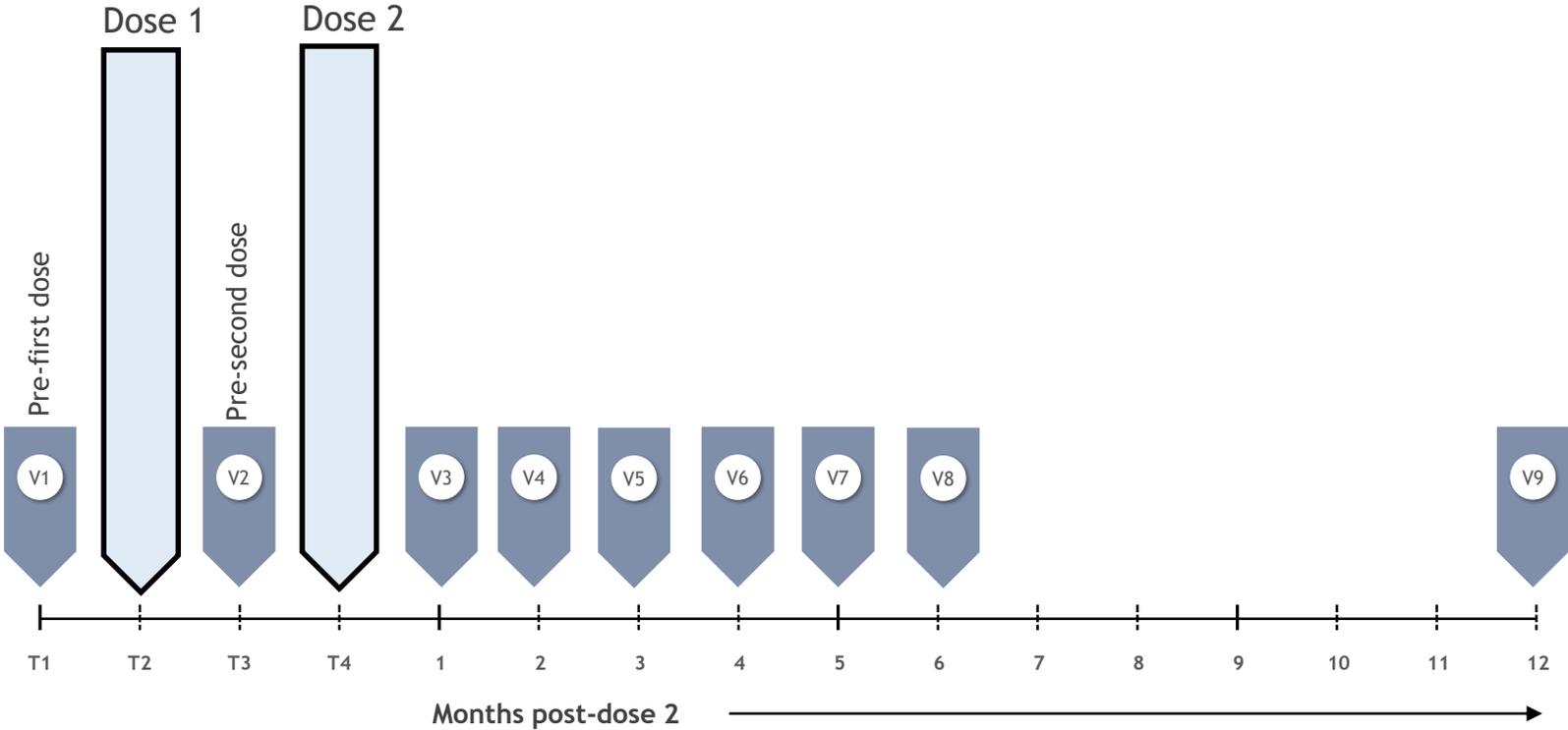
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,440 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)

BNT162b2 (Pfizer) - Comirnaty

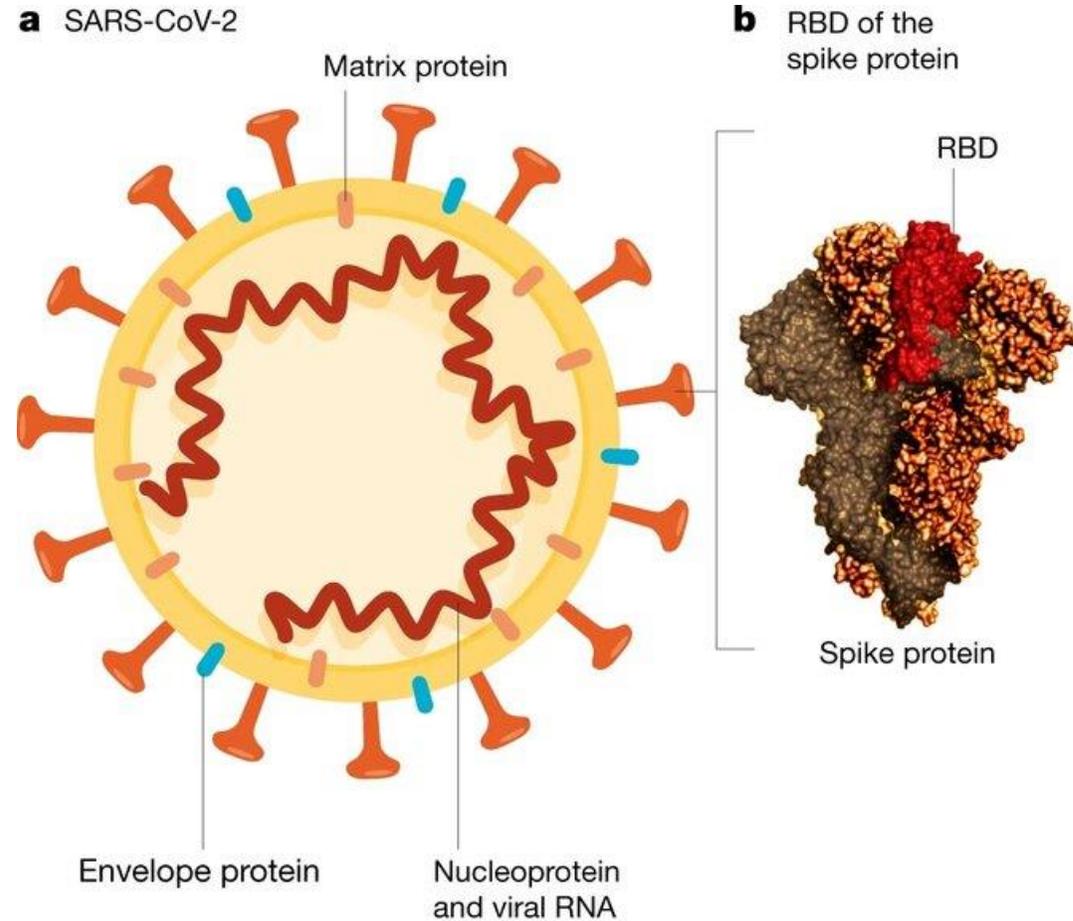
- 43,548 participants
 - 256 patients with “renal disease”

	BNT162b2 (30 µg) (N ^a =18860)	Placebo (N ^a =18846)	Total (N ^a =37706)
Charlson Comorbidity Index Category	n^b (%)	n^b (%)	n^b (%)
Participants with any Charlson comorbidity	3934 (20.9)	3809 (20.2)	7743 (20.5)
Moderate or severe liver disease	1 (0.0)	2 (0.0)	3 (0.0)
Myocardial infarction	194 (1.0)	188 (1.0)	382 (1.0)
Peptic ulcer disease	52 (0.3)	71 (0.4)	123 (0.3)
Peripheral vascular disease	124 (0.7)	117 (0.6)	241 (0.6)
Renal disease	123 (0.7)	133 (0.7)	256 (0.7)

Serologic Evaluation in Dialysis Patients



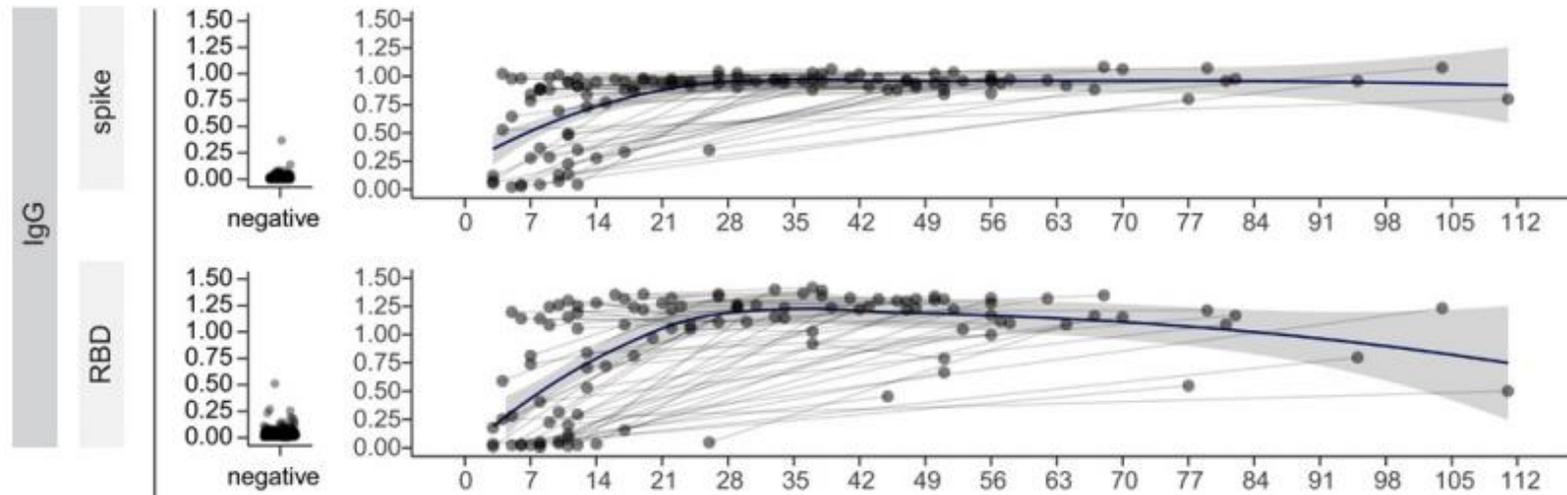
SARS-CoV-2 Antibodies



Detection of Antibodies

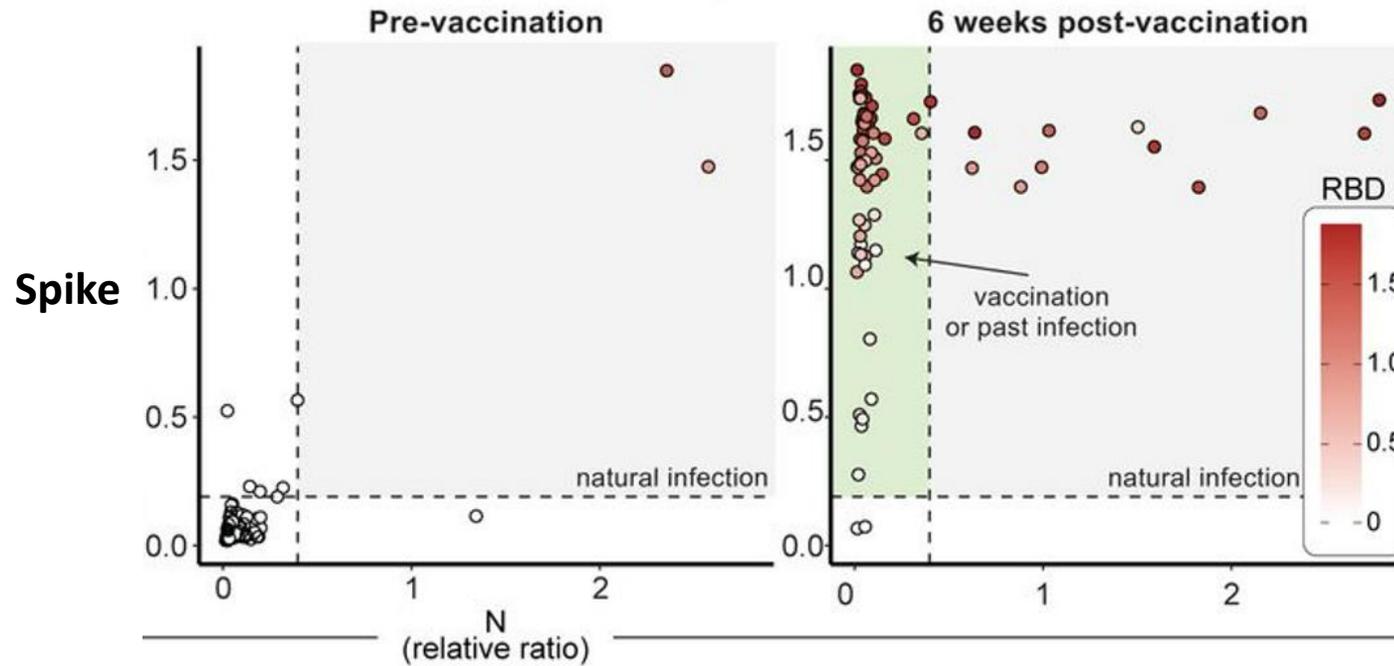
- Reported as Relative Ratios to Reference Curve
 - Can be converted to BAU/mL
- Thresholds for Positivity (Seroconversion)
 - 3 SD above mean of negative controls
- Comparison to Convalescent Serum
 - 211 patients with prior COVID-19

Convalescent Serum Antibody Levels



Isho *et al.* Science Immunology 2020

Serology Pre and Post-Vaccination



Antibody	Seropositive	Sensitivity	Specificity
Anti-spike	0.190	94.4%	98.9%
Anti-RBD	0.186	89.0%	100%
Anti-NP	0.396	78.6%	99.3%

Dried Blood Spot for CKD Patients



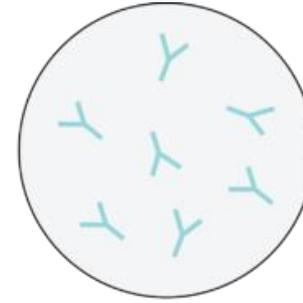
Blood from a fingerprick is placed onto a dried blood spot (DBS) card.



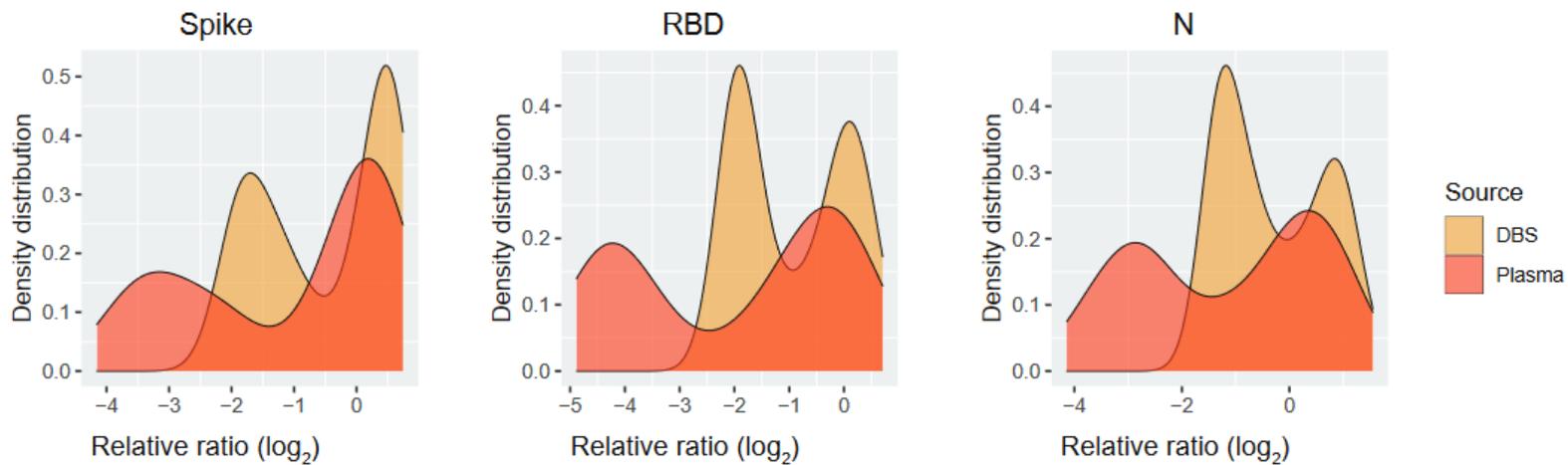
The completed DBS is sealed, packaged, labelled and shipped to a lab.



DBS samples are then analyzed for the presence of antibodies against SARS-CoV-2.



Different types and targets of SARS-CoV-2 antibodies can be detected in a positive sample.



Original Investigation | Nephrology

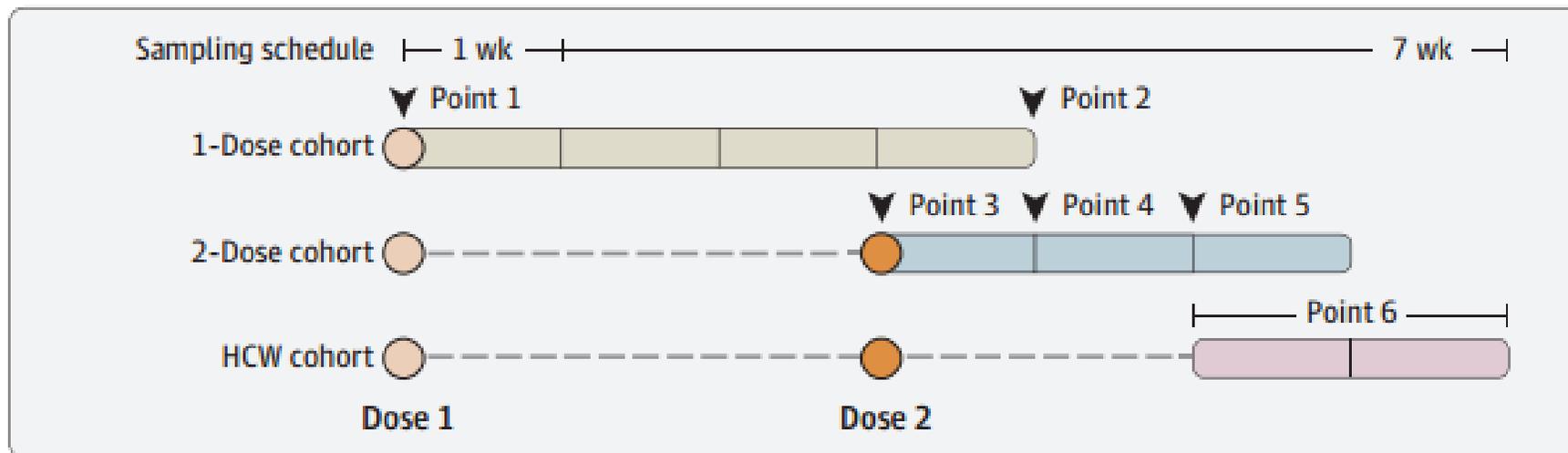
Evaluation of the SARS-CoV-2 Antibody Response to the BNT162b2 Vaccine in Patients Undergoing Hemodialysis

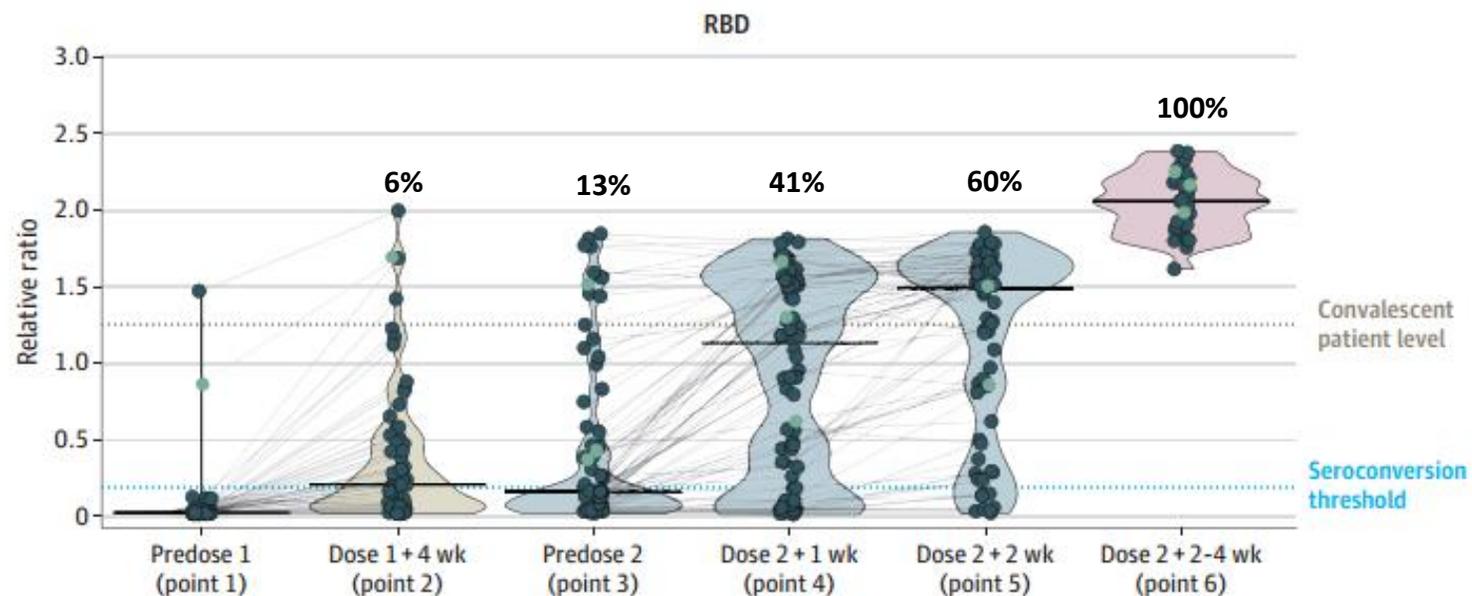
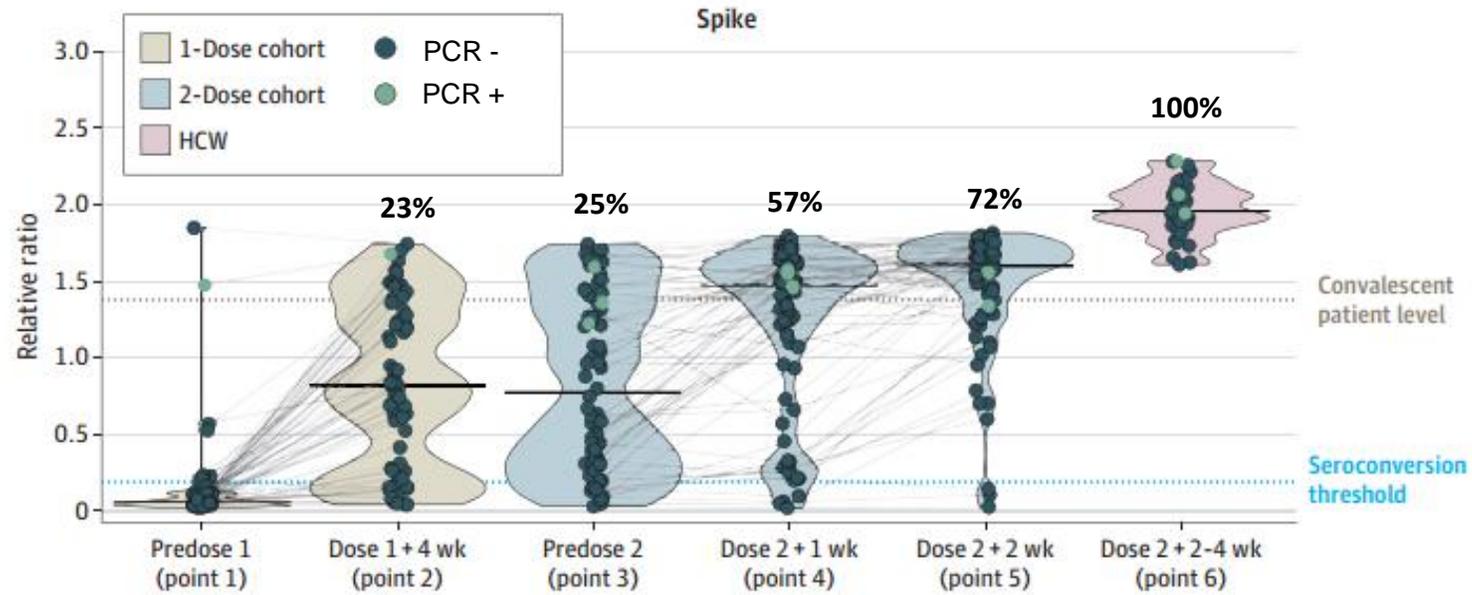
Kevin Yau, MD; Kento T. Abe, BSc; David Naimark, MD, MSc; Matthew J. Oliver, MD, MHS; Jeffrey Perl, MD, SM; Jerome A. Leis, MD, MSc; Shelly Bolotin, MSc, PhD, MScPH; Vanessa Tran, PhD; Sarah I. Mullin, BSc; Ellen Shadowitz; Anny Gonzalez, BSc; Tatjana Sukovic, BSc; Julie Garnham-Takaoka, BScN; Keelia Quinn de Launay, MSc; Alyson Takaoka, MSc; Sharon E. Straus, MD, MSc; Allison J. McGeer, MD; Christopher T. Chan, MD; Karen Colwill, PhD; Anne-Claude Gingras, PhD; Michelle A. Hladunewich, MD, MSc

Table 1. Clinical Characteristics of 142 Patients Undergoing Hemodialysis Receiving BNT162b2 Vaccine

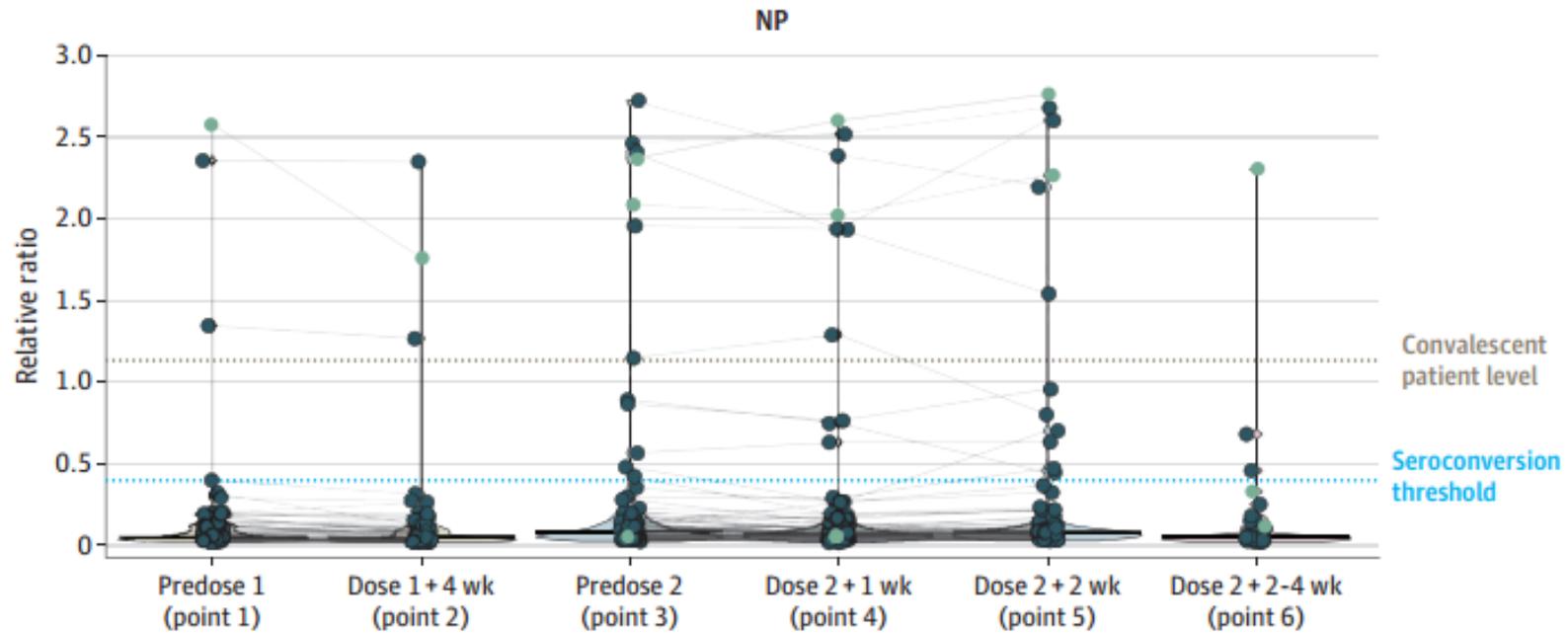
Characteristic	No. (%)			P value ^a
	Total (n = 142)	1 Dose (n = 66)	2 Doses (n = 76)	
Age, median (IQR), y	72 (62-79)	72 (59-76)	75 (64-82)	.04
Age group				
≤55 y	19 (13)	10 (15)	9 (12)	.41
>55 y	123 (87)	56 (85)	67 (88)	
Sex				
Female	48 (34)	18 (27)	30 (39)	.13
Male	94 (66)	48 (73)	46 (61)	
Prior COVID-19 ^b	3 (2)	1 (2)	2 (3)	>.99
Positive baseline anti-NP ^c	15 (11)	3 (5)	12 (16)	.05
Dialysis vintage, median (IQR), y	2.65 (1.5-4.6)	2.56 (1.2-4.8)	2.6 (1.6-4.6)	.81
Cause of end-stage kidney disease				
Diabetes	63 (44)	26 (39)	37 (49)	.03
Ischemic nephropathy	27 (19)	8 (12)	19 (25)	
Glomerulonephritis	20 (14)	13 (20)	7 (9)	
Other/unknown	32 (22)	19 (29)	13 (17)	
Comorbidities				
Immunosuppressive treatment ^d	9 (6)	5 (8)	4 (5)	.41
Autoimmune disease	8 (6)	4 (6)	4 (5)	.56
Diabetes	74 (52)	29 (44)	45 (59)	.07
Cancer	23 (16)	12 (18)	11 (14)	.36
Coronary artery disease	53 (37)	22 (33)	31 (41)	.62
Congestive heart failure	37 (26)	15 (23)	22 (29)	.36
Chronic obstructive lung disease	13 (9)	5 (8)	8 (11)	.81
Hypertension	135 (95)	65 (98)	70 (92)	.12
Obesity ^e	10 (7)	2 (3)	8 (11)	.08
Hepatitis B nonresponder ^f	11 (8)	3 (4)	8 (11)	.16

Figure 1. Immunoglobulin G (IgG) Response to Spike, Receptor Binding Domain (RBD), and Nucleocapsid Protein (NP) Antigens of SARS-CoV-2 Following 1 vs 2 Doses of BNT162b2 Vaccine in Patients Receiving Maintenance Hemodialysis





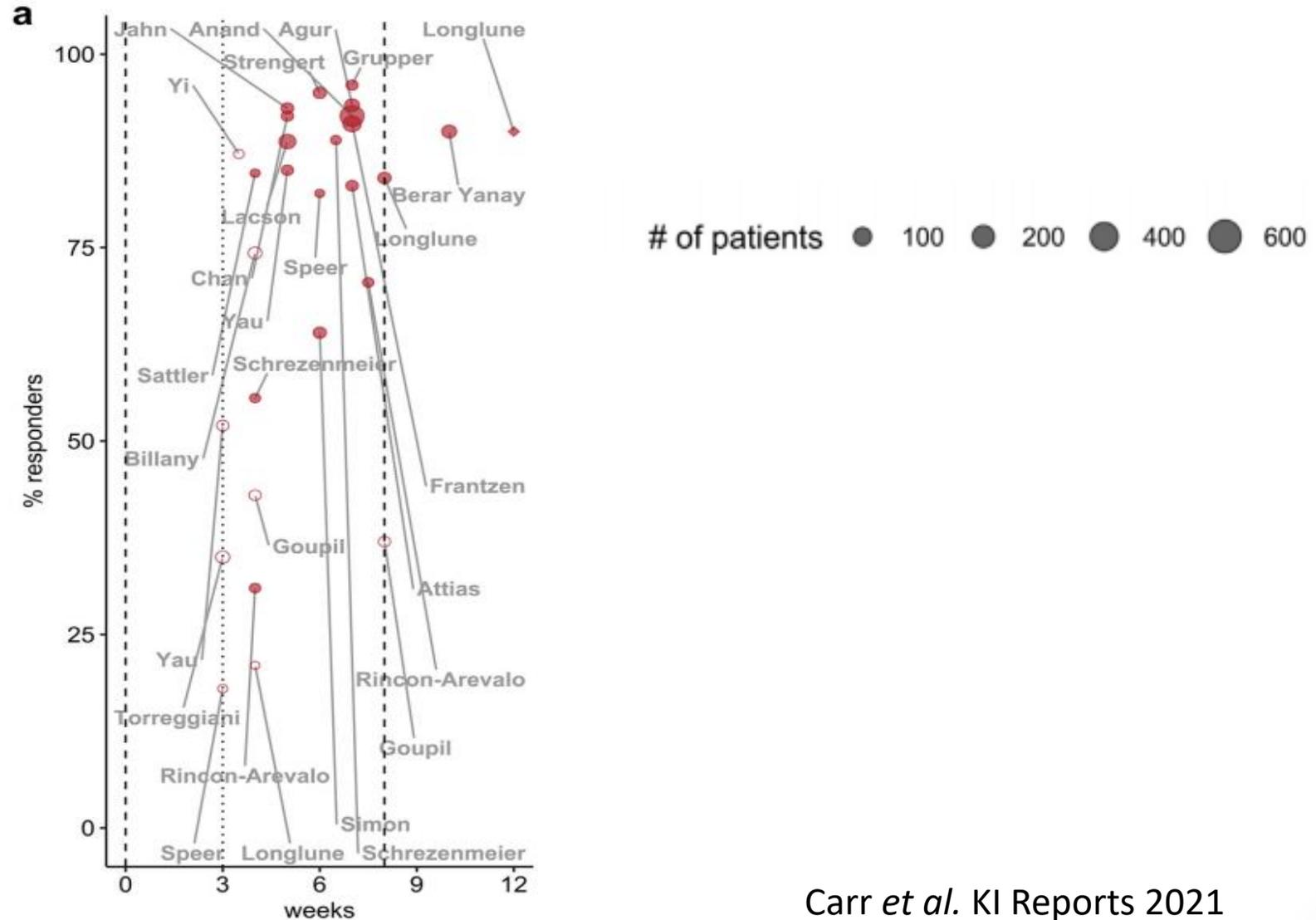
Anti-Nucleocapsid



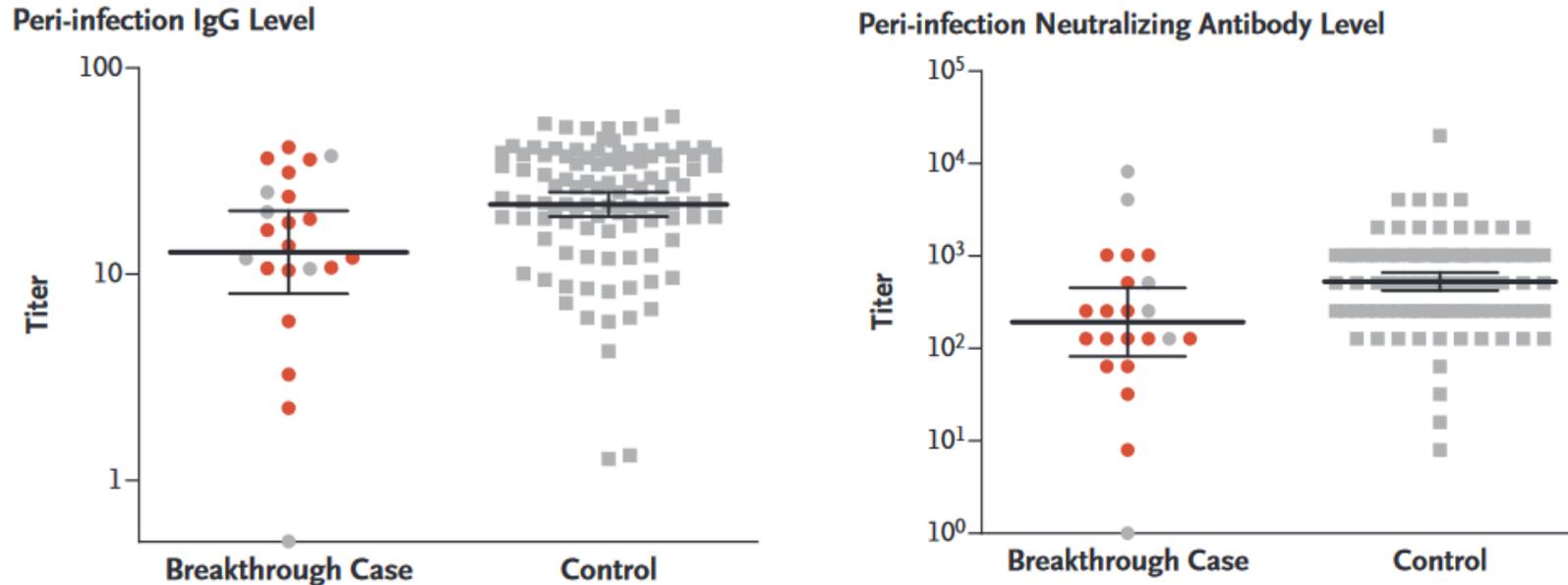
Predictors of Seroconversion for Anti-RBD

Variable	Anti-RBD seroconversion ^a		Anti-RBD reaching median convalescent serum level ^b	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.01 (0.97-1.06)	.58	0.98 (0.94-1.01)	.22
Male sex	1.33 (0.25-7.24)	.74	0.45 (0.16-1.28)	.13
Vaccine reactogenicity ^c	22.86 (2.46-212.83)	.006	1.96 (0.70-5.50)	.20

Early Serologic Studies in Dialysis Patients

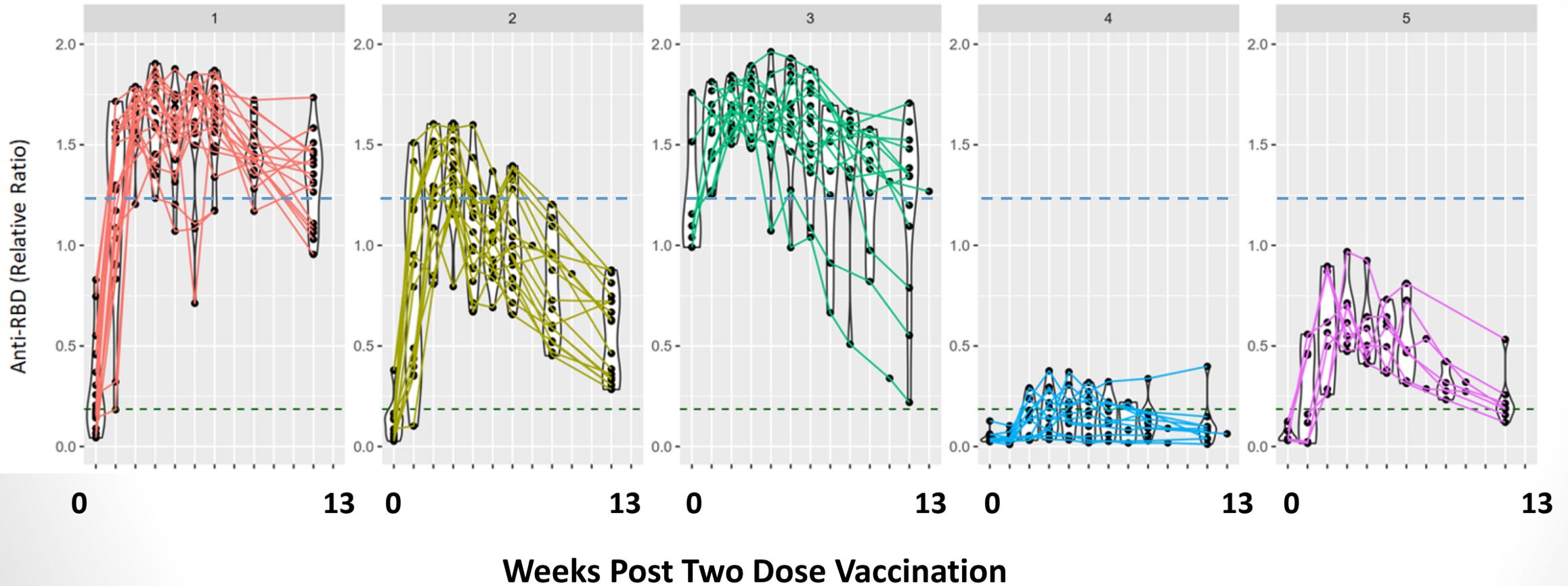


Antibodies as a Correlate of Protection?

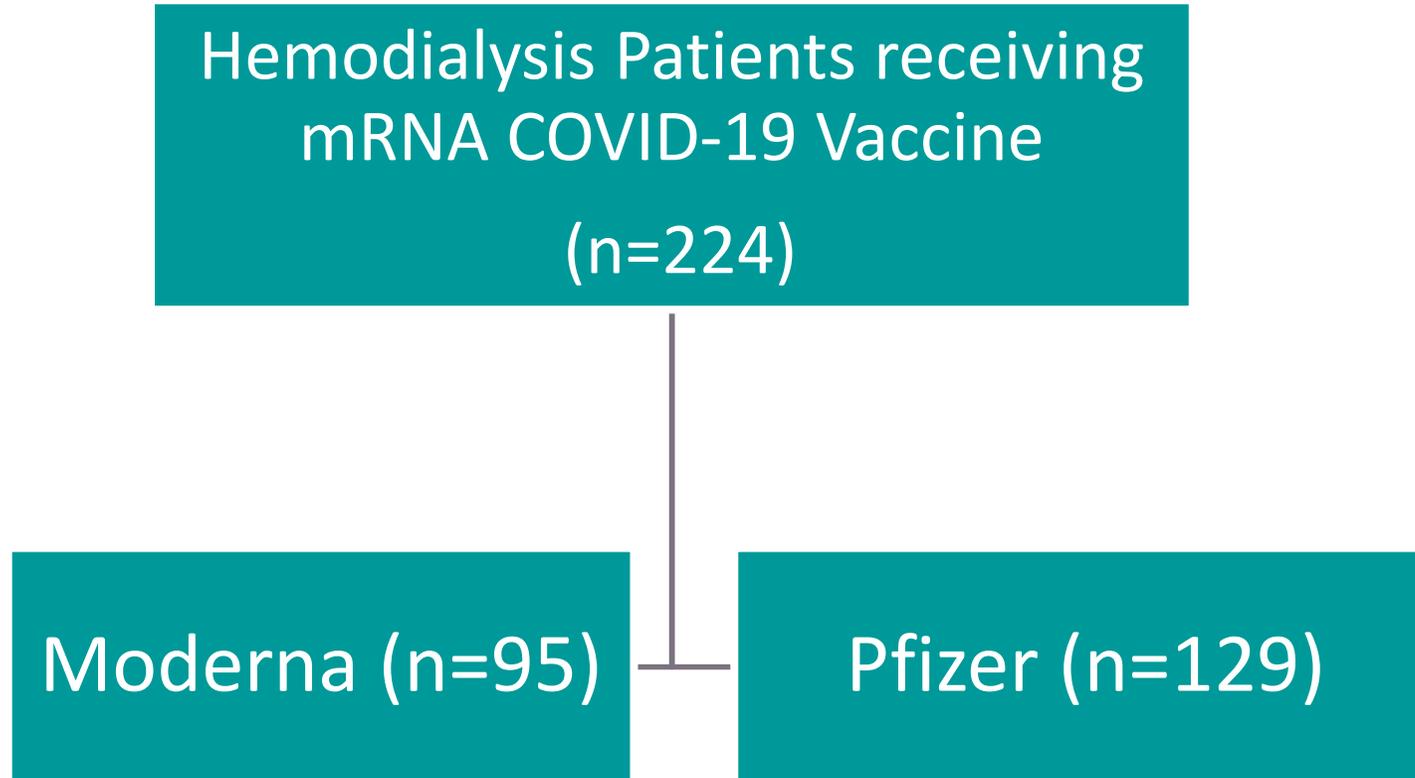


- 39 Fully Vaccinated HCW with breakthrough COVID-19
- Lower Anti-Spike IgG (Ratio 0.514; 95% CI 0.28-0.94)
- Lower Neutralizing Antibody Titers (Ratio 0.361; 95% CI 0.17-0.79)

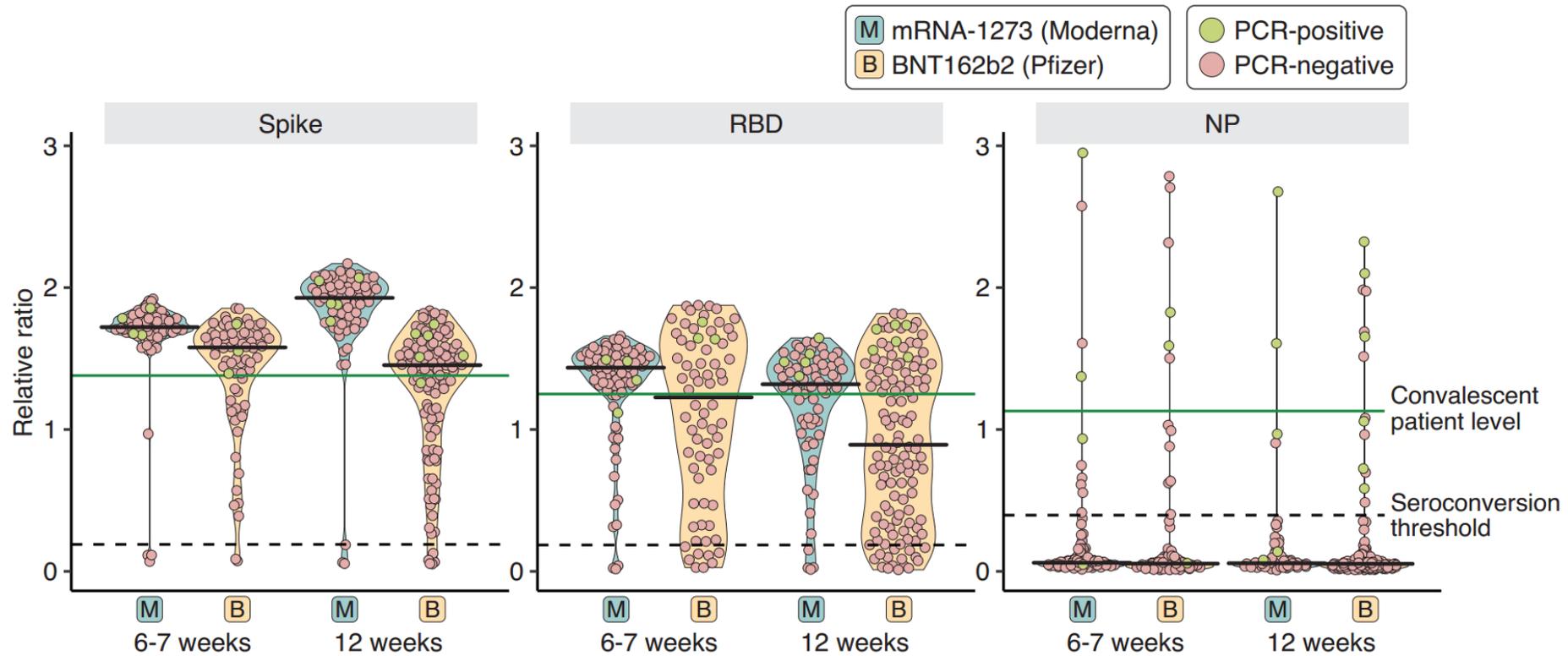
Trajectories of Anti-RBD Response up to 13 weeks (BNT162b2)



Difference in immunogenicity by mRNA vaccine type?



Moderna versus Pfizer in Hemodialysis



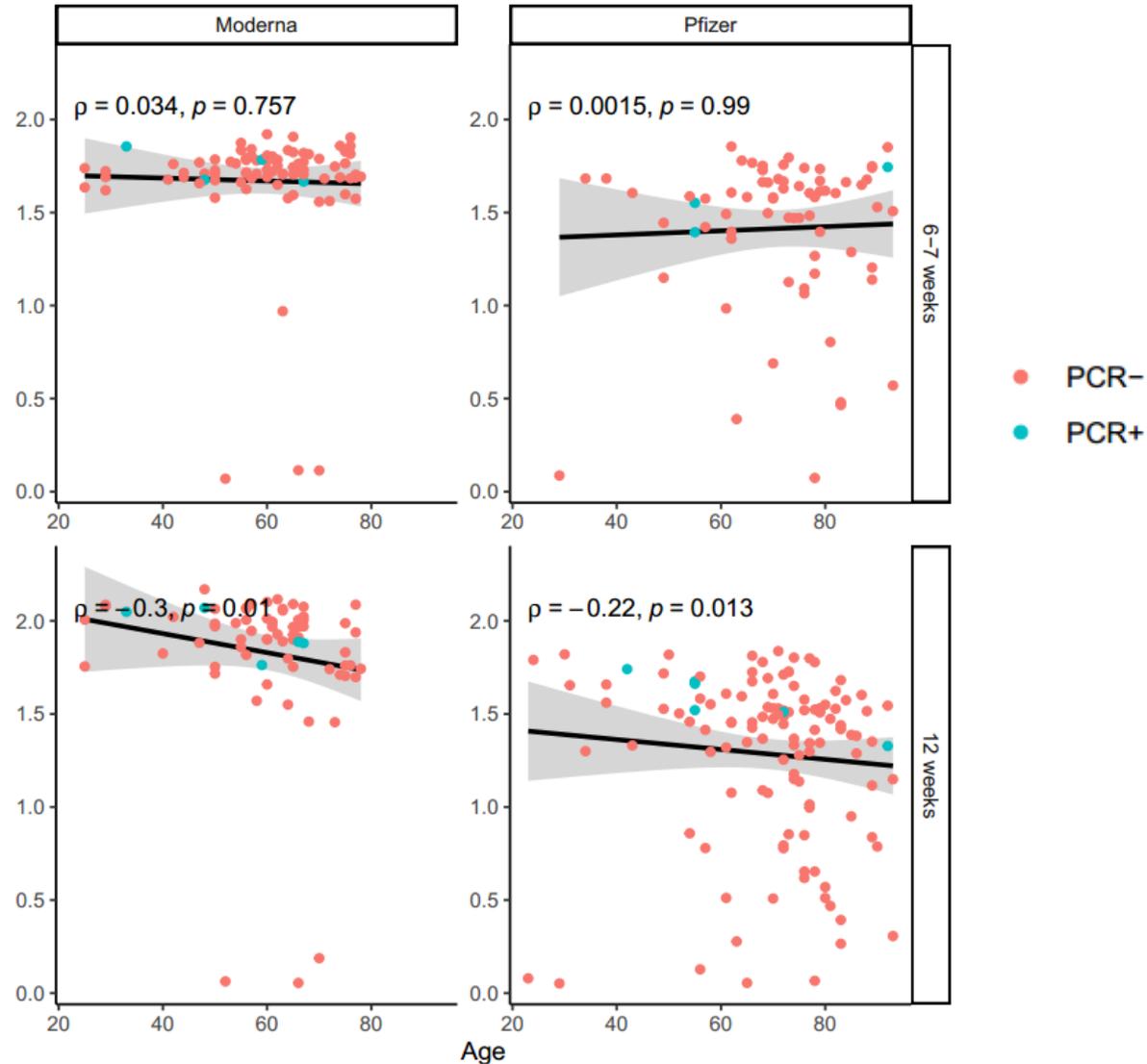
- Three breakthrough COVID-19 infections in Pfizer group

Odds of Reaching Convalescent Level at 12 weeks

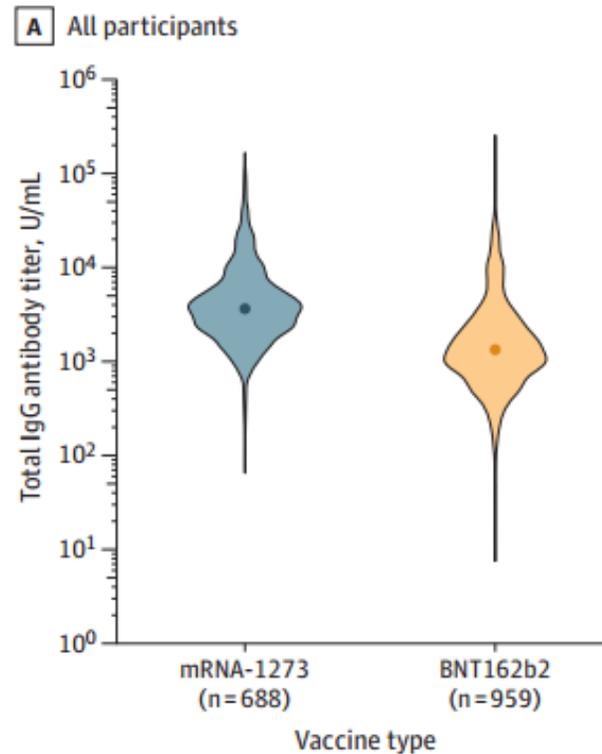
Antibody	Vaccine	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	p value
Anti-Spike	Moderna	7.7 (2.5-24.0)	10.8 (2.5-47.8)	0.002
Anti-RBD	Moderna	3.8 (1.9-7.7)	6.3 (2.4-16.3)	<0.001

*Adjustment for age, sex, immunosuppression, diabetes, coronary artery disease

Moderna versus Pfizer Anti-Spike by Age

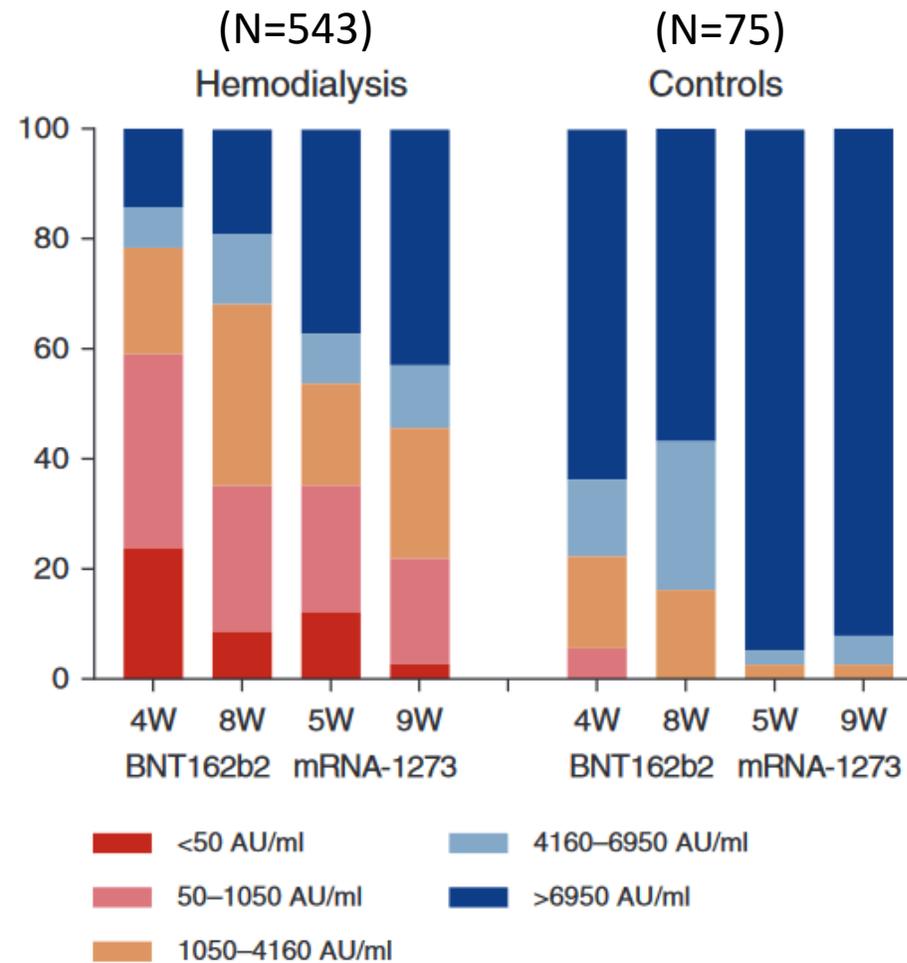


Greater Immunogenicity with mRNA-1273 (Moderna)

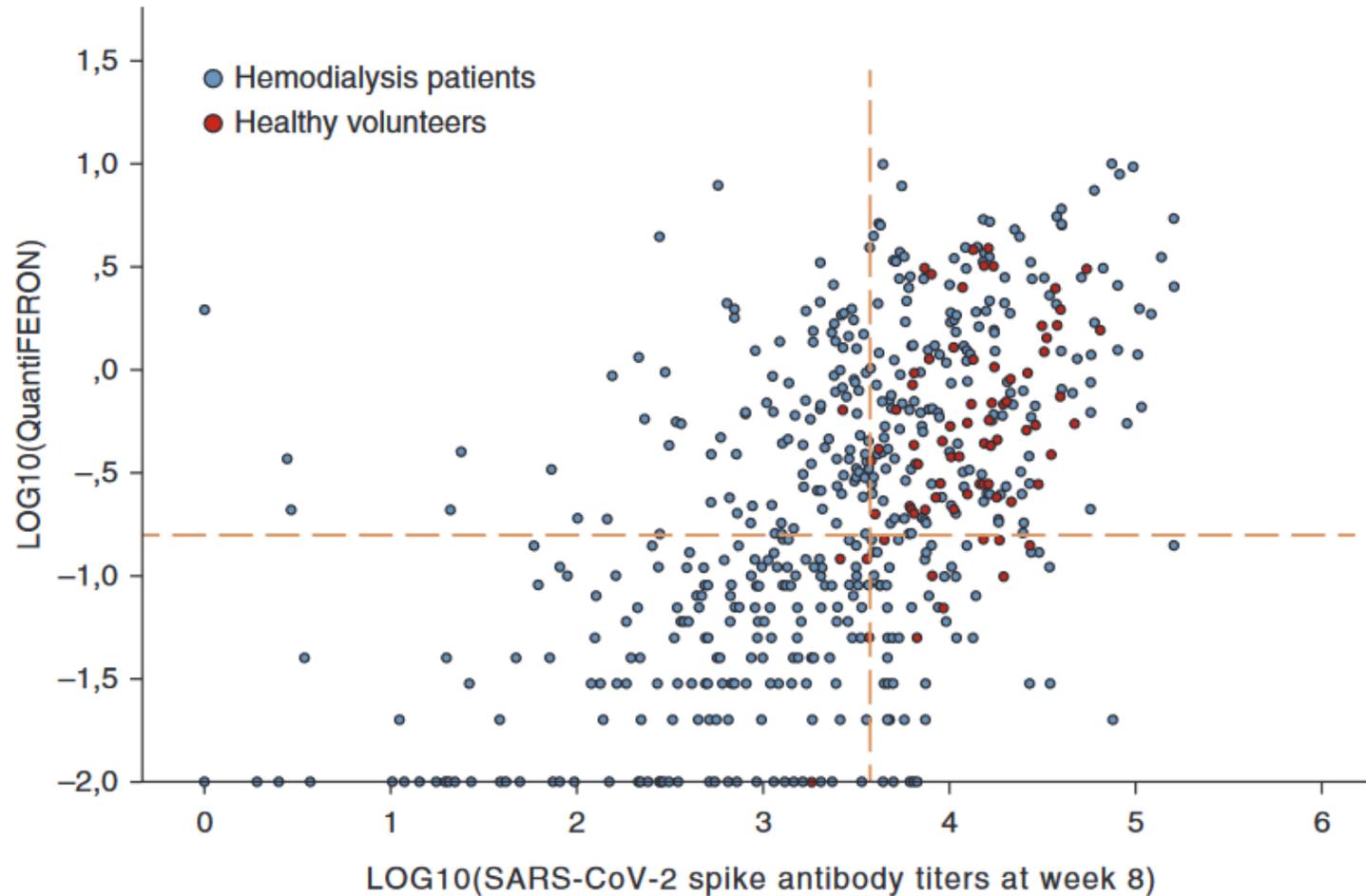


- 1647 Health Care Workers in Belgium
- Anti-RBD 6-10 weeks post 2nd dose

Anti-Spike in Hemodialysis Patients versus Controls



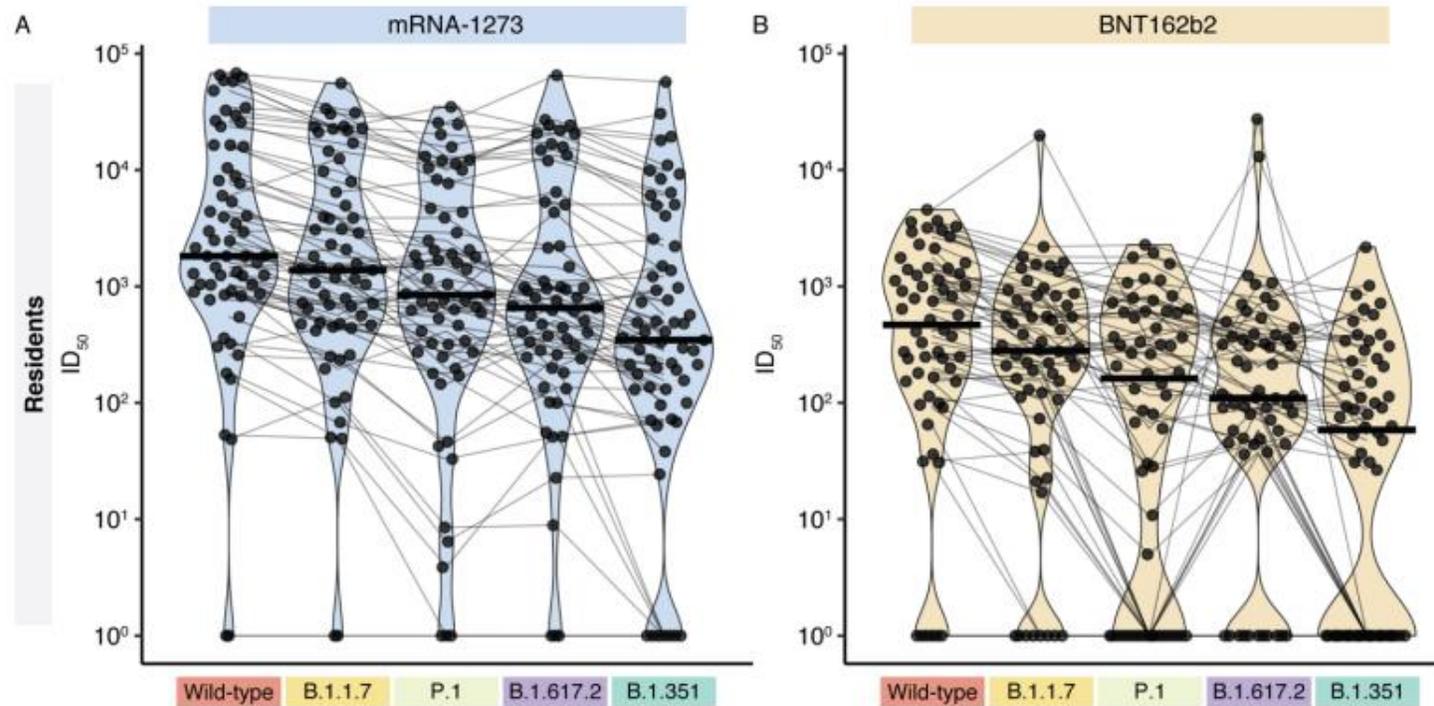
Correlation between Humoral and Cellular Immunity



Greater Immunogenicity with mRNA-1273

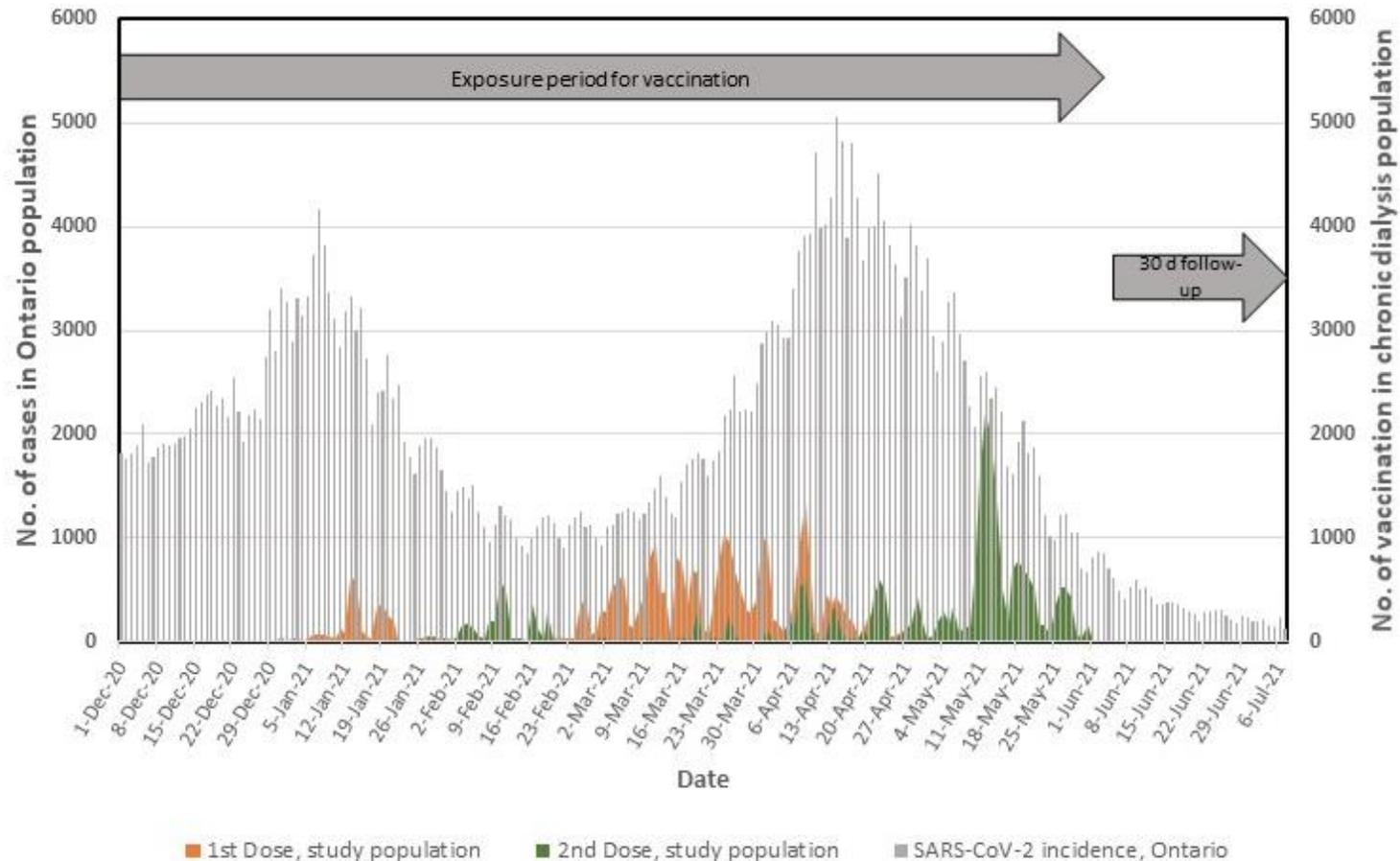
Possible Reason	mRNA-1273 (Moderna)	BNT16b2 (Pfizer)
Dose	100 µg	30 µg
Timing Between Doses	4 weeks	3 weeks

Decreased Neutralization Against Variants of Concern



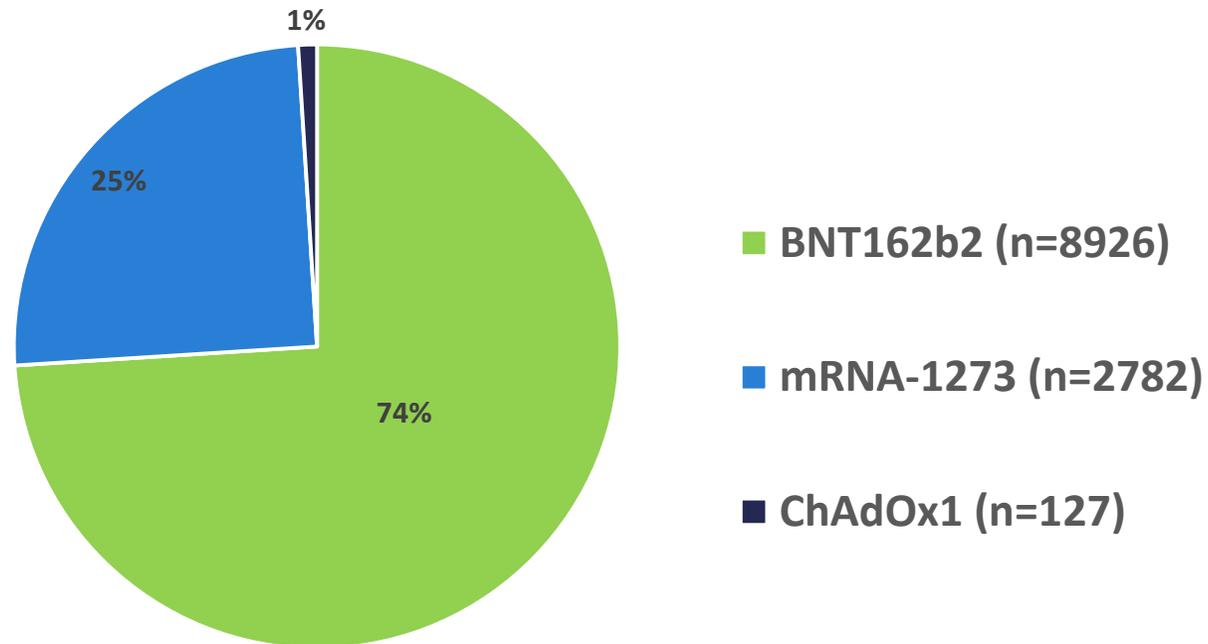
Thresholds of antibody relative ratios predicted to neutralize wild-type strain increased against variants of concern

Vaccine Effectiveness in Ontario Dialysis Patients



Vaccination of Dialysis Patients in Ontario

- Dec 20, 2020 to May 31, 2021
 - 13,888 maintenance dialysis patients



Adapted from Oliver *et al.* Under Revision

Event Rates by Vaccination Status

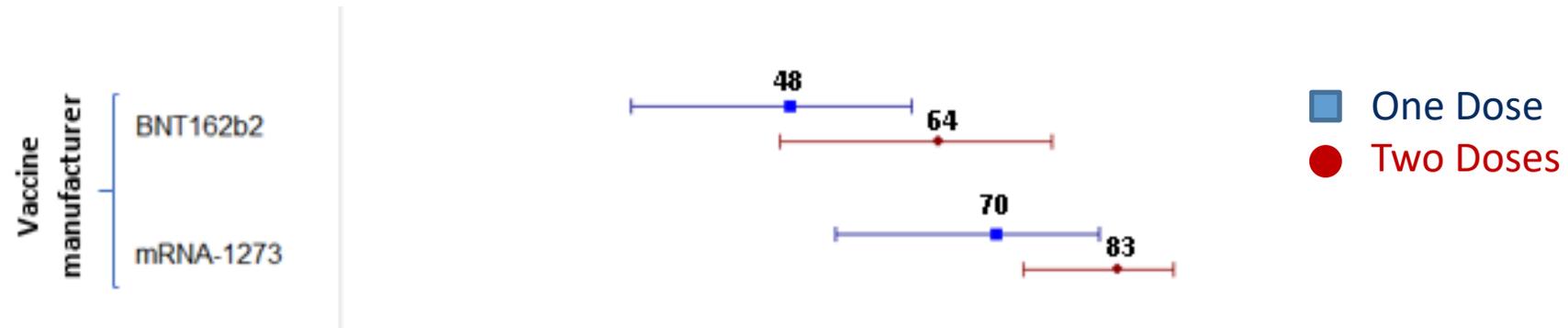
	Unvaccinated	One Dose	Two Doses
Follow-up, days	1,398,544	424,427	563,396
SARS-CoV-2 infections, N	488	112	63
Infection rate, per 100,000 days	34.9	26.4	11.3
Hospitalizations, N (% of cases)	256	49	18
Hospitalization rate, per 100,000 days	18.32	11.54	3.20
Mortality, N (% of cases)	77	11	6
Mortality rate, per 100,000 days	5.50	2.59	1.06

Adjusted Vaccine Effectiveness

	Unvaccinated	One Dose		Two Doses	
		Unadjusted	Adjusted	Unadjusted	Adjusted
		Vaccine Effectiveness (95% CI)		Vaccine Effectiveness (95% CI)	
SARS-CoV-2 infections	1 (ref.)	32% (13-48%)	41% (24-54%)	51% (32-64%)	69% (58-78%)
Severe outcomes	1 (ref.)	33% (3-54%)	48% (25-64%)	70% (47-82%)	84% (72-91%)
Hospitalizations	1 (ref.)	36% (7-56%)	49% (27-65%)	71% (49-83%)	84% (72-91%)
Mortality	1 (ref.)	63% (22-83%)	73% (43-87%)	75% (35-91%)	90% (72-96%)
Sensitivity analyses					
SARS-CoV-2 infections No lag period	1 (ref.)	33% (15-47%)	37% (21-50%)	44% (25-59%)	65% (52-74%)

*Adjusted for age, sex, ethnicity, GTA/Non-GTA, dialysis modality, Charlson comorbidity index, income quintiles, LTC, dialysis vintage, number of RT-PCR tests, and monthly Public Health Unit Region SARS-CoV-2 infection rate

Vaccine Effectiveness by Subgroups



Limitations/Conclusions

- Limited protection with one dose
- Majority of second doses during decline of 3rd wave
 - Bias towards vaccine effectiveness
- Not matched

Breakthrough Infections January 1- July 31, 2021

Characteristics of patients with breakthrough infections	Patients with breakthrough infections, Total N = 1810
Age in years—median (IQR)	66 (56-74)
Sex—no. (%)	
Male	1054 (58.2)
Vaccines received—no.(%) ¹	
Two doses of Pfizer-BioNTech	826 (45.6)
Two doses of Moderna	729 (40.3)
One dose of J&J/Janssen	236 (13.0)
At least one immunocompromising condition ^{2,3} —no(%)	95/923 (10.3)
Symptomatic ³ —no.(%)	340/494 (68.8)
Hospitalized in the 2 weeks following diagnosis—no.(%)	778 (43.0)
30-day mortality ⁵ —no.(%)	133 (7.5)

Preliminary Data from the CDC presented at ASN Kidney Week 2021

Breakthrough Infections Pre vs. Post-Delta Variant

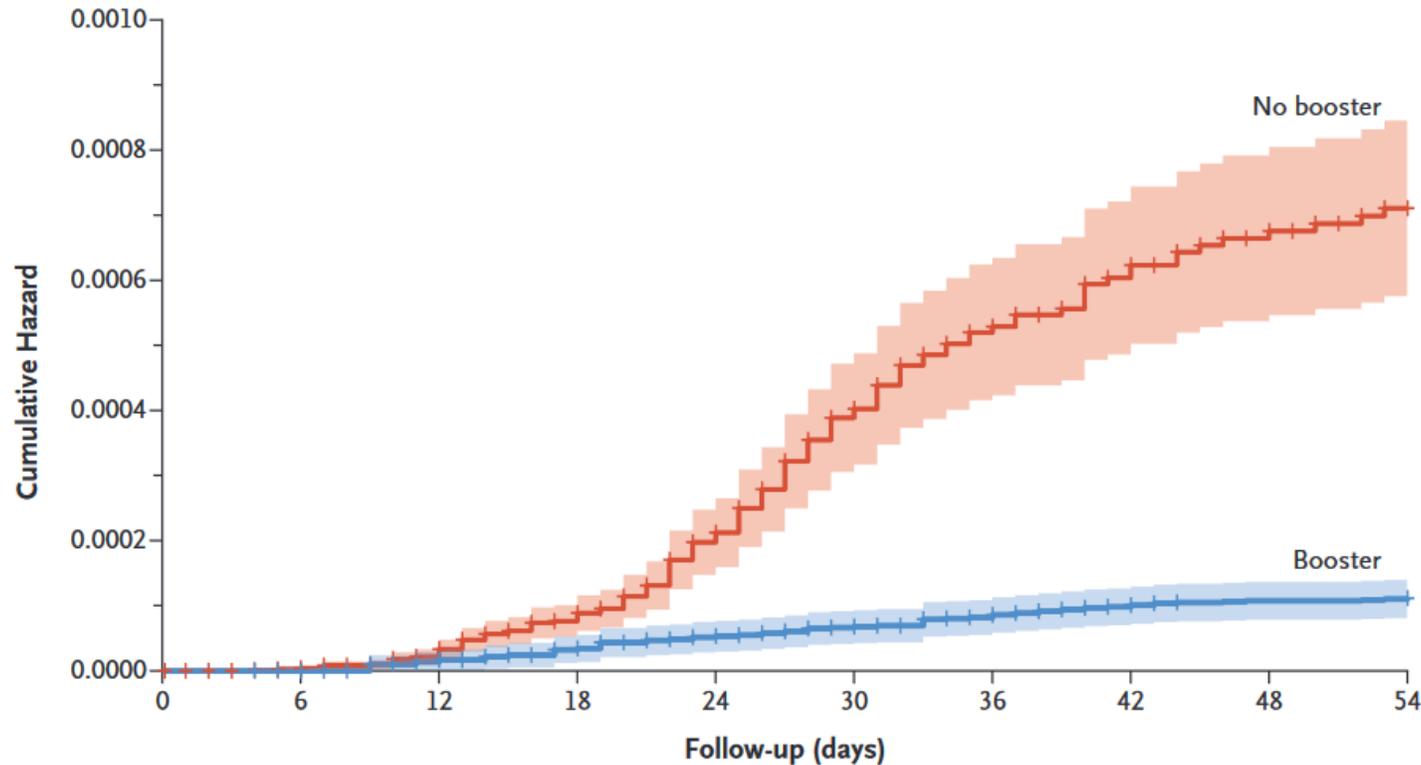
Characteristics of patients with breakthrough infections	Patients with breakthrough infections	
	01/01/21 – 06/15/21 N = 818	06/16/21 – 07/31/21 N = 992
Symptomatic ¹ –no.(%)	201/328 (61.3)	139/166 (83.7)
Hospitalized in the 2 weeks following diagnosis–no.(%)	357/818 (43.6)	421/992 (42.4)
30-day mortality ² –no.(%)	52/814 (6.4)	81/962 (8.4)

Preliminary Data from the CDC presented at ASN Kidney Week 2021

Boosters



Reduction in Mortality with BNT162b2 Booster in \geq Age 50



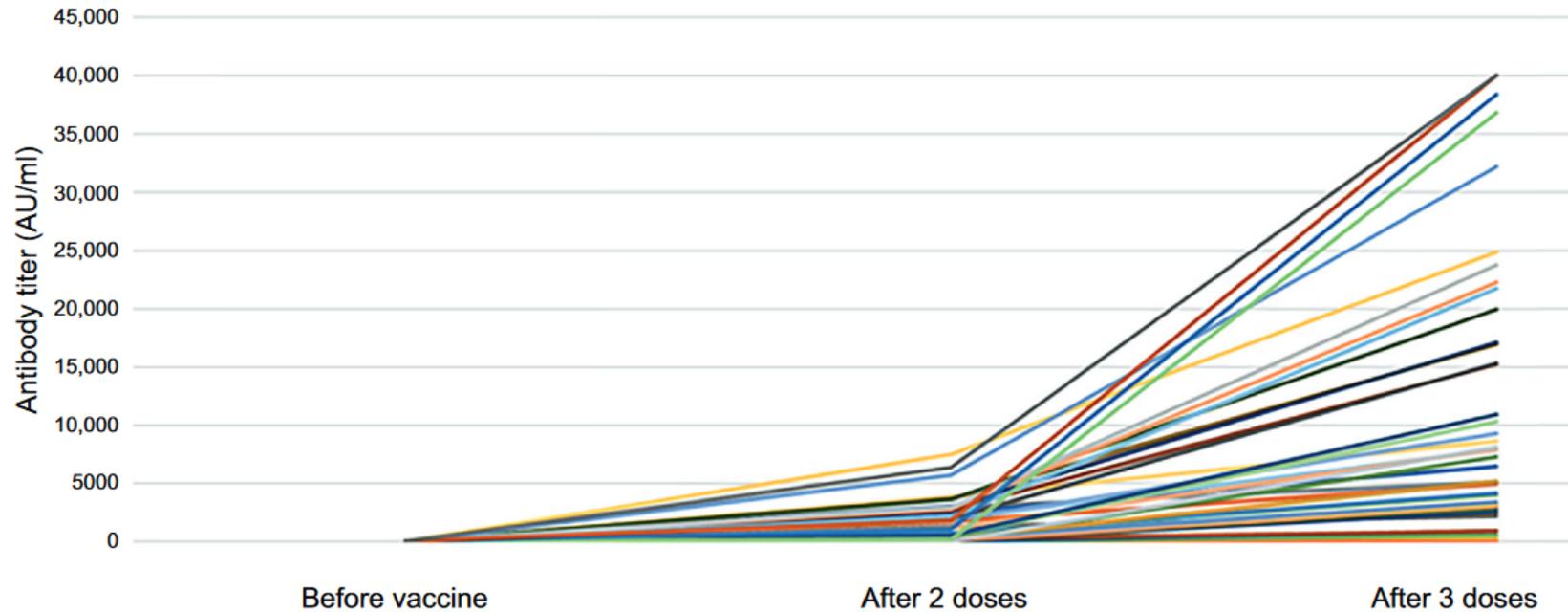
No. at Risk

No booster	841,428	723,609	520,459	326,741	202,797	145,021	111,761	101,695	90,036	83,989
Booster	46,259	119,332	322,203	515,639	639,315	696,859	729,971	739,945	756,591	757,614

Cumulative No. of Events

No booster	0	3	20	43	72	103	119	129	134	137
Booster	0	0	4	12	23	33	46	57	62	65

Three doses BNT162b2 in Hemodialysis



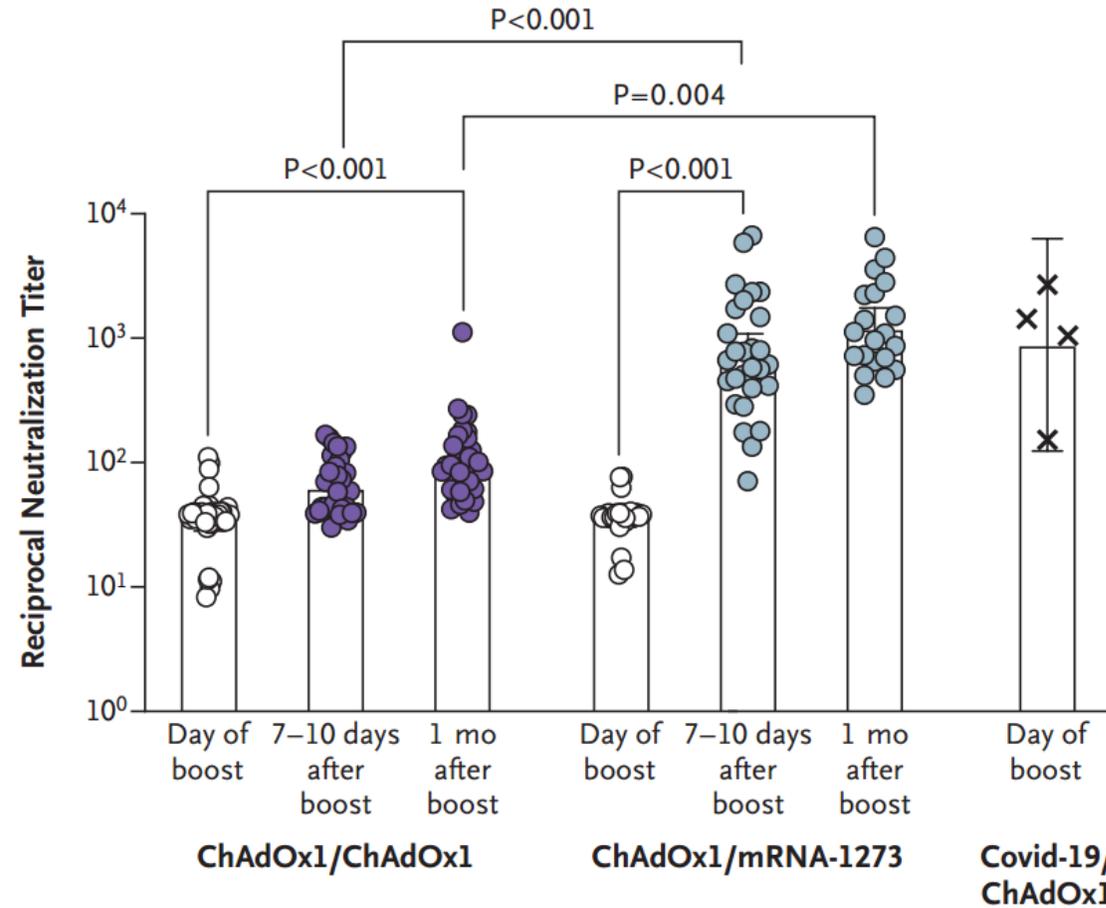
- **Median increase in RBD 580% after 3rd dose (n=45)**

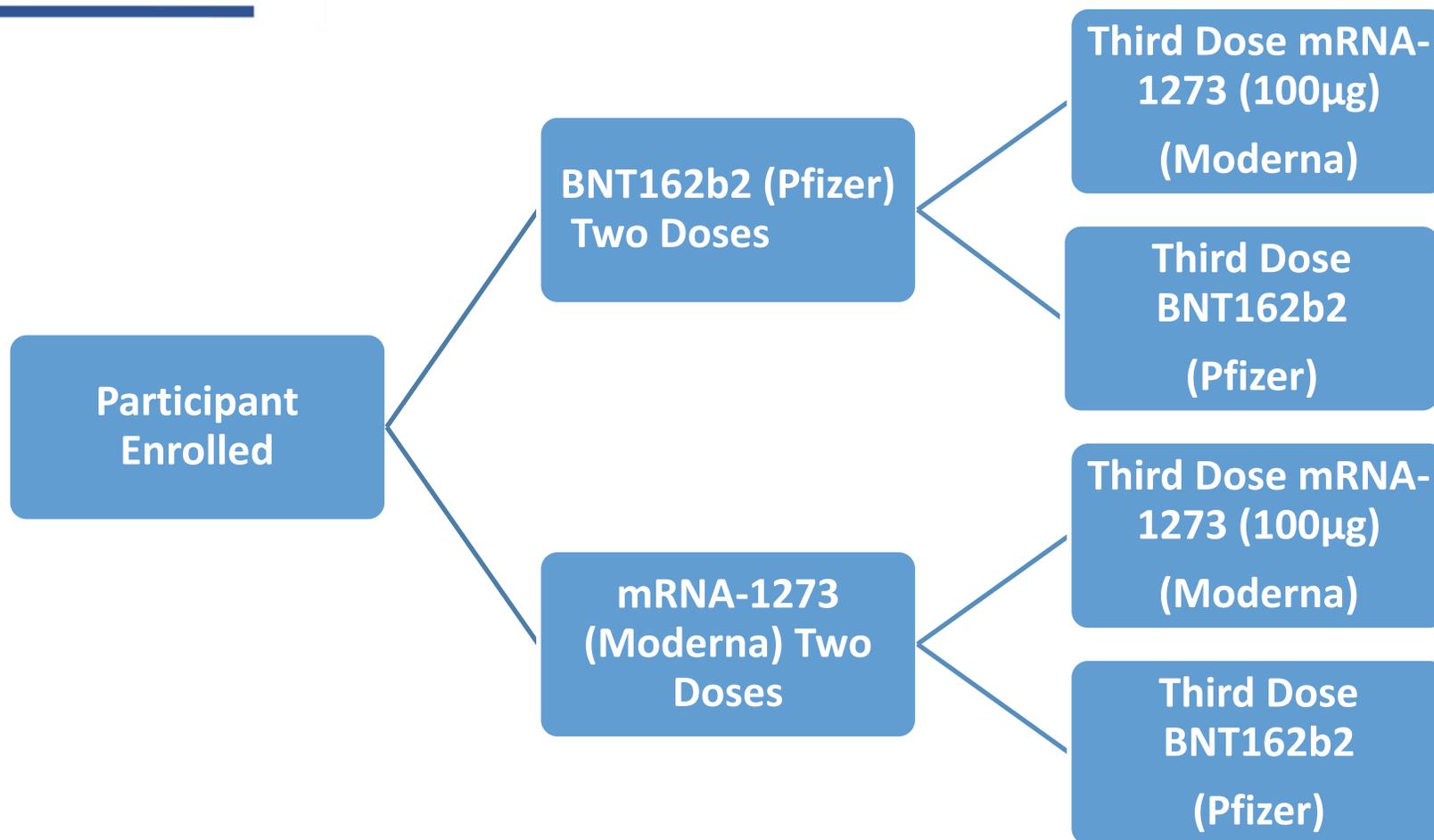
Polling Question 2

- Do you think that a different third dose of COVID-19 vaccine from the first two doses will provide greater vaccine effectiveness (e.g. Pfizer for the first two doses and Moderna for the third dose)?
 - 1. Yes
 - 2. No

Is Heterologous Vaccination Better?

A SARS-CoV-2 Neutralization Based on Immunofluorescence





Some Patients Have Strong Loyalty



Conclusions

- Dialysis patients respond poorly to one dose of vaccine
- COVID-19 vaccine effectiveness is high in Ontario dialysis patients
- Immunogenicity of mRNA-1273 greater than BNT162b2
- Booster doses in CKD/Dialysis remain under investigation



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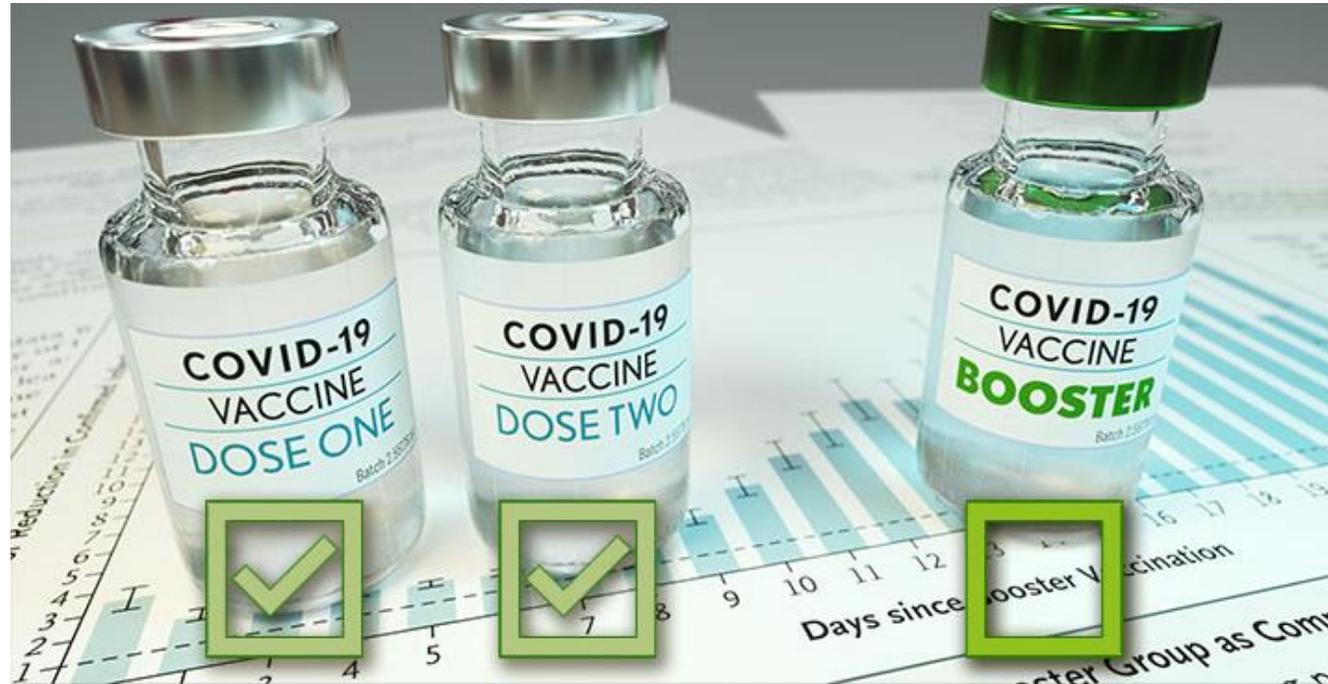
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Questions/Discussion



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