# COVID-19 Vaccine in Transplant & Immunocompromised Populations - March 25, 2021





Welcome & Introductions:

Dana Wollins, DrPH, MGC
Vice President, Clinical Affairs & Guidelines
Infectious Diseases Society of America



Moderator:

Emily Blumberg, MD
Director of the Transplant Infectious Diseases Program and the Infectious Diseases Fellowship
University of Pennsylvania
Current Past President, American Society of Transplantation



COVID-19 Vaccine in Transplant & Immunocompromised Populations



Robin K. Avery, MD, FIDSA, FAST Professor of Medicine Division of Infectious Diseases Johns Hopkins Hospital



Deepali Kumar, MD, MSc, FRCP(C)
Professor of Medicine
Transplant Infectious Diseases
University Health Network, Toronto



Lara Danziger-Isakov, MD, MPH
Director, Immunocompromised Host Infectious Disease
Professor, Department of Pediatrics
Cincinnati Children's Hospital



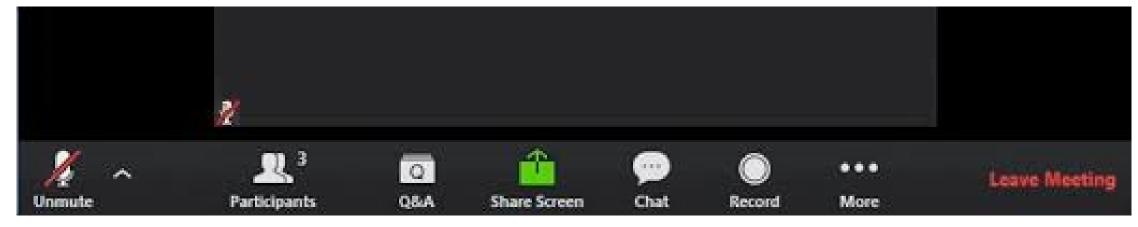
Cameron R. Wolfe, MBBS, MPH, FIDSA Associate Professor of Medicine Transplant Infectious Diseases Duke University

# Question? Use the "Q&A" Button





Comment?
Use the "Chat" Button



### **Disclosures**

Emily Blumberg, MD -

Grant support Takeda, Merck, Hologic DSMB - Amplyx

Robin K. Avery, MD, FIDSA, FAST -

Study/grant support from Aicuris, Astellas, Chimerix, Merck, Oxford Immunotec, Qiagen, Takeda/Shire

Kumar Deepali, MD, MSc, FRCP(C)

research grants from GSK, Roche consultancy fees from GSK, Roche, Sanofi

Lara Danziger-Isakov, MD, MPH

Consultant – Takeda, Merck Contracted Clinical Research support paid to my institution: Ansun Biopharma, Astellas, Merck, Takeda, Viracor

Cameron R. Wolfe, MBBS, MPH, FIDSA - has nothing to disclose.

# Johns Hopkins SARS-CoV-2 National Vaccine Safety and Immunogenicity Study in Solid Organ Transplant Recipients



### Disclosures/Acknowledgments

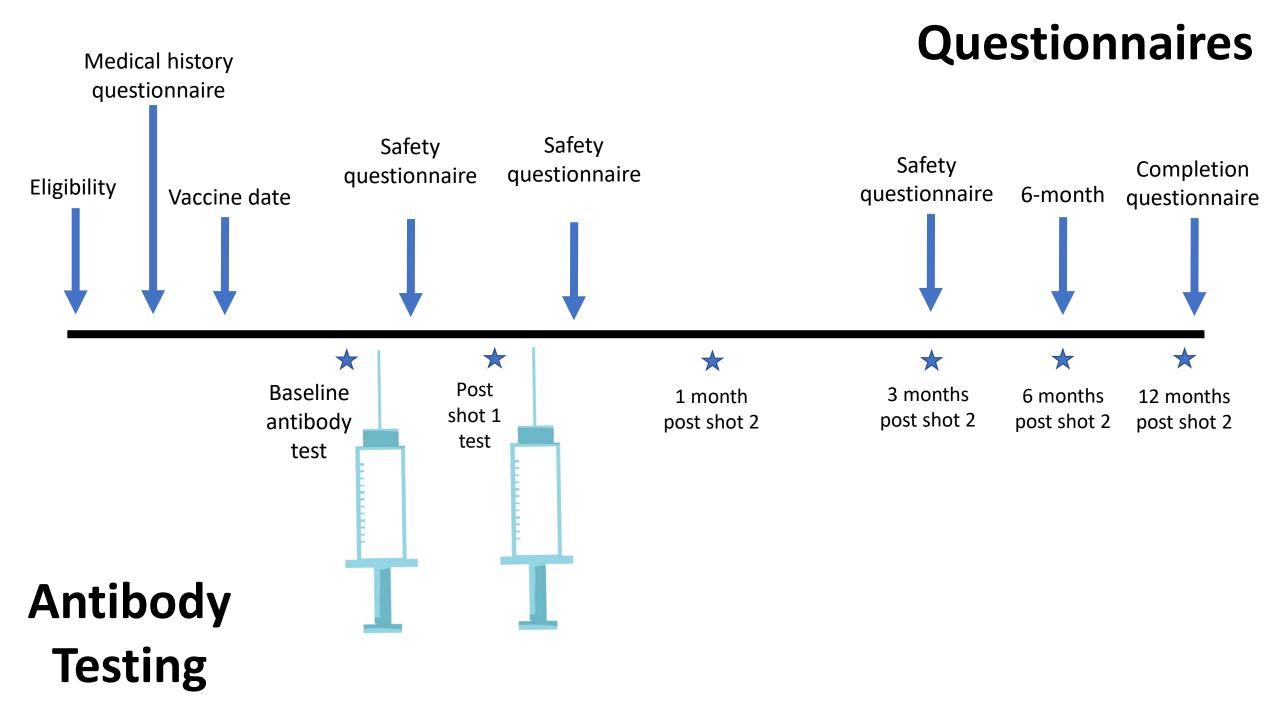
Robin Avery MD: Study/grant support from Aicuris, Astellas, Chimerix,
 Merck, Oxford Immunotec, Qiagen, Takeda/Shire

• Thanks to Brian Boyarsky MD PhD, Pl of the vaccine study, for the kind loan of his slides, which I have adapted (Brian is at the far left in the photo at right, when President Obama signed the HOPE Act, 2013)



### Study Design: Prospective Cohort

- Goal: Vaccine safety and immunogenicity in transplant recipients
- Population: Solid organ transplant recipients in the US
  - Eligibility: age 18+, intention to be vaccinated, prior COVID-19 is not an exclusion
- Recruitment: Open enrollment (online); started Dec 9, 2020
- Exposure: SARS-CoV-2 vaccination (not supplied by the study)
- Outcome:
  - <u>Safety</u>: local & systemic adverse effects; allergy; rejection; neurologic diagnoses; infections; COVID-19 diagnosis
  - Immunogenicity: Serial SARS-CoV-2 anti-spike protein Ab
- <u>Hypothesis</u>: Immunosuppression may impact Ab development



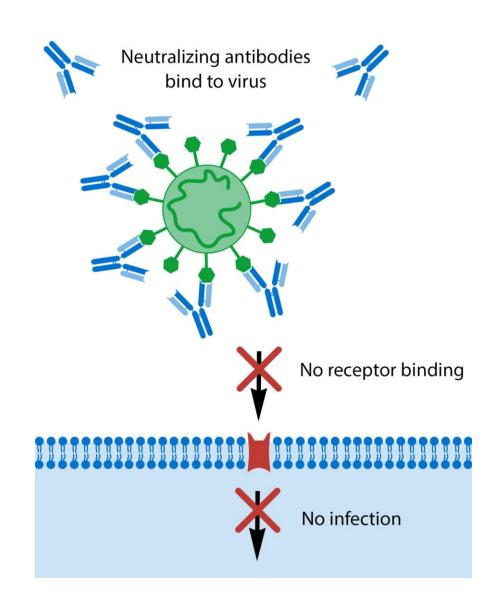
## Antibody Testing

EUROIMMUN Anti-SARS-CoV-2 ELISA



Roche Elecsys® Anti-SARS-CoV-2 S





### Enrollment: December 9 - March 16

Enrolled	3,200
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Received first dose	1611
Post first-dose Ab testing	804

Received second dose	926
Post second-dose Ab testing	211

#### Recruitment

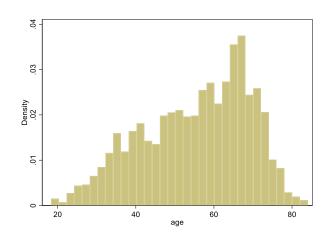
- Social media! Highly effective to spread the word
- Email announcements to major transplant organization members
- National and local organizations, support groups
- Special thanks to patients and to transplant clinicians who advocated energetically (e.g. Dr. Steve Pergam, right)





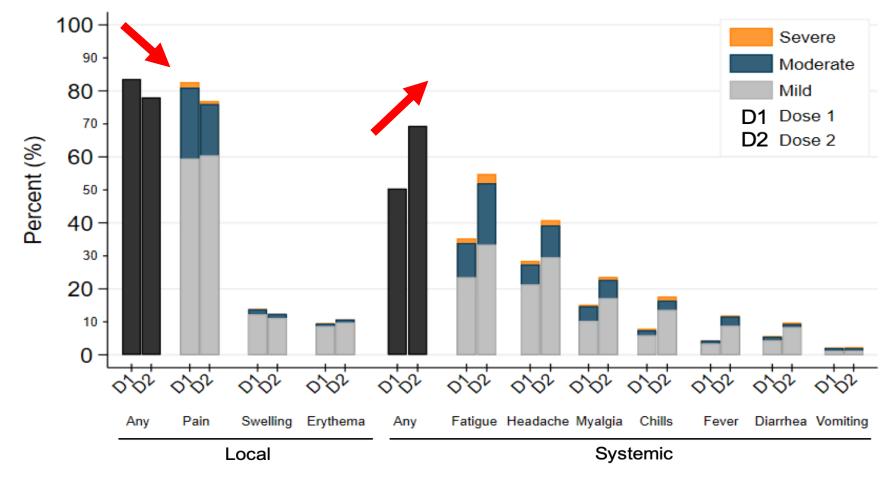
### Enrollment demographics

- Median (IQR) age, years: 58 (45-66)
- Median (IQR) years since txp: 6 (3-12)
- Transplant type: kidney (48%), liver (21%), heart (13%), lung (11%), KP (3%), pancreas (2%), multi-organ (2%)
- **Female**: 55%
- Non-white: 10%
- Hispanic: 5%
- Education: 73% college or graduate degree
- Prior COVID diagnosis: 3%
- Recruitment: 41% social media, 24% other advert, 35% transplant team



### Reactogenicity of Complete Vaccine Series

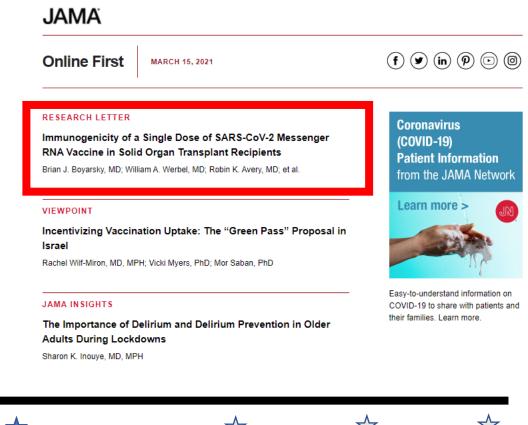
- N=742 (54%)
   Pfizer, 46%
   Moderna)
- No COVID-19
- 1 acute rejection (D2)
- No neurologic conditions
- Infections 3% D1, 0% D2
- Younger patients, females (<65 yo): 个D1, D2 systemic reactions</li>

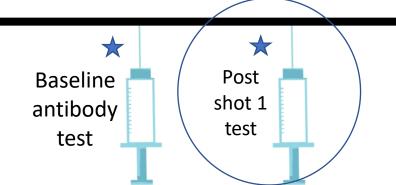


Adverse symptoms

### First dose (limited) immunogenicity

- N=436
- No prior COVID diagnosis
- Antibody was detectable in only 76/436 (17%) of participants (95% CI 14-21%) at a median (IQR) of 20 (17-24) days after the first dose







1 month post shot 2



3 months post shot 2



6 months post shot 2

12 months post shot 2

	Detectable antibody (n=76)	Undetectable antibody (n=360)	IRR bivariable (95% CI) p-value	aIRR multivariable (95% CI) p-value	
Age category, years					
18-39	30 (39)	69 (19)	0.81 (0.71-0.93)	0.83 (0.73-0.93)	
40-59	18 (24)	132 (37)	p=0.003	p=0.002	
≥60	28 (37)	159 (44)	ρ=0.003		
<b>Sex</b> , no. (%)					
Female	48 (64)	212 (59)	1.12 (0.73-1.73)		
Male	27 (36)	138 (41)	p=0.60		
Race, no (%)					
Non-white	8 (11)	38 (11)	0.99 (0.51-1.94)		
White	67 (89)	312 (89)	p=0.99		
<b>Organ,</b> no. (%)					
Kidney	31 (41)	188 (53)			
Liver	28 (37)	50 (14)			
Heart	9 (12)	57 (16)	0.68 (0.45-1.04)		
Lung	4 (5)	45 (13)	p=0.07		
Pancreas	1 (1)	4 (1)			
Other multi-organ	2 (3)	12 (3)			
Years since transplant					
<3	13 (17)	106 (30)			
3-6	12 (16)	77 (22)	1.88 (1.21-2.93)	1.45 (0.96-2.20)	
7-11	19 (25)	82 (23)	p=0.005	p=0.08	
≥12	31 (41)	89 (25)			
Maintenance					
immunosuppression, no. (%)					
Includes anti-metabolite	28 (37)	292 (81)	0.21 (0.14-0.32) 0.22 (0	0.22 (0.15-0.34)	
Does not include anti-metabolite	48 (63)	68 (19)	p<0.001	p<0.001	
Vaccine, no. (%)					
Moderna	52 (69)	152 (43)	2.14 (1.24-3.69)	2.15 (1.29-3.57)	
Pfizer/BioNTech	23 (31)	200 (57)	p=0.006	p=0.003	

### Limitations

- Correlates of protection are not yet fully understood
- First dose preliminary data only (more to come!)
- Unmeasured confounding
  - Lymphodepletion
  - Rejection
  - Drug levels
- Assays validated for response to infection (vs. vaccination)

### Conclusions

- SARS-CoV-2 mRNA vaccines have similar safety profiles in SOT recipients compared to the clinical trial populations
- No safety signals for rejection or neurologic syndromes
- Poor anti-spike antibody responses after Dose 1 of mRNA vaccines
  - Anti-metabolite, older age associated with decreased response;
     mRNA 1273 associated with increased response
  - However, too early to modify guidelines
- SOT recipients may continue to be at higher risk for SARS-CoV-2 despite vaccination, and should continue all safety measures

### Ongoing or Future Studies

- Dose 2 immunogenicity (submitted)
- Followup antibody testing out to 12 months
- Investigation of strategies to increase vaccine responses
- Correlation between reactogenicity and immunogenicity
- Memory B cell responses
- T cell responses
- Parallel studies in other immunocompromised populations

#### Dorry Segev, MD, PhD **Founder and Director**

Leadership and Core Faculty

Jacqueline Garonzik-Wang, MD, PhD

Director of Training and Education Associate Professor of Surgery

Macey Levan, JD, PhD

Director of Policy and External Affairs Assistant Professor of Surgery & Nursing

Allan Massie, PhD

Director of Data and Analytics Assistant Professor of Surgery and Epidemiology

Tanjala Purnell, PhD, MPH

Director of Community and Stakeholder Engagement Assistant Professor of Epidemiology and Surgery

> Andrew Cameron, MD, PhD **Division Chief, Transplant Surgery**

> > Professor of Surgery

Elizabeth King, MD, PhD

Assistant Professor of Surgery

Sunjae Bae, KMD, PhD Instructor of Surgery

Christine Durand, MD

Associate Professor of Medicine

Sommer Gentry, PhD

**Professor of Mathematics** United States Naval Academy

Mara McAdams-DeMarco, PhD, MS

Associate Professor of Surgery and Epidemiology

Douglas Mogul, MD, PhD

Assistant Professor of Pediatrics Hepatology and Nutrition

Abimereki Muzaale, MD, MPH

**Assistant Professor of Surgery** 

Lauren Nicholas, PhD

Associate Professor of Health Policy and Management

Fellows, Residents, Medical and Graduate Students

**Transplant Surgery Fellows** 

Michelle Nguyen, MD Eliza Lee, MD Sharon Weeks. MD

**Surgery Residents** 

Andrew Arking, MD Victoria Bendersky, MD Brian Boyarsky, MD Mackenzie Eagleson, MD Andrew Hallett, MD Kayleigh Herrick-Reynolds, MD Jessica Ruck, MD Amber Kernodle, MD

Fellows & Grad Students

Jamilah Perkins, MD, MHS Aly Strauss, MD, MIE Alvin Thomas, MSPH William Werbel, MD

**Medical Students** 

Ashton Shaffer, PhD Mary Grace Bowring, MPH Michael Ou **Darius Johnson** Jake Ruddy

Madeleine Waldram

Data Analysts

Tanveen Ishaque Jennifer Motter Michael Mankowski **Yijing Feng** Sarah Van Pilsum Rasmussen Karen Vanterpool, PhD Hannah Sung, PhD





#### Research Staff

Maria (Malu) Lourdes Perez, DVM

Research Program Manager

Research Program Coordinators

Ross Greenberg, BS Amrita Saha, MSPH

Carolyn Sidoti, BS

Alexander Ferzola, BS

Leyla Herbst, BS

Shivani Bisen, BS

Abigail Shegelman, MSPH

Research Assistants

**Briana Dang** 

Max Downey

**Kevin Gianaris** 

Archita Goyal

Nicole Hada

Michael Irving

Jamie Klunk

**Anna Kinter** 

Michelle Krach

Molly Ma

**Alexis Mooney** 

Kathryn Marks

Mimi Mensah

Marie Nunez

**Georgia Parsons** 

**Chantal Riggs** 

Chia-Chen (Wendy) Tsai

**Aura Teles** 

Wasurut Vihokrut

**Adam Wight** 

**Adam Zois** 

Alexandra Zois

#### **Affiliates**

Fawaz Al Ammary, MD, PhD

Medical Director, Living Donation

Robin Avery, MD

Transplant Infectious Diseases

Anna Beavis, MD

Gynecology

Gerald Brandacher, MD

Plastics and Reconstructive Surgery

Daniel Brennan, MD

Medical Director, Comprehensive Transplant Center

Errol Bush. MD

Director, Lung Transplant Program

Olga Charnaya, MD

Pediatric Nephrology

Victor Chen, MD

Transplant Hepatology

Josef Coresh, MD, PhD

Epidemiology

Morgan Grams, MD, PhD

Nephrology

Nirai Desai, MD

Transplant Surgery

Elliott Haut, MD, PhD Trauma Surgery

Shane Ottman, MD

**Transplant Surgery** 

Lindsay Toman, PharmD

Transplant Pharmacy

Aliaksei Pustavoitau, MD

Anesthesiology

Daniel Scharfstein, ScD

**Biostatistics** 

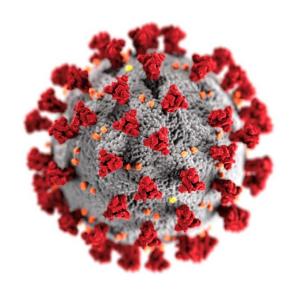
Daniel Warren, PhD

Islet Transplantation

Jason Wheatley, LCSW-C

Transplant Social Work

#### Making Guidelines for COVID-19 Immunization in Solid Organ Transplant – Lessons Learned from Influenza Vaccine

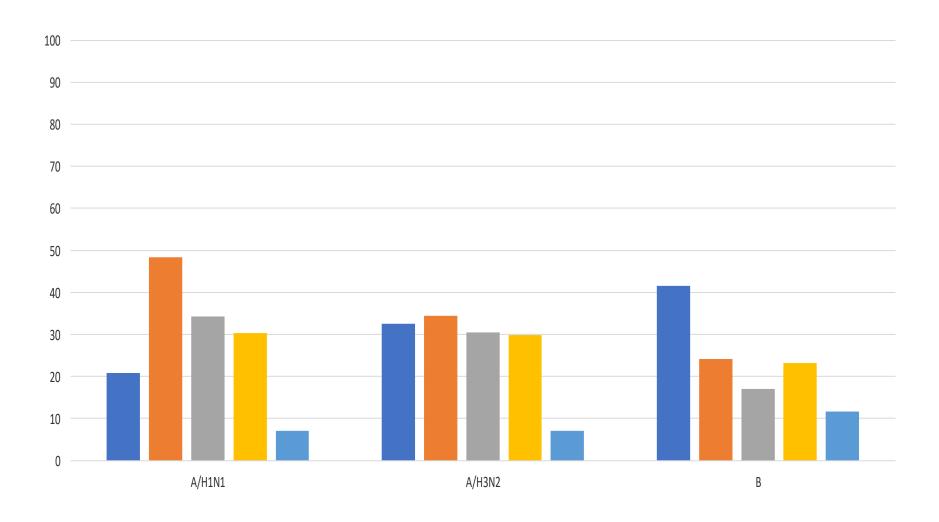




#### Where do we start

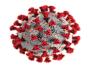
- Majority of SOT vaccine guidelines are extrapolation of recommendations in healthy persons
- Vaccine efficacy studies are difficult to do in transplantation
  - Most studies rely on immune response
  - Correlates of protection (antibody levels, T-cell responses) are often unknown or may differ in an immunosuppressed population
- Vaccine immunogenicity is suboptimal for many vaccines
- Patients are heterogeneous (type of transplant, immunosuppression)
- Adverse event concerns are different than the general population
  - Live vaccines may cause disease
  - Rejection of graft

# Seroconversion rates (%) in influenza vaccine studies of organ transplant recipients are low



Mycophenolate

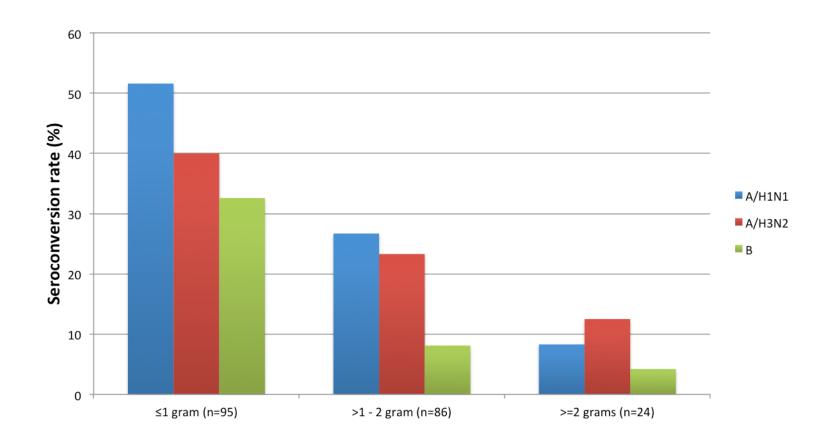
# LESSON #1: SOME IMMUNOSUPPRESSIVES IMPACT VACCINE RESPONSE MORE THAN OTHERS



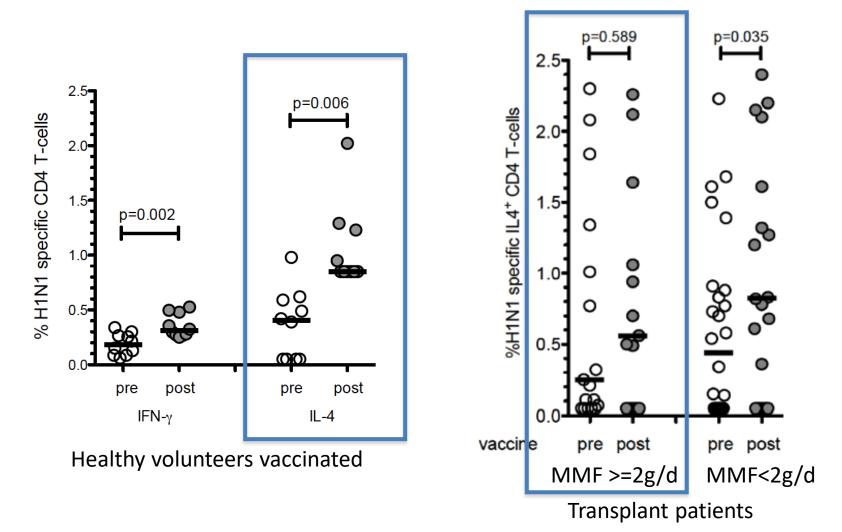


# Effect of Immunosuppression (Mycophenolate and Influenza Vaccine)

 Several studies have shown that MMF in high doses reduces the immunogenicity of influenza vaccine



# Mycophenolate blunts influenza-specific IL4 response in transplant patients

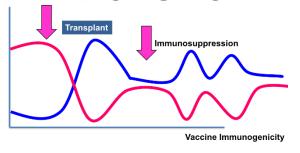


Egli et al., JID, 2015

- Pre-transplant: Immunize at least 2 weeks before transplant
- Vaccine series started in the pre-transplant period can be completed posttransplant
- Post-transplant: Restart immunization at >1 month
- After therapy for acute rejection, restart immunization at 1 month post-steroid bolus or 6 months post-rituximab

Danziger-Isakov & Kumar, ClinTransplant, 2019

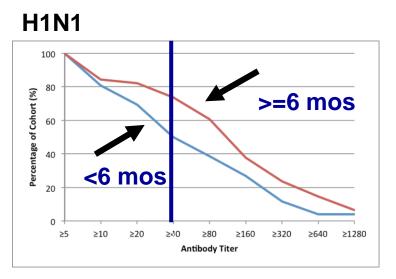
# LESSON #2: TIMING OF VACCINATION IS CRITICAL IN ACHIEVING OPTIMAL VACCINE RESPONSE

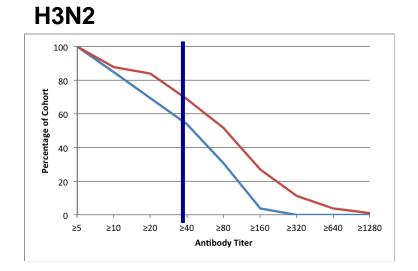


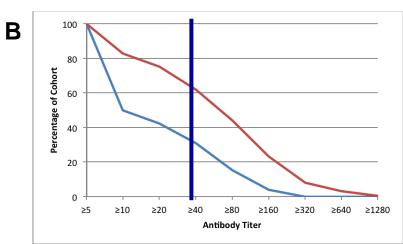




# Influenza Vaccine Response: Time from transplant (n=228)







Seroconversion to at least one antigen:
19.2% in those <6 mos from transplant vs.
53.2% in those >6 months, p=0.001

Multiple doses Higher doses

# LESSON #3: VACCINE DOSING CAN BE VARIED TO IMPROVE IMMUNE RESPONSES



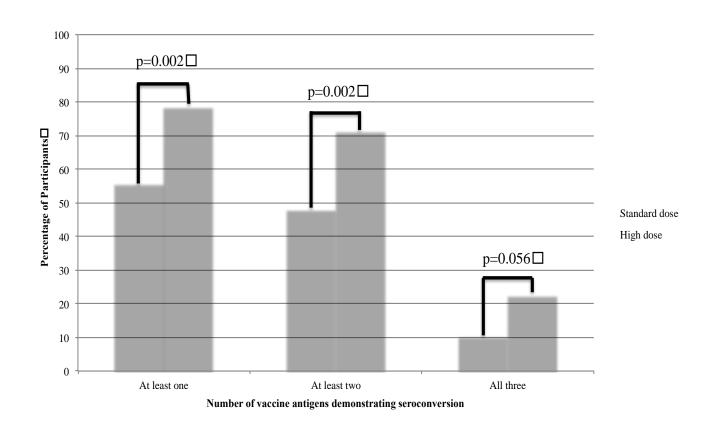


### Two doses of influenza vaccine

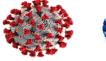
Variable	Single-Dose Vaccination Group (n = 213)	Booster Dose Vaccination Group (n = 211)	OR (95% CI)/ β Coefficient (95% CI)	NNT (ARR, %) With Booster Dose
Short-term seroconvers	sion rate			
A(H1N1)pdm	33 (32.7)	43 (46.7)	1.81 (1.009–3.24)*	12 (14.1)
A(H3N2)	38 (30.2)	45 (39.1)	1.49 (.87–2.54)	8 (9)
Influenza B	53 (63.9)	63 (75.9)	1.78 (.91–3.50)	9 (12)
Long-term seroconvers	sion rate			
A(H1N1)pdm	20 (19.8)	19 (20.7)	1.05 (.52-2.13)	
A(H3N2)	57 (45.2)	47 (40.9)	0.84 (.50-1.40)	
Influenza B	42 (50.6)	53 (63.9)	1.73 (.93–3.21)	
Short-term seroprotect	ion rate			
A(H1N1)pdm	92 (43.2)	114 (54)	1.54 (1.05–2.27)*	10 (10.8)
A(H3N2)	97 (45.5)	120 (56.9)	1.58 (1.08–2.31)*	9 (11.3)
Influenza B	153 (71.8)	176 (83.4)	1.97 (1.23-3.16)**	9 (11.6)

N=499 adult SOT patients randomized 1:1 to receive single dose or two doses of influenza vaccine 5 wks apart

# RCT of High dose vs. standard dose influenza vaccine in adult SOT (n=172)



# LESSON #4: VACCINATION MAY ATTENUATE DISEASE EVEN IF IT DOESN'T PREVENT

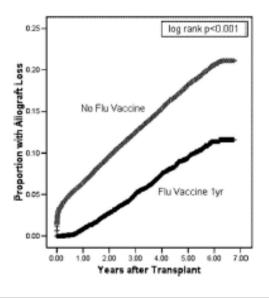




#### N=616 transplant patients with influenza

#### **Benefits of being vaccinated**

Unadjusted Analysis of Allograft Loss (death-censored)

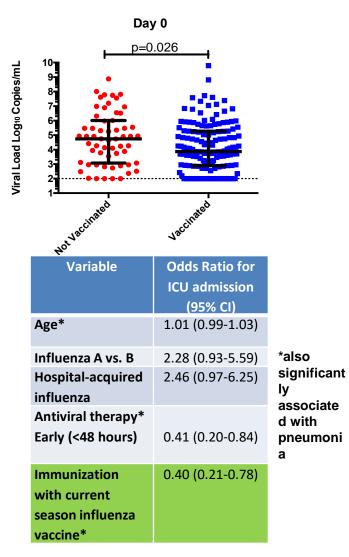


Vaccinations more likely in:

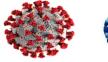
- diabetics
- -Older age
- -Vaccine less likely to be given if:
- -- African-American
- -- high PRA
- --induction immunosuppression

Figure 1. | Time to allograft loss (death-censored) among adult Medicare primary renal transplant recipients who did or did not have Medicare claims for influenza vaccine in the first year posttransplantation.

Hurst et al, Clin J Am Soc Nephrol 2011



#### **LESSON #5: VACCINATION DOES NOT LEAD TO REJECTION**







The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

# Does vaccination in solid-organ transplant recipients result in adverse immunologic sequelae? A systematic review and meta-analysis



William R. Mulley, BMed, PhD, a,b Claire Dendle, MBBS,b,c Jonathan E.H. Ling, MBChB, a,b and Simon R. Knight, MChir, MAd,e

# Does Influenza Vaccine Induce de novo DSA (donor-specific antibody)?

Study (first author, year)	Transplant type	Vaccine	Method	Incidence of de novo DSA
Kumar, 2010	Lung	Influenza	Screen/SAq	0 of 59 (0%) at 56 days
Kimball, 2000	Heart	Influenza	Screen/SAg	0 of 29 (0%) at 21 days
Danziger-Isakov, 2010	Mixture	Influenza	Screen/SAg	0 of 17 (0%) at 94 days
Vermeiren, 2014	Mixture	H1N1 + influenza	Screen/SAg	0 of 169 (0%) at 28 days
Baluch, 2013	Mixture	Influenza	Screen/SAg	0 of 229 (0%) at 30 days
Mujtaba, 2015	Kidney	H1N1 + influenza	SAg	0 of 47 (0%) at 28 days
Mujtaba, 2013	Kidney	H1N1 + influenza	SAg	0 of 57 (0%) at 50 days
Kumar, 2016	Kidney	Influenza	SAg	0 of 34 (0%) at 30 days
Rinaldi, 2014	Kidney	Influenza	Screen/SAg	0 of 81 (0%) at 21 days
LeCorre, 2012	Kidney	H1N1	SAg	1 of 121 (0.82%) at 21 days
Fairhead, 2012	Kidney	H1N1	Screen/SAg	3 of 124 (2.4%) at 30 days
Candon, 2009	Kidney	Influenza	SAg	3 of 66 (4.55%) at 30 days
Brakemeier, 2012	Kidney	H1N1	Screen/SAg	3 of 60 (5%) variable follow-up
Katerinis, 2011	Kidney	H1N1	Screen/SAg	13 of 151 (8.60%) at 42 days
Total				23 of 1,244 (1.85%) at 21 to 94 d

Mulley et al. JHLT, 2018

#### www.myast.org/covid-19-vaccine-faq-sheet



Emily Blumberg Lara Danziger-Isakov Deepali Kumar Marian Michaels Nicole Theodoropoulos Shweta Anjan

Valida Bajrovic

Emily Blodget

Jennifer Chow

Anmary Fernandez

Jay Fishman

Michael Ison

Carol Kao

Olivia Kates

**Daniel Kaul** 

Rosy Priya Kodiyanplakkal

Camille Kotton

Vineeta Kumar

Maricar Malinis

Megan Morales

Hannah Nam

**Ronald Parsons** 

Marcus Pereira

Stephanie Pouch

Joanna Schaenman

Aruna Subramanian

Cameron Wolfe

Ann Woolley

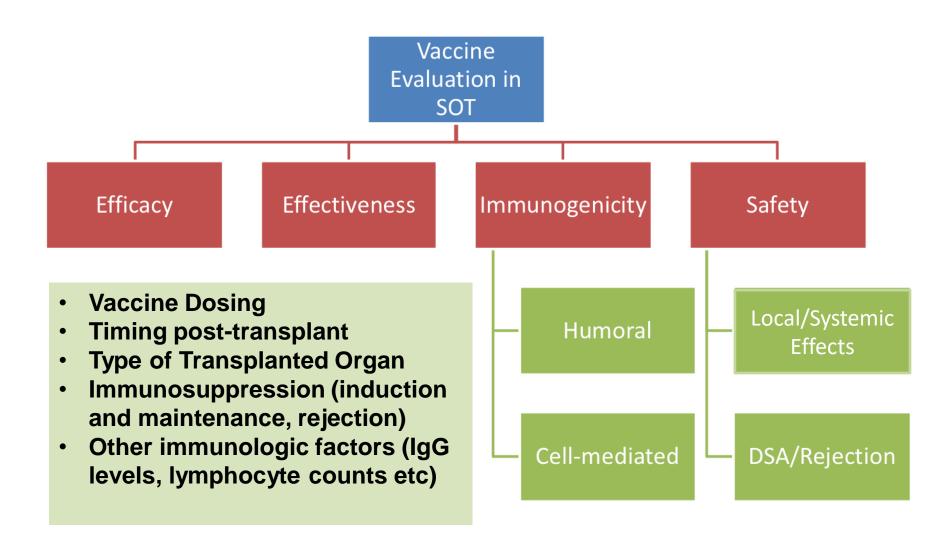
#### **COVID-19: VACCINE FAQ SHEET**

The AST has received queries from transplant professionals and the community regarding the COVID-19 vaccine. The following FAQ was developed to relay information on the current state of knowledge. This document is subject to change and will be updated frequently as new information or data becomes available.

**READ MORE** 

View all COVID-19 Resources

#### Questions that need to be answered for COVID vaccine

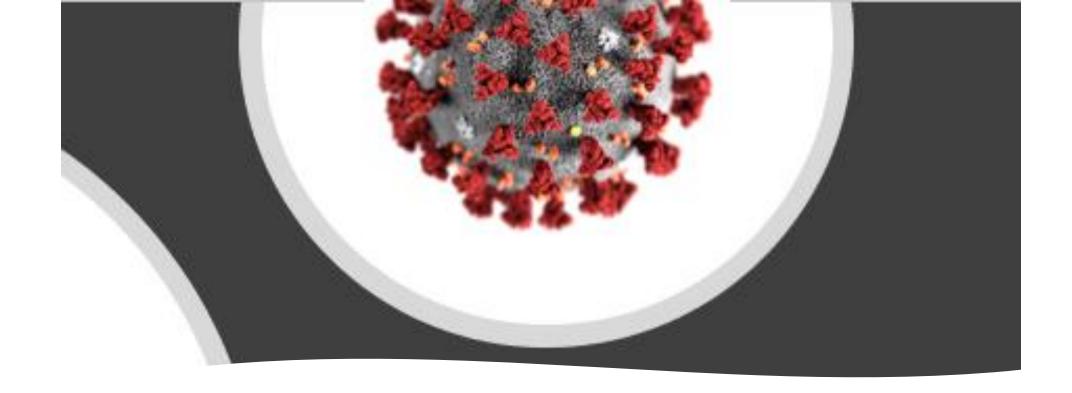


## **Q&A** and Discussion

#### References for articles mentioned in the webinar

- Boyarsky BJ, Ou MT, Greenberg RS, et al. Safety of the first dose of SARS-CoV-2 vaccination in solid organ transplant recipients. Transplantation 2021 Feb 4; doi: 10.1097/TP.000000000003654
- Boyarsky BJ, Werbel WA, Avery RK, et al. Immunogenicity of a single dose of SARS-CoV-2 messenger RNA vaccine in solid organ transplant recipients. JAMA 2021 March 15; doi: 10.1001/jama.2021.4385
- Mulley WR, Visvanathan K, Hurt AC, et al. Mycophenolate and lower graft function reduce the seroresponse of kidney transplant recipients to pandemic H1N1 vaccination. Kidney International 2012; 82: 212-219.
- Salles MJC, Sens YAS, Boas LSV, Machado CM. Influenza virus vaccination in kidney transplant recipients: serum antibody response to different immunosuppressive drugs. Clin Transpl 2010; doi: 10.1111/j.1399-0012.2009.01095
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- Haddadin Z, Krueger K, Thomas LD, Overton ET, Ison M, Halasa N. Alternative strategies of posttransplant influenza vaccination in adult solid organ transplant recipients. Am J Transplant. 2021 Mar;21(3):938-949. doi: 10.1111/ajt.16295. Epub 2020 Sep 23. PMID: 32885604.
- Danziger-Isakov L, Kumar D; AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant. 2019 Sep;33(9):e13563. doi: 10.1111/ctr.13563. Epub 2019 Jun 5. Erratum in: Clin Transplant. 2020 Mar;34(3):e13806. PMID: 31002409.





AST
Resources for
Professionals
and Patients

https://www.myast.org/covid-19-vaccine-faq-sheet

https://www.myast.org/covid-19-information





An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.



www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19

### **SPECIAL NOTICE - UPCOMING WEBINAR**

# ASCO/IDSA Global Webinar: COVID-19 Vaccines and Cancer Care

Tuesday, March 30<sup>th</sup> - 8 a.m. ET/ 11 a.m. PT

Join ASCO and IDSA for an important COVID-19 vaccines webinar at 8 a.m. EST on March 30th.

Following a short presentation on currently available vaccines, a panel of invitees from the Infectious Diseases Society of America (IDSA), a nurse, a medical oncologist, a hematologist, and a patient advocate will discuss and answer questions for the remaining hour. Shaheenah S. Dawood, MBBCh, MPH, FACP, FRCP a Consultant Medical Oncologist at Mediclinic Middle East in Dubai, UAE will moderate.

This webinar is not part of the CDC/IDSA COVID-19 Clinician Call series and requires separate registration.

To Register: <a href="https://asco1.zoom.us/webinar/register/WN">https://asco1.zoom.us/webinar/register/WN</a> B5a0zz4JR1yqdb4zseu6jA





# Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19



#### Thank You!

A recording of this call will be posted at

www.idsociety.org/cliniciancalls

And

www.myAST.org/covid