Community or clinic? Generating insights into COVID-19 transmission, severity, and response to vaccination with at-home antibody testing

Thom McDade, PhD

Northwestern University, Department of Anthropology and Institute for Policy Research

Photo: https://www.niemanlab.org/2020/05

https://scan.northwestern.edu/

Northwestern

SCAN

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Screening for Coronavirus Antibodies in Neighborhoods (SCAN)

About the Study

The purpose of the SCAN Study is to find out how many people in specific areas have been exposed to SARS-CoV-2 (also known as coronavirus or COVID-19) and developed antibodies to the virus. The SCAN Study will also help researchers learn if these antibodies protect people against re-infection.

We will test your blood for antibodies to SARS-CoV-2, the virus that causes COVID-19. The timing of antibodies appearing in the blood stream is not fully known, some appear sooner than others, and some people develop antibodies without having symptoms of disease. We will test for antibodies, including those that can remain in the blood for a long time. In other types of infection, these antibodies often indicate immunity or a sign that the body has recovered from infection.

If you are interested in joining the SCAN Study, please answer a few questions in the form below to find out if you are eligible. Your responses are

An interdisciplinary research team

Institute for Sexual and Gender Minority Health and Wellbeing (ISGMH)
Brian Mustanski
Rana Saber
Dan Ryan
Melissa Mongrella
Jack Novotny
Krystal Madkins
Reno Stephens
Joshua Schrock
Michael Newcomb

Third Coast Center for AIDS Research (TC-CFAR)
Richard D'Aquila
Nanette Benbow

Department of Anthropology
Thomas McDade
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Amelia Sancilio

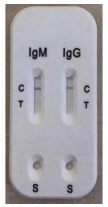
Center for Genetic Medicine
Elizabeth McNally
Alexis Demonbreun
Aaron Zelikovich
Katherine Fallon
Lauren Vaught
Nina Reiser
Jodi Curtain
Matt Velez
Ryan Hseih
Lorenzo Pesce

The promise (and perils) of antibody testing

- *Seroprevalence and the "denominator problem"*
  - *How many cases, where, whom?*
- *Evaluation of policies/behaviors that mitigate transmission in the community*
- *Origins of social inequities in COVID-19*
  - *asymptomatic vs. mild vs. serious infection*
- *Lasting effects of exposure/infection (Long COVID)*

- *Does antibody = immunity?*
  - *antibody "passports"*
  - *politics of seroprevalence*

Antibody testing in the community vs. the lab



lateral flow immunoassay

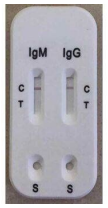
+	-
Point-of-care	Qualitative
Finger stick	QC/QA issues
Rapid (<15 min)	HCW required
Community-based collection	Single test

Antibody Test, Seen as Key to Reopening Country, Does Not Yet Deliver

The tests, many made in China without F.D.A. approval, are often inaccurate. Some doctors are misusing them. The rollout is nowhere close to the demand.

A Long Island resident's blood was screened for coronavirus antibodies on Tuesday in Hempstead, N.Y. Seth Wenig/Associated Press

Antibody testing in the community vs. the lab



lateral flow immunoassay

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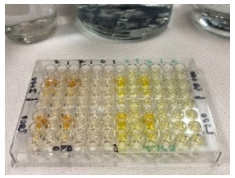

Immunoassay
(in various forms)

+	-
Quantitative	Slow (3-5 hrs)
↑ accuracy	Lab infrastructure
Retesting possible	Serum/plasma

Clinic-based collection

Travel to clinic

Licensed HCW

Collection materials
PPE

"The filter paper blood collection device has achieved the same level of precision and reproducibility that analytical scientists and clinicians have come to expect from standard methods of collecting blood"

→ Mei et al. (2001). *Journal of Nutrition* 131:1631-6S.

Clinical Chemistry 64:4
000–000 (2018)

Reviews

State of the Science in Dried Blood Spots

Jeffrey D. Freeman,[1*] Lori M. Rosman,[2] Jeremy D. Ratcliff,[3] Paul T. Strickland,[4] David R. Graham,[5] and Ellen K. Silbergeld[4]

BACKGROUND: Advancements in the quality and availability of highly sensitive analytical instrumentation and methodologies have led to increased interest in the use of microsamples. Among microsamples, dried blood spots (DBS) are the most well-known. Although there have been a variety of review papers published on DBS, there has been no attempt at describing the full range of analytes measurable in DBS, or any systematic approach published for characterizing the strengths and weaknesses associated with adoption of DBS analyses.

CONTENT: A scoping review of reviews methodology was used for characterizing the state of the science in DBS. We identified 2018 analytes measured in DBS and found every common analytic method applied to traditional liquid samples had been applied to DBS samples. Analytes covered a broad range of biomarkers that included genes, transcripts, proteins, and metabolites. Strengths of DBS enable its application in most clinical and laboratory settings, and the removal of phlebotomy and the need for refrigeration have expanded biosampling to hard-to-reach and vulnerable populations. Weaknesses may limit adoption in the near term because DBS is a nontraditional sample often requiring conversion of measurements to plasma or serum values. Opportunities presented by novel methodologies may obviate many of the current limitations, but threats around the ethical use of residual samples must be considered by potential adopters.

SUMMARY: DBS provide a wide range of potential applications that extend beyond the reach of traditional samples. Current limitations are serious but not intractable. Technological advancements will likely continue to minimize constraints around DBS adoption.

Recent advancements in the quality and availability of highly sensitive analytical instrumentation have led to increased interest in the use of microsamples (i.e., biological samples of <50 μL) *(1–3)*. Microsamples have been applied for basic and clinical research, public health, and clinical medicine *(4–9)*. Interest in microsampling has been driven, in part, by the development of sophisticated computer software programs and methodological platforms for improved qualitative and quantitative analysis *(10–13)*. Among microsampling methods, dried blood spots (DBS)[6] are the most well-known and researched. DBS are a minimally invasive method for the collection of small quantities of whole blood from finger or heel stick with application to specially prepared filter paper for drying *(14, 15)*. DBS samples do not require phlebotomy, and DBS can be stored and shipped under ambient conditions, although a comprehensive assessment of analyte stability has not been performed *(16, 17)*. Existing stability studies for DBS, although limited, have demonstrated analyte stability across a wide range of storage conditions *(18)*.

To date, DBS have a range of applications in clinical practice, basic research, and population-based research *(4, 5, 15, 19, 20)*. The most common and widely accepted clinical use of DBS is for newborn screening programs, which are primarily concerned with the detection of metabolic disorders *(21)*. Other clinical applications in the published literature have focused on HIV surveillance, therapeutic drug monitoring, and clinical chemistry *(8, 21–24)*. Basic research applications for DBS include biomarker development and validation, drug discovery and development, forensic science, systems biology, and toxicology *(5, 17, 25–27)*. Population-based research applications are variable but may be broadly categorized into human epidemiological studies and environmental population studies *(5, 17, 28, 29)*.

[1] National Health Mission Area, Johns Hopkins University Applied Physics Laboratory, Laurel, MD; [2] Welch Medical Library, Johns Hopkins University, Baltimore, MD; [3] Public Health Studies Program, Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, MD; [4] Department of Environmental Health and Engineering, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; [5] Department of Molecular and Comparative Pathobiology, School of Medicine, Johns Hopkins University, Baltimore, MD.
* Address correspondence to this author at: JHUAPL, 11100 Johns Hopkins Road, Rm. 21-5360, Laurel, MD 20723. Fax 410-955-0617; e-mail jeffrey.freeman@jhuapl.edu.
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Previously published online at DOI: 10.1373/clinchem.2017.275966

[6] Nonstandard abbreviations: DBS, dried blood spots; SRR, scoping review of reviews; SWOT, Strengths, Weaknesses, Opportunities, and Threats; VOC, volatile organic compound.

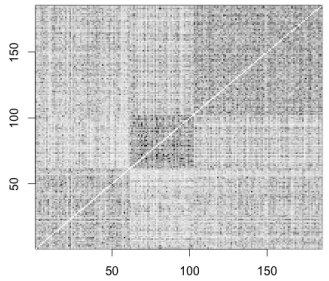
Nutrition/metabolism
Adiponectin, leptin, insulin transferrin receptor, vitamin D

Inflammation
CRP, IL1b, IL2, IL4, IL6, IL10, TNFa, IFNg

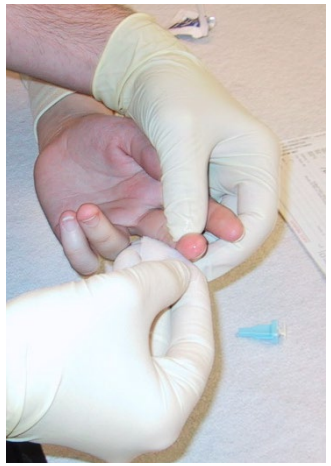
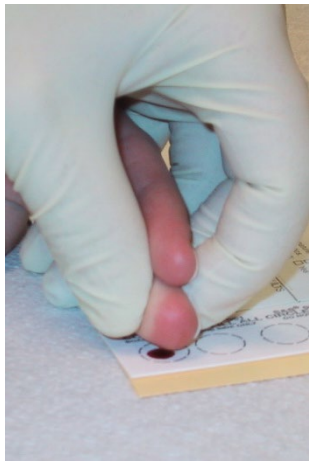
Toxic metals
Lead, mercury, arsenic, cadmium

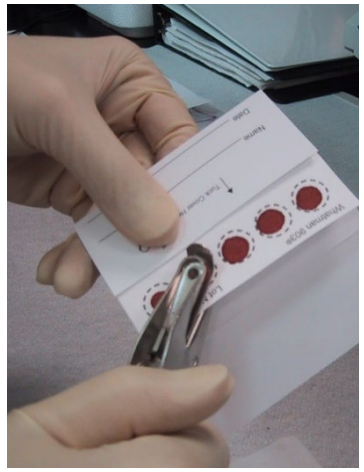
Antibodies against:
Epstein-Barr virus
Cytomegalovirus
HSV1
H. Pylori

Gene expression



Dried blood spots (DBS):
Tool for bridging the field and the lab

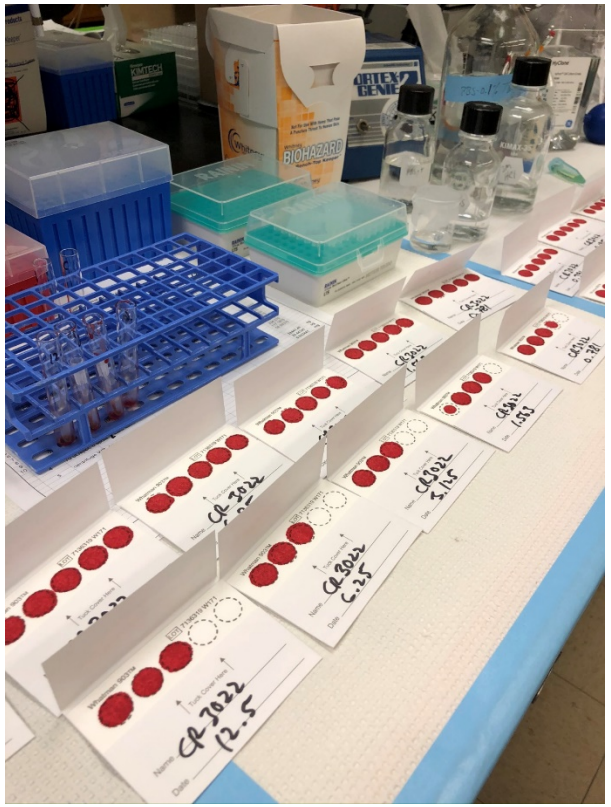


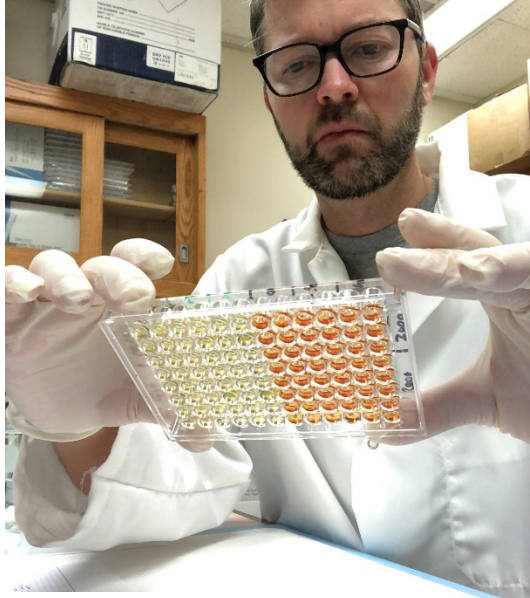
Convenience and reach of community-based sampling

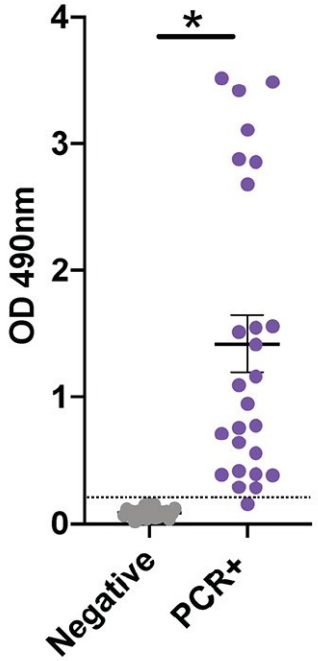
+

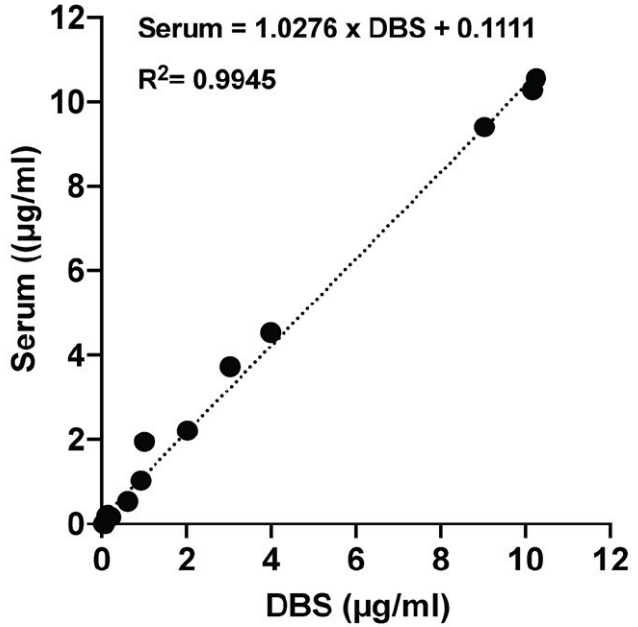
Accuracy and quantitation in the lab

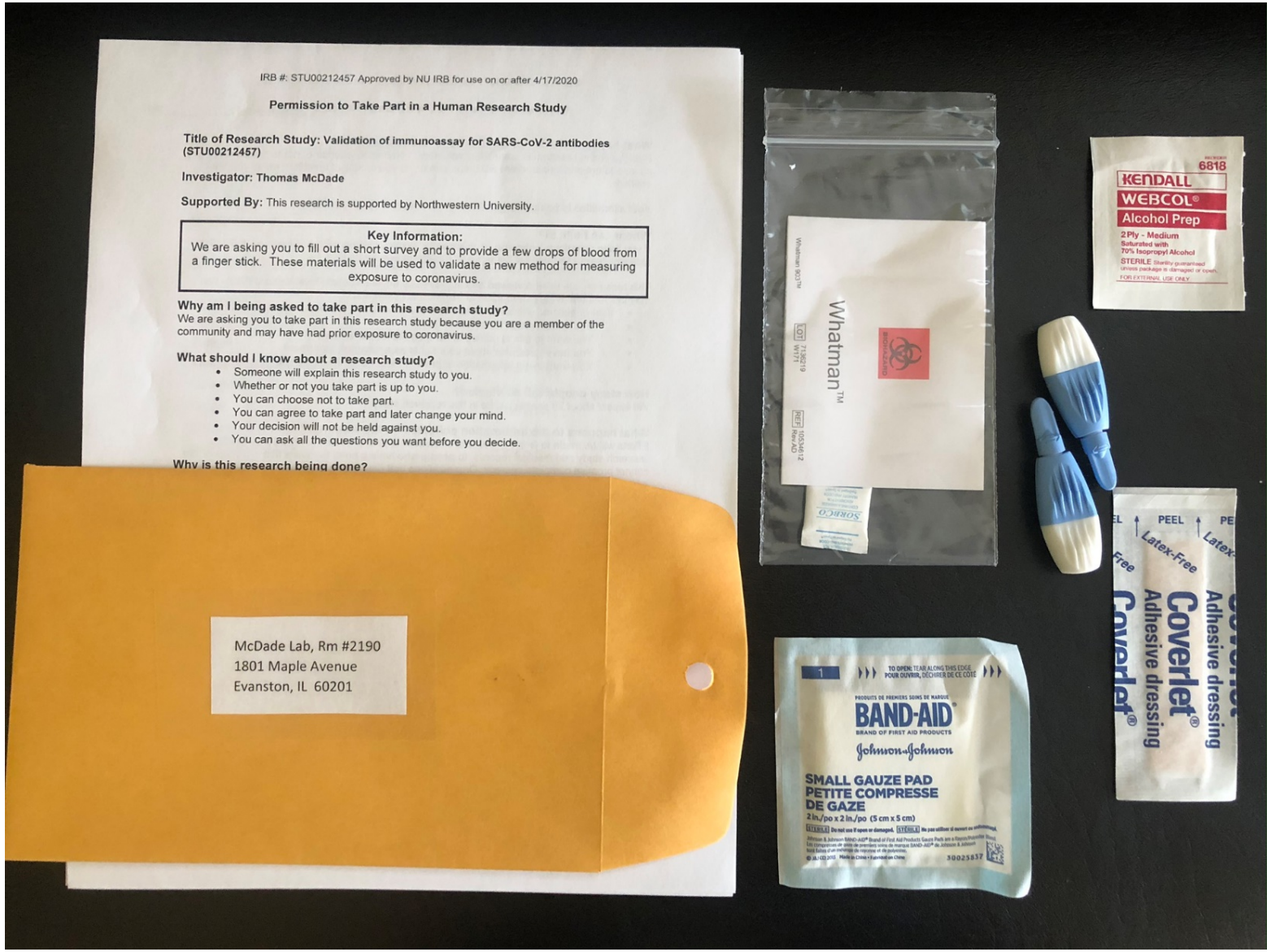
Developing a DBS immunoassay for measuring SARS-CoV-2 antibodies










IRB #: STU00212457 Approved by NU IRB for use on or after 4/17/2020
Permission to Take Part in a Human Research Study
Title of Research Study: Validation of immunoassay for SARS-CoV-2 antibodies (STU00212457)
Investigator: Thomas McDade
Supported By: This research is supported by Northwestern University.
Key Information:
We are asking you to fill out a short survey and to provide a few drops of blood from a finger stick. These materials will be used to validate a new method for measuring exposure to coronavirus.
Why am I being asked to take part in this research study?
We are asking you to take part in this research study because you are a member of the community and may have had prior exposure to coronavirus.
What should I know about a research study?
Someone will explain this research study to you.
Whether or not you take part is up to you.
You can choose not to take part.
You can agree to take part and later change your mind.
Your decision will not be held against you.
You can ask all the questions you want before you decide.
Why is this research being done?
McDade Lab, Rm #2190
1801 Maple Avenue
Evanston, IL 60201
Whatman
KENDALL
WEBCOL
Alcohol Prep
2 Ply - Medium
70% Isopropyl Alcohol
STERILE
FOR EXTERNAL USE ONLY
BAND-AID
Johnson & Johnson
SMALL GAUZE PAD
PETITE COMPRESSE
DE GAZE
2 in./po x 2 in./po (5 cm x 5 cm)
PEEL
Latex-Free
Coverlet
Adhesive dressing

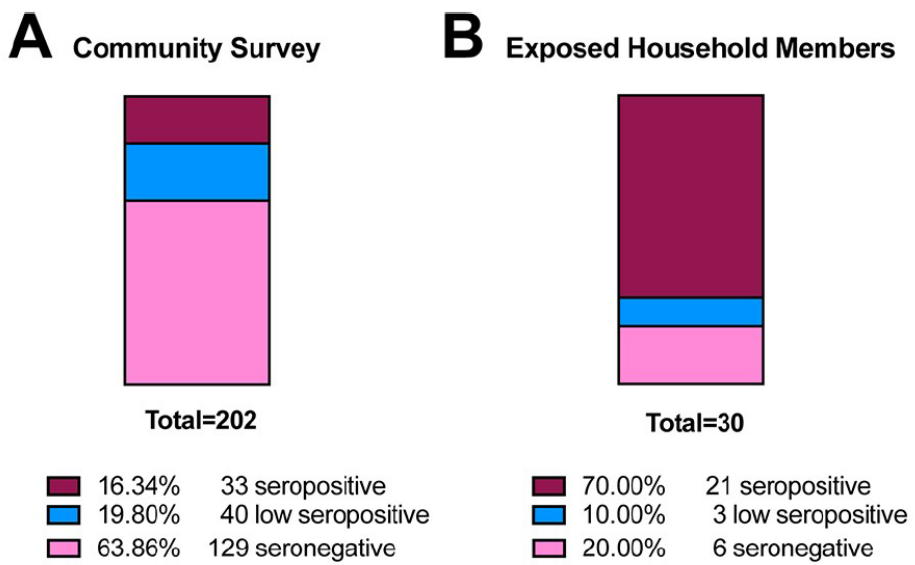

Permission to Take Part in a Human Research Study
What happens if I do not want to be in this research?
Who can I talk to?
Whom may I contact with my questions, concerns or complaints?
How many people will be studied?
What happens to the information collected for the research?
Data Sharing
Signature of Participant
Date
Printed Name of Participant
Page 1 of 3

PLOS ONE

RESEARCH ARTICLE

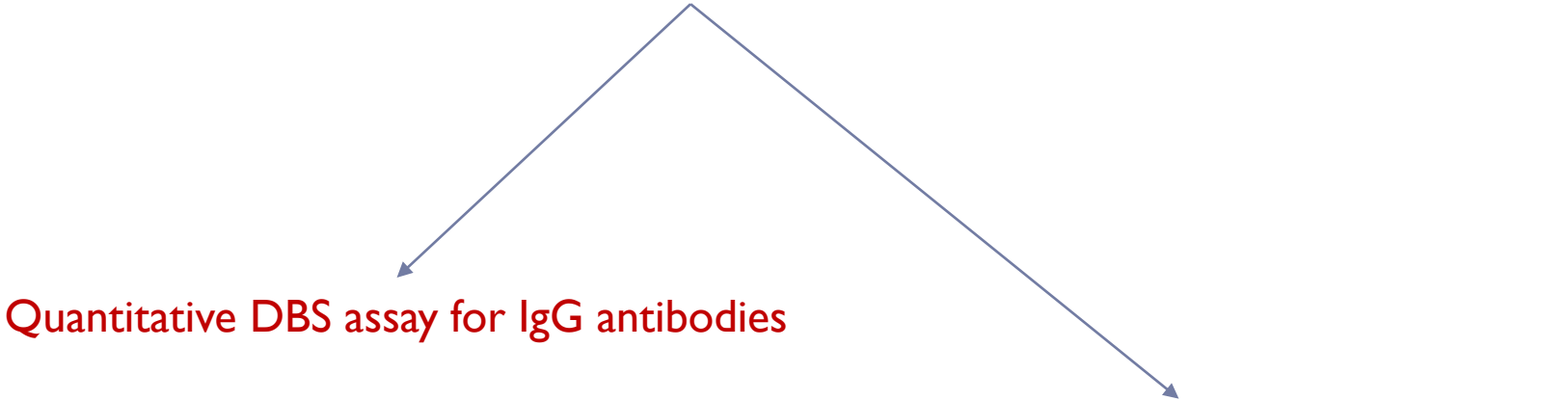
High seroprevalence for SARS-CoV-2 among household members of essential workers detected using a dried blood spot assay

Thomas W. McDade[1,2☯*], Elizabeth M. McNally[3,4,5☯], Aaron S. Zelikovich[3,4], Richard D'Aquila[6], Brian Mustanski[7], Aaron Miller[1], Lauren A. Vaught[3,4], Nina L. Reiser[3,4], Elena Bogdanovic[3,4], Katherine S. Fallon[3,4], Alexis R. Demonbreun[3,8☯]



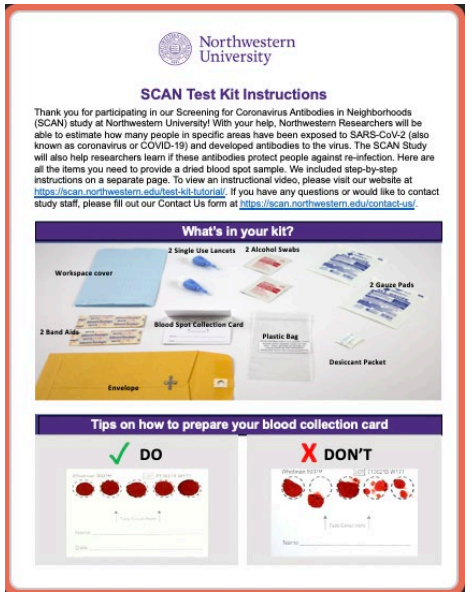
SCAN screening for coronavirus antibodies in neighborhoods

A "no contact" approach to SARS-CoV-2 antibody testing.



Dried blot spot collection training material

Detailed inserts

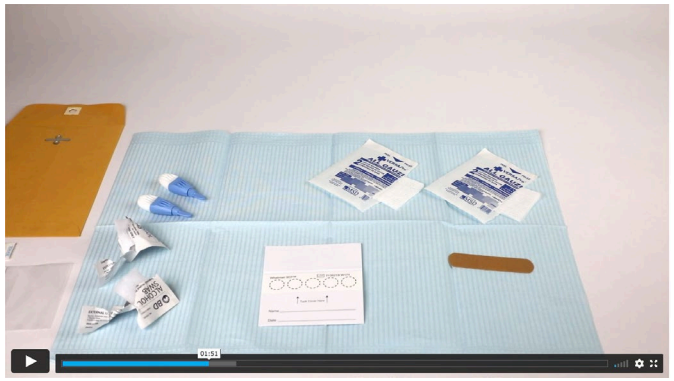


Northwestern University

SCAN Test Kit Instructions

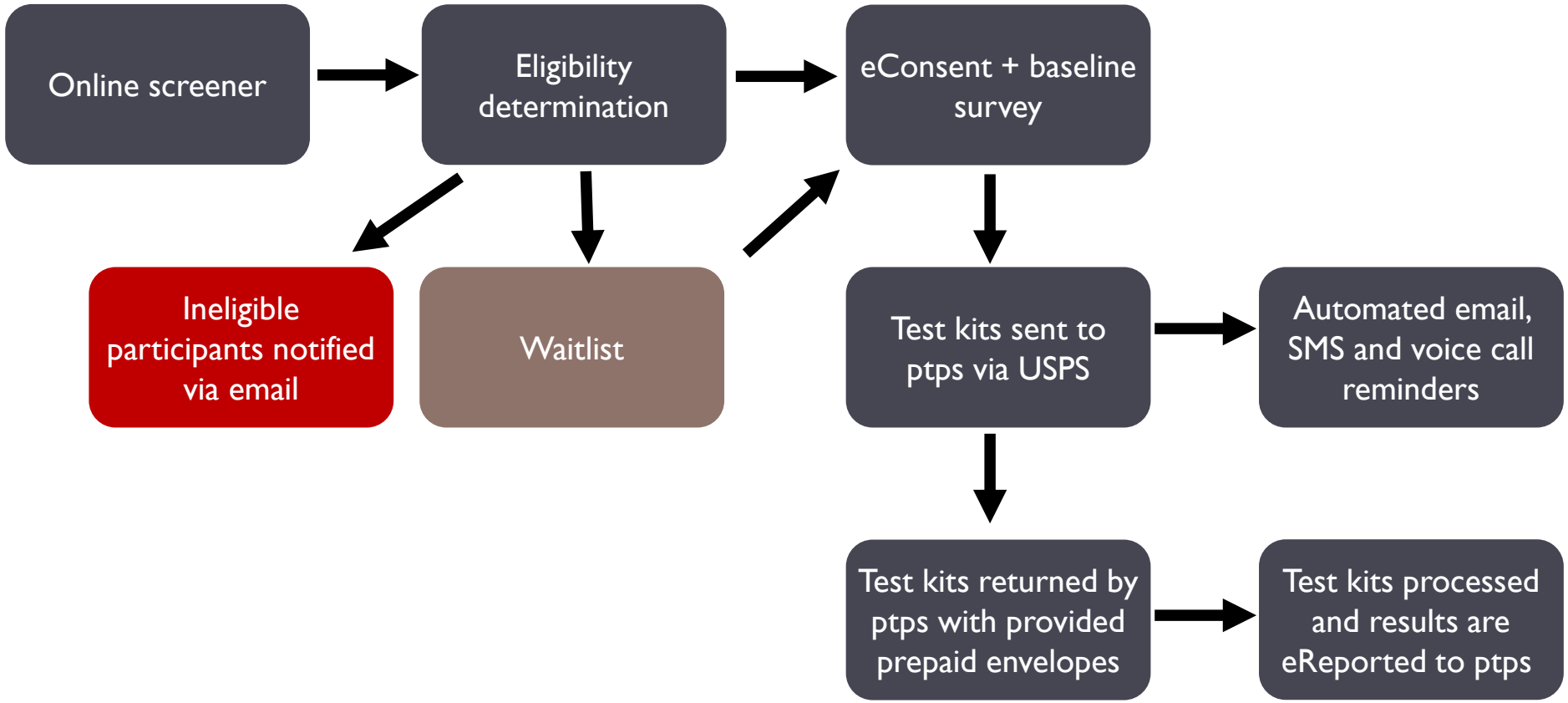
Thank you for participating in our Screening for Coronavirus Antibodies in Neighborhoods (SCAN) study at Northwestern University! With your help, Northwestern Researchers will be able to estimate how many people in specific areas have been exposed to SARS-CoV-2 (also known as coronavirus or COVID-19) and developed antibodies to the virus. The SCAN Study will also help researchers learn if these antibodies protect people against re-infection. Here are all the items you need to provide a dried blood spot sample. We included step-by-step instructions on a separate page. To view an instructional video, please visit our website at https://scan.northwestern.edu/test-kit-tutorial/. If you have any questions or would like to contact study staff, please fill out our Contact Us form at https://scan.northwestern.edu/contact-us/.

Step by step video tutorials

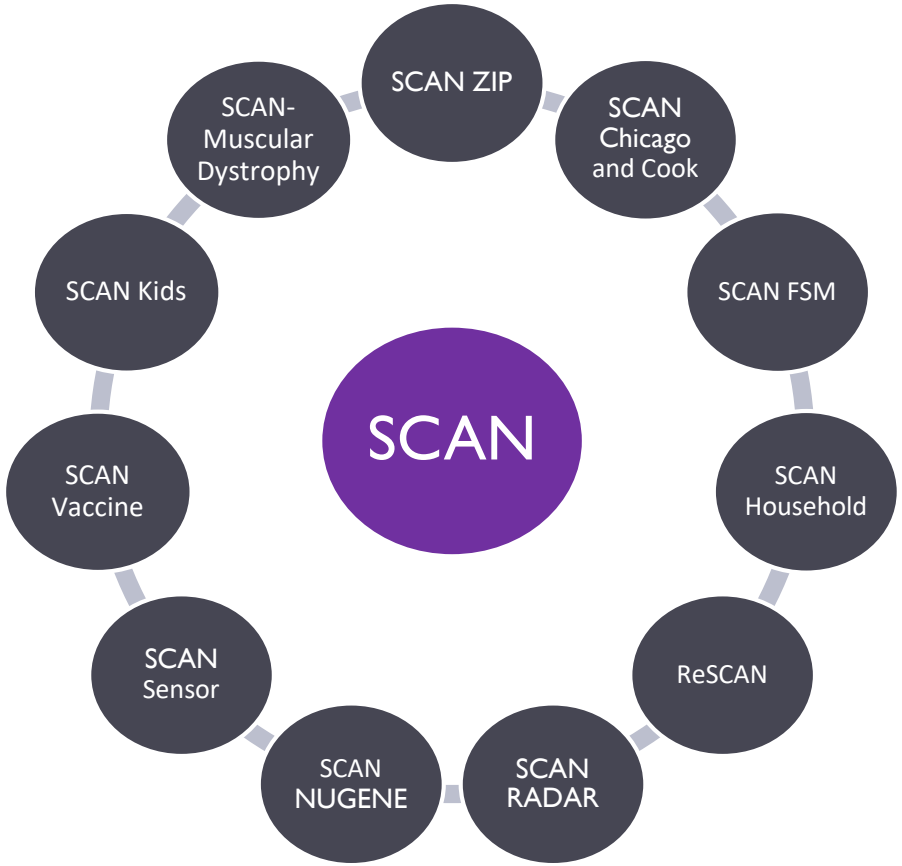


Remaining questions: scan@northwestern.edu

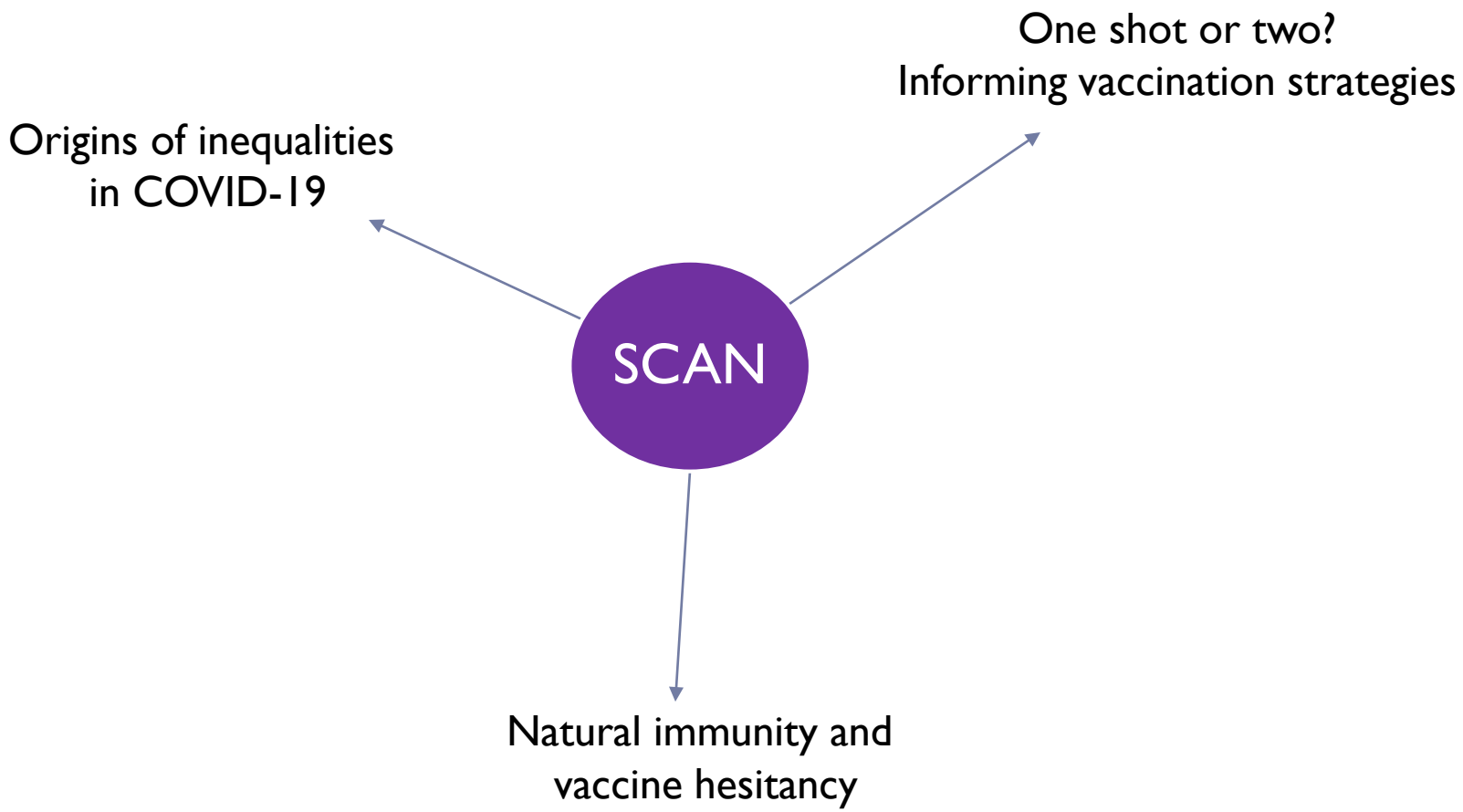
No-contact research platform



SCAN substudies

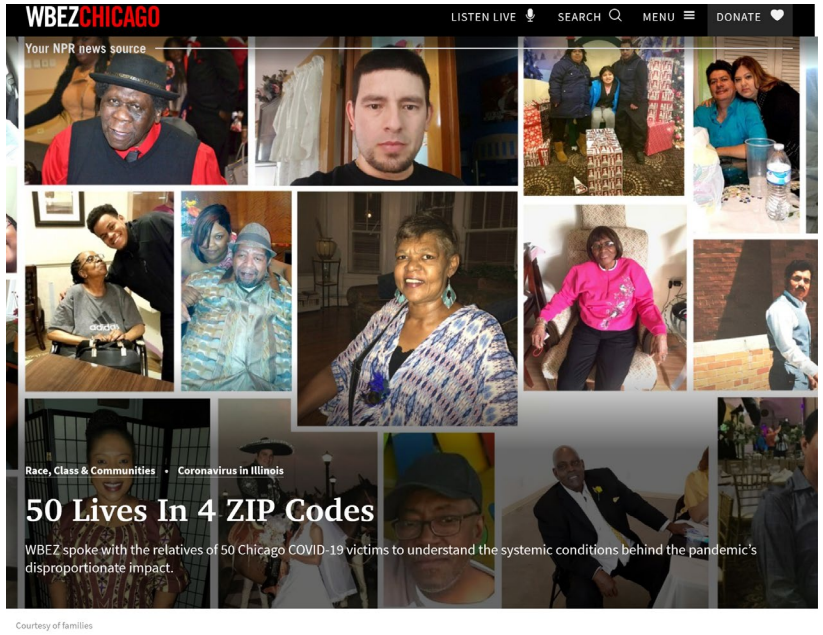


Key findings



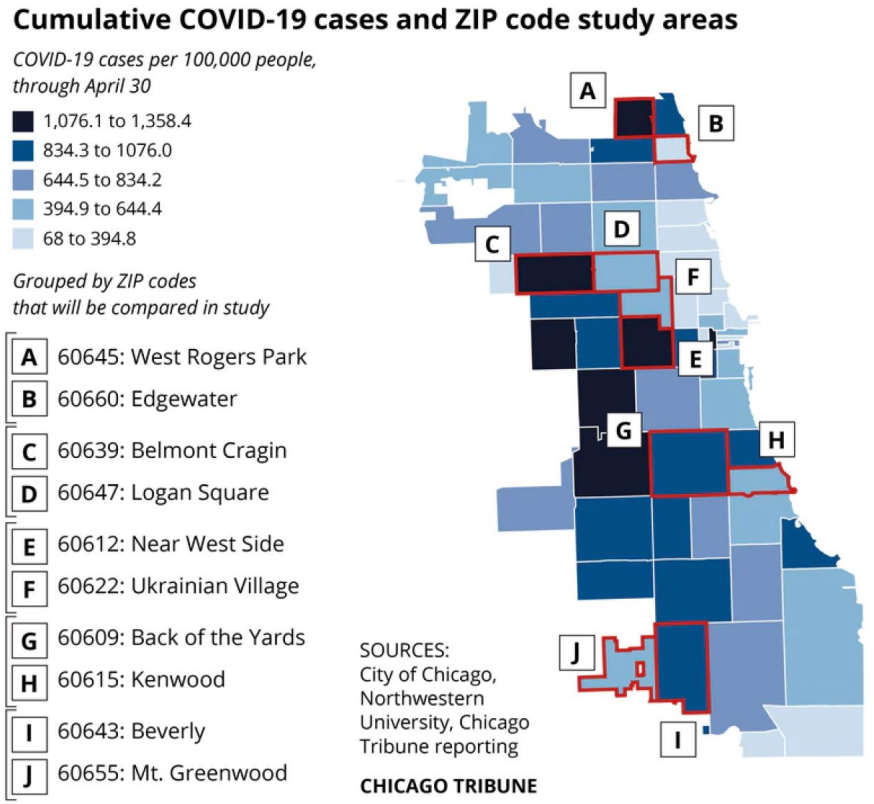
Pre-prints (peer-review is too slow!)

SCAN: 10 neighborhoods

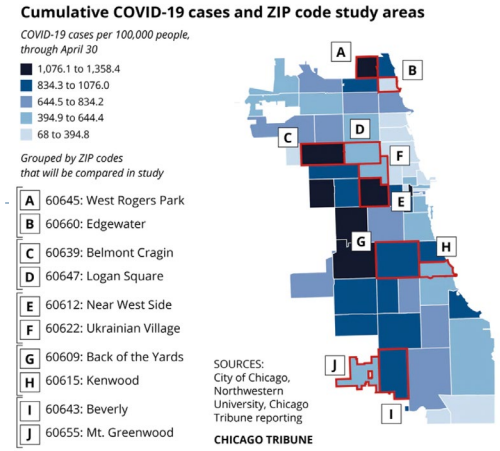


Courtesy of families

By Esther Yoon-Ji Kang, Natalie Moore, María Inés Zamudio
Aug. 17, 2020, 6 a.m. CT



SCAN: 10 neighborhoods

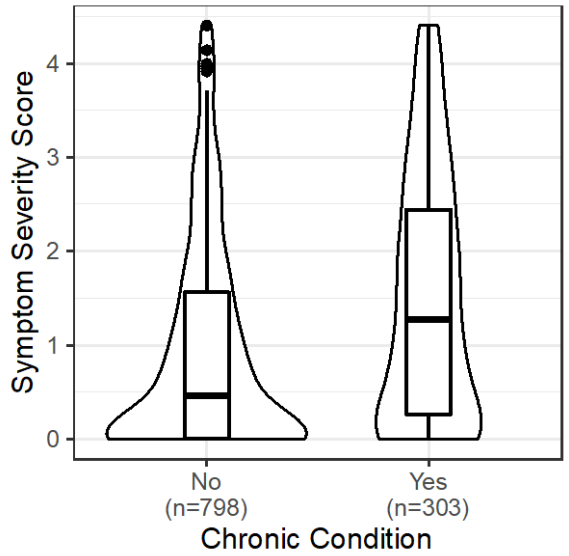


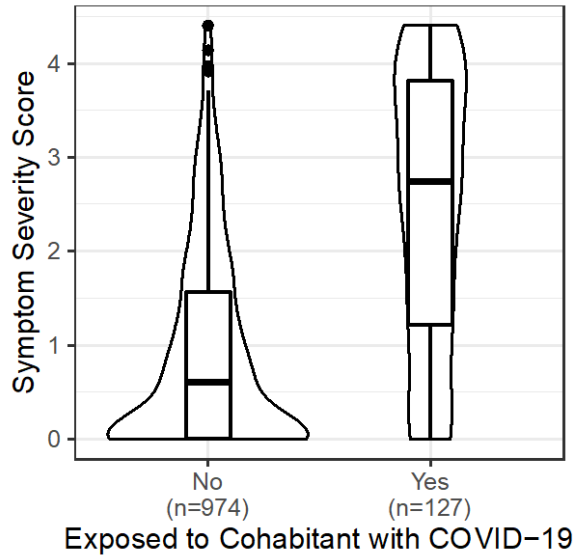
pair	neighborhood(s)	zipcode		wk32caserate	covidyou (%)	housedx (%)	PCR+	Ab pos (%)
2	Belmont Cragin (majority), H	60639		4475.4	18.64	16.95	6.8	27.12
3	New City (all), Fuller Park (all	60609		3522.2	6.52	10.87	2.2	17.39
1	West Ridge (majority), Roger	60645		2568.5	6.82	3.41	1.14	15.91
4	East Garfield Park (half), Nea	60612		2468.6	3.9	2.6	1.3	14.29
2	Logan Square (majority), Hur	60647		2111.8	11.4	5.26	0.9	19.3
5	Morgan Park (majority),Beve	60643		2023.3	8.6	5.38	4.3	22.58
4	West Town (half), Logan Squ	60622		1697.2	5	2.86	1.4	20
5	Mount Greenwood (all), Beve	60655		1482.4	7.61	6.52	3.3	21.74
1	Edgewater(majority), West R	60660		1352.9	5.5	2.75	0.9	19.27
3	Kenwood (half), Hyde Park (h	60615		1328.1	0.85	0.85	0.9	16.1
		Overall			*6.94*	*4.81*	*2*	*19.23*
		X2			*25.50*	*30.80*	*12.90*	***6.10***
		p value			*0.00*	*0.00*	*0.17*	***0.73***

Big differences in clinical cases across neighborhoods.

NO significant differences in seropositivity.

What explains the paradox of big differences in clinical cases vs. no differences in seropositivity?





Inequitable distribution of pre-existing health conditions

Higher "doses" of viral exposure

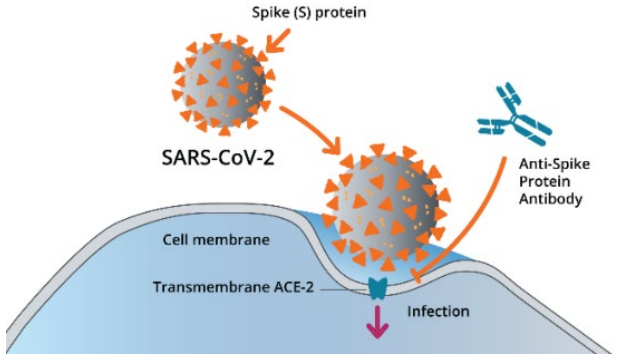
→ *inequities in more severe COVID-19?*

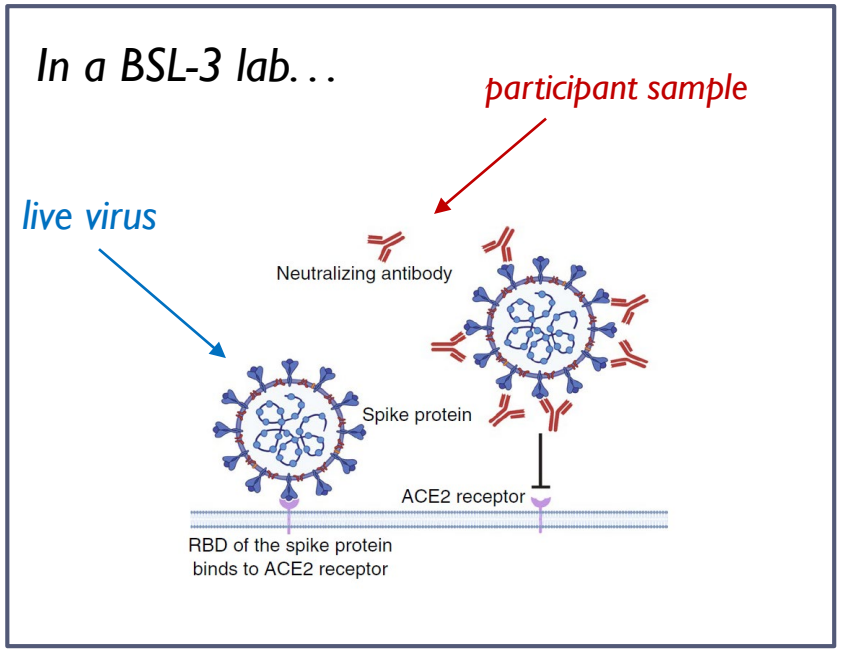
One shot or two?

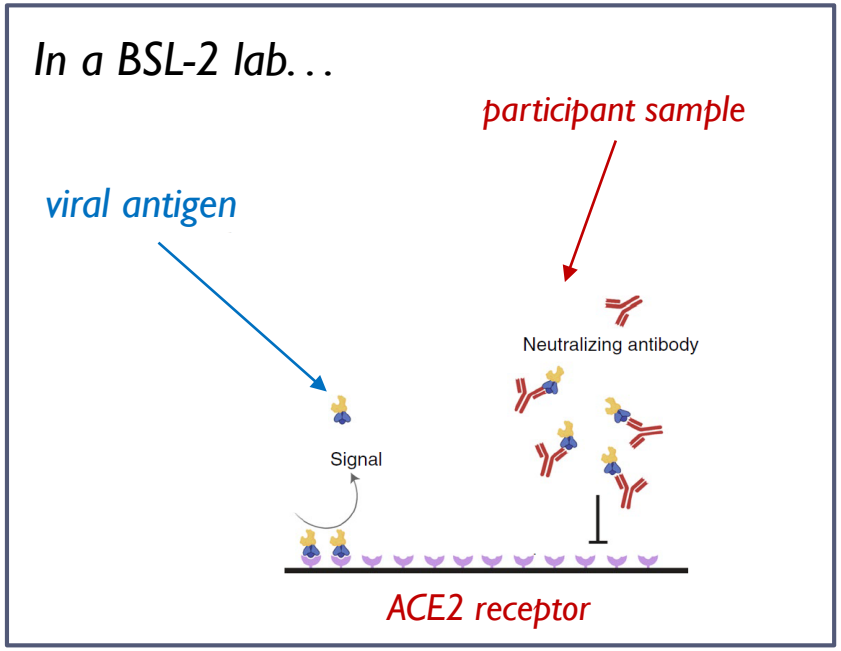
People Who Have Had Covid Should Get Single Vaccine Dose, Studies Suggest

New studies show that one shot of a vaccine can greatly amplify antibody levels in those who have recovered from the coronavirus.

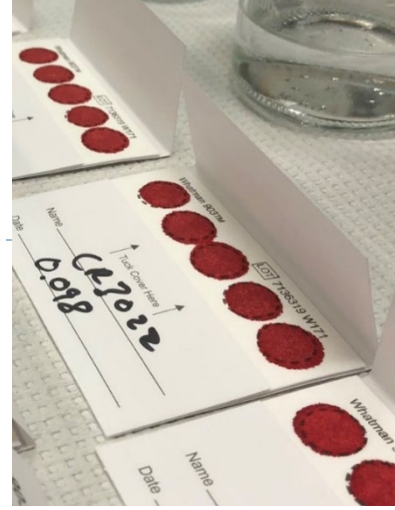
Surrogate virus neutralization test (sVNT): Functional measure of antibody-mediated neutralization

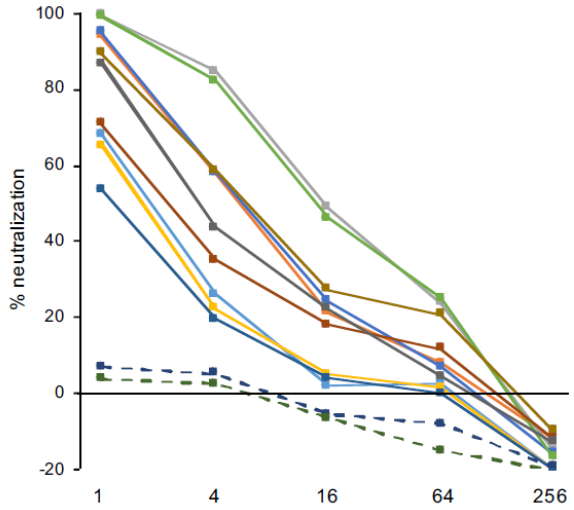


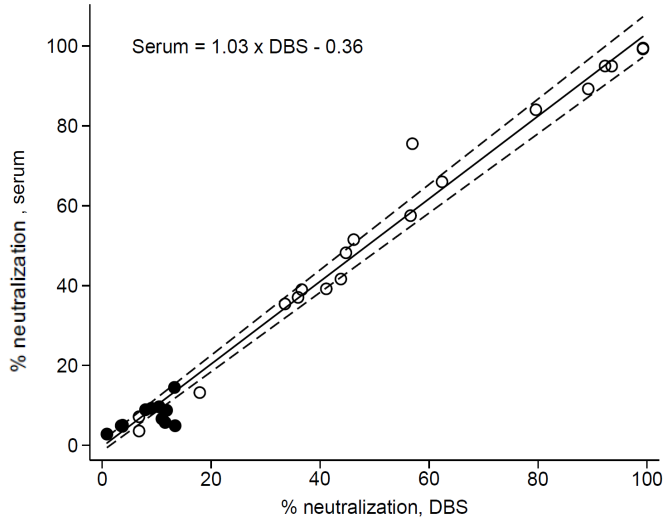


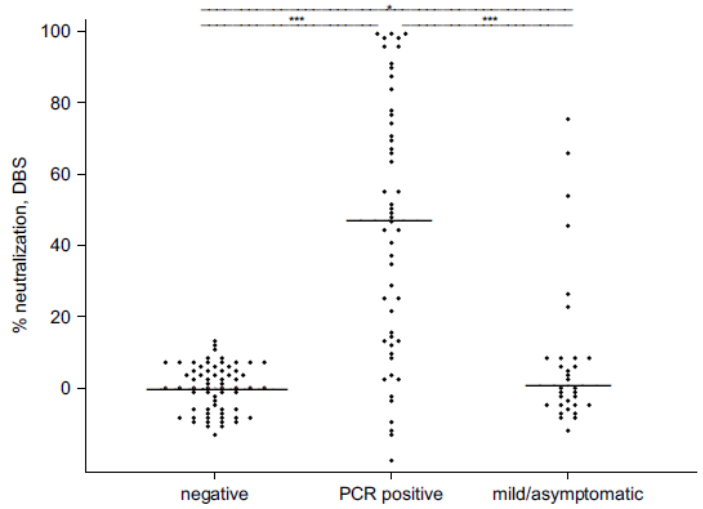


Quantifying neutralizing antibodies (sVNT) in DBS





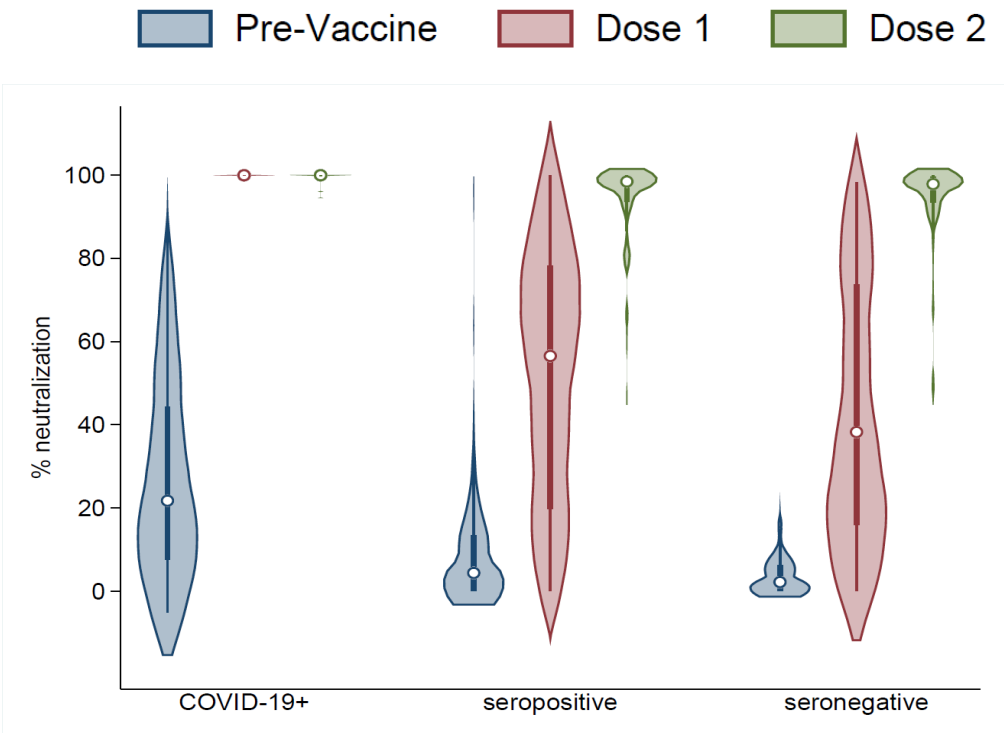




- Sancilio et al. (2021). *Scientific Reports* 11:15321.

One shot or two? *The answer depends on how you define prior exposure to SARS-CoV-2*

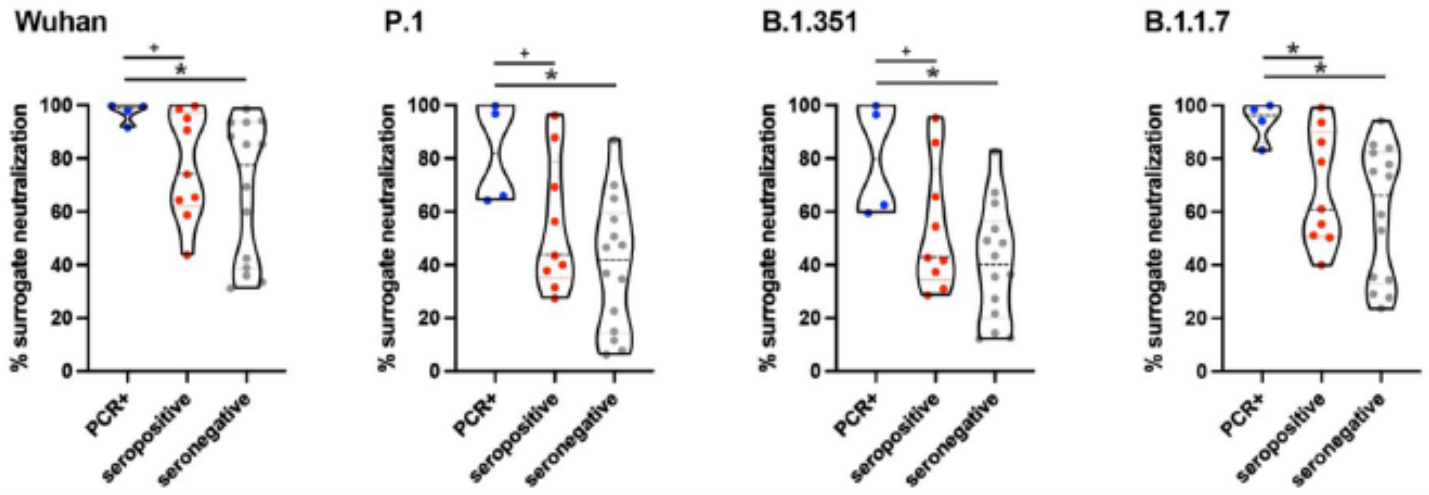
One shot or two?



- Demonbreun et al. (2021). *EClinicalMedicine* 101018.

Does durability of neutralization response vary by exposure history?

3 months post-second dose, by exposure history



→ *~20% higher neutralization for COVID-19 cases in comparison with seronegatives AND seropositives*

→ *Reduced neutralization of P.1 (Gamma) and B.1.351 (Beta) for all groups*

→ *For seropositive/seronegative participants: Level of variant neutralization comparable to one dose mRNA*

McDade et al. (2021). *Scientific Reports* 11: 17325.

Natural immunity:
Clinical vs. community-based perspectives

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibody Status and Incidence of SARS-CoV-2 Infection in Health Care Workers

S.F. Lumley, D. O'Donnell, N.E. Stoesser, P.C. Matthews, A. Howarth, S.B. Hatch, B.D. Marsden, S. Cox, T. James, F. Warren, L.J. Peck, T.G. Ritter, Z. de Toledo, L. Warren, D. Axten, R.J. Cornall, E.Y. Jones, D.I. Stuart, G. Screaton, D. Ebner, S. Hoosdally, M. Chand, D.W. Crook, A.-M. O'Donnell, C.P. Conlon, K.B. Pouwels, A.S. Walker, T.E.A. Peto, S. Hopkins, T.M. Walker, K. Jeffery, and D.W. Eyre, for the Oxford University Hospitals Staff Testing Group*

ABSTRACT

BACKGROUND

The relationship between the presence of antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the risk of subsequent reinfection remains unclear.

METHODS

We investigated the incidence of SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) in seropositive and seronegative health care workers attending testing of asymptomatic and symptomatic staff at Oxford University Hospitals in the United Kingdom. Baseline antibody status was determined by anti-spike (primary analysis) and anti-nucleocapsid IgG assays, and staff members were followed for up to 31 weeks. We estimated the relative incidence of PCR-positive test results and new symptomatic infection according to antibody status, adjusting for age, participant-reported gender, and changes in incidence over time.

RESULTS

A total of 12,541 health care workers participated and had anti-spike IgG measured; 11,364 were followed up after negative antibody results and 1265 after positive results, including 88 in whom seroconversion occurred during follow-up. A total of 223 anti-spike–seronegative health care workers had a positive PCR test (1.09 per 10,000 days at risk), 100 during screening while they were asymptomatic and 123 while symptomatic, whereas 2 anti-spike–seropositive health care workers

JAMA Internal Medicine | Original Investigation

Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection

Raymond A. Harvey, MPH; Jeremy A. Rassen, ScD; Carly A. Kabelac, BS; Wendy Turenne, MS; Sandy Leonard, MPH; Reyna Klesh, MS; William A. Meyer III, PhD, D(ABMM), MLS(ASCP)CM; Harvey W. Kaufman, MD, MBA; Steve Anderson, PhD; Oren Cohen, MD; Valentina I. Petkov, MD, MPH; Kathy A. Cronin, PhD; Alison L. Van Dyke, MD, PhD; Douglas R. Lowy, MD; Norman E. Sharpless, MD; Lynne T. Penberthy, MD, MPH

IMPORTANCE Understanding the effect of serum antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on susceptibility to infection is important for identifying at-risk populations and could have implications for vaccine deployment.

OBJECTIVE The study purpose was to evaluate evidence of SARS-CoV-2 infection based on diagnostic nucleic acid amplification test (NAAT) among patients with positive vs negative test results for antibodies in an observational descriptive cohort study of clinical laboratory and linked claims data.

DESIGN, SETTING, AND PARTICIPANTS The study created cohorts from a deidentified data set composed of commercial laboratory tests, medical and pharmacy claims, electronic health records, and hospital chargemaster data. Patients were categorized as antibody-positive or antibody-negative according to their first SARS-CoV-2 antibody test in the database.

MAIN OUTCOMES AND MEASURES Primary end points were post-index diagnostic NAAT results, with infection defined as a positive diagnostic test post-index, measured in 30-day intervals (0-30, 31-60, 61-90, >90 days). Additional measures included demographic, geographic, and clinical characteristics at the time of the index antibody test, including recorded signs and symptoms or prior evidence of coronavirus 2019 (COVID) diagnoses or positive NAAT results and recorded comorbidities.

RESULTS The cohort included 3 257 478 unique patients with an index antibody test; 56% were female with a median (SD) age of 48 (20) years. Of these, 2 876 773 (88.3%) had a negative index antibody result, and 378 606 (11.6%) had a positive index antibody result. Patients with a negative antibody test result were older than those with a positive result (mean age 48 vs 44 years). Of index-positive patients, 18.4% converted to seronegative over the follow-up period. During the follow-up periods, the ratio (95% CI) of positive NAAT results among individuals who had a positive antibody test at index vs those with a negative antibody test at index was 2.85 (95% CI, 2.73-2.97) at 0 to 30 days, 0.67 (95% CI, 0.6-0.74) at 31 to 60 days, 0.29 (95% CI, 0.24-0.35) at 61 to 90 days, and 0.10 (95% CI, 0.05-0.19) at more than 90 days.

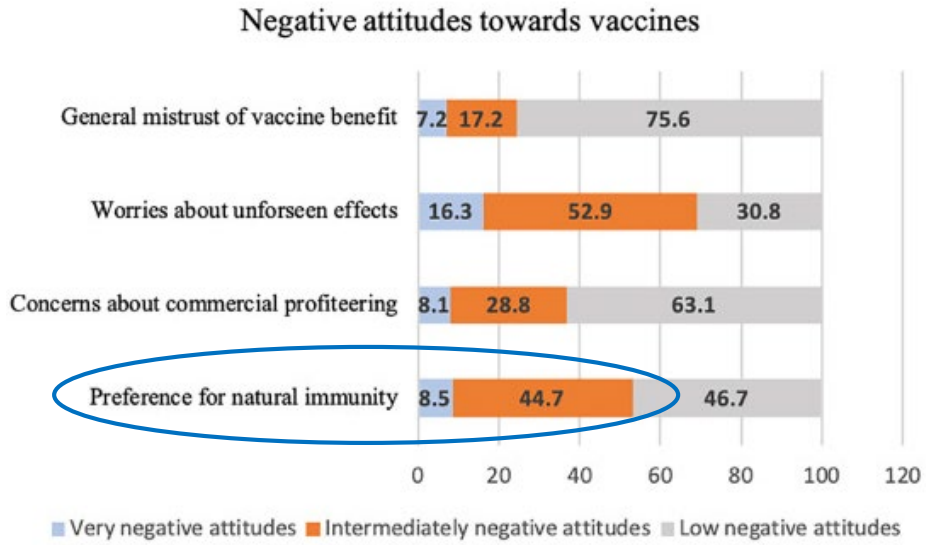
CONCLUSIONS AND RELEVANCE In this cohort study, patients with positive antibody test results were initially more likely to have positive NAAT results, consistent with prolonged RNA shedding, but became markedly less likely to have positive NAAT results over time, suggesting that seropositivity is associated with protection from infection. The duration of protection is unknown, and protection may wane over time.

Natural immunity: A justification for vaccine hesitancy

The Lancet Regional Health - Europe 1 (2021) 100012

Attitudes towards vaccines and intention to vaccinate against COVID-19: Implications for public health communications

Elise Paul, Andrew Steptoe, Daisy Fancourt*



Variable	No, *n* = 279 [1]	Wait for Review, *n* = 1953 [1]	Yes, *n* = 1247 [1]	*p*-Value [2]
Do you think you are at risk of getting COVID-19 in next 1 year?				<0.001 *
I believe I already have the disease and I am immune to it (Not diagnosed by a test)	30 (22%)	68 (49%)	40 (29%)	
No, I am confident I won't get infected	71 (27%)	128 (48%)	67 (25%)	
No, I already have recovered and won't get re-infected (Diagnosed by a test)	4 (12%)	18 (53%)	12 (35%)	
Yes, I am concerned that I will get mild symptoms which will probably not require hospitalization	153 (6.7%)	1283 (56%)	858 (37%)	
Yes, I am concerned that I will get moderate symptoms which will probably need hospitalization	15 (2.6%)	350 (61%)	207 (36%)	
Yes, I am concerned that I will get severe symptom which will probably require admission to the Intensive care unit	6 (3.4%)	106 (61%)	63 (36%)	

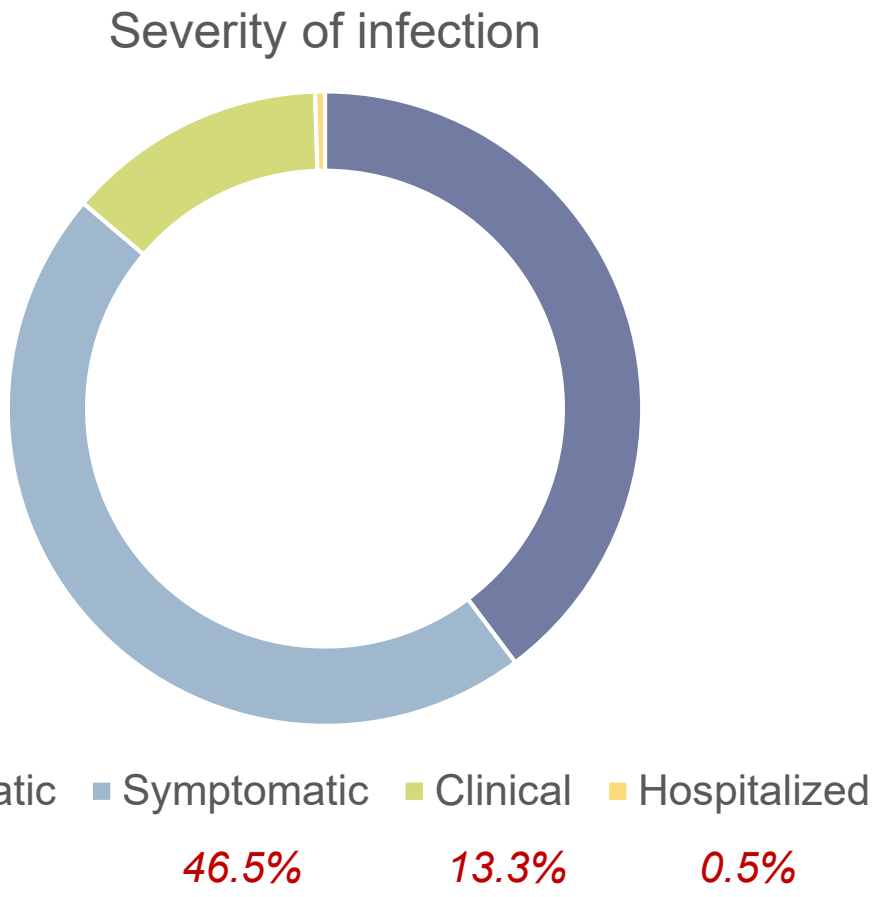
Vaccines **2021**, *9*, 119. https://doi.org/10.3390/vaccines9020119

Article

COVID-19 Vaccine Acceptance among Health Care Workers in the United States

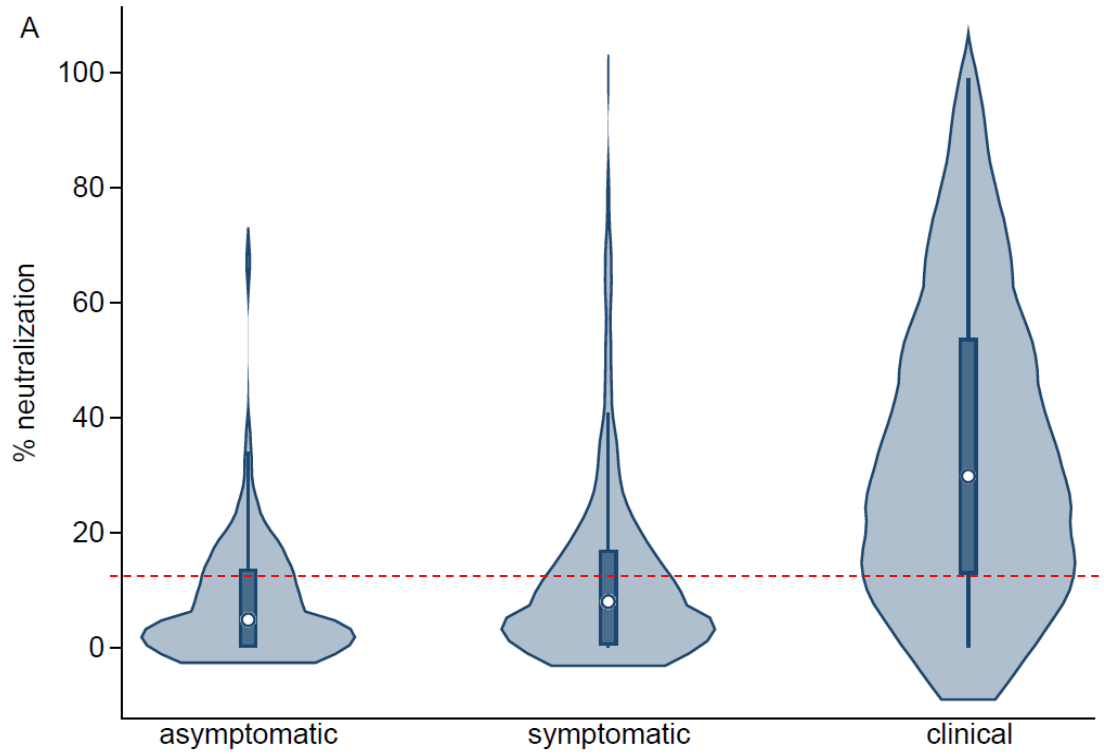
Rahul Shekhar [1], Abu Baker Sheikh [1,*], Shubhra Upadhyay [1], Mriganka Singh [2], Saket Kottewar [3], Hamza Mir [4], Eileen Barrett [1] and Suman Pal [1]

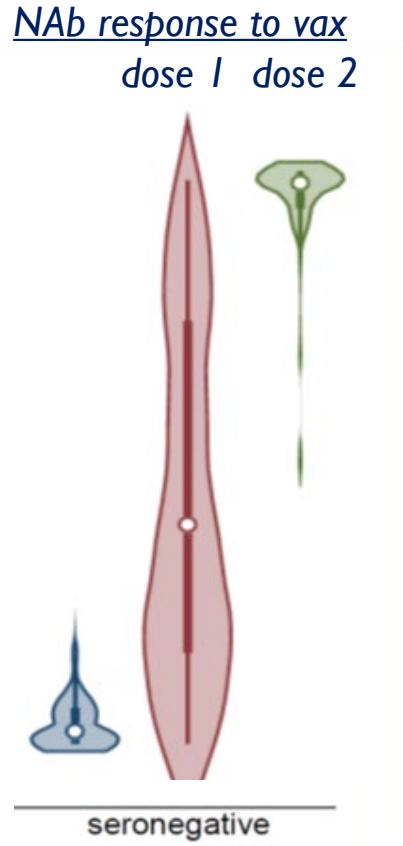
Protective immunity: Clinical vs. community-based perspectives



- McDade et al. (under review).

Protective immunity: Clinical vs. community-based perspectives





Prior infection ≠ protective immunity comparable to vaccination

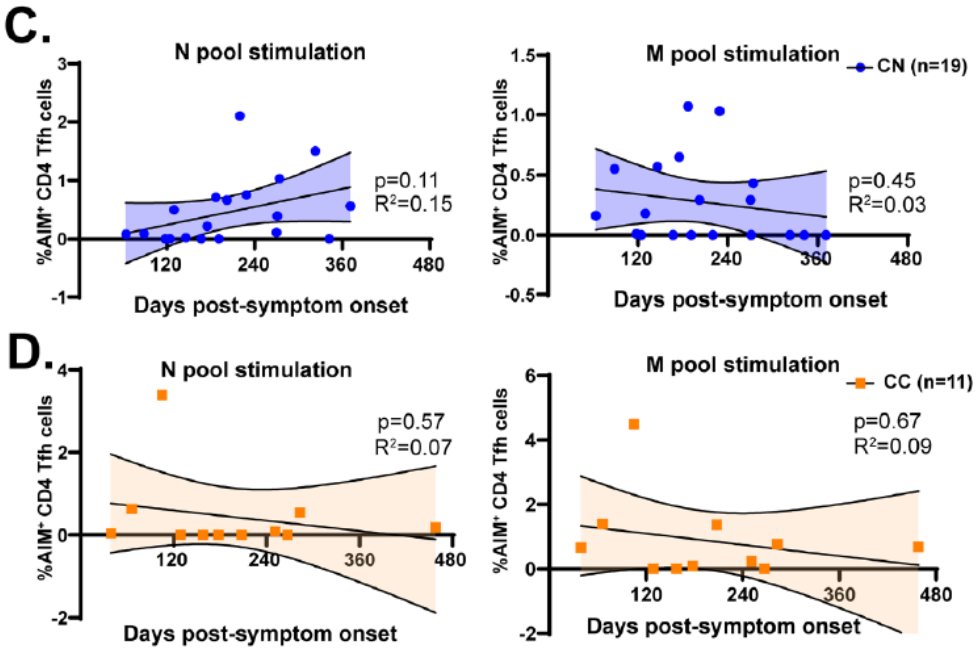
- McDade et al. (under review).

Cellular immunity to SARS-CoV-2

medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES

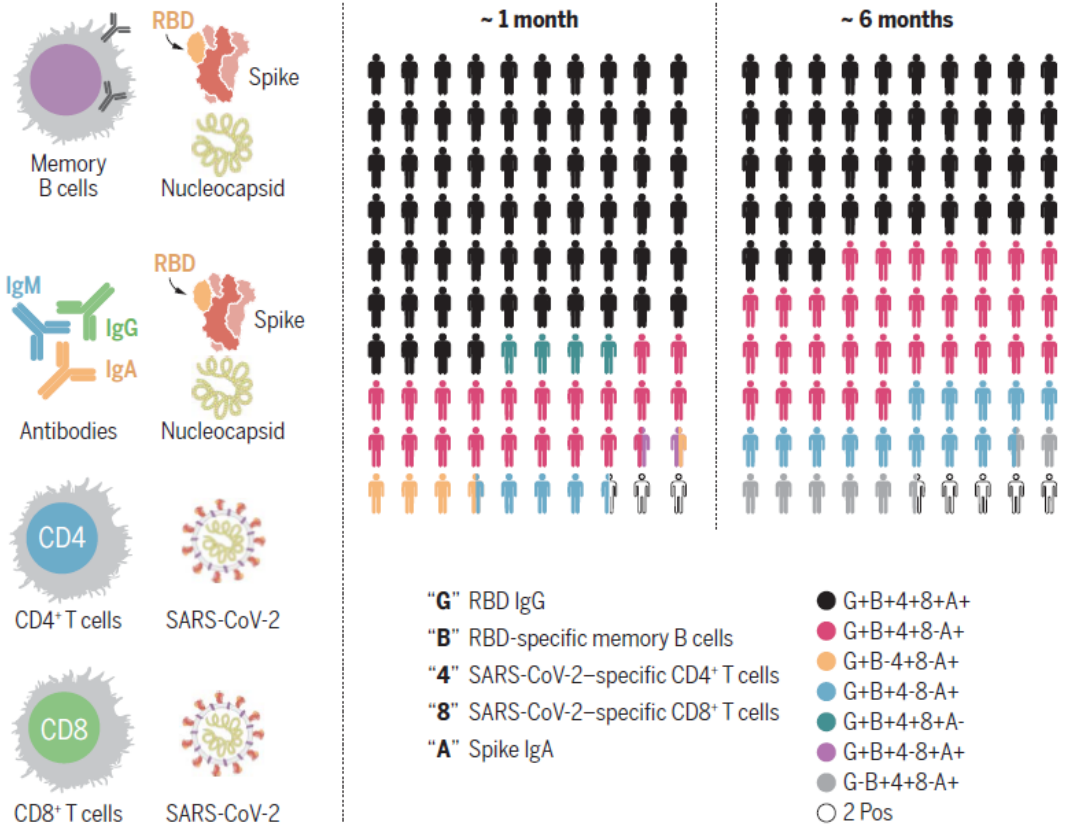
Neuro-COVID long-haulers exhibit broad dysfunction in T cell memory generation and responses to vaccination

Lavanya Visvabharathy[1*¶], Barbara Hanson[1,3], Zachary Orban[1], Patrick H. Lim[1], Nicole Palacio[2], Rishi Jain[1], Eric Michael Liotta[1], Pablo Penaloza-MacMaster[2], Igor J. Koralnik[1*]



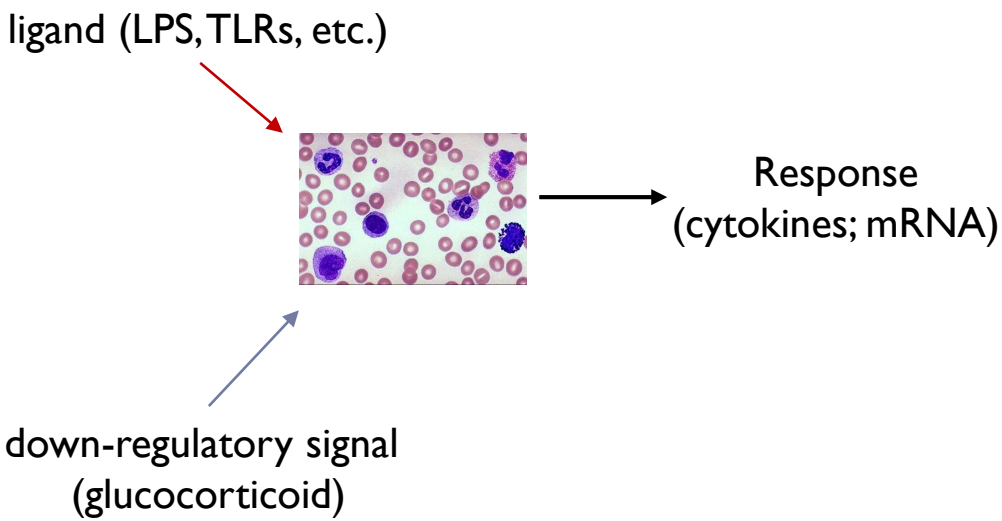
Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection

Jennifer M. Dan[1,2*], Jose Mateus[1*], Yu Kato[1*], Kathryn M. Hastie[1], Esther Dawen Yu[1], Caterina E. Faliti[1], Alba Grifoni[1], Sydney I. Ramirez[1,2], Sonya Haupt[1], April Frazier[1], Catherine Nakao[1], Vamseedhar Rayaprolu[1], Stephen A. Rawlings[2], Bjoern Peters[1,3], Florian Krammer[4], Viviana Simon[4,5,6], Erica Ollmann Saphire[1,2], Davey M. Smith[2], Daniela Weiskopf[1†], Alessandro Sette[1,2†], Shane Crotty[1,2†]



Out of the lab and into the field:

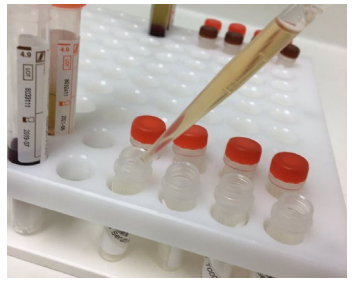
Miniaturized cell culture protocols to advance research on the regulation of inflammation



Culturing cells is hard to do outside of the clinic. . .

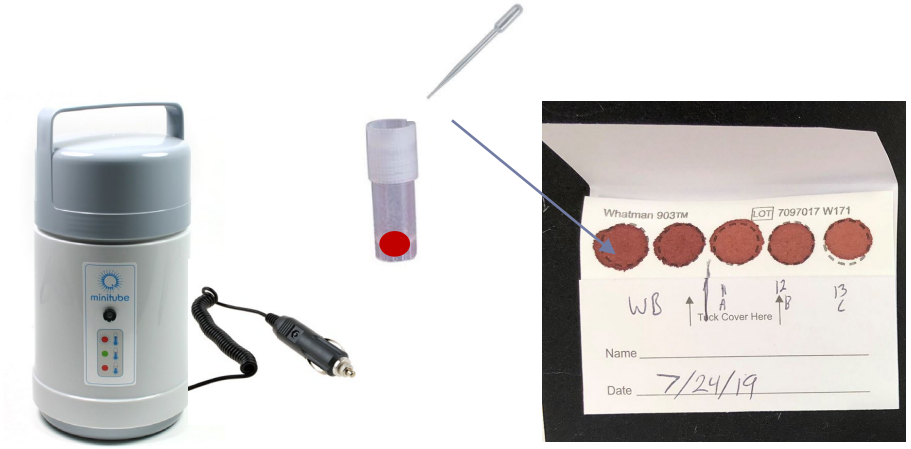




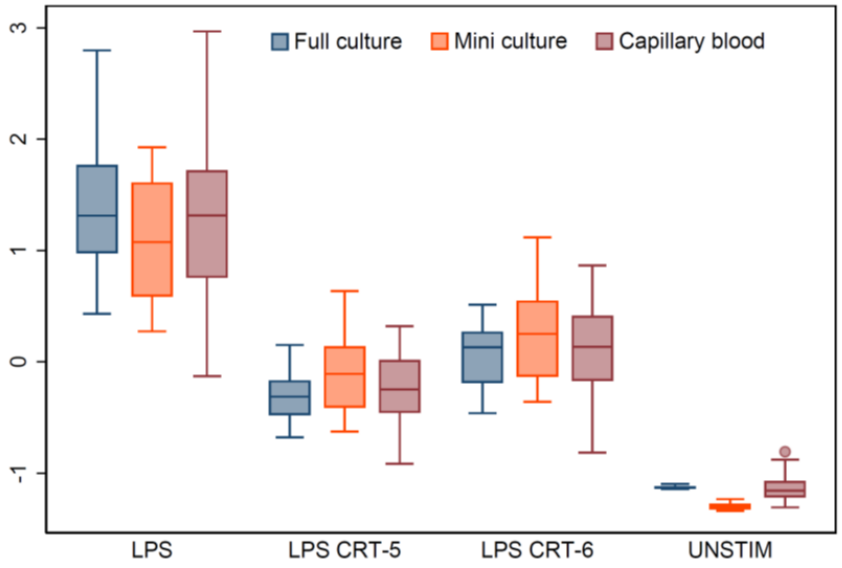



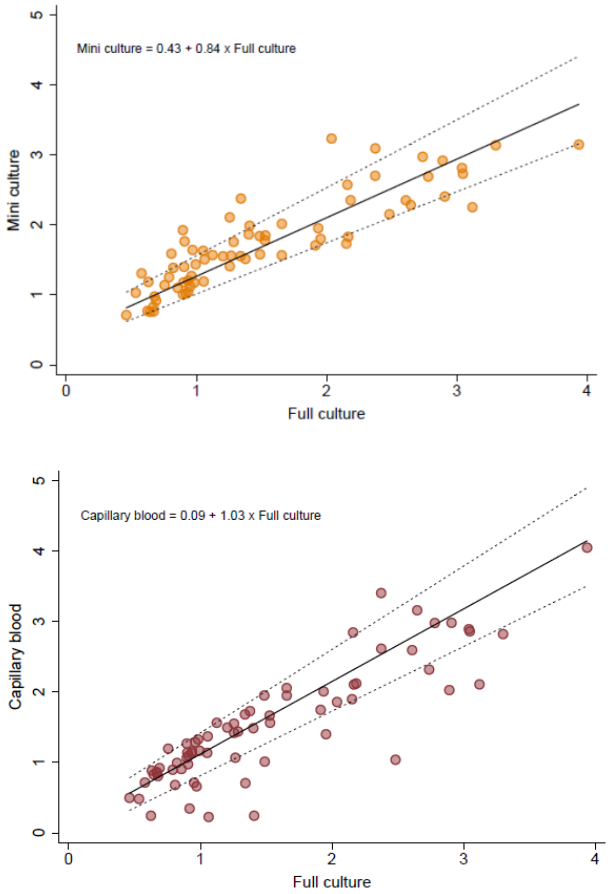
. . . but not impossible.



Agreement in results across culture protocols

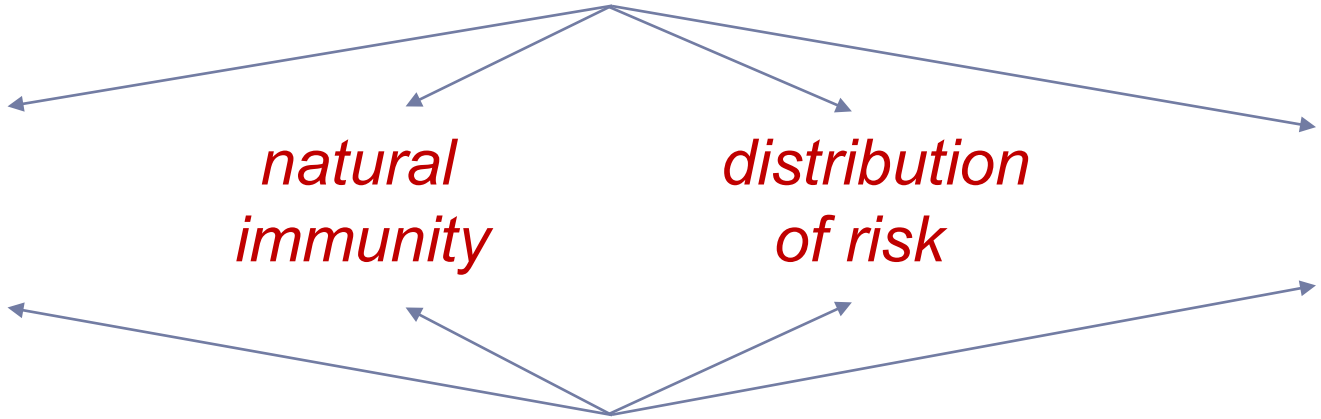




McDade, Aronoff, Leigh, Finegood, Weissman-Tsukamoto, Brody, Miller (2021). *Psychosom Med* 83: 283-90.

Community or clinic?

*The vast majority of SARS-CoV-2 infections **in the community** are mild or asymptomatic, and do not generate high levels of protective immunity.*



*Scientific understandings of the immunobiology of SARS-CoV-2 are based primarily on the study of more severe cases of COVID-19 **in the clinic**.*