COVID in the VA: Researching the effects on health & the health system

Maciej Gonek, PhD AAAS S&T Policy Fellow VA HSRD

George Ioannou, MD – Puget Sound VAHCS

Yinong Young-Xu, ScD – White River Junction VA

Caroline Korves, ScD – White River Junction VA

David Atkins, MD, MPH – VA HSRD

Building A Plane While You Are Flying in a Storm: Launching Research in the Veterans Administration During the COVID-19 Pandemic

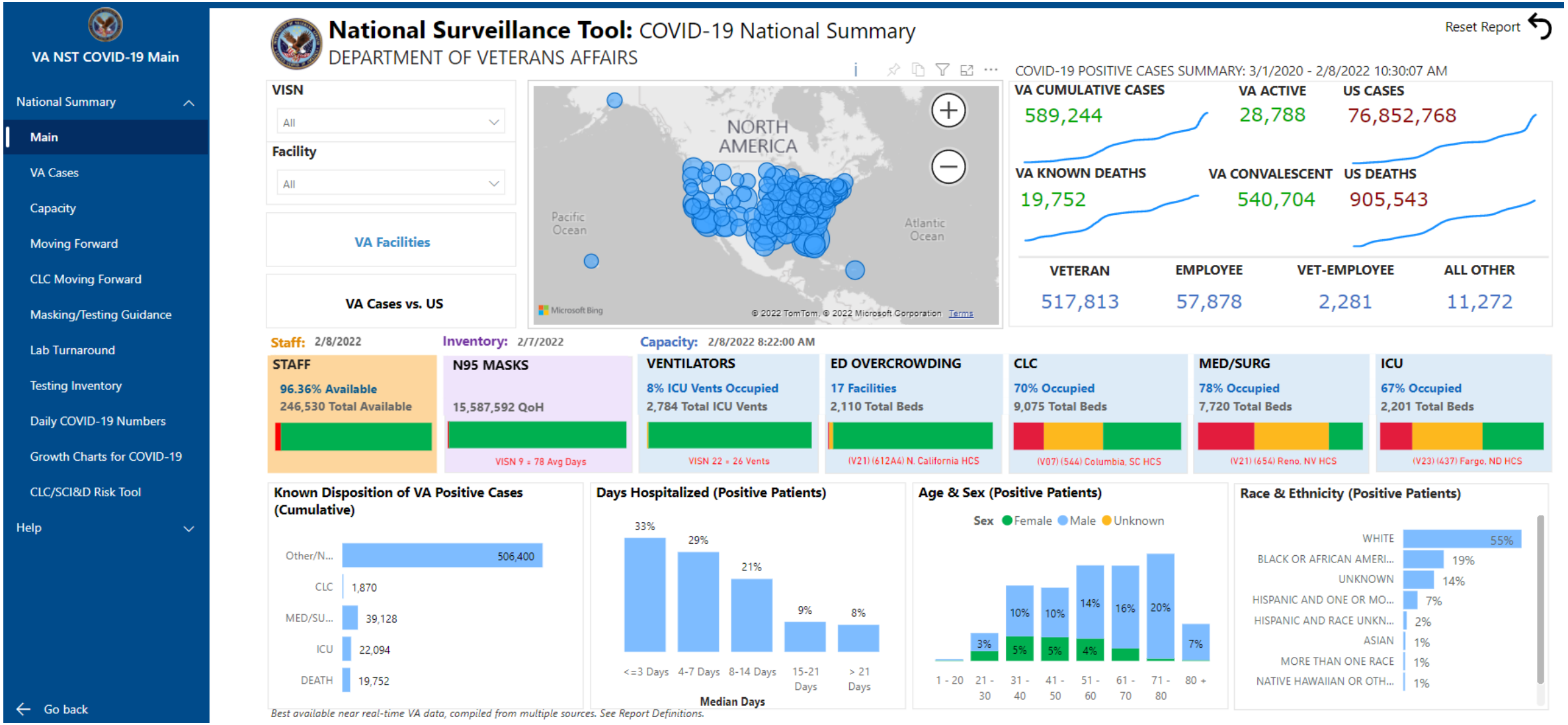
2020-2021 Critical Questions:

- How do we **keep track** of who is infected?
- How do we **keep up** with what people are learning about COVID?
- How do we quickly **enable** research?
- Do any **therapies look promising** (e.g., repurposed medications)?
- What are **risk factors** for COVID mortality?

Responses:

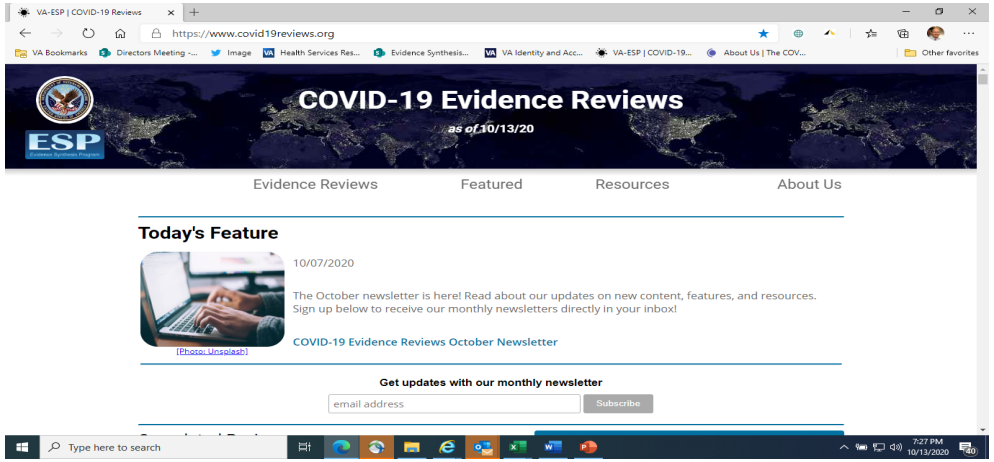
- VA National Surveillance tool
- Evidence Synthesis Program – rapid evidence syntheses
- FDA Evidence Accelerator: Health system collaborations with real world data
- Modeling with EHR data – multiple teams using VA corporate data
- Rapid response studies – mental health, homelessness, SUD, nursing home patients
- COVID Shared Data Resource
- Million Veteran Project

VA-NST: Strategic (National Summary)



Evidence Synthesis Program (ESP)

Resource for Clinical and Operational Leadership to Support Decision-making for COVID-19



COVID-19 Evidence Review Website

www.covid19reviews.org

–Developed in cooperation with WHO

–Pulls from 15 international sources

–Over 500 new reviews/protocols per month

Ultra-Rapid Reviews & Living Reviews

–Within 7-10 days of request of VA partners

–8 completed (2 living reviews)

- COVID-19: Intensive care unit length of stay and ventilation days
- Racial and Ethnic Disparities in COVID-19–Related Infections, Hospitalizations, and Deaths: A Systematic Review: Annals of Internal Medicine: Vol 174, No 3 (acpjournals.org)

Critical Appraisal of New Research

–Critical appraisal of individual high-priority studies, including pre-prints

– 6 completed:

- PREPRINT REVIEW: Outcomes of hydroxychloroquine usage in COVID

Please let us know if you'd like to receive email notifications for reports in progress: covid19reviews@gmail.com

VA COVID-19 Shared Data Resource

VA established a database of all VA patients who have:

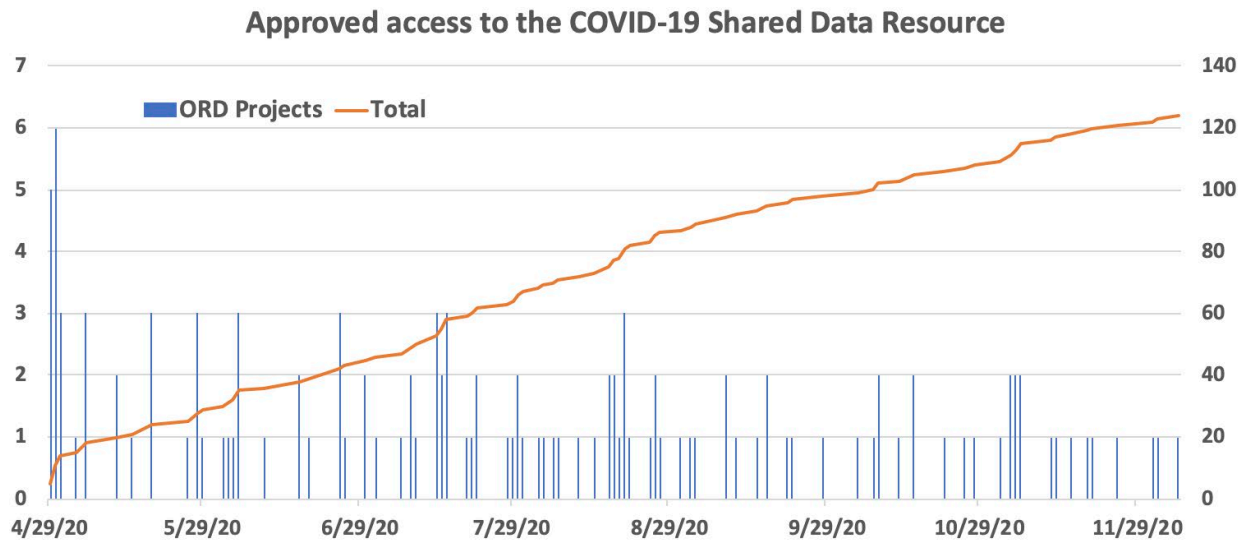
- received a COVID-19 laboratory test (positive or negative) within VA
- tested positive outside VA with information recorded in VA clinical notes

190 data elements/phenotypes

- Pre-existing conditions
- Pharmacological and non-pharmacological interventions
- Specific Patient outcomes
- Community data

- This data resource draw from the VA electronic health record and have been used for hundreds of VA studies
- **Over 300 protocols have requested data from CSDR to date.**

Vast longitudinal data for quick turnaround of studies



VA Pharmacy Surveillance and Real -World Evidence: with FDA and other Federal Partners

FDA Evidence Accelerator

Collaboratory of researchers examining real-world effectiveness of COVID therapies health system data

- VA published results showing reduced mortality with preventive anticoagulation
- VA published study showing remdesivir did not shorten hospital stays

Medication Safety Initiative -- Pharmacy Benefits Management Office

Evaluates adverse drug events (ADEs) and conducts medication safety projects at the regional and national levels; providing interventions to decrease preventable ADEs; and educating the field on safe and best practices to minimize ADEs *(with FDA)*

Real-world Evaluation of New Therapeutics

Evaluating the effectiveness of Pfizer's Paxlovid versus Merck's Molnupiravir). Collaborating with BARDA to design study using our EHR to examine how drugs are being used, in which patients and with what other therapies, in order to examine their clinical impact.

Early and significant signals of therapies

Million Veteran Program (MVP) – COVID Research

- MVP includes genomic and lifestyle data on over 850,000 Veterans; > 40,000 SARS-CoV-2 positive Veterans
  - Genetic basis of infection, severity, complications and death
  - Response to treatments
  - Disease mechanisms
  - **Risk Factors**
- COVID survey sent to over 700,000 living MVP participants
  - 250,000 completed surveys obtained
  - Assessing experience with COVID-19, including preventive measures, symptoms, complications, hospitalization, treatment, impact on routine care
- **New survey being fielded to target COVID-infected participants**

Building A Plane While You Are Flying in a Storm: 2021-22 Critical Questions About the COVID-19 Pandemic

- What is the effectiveness of vaccines over time and the role of variants?
- What are the long-term effects in patients who have recovered from COVID and how to best treat them?
- How has the pandemic affected health care and health outcomes in the VA Health System

Responses:

- FDA funded negative-case-control study of vaccine effectiveness
  - Yinong Young-Xu
- VA COVID-19 Observational Research Collaboratory (CORC) -- Long Term Outcomes Study
  - George Ioannou
- The Disrupted Care National Project
  - Caroline Korves

ACADEMY OF HEALTH ARM 2022

COVID-19 VACCINE EFFECTIVENESS RESEARCH STRATEGIES AND METHODS

YINONG YOUNG-XU, SCD, MA, MS

CLINICAL EPIDEMIOLOGY PROGRAM, VETERANS AFFAIRS MEDICAL CENTER,

WHITE RIVER JUNCTION, VERMONT, USA

JUNE 2022

VA | U.S. Department of Veterans Affairs

VETERANS ADMINISTRATION

CLINICAL EPIDEMIOLOGY PROGRAM

- VA has a robust research capability for conducting national-level near real-time research projects leveraging data from the electronic medical record of the VA, the single largest integrated health care system in the United States.
  - 170 medical centers and 1074 community-based outpatient clinics
  - Approximately 6 million (18+) Veterans use the VHA regularly
  - VHA has fully vaccinated nearly 1.5 million Veterans and 250,000 employees since December 2020
- Only the VA has a fully established data system in place to bring together test results, prescriptions, and entire patient health records which are readily accessible to the VA researchers and refreshed daily.

CLINICAL EPIDEMIOLOGY PROGRAM

FRONT LINE COVID- 19 RESEARCH

- Since Fall 2020, VA has been focused on studies of COVID-19 among Veterans
  - Charting epidemiological trends in the VA population
  - Developing risk models for infection and severity
  - Assessing the safety and real-world effectiveness of EUA COVID-19 vaccines and treatments
  - Working with external partners, CDC, DoD, FDA to predict and model variant and surge impact
- Variants sequencing, vaccine and treatment effectiveness, and long COVID are key research priorities of VA

ENTERPRISE STRATEGY FOR COVID-19 RESEARCH

Our COVID-19 research response took an enterprise-wide strategy that:

Coordinated across offices and research groups

Leveraged existing infrastructure and capabilities

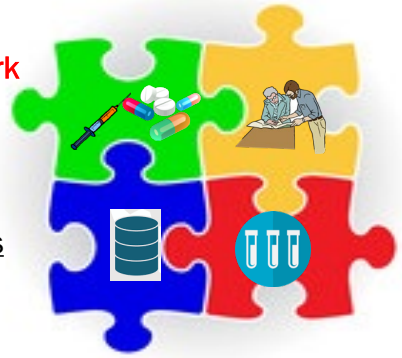
Accelerated culture & expectations for a post-COVID-19 world

VISNs/ Clinical operations
Pharmacy Benefits Management
National Ctr for Health Promotion & Disease Prevention

Ofc of Information Technology
VHA Information & Analytics Ofc

Clinical research
- Clinical trials network
- Treatment IND / Expanded Access network

Informatics / Analytics
- Consolidated data resource
- Data scientists/ epidemiologists
- Evidence synthesis program



Observational studies
- Cohort creation
- Longitudinal follow-up
- Data linkages

Biorepository network
- Specimen collection
- Standard data elements

Pathology & Lab Medicine
Public Health Reference Laboratory

COVERAGE AND ESTIMATED EFFECTIVENESS OF MRNA COVID-19 VACCINES AMONG US VETERANS (JANUARY TO MARCH 2021)

VE, % (95% CI)		VE, % (95% CI)	
Full vs No Vaccination		**Partial vs No Vaccination**	
Unadjusted	Adjusted	Unadjusted	Adjusted
Laboratory Confirmed SARS-Cov-2 Infection			
97 (95 to 97)	95 (93 to 96)	75 (71-78)	64 (59-68)
Adjusted VE, % (95% CI)			
Full Vaccination		Partial Vaccination	
From 7 d after dose 2	From 14 d after dose 2	7 d after dose 1 until dose 2	14-20 d after dose 1	14 d after dose 1 until dose 2
94 (92-95)	95 (93-96)	58 (54-62)	63 (57 to 69)	64 (59-68)
Hospitalization			
89 (80-94)	91 (83-95)	41 (24-54)	48 (32-60)
Death			
100	100	47 (3-71)	63 (24-81)
Data for the overall study population. VE Estimates were similar across all age groups, sex, race and ethnicity, or urban vs rural status, with overlapping 95% CIs.			
The adjusted variables include the following: age, body mass index, cancer, congestive heart failure, chronic kidney disease, hypertension, immunocompromised, priority level, race and ethnicity, sex, and rurality.			

Young-Xu Y, Korves C, Roberts J, et al. Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines Among US Veterans. *JAMA Netw Open.* 2021;4(10):e2128391.

Estimated Effectiveness of COVID-19 Messenger RNA Vaccination Against SARS-CoV-2 Infection Among Older Male Veterans Health Administration Enrollees, January to September 2021.

Table. Change in Estimated Messenger RNA Vaccine Effectiveness Against Laboratory-Confirmed SARS-CoV-2 Infections, January to September 2021

	Adjusted vaccine effectiveness by month from full vaccination, % (95% CI)[a]		
Month	Pre-Delta (January to April)	Rising Delta (May to June)	High Delta (July to September)
1	94.5 (90.7-96.7)	92.1 (87.2-95.1)	62.0 (45.6-73.5)
2	88.5 (86.1-90.5)	90.6 (87.8-92.7)	60.9 (51.5-68.4)
3	87.9 (85.9-89.5)	87.3 (80.8-91.7)	57.8 (52.5-62.5)
4	NA	86.6 (83.0-89.5)	38.3 (33.5-42.7)
5	NA	67.3 (63.2-70.9)	18.9 (13.7-23.8)
6	NA	NA	18.4 (13.3-23.3)
7	NA	NA	23.4 (17.3-29.0)
8	NA	NA	24.8 (18.8-30.4)

Abbreviation: NA, not applicable.

[a] Male veterans aged 65 years or older with positive SARS-CoV-2 test results (cases) or negative test results (controls) were matched 1:4 on time of test and geographic region. Adjusted variables included the following: age, body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, hypertension, immunocompromised status, priority level, race and ethnicity, and rurality. See eTable 1 in the Supplement in Young-Xu et al[1] for definitions of these variables.

Young-Xu Y, Zwain GM, Powell EI, Smith J. Estimated Effectiveness of COVID-19 Messenger RNA Vaccination Against SARS-CoV-2 Infection Among Older Male Veterans Health Administration Enrollees, January to September 2021. *JAMA Netw Open.* 2021;4(12):e2138975.

Effectiveness of mRNA COVID-19 Booster Vaccines against Omicron and Delta Variants among US Veterans

Young-Xu Y, Zwain G, Izurieta H, et al.
Under review, March 2022

Estimated Vaccine Effectiveness Against Laboratory Confirmed SARS-Cov-2 Infection, Covid-19 related Hospitalization and Death by Dose and Variant

	VE INTERVAL (14+ DAYS AFTER VACCINATION)	VE (95% CI)
LABORATORY CONFIRMED SARS-COV-2 INFECTION		
OMICRON	2nd dose	12% (10, 15)
OMICRON	3rd dose	64% (63, 65)
DELTA	2nd dose	54% (50, 57)
DELTA	3rd dose	90% (88, 92)
HOSPITALIZATION		
OMICRON	2nd dose	63% (58, 67)
OMICRON	3rd dose	89% (88, 91)
DELTA	2nd dose	75% (69, 80)
DELTA	3rd dose	94% (90, 96)
DEATH		
OMICRON	2nd dose	77% (67, 83)
OMICRON	3rd dose	94% (90, 96)
DELTA	2nd dose	92% (83, 96)
DELTA	3rd dose	96% (87, 99)

Above numbers exclude Johnson & Johnson's Janssen vaccines as of the date of the Johnson & Johnson's Janssen vaccine. 2nd and 3rd doses are for mRNA vaccines compared to no vaccination in the indicated period beginning 14 days after vaccination. Tests occurring in 0-13 days after vaccination were excluded.

Cases and controls were matched 1:4 (max) without replacement on HHS and lab test date within three weeks. The adjusted variables include the following: age (continuous), body mass index, cancer, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, immunocompromised, priority level, race/ethnicity, and rurality.

mRNA Vaccine Efficacy:

Test Negative Design

Pfizer Clinical Trial

Moderna Clinical Trial

Emulated Target Trial

	Cases	Time period	VE, % (95% CI)
Overall mRNA[1] Among US Veterans	15,110	12/2020 – 03/2021	95 (93-96)
BNT162b2 Clinical trial[2]	18,198	07/2020-11/2020	95 (90.0-97.9)
mRNA-1273 Clinical trial[3]	14,134	07/2020-10/2020	94.1 (89.3-96.8)

	Dickerman et al, Event Rates[4]	Young-Xu, et al Vaccine Effectiveness
BNT162b2	5.75 (95% CI, 5.39-6.23)	94% (90-98%)
mRNA-1273	4.52 (95% CI, 4.17-4.84)	96% (93-99%)

[1] Young-Xu Y, Korves C, Roberts J, et al. Coverage and Estimated Effectiveness of mRNA COVID-19 Vaccines Among US Veterans. *JAMA Netw Open.* 2021;4(10):e2128391.

[2] Polack, Fernando P et al. "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine." *The New England journal of medicine* vol. 383,27 (2020): 2603-2615. doi:10.1056/NEJMoa2034577

[3] Baden, Lindsey R et al. "Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine." *The New England journal of medicine* vol. 384,5 (2021): 403-416. doi:10.1056/NEJMoa2035389

[4] Dickerman, Barbra A., et al. "Comparative effectiveness of BNT162b2 and mRNA-1273 vaccines in US veterans." *New England Journal of Medicine* 386.2 (2022): 105-115

mRNA Vaccine Efficacy

Study Population Characteristics

	Young-Xu et al Test Negative Case Control[1]		Dickerman et al Emulated Target Trial[4]		mRNA-1273 Clinical Trial[3]		BNT162b2 Clinical Trial[2]	
	Enrollees, No.	Vaccinated enrollees, No. (%)	BNT162b2 Recipients (%)	mRNA-1273 Recipients (%)	Enrollees, No.	Recipients, No. (%)	Enrollees, No.	Recipients, No. (%)
	6,647,733	1,363,180 (21)	219,842	219,842	30,351	15,181	37,706	18,846
Age range (y)	**<65**		**<60**		**<65**		**≤55**	
	3,297,360	280,763 (.20)	21,319 (24)	21,319 (24)	22,839	11,418 (75)	21,785	10,889 (58)
	≥65		**≥60**		**≥65**		**>55**	
	3,350,373	1,082,417 (79)	167,468 (76)	167,468 (76)	7,512	3,763 (25)	15,921	7,971 (42)
	≥85		**≥80**					
	473,266	149,041 (11)	22,753 (10)	22,753 (10)				
Female	632,935	74,795 (12)	16,116 (7)	16,116 (7)	14,366	7,258 (48)	18,631	9,410 (50)
Non-Hispanic White	4,361,621	940,691 (22)	163,759 (74)	163,759 (74)	24,024	12,029 (79)	31,266	15,636 (83)
Non-Hispanic Black	1,102,471	234,363 (21)	44,967 (21)	44,967 (21)	3,090	1,563 (10)	3,492	1,729 (9)
Hispanic	461,645	81,480 (18)	14,939 (7)	20,493 (9)	6,235	3,121 (21)	10,543	5,266 (28)
Other	381,648	70,080 (18)	4,380 (2)	4,380 (2)	637	321 (2)	2,740	1,402 (7)
Missing	340,348	36,566 (11)	6,736 (3)	6,736 (3)	282	155 (1)	208	93 (0.5)
				Comorbidities & Risk factors				
Obese			101,740 (46)	102,280 (47)	2046	1025 (7)	13,218	6,556 (34.8)
Chronic Lung Disease	684,318*	255,404 (19)	36,793 (17)†	40,166 (18)	1,454	744 (5)		
Cardiac Disease	111,379	44,097 (3)	60,311 (27)	60,423 (28)	1,496	744 (5)		
Diabetes	953,054	347,594 (37)	73,884 (34)	80,061 (36)	2,875	1,440 (10)		
Liver Disease	35,163	100,280 (3)	859 (0.4)	784 (0.4)	196	96 (0.6)		
HIV	19,279	6703 (35)			179	87 (0.6)		
Cancer	186,911	85,194 (46)	30,870 (14)	29,151 (13)				
Hypertension	1,453,671	517,021 (36)	139,451 (63)	142,733 (65)				
Chronic Kidney Disease	212,003	93,517 (44)	21,100 (10)	22,186 (10)				

*Chronic lung disease includes asthma and chronic obstructive pulmonary disease

†Chronic lung disease includes asthma, bronchitis, and chronic obstructive pulmonary disease

WHAT ARE THE CRITICAL QUESTIONS TO ADDRESS?

2021 Research driving questions:

- What is the real-world effectiveness of available vaccines in the Veteran population?
  - Does it differ in high-risk groups (e.g., CLC patients)?
  - Does it differ across vaccine products?
  - Does it diminish with time?

New research questions for 2022:

- Current questions focus on duration of vaccine effectiveness for each vaccine, emerging variants and sub-groups
- Answers will inform the need for booster vaccinations, re-vaccination against variants and additional essential therapies for at risk populations
  - Use of Tixagevimab/Cilgavimab for prevention of COVID-19 among immunocompromised Veterans
  - Interactions between vaccines and monoclonal antiviral treatments
  - Deliver treatments to those need them the most

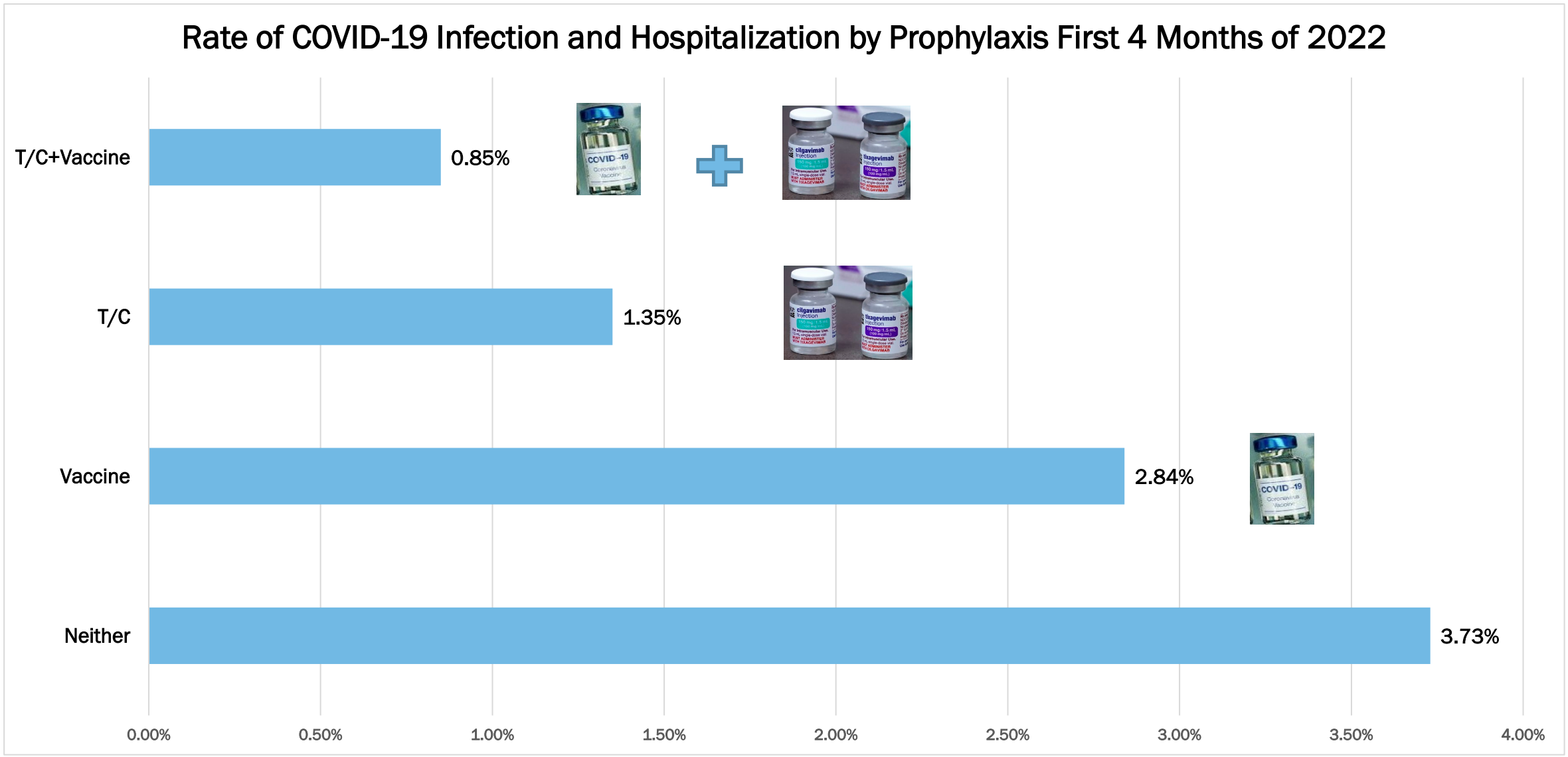
DISEASE BURDEN BY TREATMENT TYPE IN 3 MONTHS BEFORE AND AFTER TIXAGEVIMAB/CILGAVIMAB

	Outcomes (%)/Month	October 21	November 21	December 21		January 22	February 22	March 22
tixagevimab/cilgavimab	Covid-19 Infection (positive PCR test)	0.44%	0.81%	0.30%		0.15%	0.00%	0.00%
	Covid-related Hospitalization	0.22%	0.07%	0.45%		0.00%	0.13%	0.00%
	All-cause Mortality	N/A	N/A	N/A		0.22%	0.13%	0.00%
	Number of Eligible Patients	1,353	1,353	1,353		1,353	796	302
Immunosuppressed but did not receive tixagevimab/cilgavimab	Covid-19 Infection (positive PCR test)	0.27%	0.63%	0.24%		0.76%	0.86%	0.27%
	Covid-related Hospitalization	0.09%	0.06%	0.36%		0.40%	0.39%	0.08%
	All-cause Mortality	0.45%	0.39%	0.98%		0.97%	0.80%	0.78%
	Number of Eligible Patients	192,842	191,975	191,227		189,355	187,517	186,020

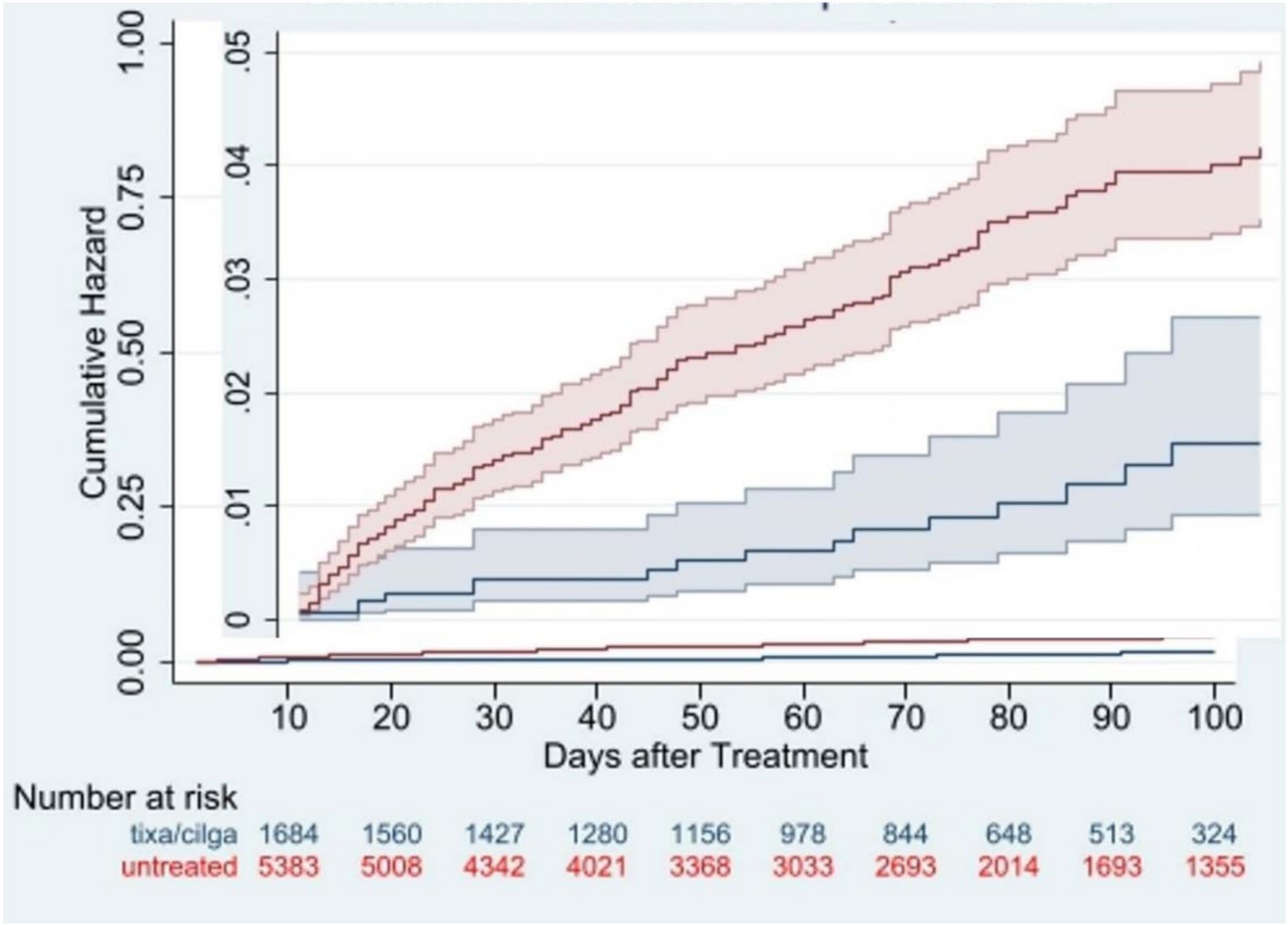
TIXAGEVIMAB/CILGAVIMAB

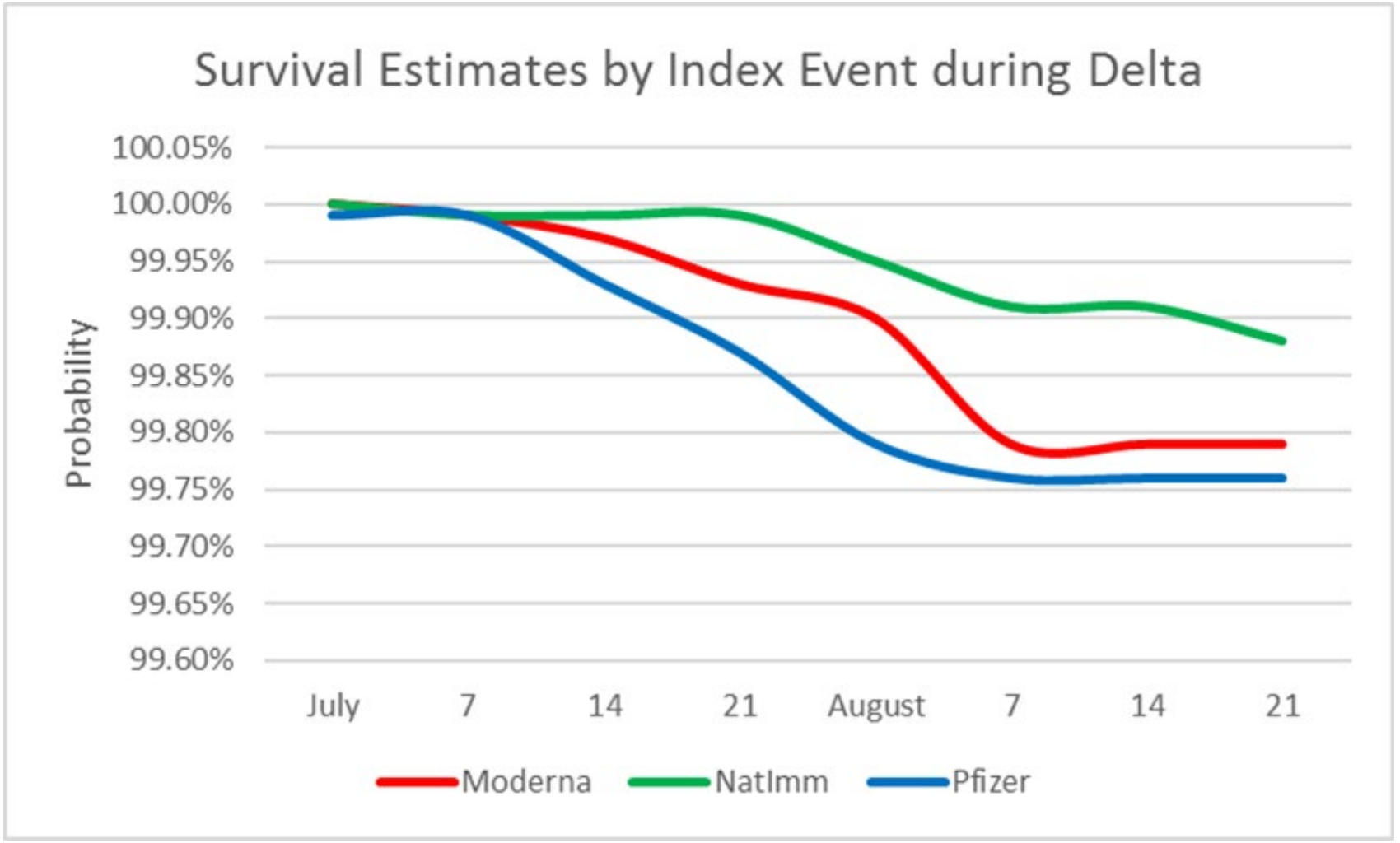
21A (Delta)
21I (Delta)
21J (Delta)
21K (Omicron)
21L (Omicron)

Rate of COVID-19 Infection and Hospitalization by Prophylaxis First 4 Months of 2022



Cumulative risk of composite COVID-19 outcomes for tixagevimab-cilgavimab recipients compared to untreated controls



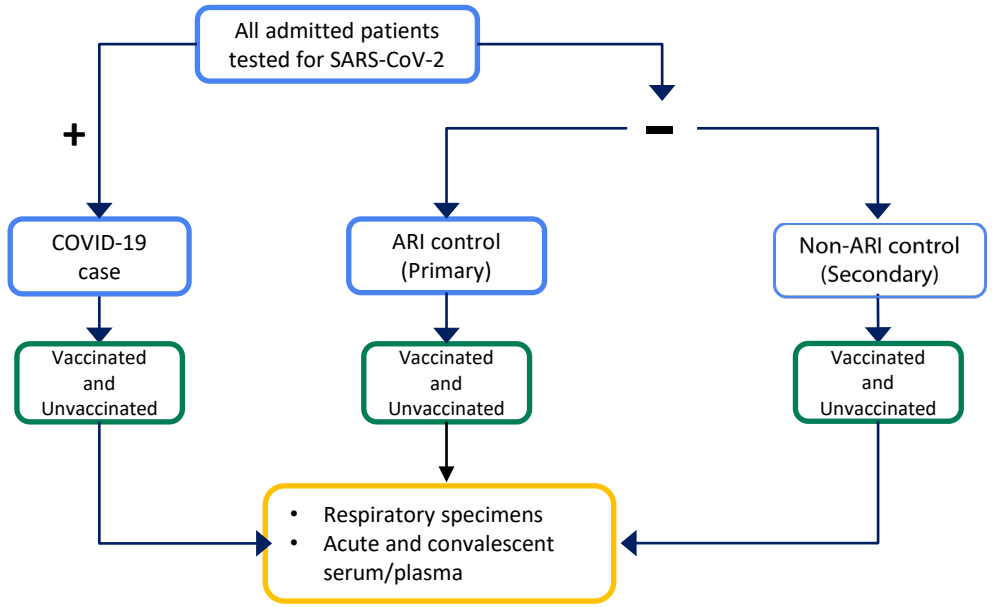

Survival Estimates by Index Event during Delta
100.05%
100.00%
99.95%
99.90%
99.85%
99.80%
99.75%
99.70%
99.65%
99.60%
Probability
July
7
14
21
August
7
14
21
Moderna
NatImm
Pfizer

COVID-19 VACCINE SURVEILLANCE (CVS)

- National VA study funded by FDA in collaboration with CDC
- Case-control study including ALL new COVID-19 cases and matched set of COVID-negative controls (test negative design)
- Using Vaccine Effectiveness as a public health measure like infection, hospitalization, and mortality rates
- Can estimate, sequentially, in a surveillance framework:
  - Vaccine effectiveness overall and in subgroups (age, underlying conditions, race/ethnicity, regions, income, etc.)
  - Duration of protection (evaluation at 2-week intervals for one year, longer if needed)
  - Comparative effectiveness of vaccine products
  - Effectiveness of complete vaccinations and incomplete vaccinations

COVID-19 VACCINE SURVEILLANCE

- In collaboration with the FDA and the CDC
- Researchers looking at vaccine effectiveness conduct a case-control study using a test-negative design as well as a second set of controls (patients hospitalized for non-respiratory illness who also test negative for SARS-CoV-2).
- Collecting respiratory specimens (primarily nasopharyngeal swabs) and sequencing for breakthrough infections and allow for assessment of protection against specific variants



VA SHIELD
SCIENCE AND
HEALTH **I**NITIATIVE
TO COMBAT
INFECTIOUS AND
EMERGING **L**IFE-
THREATENING
DISEASES

Retrospective analysis can demonstrate vaccine effectiveness against known variants, we are not able to predict the effectiveness against future strains in real world clinical settings. To help address this issue, the VA has launched several initiatives including VA SHIELD, a comprehensive biorepository of specimens from a cohort of affected Veterans with accompanying clinical data.

As part of the future of VA SHEILD, clinical specimens will be collected prospectively from patients, which will help identify emerging strains as well as developing resistance in real world clinical settings. Obtaining this information rapidly will help public health officials, clinicians and researchers make important, timely decisions regarding diagnostics, prophylaxis, and therapeutics.

Department of Veterans Affairs	Collaborators
Office of Research and Development	Rachel Ramoni, David Atkins, Jane Battles, Vicky Davey, Maciej Gonek, Grant Huang, Saiju Pyarajan, Wendy Tenhula, Sarah Wonders, Amanda Garcia
National Pathology and Laboratory Medicine Program Office	Jessica Wang-Rodriguez
Office of Public Health Surveillance	Mark Holodniy
Office of Patient Care Services/Public Health	Larry Mole
VA Informatics and Computing Infrastructure (VINCI)	Scott DuVall
CVS, Clinical Epidemiology Program, White River Junction VA Medical Center	Yinong Young-Xu, Caroline Korves, Ethan Powell, Gabrielle Zwain, Jeremy Smith
Centers for Disease Control and Prevention	
National Center for Emerging and Infectious Diseases (NCEZID)	Marc Fischer
National Center for Immunization and Respiratory Diseases (NCIRD)	Summer Galloway, Meredith McMorrow, Diya Surie, Jennifer Verani
Food and Drug Administration	
Office of Vaccines Research and Review, Center for Biologics Evaluation and Research	Jeff Roberts, Hector S. Izurieta
Office of the Commissioner	Tamar Lasky, Aloka Chakravarty
Center for Drug Evaluation Research	David Graham

COVID-19 Observational Research Collaboratory

CORC
VA COVID-19 Observational Research Collaboratory

Long-COVID in the VA:
Post Acute Sequelae of COVID-19

George N. Ioannou, BMBCh, MS, FAASLD

Director Hepatology
Veterans Affairs Puget Sound Health Care System
Professor of Medicine
University of Washington
SEATTLE

What is long-COVID or PASC? POST-COVID SYMPTOMS

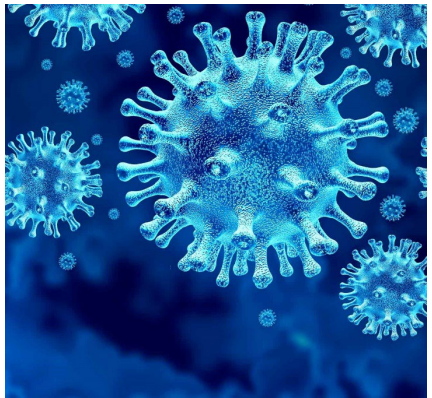
Persistent SYMPTOMS
Fatigue
Shortness breath
Cognitive dysfunction / brain fog
Post-exertional malaise
Memory issues
Muscle pain/spasms
Cough
Sleep disorders
Tachycardia/palpitations
Altered smell/taste
Headache
Chest pain
Joint pain
Depression

World Health Organization

Delphi Consensus

SYMPTOMS:

- At least 3 months after infection
- Symptom duration >2 months
- No alternative explanation
- Impact on functioning

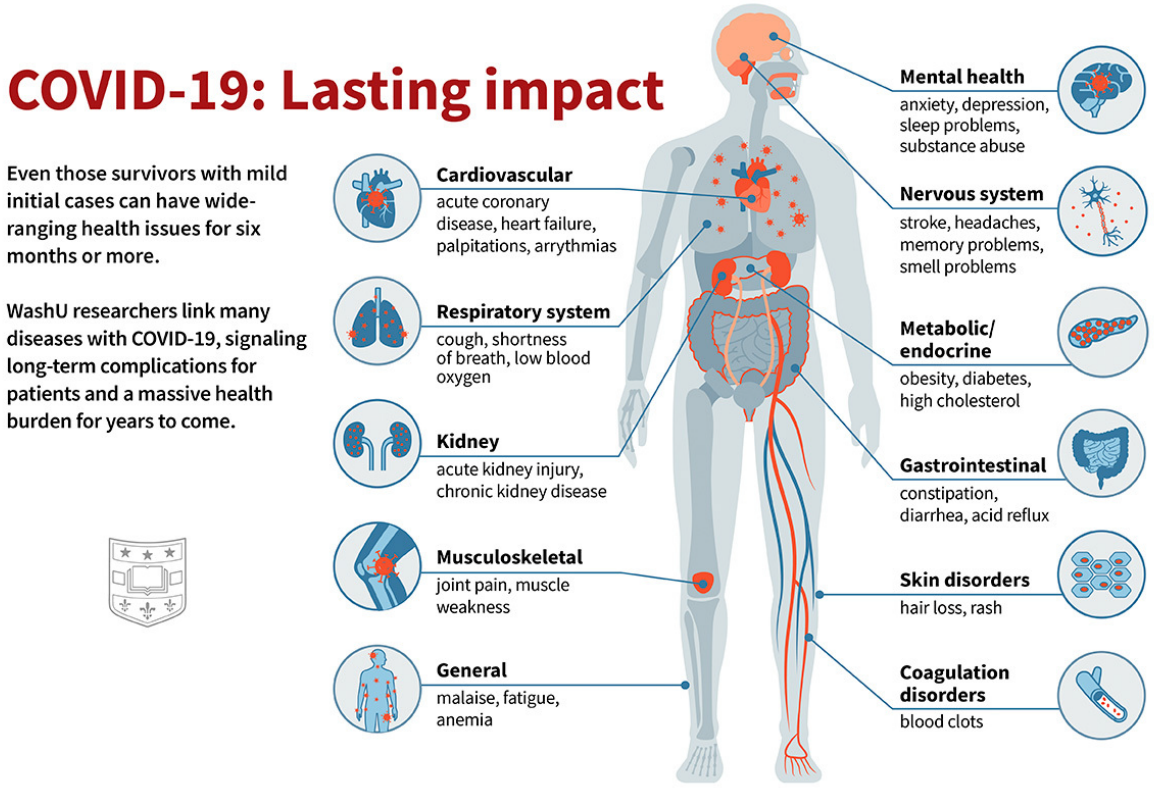


What is long-COVID or PASC? POST-COVID CONDITIONS

CARDIOVASCULAR	Acute MI
	Cardiac Dysrhythmias
	Cardiovascular Disease
	Myocarditis and cardiomyopathy
PULMONARY	Acute pulmonary embolism
	Respiratory symptoms
	Asthma
RENAL	Renal Failure
	Chronic Kidney Disease
COAGULOPATHY & VASCULAR	Thromboembolic event
	Cerebrovascular disease
	Coagulation and hemorrhagic
GI	GI and esophageal

NEUROLOGIC	Neurologic conditions
	Smell and taste disturbances
MENTAL HEALTH	Mood disorders
	Other mental conditions
	Anxiety and fear related
	Sleeping disorders
MUSCOLO-SKELETAL	Malaise and fatigue
	Muscle disorders
	Musculoskeletal pain
ENDOCRINE	Diabetes type 2
	Diabetes type 1

Bull-Otterson MMWR 2022



- SARS-CoV-2 infection ass/d with increased risk of these conditions
- Follow-up to 6 or 12 months

		EHR	
Al-Aly 2021	Nature, BMJ, Nature Comm	Veterans Affairs	Matched Infected vs uninfected cohorts
Al-Aly 2022	Nature Medicine	Veterans Affairs	Matched infection vs breakthrough infection vs no infection
Cohen 2022	BMJ	Medicare Advantage	Matched Infected vs uninfected cohorts
Bull-Otterson 2022	MMWR	Cerner	Matched Infected vs uninfected cohorts

Multi-systemic long-term complications. ETIOLOGY?

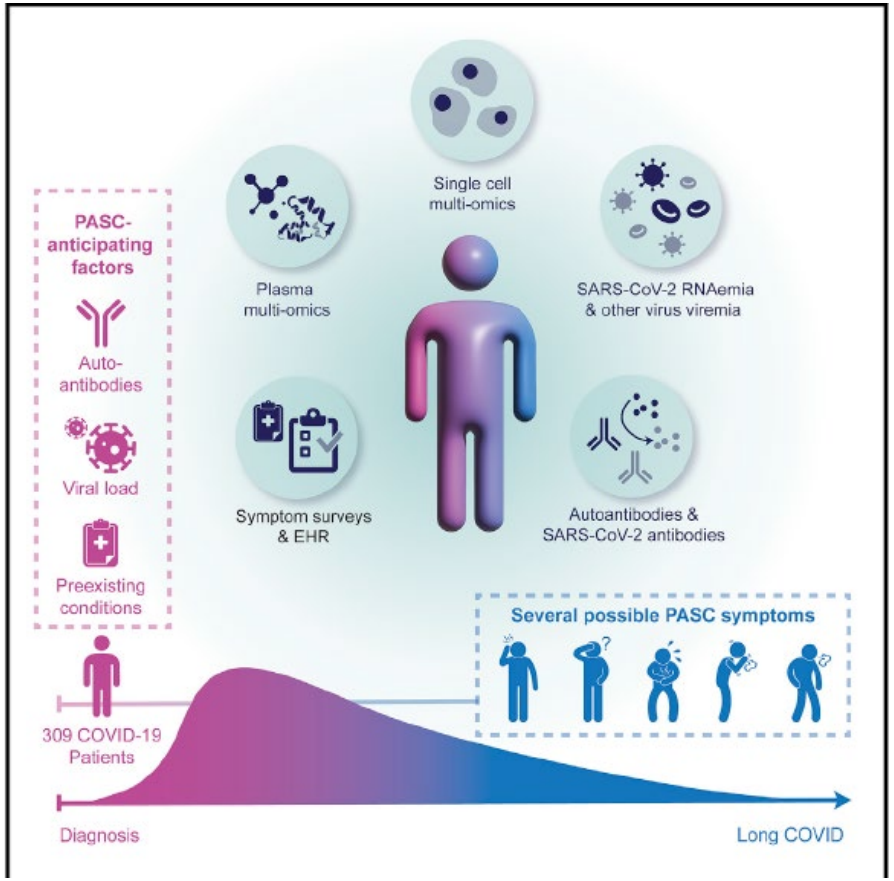
- Tissue invasion via ACE2 receptors (lungs, heart, kidneys, CNS)
- Immunologic activation, “cytokine storm”
- Hypercoagulability
- Post-ICU syndromes
- Post-viral syndromes

Su et al. Cell 2022

❖ Anticipating Factors

- Diabetes
- SARS-CoV-2 viremia
- EBV viremia
- Auto-antibodies

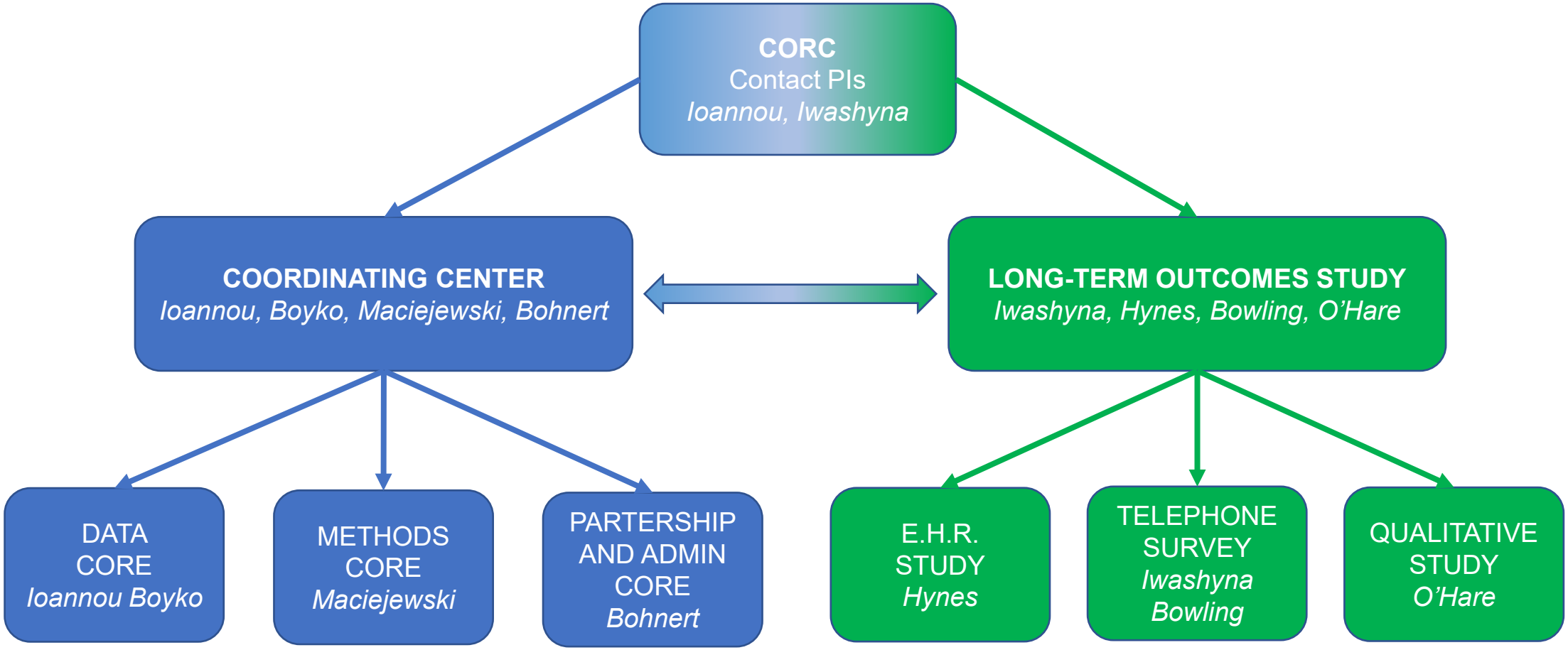
❖ Different immunologic signatures for different PASC phenotypes



COVID-19 Observational Research Collaboratory

What is it?

- VA HSR&D funded research program
- **Overarching Aim**: To support and conduct observational research on the LONG-TERM manifestations of SARS-CoV-2 infection in VA enrollees
- **Duration**: 3 years
- **Funding start date**: May 1, 2021
- **Participating Institutions**:
  - Puget Sound
  - Portland
  - Palo Alto
  - Ann Arbor
  - Durham


CORC
Contact PIs
Ioannou, Iwashyna
COORDINATING CENTER
Ioannou, Boyko, Maciejewski, Bohnert
LONG-TERM OUTCOMES STUDY
Iwashyna, Hynes, Bowling, O'Hare
DATA CORE
Ioannou Boyko
METHODS CORE
Maciejewski
PARTERSHIP AND ADMIN CORE
Bohnert
E.H.R. STUDY
Hynes
TELEPHONE SURVEY
Iwashyna
Bowling
QUALITATIVE STUDY
O'Hare

COVID Observational Research Collaboratory (CORC)

CORC
VA COVID-19 Observational Research Collaboratory

1. **Electronic Health Record (EHR) analysis of Veterans with SARS-CoV-2 infection and matched uninfected comparators**
   - 208,536 Veterans infected between March 2020 and April 2021 and matched uninfected comparators
   - COMPARE: long-term adverse outcomes, healthcare utilization and costs
   - UPDATE: Continually update these matched cohorts
   - SHARE: analytic datasets, analytic code and methods

2. **Structured Telephone Surveys will be administered to 1200 Veterans**
   - Infected patients (n=600) and matched uninfected comparators (n=600) – Initial sampling
   - Up to 36 months after infection or index date
   - Survey domains include: General health, Functional Status, Health-Related Quality of Life, Financial Toxicity, Mental health, Fatigue, Life Space Mobility, Unmet care needs

3. **Qualitative Interviews**
   - 45 semi-structured interviews of Veterans with long-COVID diagnosis
   - Video recorded
   - DIPEx (Directory of Patient Experiences) methodology: identify themes of patient illness, experience and care

4. **Qualitative Chart Extraction-Abstraction**
   - 200 charts of randomly-selected patients with long-COVID ICD-10 codes
   - Electronic-assisted abstraction of all text notes pertaining to COVID-19
   - Inductive content analysis: **1. CLINICAL UNCERTAINTY 2. CARE FRAGMENTATION**

Rates and Predictors of DOCUMENTATION of long-COVID Care

OBJECTIVES

- Determine rates, clinical setting and factors associated with documented receipt of COVID-19 related care ≥3 months after acute infection

DESIGN

- Retrospective Cohort Study based on Veterans Affairs Electronic Health Records

STUDY POPULATION

- Positive SARS-CoV-2 test from 02/01/2020 to 04/30/2021
- Alive 3 months after infection
- No evidence of re-infection
- N=198,601

OUTCOME

- Documentation of COVID-19 related ICD-10 codes ≥3 months after infection(U07.1, Z86.16, U09.9, J12.82)
- Follow-up extending to 12/31/2021 (i.e. 8 months to 22 months, mean 13.5 months)

STATISTICAL ANALYSIS

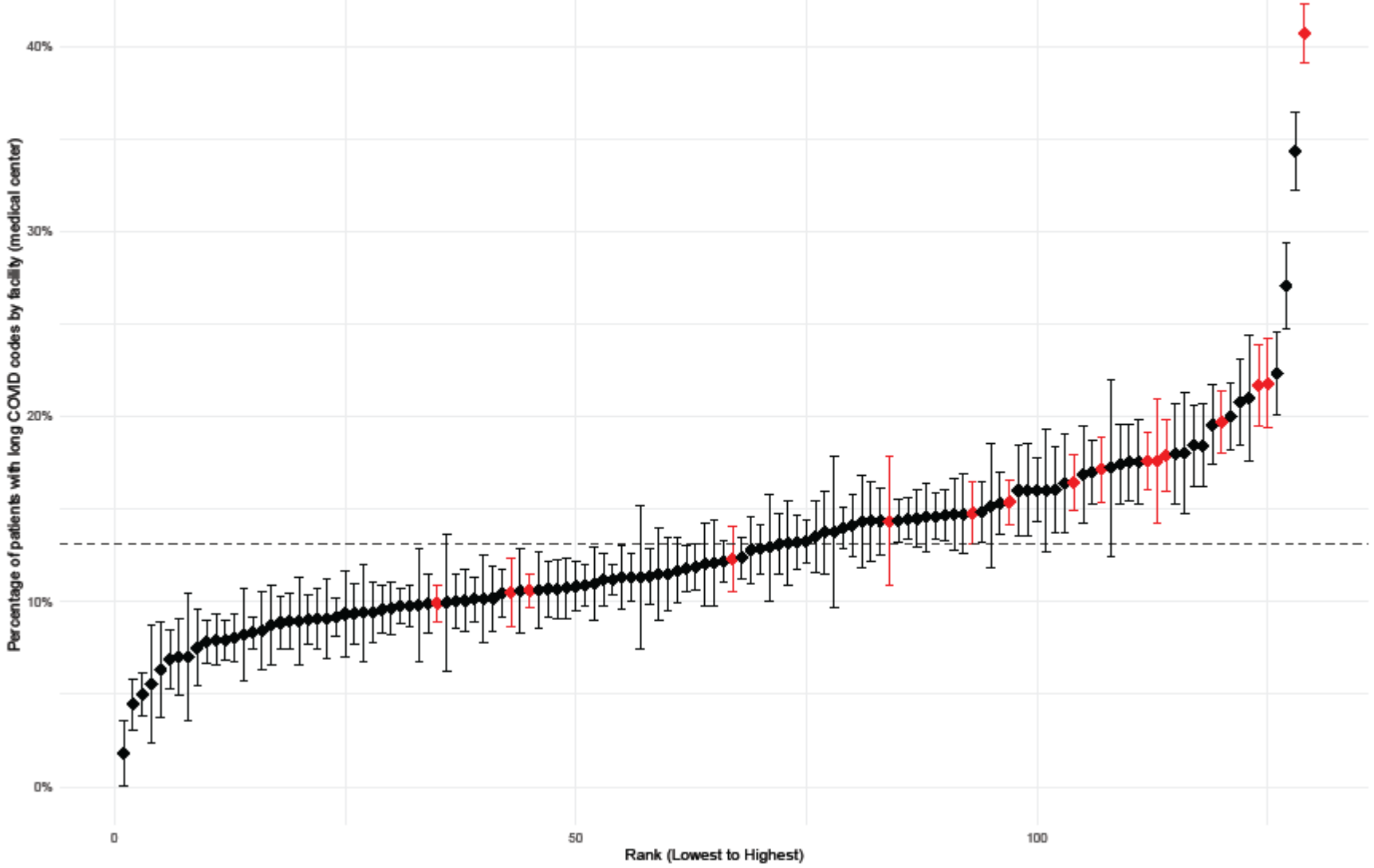
- **Multivariable logistic regression adjusted for** *age, sex, race, ethnicity, urban/rural residence, CCI, VISN, time period of infection,* and number of primary care, mental health and specialty care encounters in the two year prior to infection.

Which Clinics Documented Long COVID care?

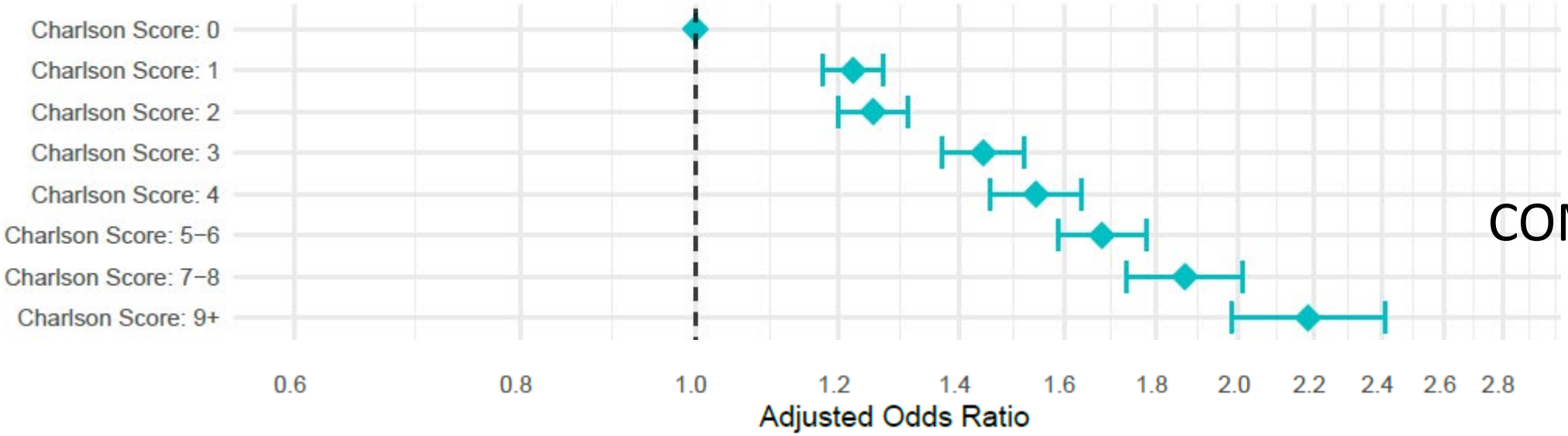
	CLINIC
Primary care/General Internal Medicine	33.1%
Pulmonary	13.1%
Geriatrics	9.7%
Mental Health	3.5%
Physical Therapy	3.2%
Rehabilitation Medicine	2.6%
Cardiology	2.2%
Occupational Therapy	1.5%
Nephrology	0.9%
Neurology	0.8%

High Variability of documented long COVID care across sites

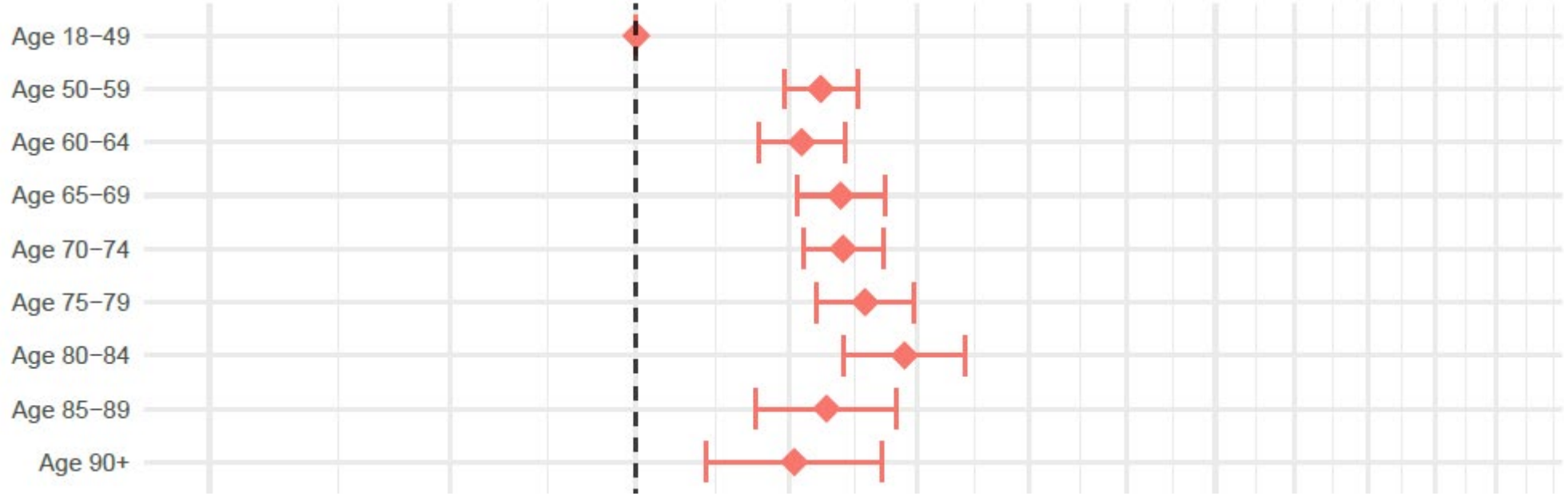
Proportion of Patients with Documented Long COVID care
Overall=13.5%



Factors Associated with Documentation of Long-COVID care

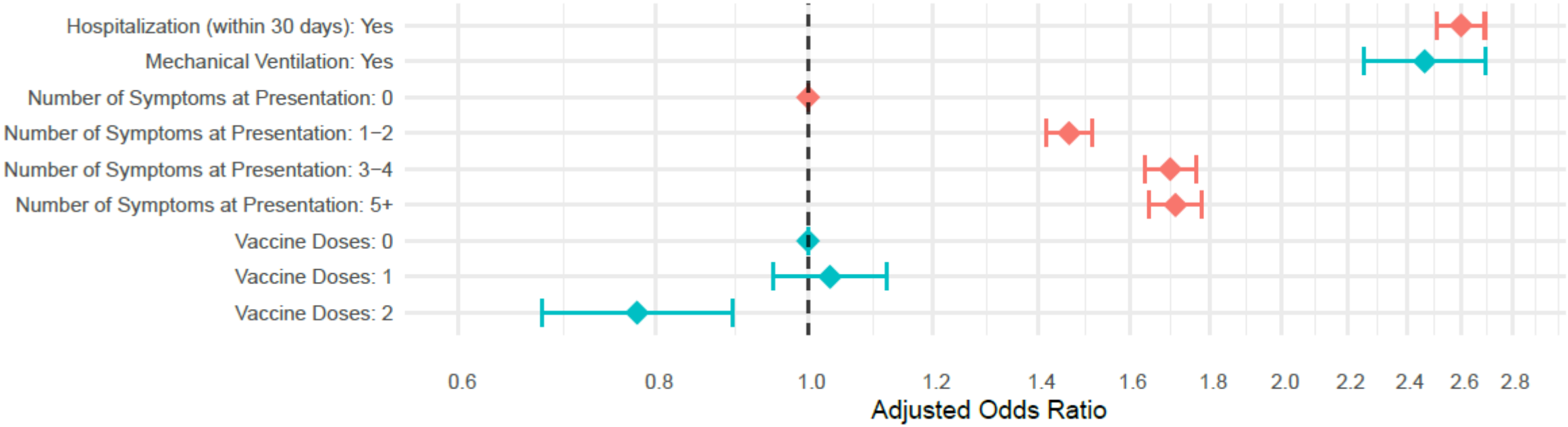


COMORBIDITIES



AGE

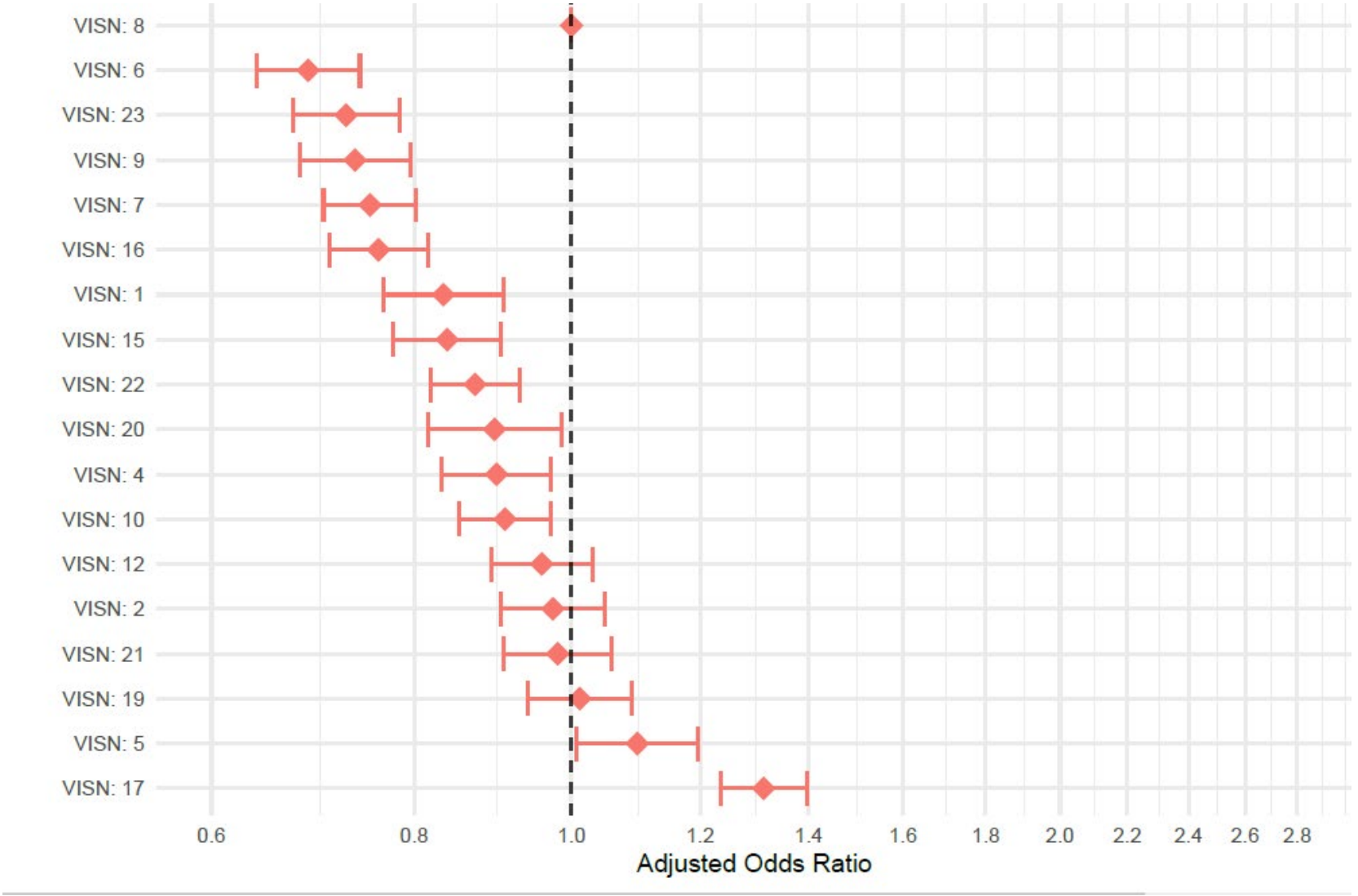
Factors Associated with Documentation of Long-COVID care



- More severe acute presentation → more likely to have documented long-COVID care
- Vaccinated ("breakthrough" infection) → less likely to have documented long-COVID care

Factors Associated with Documentation of Long-COVID care

VA Region: VISN



CONCLUSIONS on “Long COVID”

POST-ACUTE SYMPTOMS

- A proportion of patients experience persistent symptoms for months after infection
- Fatigue, shortness of breath, cognitive dysfunction/brain fog

POST-ACUTE CONDITIONS

Persons with SARS-CoV-2 infection appear to be at increased risk of:

- Pulmonary
- Cardiovascular disease
- Metabolic/Diabetes
- Renal
- Neurologic
- Thromboembolic

POST-ACUTE CARE

- Clinical uncertainty
- Care Fragmentation
- Variability across site
- Variable clinical settings

FUTURE DIRECTIONS & CHALLENGES

- **PREVENTION OF POST-ACUTE SYMPTOMS AND CONDITIONS**
  - VACCINATION?
  - ANTIVIRAL TREATMENTS?

- **TREATMENT OF POST-ACUTE SYMPTOMS**
  - SPECIALIZED LONG-COVID MULTI-DISCIPLINARY CLINICS?
  - REPURPOSING OF EXISTING CLINICS?
  - DIFFERENT FOR DIFFERENT LONG-COVID PHENOTYPES?

- **MONITORING OR TREATMENT OF POST-ACUTE CONDITIONS**
  - HOW LONG DOES THIS INCREASED RISK LAST FOR?

- **WHAT IS A USEFUL DEFINITON OF LONG-COVID?**
  - WHAT IS THE PURPOSE/UTILITY OF A “CLINICAL CASE DEFINITION”?
  - POST-ACUTE SYMPTOMS ONLY?
  - POST-ACUTE SYMPTOMS + CONDITIONS?

Academy Health ARM 2022
COVID in the VA: Researching the effects on health & the health system

Presented by Caroline Korves, ScD on behalf of
The Disrupted Care National Project (DCNP)
June 6, 2022

Acknowledgements

DCNP Principal Investigators

- Louise Davies, White River Junction VA Medical Center
  Amy Justice, West Haven VA Medical Center
- Anita Vashi, Palo Alto VA Medical Center

Executive Committee

- Philip Goodney, White River Junction VA Medical Center
- Caroline Korves, White River Junction VA Medical Center
- Brian Lucas , White River Junction VA Medical Center
- Christopher Rentsch, West Haven VA Medical Center
- Liam Rose, Palo Alto VA Medical Center
- Daniel Weinberger, West Haven VA Medical Center

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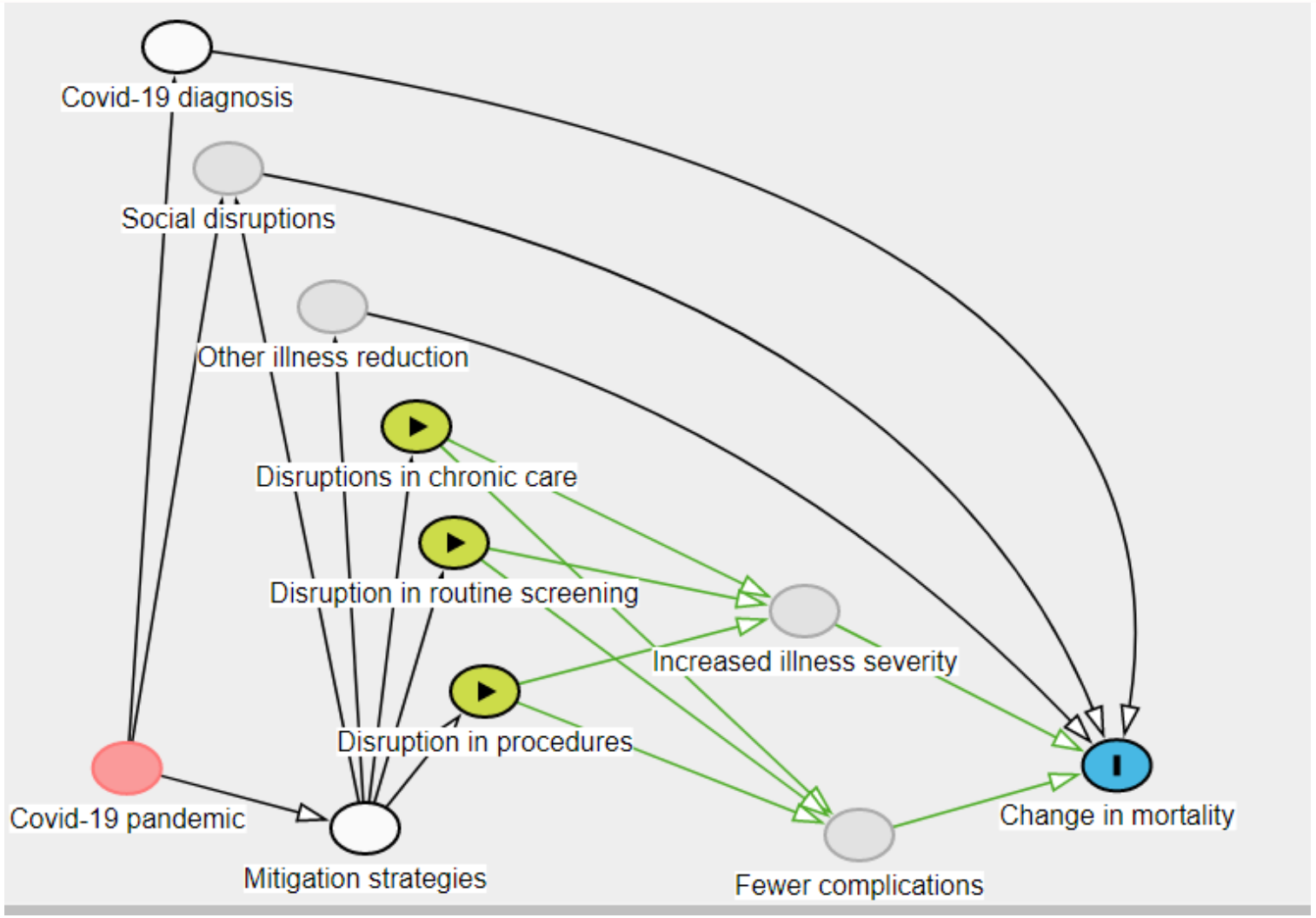
- Yinong Young-Xu, Nabin Nepuane, and Jeremy Smith

DCNP Conceptual Framework



Study Aims

1. How much did all-cause mortality increase in 2020 in the VA population compared to the general US population?

2. How was the management of sentinel conditions disrupted during the pandemic?

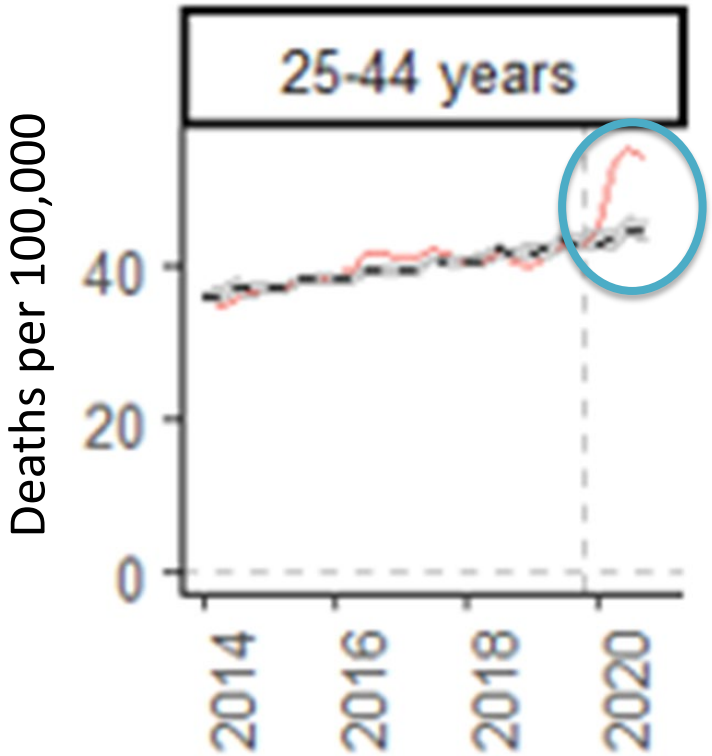
Specific sentinel conditions include:

a) HIV

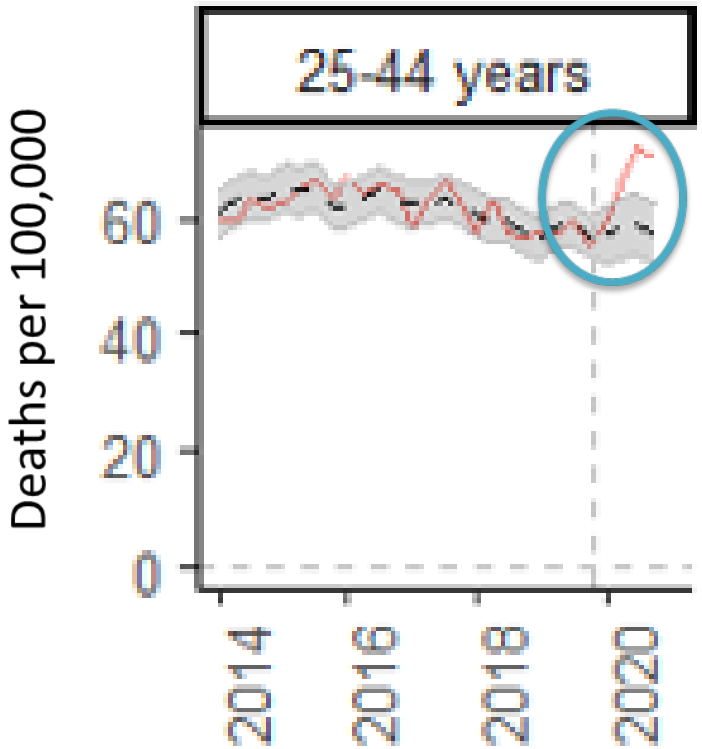
b) Hypertension

Observed vs expected mortality US population vs VA enrollees

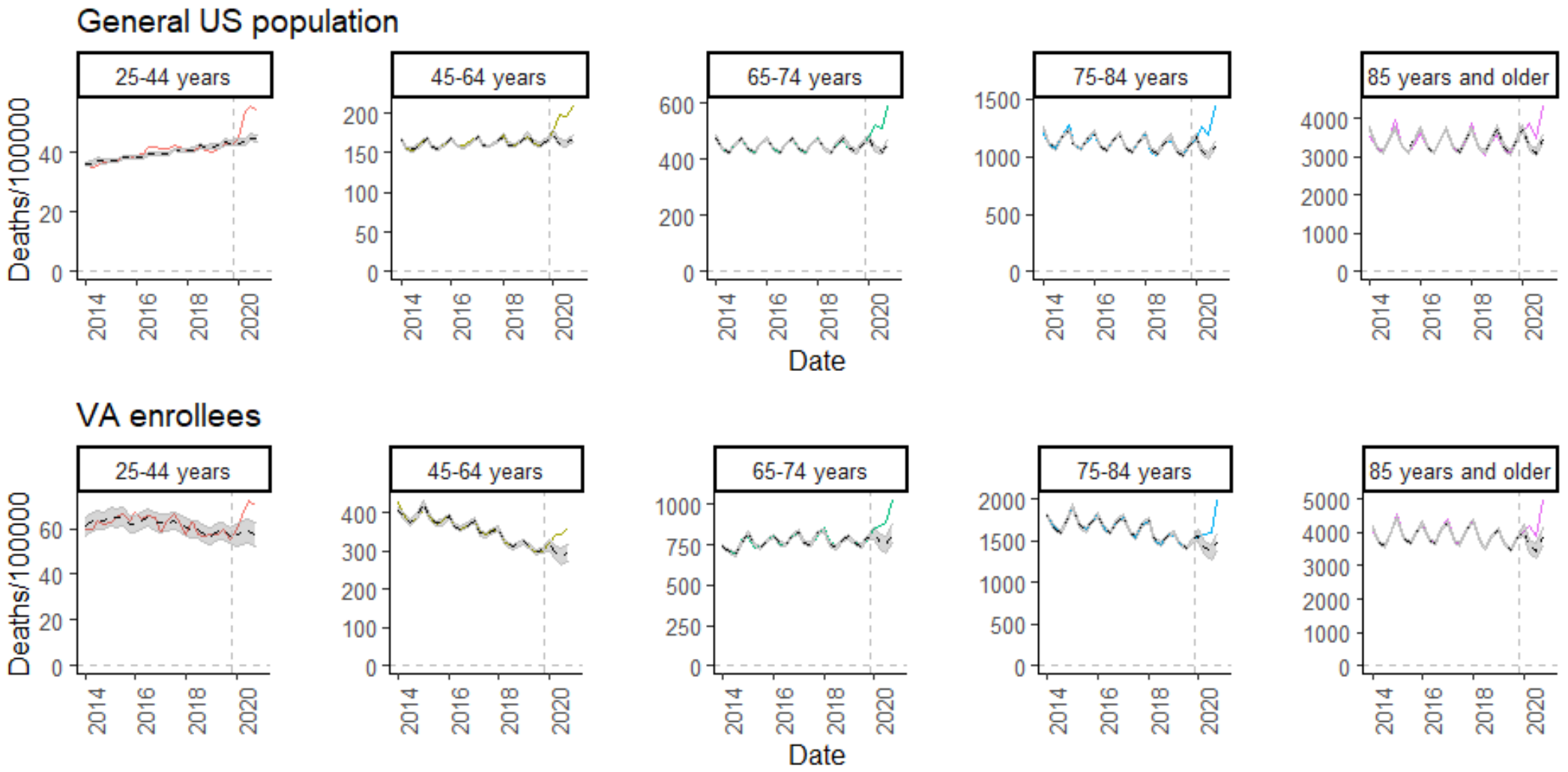
US population



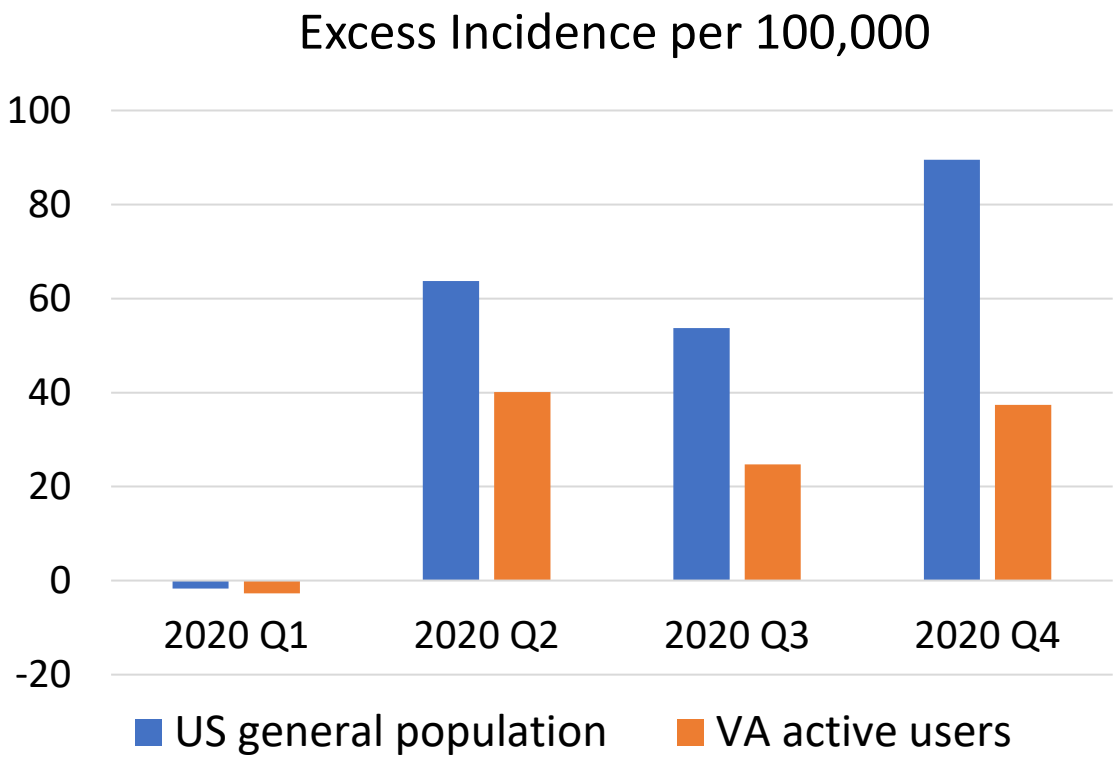
VA enrollees



AIM 1. Observed vs expected mortality in US population compared to VA enrollees



AIM 1. Population-standardized excess mortality and relative change



Rate Ratio

	2020 Q1	2020 Q2	2020 Q3	2020 Q4
US general population	1.02	1.22	1.21	1.25
VA active users	1.00	1.10	1.13	1.19

AIM 2. Assessing Quality of Care Metrics for Sentinel Conditions: Analysis Framework

Study Population

- Persons with sentinel condition (e.g., HIV, hypertension) active in VA
- Survived pandemic and never diagnosed with COVID 19

Analysis

- Descriptive statistics for pre-pandemic and pandemic periods
  - Virtual vs face to face visits
  - Adherence measures
  - Proportion tested
  - Proportion of those tested meeting relevant quality metrics for viral suppression (HIV), blood pressure (HTN)

AIM 2a. Assessing Quality of Care Metrics for Persons with HIV

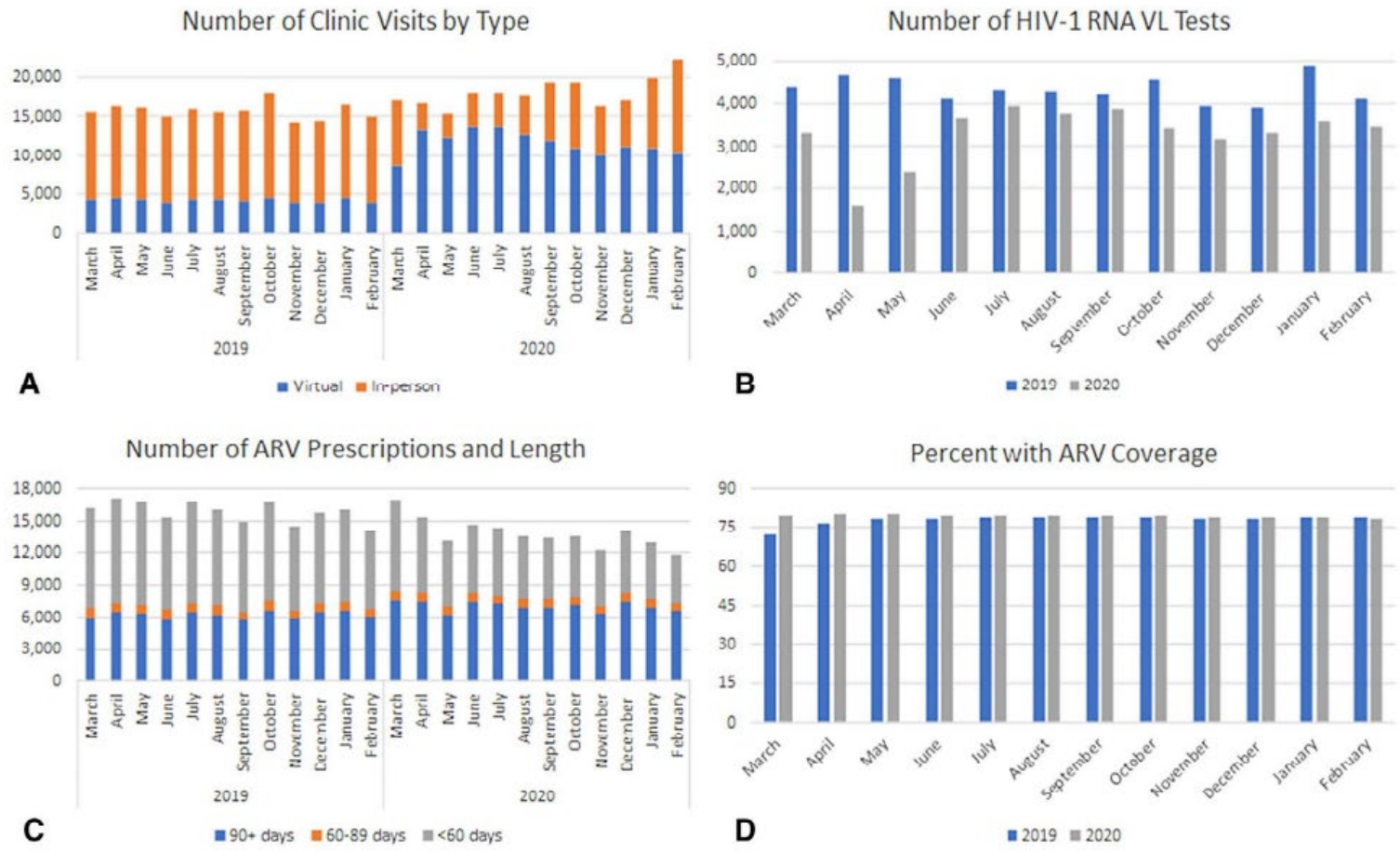


Figure 1. Healthcare services among 27,674 PWH in 2019 and 2020
ARV, antiretroviral therapy; VL, viral load; 2019, 1 March 2019 to 28 February 2020; 2020, 1 March 2020 to 29 February 2021.

McGinnis KA, et al. 2021 JIAS

AIM 2b. Assessing Quality of Care Metrics for Individuals with Hypertension: Methods

Study period: March 2019- February 2022

Study population:

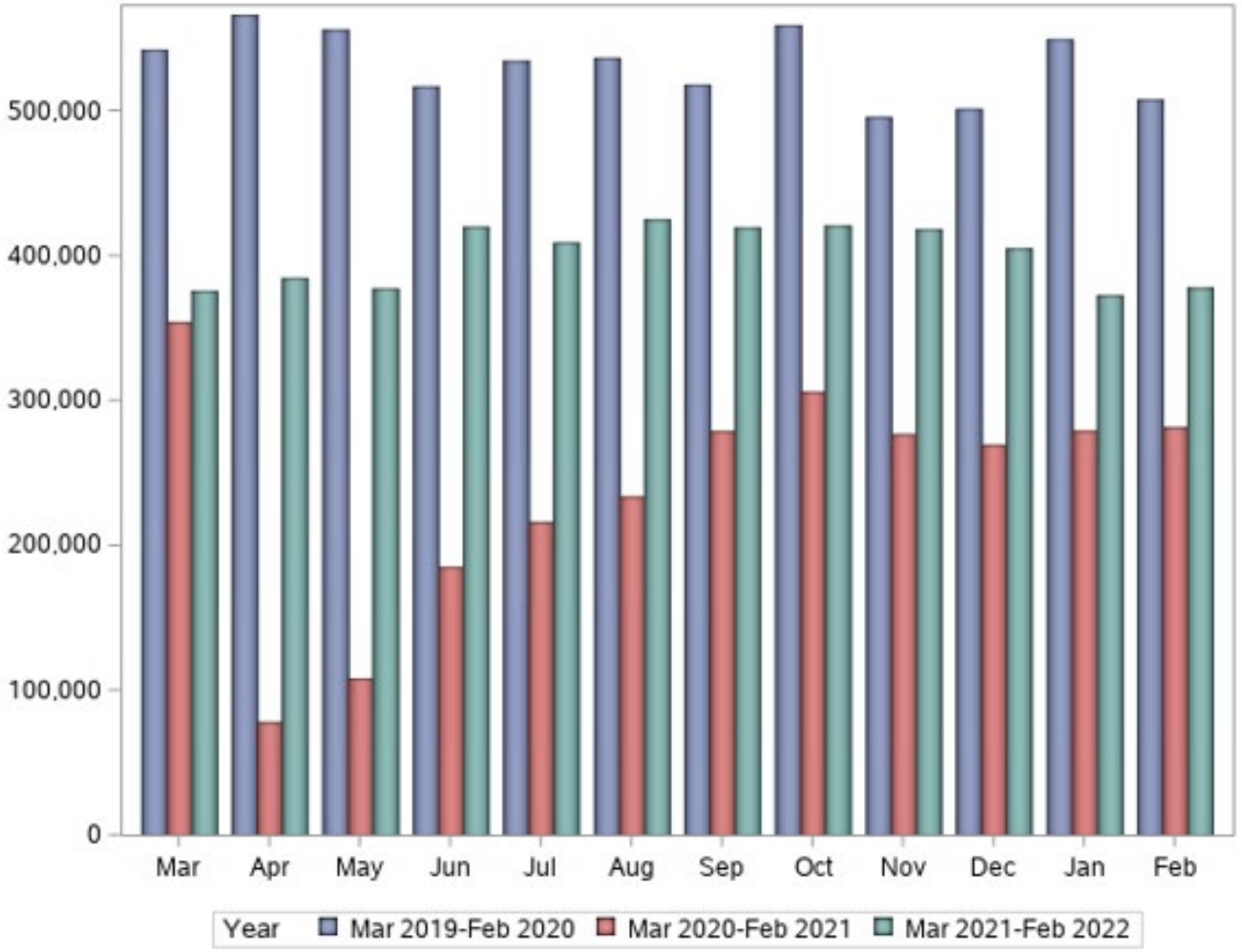
- Adults, ≥1 HTN diagnosis in inpatient or outpatient setting in the 2-year period prior to study period, and
- Outpatient treatment for HTN in the 1-year period prior to study period, and
- Survived pandemic and never diagnosed with COVID 19

Outcomes and Analysis

Descriptive statistics for pre-pandemic and pandemic period:

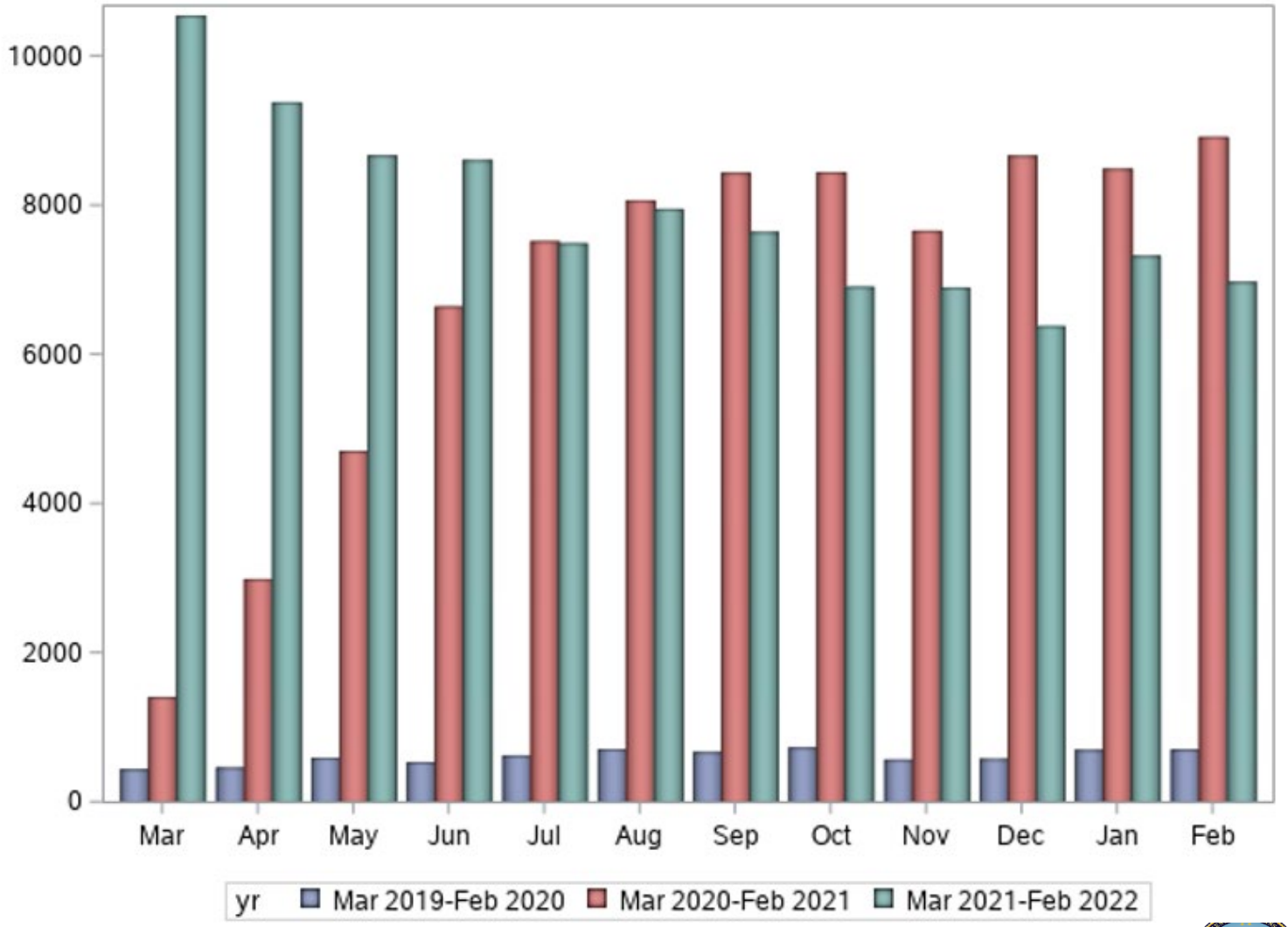
- Number of blood pressure readings from non-acute settings
- Number of virtual visits with blood pressure readings

Aim 2b. Assessing Quality of Care Metrics for Individuals with Hypertension: Number of blood pressure readings in non-acute settings



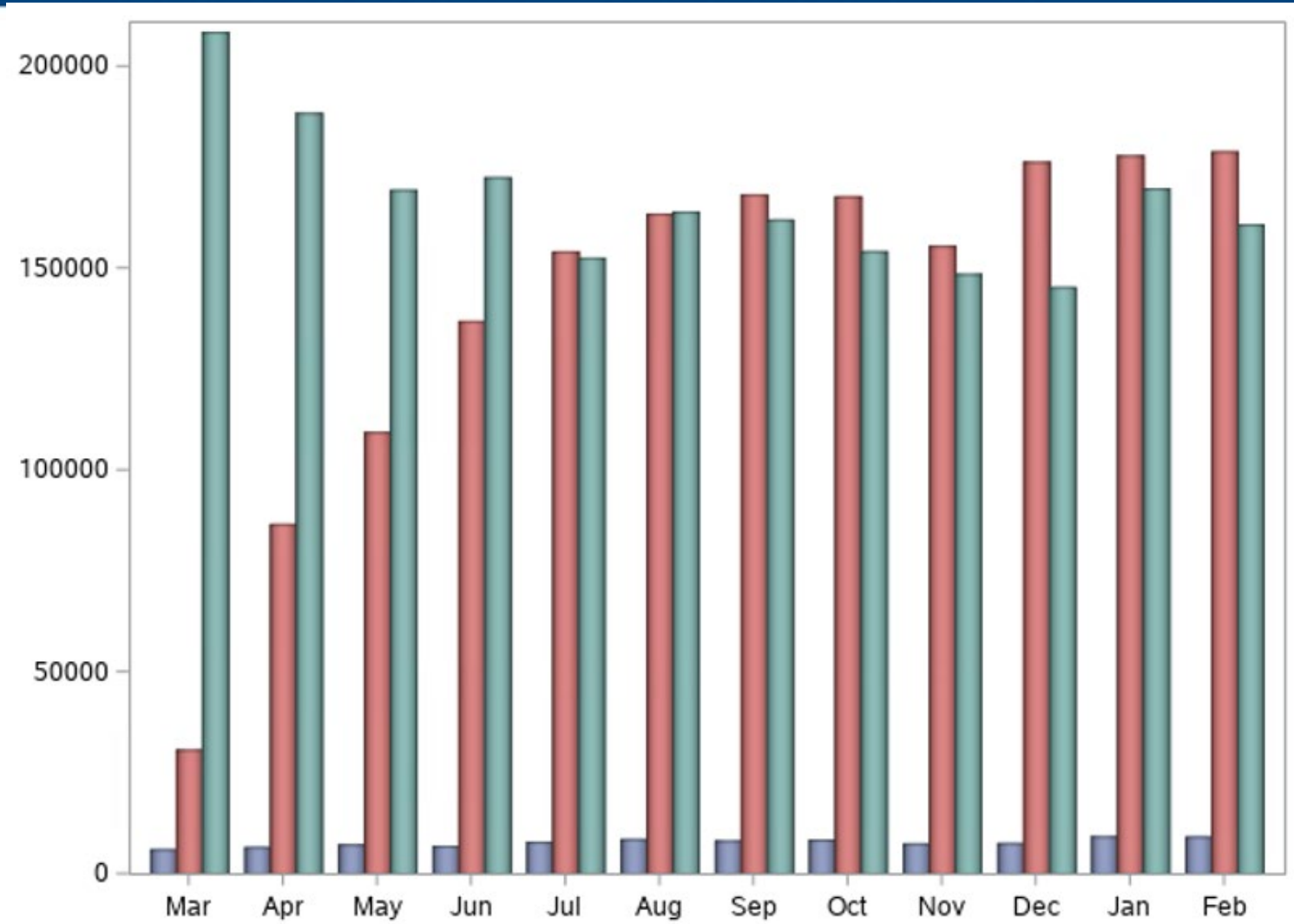
Study population
N=1,672,073

Aim 2b. Assessing Quality of Care Metrics for Individuals with Hypertension: Number of video visits with blood pressure reading



Study population
N=1,672,073

Aim 2b. Assessing Quality of Care Metrics for Individuals with Hypertension: Number of video visits



Study population
N=1,672,073

AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: Methods

Study period: March 2019- February 2022

Study population:

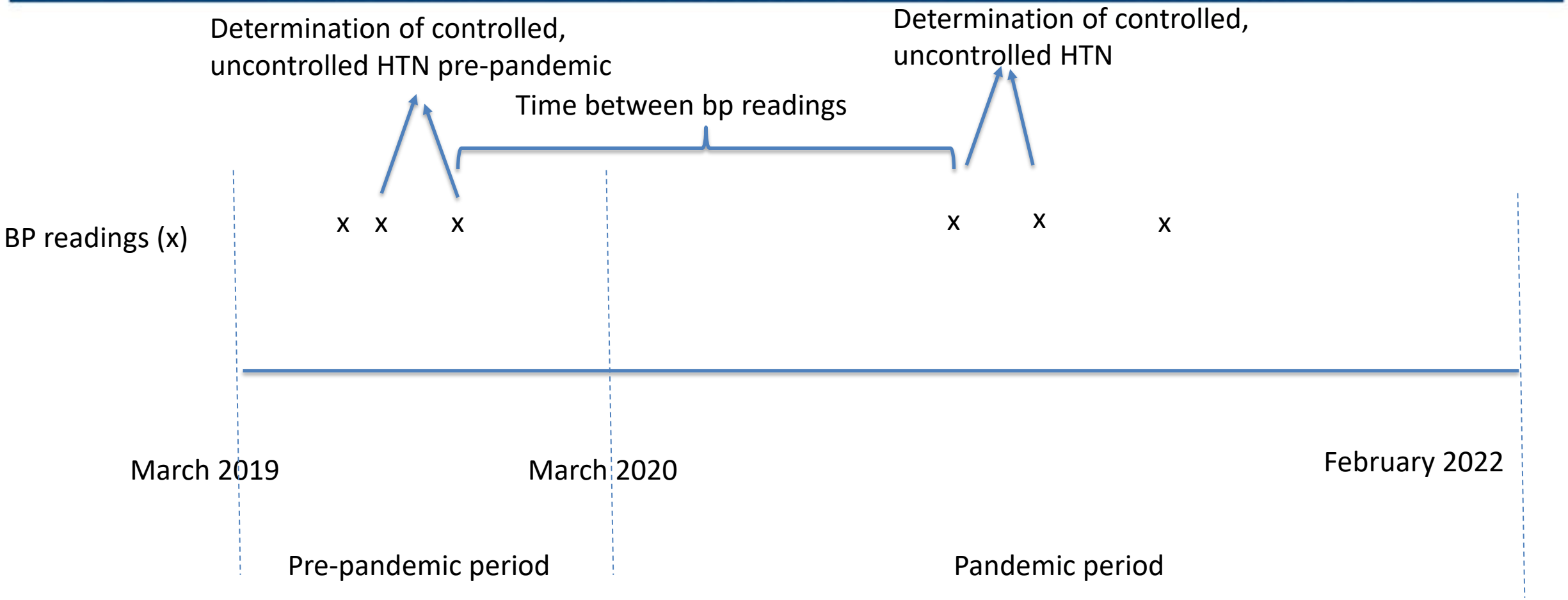
- Adult with ≥1 HTN diagnosis, and
- Outpatient treatment for HTN, and
- ≥2 blood pressure readings pre-pandemic and in the pandemic period, and
- Excluded individuals pregnant, resident in nursing home, or with SARS-CoV-2 during the study period

Outcomes: Controlled HTN, uncontrolled HTN, based on first two blood pressure readings during the pandemic

Exposure: Time between last pre-pandemic and first pandemic blood pressure reading

Analysis: Adjusted logistic regression

AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: Study design



AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: Time between last pre-pandemic period and first pandemic period blood pressure readings

		Time between blood pressure readings (days) [median (IQR)]
Pre-pandemic period HTN classification	Controlled HTN N=184,325	190 (78, 348)
	Uncontrolled HTN N=644,976	201 (91, 354)

AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: HTN classification for pre-pandemic and pandemic periods

		Pandemic period		
		Controlled	Uncontrolled	Indeterminate
Pre-pandemic period	Controlled N=184,325	63,581 (34%)	50,627 (27%)	70,117 (38%)
	Uncontrolled N=644,976	37,158 (6%)	450,122 (70%)	157,696 (24%)

AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: Blood pressure control and time between blood pressure readings

Association between development of uncontrolled HTN and time between readings among individuals with controlled HTN pre-pandemic		
	Unadjusted OR (95%CI)	Adjusted OR (95%CI)*
≥6 months vs. <6 months between last pre-pandemic bp reading and first pandemic bp reading	1.52 (1.49, 1.56)	1.38 (1.35, 1.42)

*Adjustment for age, sex, black race, Hispanic ethnicity, rurality, VA priority level, CVD, CHF, diabetes, cancer, overweight/obesity, current/former smoking.

AIM 2. Management of Sentinel Conditions: Next steps

- Apply the current framework for evaluating management of sentinel conditions during the pandemic to other conditions
  - » Lung cancer screening for smokers
  - » Procedural care

DCNP's Role in Coordinating the VA's Disrupted Care Research Agenda

- Accelerate progress through collaboration and engagement
- Create a community of research to advance the science and promote comparability of work
- Develop forums for the curation of data and methodologies

Filling In the Picture on “ Long COVID”
VA’s Portfolio of Research

David Atkins, MD, MPH
Director, Health Services Research

Why Are the Data on Long COVID So Variable?

- Varying case definition for long COVID – WHO, CDC
- Differing populations with long term effects of COVID
  - Patients with lasting effects of damage from acute COVID
    - Irreversible damage to lungs, heart, kidneys
    - Prolonged but reversible effects of severe illness
  - Patients with persisting unexplained symptoms suggestive of ongoing process
  - Patients with increased risk of new disorders post acute phase (DM,
- Studies relying on EHR diagnoses may suffer from both *over- and under-detection*
  - Many persistent symptoms may not be recorded
  - New ICD codes may not be indicative of long COVID

Draft Recommendations of the National Research Action Plan on Long COVID

- White House executive order established an ICC chaired by Sec HHS, involving members of other cabinet agencies.
- A Research WG was tasked with developing a National Research Action Plan.
  - Co-Chaired by Debra Porterfield (ASPE) and Ziyad Al-Aly.
- Selected major recommendations relevant to VA:
  - Develop consensus on surveillance **definition for long COVID**
  - Rapid implementation models for **clinical trials**
  - National Long COVID **Real World Evidence Center**
  - Standardize an approach in all **Long COVID cohort research**
  - Ensure that the **Long COVID Centers of Excellence** become a gold-standard patient-engaged care delivery research network
  - Expand **voice of the patient** in Long COVID research

Elements of VA Long COVID Research Strategy

- **COVID Outcomes Research Collaboratory (CORC) – Track and coordinate other activities**
- *Al-Aly Studies – EHR to examine long terms outcomes of cases vs. controls*
- *CORC Long Term Outcomes Study – Population-based controlled study using VA EHR records, Medicare, sample surveys, semi-structured interviews and chart review*
- CSP 2028 – Longitudinal follow- up of new cases over 24 months with EHR, survey and blood samples (Partnership on protocol with DOD study of active duty mil)
- Long COVID Collaborative Programs – projects linking basic, clinical, rehab and health services research around specific problems (in review)
- Long COVID Integrated Project Team – clinical initiative to ensure care throughout VA
- Long COVID Clinic Practice Based Research Network – network of all VA long COVID clinics to standardize data and examine outcomes (in planning)

Cooperative Study #2028: Epidemiology, Immunology and Clinical Characteristics of COVID-19 (EPIC^3) within the Veterans Health Administration

- **Study goals:** Among inpatient and outpatient Veterans with and without SARS-CoV-2 infection and/or COVID-19 disease,
  - Identify patterns of SARS-CoV-2 viral shedding;
  - characterize development of immunity;
  - determine predictors of infection and disease course, severity and related death
- **Study design:** Longitudinal follow-up of Veterans receiving health care from the VHA, involving collection of survey questionnaires; information from the electronic health record; and blood, respiratory, and stool specimens at 9-11 study visits over a 24-month period
- **Core biomarker assays:** RT-PCR and viral sequencing of respiratory specimens, serologic assays for SARS-CoV-2 antibodies, cytokine/chemokine/growth factors panels, RNA sequencing, and cellular immunity assays.
- **Current progress:** Enrollment and the conduct of core laboratory assays continue. As of May 12, 2022, 2331 enrolled – 630 inpatients, 1526 outpatients, and 175 community living center residents.

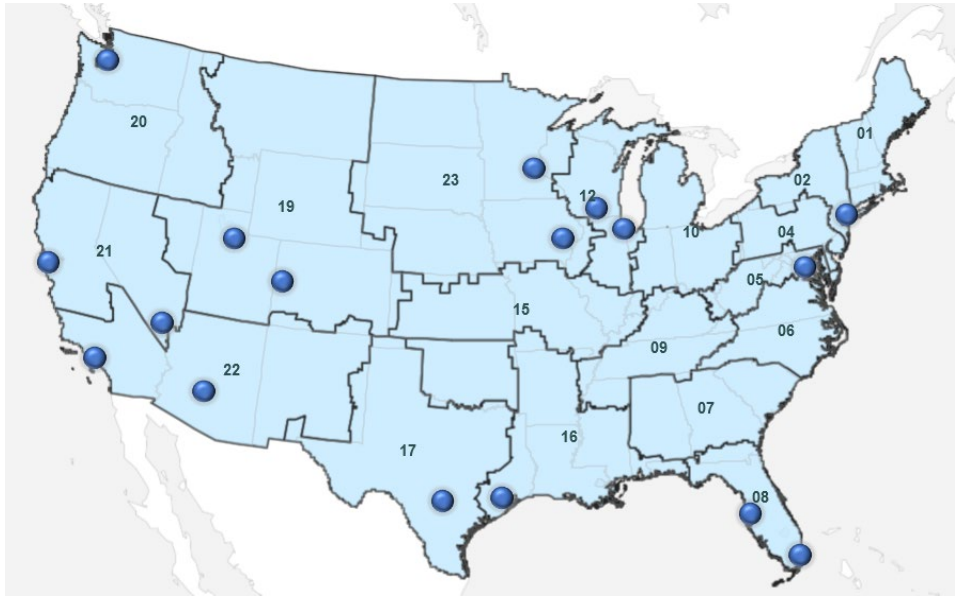
Post COVID Conditions Collaborative Merit

- Cross-Service RFA
- The aim of this RFA is to support pre-planned collaboration across multiple investigators in all 4 research services and allowing investigators with different expertise to examine different aspects of a single, high-priority problems: cognitive problems, cardiac, renal, pulmonary sx.
- Composition of three I01's.
- Current Status: 22 proposals in 7 programs have been sent out to reviewers and reviewer panel meeting is June 27 & 28th.

1. GBD Long COVID Collaborators. Surviving COVID-19: a global systematic analysis of long COVID disability in 2020

Environmental Scan Findings

17 Established Long COVID Programs



South Texas began enrolling patients into their Long COVID Care program in March 2020, several months before any other facility.

25 facilities are considering establishing a program

Growing to >2X the number of Long COVID programs	In areas with few Long COVID programs	**22** describe care pathways in place

Long COVID Practice Based Research Network (PBRN)

- AIM: Generate more rapid insights into the care and outcomes of patients presenting in VA with symptoms of Long COVID.
- Solicitation to be released by end of month
- Will involve all willing sites with Long COVID clinics
- Partnership of researchers and clinical leads to:
  - Collect uniform set of critical data on long COVID symptoms
  - Facilitate analyses of aggregated data
  - Generate new clinical questions from front-line providers
  - Conduct rapid analyses and targeted pilot studies
  - Involve voice of patients in research
- Will serve as platform for recruiting patients into treatment trials

EXTRA

Long COVID IPT

- Purpose
  - Organize, support, and report the progress in establishing clinical guidance and a system in which Long COVID care, support, and services are accessible to all Veterans across VA no matter where they live. Develop an enterprise-wide LONG COVID Learning Healthcare System

- Led by CORE Team

- Data & Metrics Workstream
  - Pull together Long COVID data definitions and sources
  - Determine Gaps and challenges in data collection
  - Help develop tools for capturing data, reporting, etc. with other workstreams