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

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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

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

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

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 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.
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

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

Biorpository network
- Specimen collection
- Standard data elements

VISNs/ Clinical operations
Pharmacy Benefits Management
National Ctr for Health Promotion & Disease Prevention
Ofc of Information Technology
VHA Information & Analytics Ofc

Pathology & Lab Medicine
Public Health Reference Laboratory
<table>
<thead>
<tr>
<th>Lab Confirmed SARS-CoV-2 Infection</th>
<th>VE, % (95% CI)</th>
<th>VE, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>97 (95 to 97)</td>
<td>95 (93 to 96)</td>
<td>75 (71-78)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory Confirmed SARS-CoV-2 Infection</th>
<th>VE, % (95% CI)</th>
<th>VE, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Vaccination</td>
<td></td>
<td>Partial Vaccination</td>
</tr>
<tr>
<td>From 7 d after dose 2</td>
<td>94 (92-95)</td>
<td>From 14 d after dose 2</td>
</tr>
<tr>
<td>From 14 d after dose 2</td>
<td>95 (93-96)</td>
<td>58 (54-62)</td>
</tr>
<tr>
<td>7 d after dose 1 until dose 2</td>
<td>63 (57 to 69)</td>
<td>64 (59-68)</td>
</tr>
<tr>
<td>14 d after dose 1 until dose 2</td>
<td>89 (80-94)</td>
<td>91 (83-95)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>41 (24-54)</td>
<td>48 (32-60)</td>
</tr>
<tr>
<td>Death</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>47 (3-71)</td>
<td>63 (24-81)</td>
<td></td>
</tr>
</tbody>
</table>

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.

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>
<thead>
<tr>
<th>Month</th>
<th>Adjusted vaccine effectiveness by month from full vaccination, % (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Delta (January to April)</td>
</tr>
<tr>
<td>1</td>
<td>94.5 (90.7-96.7)</td>
</tr>
<tr>
<td>2</td>
<td>88.5 (86.1-90.5)</td>
</tr>
<tr>
<td>3</td>
<td>87.9 (85.9-89.5)</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>NA</td>
</tr>
</tbody>
</table>

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\(^b\) for definitions of these variables.

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


<table>
<thead>
<tr>
<th></th>
<th>LABORATORY CONFIRMED SARS-COV-2 INFECTION</th>
<th>VE INTERVAL (14+ DAYS AFTER VACCINATION)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMICRON</td>
<td>2nd dose</td>
<td>12% (10, 15)</td>
<td></td>
</tr>
<tr>
<td>OMICRON</td>
<td>3rd dose</td>
<td>64% (63, 65)</td>
<td></td>
</tr>
<tr>
<td>DELTA</td>
<td>2nd dose</td>
<td>54% (50, 57)</td>
<td></td>
</tr>
<tr>
<td>DELTA</td>
<td>3rd dose</td>
<td>90% (88, 92)</td>
<td></td>
</tr>
</tbody>
</table>

|                  | 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

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Time period</th>
<th>VE, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mRNA(^1) Among US Veterans</td>
<td>15,110</td>
<td>12/2020 - 03/2021</td>
<td>95 (93-96)</td>
</tr>
<tr>
<td>BNT162b2 Clinical trial(^2)</td>
<td>18,198</td>
<td>07/2020-11/2020</td>
<td>95 (90.0-97.9)</td>
</tr>
<tr>
<td>mRNA-1273 Clinical trial(^3)</td>
<td>14,134</td>
<td>10/2020</td>
<td>94.1 (89.3-96.8)</td>
</tr>
</tbody>
</table>

Dickerman et al, Event Rates\(^4\)  
Young-Xu, et al Vaccine Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Dickerman et al, Event Rates(^4)</th>
<th>Young-Xu, et al Vaccine Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2</td>
<td>5.75 (95% CI, 5.39-6.23)</td>
<td>94% (90-98%)</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>4.52 (95% CI, 4.17-4.84)</td>
<td>96% (93-99%)</td>
</tr>
</tbody>
</table>


### Study Population Characteristics

<table>
<thead>
<tr>
<th>Age range (y)</th>
<th>Young-Xu et al Test Negative Case Control</th>
<th>Dickerman et al Emulated Target Trial</th>
<th>mRNA-1273 Clinical Trial</th>
<th>BNT162b2 Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enrollees, No.</td>
<td>Vaccinated enrollees, No. (%)</td>
<td>BNT162b2 Recipients (%)</td>
<td>mRNA-1273 Recipients (%)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>6,647,733</td>
<td>1,363,180 (21)</td>
<td>219,842</td>
<td>219,842</td>
</tr>
<tr>
<td>&lt;60</td>
<td>3,297,360</td>
<td>280,763 (20)</td>
<td>213,19 (24)</td>
<td>213,19 (24)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>3,350,373</td>
<td>1,082,417 (79)</td>
<td>167,468 (76)</td>
<td>167,468 (76)</td>
</tr>
<tr>
<td>&gt;80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>473,266</td>
<td>149,041 (11)</td>
<td>22,753 (10)</td>
<td>22,753 (10)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>632,935</td>
<td>74,795 (12)</td>
<td>16,116 (7)</td>
<td>16,116 (7)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1,102,471</td>
<td>234,363 (21)</td>
<td>44,967 (21)</td>
<td>44,967 (21)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>461,645</td>
<td>81,480 (18)</td>
<td>14,939 (7)</td>
<td>20,493 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>381,648</td>
<td>70,080 (18)</td>
<td>4,380 (2)</td>
<td>4,380 (2)</td>
</tr>
<tr>
<td>Missing</td>
<td>340,348</td>
<td>36,566 (11)</td>
<td>6,736 (3)</td>
<td>6,736 (3)</td>
</tr>
</tbody>
</table>

### Comorbidities & Risk factors

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>mRNA-1273 Clinical Trial</th>
<th>BNT162b2 Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese</td>
<td>101,740 (46)</td>
<td>102,280 (47)</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>684,318 *</td>
<td>255,404 (19)</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>111,379</td>
<td>44,097 (3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>953,054</td>
<td>347,594 (37)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>35,163</td>
<td>100,280 (3)</td>
</tr>
<tr>
<td>HIV</td>
<td>19,279</td>
<td>6703 (35)</td>
</tr>
<tr>
<td>Cancer</td>
<td>186,911</td>
<td>85,194 (46)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,453,671</td>
<td>517,021 (36)</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>212,003</td>
<td>93,517 (44)</td>
</tr>
</tbody>
</table>

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

mRNA Vaccine Efficacy
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

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

| Number of Eligible Patients               | 192,842    | 191,975     | 191,227     | 189,355    | 187,517     | 186,020  |

Legend: 21A (Delta), 21J (Delta), 21K (Omicron), 21L (Omicron)
Rate of COVID-19 Infection and Hospitalization by Prophylaxis First 4 Months of 2022

- T/C+Vaccine: 0.85%
- T/C: 1.35%
- Vaccine: 2.84%
- Neither: 3.73%
Cumulative risk of composite COVID-19 outcomes for tixagevimab-cilgavimab recipients compared to untreated controls
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
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.
<table>
<thead>
<tr>
<th>Department of Veterans Affairs</th>
<th>Collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office of Research and Development</td>
<td>Rachel Ramoni, David Atkins, Jane Battles, Vicky Davey, Maciej Gonek, Grant Huang, Saiju Pyarajan, Wendy Tenhula, Sarah Wonders, Amanda Garcia</td>
</tr>
<tr>
<td>National Pathology and Laboratory Medicine Program Office</td>
<td>Jessica Wang-Rodriguez</td>
</tr>
<tr>
<td>Office of Public Health Surveillance</td>
<td>Mark Holodniy</td>
</tr>
<tr>
<td>Office of Patient Care Services/Public Health</td>
<td>Larry Mole</td>
</tr>
<tr>
<td>VA Informatics and Computing Infrastructure (VINCI)</td>
<td>Scott DuVall</td>
</tr>
<tr>
<td>CVS, Clinical Epidemiology Program, White River Junction VA Medical Center</td>
<td>Yinong Young-Xu, Caroline Korves, Ethan Powell, Gabrielle Zwain, Jeremy Smith</td>
</tr>
<tr>
<td>Centers for Disease Control and Prevention</td>
<td></td>
</tr>
<tr>
<td>National Center for Emerging and Infectious Diseases (NCEZID)</td>
<td>Marc Fischer</td>
</tr>
<tr>
<td>National Center for Immunization and Respiratory Diseases (NCIRD)</td>
<td>Summer Galloway, Meredith McMorrow, Diya Surie, Jennifer Verani</td>
</tr>
<tr>
<td>Food and Drug Administration</td>
<td></td>
</tr>
<tr>
<td>Office of Vaccines Research and Review, Center for Biologics Evaluation and Research</td>
<td>Jeff Roberts, Hector S. Izurieta</td>
</tr>
<tr>
<td>Office of the Commissioner</td>
<td>Tamar Lasky, Aloka Chakravarty</td>
</tr>
<tr>
<td>Center for Drug Evaluation Research</td>
<td>David Graham</td>
</tr>
</tbody>
</table>
Long-COVID in the VA:
Post Acute Sequelae of COVID-19

George N. Ioannou, BMBCh, MS, FAA SDL

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**

<table>
<thead>
<tr>
<th>Persistent SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Shortness breath</td>
</tr>
<tr>
<td>Cognitive dysfunction / brain fog</td>
</tr>
<tr>
<td>Post-exertional malaise</td>
</tr>
<tr>
<td>Memory issues</td>
</tr>
<tr>
<td>Muscle pain/spasms</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Sleep disorders</td>
</tr>
<tr>
<td>Tachycardia/palpitations</td>
</tr>
<tr>
<td>Altered smell/taste</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Joint pain</td>
</tr>
<tr>
<td>Depression</td>
</tr>
</tbody>
</table>

**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?**

<table>
<thead>
<tr>
<th>CARDIOVASCULAR</th>
<th>Acute MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac Dysrhythmias</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td></td>
<td>Myocarditis and cardiomyopathy</td>
</tr>
<tr>
<td>PULMONARY</td>
<td>Acute pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Respiratory symptoms</td>
</tr>
<tr>
<td></td>
<td>Asthma</td>
</tr>
<tr>
<td>RENAL</td>
<td>Renal Failure</td>
</tr>
<tr>
<td></td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>COAGULOPATHY &amp; VASCULAR</td>
<td>Thromboembolic event</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
<tr>
<td></td>
<td>Coagulation and hemorrhagic</td>
</tr>
<tr>
<td>GI</td>
<td>GI and esophageal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEUROLOGIC</th>
<th>Neurologic conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smell and taste disturbances</td>
</tr>
<tr>
<td>MENTAL HEALTH</td>
<td>Mood disorders</td>
</tr>
<tr>
<td></td>
<td>Other mental conditions</td>
</tr>
<tr>
<td></td>
<td>Anxiety and fear related</td>
</tr>
<tr>
<td></td>
<td>Sleeping disorders</td>
</tr>
<tr>
<td>MUSCOLO-SKELETAL</td>
<td>Malaise and fatigue</td>
</tr>
<tr>
<td></td>
<td>Muscle disorders</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain</td>
</tr>
<tr>
<td>ENDOCRINE</td>
<td>Diabetes type 2</td>
</tr>
<tr>
<td></td>
<td>Diabetes type 1</td>
</tr>
</tbody>
</table>
### COVID-19: Lasting impact

Even those survivors with mild initial cases can have wide-ranging health issues for six months or more.

WashU researchers link many diseases with COVID-19, signaling long-term complications for patients and a massive health burden for years to come.

#### SARS-CoV-2 infection associations with increased risk of these conditions

- Follow-up to 6 or 12 months

#### Example studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal(s)</th>
<th>EHR</th>
<th>Data Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Aly 2022</td>
<td>Nature Medicine</td>
<td>Veterans Affairs</td>
<td>Matched infection vs breakthrough infection vs no infection</td>
</tr>
<tr>
<td>Cohen 2022</td>
<td>BMJ</td>
<td>Medicare Advantage</td>
<td>Matched Infected vs uninfected cohorts</td>
</tr>
<tr>
<td>Bull-Otterson 2022</td>
<td>MMWR</td>
<td>Cerner</td>
<td>Matched Infected vs uninfected cohorts</td>
</tr>
</tbody>
</table>
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
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
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?

<table>
<thead>
<tr>
<th>CLINIC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care/General Internal Medicine</td>
<td>33.1%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>13.1%</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>9.7%</td>
</tr>
<tr>
<td>Mental Health</td>
<td>3.5%</td>
</tr>
<tr>
<td>Physical Therapy</td>
<td>3.2%</td>
</tr>
<tr>
<td>Rehabilitation Medicine</td>
<td>2.6%</td>
</tr>
<tr>
<td>Cardiology</td>
<td>2.2%</td>
</tr>
<tr>
<td>Occupational Therapy</td>
<td>1.5%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>0.9%</td>
</tr>
<tr>
<td>Neurology</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
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**
- Charlson Score: 0
- Charlson Score: 1
- Charlson Score: 2
- Charlson Score: 3
- Charlson Score: 4
- Charlson Score: 5-6
- Charlson Score: 7-8
- Charlson Score: 9+

**AGE**
- Age 18-49
- Age 50-59
- Age 60-64
- Age 65-69
- Age 70-74
- Age 75-79
- Age 80-84
- Age 85-89
- Age 90+
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 definition 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

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• 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

Analytic and Programming Support from the White River Junction VA Medical Center Clinical Epidemiology Program

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

Deaths per 100,000

VA enrollees

Deaths per 100,000
AIM 1. Observed vs expected mortality in US population compared to VA enrollees

General US population

25-44 years
45-64 years
65-74 years
75-84 years
85 years and older

Deaths/100,000

Date

VA enrollees

25-44 years
45-64 years
65-74 years
75-84 years
85 years and older

Deaths/100,000

Date
AIM 1. Population-standardized excess mortality and relative change

Excess Incidence per 100,000

-20 0 20 40 60 80 100

2020 Q1 2020 Q2 2020 Q3 2020 Q4

Rate Ratio

<table>
<thead>
<tr>
<th></th>
<th>2020 Q1</th>
<th>2020 Q2</th>
<th>2020 Q3</th>
<th>2020 Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>US general population</td>
<td>1.02</td>
<td>1.22</td>
<td>1.21</td>
<td>1.25</td>
</tr>
<tr>
<td>VA active users</td>
<td>1.00</td>
<td>1.10</td>
<td>1.13</td>
<td>1.19</td>
</tr>
</tbody>
</table>
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

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

Determination of controlled, uncontrolled HTN pre-pandemic

Time between bp readings

Determination of controlled, uncontrolled HTN

BP readings (x)

March 2019 Pre-pandemic period

March 2020 Pandemic period

February 2022
### AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control:
Time between last pre-pandemic period and first pandemic period blood pressure readings

<table>
<thead>
<tr>
<th>Pre-pandemic period HTN classification</th>
<th>Time between blood pressure readings (days) [median (IQR)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled HTN N=184,325</td>
<td>190 (78, 348)</td>
</tr>
<tr>
<td>Uncontrolled HTN N=644,976</td>
<td>201 (91, 354)</td>
</tr>
</tbody>
</table>
AIM 2c. Evaluating Association Between Disruption and Blood Pressure Control: HTN classification for pre-pandemic and pandemic periods

<table>
<thead>
<tr>
<th></th>
<th>Pre-pandemic period</th>
<th>Pandemic period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled</td>
<td>Uncontrolled</td>
</tr>
<tr>
<td>Controlled</td>
<td>N=184,325</td>
<td>63,581 (34%)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>N=644,976</td>
<td>37,158 (6%)</td>
</tr>
</tbody>
</table>

Pre-pandemic period:

- Controlled: 63,581 (34%)
- Uncontrolled: 50,627 (27%)
- Indeterminate: 70,117 (38%)

Pandemic period:

- Controlled: 37,158 (6%)
- Uncontrolled: 450,122 (70%)
- Indeterminate: 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

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted OR (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6 months vs. &lt;6 months between last pre-pandemic bp reading and first pandemic bp reading</td>
<td>1.52 (1.49, 1.56)</td>
<td>1.38 (1.35, 1.42)</td>
</tr>
</tbody>
</table>

*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 (EPIC³) 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.
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.
Environmental Scan Findings

17 Established Long COVID Programs

South Texas
1,304
Highest number of patients enrolled-to-date (as of Nov. 2021)

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
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