Update: Serologic Science and More at the Frederick National Laboratory

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Deputy Director, National Cancer Institute

FNLAC Virtual Meeting
February 23, 2021

Today's topics

- Some NCI SARS-CoV-2 serology projects
  - FNL & Serology
  - SeroNet; SeroHub
- SARS-CoV-2 in cancer patients; immune responses of cancer patients to SARS-CoV-2 vaccination
- SARS-CoV-2 antibodies are associated with a decreased risk of new infection

NCI's initial involvement with SARS-CoV-2 serology

- Converted part of HPV serology lab at Frederick National Laboratory to SARS-CoV-2 serology lab
- FDA asked NCI to help FDA evaluate quality of commercial serology devices submitted to FDA
  - Informal HHS agency collaborations essential for success: NIAID, CDC, BARDA, NCI-designated cancer centers

Congressional funding for serology research

- April 24, 2020, NCI receives $306 million to "develop, validate, improve, and implement serological testing and associated technologies"
  - Part of Paycheck Protection Program and Healthcare Enhancement Act (HR 266)
- This funding has allowed NCI to support a wide range of SARS-CoV-2 research related to serology

FNL/NCI serology leadership group

Troy Kemp, Ph.D.
FNL

Ligia Pinto, Ph.D.
FNL

Jim Cherry, Ph.D.
NCI

NCI COVID-19 Response

FOUNDATIONAL SEROLOGY

Serological Sciences Network (SeroNet)

- 8 Centers of Excellence
- 13 Research Projects
- 4 Capacity Building Centers
- FNL Serology Lab & Network Coordinating Center

CLINICAL & TRANSLATIONAL SEROLOGY

Sero-protection Studies:

- Mount Sinai, University of Arizona
- NIH All of Us
- NCI SEER + Health Verity

COVID-19 Seroprevalence Studies Hub (SeroHub)

Antibody test performance evaluation, with FDA

Standard reference serum

Clinical trials for COVID-19 therapeutics

- BTK inhibitors
- Tocilizumab

SUPPORT FOR CANCER RESEARCH AND CARE AMID THE PANDEMIC

NCI COVID-19 in Cancer Patients Study (NCCAPS)

Flexibilities for grantees

Clinical trials adaptations

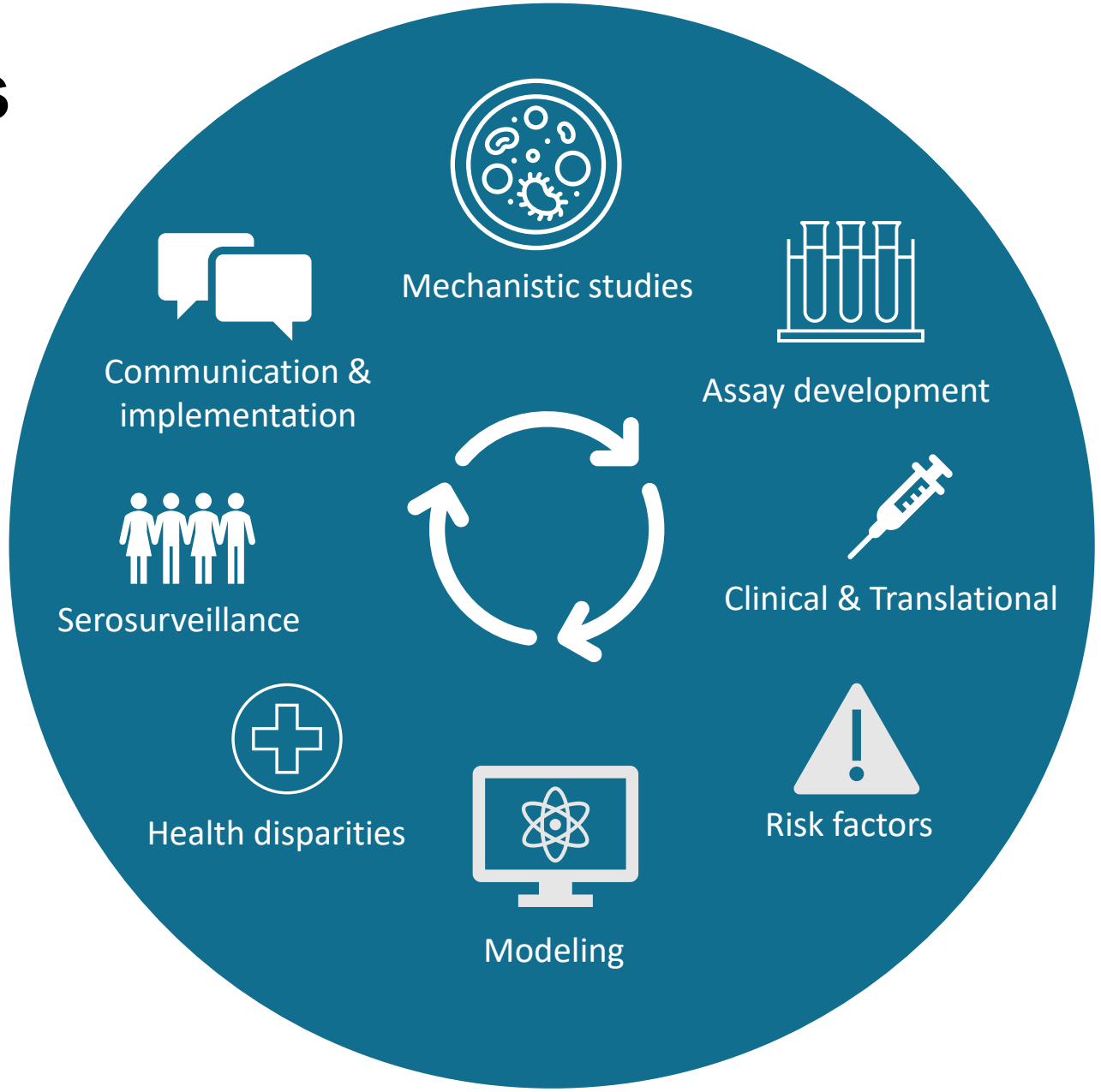
Modeling to predict long-term cancer outcomes

ADDITIONAL COVID-19 RESEARCH

- Excess Mortality Study
- Digital Health Solutions (with NIBIB)
- ACTIV (trans-NIH)

Some SeroNet Objectives

- Develop novel serological assays and deploy them broadly
- Characterize the biological mechanisms driving the innate humoral and cellular responses to SARS-CoV-2
- Determine factors that modulate the immune response



Some Highlights

- Designed to be a highly interactive network
- Sharing of data and resources
- Open access publication

SeroNet & SARS-CoV-2 Vaccination: Serologic response of cancer patients

- **Some important questions:** 1) Are there specific groups whose immune response is similar to the general population vs. those whose initial or long-term response is inferior? 2) Would those with an inferior response benefit from an additional booster vaccine dose and/or an earlier booster dose?
- **Conducted through SeroNet and other networks**
  - Include Black and Hispanic cancer patients

NCI COVID-19 Response

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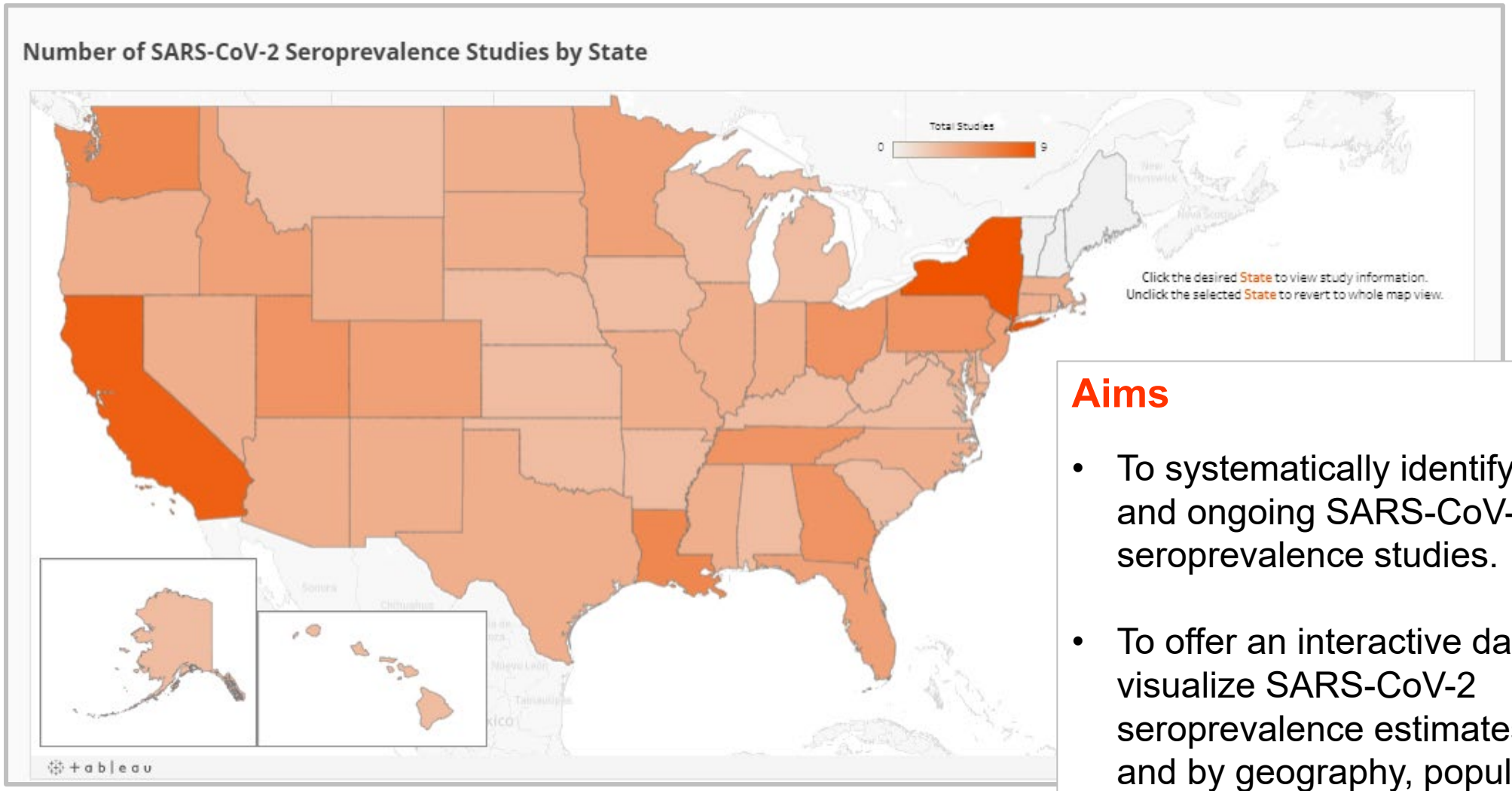
covid19serohub.nih.gov/



Aims

- To systematically identify published and ongoing SARS-CoV-2 seroprevalence studies.
- To offer an interactive dashboard to visualize SARS-CoV-2 seroprevalence estimates over time and by geography, population, and other factors.

In collaboration with CDC and NIAID

U.S. SARS-CoV-2 Serology Standard

A tool to enable serology assay harmonization and to increase comparability of results across different serology studies

- Large volume of pooled plasma samples for use as an **assay calibrator** by laboratories conducting SARS-CoV-2 serology testing
- The main goal is to **harmonize assays** that measure anti-SARS-CoV-2 antibodies to **increase comparability** of results from different studies, including different candidate vaccines
- Will be calibrated to the **WHO International Standard** when it becomes available

Now widely available:
e.g., Operation Warp Speed, SeroNet, academic institutions

Download request form at

https://frederick.cancer.gov/seronet/serology-standard

SARS-CoV-2 Serology Validation Program: Overview

Collaborative effort between NCI, NIAID, FDA, CDC, BARDA and several academic groups

GOAL: Performance evaluation of ELISA assays, Lateral Flow Devices and Automated Chemiluminescent Immunoassays to assist the FDA in determining suitability for EUA approval

Evaluation Panel: Production and Qualification

1. **Sample acquisition**
2. **Sample Characterization at multiple dilutions**

CDC Assays:

- SARS-CoV-2 Spike IgG and IgM ELISA
- SARS-CoV-2 Spike Total Ig

FNLCR Assays:

- SARS-CoV-2 Spike IgG and IgM ELISA
- SARS-CoV-2 Spike Total Ig
- SARS-CoV-2 RBD IgG

Evaluation Panel

Positive samples:

- 30 PCR+ patient's sera

Negative samples:

- 80 pre-pandemic negative controls plasma, including 10 HIV-positive samples

Sample Characterization: CDC and FNLCR

Commercial Assay Performance Evaluation

1. Entities submit their serology assays for evaluation by this program
2. Testing is done at FNLCR according to corresponding protocol using evaluation panels
3. Data is sent to FDA
4. Sensitivity and Specificity are determined

FDA uses the antibody test performance in regulatory decision making and makes those decisions publicly available

The FDA's Experience with Covid-19 Antibody Tests

Jeffrey Shuren, M.D., J.D., and Timothy Stenzel, M.D., Ph.D.

N ENGL J MED 384;7 NEJM.ORG FEBRUARY 18, 2021

Recommendation for future epidemics: "We should establish the capacity within or on behalf of the federal government to evaluate test performance before outbreaks occur so that independent evaluation can be performed quickly during an outbreak. **Our collaboration with the NCI showed us the value of this approach**."

Title: Association of SARS-COV-2 seropositive antibody test with risk of future infection

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Author Affiliation:[1] Aetion, Inc., New York, NY [2] HealthVerity, Philadelphia, PA [3] Quest Diagnostics, Secaucus, NJ [4] LabCorp, Burlington, NC [5] National Cancer Institute, Bethesda, MD

Main question: *Are serum antibodies that develop after SARS-CoV-2 infection associated with a decreased risk of a new infection?*

Secondary question: *Can this question be addressed with anonymized "real-world data"?*

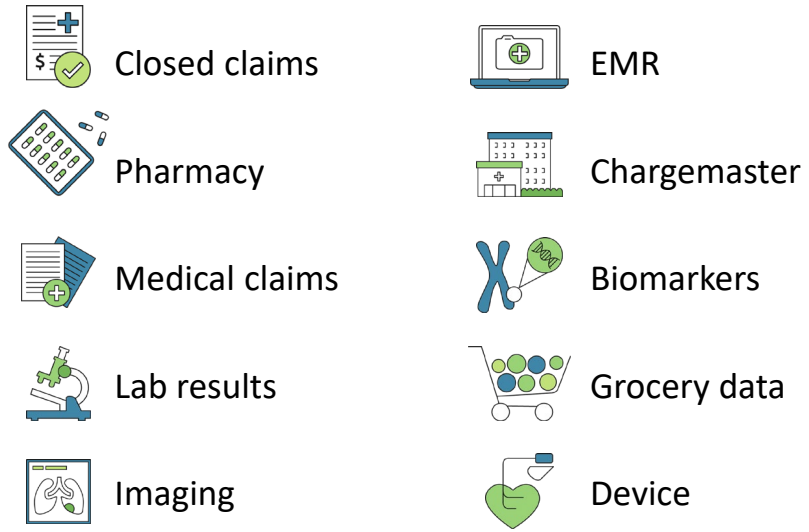
Manuscript available on preprint server: https://www.medrxiv.org/content/medrxiv/early/2020/12/20/2020.12.18.20248336.full.pdf

Manuscript in press: JAMA Internal Medicine

The HealthVerity data ecosystem

A Real-World Data aggregation system that:

- provides an infrastructure to connect data from **>75 unique data sources**
- uses a secure encrypted linkage process
- permits access to the broad categories of data on millions of individuals
- **uses anonymized but linkable commercial laboratory data, medical claims, and electronic medical records (EMR) data**

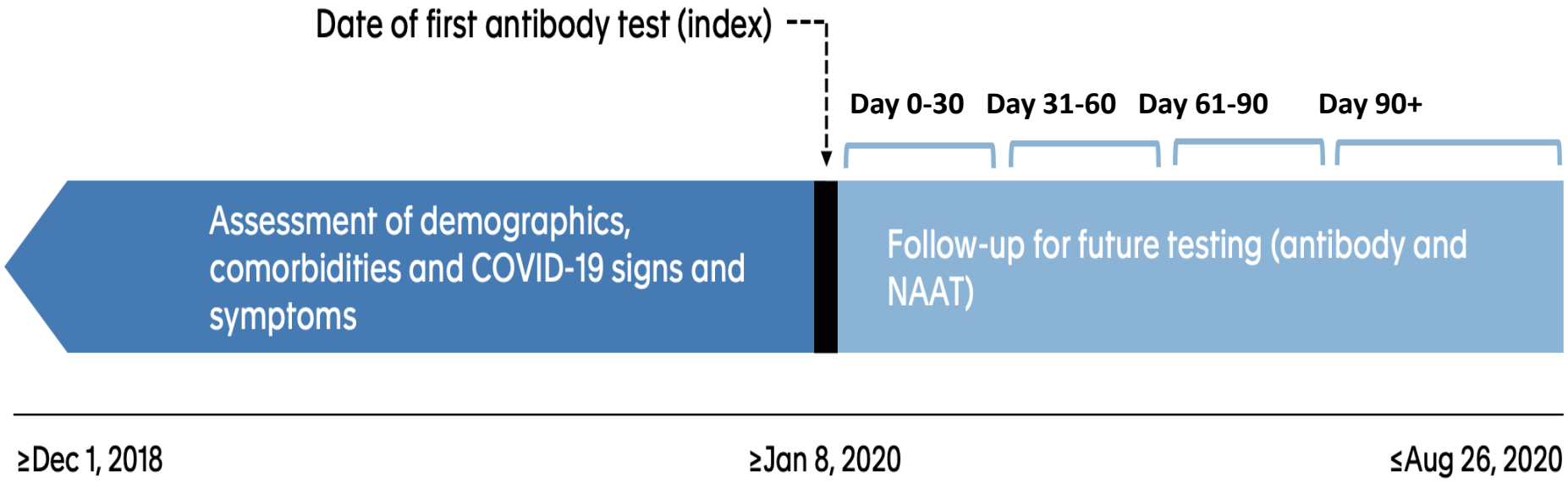


HealthVerity SARS-CoV2 has serum antibody tests on ~4 million patients and viral RNA tests on ~20 million patients (through Sept. 10, 2020)

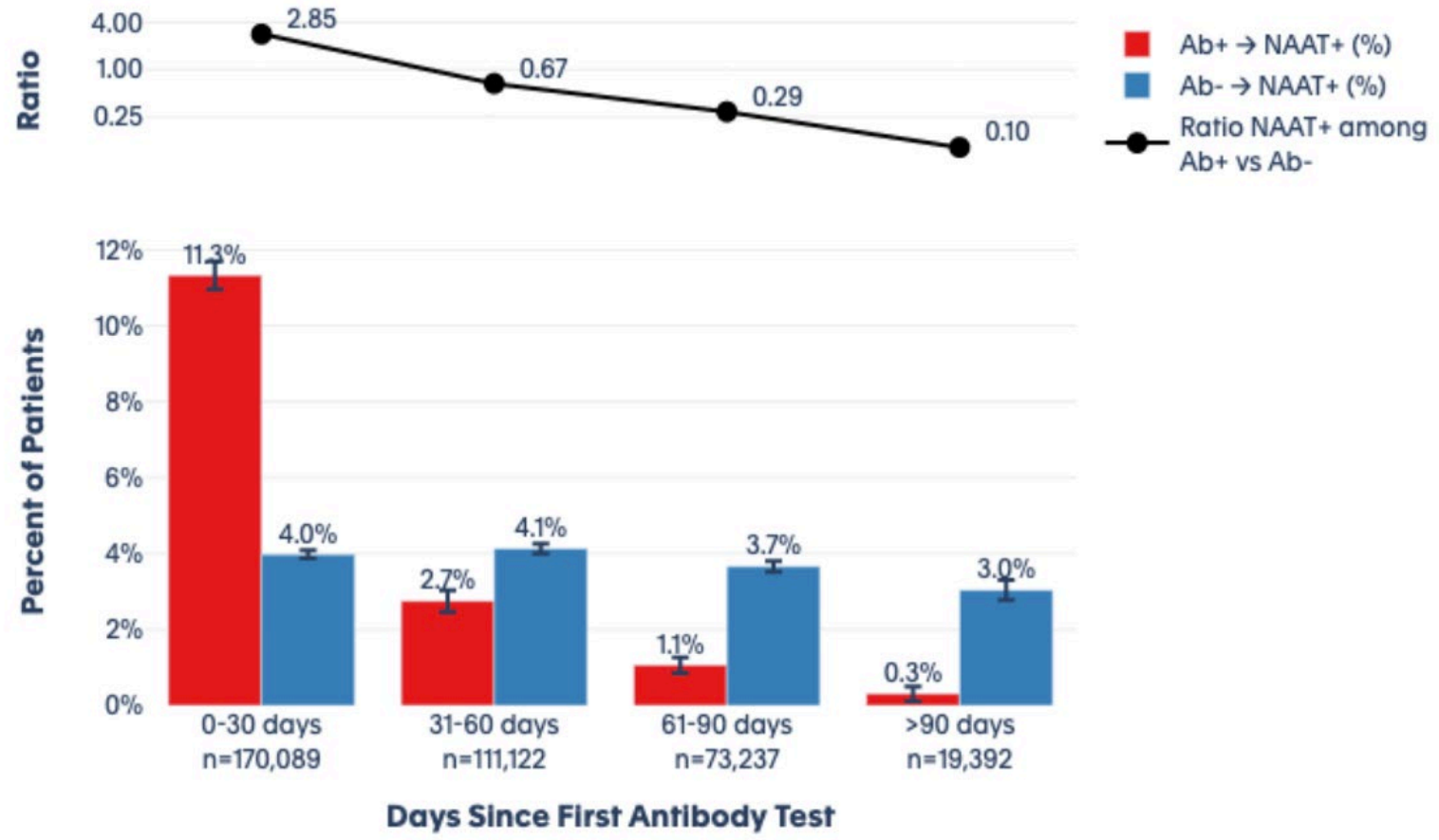
Commercial Lab Data Cumulative Volume			
Data Supplier	**Tests**	**Patients**	**Positive Test Rate***
Antibody Test**			
Total	**5,003,166**	**3,954,891**	**11.13%**
LabCorp	2,608,207	1,862,286	8.50%
Quest Diagnostics	2,135,960	1,863,576	13.15%
Other Commercial Labs	258,999	253,576	20.92%
Diagnostic Test			
Total	**31,183,960**	**19,665,278**	**8.59%**
LabCorp	11,860,271	9,666,871	8.54%
Quest Diagnostics	7,234,350	5,763,210	9.95%
Other Commercial Labs	12,089,339	7,231,571	8.20%

Study Design

- **Index Event:** 88.3% antibody-negative; 11.6% antibody-positive, 0.1% inconclusive
- **Study index date:** date for each patient of first SARS-CoV-2 antibody test (after Jan 8, 2020).
- **Follow-up:** captured in 30-day increments after index date: (0-30, 31-60, 61-90 and >90 Days); to monitor viral RNA shedding (nucleic acid amplification test; NAAT)



Positive diagnostic viral RNA tests (NAAT): Antibody-negative patients (blue) had similar positive rate over multiple 30 Day Intervals; Antibody-positive patients (red) had progressively declining positive rate



Diagnostic viral RNA test results for subsequent 30 Day intervals after index antibody test: Progressive decrease in ratio of positive viral RNA among Index antibody-positive/antibody-negative (AB+/Ab-, 95% CI)

Days since index antibody test	Ratio of viral RNA positives for Antibody-pos/Antibody-neg	95% confidence interval
0-30	**2.85**	2.73-2.97
31-60	**0.67**	0.60-0.74
61-90	**0.29**	0.24-0.35
>90	**0.10**	0.05-0.19

Some considerations

- Reduced infection rate among antibody-positive patients was not attributable to them getting fewer viral RNA tests; antibody-positive people had more tests per person than antibody-negative people
- The Inferred level of protection could be an overestimate or an underestimate
  - An overestimate: Possible confounding biases from observational study
  - An underestimate: If antibody-positive people thought they were protected, they might have engaged in riskier behavior

Main conclusion

- The presence of antibodies to SARS-CoV-2 is associated with a reduced risk of developing a subsequent symptomatic SARS-CoV-2 infection; the observed decrease in risk during the >90 day period was ~10-fold
- Similar conclusions drawn by Lumley et al, NEJM, Dec 23, 2020
  - ~10-fold decrease in risk for SARS-CoV-2 antibody-positive health care workers (HCW) in United Kingdom over 6 month period; evaluated 12,629 HCW, 10% were antibody-positive; antibody test was developed by Oxford University

Possible implications

- Commercial SARS-CoV-2 antibody tests are reliable
  - The risk of new infection differs for antibody-positive and antibody-negative people
- When considering herd immunity, the population who are antibody-positive after natural infection could be added to the population who are antibody-positive after vaccination
- In future, if a given activity is going to require proof of vaccination – by the private sector or public sector – a positive antibody test might be an acceptable alternative
  - Could be a “safety valve” for people who lack documentation of vaccination

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