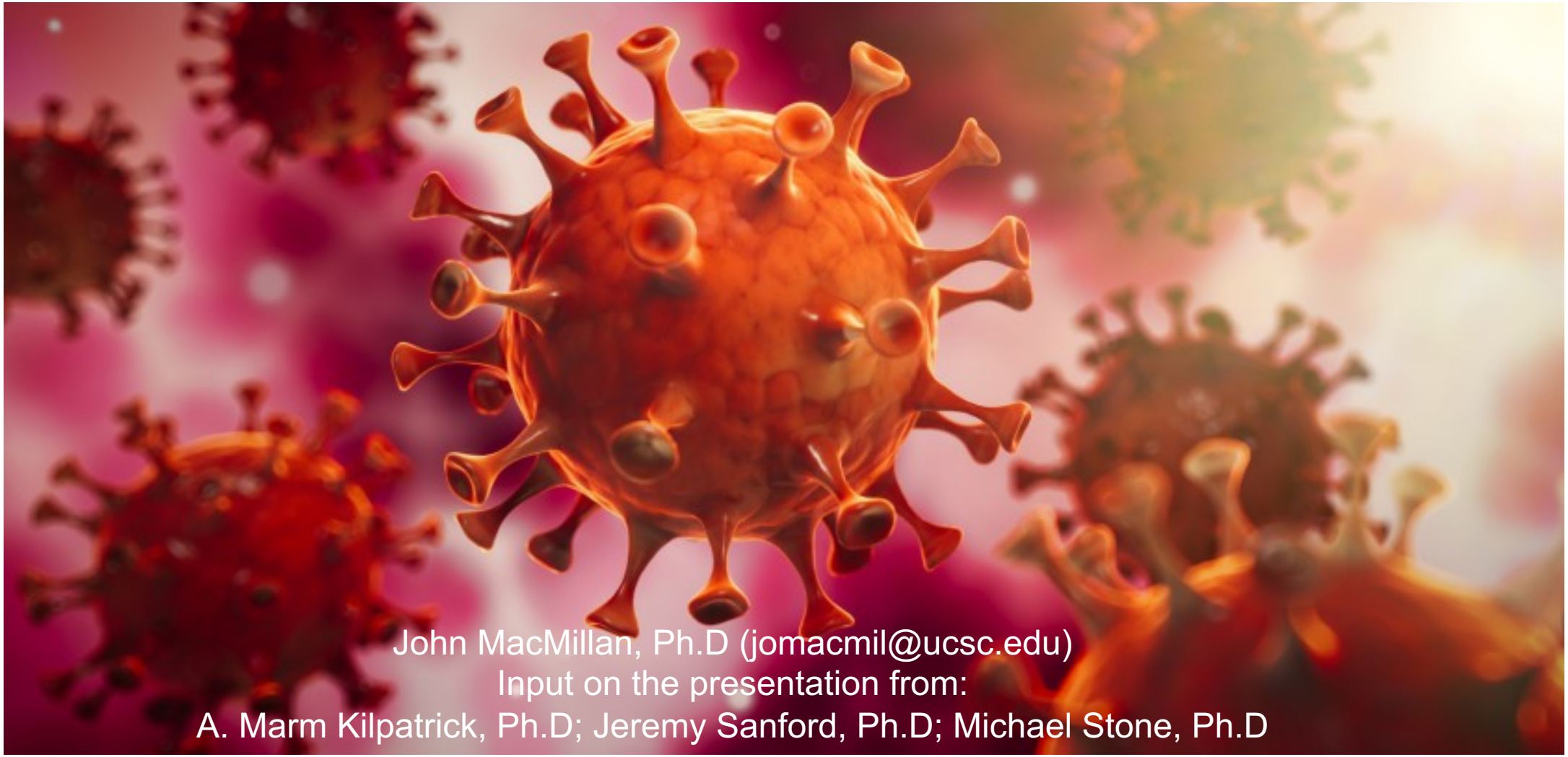
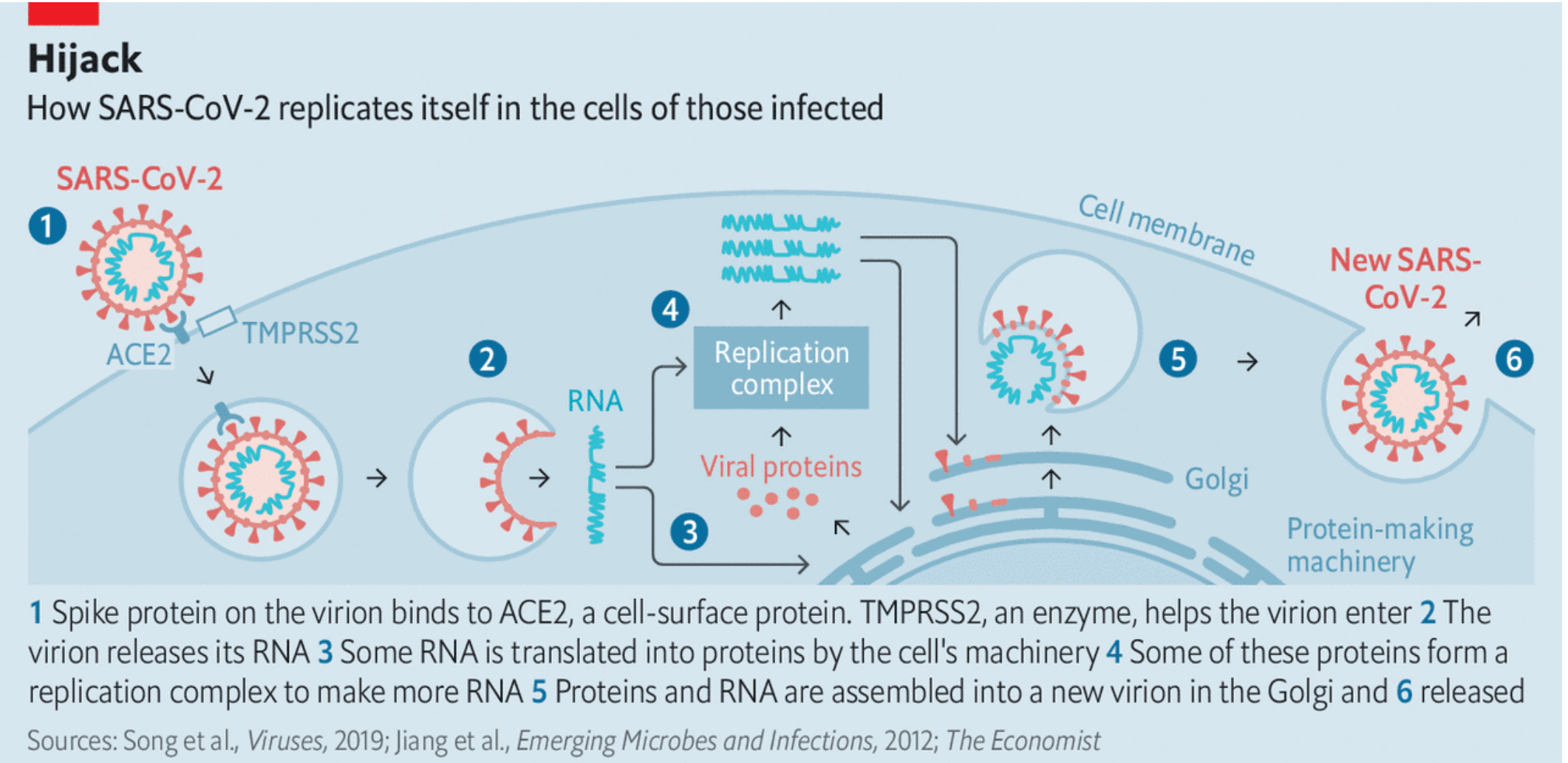
Role of COVID-19 Diagnostic Testing

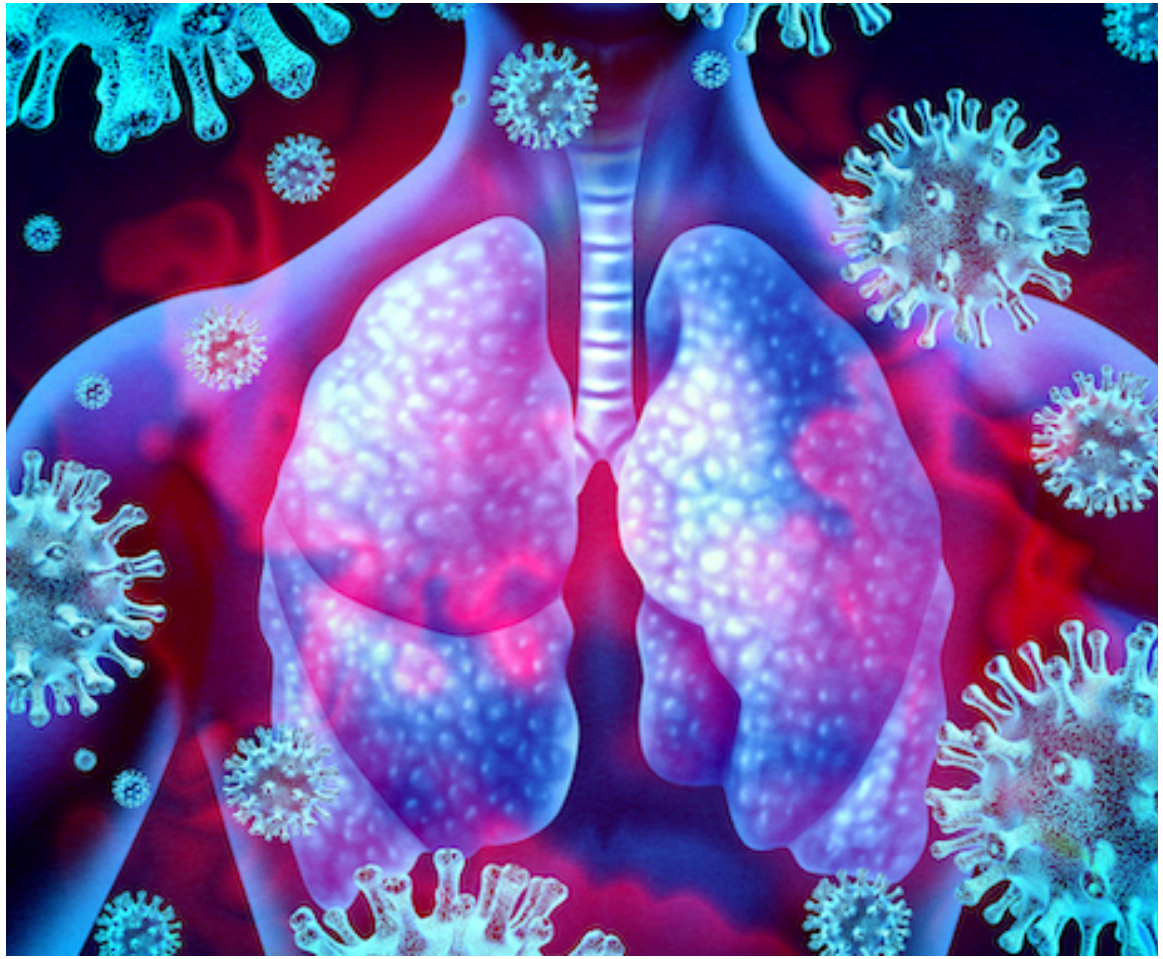


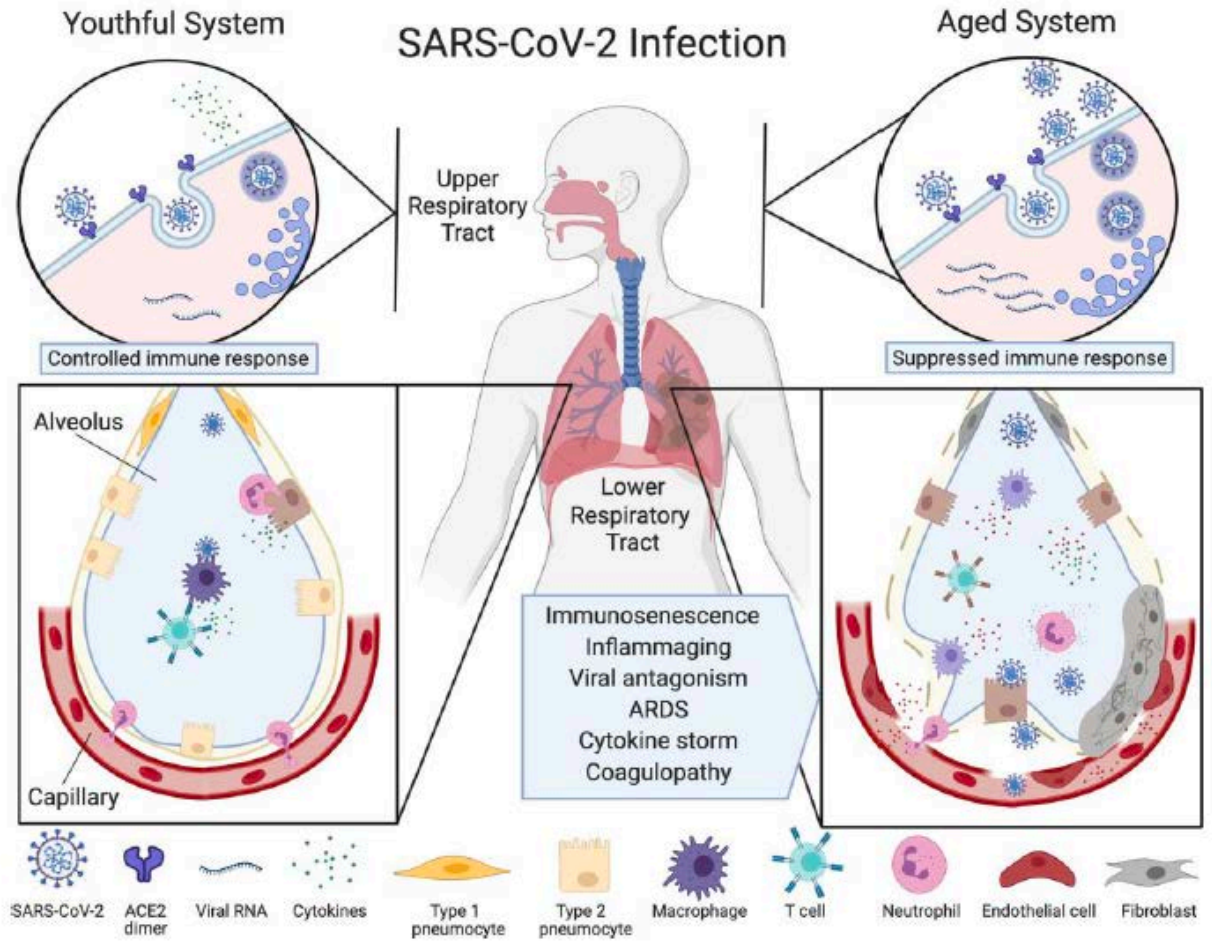
John MacMillan, Ph.D (jomacmil@ucsc.edu)
Input on the presentation from:
A. Marm Kilpatrick, Ph.D; Jeremy Sanford, Ph.D; Michael Stone, Ph.D

SARS-CoV-2


Hijack
How SARS-CoV-2 replicates itself in the cells of those infected
SARS-CoV-2
1
ACE2
TMPRSS2
2
RNA
4
Replication complex
Viral proteins
3
Cell membrane
5
Golgi
Protein-making machinery
New SARS-CoV-2
6
1 Spike protein on the virion binds to ACE2, a cell-surface protein. TMPRSS2, an enzyme, helps the virion enter 2 The virion releases its RNA 3 Some RNA is translated into proteins by the cell's machinery 4 Some of these proteins form a replication complex to make more RNA 5 Proteins and RNA are assembled into a new virion in the Golgi and 6 released
Sources: Song et al., Viruses, 2019; Jiang et al., Emerging Microbes and Infections, 2012; The Economist

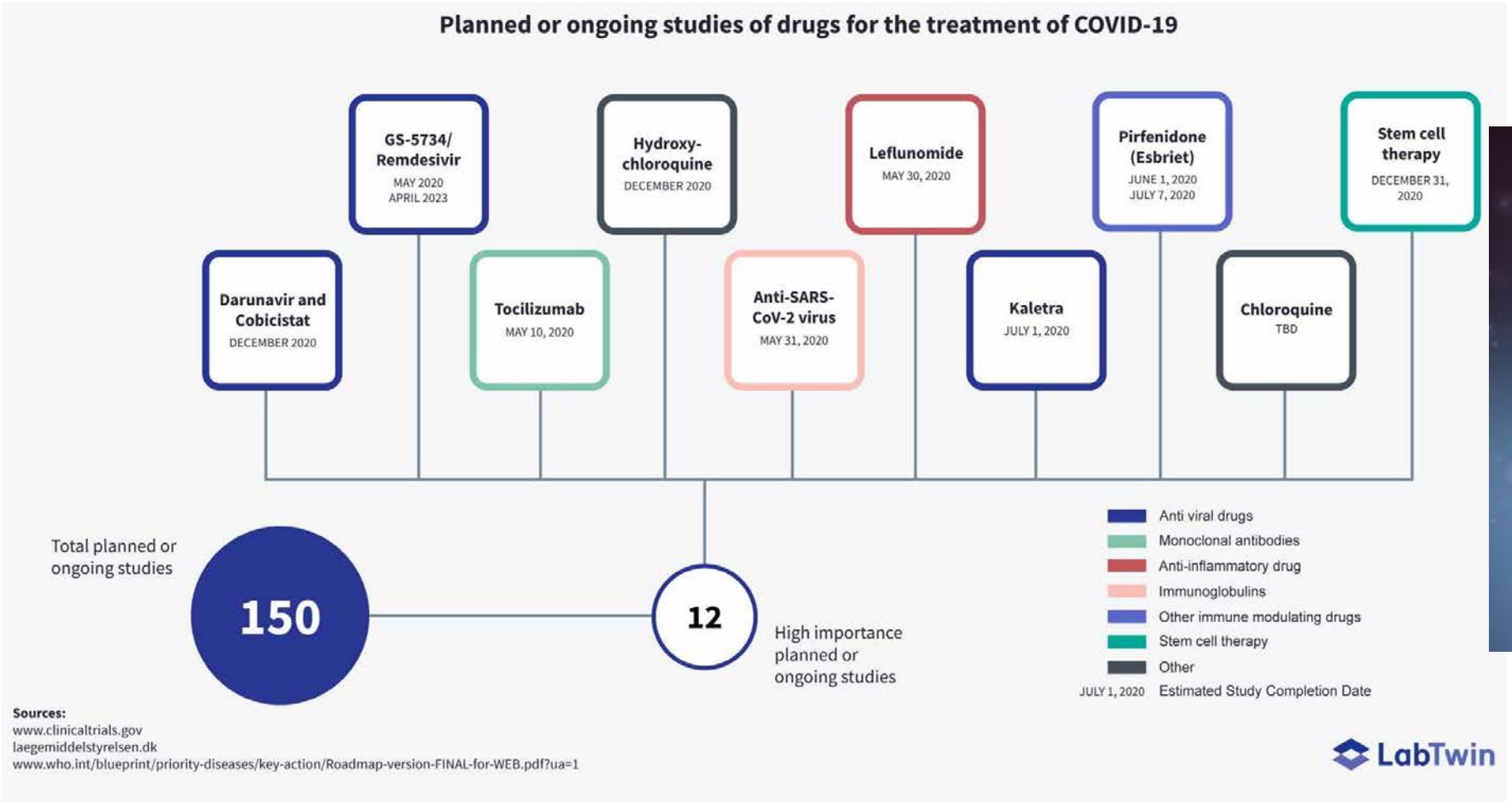
SARS-CoV-2 and Immune System

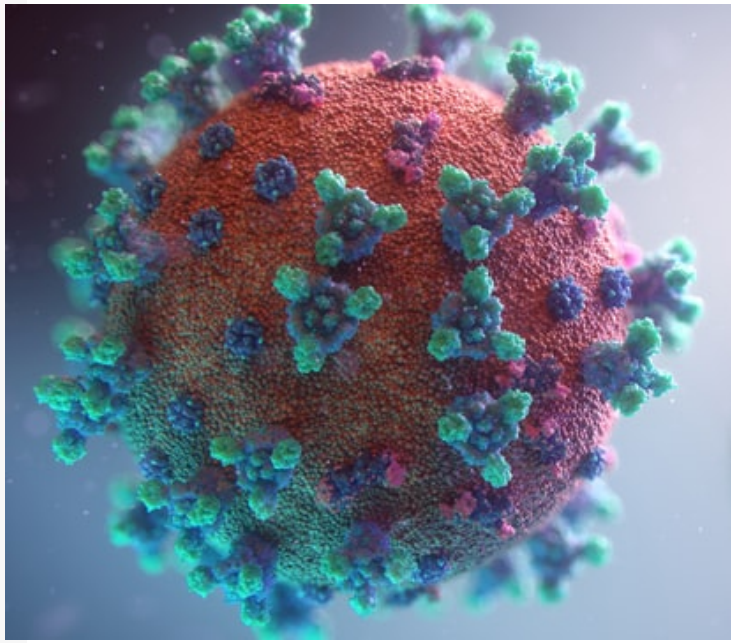




The Lancet, **2020,** *395,*1517-1520

Drugs Undergoing Evaluation for COVID-19





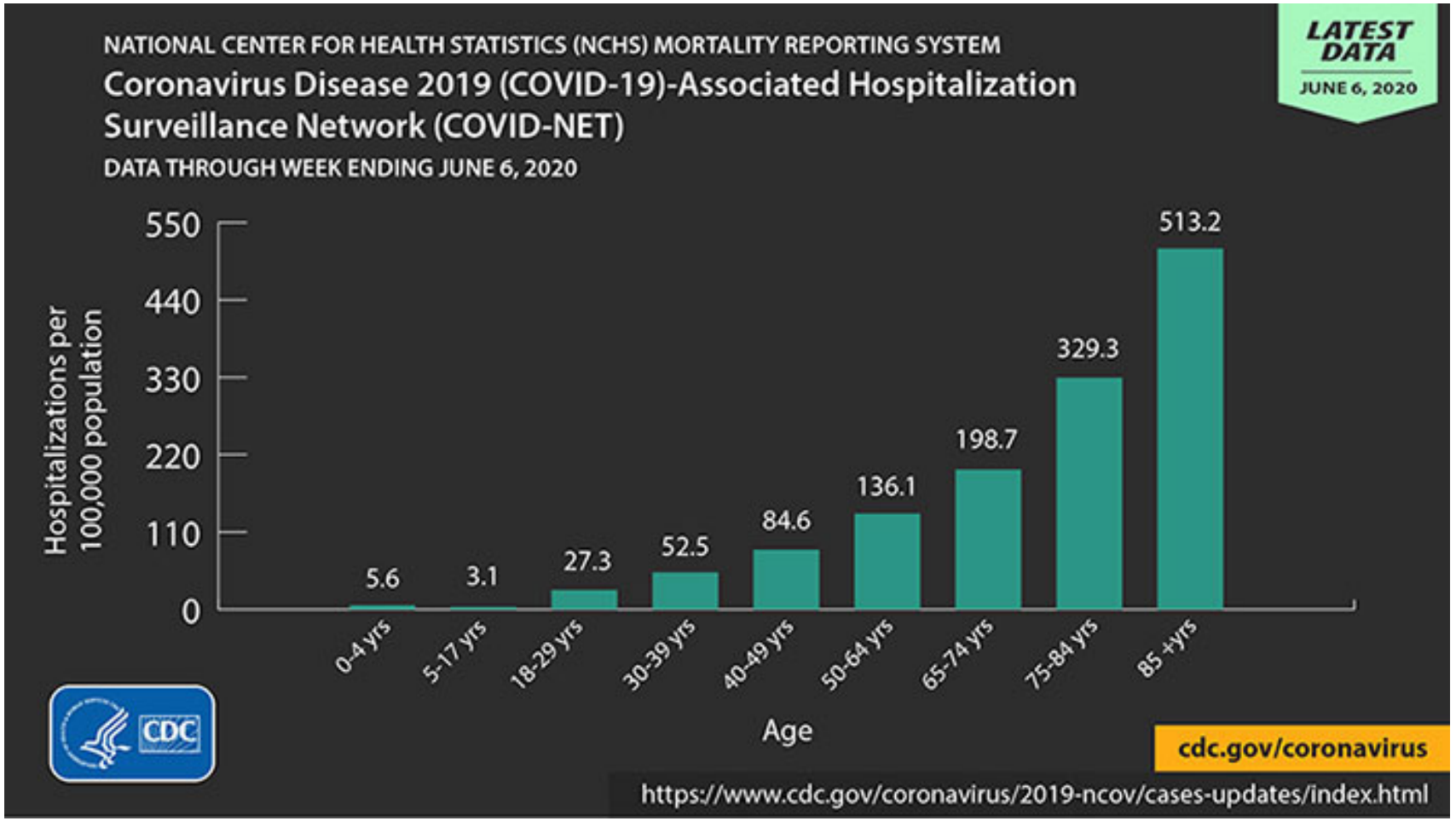
Who is at highest risk for severe illness and death from COVID-19?

Older people with pre-existing illnesses

Older adults are more likely to already have underlying conditions such as cardiovascular disease, diabetes, or respiratory illness — comorbidities that we now know raise the risk of severe COVID-19 and COVID-19-related death

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html

COVID-19 Associated Hospitalization



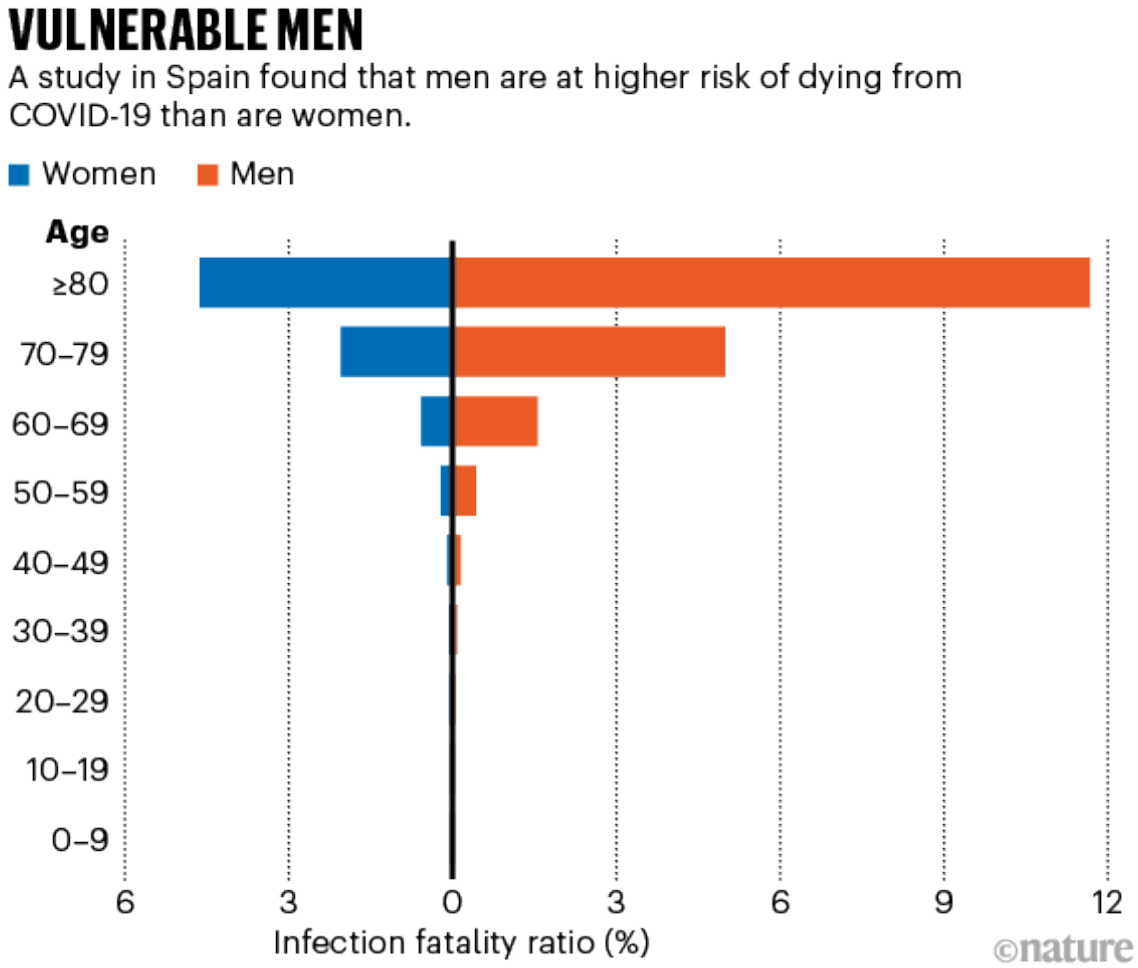
https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html

Age-specific Fatality of COVID-19

Age	Infection Fatality Rate
1-49	<0.17%
50-9	0.6%
60-9	1.9%
70-9	4.3%
80+	7.8%

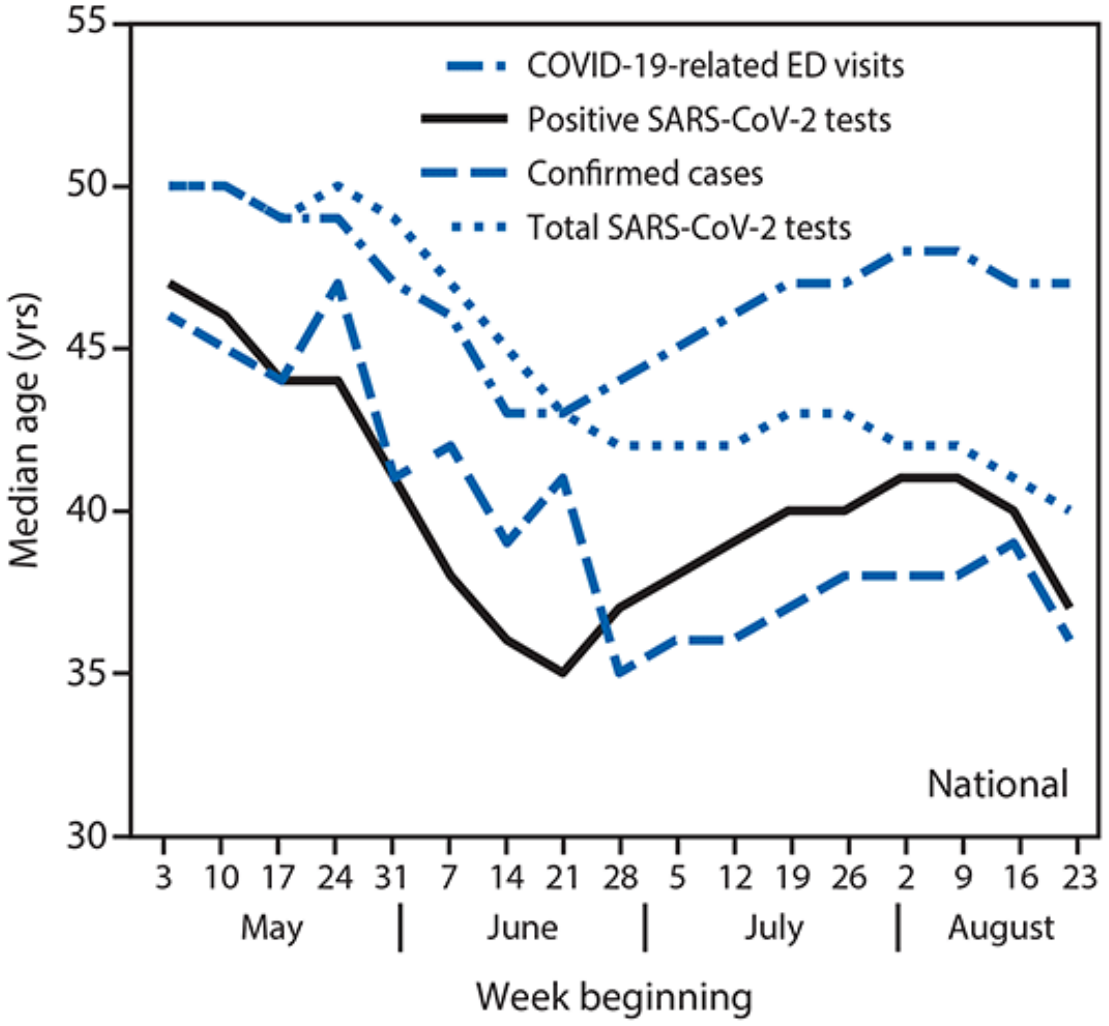
- Men 1.5-3x higher
- Other illnesses can increase chance of dying by 3x (obesity, severe diabetes, some cancers)
- Infection can cause longer-term illness (months!)

Verity et al 2020 Lancet



How will this enormous effect of age influence epidemic outcome over time?

Shifting age of infection: getting younger

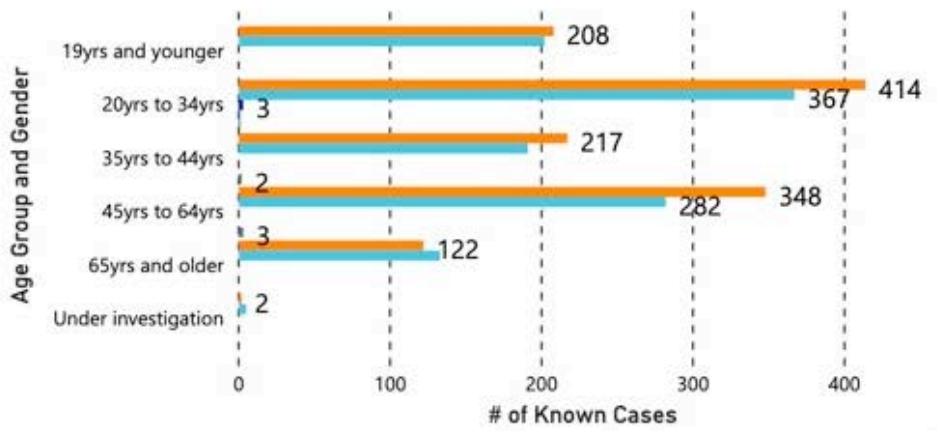


- **From CDC National Syndromic Surveillance Program (NSSP)**
- **Due to testing more mild cases, increased social activities w/ lifting lockdowns**
- **Open question: How much will infection spillover to older & at-risk individuals?**

Conditions in Santa Cruz County: Current Demographics

For additional dashboard details and data definitions select the information icon:

Known cases by age group and gender



Known cases by race/ethnicity

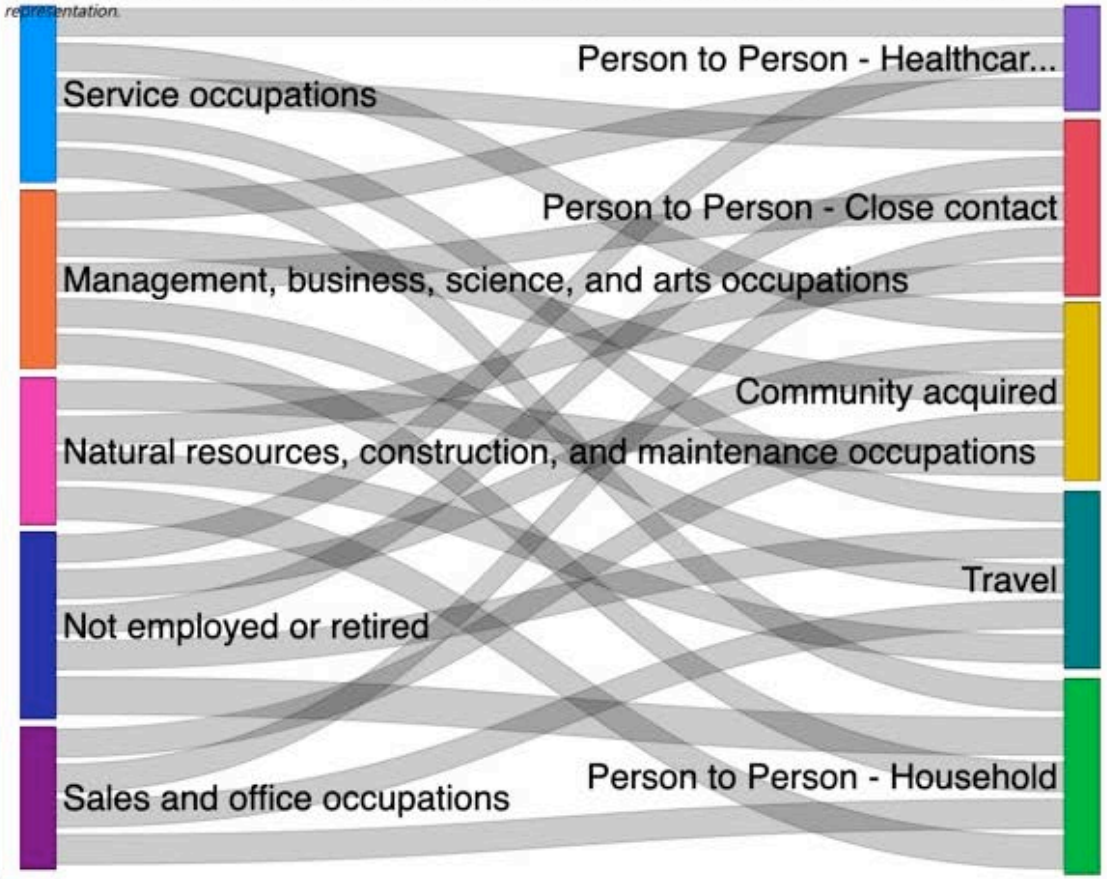
Race / Ethnicity	# Known Cases	% Known Cases	% County Population
Asian Alone	36	1.44	4.43
Black or African American Alone	13	0.52	0.86
Hispanic/Latino	1,566	62.61	33.49
Multiple Races	24	0.96	3.28
Other	58	2.32	0.40
Unknown	363	14.51	0.00
White/Caucasian Alone	441	17.63	57.55
Total	**2,501**		

**Race/Ethnicity categories with 5 or less reported cases have been reported as "Other."*

***% County Population is a 2018 Census Population Estimate.*

Known cases by occupation and identified likely source of exposure

**Recent cases may not be included in the visual representation. **Cases currently under investigation are not included in the visual representation.*

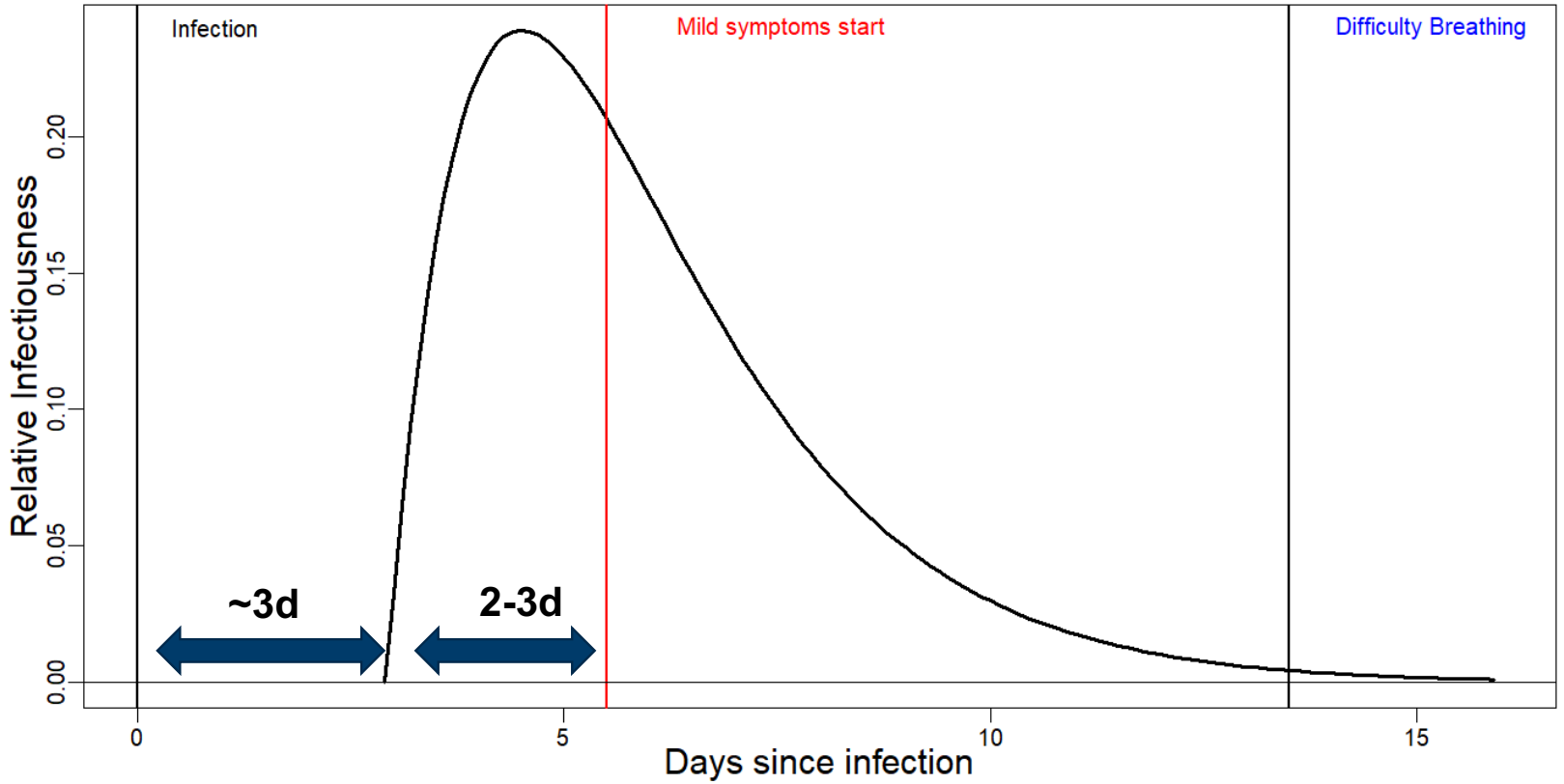


Who can spread the virus and when are they most likely to do so?

Why can’t we stop transmission by asking sick people to stay at home?

When do people become infectious?

Data: case investigation & timing of contact between infector-infectee pairs



- Mild symptoms (cough, fever, etc.) start ~5.5d (3-14) after infection, but
- People become infectious 2-3d before they feel any symptoms
- People without symptoms can infect others!
- Need to wear mask & avoid high risk activities even if you feel fine & get tested at first sign of mild symptoms

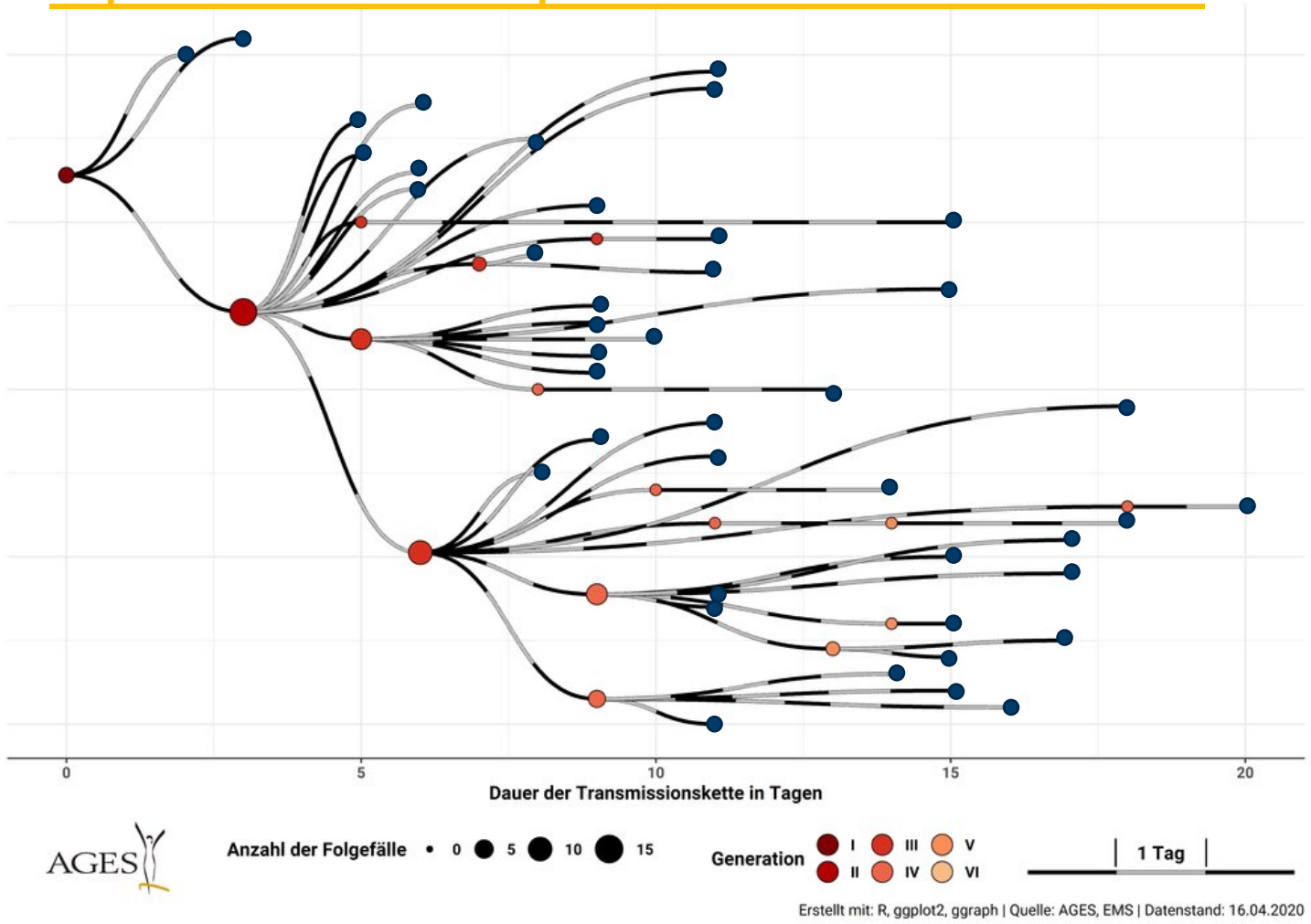
Adapted from He et al 2020 Nat Med; Zhou et al 2020 Lancet

Super spreading events

https://twitter.com/kakape/status/1262869552163160067

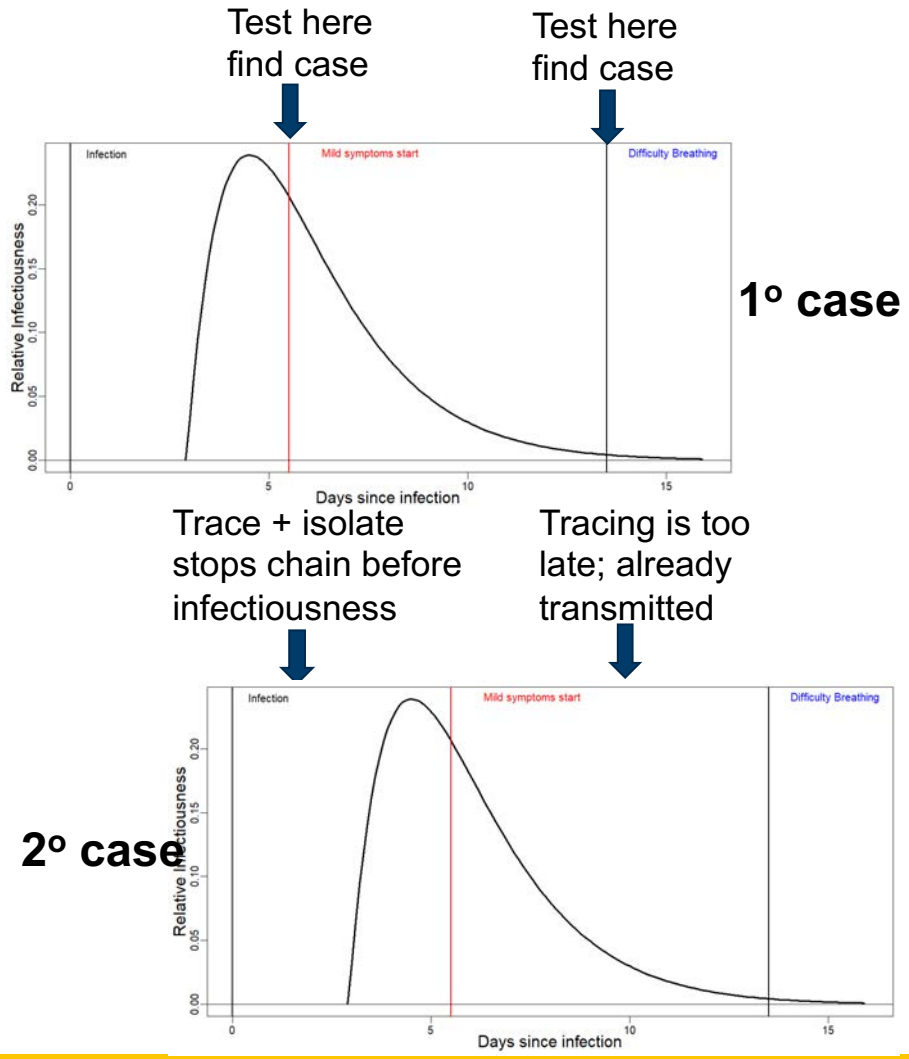
- **Truism for ALL diseases including COVID-19: a few cases cause most infection; most cases infect few or none (20:80 rule)**
  - **e.g. Austrian outbreak: 57 infections 41 R=0 dead-ends (blue): 16 pink R=1-10 (10 twice!)**

- **Examples you may have heard of: choir practice, call center, bars, exercise class, bus trip, meat-packing factories, migrant worker dorms, weddings, birthday party, etc.**



Need Access to Rapid Testing: Test-Trace-Isolate

- To stop transmission via contact tracing, people need to get tested at first sign of mild symptoms or in higher density living carry out asymptomatic testing
- Need to incentivize testing by making it easy; need results fast (~ 24hr)
- Asymptomatic testing of high risk groups, such as communal living
- Improvements in testing: Pooled testing, saliva, self-collected swabs
- Need to provide safe isolation space for cases and contacts



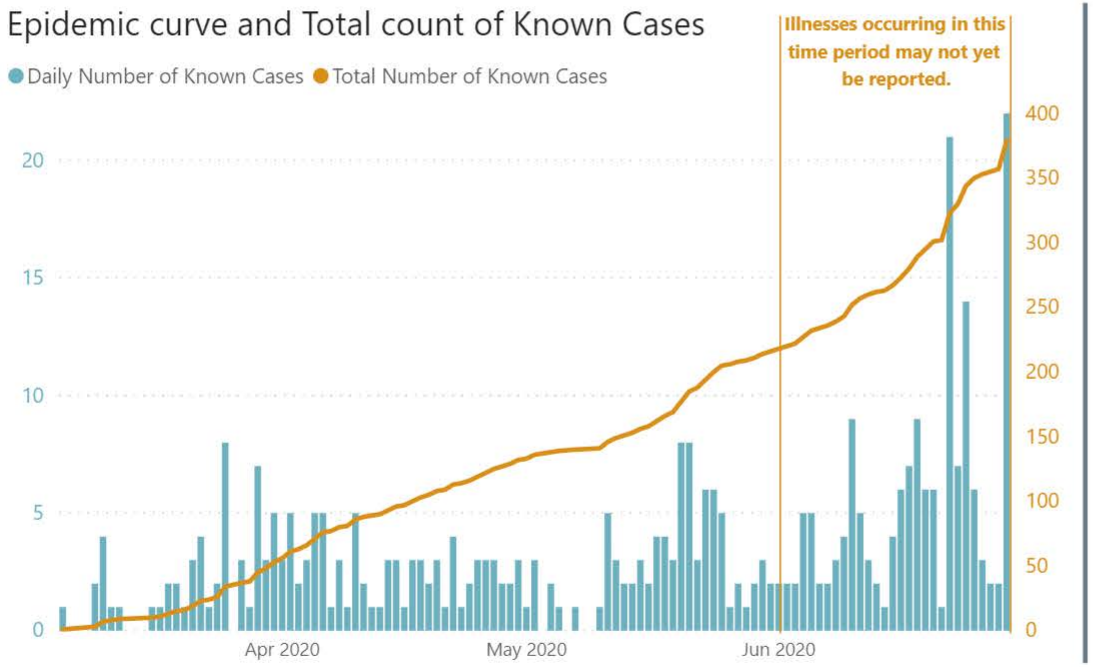
https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1.full.pdf
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30362-5/fulltext

Conditions in Santa Cruz County: Late June

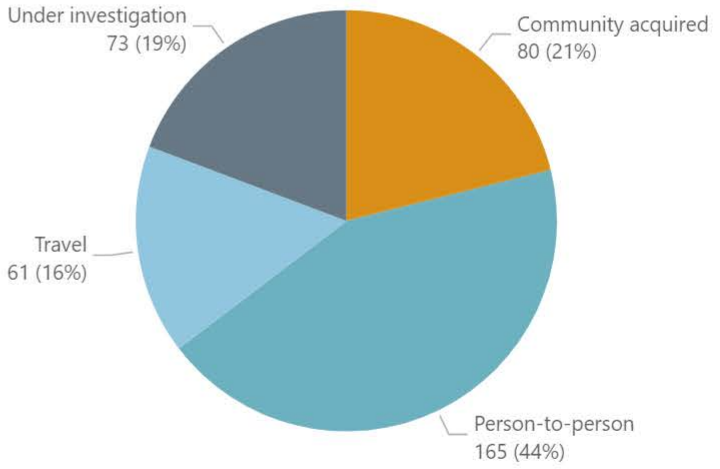
COVID-19 Data Dashboard: Counts of Known Cases Among Santa Cruz County Residents

379	=	129	+	247	+	3 ⓘ	45	16,738
Total Known Cases of COVID-19		Active Known Cases		Recovered Known Cases		Deaths due to COVID-19	Required Hospitalization while ill with COVID-19	Total number of Negative Lab Test Results

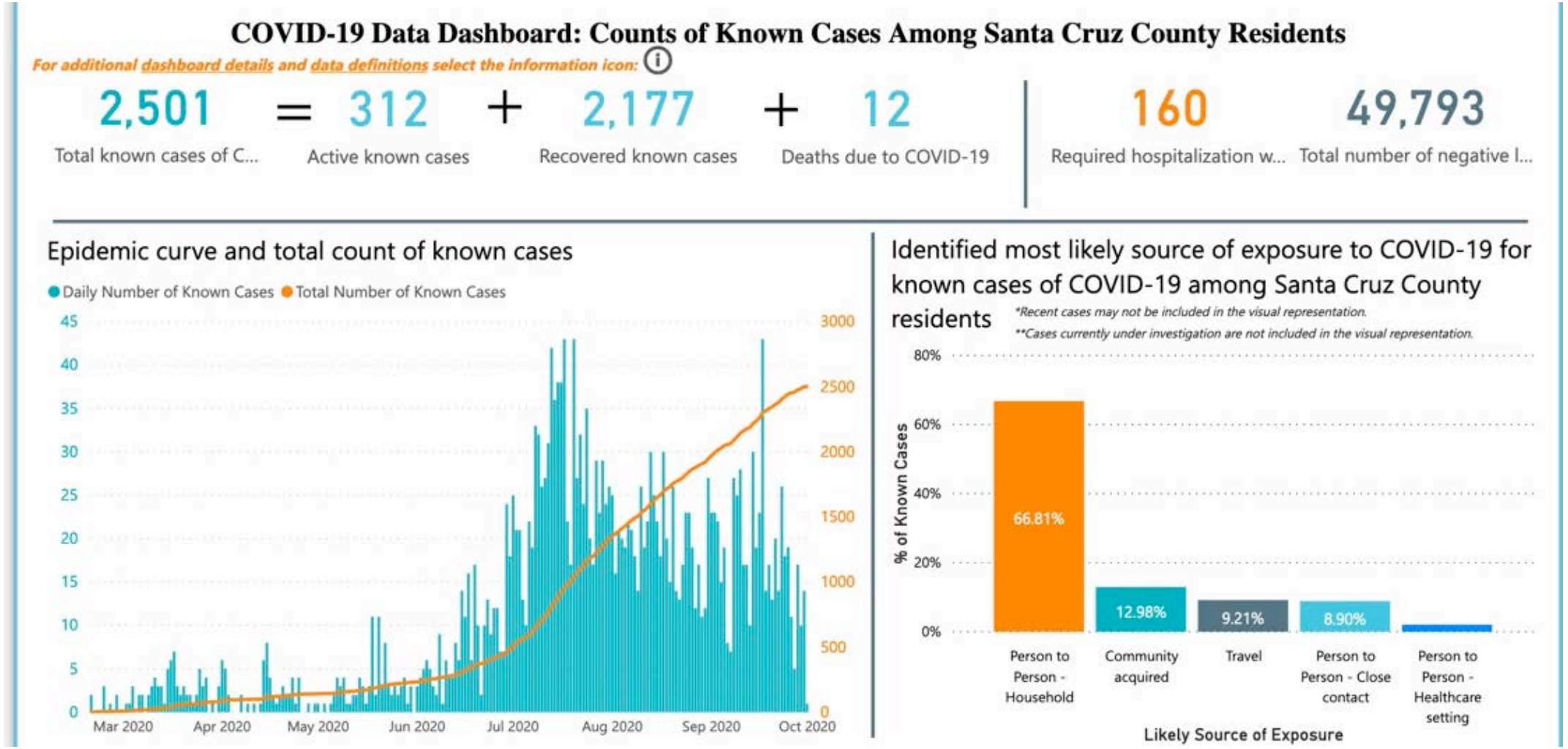
Epidemic curve and Total count of Known Cases



Most likely source of exposure to COVID-19 for Known Cases of COVID-19 among Santa Cruz County Residents



Conditions in Santa Cruz County: Current



Development of the UC-Santa Cruz Molecular Diagnostics Lab to ExpandTesting Capacity in Santa Cruz County

The UCSC Molecular Diagnostic Lab (MDL)

Our Mission: To help our Santa Cruz community by increasing testing capacity and providing a quick turnaround of testing results for populations vital to the recovery of Santa Cruz.

https://sites.google.com/ucsc.edu/molecular-diagnostic-lab

Why establish the UCSC Molecular Diagnostic Lab?

- Mobilize the scientific expertise and resources present at UCSC to serve the Santa Cruz community during the SARS-CoV-2 pandemic.
- Create a campus resource to facilitate ‘Return-to-Learn’ efforts for UCSC students when appropriate.
- Forge a long-term, mutually beneficial, partnership between UCSC and Santa Cruz County

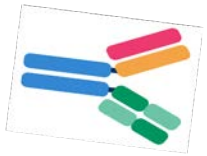
How did we convert a research laboratory to a clinical laboratory in about a month?

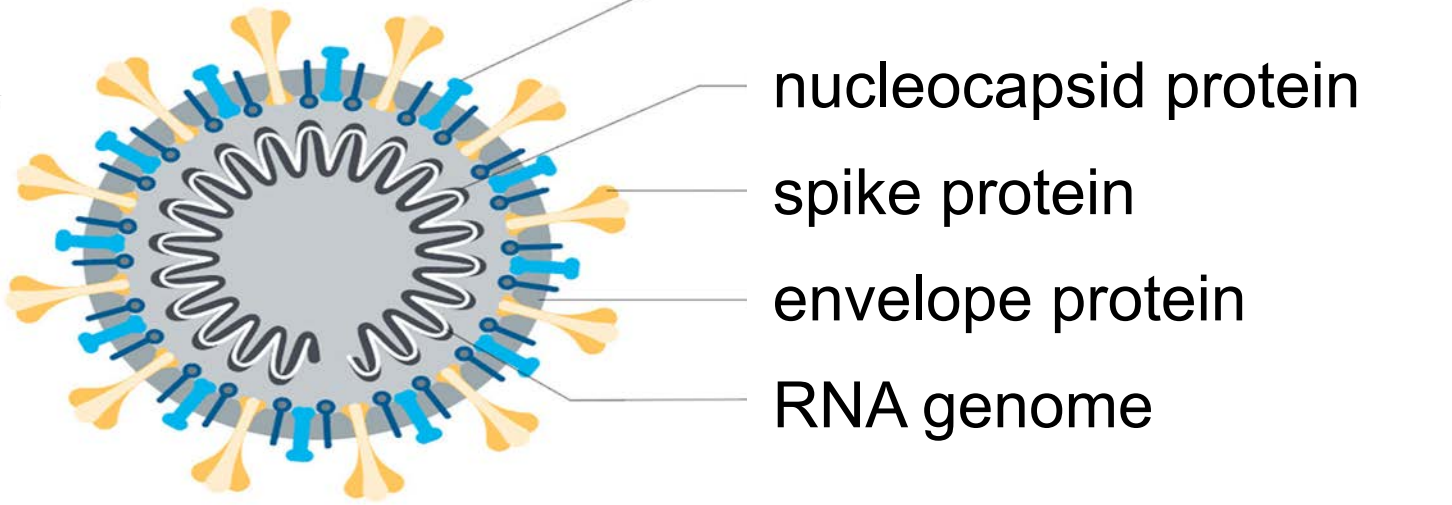
	Research Laboratory	Clinical Laboratory
Primary purpose	Derive new scientific knowledge	Return results to patients to be used in clinical care
Process	Laboratory notebook	Worksheets, Standard Operating Procedures, Proficiency, Equipment
Protected Health Information	None	Integral part (HIPAA, information security requirements)
Oversight	No licensing	CLIA, State, FDA, highly regulated

- Clinical Laboratory Improvements Amendment (CLIA) Legislature of 1988 to establish quality standards for all laboratory testing

Molecular Diagnostic tests for SARS-CoV-2

SARS-CoV-2 antibody





Adapted from Periris el al. Nat Med 2004

Nucleic Acid Tests - *test directly for viral RNA genome*
- Real Time Quantitative Polymerase Chain Reaction (RT-qPCR) - **'gold standard'**

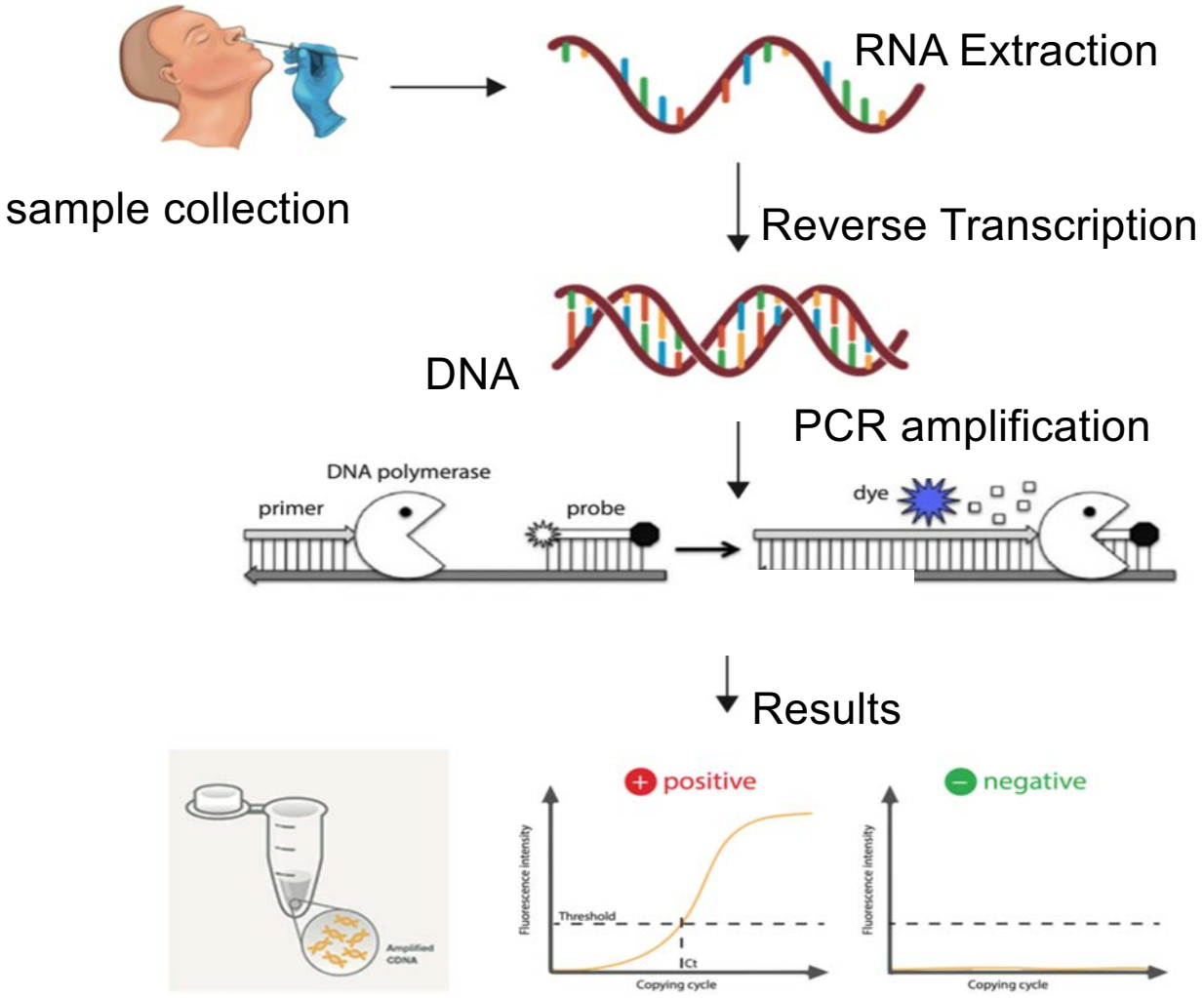
Antigen Tests - *test directly for presence of viral proteins*

Serological Tests - *test for the presence of SARS-CoV-2 antibodies*
- UCSC Serology Research Project - Rebecca Dubois, Jaqueline Kimmey, A. Marm Kilpatrik

Molecular Diagnostic tests for SARS-CoV-2: Antigen

- Ideal test: Cheap, fast and accurate
- Antigen Tests – Cheap and fast
- Rapid antigen tests are commonly used in the diagnosis of respiratory pathogens, including influenza viruses and respiratory syncytial virus (RSV). Has been recent approval for SARS-CoV-2.
- Rapid antigen tests perform best when the person is tested in the early stages of infection with SARS-CoV-2 when viral load is generally highest.
- Rapid antigen tests can be used for screening testing in high-risk congregate settings.

Real-time quantitative PCR (RT-qPCR) SARS-CoV-2 Test

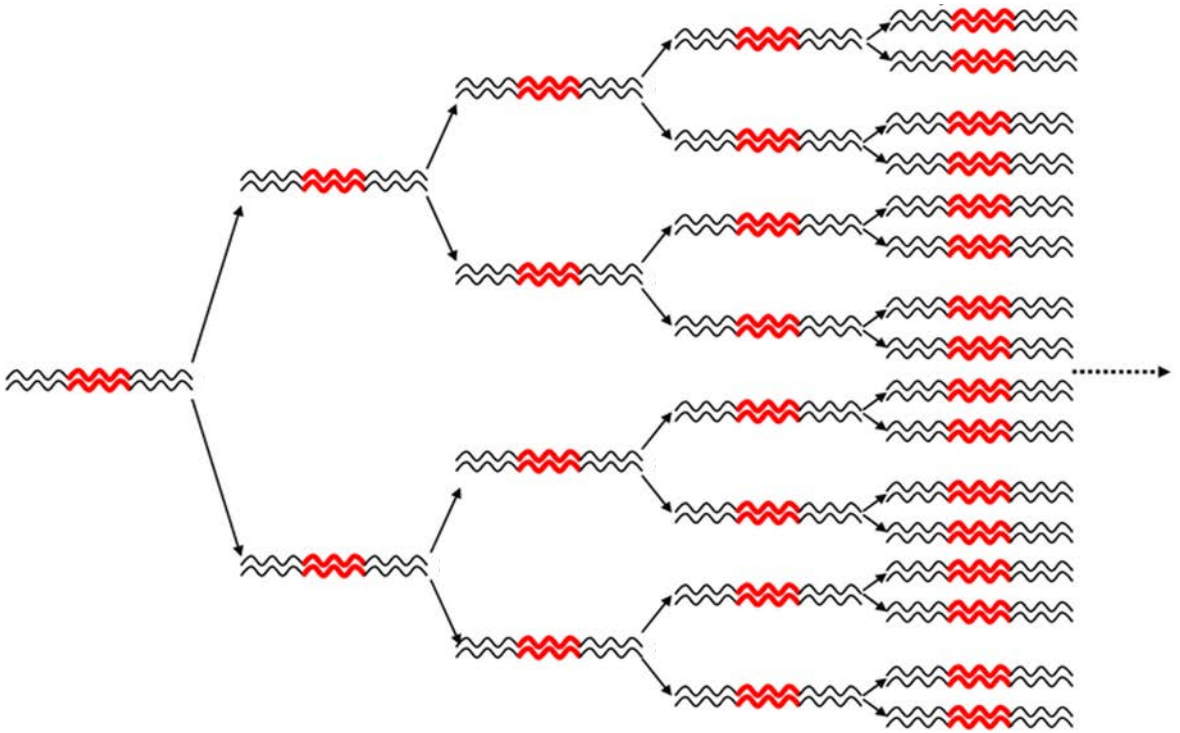


- Ideal test: Cheap, fast and accurate
- PCR tests – accurate
- Designed to be very specific for SARS-CoV-2
- Require the use of specialized equipment, chemicals and reagents (supply chain)
- Can develop methods to “pool” samples
- This is the method the UCSC MDL utilizes

The Polymerase Chain Reaction (PCR)

Exponential amplification by PCR permits detection down to one viral genome

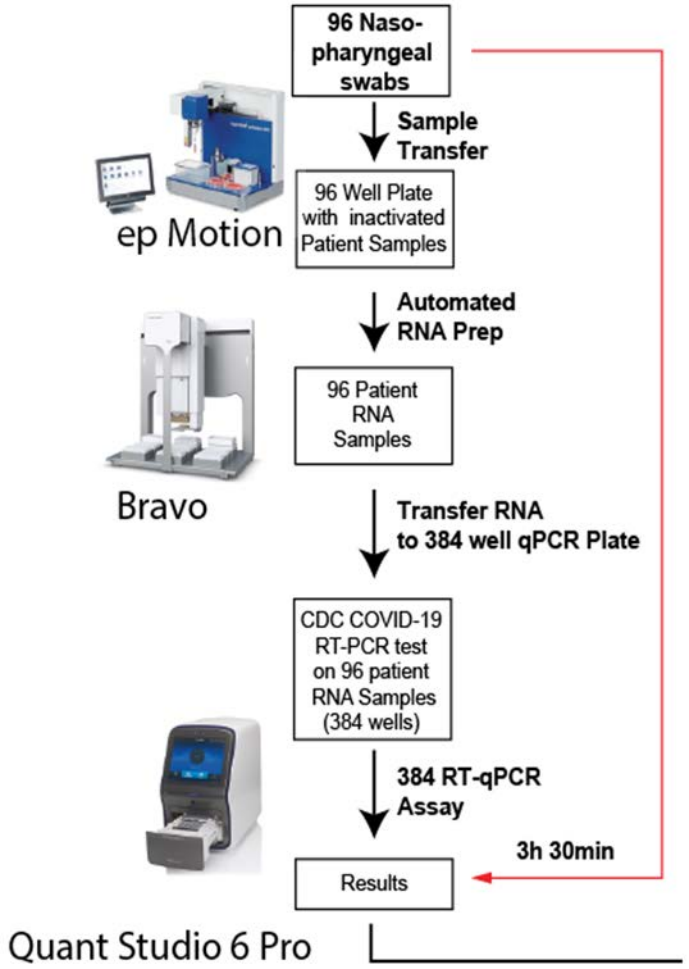
1
molecule



2^{40} = 1000
billion

$2^1 = 2$ $2^2 = 4$ $2^3 = 8$ $2^4 = 16$

UCSC MDL test details, automation, and capacity



The CDC SARS-CoV-2 Test - *validated*

- high analytical specificity
- good analytical sensitivity, ***~1500 viral genomes per mL***
- testing capacity ***~200-400 tests per day***

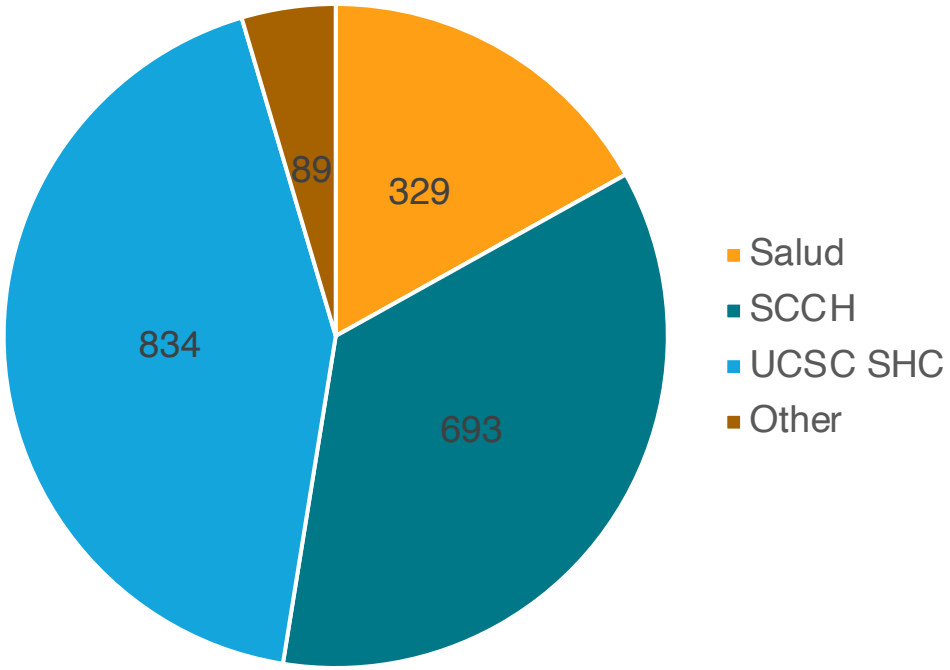
Multiplex SARS-CoV-2 Test - *validated, in process of transitioning to this test*

- ~ **7-fold boost in sensitivity**, ***~200 viral genomes per mL***
- will boost capacity to ***~1000 tests per day***

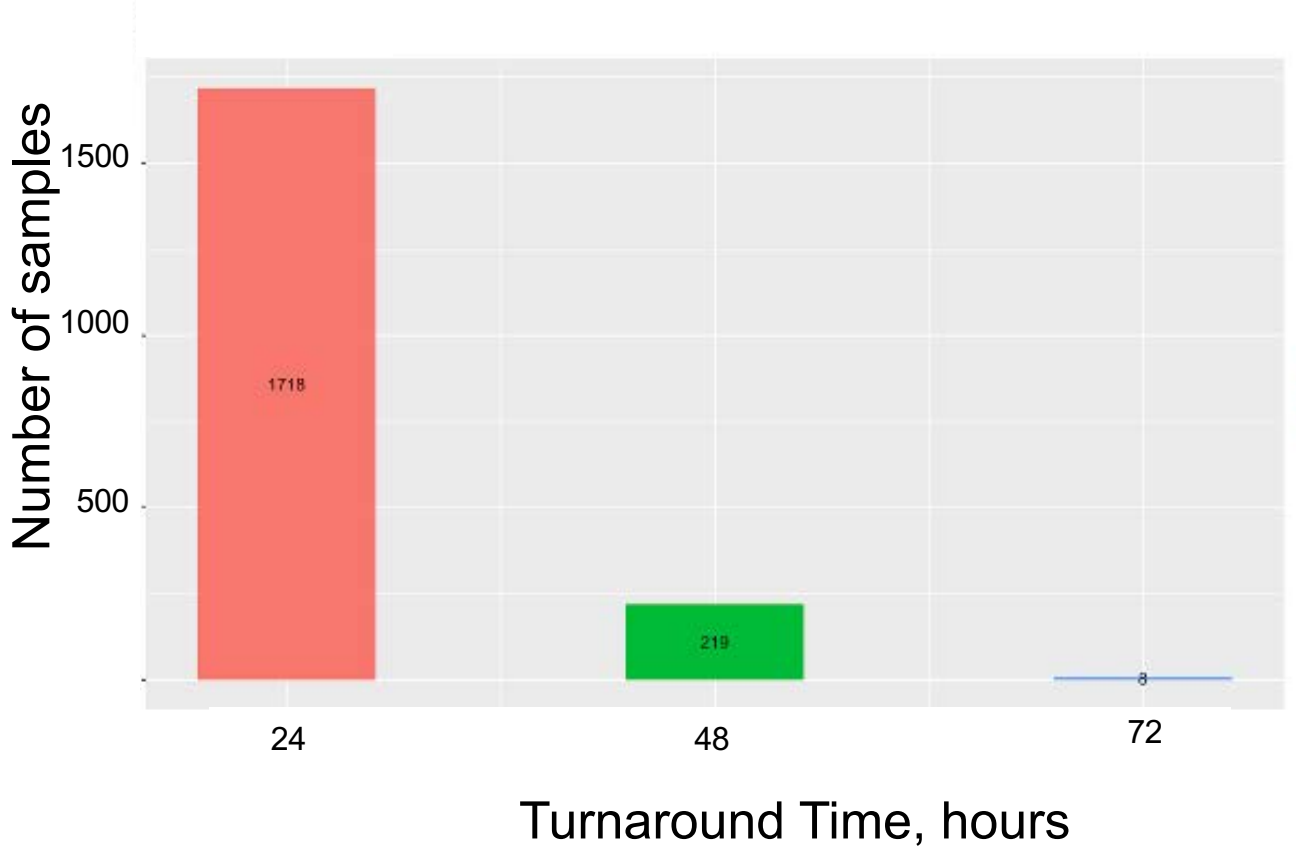
Dr. Nischay Mishra and Dr. W. Ian Lipkin
Columbia University

Processing Samples from clinical providers serving Santa Cruz County

Samples processed from 5/6/20-7/21/20



Importance of Turn Around Time: Average 28.9 hours



Sample turnaround time is the time from sample receipt to report sent to the clinical provider

Community Partners

Santa Cruz Women's Health Center

East Cliff Family Health Center

Santa Cruz Community Health Centers

Salud Para La Gente
A Network of Family Community Health Clinics

encompass
COMMUNITY SERVICES

COMMUNITY FOUNDATION
SANTA CRUZ COUNTY

Swab-a-Slug: Campus Asymptomatic Testing Program

- Main goal is to maintain the health and safety of our campus community.

- The majority of our students are in the 18-29 year old age group. This age group is known to have a high rate of SARS-CoV-2 infection without symptoms (asymptomatic), despite not having symptoms they are shedding virus and infectious to others.

- Acknowledge that students are social and will engage in riskier behaviors that could put them at higher risk of viral transmission. Routine testing will help identify positive before they spread.

- Controlling spread in campus population carries over to the Santa Cruz community.

Molecular Diagnostics Lab Team

Leadership Team
Jeremy Sanford
Olena Vaske
Isabel Bjork
Michael Stone
John MacMillan

Epidemiology
A. Marm Kilpatrik

UCSC Student Health Center Ralph Green, *Clinical Lab Director*
Elizabeth Miller, *Medical Director*
Frank Dang, IT

UCSC Legal Counsel
Erendira Rubin

Lab Technical Team
Namrita Dhillon
Jolene Draper
Terren Chang
Hannah Maul-Newby
Savanna Randi

Lab Operations Team
Anouk van den Bout
Yvonne Vasquez
Scott La
Ellen Kephart
Thea EgelHofer
Cayla McEwen

UCSC ITS
Brad Smith and Glenn Blackler

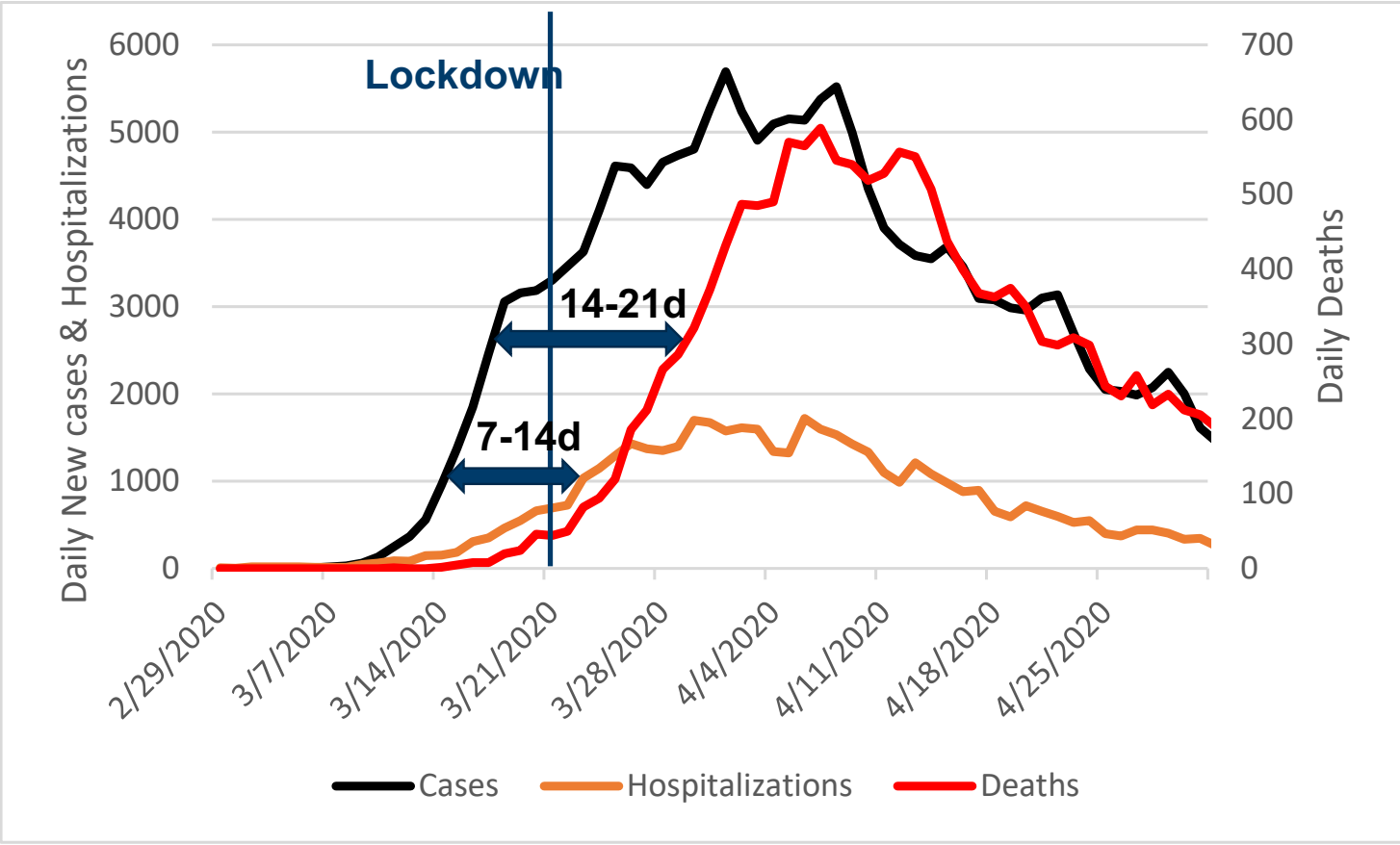
UCSC Administration
Chancellor Cindy Larive

Lori Kletzer (EVC and Provost)
Scott Brandt (VC of Research)
Sarah Latham (VC of BAS)

Relaxations of Federal and State regulatory guidelines helped

- **Laboratory CLIA License**
  - Extended CLIA license from UCSC Student Health Center to vacant UCSC research lab
- **Staff Licensing**
  - Requirements relaxed by Gov. Newsom's Executive Order of March 12, 2020
  - Any CA licensed Clinical Laboratory Scientist (CLS) can oversee COVID-19 testing
- **US FDA regulations**
  - Emergency Use Authorization (EUA) process

Threat of COVID-19: Ex. 1: speed & delays in NYC



- In 7d, confirmed cases went from 70 to 2455
- Lockdown March 22
- Confirmed cases increased for 2 weeks due to within-household transmission & delay b/w infection & illness
- Hospitalizations occur 7-14 d after cases
- Deaths occur 7-14 d after hospitalizations
- Lockdown was too late!