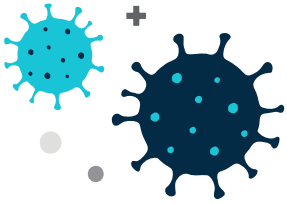

Webinar Slides

Virtual Grand Rounds: Post-Acute COVID Syndrome – In it for the Long Haul?

Overview

Our goal for this session is that you will be able to:

- Define post-acute COVID syndrome and summarize the current state of knowledge on this syndrome.
- Discuss the multi-symptom nature of this syndrome and consider strategies to diagnose and follow patients with prolonged symptoms attributed to COVID-19.
- Care for and counsel patients who experience prolonged symptoms of COVID-19.

These webinars will be available for on-demand playback at **cmadocs.org/webinars** and **covidroundsca.org**

April 13, 2021

CHHS California Health & Human Services Agency | CALIFORNIA MEDICAL ASSOCIATION | IN PARTNERSHIP WITH | CAPA

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Disclosure

The following speakers disclose no relevant financial relationships with commercial interests.

Kimberly Newell Green, M.D.; Michael Peluso, M.D.; Lekshmi Santhosh, M.D., MA.Ed.; and Erica Pan, M.D., MPH.

All other planners, staff and others involved with this activity have reported no relevant financial relationships with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients

This activity has not received commercial support.

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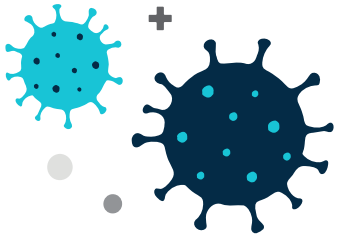
Agenda



- **Post-Acute Sequelae of COVID-19 (PASC) from the Bench to the Bedside.**
  - Michael Peluso, M.D., MPhil, MHS, DTM&H.
  - Lekshmi Santhosh, M.D., MA.Ed.
- **COVID-19 California Epidemiology and Vaccine Update**
  - Erica Pan, M.D., MPH
- **Q&A**

 3

3

Continuing Medical Education (CME) Offered

Learning Objectives:

- Define post-acute COVID syndrome and summarize the current state of knowledge on this syndrome.
- Discuss the multi-symptom nature of this syndrome and consider strategies to diagnose and follow patients with prolonged symptoms attributed to COVID-19.
- Care for and counsel patients who experience prolonged symptoms of COVID-19.

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Kimberly Newell Green M.D. – Moderator

Immediate Past President, San Francisco Marin Medical Society

Associate Clinical Professor, University of California, San Francisco

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University of California, San Francisco

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Lekshmi Santhosh, M.D., MA.Ed.

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University of California, San Francisco

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Post-acute sequelae of COVID-19 (PASC):
From the Bench to the Bedside

California Medical Association Grand Rounds

April 2021

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Disclosures

We have no disclosures to report.

9

9

Learning Objectives

By the end of this talk, you will be able to:

- **Discuss the different definitions & epidemiology of PASC (post-acute sequelae of COVID-19)**
- **Discuss possible biological mechanisms associated w/ PASC**
- **Discuss treatment strategies for patients w/ PASC done in post-COVID clinics**

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Case Definitions & Epidemiology

11

The scale of the SARS-CoV-2 pandemic is tremendous

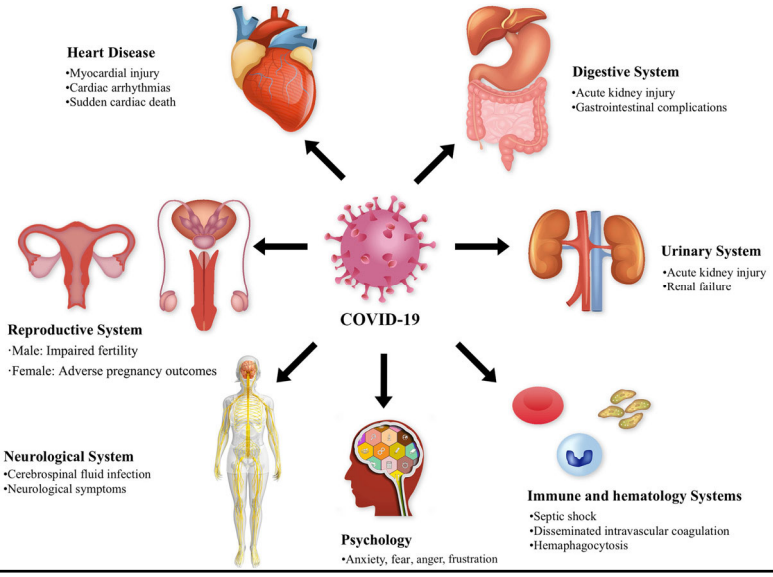
As of April 12, 2021:

			
Globally	136 million cases	2.94 million deaths	>130 million recovered
U.S.	31.2 million cases	562 thousand deaths	>30 million recovered

But not all COVID-19 recovery is the same

12

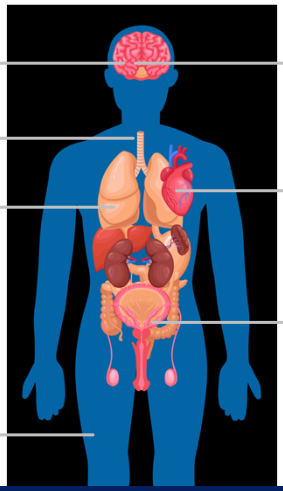
COVID-19 has multi-system effects during the acute phase



Zheng Medical Virology 2020

13

It is now clear that there is variability in COVID-19 recovery as well



Symptoms of distress

Loss of taste/smell

Chronic cough

Shortness of breath

Muscle aches
Neuropathy
Joint pain

Headaches

Trouble concentrating

Fatigue

Sleep disturbances

Palpitations

Chest pain

Orthostasis/POTS

Nausea or diarrhea
Poor appetite
Weight loss

Inter-patient variability
Waxing and waning
Hospitalized / Non-hospitalized
Decreased quality of life

14

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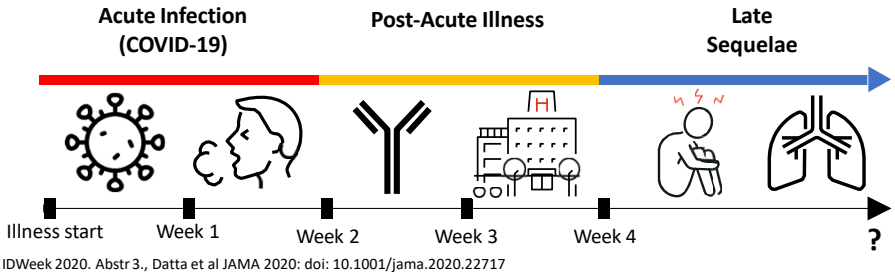
Timeline of SARS-CoV-2 Infection and Sequelae



Source: Datta. IDWeek 2020. Abstr 3., Datta et al JAMA 2020: doi: 10.1001/jama.2020.22717

For many people, COVID is not just a 10 to 14 day illness

Many notable efforts at UCSF, including:
Post-COVID clinics at UCSF/SFGH (OPTIMAL), PRIORITY study (pregnant/postpartum women and their newborns)


Lekshmi Santhosh


Josh Vasquez


Neeta Thakur


Vanessa Jacoby

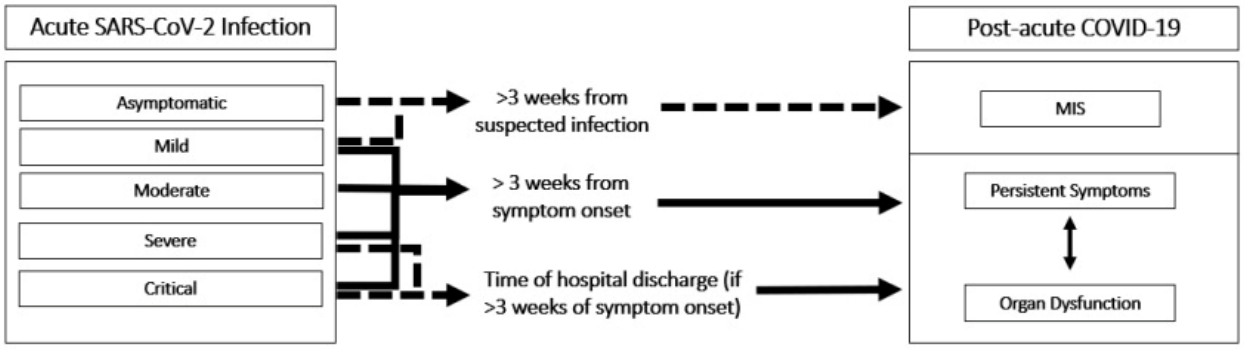

Stephanie Gaw


Valerie Flaherman

15

15

Symptoms Not Necessarily = Organ Dysfunction



Amenta OFID 2020

16

Key Question 1: How should PASC be defined?

- Currently, there is no accepted case definition for PASC
- What symptoms should be included?
  - Is someone with fatigue + cognitive issues the same as someone with GI issues or cardiopulmonary issues?
- What signs/objective findings should be included?
  - Are symptoms sufficient?
  - Are objective findings necessary? What if there are objective findings without symptoms?
- On what time-scale?
  - 3 weeks? Most people will get better.
  - 3 months? Some people could still get better.

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Reports of post-acute symptoms in hospitalized and non-hospitalized patients emerged early in the pandemic

Vox

The emerging long-term complications of Covid-19, explained

"It is a true roller coaster of symptoms and severities, with each new day offering many unknowns."

By Lois Parshley | May 8, 2020, 1:10pm EDT

The New York Times

Surviving Covid-19 May Not Feel Like Recovery for Some

Debilitating symptoms can last long after a person's body has gotten rid of the coronavirus, a reality Italians are now confronting.

npr

PRESS PLAY WITH MADELEINE BRAND

Think COVID-19 lasts 2 weeks? This patient has been suffering for months

Hosted by Madeleine Brand • Jul. 24, 2020 CORONAVIRUS

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More recently, these observations have been confirmed in the scientific literature

Office for National Statistics

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 1 April 2021

- Using population survey and NHS data (20,000 participants):
  - 13.7% experienced symptoms beyond 12 weeks

nature medicine

Attributes and predictors of long COVID

- 4182 incident cases (no prior issues)
  - Symptoms > 4 weeks: 13.3%
  - Symptoms > 8 weeks: 4.5%
  - Symptoms > 12 weeks: 2.3%

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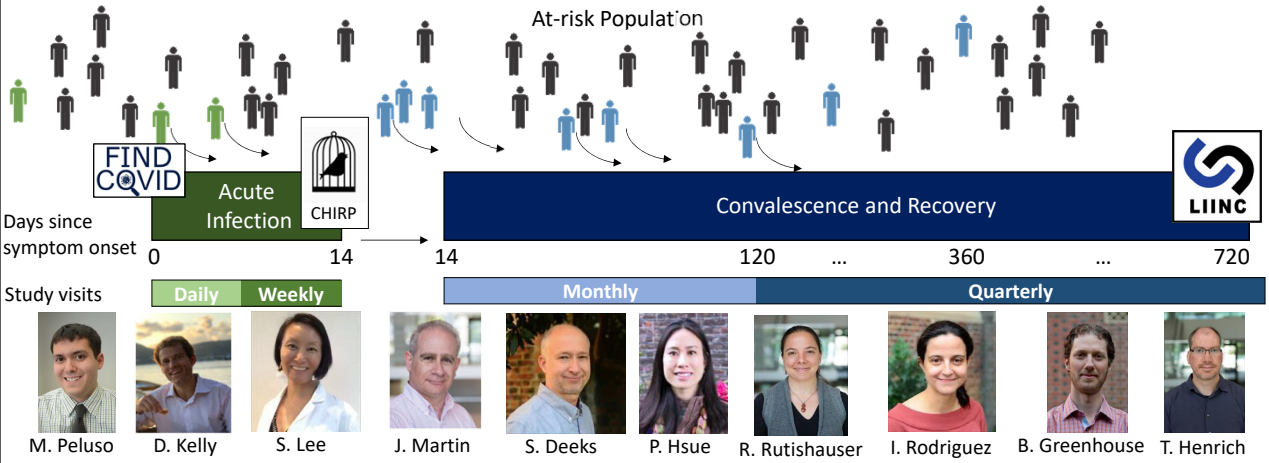
The LIINC study investigates COVID sequelae



Many key partners: IRB, Dept of Medicine, ID Divisions across hospitals, Div Exp Med, DPH, CTSI

300+ enrolled (~130 with PASC) and deeply phenotyped, many now with ~1 year of follow-up; thousands of samples collected and distributed

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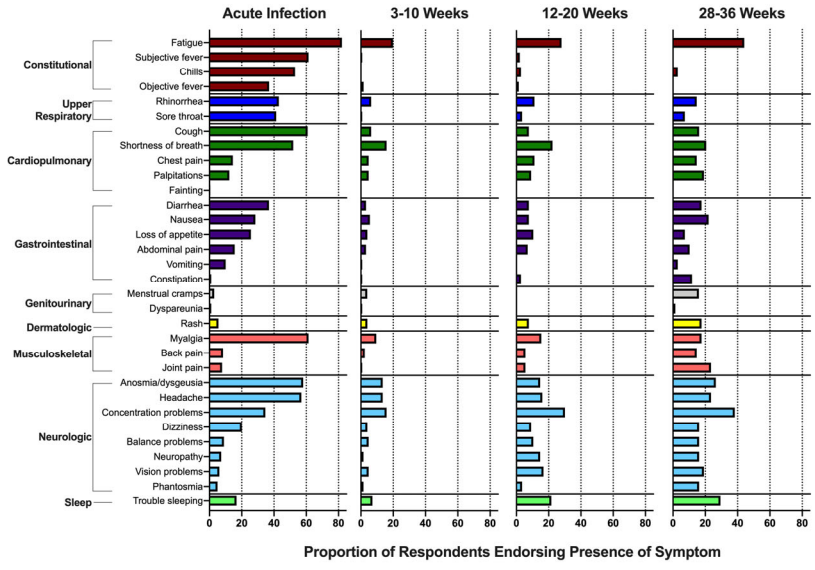
Many LIINC participants have persistent symptoms not present prior to acquiring COVID-19



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There appears to be a small but significant effect on quality of life

Quality of Life Domain	Response	Before Illness (n=92)	Worst Point (n=179)	Week 16 (n=117)	Week 32 (n=66)
Mobility	No problems	91%	39%	85%	77%
"Which of the best describes your ability to walk about?"	Slight problems	6.0%	10%	9.0%	11%
	Moderate problems	2.0%	29%	4.0%	8.0%
	Severe problems	0%	4.0%	1.0%	4.0%
	Unable to walk	1.0%	18%	0.0%	0.0%
Self-care	No problems	95%	60%	96%	90%
"Which of the following describes your ability to wash and dress yourself?"	Slight problems	1.0%	6.5%	1.0%	6.0%
	Moderate problems	4.0%	17%	2.0%	4.0%
	Severe problems	0%	1.5%	1.0%	0%
	Unable to wash or dress	0%	15%	0%	0%
Usual activities	No problems	95%	31%	81%	77%
"Which of the following describes your ability to perform your usual activities?"	Slight problems	2.0%	11%	11%	14%
	Moderate problems	1.0%	23%	6.0%	1.0%
	Severe problems	2.0%	7.0%	2.0%	5.0%
	Unable to do usual activities	0%	28%	0%	3.0%
Pain/discomfort*	No pain or discomfort	70%	27%	65%	52%
"Which of the following describes how much pain or discomfort you felt?"	Slight pain or discomfort	20%	13%	14%	26%
	Moderate pain or discomfort	7.0%	26%	17%	15%
	Severe pain or discomfort	3.0%	24%	3.0%	2.0%
	Extreme pain or discomfort	0%	10%	1.0%	5.0%
Anxiety/depression*	No anxiety or depression	51%	18%	48%	43%
"Which of the following describes how anxious or depressed you felt?"	Slight anxiety or depression	27%	23%	31%	32%
	Moderate anxiety or depression	17%	24%	15%	14%
	Severe anxiety or depression	2.0%	17%	4.0%	6.0%
	Extreme anxiety or depression	3.0%	18%	2.0%	5.0%
Visual analogue scale					
"On a scale of 0 to 100, we would like to know how good or bad your health was…"		85 (75 to 90)	50 (25 to 65)	80 (70 to 90)	80 (75 to 90)

Rapid implementation of a cohort for the study of post-acute sequelae of SARS-CoV-2 infection/COVID-19

Michael J. Peluso[1,4,5], J. Daniel Kelly[2,3+], Scott Lu[2], Sarah A. Goldberg[2], Michelle C. Davidson[2], Sujata Mathur[2], Matthew S. Durstenfeld[4], Matthew A. Spinelli[1], Rebecca Hoh[1], Viva Tai[1], Emily A. Fehrman[1], Leonel Torres[1,5], Yanel Hernandez[1], Meghann C. Williams[1], Mireya I. Arreguin[1], Jennifer A. Bautista[1], Lynn H. Ngo[1], Monika Deswal[1], Sadie E. Munter[1,5], Enrique O. Martinez[1,5], Khamal A. Anglin[2], Mariela D. Romero[2], Jacqueline Tavs[2], Paulina R. Rugart[2], Jessica Y. Chen[2,3], Hannah M. Sans[2], Victoria W. Murray[1], Payton K. Ellis[2], Kevin C. Donohue[2], Jonathan A. Massachi[2], Jacob O. Weiss[2], Irum Mehdi[2], Jesus Pineda-Ramirez[2], Alex F. Tang[2], Megan Wenger,[2] Melissa Assenzio,[2] Yan Yuan,[2] Melissa Krone,[2] Rachel L. Rutishauser[2], Isabel Rodriguez-Barraquer[1], Bryan Greenhouse[1], John A. Sauceda[6], Monica Gandhi[1], Priscilla Y. Hsue[4], Timothy J. Henrich[3], Steven G. Deeks[1], Jeffrey N. Martin[2]

Severe symptomology occurs and persists, but is uncommon

22

LIINC: Mental health assessments

Mental Health Symptoms and Severity	Week 16 (n = 119)*	Week 32 (n = 65)*
Symptoms of anxiety (GAD-7 total score)†		
Minimal (0 to 4)	68 (44%)	33 (51%)
Mild (5 to 9)	86 (56%)	32 (49%)
Moderate (10 to 14)	0 (0%)	0 (0%)
Severe (15 to 21)	0 (0%)	0 (0%)
Symptoms of depression (PHQ-8 total score)†		
None (0 to 4)	70 (54%)	39 (54%)
Mild (5 to 9)	19 (17%)	12 (20%)
Moderate (10 to 14)	13 (12%)	5 (8.0%)
Moderately severe (15 to 19)	4 (3.5%)	3 (5.0%)
Severe (20 to 24)	4 (3.5%)	2 (3.0%)
Symptoms of post-traumatic stress disorder (PCL-5 total score)†,§		
Score ≥ 10	6 (6.0%)	7 (11%)

Post-COVID symptoms of distress are common

23

Evidence of organ system abnormalities in late recovery

Journal of NeuroVirology — Dedicated to Neurological Infections

Persistent COVID-19-associated neurocognitive symptoms in non-hospitalized patients

First report of persistent neurocognitive symptoms; impetus for Coronavirus Neurocognitive Study (CNS, PI: J. Hellmuth)

THE LANCET

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Persistent symptoms associated with abnormal chest imaging; now working to characterize pulmonary recovery (PI: L. Huang)

JAMA Cardiology

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

High proportion of abnormal cardiac MRI findings; impetus for Cardiovascular Impact Study (PI: P. Hsue)

Efforts now underway to deeply characterize PASC, there might be several different "phenotypes" of PASC

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Key Question 1: How should PASC be defined?

Cardiovascular Impact Study
(P. Hsue, M. Durstenfeld)

Pulmonary Recovery Study
(L. Huang)

Coronavirus Neurocognitive Study
(J. Hellmuth, F. Chow, M. Greene)

No agreed upon definition.
There might be several different "phenotypes" of PASC.

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Key Question 2: How common is PASC?

- Prevalence of 2-90% has been reported
- Most study populations <u>not representative</u>:
  - Are people who are not feeling well motivated to enroll (over-represented)?
  - Are people who are not feeling well too disabled to participate (under-represented)?

No one knows. But even if uncommon (<5%),
the sheer numbers are problematic (5% of 30M is 1.5M).

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Key Question 3: Who gets PASC?

- Determining who may develop PASC can guide care and research

nature medicine

Attributes and predictors of long COVID

- Increasing age (up to 70)
- Increasing BMI
- Female sex
- >5 symptoms during first week of illness
- Pre-existing, activity-limiting conditions
- Lower socioeconomic status

Office for National Statistics

Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK:

Predictors of clinical symptoms, objective findings, and symptom trajectory will all need to be identified.

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Biology of PASC

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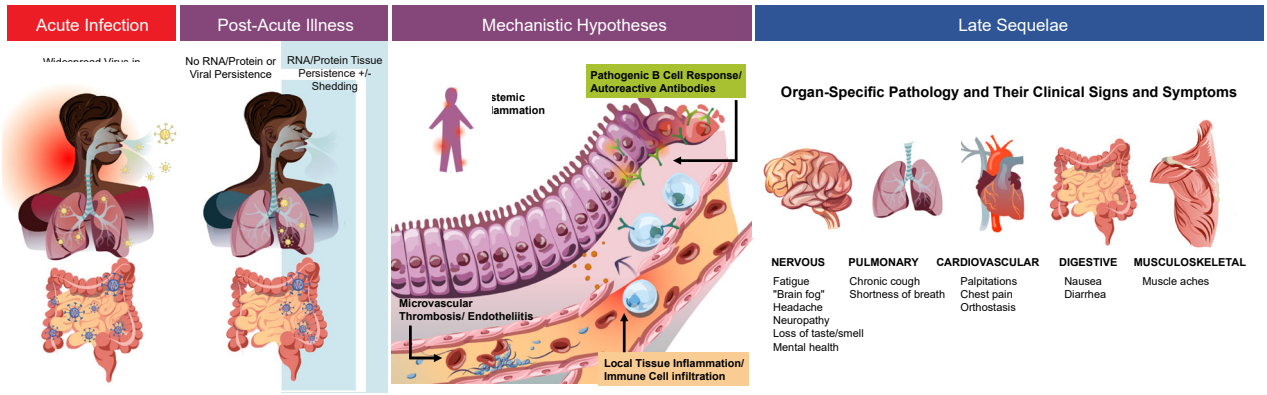
Key Question 4: What is the biology of PASC?



Artwork: Shirley Shao, UCSF MS2

Studies like LIINC are well-positioned to answer these questions

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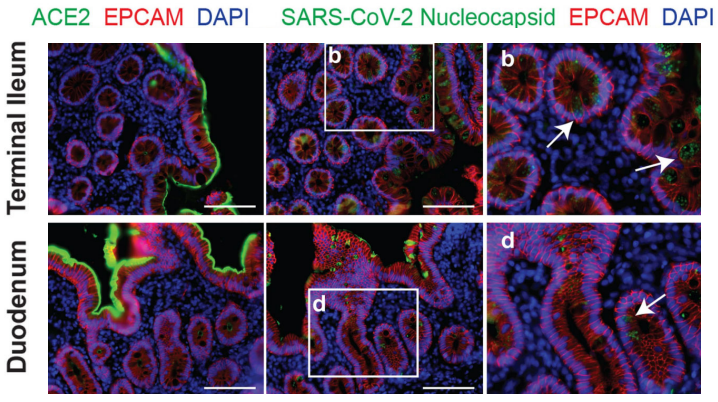
SARS-CoV-2 persists in gut tissue for > 6 months

nature

Evolution of antibody immunity to SARS-CoV-2

Christian Gaebler, Zijun Wang, Julio C. C. Lorenzi, Frauke Muecksch, Shlomo Finkin, Minami Tokuyama, Alice Cho, Mila Jankovic, Dennis Schaefer-Babajew, Thiago Y. Oliveira, Melissa Cipolla, Charlotte Viant, Christopher O. Barnes, Yaron Bram, Gaëlle Breton, Thomas Hägglöf, Pilar Mendoza, Arlene Hurley, Martina Turroja, Kristie Gordon, Katrina G. Millard, Victor Ramos, Fabian Schmidt, Yiska Weisblum, Divya Jha, Michael Tankelevich, Gustavo Martinez-Delgado, Jim Yee, Roshni Patel, Juan Dizon, Cecille Unson-O'Brien, Irina Shimeliovich, Davide F. Robbiani, Zhen Zhao, Anna Gazumyan, Robert E. Schwartz, Theodora Hatziioannou, Pamela J. Bjorkman, Saurabh Mehandru, Paul D. Bieniasz, Marina Caskey & Michel C. Nussenzweig -Show fewer authors



Memory B cells display clonal turnover after 6 months, and express a continually evolving antibody response

Viral activity detectable in intestinal biopsies obtained from asymptomatic individuals at month 4 in 7 out of 14people

30

Immune dysregulation is associated with adverse outcomes in acute COVID-19

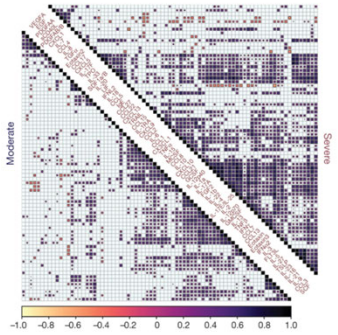
nature

Article

Longitudinal analyses reveal immunological misfiring in severe COVID-19

https://doi.org/10.1038/s41586-020-2588-y
Received: 23 June 2020
Accepted: 21 July 2020
Published online: 27 July 2020
Check for updates

Carolina Lucas[1,17], Patrick Wong[1,17], Jon Klein[1,17], Tiago B. R. Castro[2,17], Julio Silva[1], Maria Sundaram[3], Mallory K. Ellingson[3], Tianyang Mao[1], Ji Eun Oh[1], Benjamin Israelow[1,4], Takehiro Takahashi[1], Maria Tokuyama[1], Peiwen Lu[1], Arvind Venkataraman[1], Annsea Park[1], Subhasis Mohanty[4], Haowei Wang[4], Anne L. Wyllie[3], Chantal B. F. Vogels[3], Rebecca Earnest[3], Sarah Lapidus[3], Isabel M. Ott[3], Adam J. Moore[3], M. Catherine Muenker[3], John B. Fournier[4], Melissa Campbell[4], Camila D. Odio[4], Arnau Casanovas-Massana[3], Yale IMPACT Team*, Roy Herbst[5], Albert C. Shaw[4], Ruslan Medzhitov[1,6], Wade L. Schulz[7,8], Nathan D. Grubaugh[3], Charles Dela Cruz[9], Shelli Farhadian[4], Albert I. Ko[3,4], Saad B. Omer[3,4,10] & Akiko Iwasaki[1,4]✉



- **Core COVID signature: IL-1a, IL-1b, IL-17A, IL12p70, IFN-a**
- **Identified cytokine clusters present early that was associated with longer hospitalization and death**
- **We are actively working to define this in COVID recovery**

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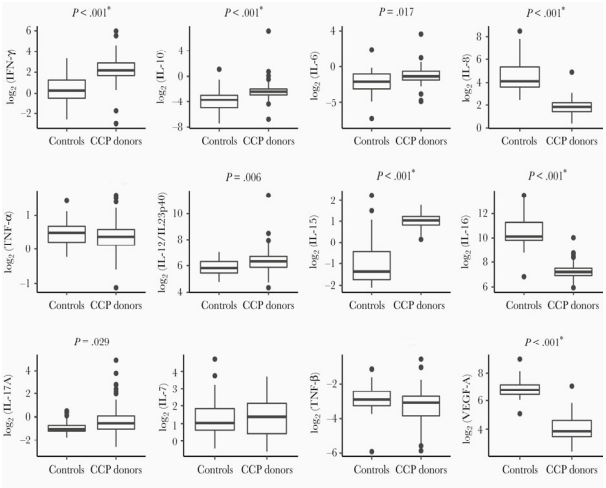
Some early data showing interesting trends during COVID recovery, even in people who feel well

Open Forum Infectious Diseases

Cytokine and Chemokine Levels in Coronavirus Disease 2019 Convalescent Plasma

- Cross-sectional study of 140 convalescent plasma donors at median 44 days
- Compared to pre-pandemic healthy donors



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Early data regarding autoimmunity

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

New-Onset IgG Autoantibodies in Hospitalized Patients with COVID-19

- Autoantibodies in 50% of COVID-19 patients but 15% of controls that tracked with anti-SARS-CoV-2 IgG

Distinct Autoimmune Antibody Signatures Between Hospitalized Acute COVID-19 Patients, SARS-CoV-2 Convalescent Individuals, and Unexposed Pre-Pandemic Controls

- Autoantibodies in 5/5 with persistent symptoms and 2/4 without symptoms

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

Exploratory neuroimmune profiling identifies CNS-specific alterations in COVID-19 patients with neurological involvement

- CSF antibodies differed from serum antibodies
- Significant burden of CNS autoimmunity

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NIH prioritization for studying PASC

NIH National Institutes of Health
Turning Discovery Into Health

Research Opportunity Announcement
OTA-21-015B
Post-Acute Sequelae of SARS-CoV-2 Infection Initiative:
SARS-CoV-2 Recovery Cohort Studies

We and others from UCSF are pursuing these opportunities to answer key questions for clinicians and patients.

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Management of PASC

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Key Question 5: How do we manage PASC?

- Will new preventative (vaccines) or therapeutic (monoclonal antibodies) interventions change the incidence of PASC?
- Do certain interventions help patients manage PASC symptoms?
- Do certain interventions treat PASC and cause it to resolve?

There is an urgent need for interventional studies, which may also help to define the underlying biology.

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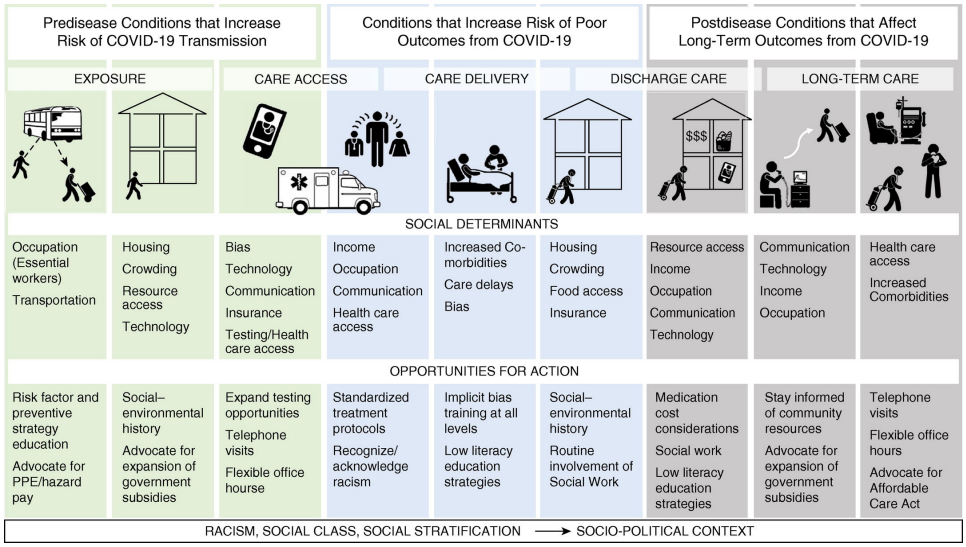
There are several early studies suggesting disparities in PASC



Thakur AJRCCM 2020

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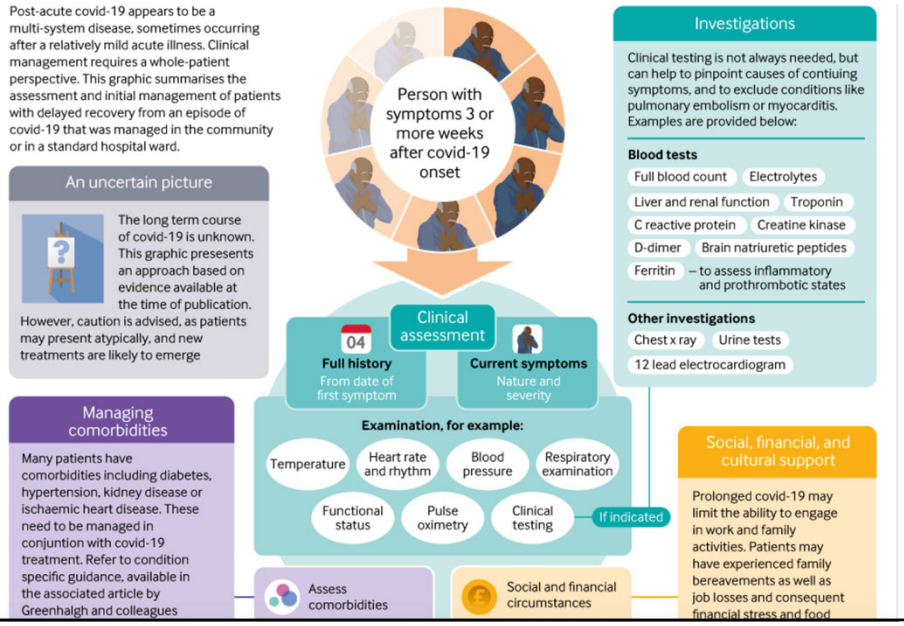
What do the guidelines say? BMJ Recs



Greenhalgh BMJ 2020

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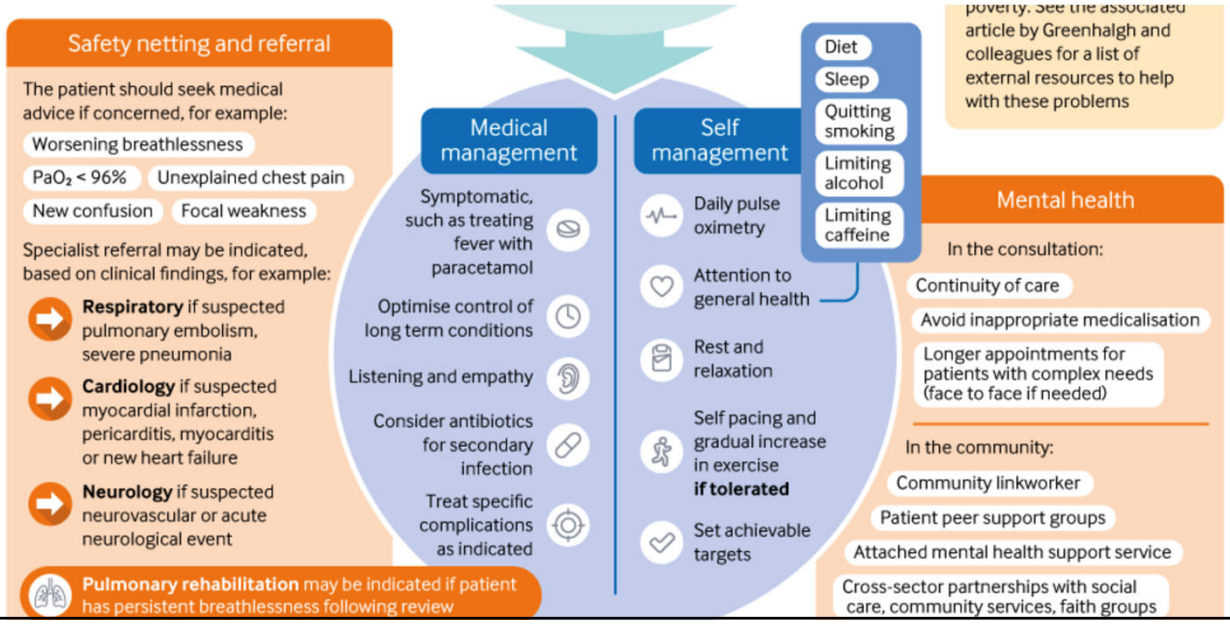
BMJ Recs Continued



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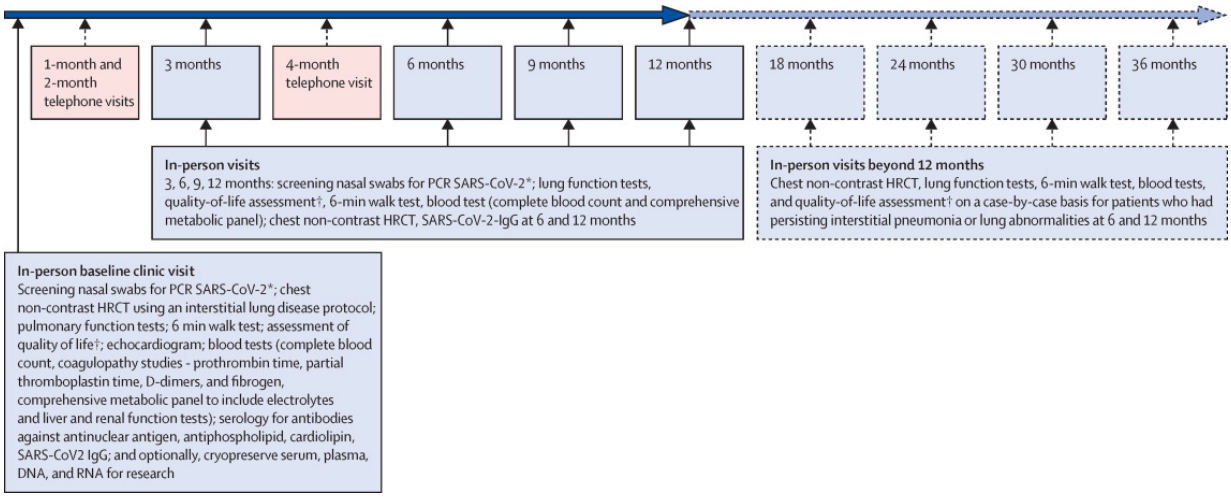
How Long to Follow Patients?



Raghu Lancet 2020

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ATS/ERJ Recs: More Research Qs than As!

The Task Force identified the following research needs for previously hospitalized patients with COVID-19 pneumonia who were discharged in the past 30–60 days
Routine testing to establish a new baseline?
Pulmonary function testing
6-min walk test
Computed tomography of the chest
Transthoracic echocardiography
Routine screening for:
Cognitive impairment
Depression
Anxiety & PTSD
Post-traumatic stress disorder

Bai Eur Resp Review 2020

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ATS/ERJ Recs: More Research Qs than As!

Continue prophylactic anticoagulant therapy as outpatients until the D-dimer normalises?
Serological testing to assess immune response to the infection?
Attending medical visits without screening for active infection if serological tests positive?
Serological testing of household contacts to determine if mild or asymptomatic infection?
Referral to a multidisciplinary clinic for post-intensive care syndrome?
Referral to pulmonary rehabilitation regardless of lung function?
Routine referral for mental health counselling?

Bai Eur Resp Review 2020

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One of my patients: from COVID ICU to post-COVID Clinic

Mrs. L is an 83-year-old Spanish-speaking woman recently discharged following hospitalization for COVID-19 pneumonia. She has T2DM, HTN, and hearing loss. She lives with her daughter, who is her DPOA.

She is discharged to subacute rehab at a local skilled nursing facility.

During hospitalization she required HFNC in the ICU. She is discharged home on room air, yet remains breathless, anxious, and socially isolated.

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Ambulatory Follow-Up for COVID-19: The OPTIMAL Clinic (pOst-covid/PosT-Icu MultidisciplinAry cLinic)

- New at UCSF - Multidisciplinary Clinic b/w Pulm, Geriatrics, Psych, Integrative Medicine, & partnerships with Cardiology, Neurology
- Integrated clinical follow-up and research arms
- Will see patients ~4 weeks post-discharge (virtual visit), 3 month, 6 month, 9 month, 12 months post-discharge
- Please refer any pts who were admitted to the ward or ICU w/ COVID

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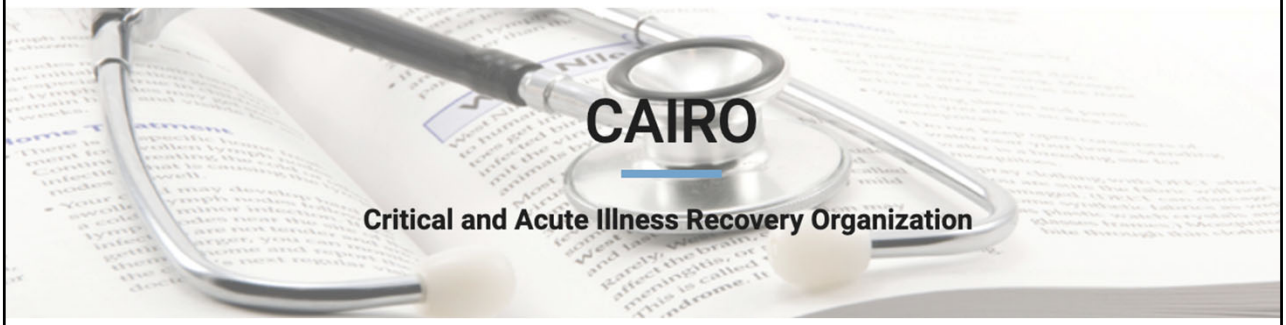
OPTIMAL Demographics: > 300 Pts Seen



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Ambulatory Follow-Up for COVID-19: The OPTIMAL Clinic (pOst-covid/PosT-Icu MultidisciplinAry cLinic)

Journal Pre-proof

"How I Do It: Rapid Design & Implementation of Post-COVID Clinics"

Lekshmi Santhosh, M.D., M.A.Ed, Brian Block, M.D., Soo Yeon Kim, M.D., Sarath Raju, M.D., M.P.H., Rupal J. Shah, M.D., M.S., Neeta Thakur, M.D., M.P.H., Emily Pfeil Brigham, M.D., M.H.S., Ann Marie Parker, M.D. PhD

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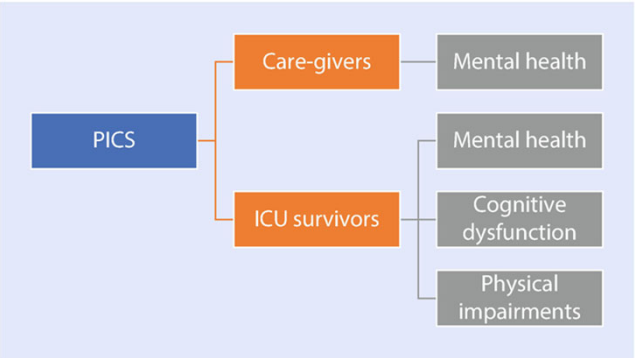
Post-Intensive Care Syndrome (PICS) Framework

- Holistic approach to caregivers & patients - translatable to COVID
  - Pulmonary impairments
  - Physical impairments
  - Cognitive dysfunction
  - Mental Health



Flaaten 2019 PICS

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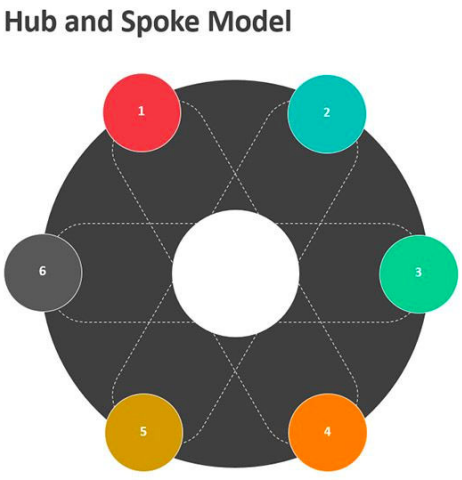
Outpatient Follow-Up Structure

OPTIMAL Hub with Collaborations:

- Integrative Medicine
- Cardiology
- Electrophysiology
- Neuro Recovery Clinic
- Pulmonary Rehab
- Virtual Support Groups
- Psychiatry & Behavioral Health
- Infection Control
- Primary Care



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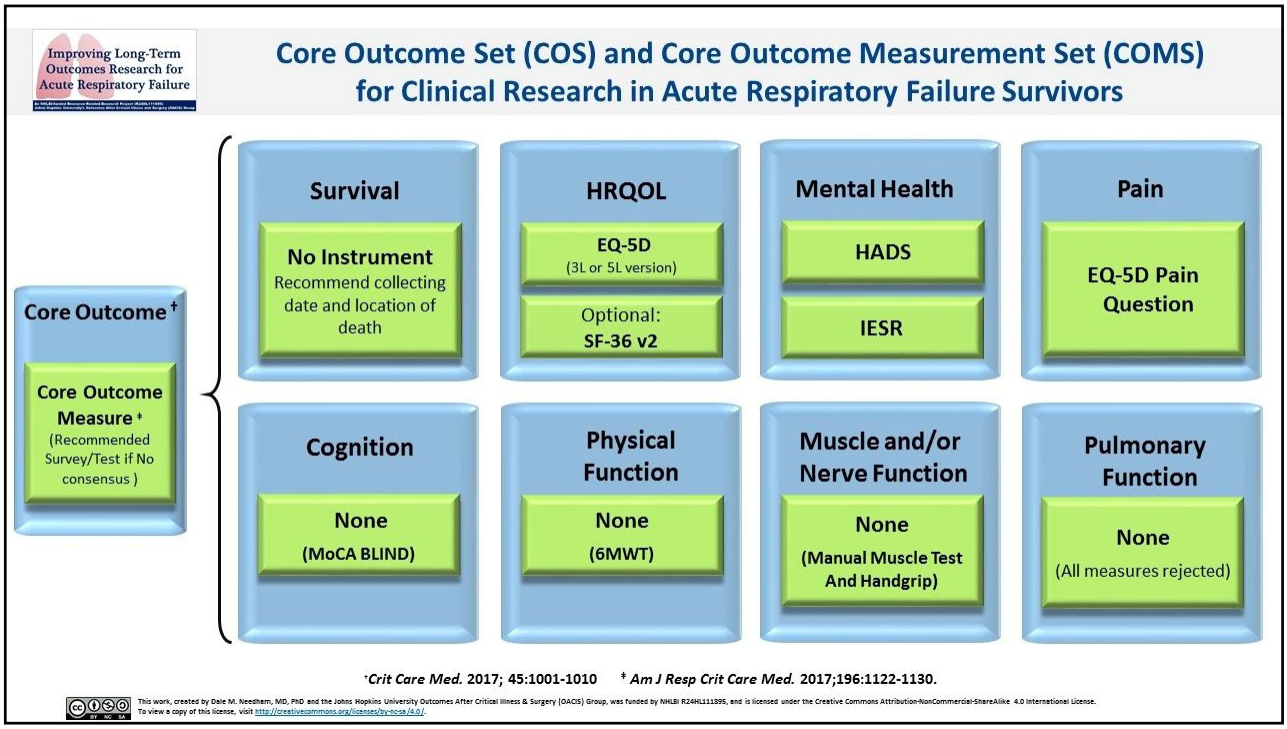

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Outpatient Follow-Up Structure

- Trained mental health research assistant administers structured instruments for:
  - Breathlessness (MMRC, BCSS)
  - Anxiety (GAD-7)
  - Depression (PHQ-9)
  - Cognitive function (MOCA)
  - PTSD (PCL-15)
  - Physical function (AMPAC)
  - Screening for SDOH
- Detailed Med Rec By Pharmacists
- Counseling re: Activity
- Reassurance & Linkage to Resources

Illustration: Anna & Elena Balbusso, UCSF Magazine

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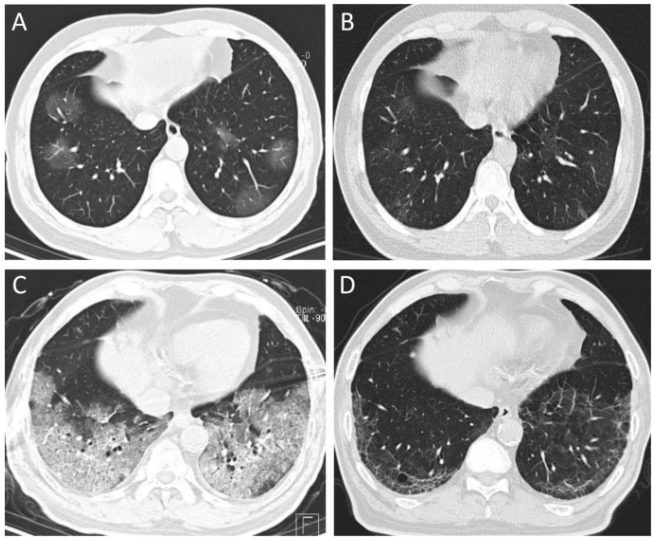
Persistent Pulmonary Issues: Compared to?



Huang Resp Research 2020

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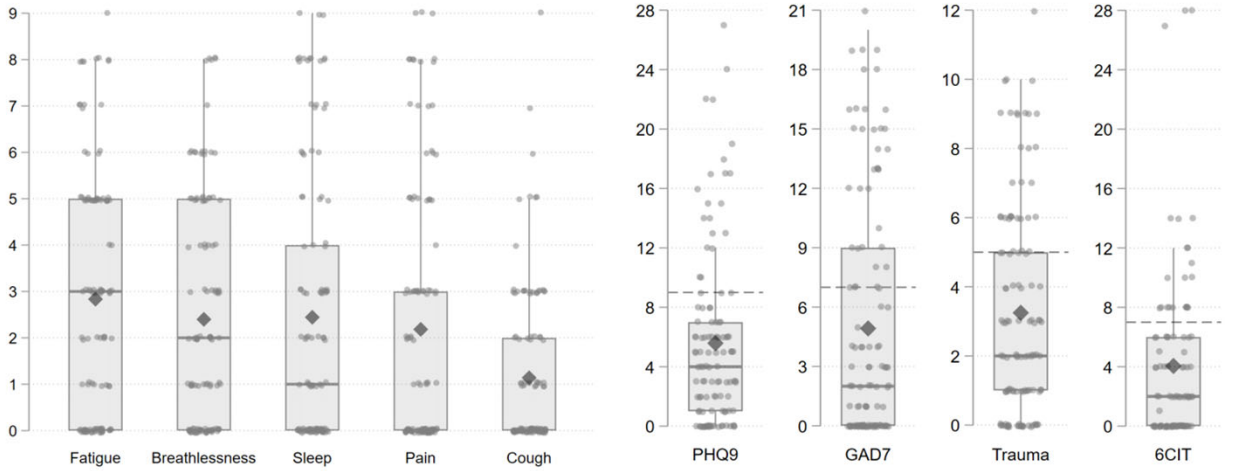
ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia



D'Cruz ERJ 2020

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Lessons from the Post-ARDS Literature

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2011 VOL. 364 NO. 14

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

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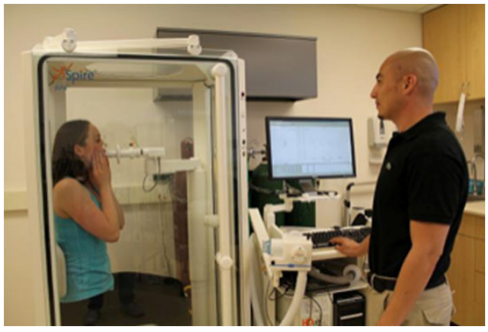
UCSF OPTIMAL Approach to Diagnostics

- Pulmonary Function Tests
  - I like to include 6MWT
- If DLCO is low, consider CT chest
- Also consider TTE
- Labs:
  - CBC diff, ESR/CRP, Thyroid, +/- CPK



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[Critical Care Original Research] CHEST

Fatigue Symptoms During the First Year Following ARDS

Karin J. Neufeld, MD, MPH; Jeannie-Marie S. Leoutsakos, PhD, MHS; Haijuan Yan, PhD; Shihong Lin, MS; Jeffrey S. Zabinski, MD; Victor D. Dinglas, MPH; Megan M. Hosey, PhD; Ann M. Parker, MD; Ramona O. Hopkins, PhD; and Dale M. Needham, MD, PhD

BACKGROUND: Fatigue is commonly reported by ARDS survivors, but empirical data are scarce.

RESEARCH QUESTION: This study evaluated fatigue prevalence and associated variables in a prospective study of ARDS survivors.

STUDY DESIGN AND METHODS: This analysis is part of the ARDSNet Long-Term Outcomes Study (ALTOS) conducted at 38 US hospitals. Using age- and sex-adjusted, time-averaged random effects regression models, we evaluated associations between the validated Functional Assessment of Chronic Illness Therapy-Fatigue Scale with patient and critical illness variables, and with physical, cognitive, and mental health status at 6 and 12 months following ARDS.

RESULTS: Among ARDS survivors, 501 of 711 (70%) and 436 of 659 (66%) reported clinically significant symptoms of fatigue at 6 and 12 months, respectively, with 41% and 28% reporting clinically important improvement and worsening (n = 638). At 6 months, the prevalence of fatigue (70%) was greater than that of impaired physical functioning (50%), anxiety (42%), and depression (36%); 46% reported both impaired physical function and fatigue, and 27% reported co-existing anxiety, depression, and fatigue. Fatigue was less severe in men and in those employed prior to ARDS. Critical illness variables (eg, illness severity, length of stay) had little association with fatigue symptoms. Worse physical, cognitive, and mental health symptoms were associated with greater fatigue at both the 6- and 12-month follow-up.

INTERPRETATION: During the first year following ARDS, more than two-thirds of survivors reported clinically significant fatigue symptoms. Due to frequent co-occurrence, clinicians should evaluate and manage survivors' physical, cognitive, and mental health status when fatigue is endorsed.

CHEST 2020; 158(3):999-1007

KEY WORDS: acute lung injury; cognitive function; depression; disability; rehabilitation

FOR EDITORIAL COMMENT, SEE PAGE 848

ABBREVIATIONS: APACHE III = Acute Physiology and Chronic Health Evaluation III; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; SF-36v2 = Short Form-36 Version 2

AFFILIATIONS: From the Department of Psychiatry and Behavioral Sciences (Drs Neufeld, Leoutsakos, Yan, and Zabinski; and Mr Lin), Division of Pulmonary and Pulmonary and Critical Care Medicine (Mr Dinglas and Drs Parker and Needham), Department of Physical Medicine and Rehabilitation (Drs Hosey and Needham), and, Outcomes After Critical Illness and Surgery (OACIS) Group, (Drs Neufeld, Leoutsakos, Hosey, Parker, and Needham; and Mr Dinglas) Johns Hopkins University School of Medicine, Baltimore, MD; Neuroscience Center and Psychology Department (Dr Hopkins), Brigham Young University, Provo, UT; and Pulmonary and Critical Care Medicine (Dr Hopkins), Intermountain Healthcare, and Center for Humanizing Critical Care (Dr Hopkins), Intermountain Medical Center, Murray, UT.

FUNDING/SUPPORT: This research was supported by the National Heart, Lung, and Blood Institute [Grants R24 HL111895, R01HL091760, and R01HL091760-02S1], the Johns Hopkins Institute for Clinical and Translational Research [Grant UL1 TR 000424-06], and the Albuterol for Treatment of Acute Lung Injury Trial (ALTA), Early Versus Delayed Enteral Nutrition Trial (EDEN), Omega Nutrition Supplement Trial (OMEGA), and Statins for Acutely Injured Lungs from Sepsis Trial (SAILS) [National Heart, Lung, and Blood Institute contracts HHSN268200536165C to HHSN268200536179C, and HHSN268200536179C].

CORRESPONDENCE TO: Karin J. Neufeld, MD, MPH, A4Center, Ste 457, Johns Hopkins Bayview Medical Center, 4940 Eastern Ave, Baltimore, MD 21224; e-mail: kneufel2@jhu.edu

DOI: https://doi.org/10.1016/j.chest.2020.03.059

More than 2/3rds of ARDS survivors reported clinically significant fatigue symptoms 1 year after discharge.

Neufeld CHEST 2020

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ACPOHE
PHYSIOS FOR WORK AND HEALTH

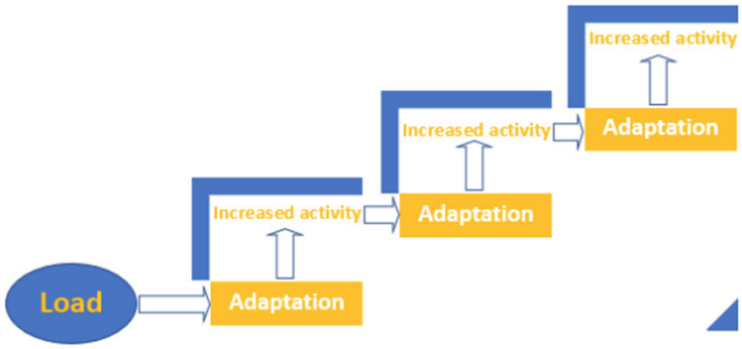

Figure 3: Progressive or graded increase in activity to increase functional capacity

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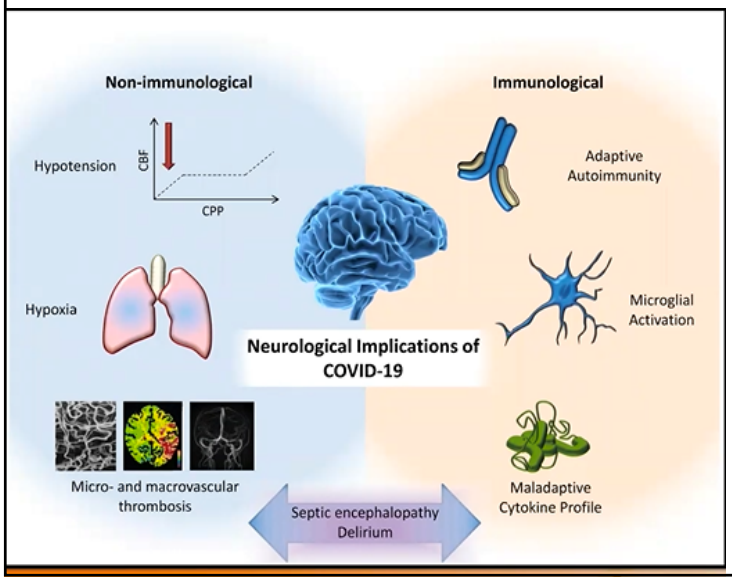
As Many as 1 in 3 w/ Neuro/Psych Sx



Taquet Lancet 2021
Varatharaj Lancet Psych 2020
Mao JAMA Neurol 2020
Needham Neuro Crit Care 2020
Liotta Annals Clin Transl Neur 2020

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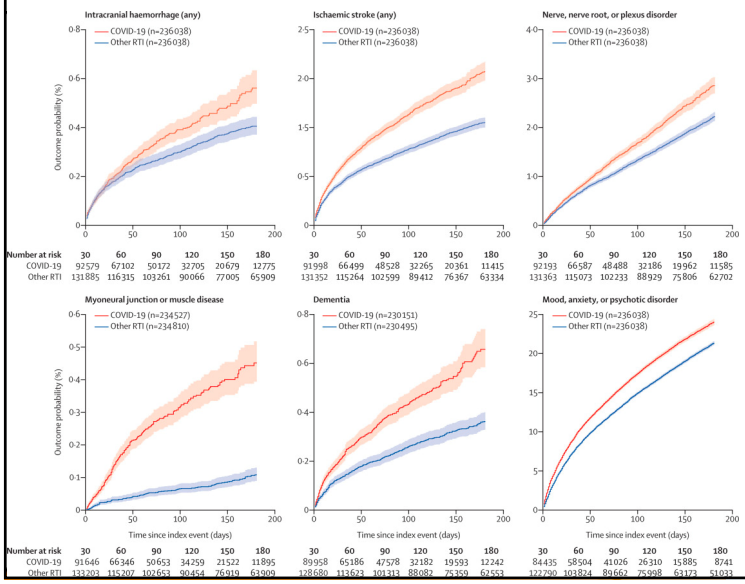
As Many as 1 in 3 w/ Neuro/Psych Sx



Taquet Lancet 2021
Varatharaj Lancet Psych 2020
Mao JAMA Neurol 2020
Needham Neuro Crit Care 2020
Liotta Annals Clin Transl Neur 2020

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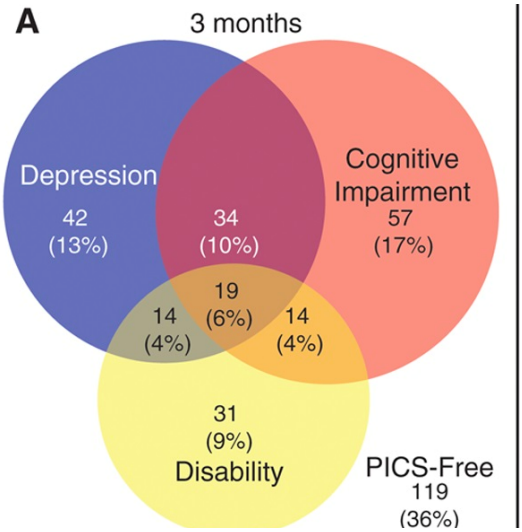
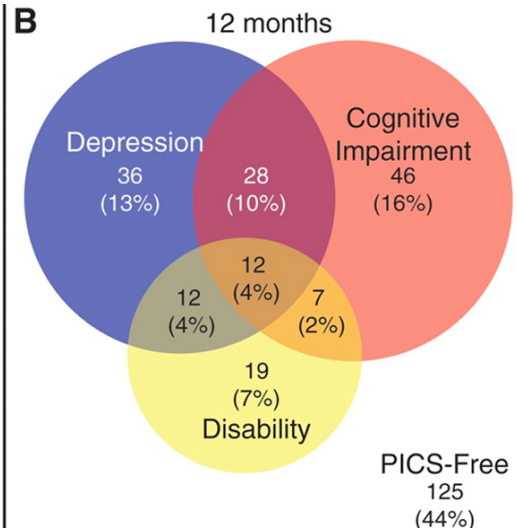
Depression, Cog Issues & Disability Intertwined





Marra CCM 2018

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COVID is a "Delirium Factory" – Dr. Wes Ely

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COVID Recovery Resources: Power of AVS

- **Mental Health:** Reassurance and coping strategies are key, peer support, assess for psych referral/needs for meds
- **Social Isolation/Loneliness:** Older adults and those with many medical problems are at particular risk. Discuss safe socialization and IADL logistics

Perissinotto Archives 2012

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One Key Point

All that "Long-Hauls" is not COVID.

Avoid anchoring & keep ddx broad throughout.

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One of my Patients: From COVID ICU to Post-COVID Clinic

During our OPTIMAL Clinic visit, we assessed Mrs. L & counseled her and her daughter about anticipated recovery. We recommended gradual aerobic exercise, using a home pulse oximeter, & consideration of PRN inhalers. The integrated mental health support of the visit greatly alleviated the patient's stresses & she "felt a lot better after talking to them." We provided reassurance & recommendations for local resources & set f/u appointment for 3 months.

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Take Home Points

- COVID long-term symptoms & complications can affect **multiple organs**
- The **biological basis** of PASC is under investigation in multiple organ systems
- A comprehensive **multidisciplinary** approach is important to address disability, fatigue, neuropsych symptoms
- Lots of **uncertainty** remains & further research will help outline best next steps

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Thank You!
Questions?

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@LekshmiMD

Do you have a patient who lives in the SF Bay Area and wants to participate in research?
(Requires COVID+ PCR and ability to attend visits at San Francisco General Hospital)

Refer them to our website www.liincstudy.org or have them email LIINC@UCSF.edu

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Erica Pan, M.D., MPH

California State Public Health Officer, and Epidemiologist

Deputy Director, California Department of Public Health (CDPH) Center of Infectious Diseases

CHHS California Health & Human Services Agency | CALIFORNIA MEDICAL ASSOCIATION | IN PARTNERSHIP WITH | CAPA

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Vaccinate ALL 58

Together we can end the pandemic.
Juntos podemos acabar con la pandemia.
我們可以一起終止疫情。

COVID-19 California Epidemiology and Vaccine Update

Dr. Erica Pan, MD, MPH, FAAP
California State Epidemiologist
Deputy Director, Center for Infectious Diseases
California Department of Public Health

UCSF Clinical Professor
Pediatric Infectious Diseases

April 13, 2021

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Agenda

- Epidemiology
- Variants
- Vaccine Coverage and Updates
- Possible Long Term CDPH COVID-19 Activities
- Question & Answer

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COVID-19 Overview

SEE THE NUMBERS

Tracking COVID-19

As of April 12, California has 3,602,827 confirmed cases of COVID-19, resulting in 59,249 deaths.

Cases	Deaths	Tests	Vaccines Administered
3,602,827 Total	**59,249** Total	**56,593,271** Total	**22,974,654** Total
2,649 Today	31 Today	229,596 Today	
↘ 4.7 New cases per 100K	↘ 0.1 New deaths per 100K	↘ 1.5% Test positivity	

Updated April 12, 2021 at 10:00 AM with data from April 11, 2021

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https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/ncov2019.aspx 69

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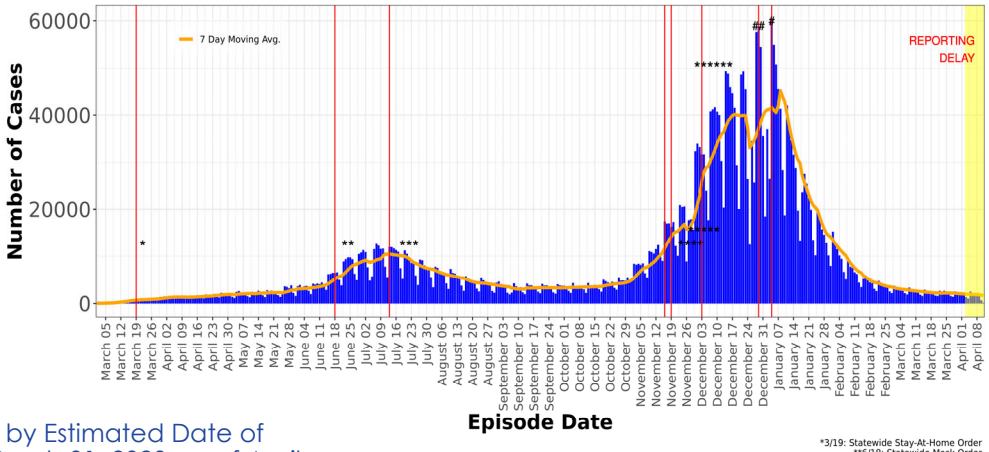
As of April 12, 2021



Cases of COVID-19 by Estimated Date of Illness Onset from March 01, 2020, as of April 12, 2021, California (n=3,604,395)

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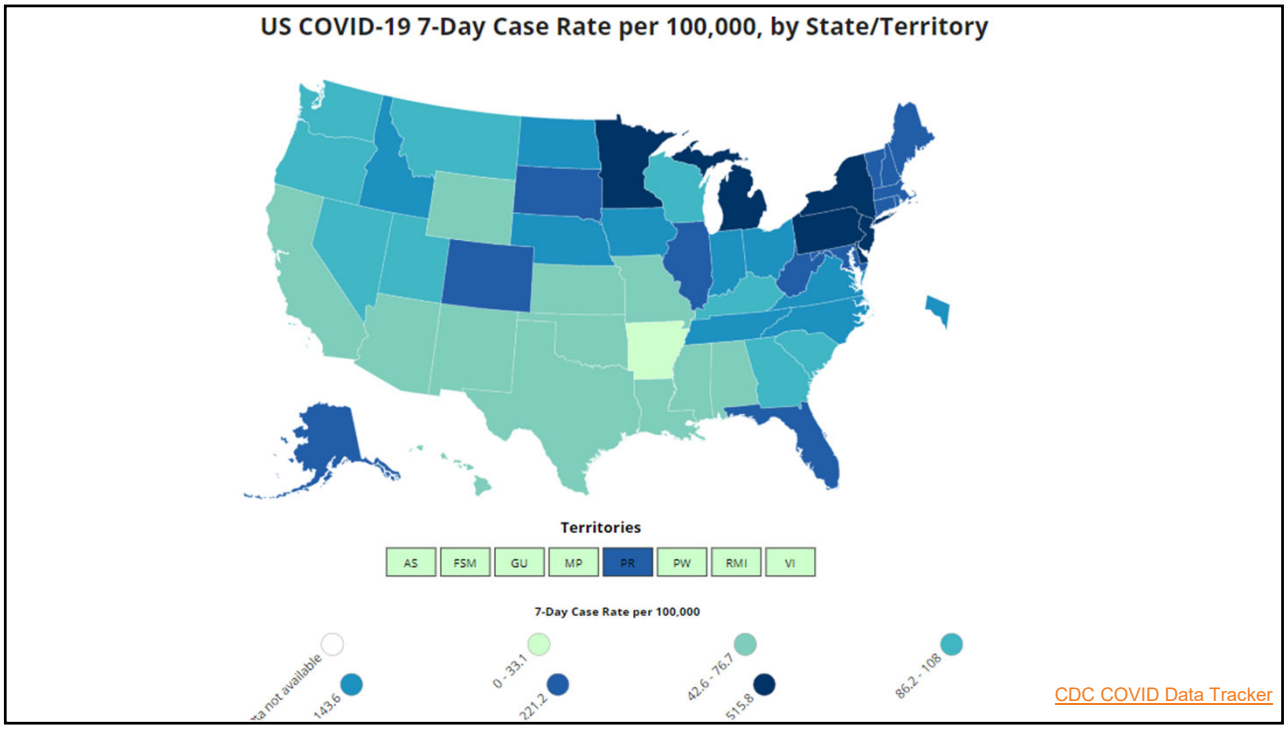

CDC COVID Data Tracker

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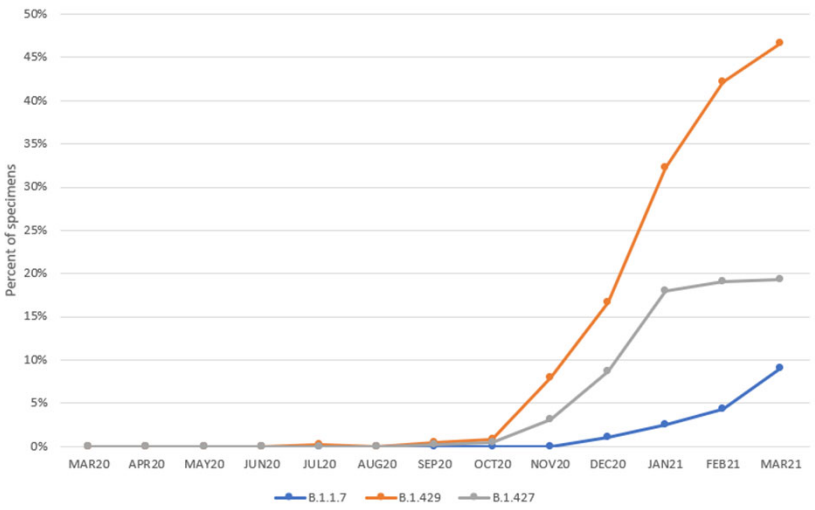
Variant Update

More Commonly Detected* Variants of Concern in California by Specimen Collection Month, March 2020-March 2021

*Only those variants with 1000 or more total detected cases are shown on the graph



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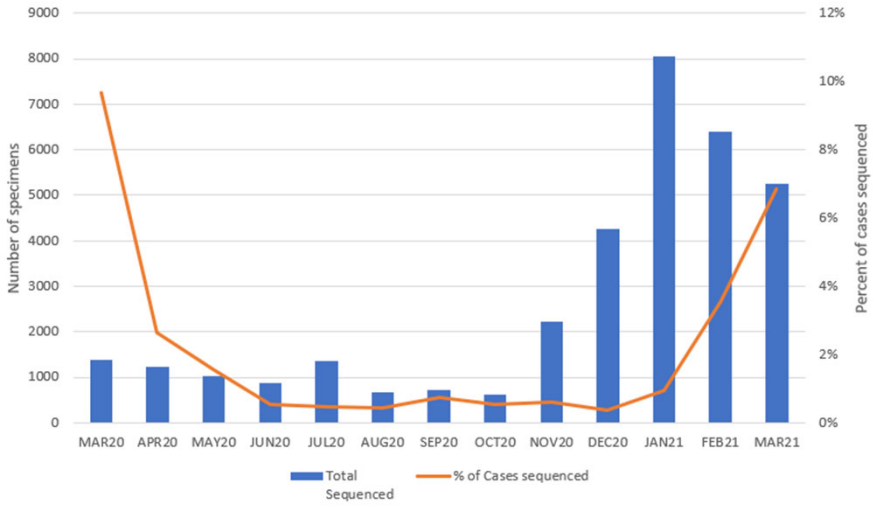
Variant Update

Sequences In California by Specimen Collection Month, March 2020-March 2021



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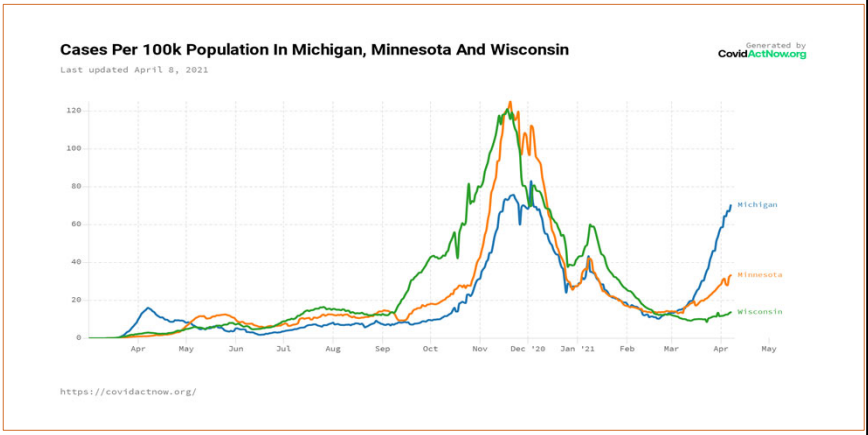
Midwestern States and VOCs

- Graph comparing cases per 100k population in 3 Midwestern states (MI, MN, WI)
- **Data from Minnesota indicate that Indications that B.1.1.7 is dominant strain, estimated 60% of recent cases**



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Graph & data courtesy of Ruth Lynfield, MN Department of Health

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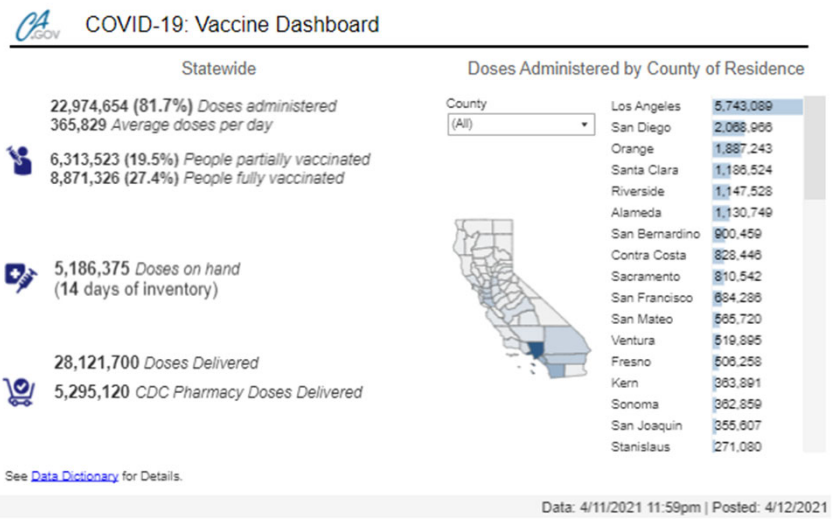
Vaccine Doses Administered in California



As of April 12, 2021

Individuals (16+) fully vaccinated:

8,871,326 (27.4%)

Individuals (65+) fully vaccinated:

3,631,828 (56.1%)

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https://covid19.ca.gov/vaccines/ 75

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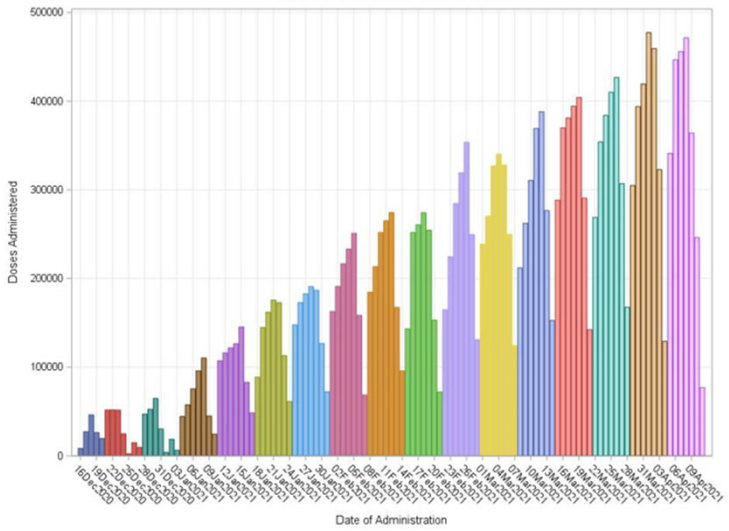
Vaccine Doses Administered by Day



As of April 12, 2021

Total Doses Administered:

22,974,654

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https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/ncov2019.aspx 76

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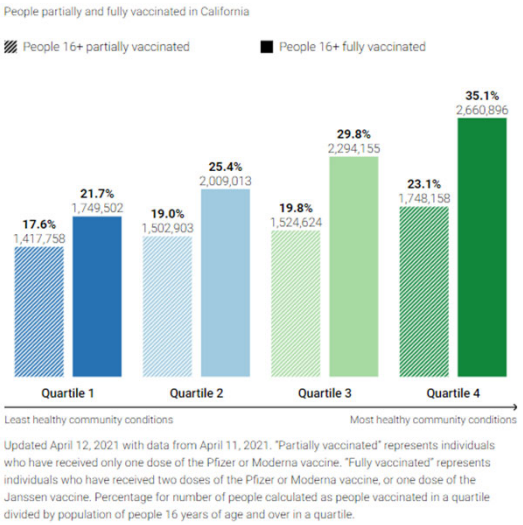
Vaccine Equity Metric

This graph compares COVID-19 vaccinations among four different levels of community health.

It uses Healthy Places Index (HPI)* measures in a zip code area that can impact health, like income, education, and access to health care. Areas are then given a score, ranging from least healthy community conditions (Quartile 1) to most healthy community conditions (Quartile 4).

The Vaccine Equity Metric also creates scores for areas that don't have an HPI score.

*A project of the Public Health Alliance of Southern California (PHASC)



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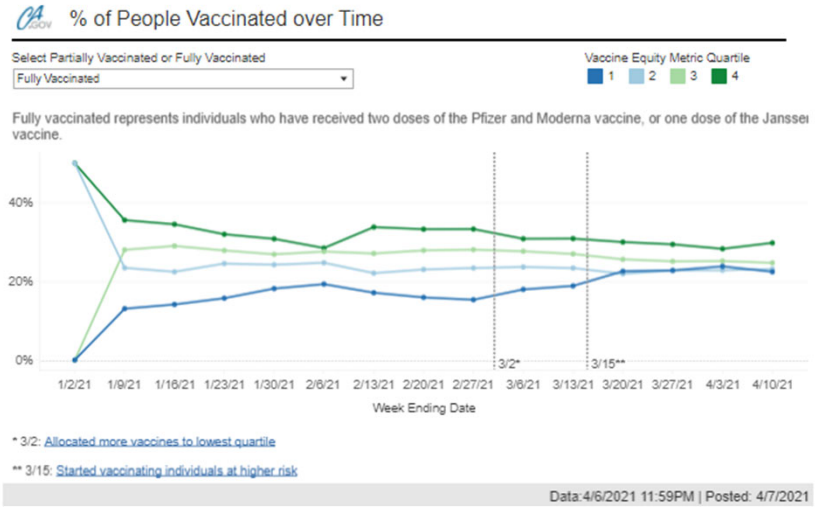
Vaccine Equity Metric

This graph shows the percent of people vaccinated by Vaccine Equity Metric quartile each week. It shows that, while administration rates in quartiles 1 and 2 have improved, there is still work to be done.



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Who Can Get Vaccinated?

Eligible Groups

- Health care workers
- Long term care and skilled nursing facility residents
- Californians 65 years and older
- Food and agriculture
- Childcare and education
- Emergency responders
- Those in high-risk congregate living spaces
- Certain public transit workers

As of **March 15,** healthcare providers may use their clinical judgement to vaccinate individuals aged 16-64 who are deemed to be at the very highest risk to get very sick from COVID-19:

- Severe health conditions
- Disabilities or illness

As of **April 1**, Individuals 50 or older

Starting **April 15**, Every Californian 16 or older

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Fully Vaccinated Guidance

- Fully vaccinated people can:
  - Visit the private households of other fully vaccinated people indoors without wearing masks or physical distancing.
  - Visit with unvaccinated people from a single household who are at low risk for severe COVID-19 disease indoors without wearing masks or physical distancing.
  - Refrain from quarantine following a known exposure if asymptomatic.

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Vaccine Verification – Capacity Increases

Fully vaccinated or tested negative attendees **only:**

For further increased numbers of guests, venues can establish vaccinated-only sections with no distancing requirements.

Tier 1 Widespread	Tier 2 Substantial	Tier 3 Moderate	Tier 4 Minimal
Existing capacity limits apply	Existing capacity limits apply	Outdoor: Existing capacity limits apply Indoor: Venues may increase capacity by an additional 50%, up to a maximum of 50% of total venue capacity.	Outdoor: Existing capacity limits apply Indoor: Venues may increase capacity by an additional 50%, up to a maximum of 75% of total venue.

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Vaccine Verification

The following are acceptable as proof of full vaccination:

- Vaccination card (which includes name of person vaccinated, type of vaccine provided, and date last dose administered), OR
- A photo of a vaccination card as a separate document, OR
- A photo of the attendee's vaccine card stored on a phone or electronic device, OR
- Documentation of vaccination from a healthcare provider.

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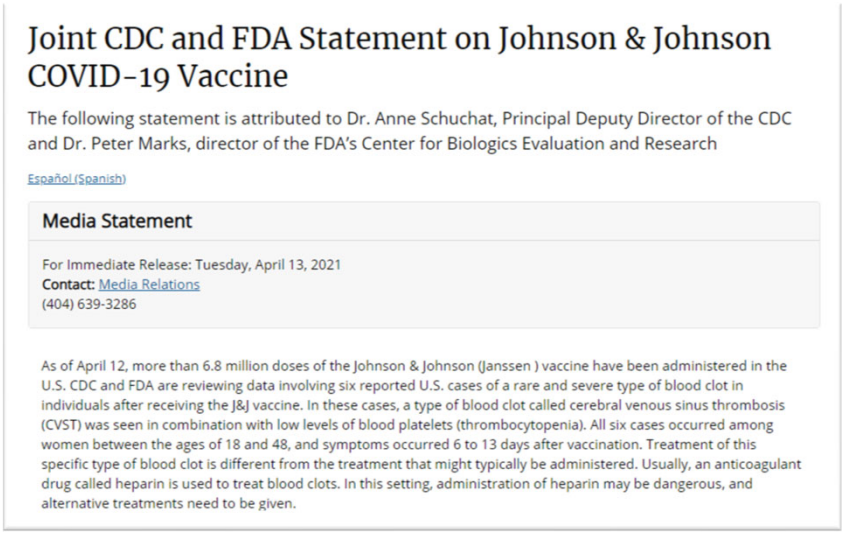
Vaccine Update – J&J Pause



Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine

The following statement is attributed to Dr. Anne Schuchat, Principal Deputy Director of the CDC and Dr. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research

Español (Spanish)

Media Statement

For Immediate Release: Tuesday, April 13, 2021
Contact: Media Relations
(404) 639-3286

As of April 12, more than 6.8 million doses of the Johnson & Johnson (Janssen) vaccine have been administered in the U.S. CDC and FDA are reviewing data involving six reported U.S. cases of a rare and severe type of blood clot in individuals after receiving the J&J vaccine. In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women between the ages of 18 and 48, and symptoms occurred 6 to 13 days after vaccination. Treatment of this specific type of blood clot is different from the treatment that might typically be administered. Usually, an anticoagulant drug called heparin is used to treat blood clots. In this setting, administration of heparin may be dangerous, and alternative treatments need to be given.

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https://www.cdc.gov/media/releases/2021/s0413-JJ-vaccine.html

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Vaccine Updates – Addressing Delaying Second Doses

- Western States Scientific Safety Review Workgroup reconvened April 8, 2021
- Modeling & projection data for delaying second doses by 2 weeks were reviewed:
  - Accelerate vaccine coverage for California by one week
  - May decrease cases if high uptake, but with NPIs and current vaccine coverage still likely lower than summer 2020 surge
- After discussing the most recent effectiveness data and evidence, the pros & cons of this new timeline with implementation and communication issues, and current levels of transmission in CA, the workgroup recommended not to increase interval to 2nd dose
- Recommendation & modeling to be further reviewed by CHHS

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Vaccine Updates – Pfizer Application

Pfizer and BioNTech Request Regulatory Agencies Expand Emergency Use of Their COVID-19 Vaccine to Adolescents

NEW YORK and MAINZ, GERMANY, April 9, 2021 — Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today requested amendments to the U.S. Emergency Use Authorization (EUA) of the Pfizer-BioNTech Vaccine (BNT162b2) to expand the use in adolescents 12 to 15 years of age. The companies plan to request similar rulings by other regulatory authorities worldwide in coming days. These requests are based on data from the pivotal Phase 3 trial in adolescents 12 to 15 years of age with or without prior evidence of SARS-CoV-2 infection, which demonstrated 100 percent efficacy and robust antibody response after vaccination with the COVID-19 Vaccine.

Topline results from an efficacy analysis on 12 to 15 year old participants through cases accured by March 31, 2021 from the Phase 3 trial were recently announced. In this analysis, BNT162b2 was well tolerated with side effects generally consistent with those observed in participants 16 to 25 years of age. All participants in the trial will continue to be monitored for long-term protection and safety for an additional two years after their second dose.

- 4/9 requested amendments to Emergency Use Authorization (EUA) to expand use in 12 to 15yo.
- Based on data from Phase 3 trial in this age group that demonstrated good efficacy and vaccine tolerance.

Vaccinate ALL 58

https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/ncov2019.aspx

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Possible Long Term CDPH COVID-19 Activities

- Exploring options for developing CA COVID-19 registry of long-term outcomes from surveillance.
- Collaborate to conduct longitudinal follow up on long term symptoms and other impacts.
- Assess and synthesize to inform economic impacts, policy and program interventions, and provide recommendations on long term recovery.

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Resources for Providers

- Vaccine Administration
  - EZIZ: https://eziz.org/covid/enrollment/
  - CalVax: https://calvax.cdph.ca.gov/s/
  - CDPH Immunization Branch: https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/COVIDVaccineEnrollment.aspx#
- The COVID-19 Call Center for Providers is dedicated to medical providers in California and their COVID-19 response, specifically addressing questions about program requirements, enrollment, and vaccine distribution.
  - Email: covidcallcenter@cdph.ca.gov
  - Phone: (833) 502-1245
  - For technical system issues with CalVax: Helpdesk.CalVax@calvax.accenture.com
- CDC Resources
  - CDC general vaccine resources: www.cdc.gov/coronavirus/2019-ncov/vaccines
  - CDC LTCF toolkit: https://www.cdc.gov/vaccines/covid-19/toolkits/long-term-care/index.html

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Question & Answer

Thank you!

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Question and Answer

Kimberly Newell Green, M.D.

Erica Pan M.D., MPH.

Michael Peluso, M.D., MPhil, MHS, DTM&H.

Lekshmi Santhosh, M.D., MA.Ed.

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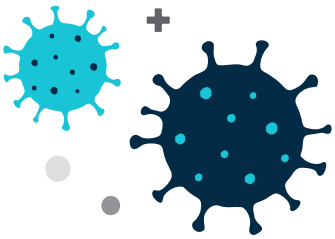
Next Webinars in Series



- **Tuesday, May 11, 2021:** COVID-19 in Pregnancy and Birth
- More information at www.covidroundsca.org

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CMA Telehealth "Tipping Point" Project

- Two Webinars per Month https://www.cmadocs.org/telehealth-webinars
- Physician Telehealth Survey https://www.surveymonkey.com/r/cmatelehealth2020
- Online Telehealth Resource Center – ***Coming Soon!***

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CME

- Will receive an email after this webinar with an evaluation around 5pm
- Upon receiving your response, you will receive a CME certificate

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