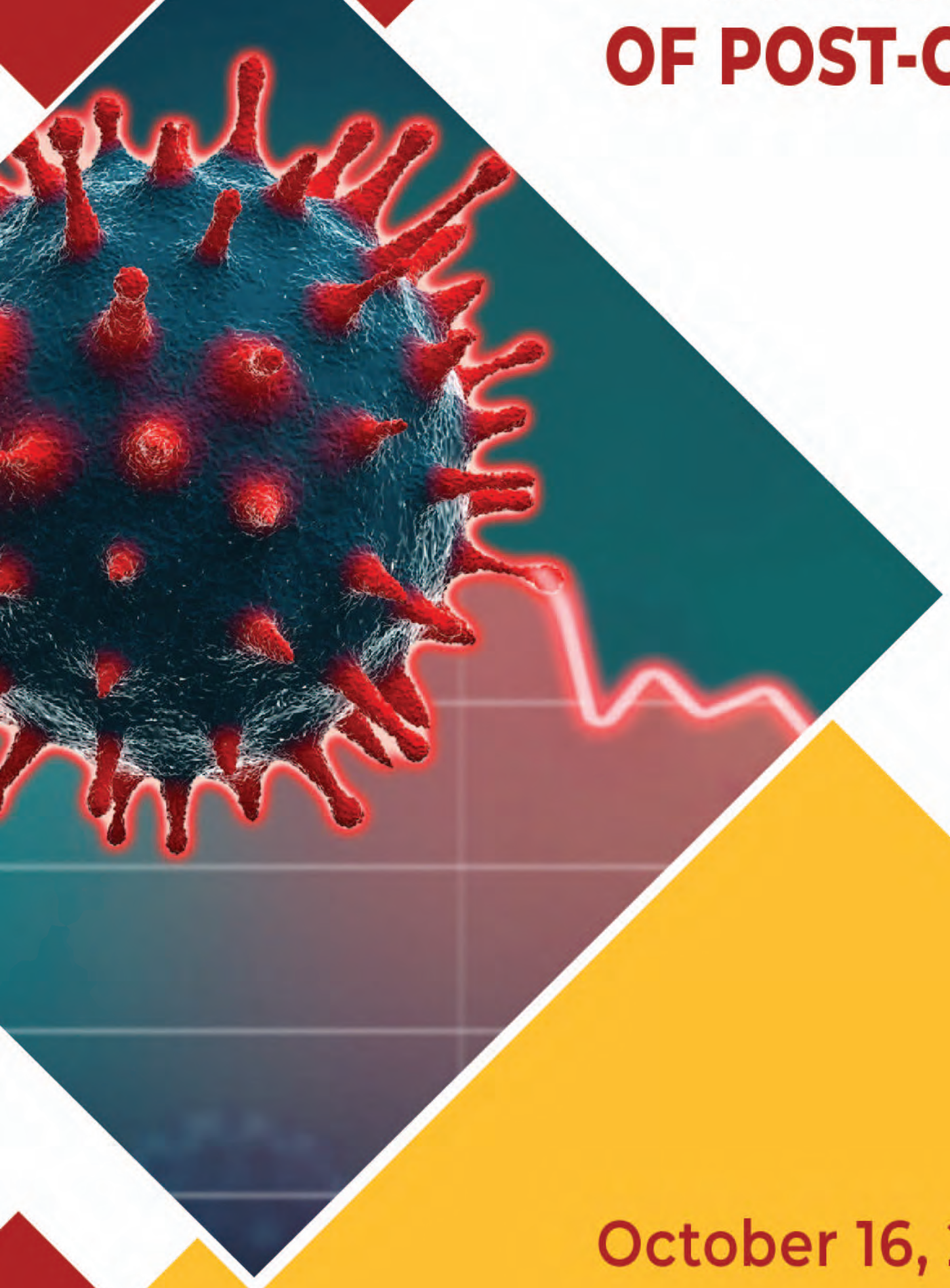
CHALLENGES IN THE MANAGEMENT OF POST-COVID SYNDROME



Maryland
DEPARTMENT OF HEALTH

OFFICE OF PHARMACY SERVICES

October 16, 2021

Continuing Education Seminar

NOTES:

Continuing Medical Education (CME) &
Pharmacy Continuing Education (ACPE) Seminar

Challenges in the Management of Post-COVID syndrome

Virtual Live program
on
October 16, 2021

Attendees must pre-register at www.mmppi.com to attend. This program will only be available virtually due to contact precautions related to COVID-19

8:30 am – Registration	
8:45 am – Introductions	Maryland Department of Health Office of Pharmacy Services
9:00 am – Presentation	Eleanor Wilson, MD Institute for Human Virology University of Maryland School of Medicine
11:00 am – Closing Remarks	Maryland Department of Health Office of Pharmacy Services
11:15 pm - Adjourn	

The views and opinions expressed by the speakers are not necessarily the views and opinions of The State of Maryland Department of Health.
****This event will be recorded for future use.***
By attending, you agree to participate in audio and/or visual recording*

CE Program Sponsorship:
This program is co-sponsored by The Maryland Department of Health (MDH) Office of Pharmacy Services (OPS) in collaboration with Health Information Designs, a Kepro company.

CE Accreditation Statement:
The Alabama Pharmacy Association Research and Education Foundation (APAREF) is accredited by the Accreditation Council for Pharmacy Education (ACPE), as a provider of continuing pharmacy education.

Statement of Credit (ACPE):
The Alabama Pharmacy Association (APA) will upload your continuing education credit information to CPE Monitor. You will be able to view and print your continuing education credits from CPE Monitor. The statement of credit should be retained as proof of attendance in the event of an audit by the State Board of Pharmacy. **In order to receive ACPE credits you must sign your name on all sign-in sheets and turn in an evaluation form for each presentation at the end of the program. You also must provide your NABP e-Profile ID # as well as the month and day of your date of birth to receive credit.**

CME Accreditation Statement:
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through joint providership of MedChi, The Maryland State Medical Society, The Maryland Department of Health Office of Pharmacy Services, and Health Information Designs/Kepro. MedChi is accredited by the ACCME to provide continuing medical education for physicians.

CME Designation:
MedChi designates this live activity for a maximum of (2) *AMA PRA Category 1 Credit(s)™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Presenter Disclosure:
Dr. Wilson states that she does not have relevant financial relationship with commercial interests and will be discussing “Off-Label” uses of products or devices. This information is on file with Health Information Designs/Kepro.

Planner Disclosure:
Dr. Boyer states that she does not have relevant financial relationships with commercial interests and will not be discussing “Off-Label” uses of products or devices. This information is on file with Health Information Designs/Kepro.

Program Disclosure:
Support provided by Health Information Designs, LLC, a Kepro company.

Activity Type: Knowledge-Based

Challenges In The Management Of Post-COVID Syndrome

A Clinician's View

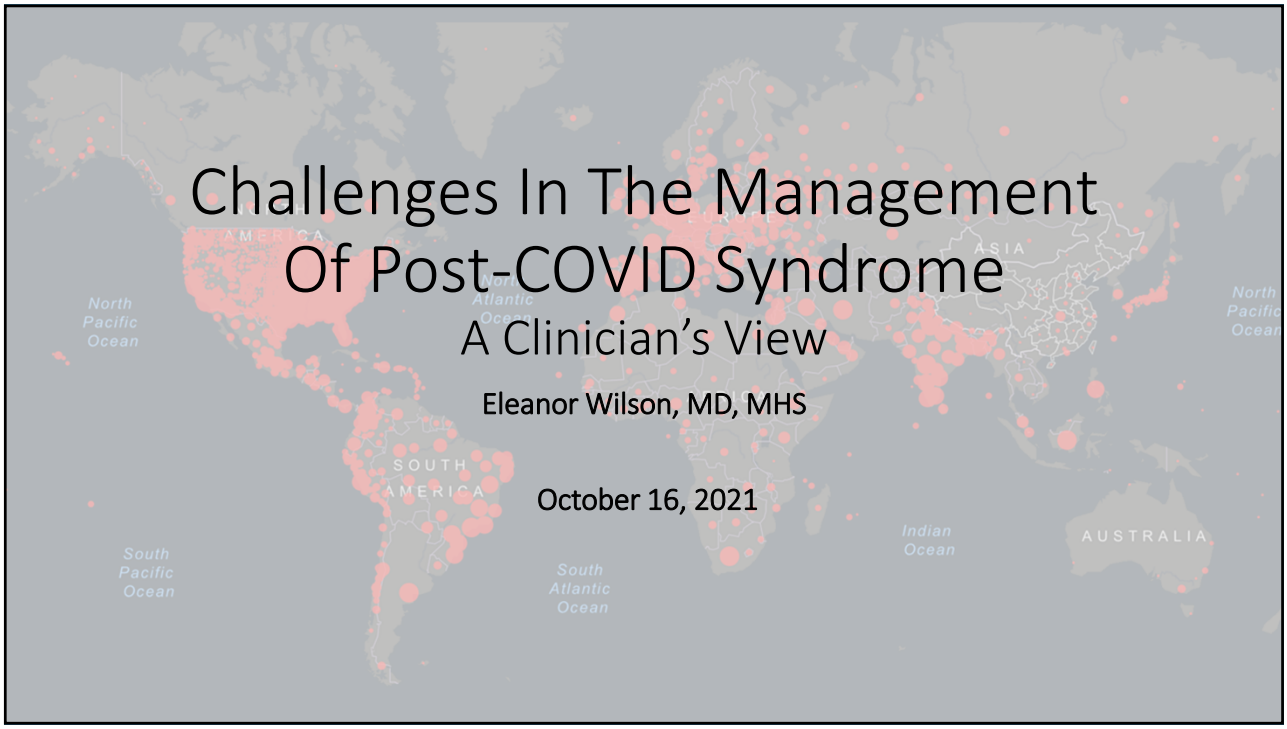
Eleanor Wilson, MD, MHS

October 16, 2021

Eleanor Wilson, MD

- Associate Professor, Institute Of Human Virology at the University of Maryland School of Medicine

Eleanor.Wilson@ihv.umaryland.edu



Challenges In The Management Of Post-COVID Syndrome

A Clinician's View

Eleanor Wilson, MD, MHS

October 16, 2021

1

Objectives

At the end of this talk, you should understand

- Common symptoms of Long COVID, or Post-Acute Sequalae of COVID-19 (PASC)
- Proposed mechanisms and host predictors underlying PASC
- Therapeutics targeting some of the common PASC manifestations
- Prevention strategies for PASC

Conflicts of Interest

I am a co-PI of an NINDS R21 evaluating long term neurologic effects following COVID-19.

I am a sub-investigator on Janssen's COVID-19 vaccine trial (NCT04509947) and other treatment trials that I will not be discussing.

2

CC: 49yoM with shortness of breath

49yo man presents with 7 days of progressive shortness of breath, 4 days of productive cough, pleuritic chest pain, and dyspnea on exertion. He bought a home oximeter, which showed SaO2 of 68%; feeling this couldn't be correct, he came to the ED for a recheck.

Review of systems: + chills, diaphoresis, sore throat, cough, shortness of breath, chest pain, myalgias, denies fever, abdominal pain, diarrhea, rash

Past Medical History: NIDDM, HgbA1c 7.2 (May 2020)

Medications: Glipizide 2.5mg daily, Metformin 1000mg BID, Atorvastatin 10mg daily

Social History: Married but separated, sexually active with women, lives with his adult daughter, no tobacco or alcohol use, works as a truck driver

3

CC: 49yoM with shortness of breath

Physical Exam:

T 37.3 °C (99.1 °F) **WT** 94.2kg (BMI 31 kg/m^2) **HR** 112 **BP** 126/89 **RR** 24 **SpO2** 72%

Gen: in acute distress, tachypneic, speaking in 3-4 word sentences

HEENT: normal, op clear

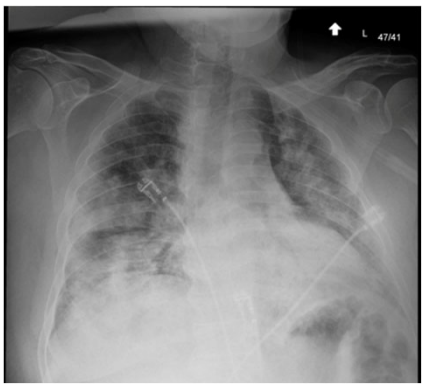
CV: Tachycardic, regular, no murmurs

Pulm: Normal breath sounds, good air movement bilaterally throughout

Abd: nontender, nondistended, no rebound, no guarding

MSK: no swelling, tenderness, or deformity, delayed cap refill

Neuro: alert and oriented, grossly intact, no focal deficits



Labs:

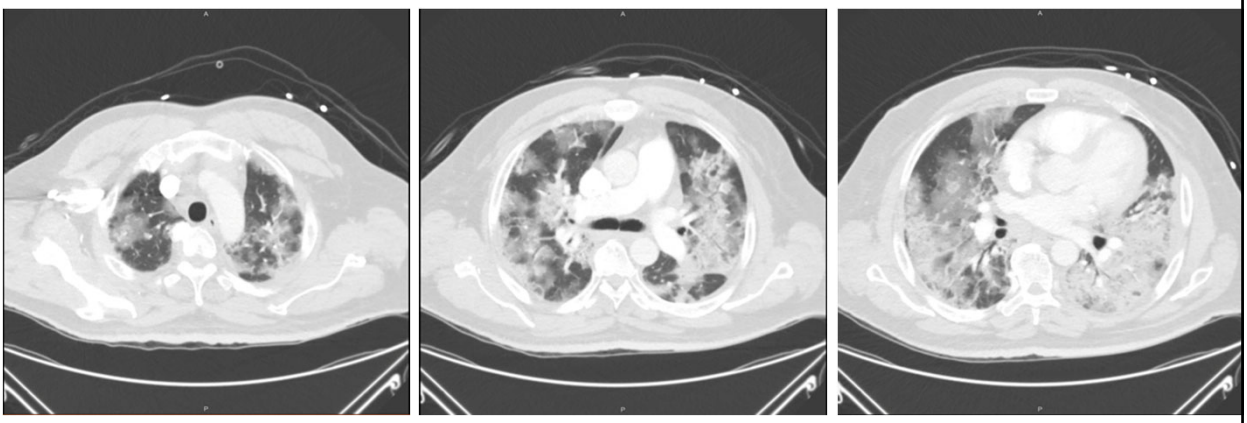
WBC 7.5 (84.7% pmns, 9.1% lymphs)	Hgb 11.6
Plt 344	

139	103	0.47
4.1	25	12

281

4

CC: 49yoM with shortness of breath



5

CC: 49yoM with shortness of breath

What is the most likely diagnosis in January 2019?

A. Influenza A
B. Parainfluenza
C. Respiratory Syncytial Virus
D. Rhinovirus
E. SARS-CoV-2 (COVID-19)

6

CC: 49yoM with shortness of breath

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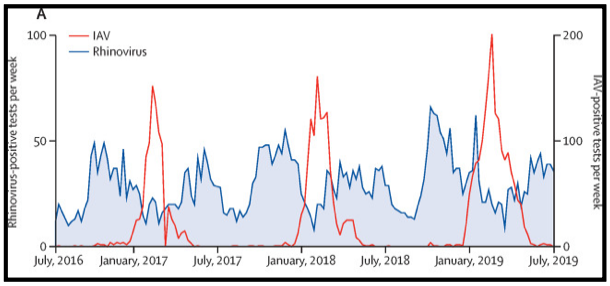


Anchi et al, Lancet Microbe Oct 1 2020;1(6):E254-62

7

CC: 49yoM with shortness of breath

What is the most likely diagnosis in January 2021?

A. Influenza A

B. Parainfluenza

C. Respiratory Syncytial Virus

D. Rhinovirus

E. SARS-CoV-2 (COVID-19)

8

COVID on the ground…

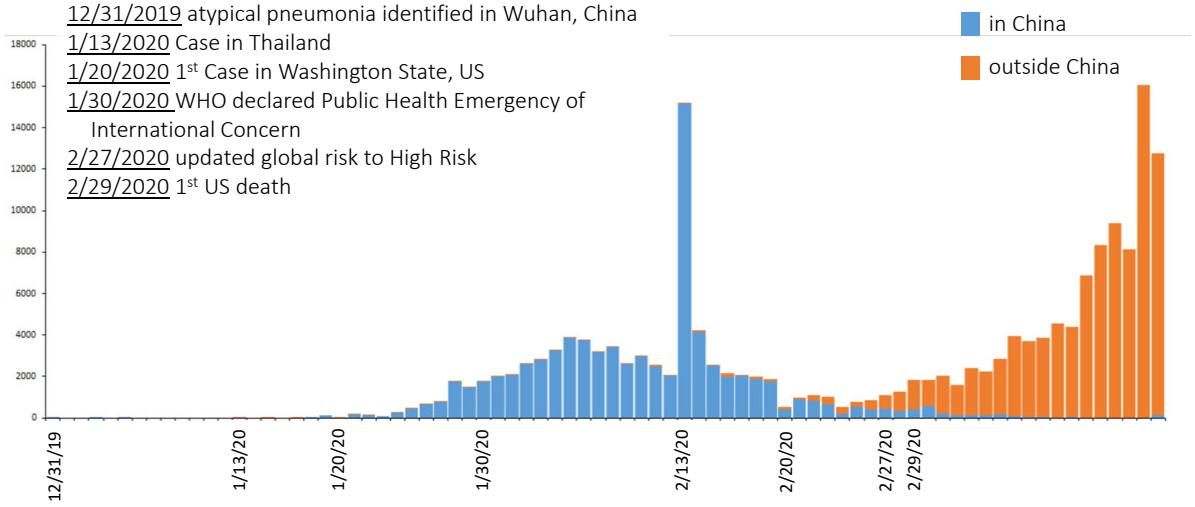
9

Behind the Covid door:

10

Coronavirus Infectious Disease 2019 (COVID-19)

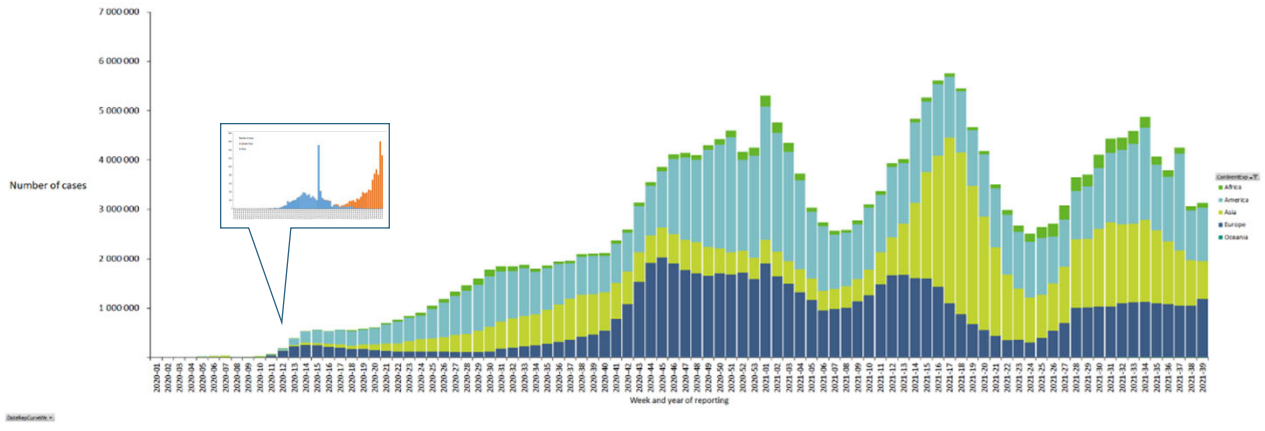
12/31/2019 atypical pneumonia identified in Wuhan, China
1/13/2020 Case in Thailand
1/20/2020 1st Case in Washington State, US
1/30/2020 WHO declared Public Health Emergency of International Concern
2/27/2020 updated global risk to High Risk
2/29/2020 1st US death



https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

11

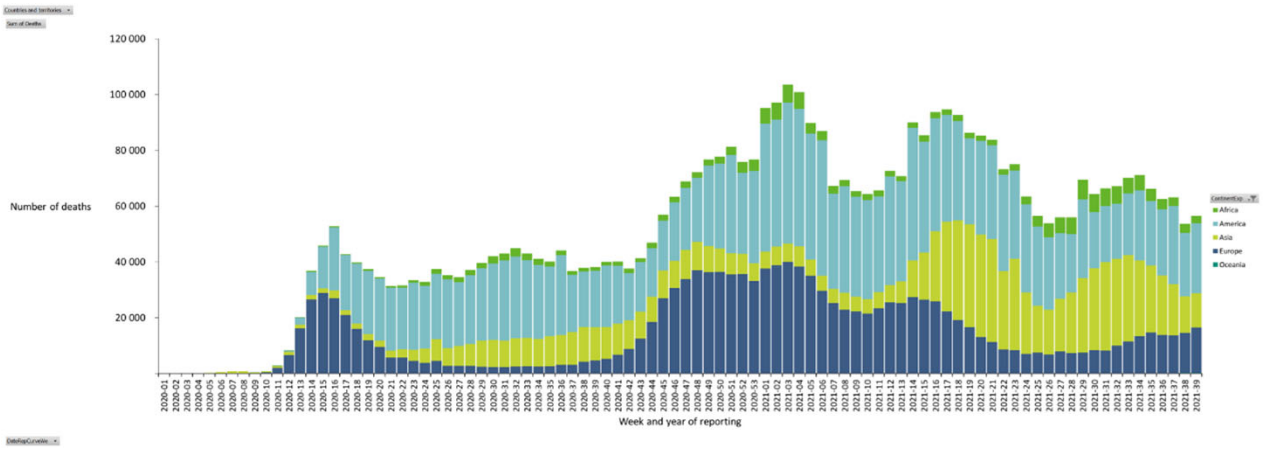
COVID-19 Cases



https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases, accessed 10/8/21

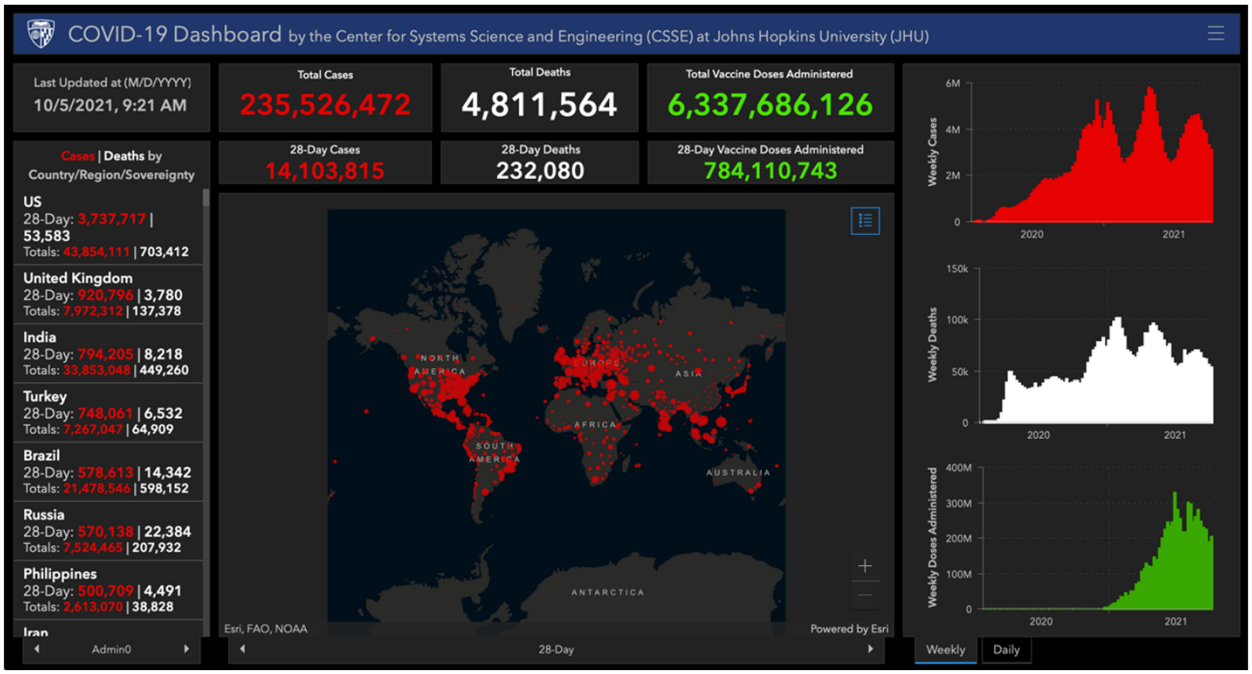
12

COVID-19 Deaths



https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases, accessed 10/8/21

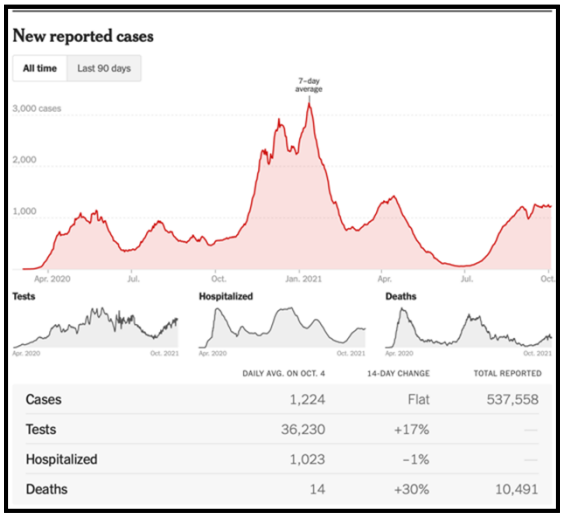
13

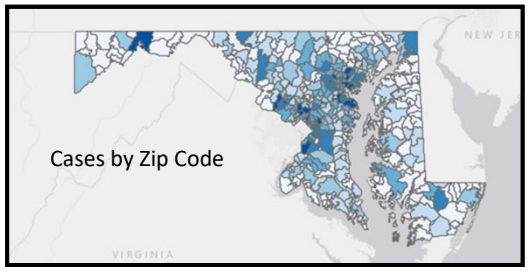


COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University, accessed October 5, 2021

14

Maryland Coronavirus Cases

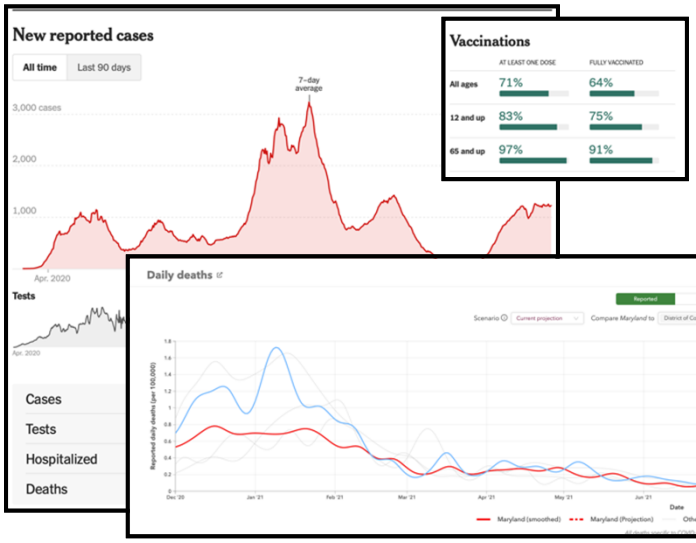


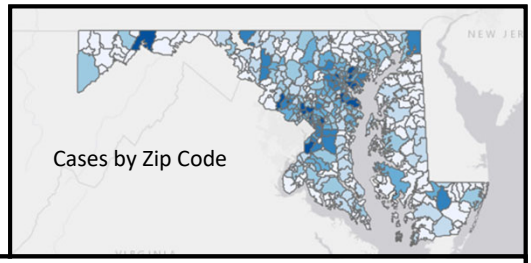


NYTimes https://www.nytimes.com/interactive/2020/us/maryland-coronavirus-cases.html, accessed Oct 5, 2021
Maryland COVID-19 Data Dashboard, https://coronavirus.maryland.gov, accessed Oct 5, 2021
IMHE Health Data https://covid19.healthdata.org/united-states-of-america/maryland?view=total-deaths&tab=trend, accessed Oct 5, 2021

15

Maryland Coronavirus Cases





NYTimes https://www.nytimes.com/interactive/2020/us/maryland-coronavirus-cases.html, accessed Oct 5, 2021
Maryland COVID-19 Data Dashboard, https://coronavirus.maryland.gov, accessed Oct 5, 2021
IMHE Health Data https://covid19.healthdata.org/united-states-of-america/maryland?view=total-deaths&tab=trend, accessed Oct 5, 2021

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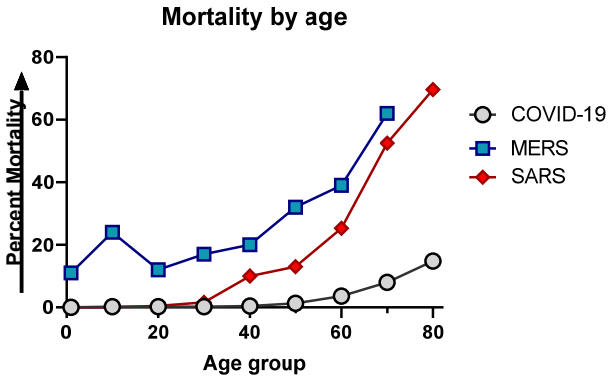
COVID-19 Spectrum of Illness

- ~80% **mild-moderate**
- 13.8% **severe**
  - dyspnea, RR ≥30/minute, O2 sat ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours
- 6.1% are **critical**
  - respiratory failure, septic shock, and/or multiple organ dysfunction/failure
  - Crude CFR 1.4-4%



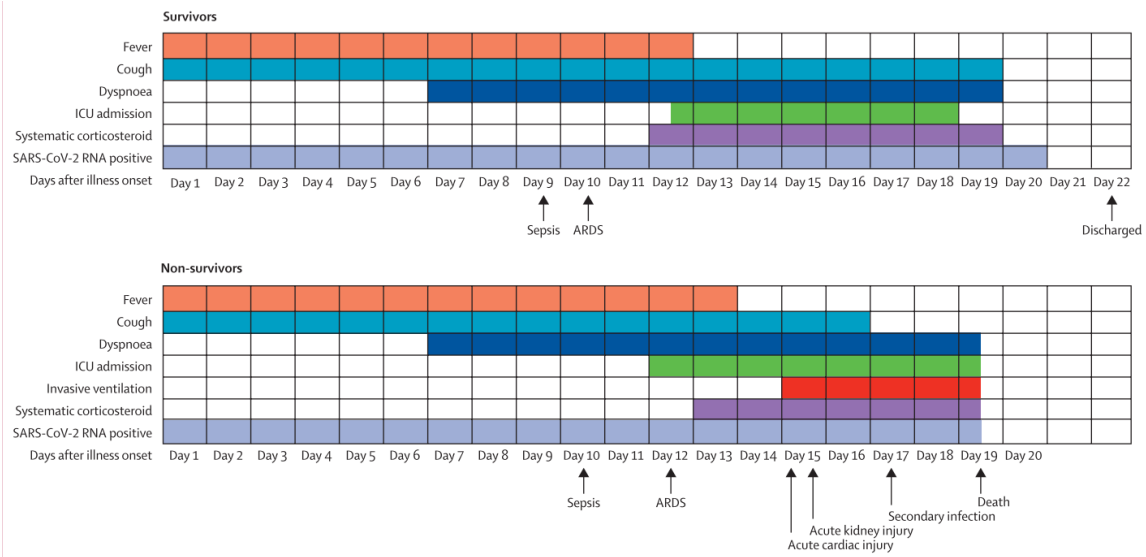
Wu, Z. et al. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China; Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. Feb 24, 2020.

Chan-yeung M, Xu R. SARS: epidemiology. Respirology 2003;8:S9–S14.
MERS mortality by age curtesy of Vineet Menachery (personal communication)

17

Clinical Course

191 patients in 2 hospitals in Wuhan, China
- 137 discharged, 54 died **(28%)**



Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;6736:1–9.

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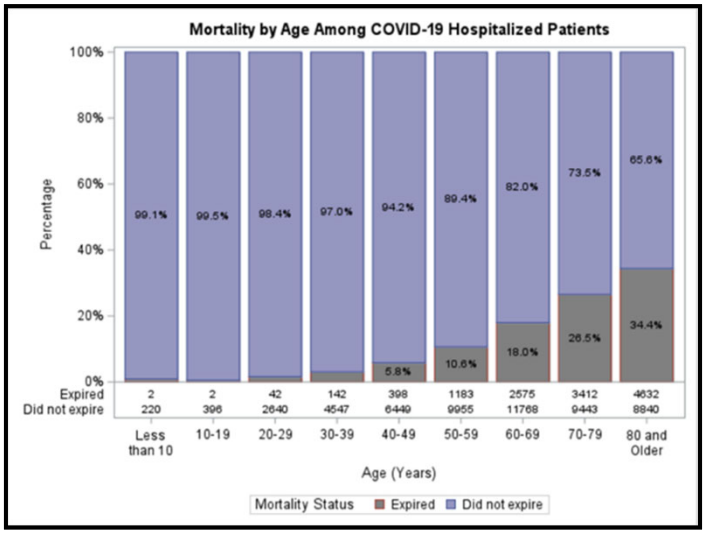
COVID-19 Cases and Deaths Stratified



Goodman KE, Impact of Sex and Metabolic Comorbidities on COVID-19 Mortality Risk Across Age Groups: 66,646 Inpatients Across 613 U.S. Hospitals. *Clin Infect Dis*. 2020 Dec 18:ciaa1787. doi: 10.1093/cid/ciaa1787.

19

CC: 49yoM with shortness of breath

Clinical Course:

1/18 Presented to the ED with hypoxia, placed on 6L NCO2, tested COVID-19 +, started steroids

1/19 Admitted to ICU, ↑ work of breathing with SpO2 60-70%, required HFNC at 40L/100%, started remdesivir

1/21 Required intubation, mechanical ventilation

1/24 Developed fevers to 39.7 °C (103.5 °F), sputum cultured

1/25 Sputum grew Klebsiella pneumonia, imaging suggestive of superimposed ventilator-associated bacterial pneumonia

2/11 Tracheostomy placed to facilitate slow wean from ventilator

2/15 Weaned to trach collar

2/21 Decannulated

2/22 Discharged to rehab facility

20

CC: 39yoW with headaches, palpitations

39yo woman presents with 6 month history of dyspnea on exertion, fatigue, daily headaches, palpitations, and "brain fog."

Diagnosed with Covid 6 months ago: develop symptoms and tested negative, but symptoms (cough, shortness of breath, and diarrhea) progressed and she tested positive three days later. Not admitted, required no oxygen or Covid-specific therapy. Previously played soccer with her son, now gets short of breath climbing a flight of stairs. Using her albuterol inhaler now ~5x per day, previously just 3-4x per year, predominantly in the winter months.

Review of systems: No fever/chills/night sweats, + fatigue, no chest pain, +palpitations, no cough, + shortness of breath especially with mild exertion, +memory loss, +brain fog

Past Medical History: Hypothyroidism, migraines, seasonal allergies, asthma (previously albuterol 3-4x/yr, now several times daily), CKD, obesity

Medications: levothyroxine, albuterol, duloxetine, gabapentin, nortriptyline, fluticasone, OCP

Social History: Married but separated, 9 year old son, denies tobacco/illicits, social alcohol, pet goldfish, employed at a desk job for the DoD, working from home since April 2020

Family History: COPD in her mother, maternal grandmother

21

CC: 39yoW with headaches, palpitations

Physical Exam: **T** 37 °C (98.6 °F) **WT** 83.9kg (BMI 28.9 kg/m^2) **HR** 112 **BP** 133/87 **RR** 16 **SpO2** 100%

Gen: No acute distress,

HEENT: normal, op clear

CV: Tachycardic, regular, no murmurs

Pulm: Dry cough, pleuritic chest pain with deep breathing

Abd: nontender, nondistended, no rebound, no guarding

MSK: no swelling, tenderness, or deformity,

Neuro: alert and oriented, grossly intact, no focal deficits

Labs: TSH 0.955 T4 1.19

Imaging: VQ Scan – negative for pulmonary embolism

PFTs – within normal limits

22

CC: 39yoW with headaches, palpitations

Which is a potential cause of her symptoms?

A. Chronic Obstructive Pulmonary Disease
B. Pulmonary embolism
C. Thyroid dysregulation
D. Depression
E. Post-Acute Sequelae of SARS-CoV-2 Infection

23

CC: 39yoW with headaches, palpitations

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24

What happens after COVID-19?

- Beginning in early summer 2020, some patients started reporting prolonged COVID symptoms, often waxing and waning after they initially recovered from COVID-19.
  - Ed Yong, "COVID-19 can last for several months" in *The Atlantic* June 4, 2020
  - Ed Yong, "Long-Haulers are redefining COVID-19" in *The Atlantic* August 19, 2020
  - Callard and Perego, ”How and why patients made Long Covid,” in *Soc Sci Med*, 2021 Jan;268:113426


Social Science & Medicine 268 (2021) 113426

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: http://www.elsevier.com/locate/socscimed

ELSEVIER

Short communication

How and why patients made Long Covid

Felicity Callard [a,*], Elisa Perego [b]

[a] University of Glasgow School of Geographical and Earth Sciences, University of Glasgow, United Kingdom
[b] University College London Institute of Archaeology, UCL, United Kingdom

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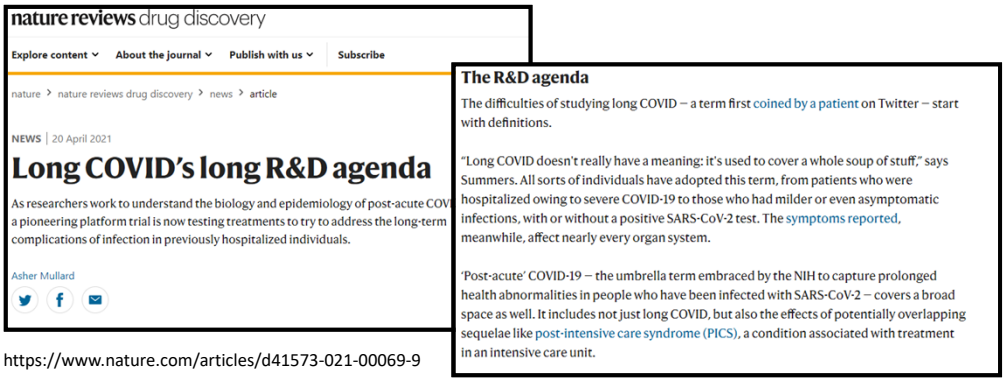
What happens after COVID-19?

Post-COVID conditions have a wide range of names, including

- long COVID
- post COVID-19 syndrome (PSC)
- chronic COVID
- long-haul COVID
- post-acute sequelae of SARS-COV-2 infection (PASC)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NEWS | 20 April 2021

Long COVID's long R&D agenda

As researchers work to understand the biology and epidemiology of post-acute COV a pioneering platform trial is now testing treatments to try to address the long-term complications of infection in previously hospitalized individuals.

Asher Mullard

The R&D agenda

The difficulties of studying long COVID – a term first coined by a patient on Twitter – start with definitions.

"Long COVID doesn't really have a meaning: it's used to cover a whole soup of stuff," says Summers. All sorts of individuals have adopted this term, from patients who were hospitalized owing to severe COVID-19 to those who had milder or even asymptomatic infections, with or without a positive SARS-CoV-2 test. The symptoms reported, meanwhile, affect nearly every organ system.

'Post-acute' COVID-19 – the umbrella term embraced by the NIH to capture prolonged health abnormalities in people who have been infected with SARS-CoV-2 – covers a broad space as well. It includes not just long COVID, but also the effects of potentially overlapping sequelae like post-intensive care syndrome (PICS), a condition associated with treatment in an intensive care unit.

https://www.nature.com/articles/d41573-021-00069-9

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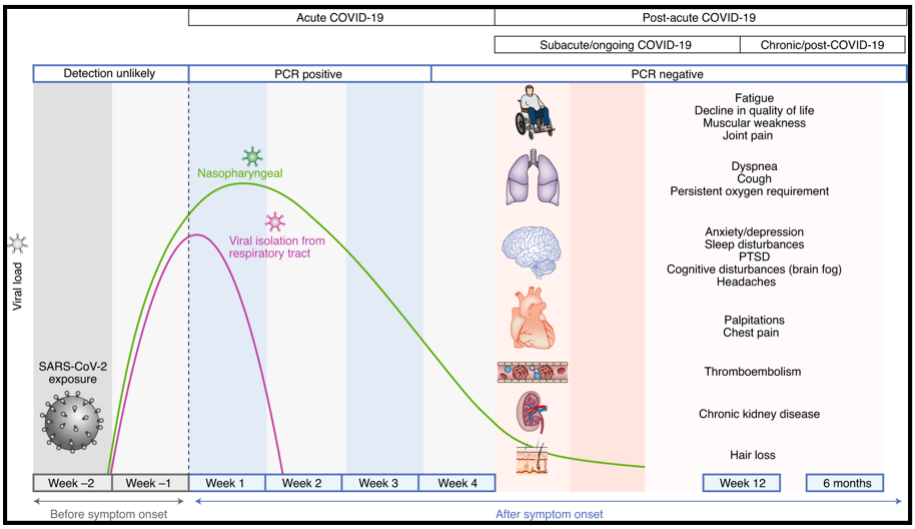
COVID-19 Timecourse



Nalbandian, A., Sehgal, K., Gupta, A. et al. *Nat Med. 2021*

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What happens after COVID-19?

Patients with PASC can present with prolonged multisystem involvement and significant disability.

- Brain fog
- Depression
- Anxiety
- Confusion
- Neurocognitive impairment
- Headache
- Persistent loss of smell/taste

- Chest pain
- Palpitations
- Tachycardia
- Orthostatic Hypotension

- Shortness of breath
- Exercise intolerance
- Cough
- Dyspnea
- Hoarseness

- Exercise intolerance
- Fatigue
- Muscle aches

- Swelling
- Redness

Seessle, et al, "Persistent Symptoms in Adult Patients One Year After COVID-19: a prospective cohort study," in CID Jul 2021 doi.org/10.1093/cid/ciab611

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What happens after COVID-19?

- Centers for Disease Control and Prevention (CDC) specified
  - Symptoms >4 weeks meet criteria for PASC
  - >4 weeks but <12 weeks is ”subacute”
  - >12 weeks is “chronic”
- In December, 2020, the National Institute for Health and Care Excellence (NICE), the Royal College of General Practitioners (RCFP), and the Scottish Intercollegiate Guidelines Network (SIGN) established a definition of so-called "Long COVID."
  - "Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis.”

CDC Centers for Disease Control and Prevention · NICE National Institute for Health and Care Excellence · RCGP Royal College of General Practitioners · SIGN Scottish Intercollegiate Guidelines Network

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PASC: Scope of the Problem

- To date, there are more than
  - 235 million cases of COVID-19 globally
  - 44 million cases of COVID-19 in the US

At risk for PASC:
– 70-188 million
– 13-35 million

- Between 30-80% of patients diagnosed with COVID-19 have one or more symptom of post-acute COVID-19
- This is the next public health crisis!

Lopez-Leon et al, “More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis,” medRxiv. 2021 Jan 30 doi: 10.1101/2021.01.27.21250617. Preprint
Proal and VanElzakker, “Long COVID or Post-acute Sequelae of COVID-19,” in Front Microbiol Jun 2021 doi:10.3389/fmicb.2021.698169

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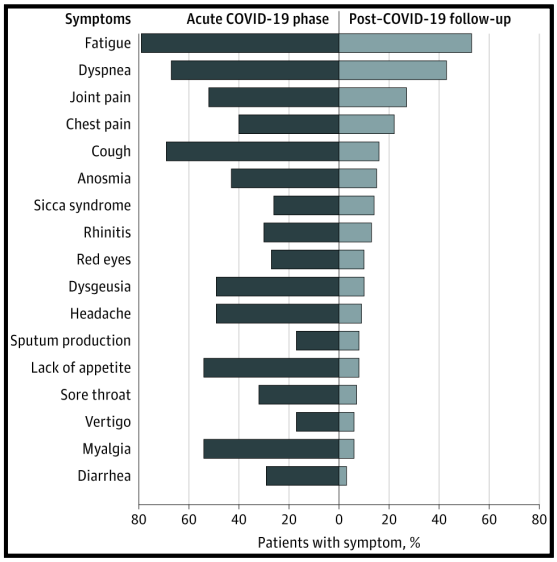
Long Term Sequelae following COVID-19



143 patients with recovered COVID-19, ~2 months post diagnosis,

- 84.4% having 1 or more persistent symptoms

JAMA Network

From: **Carfi, et al, Persistent Symptoms in Patients After Acute COVID-19**
JAMA Netw Open. July 9, 2020 324(6):603-605. doi:10.1001/jama.2020.12603

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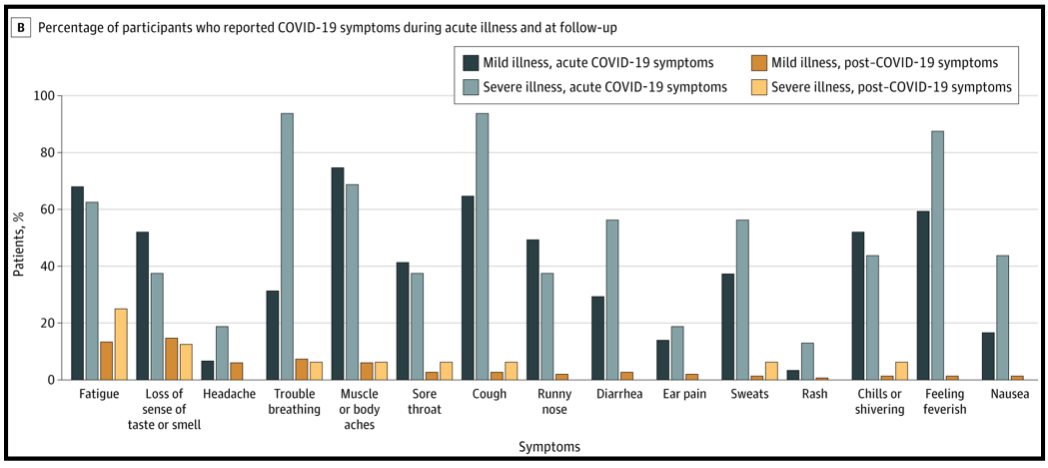
Long Term Sequelae following COVID-19



177 Patients surveyed 4-6 months after initial diagnosis

JAMA Network

From: **Logue, et al, Sequelae in Adults at 6 Months After COVID-19 Infection**
JAMA Netw Open. Feb 19, 2021;4(2):e210830. doi:10.1001/jamanetworkopen.2021.0830

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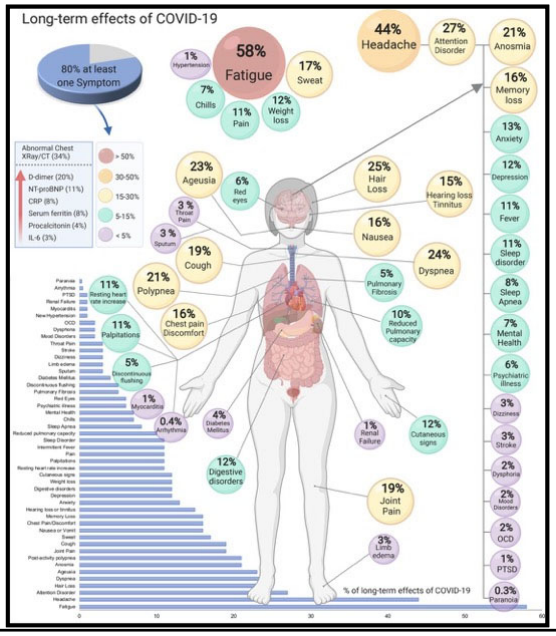
Long Term Effects of COVID-19



Metanalysis of 47,910 patient reports with ongoing symptoms

- Estimates 80% have one or more symptoms
- Assessed 2-13 weeks post-COVID
- Most common symptoms were
  - Fatigue (58%)
  - Headache (44%)
  - Attention disorder (27%)
  - Hair loss (25%)
  - Shortness of breath/Dyspnea (24%)

Lopez-Leon et al, "More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis," *Scientific Reports*. 2021

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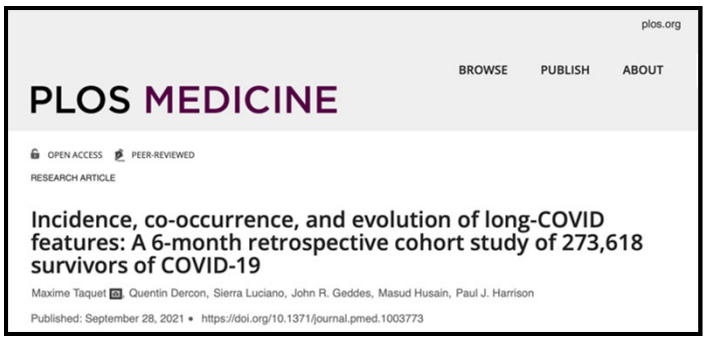
plos.org

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OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19

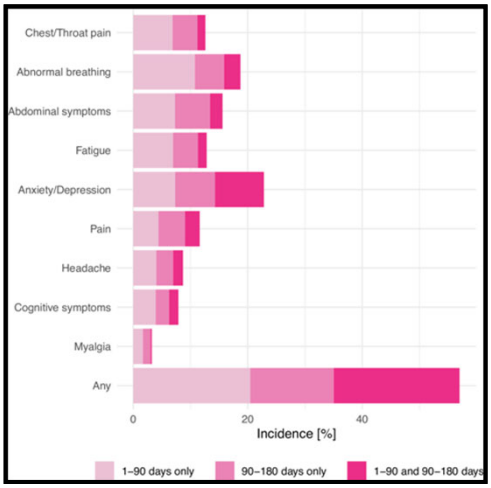
Maxime Taquet, Quentin Dercon, Sierra Luciano, John R. Geddes, Masud Husain, Paul J. Harrison

Published: September 28, 2021 • https://doi.org/10.1371/journal.pmed.1003773

Retrospective cohort study

- Electronic health records of 81 million patients
- 273,618 COVID-19 survivors
- Evaluated incidence of 9 long COVID-19 symptoms
  - Breathing difficulties
  - Fatigue/malaise
  - Chest/throat pain
  - Headache
  - Abdominal symptoms
  - Myalgia
  - Other pain
  - Cognitive symptoms
  - Anxiety/depression

Fig 1. Incidence of each long-COVID feature in the 180 days after COVID-19.



Taquet et al. (2021) *PLOS Medicine* 18(9): e1003773. https://doi.org/10.1371/journal.pmed.1003773

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Fig 2. Comparison of Long COVID-19 and Influenza

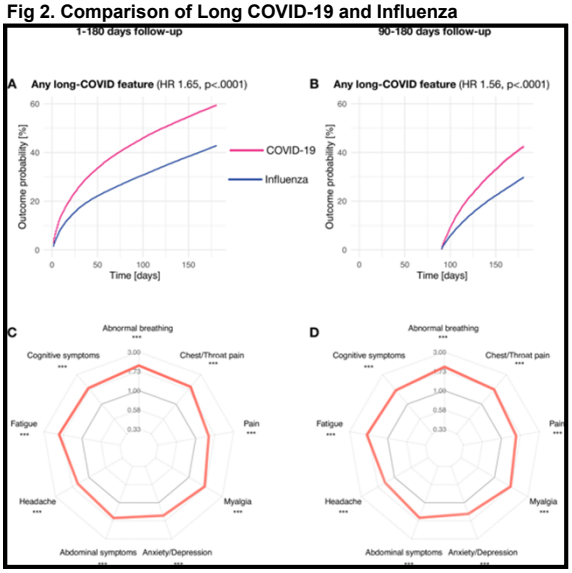

Fig 5. Spider plots summarizing the HRs for each long-COVID feature in subgroups based upon sex, age, and severity of COVID-19.

Taquet et al. (2021) *PLOS Medicine* 18(9): e1003773. https://doi.org/10.1371/journal.pmed.1003773

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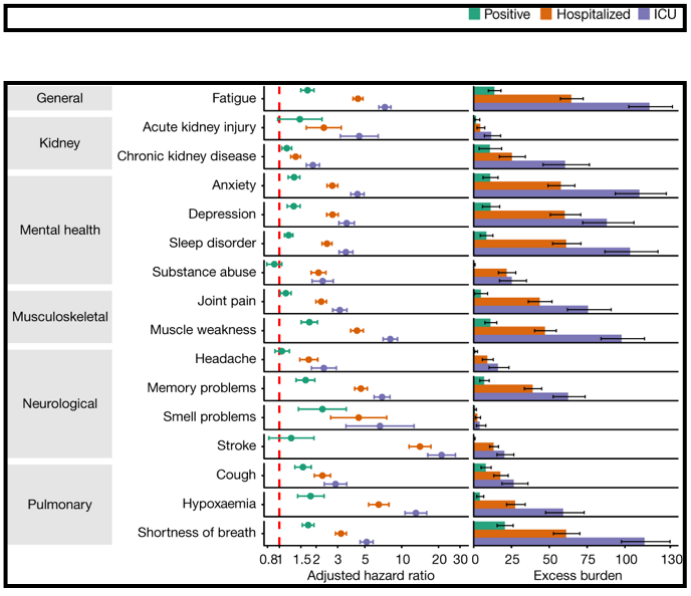
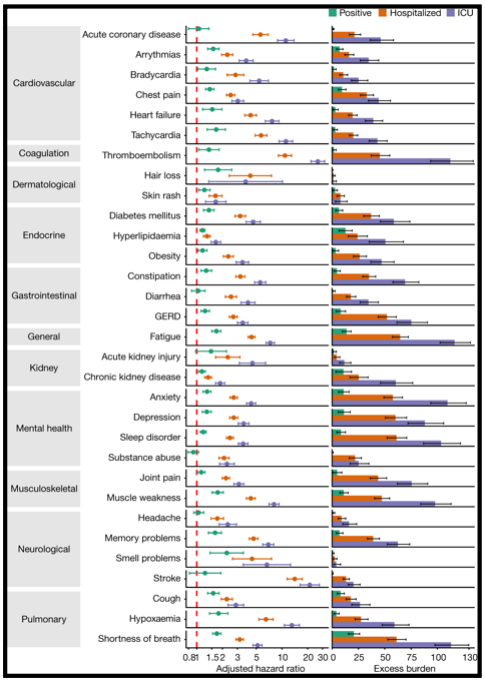
The Burden of Disease is High





Al-Aly et al. "High-dimensional characterization of post-acute sequelae of COVID-19," in *Nature,* June 2021

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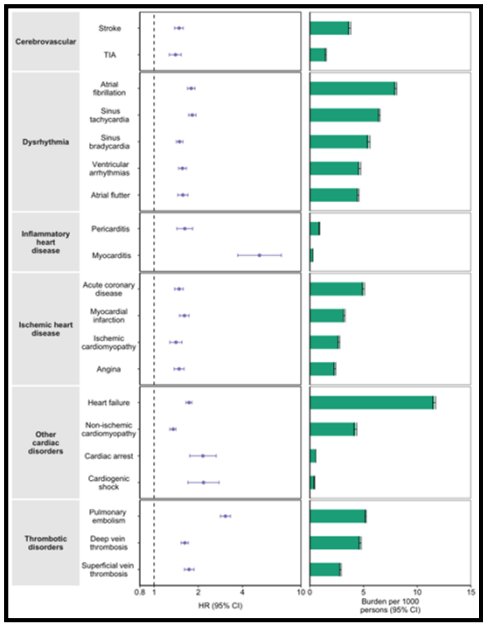
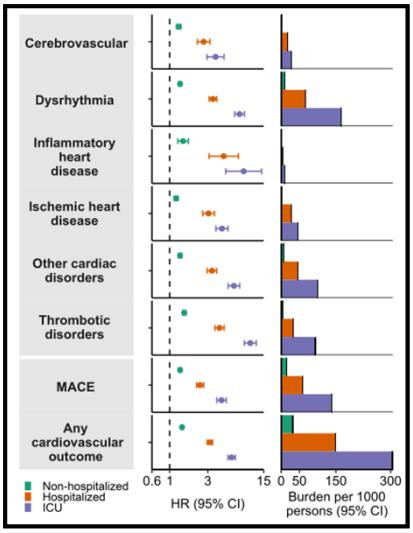
The Burden of Cardiovascular Disease is High





Al-Aly et al. One-year Risks and Burdens of Incident Cardiovascular Disease in COVID-19: Cardiovascular Manifestations of Long COVID, **Preprint**, October 2021

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The Burden of Disease is High

Cohort	Outcomes	Hazard ratio (95% confidence interval) ‡	Incident rate per 1000 at 6-months in COVID-19 group (95% confidence interval) ‡	Incident rate per 1000 at 6-months in comparison group (95% confidence interval) ‡	Excess burden per 1000 at 6-months (95% confidence interval) ‡
COVID-19 vs. VHA users *	Death	1.59 (1.46, 1.73)	22.77 (20.90, 24.81)	14.38 (13.19, 15.68)	8.39 (7.09, 9.58)
	Outpatient encounter	1.20 (1.19, 1.21)	946.69 (944.94, 948.41)	913.48 (911.11, 915.81)	33.22 (30.89, 35.58)
Hospitalized COVID-19 vs. hospitalized seasonal influenza †	Death	1.51 (1.30, 1.76)	87.92 (76.11, 101.47)	59.13 (51.07, 68.41)	28.79 (19.52, 36.85)
	Outpatient encounter	1.12 (1.08, 1.17)	990.32 (988.50, 991.90)	983.95 (981.28, 986.30)	6.37 (4.01, 9.03)

Al-Aly et al. "High-dimensional characterization of post-acute sequelae of COVID-19," in *Nature,* June 2021

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CC: 39yoW with headaches, palpitations

Which is a risk factor for our patient to develop PASC?

A. Age
B. Gender
C. Severity of initial COVID presentation
D. Whether received COVID-specific antiviral therapy
E. BMI

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40

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Which is a risk factor for our patient to develop **PASC**?

A. Age
B. Gender
C. Severity of initial COVID presentation
D. Whether received COVID-specific antiviral therapy
E. BMI

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What predicts symptom persistence?

Study of 1733 patients discharged post-COVID and assessed symptoms 6 months post infection

- Patients requiring ventilatory support (NIV, HFMC, IMV), compared to those who did not require supplemental oxygen were
  - More likely to have any symptoms, fatigue and muscle weakness
  - More problems with mobility, pain, discomfort, anxiety/depression
  - Reduced distance walked
- Patients requiring supplemental oxygen, compared to those who did not, showed
  - Reduced odds of symptoms
  - Reduced odds of fatigue/muscle weakness

How do you differentiate symptoms from deconditioning/post-ARDS/post-ICU from PASC?

Huang, et al, "6-month consequences of COVID-19 in patients discharged from hospital: a cohort study." *Lancet*. 2021; 397:220-32

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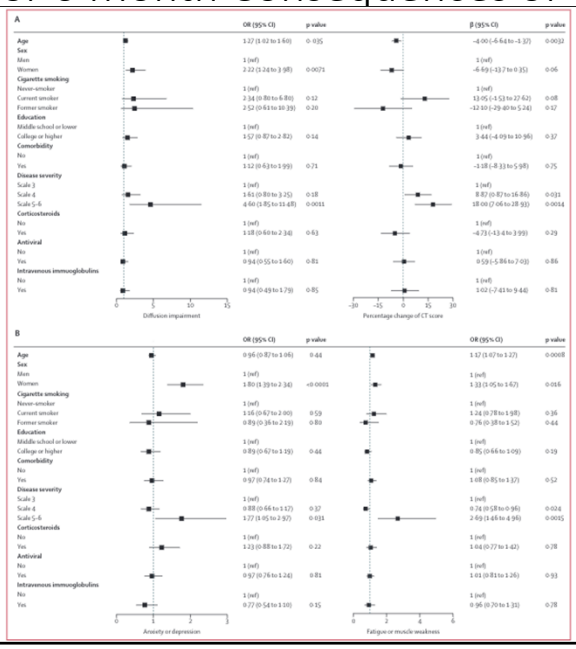
Risk Factors for 6 Month Consequences of COVID-19

Age associated with worse diffusion impairment
OR 1.27, p=0.035



Age associated with worse CT scan findings
Beta -4.0, p=0.0032

Age not associated with anxiety or depression

Age associated with fatigue and muscle weakness
OR 1.17, p=0.008

Huang, et al, *Lancet*. 2021; 397:220-32

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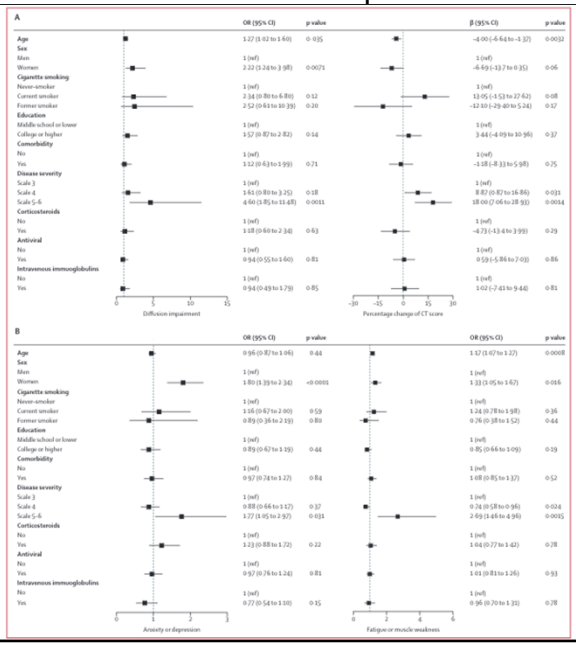
Risk Factors for 6 Month Consequences of COVID-19

Women are more likely to have diffusion impairment
OR 2.22, p=0.0071



Trend towards women having more change in CT findings
Beta 6.69, p=0.06

Women are more likely to have anxiety and depression
OR 1.8, p<0.001

Women are more likely to have fatigue/muscle aches
OR 1.33, p=0.016

Huang, et al, *Lancet*. 2021; 397:220-32

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Does initial severity predict symptom persistence?

Study of symptoms at 6 months found that

- Sleep difficulties, hair loss, smell disorder, palpitations, joint pain, appetite, taste disorder, dizziness, diarrhea, vomiting, chest pain, rash, myalgias, usual activity problems, pain or discomfort, quality of life not different between groups
- Most PFT parameters not different based on severity of acute illness
- Most CT scan findings not different based on severity of acute illness

Huang, et al, "6-month consequences of COVID-19 in patients discharged from hospital: a cohort study." *Lancet*. 2021; 397:220-32

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Persistent symptoms perhaps unrelated to severity of illness…

…but associated with age, sex, and frailty

Table 2: Relationship between respiratory outcomes and disease severity

	Abnormal chest x-ray		Distance at 6MWT		Maximal Borg at 6MWT	
	OR (95% CI)	P value	β coefficient (95% CI)	P value	β coefficient (95% CI)	P value
Disease Severity						
Non-admitted	1.0 (reference)	n/a	0 (reference)	n/a	0 (reference)	n/a
Admitted, non-ICU	2.6 (0.5 – 14.0)	0.26	-23.6 (-69.4 – 22.2)	0.31	-0.15 (-1.3 – 1.0)	0.79
Admitted, ICU	4.9 (0.8 – 30.1)	0.09	-27/1 (-85.2 – 31.0)	0.36	-0.56 (-2.0 – 0.9)	0.45
Age	1.0 (1.0 – 1.1)	0.39	-1.8 (-3.4 – -0.3)	0.02	0.01 (-0.03 – 0.04)	0.78
Sex, Female	1.1 (0.3 – 3.9)	0.85	-47.1 (-83.4 – -10.7)	0.01	0.95 (0.04 – 1.9)	0.04
CFS	0.9 (0.4 – 2.1)	0.81	-47.4 (-73.0 – -21.8)	< 0.001	0.65 (0.01 – 1.3)	0.048

6MWT = six-minute-walk test, OR = odds ratio, ICU = intensive care unit, CFS = Clinical Frailty Score

Townsend et al. *Annals of ATS*. 2021

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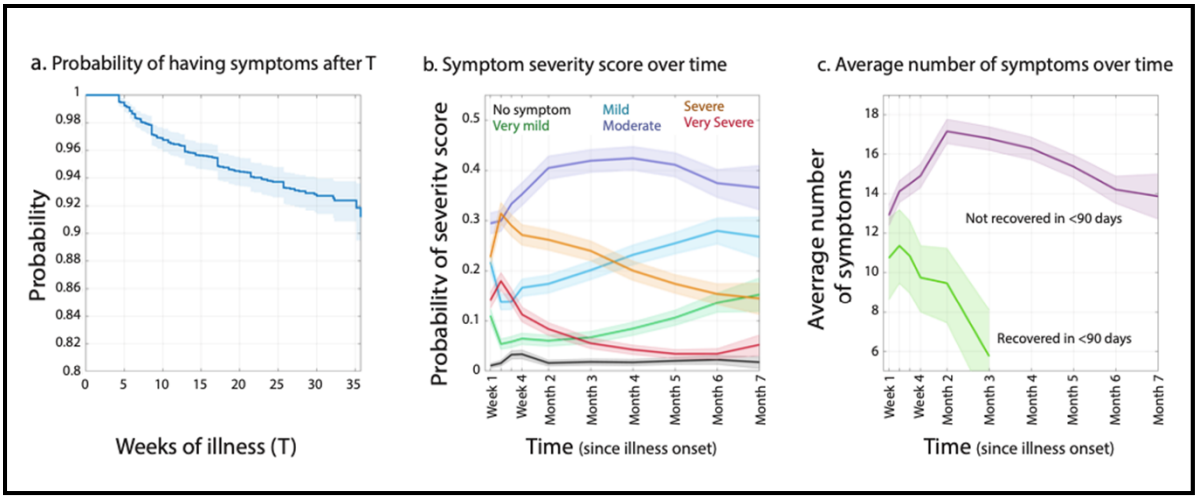
How long do symptoms last?



Davis et al, "Characterizing Long COVID in an International Cohort: 7 months of symptoms and their impact," medRxiv. 2021 Apr 5 https://doi.org/10.1101/2020.12.24.20248802 Preprint

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Plausible mechanisms

- Persistent viral reservoir? Viral fragments?
- Clotting-related damage to multiple organ systems?
- Alterations in host microbiome/virome?
- Oxidative stress?
- Auto-immune or immune dysregulated response to the virus?
  - Myocarditis
  - Neuroinvasive/neurotrophic inflammation
  - Disrupting neuroendocrine signaling

Adapted from Proal and VanElzakker, "Long COVID or Post-acute Sequelae of COVID-19 (PASC): an Overview of Biological Factors that May Contribute to Persistent Symptoms," in *Frontiers Microbiol* June 2021:12(698169).

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Differential diagnosis based on symptoms and biological plausibility

- Anxiety
- Depression
- PTSD
- Stroke

- Myocarditis
- Cardiac Ischemia
- POTS Syndrome

- Viral pneumonia
- Secondary Infection
- Pulmonary Fibrosis
- Pulmonary Embolism
- Paralyzed diaphragm

- Deconditioning
- Fatigue

- DVT

Nalbandian *et al. Nat Med.* 2021

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Symptom based approach to diagnosis

- MOCA
- HADS
- PCL-5
- Neurocognitive testing
- Psychological evaluation
- MRI

- EKG
- Orthostatic blood pressure
- Troponin
- BNP
- TTE

- Pulse ox
- CXR
- CT scan (+/- contrast)
- Full PFT
- 6MWT

- 6MWT
- Rehabilitation/PT/OT

- Vascular duplex
- CTA

Nalbandian *et al. Nat Med.* 2021

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There are no current COVID-specific therapeutic options

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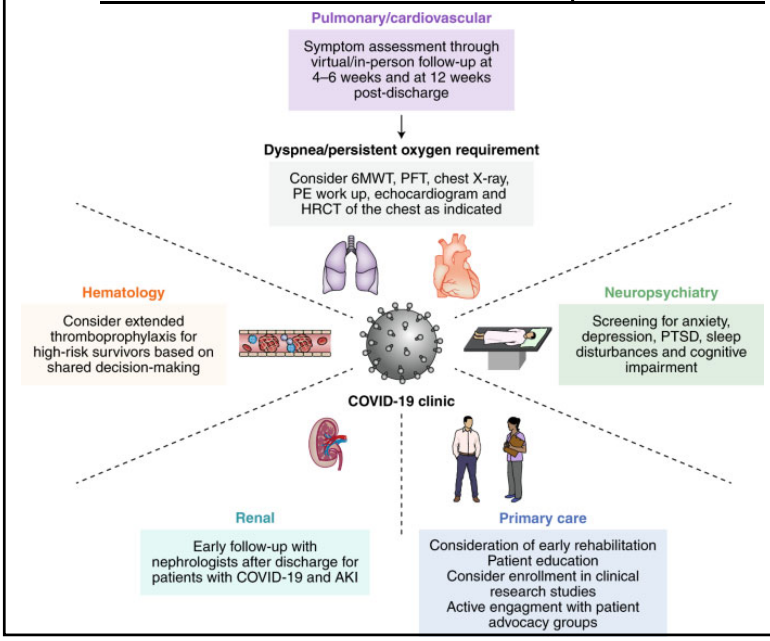
So what do we do for patients?



1. Multidisciplinary care in a post-COVID-19 clinic or with a provider familiar with the disease process
2. Practice evidence-based medicine
3. Do no harm
4. Validate patients fears/concerns
5. Refer your patients for research and clinical trials

Nalbandian *et al. Nat Med.* 2021

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Clinic Models

RECOVERY: CompREhensive Post-COVID CentER at Yale

Referral Pathway	Initial Assessment	Subsequent Care	Disposition
Inpatients (pre-discharge) **Respiratory Assessment** • Ambulatory oximetry • Pulse oximeter & incentive spirometry training **Functional Assessment** • Physical & occupational therapy evaluation • Swallow evaluation **Care Coordination** • Arrange home services • Address care barriers **Outpatients (ongoing sx)** • Referral by outpatient provider, occupational medicine provider, health system COVID-19 hotline, or self	**Visit 1 (telehealth)** • Pulmonary consultation • Subjective sx assessment • Assess for extrapulmonary complications **Initial Diagnostics** • Repeat imaging (HRCT) • PFTs, 6MWT • Repeat selected labs **Visit 2 (face-to-face)** • Ongoing pulmonary care • PT/OT assessment • Subjective sx assessment • Neurocognitive screening • Mental health screening • Additional subspecialty involvement	**MD visits** • Planned 3, 6, and 12 mo or as needed per severity • Extrapulmonary consultation as needed **Rehab** - PT/OT outpatient care - Pulmonary rehabilitation **Lung function testing** • PFT & 6MWT at 3, 6 , 12 mo • CPET for selected patients **Additional diagnostics** • VQ or CTA chest • Transthoracic Echo • Cardiac event monitoring • Functional cardiac imaging • Neurocognitive testing	**Sx resolve & PFT normal** • Transition to primary care **Sx persist or PFT abnormal** • Non-specific phenotype → continue RECOVERY clinic • Phenotype consistent with specific disease process → appropriate advanced lung disease program (e.g. interstitial lung disease, airways disease, pulmonary vascular disease)

Multi-disciplinary discussion of active cases
Translational research efforts
Revision of clinic processes to meet patient needs and evolving evidence

Lutchmansingh et al. Chest. 2021

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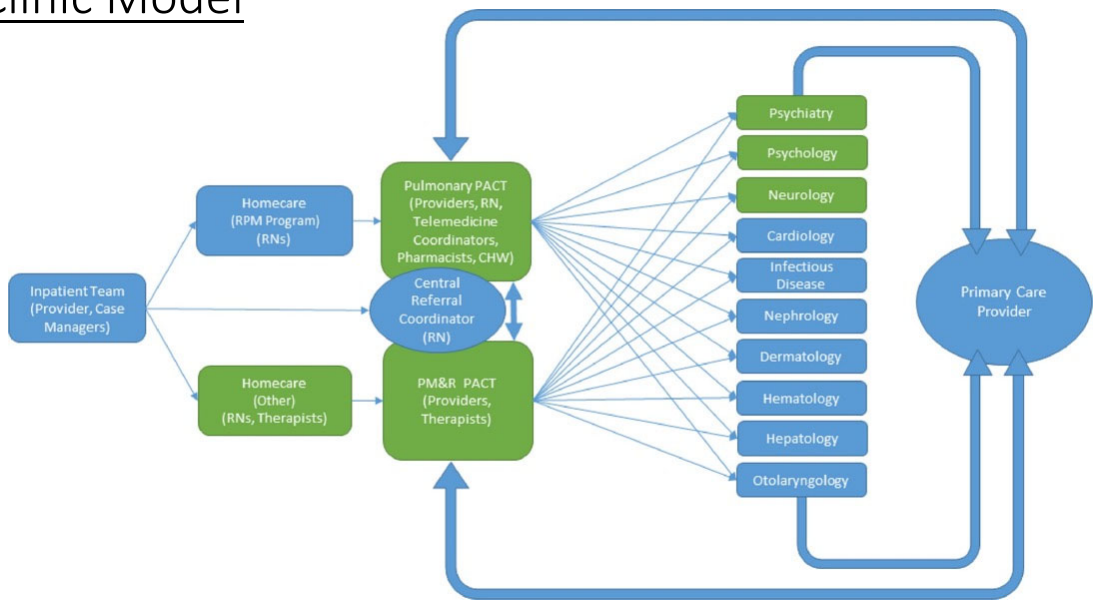
Clinic Model



Brigham et al. The American Journal of Medicine. 2021

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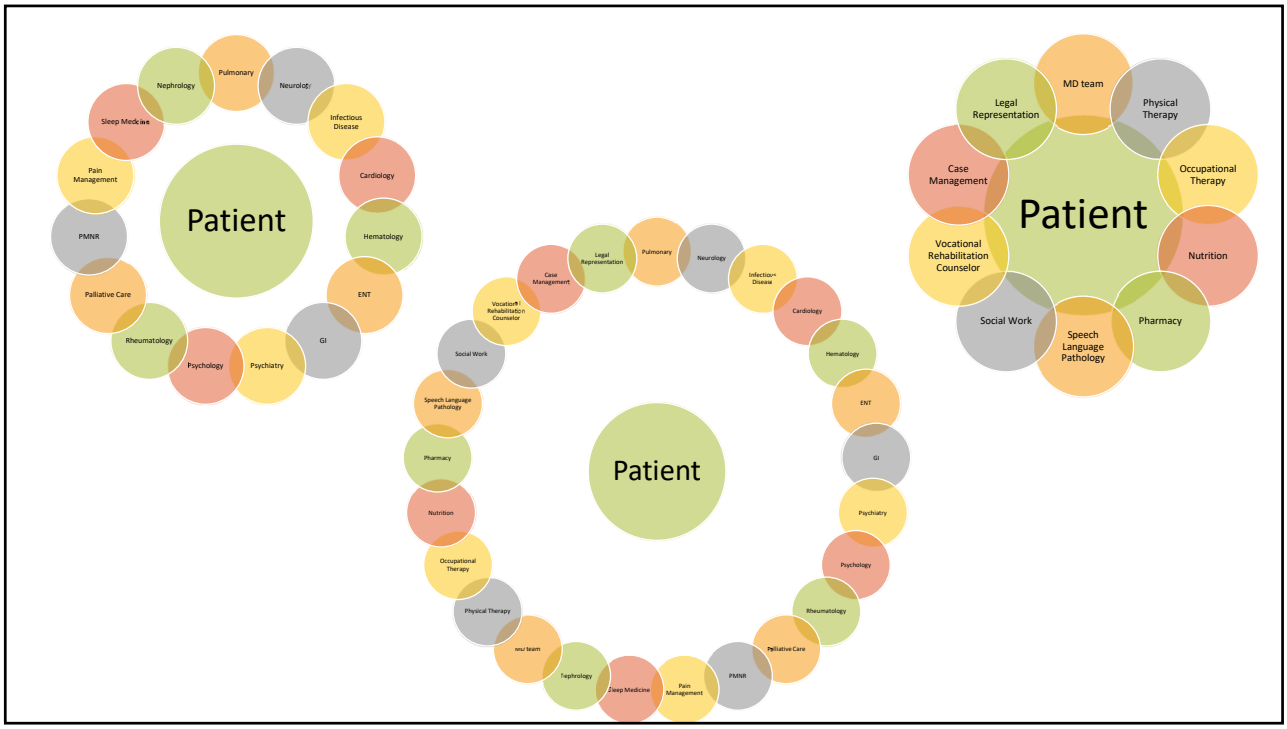

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Ongoing Problems for PASC

- Infrastructure problems
  - Not enough providers, clinic space, or appointments to accommodate new patients
  - Not enough interest/expertise in PASC
- Logistical problems
  - Who should see these patients?
  - How do we identify patients most likely to benefit from long term care?
  - How should patients be triaged?
- Knowledge problems
  - Who will have PASC? For how long?
  - There is no known treatment for PASC.
  - Good clinical practice will come through large RCTs, but access is a challenge

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A Pathway Forward for PASC

- A systematic approach to follow up post COVID-19 illness
  - Phone based or virtual screening
  - Initial visit (virtually if needed) with PCP
  - Systematic assessment of patient's needs
  - Referrals if necessary to post-COVID clinics or specialists
- Provide the support/infrastructure for multi-disciplinary clinics
- Reward and incentivize trainees to do primary care and care for patients with PASC
- Research funding for ongoing investigation into mechanisms underlying PASC and interventional trials
  - NIH RECOVER initiative, among others

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Current drug trials

- Antifibrotic therapy (LYT-100)
- Nintedanib (stopped for adverse events)
- Naltrexone and NAD+
- Niacin (Vitamin B3)
- Montelukast
- Anticoagulation to treat VTE associated with COVID
- COVID-19 vaccine itself as treatment for PASC?

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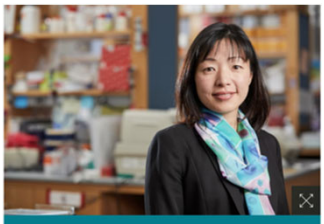
Vaccination to Treat Long COVID?

- In early spring 2021, circulating reports on social media suggested vaccination might partially alleviate PASC symptoms
- On March 17, 2021, the New York Times published about this
- By April 2021, Akiko Iwasaki, Eric Topol, and others started a clinical trial of vaccination for Long COVID patients, reporting preliminary ~30-40% response rates

NYTimes, March 17, 2021

Some Long Covid Patients Feel Much Better After Getting the Vaccine

It is too soon to tell whether the shots have a broad beneficial effect on patients with continuing issues, but scientists are intrigued and beginning to study the phenomenon.



"I've heard from people who say they no longer have 'brain fog,' their gastrointestinal problems have gone away, or they stopped suffering from the shortness of breath they've been living with since being diagnosed with COVID-19," says Akiko Iwasaki, PhD, who is focused on generating hard data on vaccinated long-haulers.

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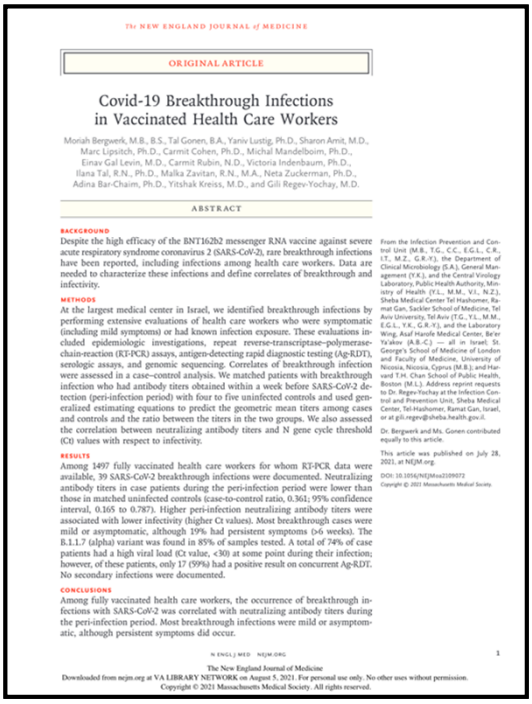
Preventing Long COVID

- Preventing COVID infection is the best way to prevent Long COVID
- Currently >90% of COVID cases occur in unvaccinated persons
  - Breakthrough infections do occur, but are less severe and less fatal

In a study of 1,497 vaccinated Israeli HCW

- 39 (2.6%) had breakthrough infections
- 19% had persistent symptoms for >6 weeks

Bergwerk, et al NEJM 2021 Jul 28. doi: 10.1056/NEJMoa2109072.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Covid-19 Breakthrough Infections in Vaccinated Health Care Workers

Moriah Bergwerk, M.B., B.S., Tal Gonen, B.A., Yaniv Lustig, Ph.D., Sharon Amit, M.D., Marc Lipsitch, Ph.D., Carmit Cohen, Ph.D., Michal Mandelboim, Ph.D., Einav Gal Levin, M.D., Carmit Rubin, N.D., Victoria Indenbaum, Ph.D., Ilana Tal, R.N., Ph.D., Malka Zavitan, R.N., M.A., Neta Zuckerman, Ph.D., Adina Bar-Chaim, Ph.D., Yitshak Kreiss, M.D., and Gili Regev-Yochay, M.D.

ABSTRACT

BACKGROUND

Despite the high efficacy of the BNT162b2 messenger RNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rare breakthrough infections have been reported, including infections among health care workers. Data are needed to characterize these infections and define correlates of breakthrough and infectivity.

METHODS

At the largest medical center in Israel, we identified breakthrough infections by performing extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known infection exposure. These evaluations included epidemiologic investigations, repeat reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case–control analysis. We matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. We also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (Ct) values with respect to infectivity.

RESULTS

Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

CONCLUSIONS

Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

From the Infection Prevention and Control Unit (M.B., T.G., C.C., E.G.L., C.R., I.T., M.Z., G.R.-Y.), the Department of Clinical Microbiology (S.A.), General Management (Y.K.), and the Central Virology Laboratory, Public Health Authority, Ministry of Health (Y.L., M.M., V.I., N.Z.), Sheba Medical Center Tel Hashomer, Ramat Gan, Sackler School of Medicine, Tel Aviv University, Tel Aviv (T.G., Y.L., M.M., E.G.L., Y.K., G.R.-Y.), and the Laboratory Wing, Asaf Harofe Medical Center, Be'er Ya'akov (A.B.-C.) — all in Israel; St. George's School of Medicine of London and Faculty of Medicine, University of Nicosia, Nicosia, Cyprus (M.B.); and Harvard T.H. Chan School of Public Health, Boston (M.L.). Address reprint requests to Dr. Regev-Yochay at the Infection Control and Prevention Unit, Sheba Medical Center, Tel-Hashomer, Ramat Gan, Israel, or at gili.regev@sheba.health.gov.il.

Dr. Bergwerk and Ms. Gonen contributed equally to this article.

This article was published on July 28, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2109072

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COVID Treatments in development

- Merck & Co. and Ridgeback Biotherapeutics called molnupiravir,
- Pfizer, known as PF-07321332
- AT-527, an antiviral produced by Roche and Atea Pharmaceuticals

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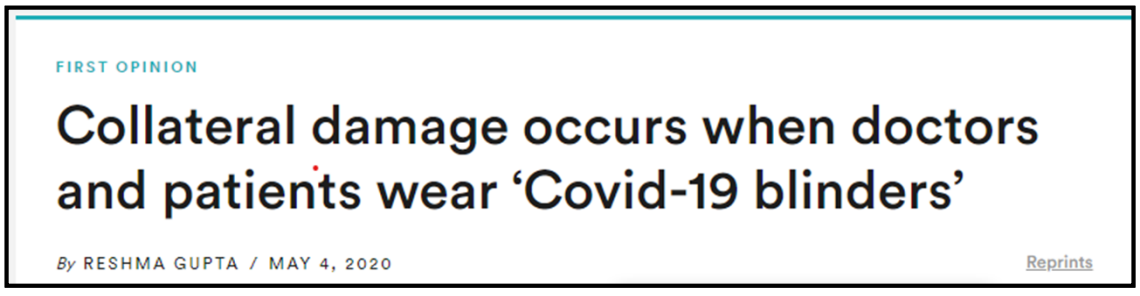
There's more to life than COVID-19



FIRST OPINION

Collateral damage occurs when doctors and patients wear 'Covid-19 blinders'

By RESHMA GUPTA / MAY 4, 2020 Reprints

Concurrent epidemics:

- HIV/STIs
- Depression
- Substance use disorders
- Influenza

https://www.statnews.com/2020/05/04/collateral-damage-occurs-when-doctors-and-patients-wear-covid-19-blinders/

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In Summary

- It is common for symptoms to persist after SARS-CoV-2 infection
- If symptoms persist more than 4 weeks after COVID infection, this is called Post-Acute Sequelae of SARS-CoV-2 infection (PASC)
- No specific therapy for PASC; make sure you evaluate for other common complications/mimics
  - Particularly important to assess for clotting problems: DVT, PE, strokes
  - Consider enrolling your patients in a study or observational cohort
- Prevention is best: get vaccinated as soon as you are able and encourage others to as well!

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Tips for Staying Safe During COVID-19
(or the next emerging infection)

Personal Hygiene & Practices

Handwashing/Hand sanitizer
Cough/Sneeze etiquette
Stay home when sick
Avoid sick contacts
Seek medical assistance

Public Health Authorities

Isolation/Quarantine
Control mass gatherings/travel
Hospitalize
- Contact/Droplet Precautions
- PPE
- ICU, mech vent support

Clear & Fast Communication
- Prevent public panic

Diagnostics

Vaccines

Therapeutics

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THANK YOU

Meagan Deming, MD, PhD
Andrea Levine, MD, MHS
Linda Chang, MD, MS

Institute of Human Virology & Center for
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COVID-19 Providers, Patients, Researchers,
First Responders and Data Fanatics

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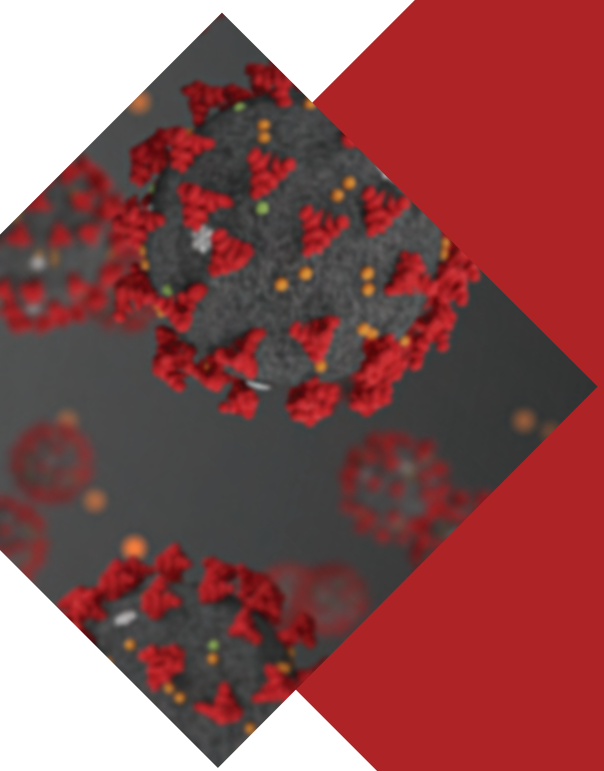
NOTES:



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