I-VAC Learning Collaborative for COVID-19 Vaccination

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Disclosures

- No one in a position to control the education content of the activity has any relevant financial disclosures with ineligible companies to disclose
- What gets said here today may change based on new data and recommendations
 - Knowledge is shared more rapidly through ECHO







Track Covid-19 in the U.S.

Updated Dec. 19, 2023







Reported COVID-19 New Hospital Admissions Rate per 100,000 Population in the Past Week, by County – United States





Wastewater Surveillance







Wastewater Surveillance



Wastewater: Effective SARS-CoV-2 virus concentration (copies / mL of sewage)









Source: Wastewater data from Biobot Analytics





Unexpectedly, given the marked difference in mutations between XBB.1.5, the target of the monovalent "updated" booster compared with JN.1, there is very good cross-reactivity as demonstrated in 3 highly regarded labs. These labs have preprint published data showing solid levels of neutralizing antibodies for the XBB.1.5 booster against JN.1

(ECHO

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From a Detour to Global Dominance - by Eric Topol (substack.com)

Weighted and Nowcast Estimates in United States for 2-Week Periods in 8/20/2023 – 12/9/2023

Nowcast Estimates in United States for 11/26/2023 – 12/9/2023

Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.





WHO designates JN.1 as separate COVID-19 variant of interest

- Due to its rapid growth and potential to add to the respiratory virus burden in Northern Hemisphere countries, the World Health Organization (WHO) today designated JN.1, part of the BA.2.86 SARS-CoV-2 lineage, as its own variant of interest
- Yesterday, scientist and infectious disease modeler J. P. Weiland projected that, based on wastewater tracking, JN.1 will become the dominant variant within a week, with nearly 1 million infections reported each day
- JN.1 has become the fastest-growing variant in the past two years. In the U.S., JN.1 is reaching dominance. But, in other countries where JN.1 is already dominant, like Europe, wastewater is uniformly and exponentially increasing, as shown below. This is even the case in Australia even though it is summer there
- Impact: The continued growth of JN.1 suggests that it is either more transmissible or better at evading our immune systems. At this time, there is no evidence that JN.1 presents an increased risk to public health relative to other currently circulating variants





"Long COVID" PASC (Post-Acute Sequelae of COVID)





Risk of New-Onset Long COVID Decreases Following Reinfection With SARS CoV-2: A Community-Based Cohort Study

- Long COVID was reported by those ≥16 years after 4.0% and 2.4% of first and second infections, respectively; the corresponding estimates among those aged <16 years were 1.0% and 0.6%.
- The aOR for long COVID after second compared to first infections was 0.72 (95% confidence interval [CI], .63–.81) for those ≥16 years and 0.93 (95% CI, .57–1.53) for those <16 years
- The risk of new-onset long COVID after a second SARS-CoV-2 infection is lower than that after a first infection for persons aged ≥16 years, though there is no evidence of a difference in risk for those <16 years

0.72 (.63 to .81) Adults





Open Forum Infectious Diseases, Volume 10, Issue 11, November 2023, ofad493, https://doi.org/10.1093/ofid/ofad493

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

- Prospective observational cohort study of adults with and without SARS-CoV-2 infection at 85 enrolling sites
- 9764 participants met selection criteria. Adjusted odds ratios were 1.5 or greater (infected vs uninfected participants) for 37 symptoms
- Symptoms contributing to PASC score included: **post-exertional malaise**, fatigue, brain fog, dizziness, gastrointestinal symptoms, palpitations, changes in sexual desire or capacity, loss of or change in smell or taste, thirst, chronic cough, chest pain, and abnormal movements.
- Among 2231 participants first infected on or after December 1, 2021, and enrolled within 30 days of infection, 224 (10%) were PASC positive at 6 months.
- Given the heterogeneity of PASC symptoms, determining whether PASC represents one unified condition or reflects a group of unique phenotypes is important. Recent evidence supports the presence of PASC phenotypes, although characterization of these phenotypes is inconsistent





Closing in on understanding "Long COVID"

- Pathophysiological model of long COVID based on the persistence of SARS-CoV-2 virus that triggers a dysregulation of the immune system, followed by increased release of inflammatory cytokines and abnormal endothelial damage, ultimately leading to the development of chronic inflammation, vascular damage, hypercoagulability, microthrombosis, and multiorgan symptoms
- There might be a correlation between the length of time the virus stays in the body and the risk of long COVID
- Rapid viral elimination in patients with persistent SARS-CoV-2 virus could be crucial.



Figure Examples of long COVID driven by persistence of SARS-CoV-2





Fig. 3: Hypothesized mechanisms of long COVID pathogenesis.

From: Long COVID: major findings, mechanisms and recommendations

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There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. *Nat Rev Microbiol* **21**, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2

Long COVID might be due to "microclots"

- *Per Dr. Pretorius:* "The spike protein has the capability to change your soluble clotting protein to insoluble little microclots and that's where everything starts," "So when you have acute COVID you will have activated platelets, you will have vascular damage in endothelial damage and you will have a micro cloud presence in some individuals." In some people, after around two weeks, the body will begin to break down those insoluble microclots and they will return to normal. But for others, those microclots hang around and they can damage blood vessels as well as block blood flow to many organs which could help explain Long COVID's wide-ranging symptoms. "You get widespread and systemic-induced ... inflammation of your blood vessels—the inside of your blood vessels. If it's systemic, it means it's in every organ. It's in every part of your body,"
- Research is ongoing, but using an assay for microclots could be a biomarker for Long COVID



Fluorescent image of a microclot from a Long COVID patient shown at 40x magnification. Mount Sinai Health System





SARS-CoV-2 Can Damage Mitochondrion in Heart, Other Organs

- The COVID-19 International Research Team (COV-IRT) and the Children's Hospital of Philadelphia (CHOP) report that they have identified abnormal mitochondrial function in the heart, kidneys, and liver after SARS-CoV-2 infection, which leads to long-term damage and may help explain long COVID.
- The team analyzed mitochondrial gene expression in tissues from COVID-19 patients' nose and throat, along with tissues from deceased patients and hamsters and mice.
- Co-senior author Douglas Wallace, PhD, of CHOP, said that the study offers strong evidence that COVID-19 is a systemic disease that affects multiple organs rather than strictly an upper respiratory illness. "The continued dysfunction we observed in organs other than the lungs suggests that mitochondrial dysfunction could be causing longterm damage to the internal organs of these patients,"
- The results also identified a potential therapeutic target, **microRNA 2392**, which was shown to regulate mitochondrial function in the human tissue samples
- Data suggest that when the viral titer first peaks, there is a systemic host response followed by viral suppression of mitochondrial gene transcription and induction of glycolysis leading to the deployment of antiviral immune defenses. Even when the virus was cleared and lung mitochondrial function had recovered, mitochondrial function in the heart, kidney, liver, and lymph nodes remained impaired, potentially leading to severe COVID-19 pathology.

AGAINST COVID



DOI: 10.1126/scitranslmed.abq1533



Possible test for Long COVID?

- Here 275 individuals with or without long COVID were enrolled in a cross-^d sectional study that included multidimensional immune phenotyping and unbiased machine learning methods to identify biological features associated with long COVID.
- Marked differences were noted in **circulating myeloid and lymphocyte populations** relative to the matched controls, as well as evidence of exaggerated humoral responses directed against SARS-CoV-2 among participants with long COVID.
- Higher antibody responses directed against non-SARS-CoV-2 viral pathogens were observed among individuals with long COVID, particularly Epstein–Barr virus.
- Levels of soluble immune mediators and hormones varied among groups, with **cortisol levels** being lower among participants with long COVID.
- Integration of immune phenotyping data into unbiased machine learning models identified the key features that are most strongly associated with long COVID status. Collectively, these findings may help to guide future studies into the pathobiology of long COVID and help with developing relevant biomarkers.



LASSO regression identifies a minimal set of immunological features differentiating participants with LC from others. Unlabelled dots are significant predictive features that were not included in the final LASSO regression model. Dots are coloured according to individual data segments: orange, flow; blue, plasma cytokines; pink, viral epitopes; green, anti-SARS-CoV-2; yellow, autoantibodies. Flow, flow cytometry; FPR, false-positive rate; TCM, T central memory cells; TPR, true-positive rate.



Nature volume 623, pages139-148 (2023)



Another Possible Biomarker?

- Researchers found elevated levels of certain components
- Four proteins in particular Ba, iC3b, C5a, and TCC predicted the presence of long COVID with 78.5% accuracy in 166 patients, 79 of whom had been diagnosed with long COVID and 87 who had not. All participants had recovered from a severe bout of acute COVID-19.
- Study revealed that long COVID was associated with inflammation of the immune system causing these complement proteins to remain dysregulated. Proteins like C3, C4, and C5 are important parts of the immune system because they recruit phagocytes, cells that attack and engulf bacteria and viruses at the site of infection to destroy pathogens like SARS-coV-2.





Serotonin reduction in post-acute sequelae of viral infection

- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling
- The study was not large, so the findings need to be confirmed with other research. Participants in some other long Covid studies, in which some patients had milder symptoms, did not always show depleted serotonin
- Trial for fluoxetine on the way





https://doi.org/10.1016/j.cell.2023.09.013

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Metformin Seems to Protect Against Long COVID

- In this phase 3 trial of outpatient treatment for COVID-19, treatment with metformin during acute COVID-19 infection reduced the risk of long COVID by day 300 by 41·3% compared with placebo, with an estimated cumulative incidence of 6·3% in the metformin group and 10·6% in the placebo group.
- This finding is consistent with the results for the primary outcome of the trial, in which metformin reduced the risk of emergency department visits, hospitalizations, and death due to COVID-19 by day 14 of study drug by 42.3% compared with placebo (odds ratio [OR] 0.58, 95% CI 0.35–0.94).
- Experimentally, metformin has shown in-vitro activity at a physiologically relevant dose against SARS-CoV-2 in cell culture and in human lung tissue

AGAINST COVID-19







NIH launched long COVID clinical trials through RECOVER Initiative, opening enrollment

- National Institutes of Health launched and is opening enrollment for phase 2 clinical trials that will evaluate at least four potential treatments for long COVID, with additional clinical trials to test at least seven more treatments expected in the coming months.
 - RECOVER-VITAL will initially focus on a treatment targeting SARS-CoV-2 persistence, which could occur if the virus stays in the body and causes the immune system to not function properly or damage to the organs. The first intervention will test a longer dose regimen of the antiviral PAXLOVID (nirmatrelvir and ritonavir) than is used for treating acute COVID to see if it improves the symptoms of patients with long COVID.
 - **RECOVER-NEURO** will examine accessible interventions for cognitive dysfunction related to long COVID, including brain fog, memory problems and difficulty with attention, thinking clearly and problem solving. Interventions under this protocol will include a web-based brain training program called BrainHQ, developed by Posit Science Corporation in San Francisco, that has been used to improve cognitive function; PASC-Cognitive Recovery, a web-based goal management training program, developed by Mount Sinai Health System, New York City, that has been used to improve executive function; and a device used for home-based transcranial direct current stimulation developed by Soterix Medical, Inc., Woodbridge, New Jersey, which has been demonstrated to help brain activity and blood flow.
 - **RECOVER-SLEEP** will test interventions for changes in sleep patterns or ability to sleep after having COVID-19. A trial for hypersomnia, or excessive daytime sleepiness, will test two wakefulness-promoting drugs compared to a placebo control. A second trial for sleep disturbances, such as problems falling or staying asleep, will test other interventions designed to improve sleep quality to learn if these interventions may help regulate sleep patterns in adults with long COVID.
 - **RECOVER-AUTONOMIC** will examine interventions to help treat symptoms associated with problems in the autonomic nervous system, which controls a range of bodily functions including heart rate, breathing and digestive system activity. The initial trial will focus on postural orthostatic tachycardia syndrome (POTS), a disorder with a number of symptoms including irregular heartbeat, dizziness and fatigue, and will have multiple study arms. The first arm will evaluate a treatment used for immune diseases versus placebo. The second arm will evaluate a drug currently used to treat chronic heart failure in people with an elevated heart rate versus placebo.



https://www.nih.gov/news-events/news-releases/nih-launches-long-covid-clinical-trials-through-recover-initiative-opening-enrollment



Vaccination may protect against long COVID

- Researchers analyzed COVID vaccine data for 1.6 million people from 10 studies published from December 2019 to April 2022. They focused on how many people had COVID symptoms lasting longer than three to four weeks after testing positive and whether or not they were vaccinated.
- The analysis found that people who got a single dose of the Pfizer, Moderna, AstraZeneca, or Johnson & Johnson vaccine before testing positive for COVID had a 35% lower risk of developing long COVID compared with unvaccinated people who got COVID.
- Unvaccinated people should still consider getting the vaccine even if they've already had the disease, according to the researchers. They found that unvaccinated people who recovered from COVID and then got a vaccine lowered their long COVID risk by 27%.







Questions?





For any questions, email us at pgower@peds.bsd.uchicago.edu

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