

Long Covid: The Forever Pandemic

“I’m frustrated I don’t feel better. One day I was fine. I had a future and goals. Now...what the hell is happening to me”

Kenneth Krell MD FACP

Director EIRMC Post Covid Clinic

Associate Director – Internal Medicine Residency

Asst. Clinical Professor University of Washington

March 28th, 2024

CONFIDENTIAL – Contains proprietary information.
Not intended for external distribution.



Current State of Covid

COVID-19 Update for the United States

Early Indicators

Test Positivity >

% Test Positivity

6.5%

(February 25 to March 2, 2024)

Trend in % Test Positivity

-1% in most recent week



Jan 13, 2024 Mar 2, 2024

Emergency Department Visits >

% Diagnosed as COVID-19

1.2%

(February 25 to March 2, 2024)

Trend in % Emergency Department Visits

-21.2% in most recent week



Jan 13, 2024 Mar 2, 2024

Severity Indicators

Hospitalizations >

Hospital Admissions

15,141

(February 25 to March 2, 2024)

Trend in Hospital Admissions

-13.6% in most recent week



Jan 13, 2024 Mar 2, 2024

Deaths >

% of All Deaths in U.S. Due to COVID-19

2.2%

(February 25 to March 2, 2024)

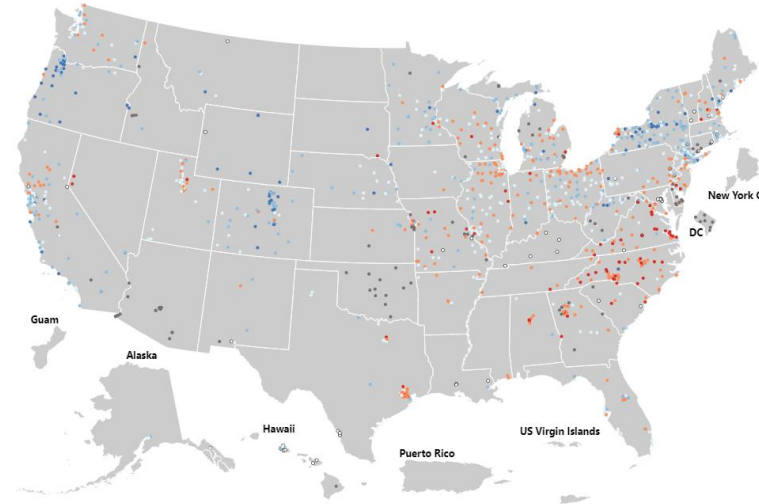
Trend in % COVID-19 Deaths

No change in most recent week



Jan 13, 2024 Mar 2, 2024

Current SARS-CoV-2 Virus Levels in Wastewater by Site, United States
Time Period: Feb 19, 2024 – Mar 04, 2024



Current SARS-CoV-2 virus levels by site, United States

Current virus levels category	Num. sites	% sites	Category change in last 7 days
New Site	50	4	25%
0% to 19%	99	8	21%
20% to 39%	313	24	10%
40% to 59%	424	33	-4%
60% to 79%	321	25	-12%
80% to 100%	85	7	-21%

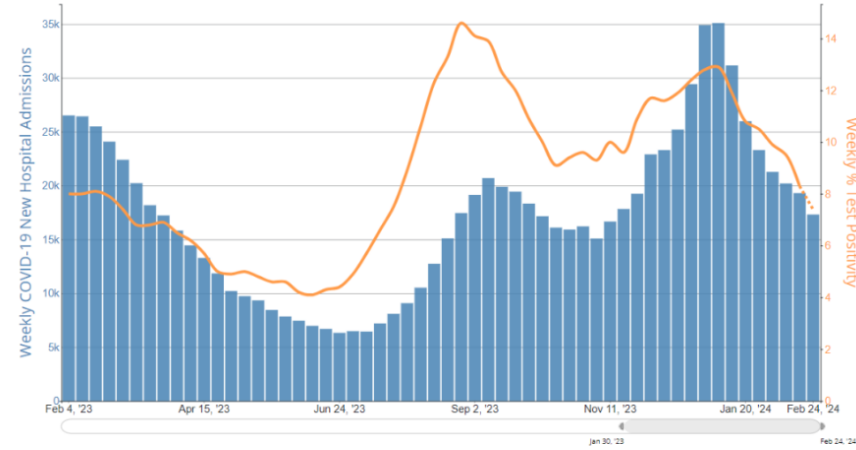
Total sites with current data: 1292
Total number of wastewater sampling sites: 1406

Select legend categories to filter points on the map.

- New site
- 0% to 19%
- 20% to 39%
- 40% to 59%
- 60% to 79%
- 80% to 100%
- No recent data

Centers for Disease Control and Prevention. COVID Data Tracker. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2024, March 11. <https://covid.cdc.gov/covid-data-tracker/>

COVID-19 New Hospital Admissions and COVID-19 Nucleic Acid Amplification Test (NAAT) Percent Positivity, by Week, in The United States, Reported to CDC



Covid-19 hospitalizations and test positivity are on the decline, according to the CDC. [Data as of March 4.](#)

CONFIDENTIAL – Contains proprietary information.
Not intended for external distribution.

- With Covid deaths decreasing life expectancy in U.S. rose 2022 by 1.1 years after 2.4 year decrease from 2019-2021
- But the JN.1 surge continues, infecting 1 million Americans each day with more than 3000 US death in past 2 weeks
- 10,000 deaths worldwide in December

CDC

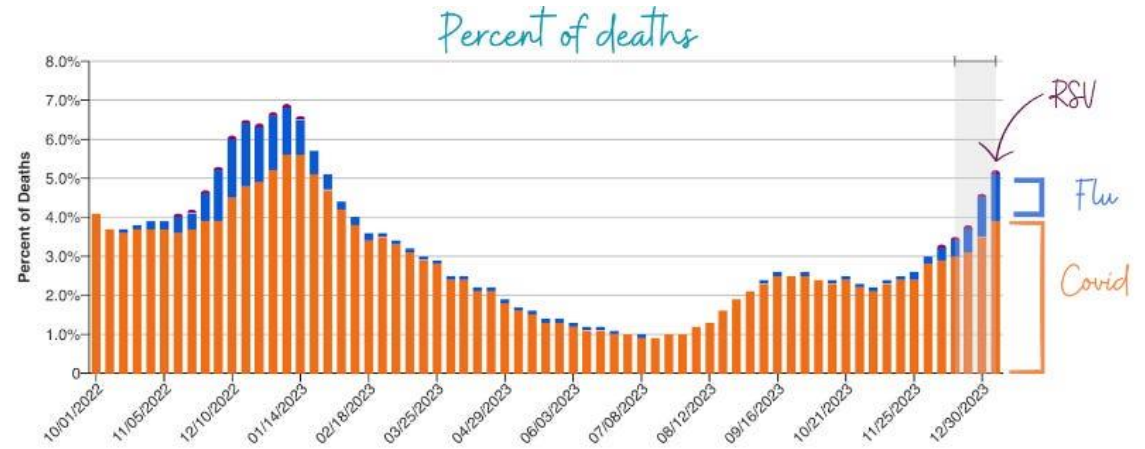
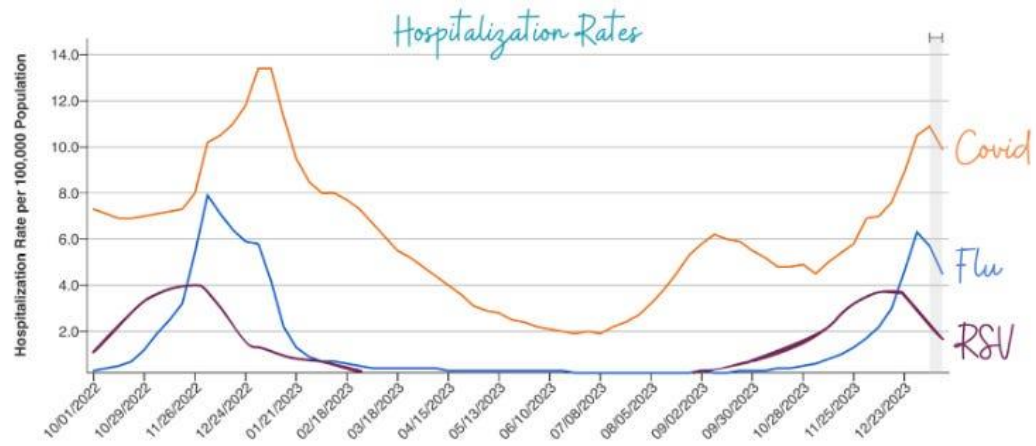
If 5% of infected COVID patients develop persistent long Covid then 50,000 new US cases each day

JN.1 Variant

- Evolved from BA.2.86
- Omicron descendent
- Good fit for current vaccine (boosts virus neutralizing antibodies against JN.1 though not specifically targeted)
- Highly contagious, more than other Omicron variants

Good and Bad News

- Higher rates of infection
 - Wastewater levels 27% higher & Positive COVID test 17% higher than 1 year ago
 - But ER visits down 21%
 - Deaths decreased from 5.2% all US deaths to 3.67% for week 12/30/23
 - 839 vs 3658 deaths



Jetelina, K 2023

Still Abysmal Vaccine rates US

- 41% over age 65 vs 75% flu vaccine

How Likely is it to Develop Long Covid

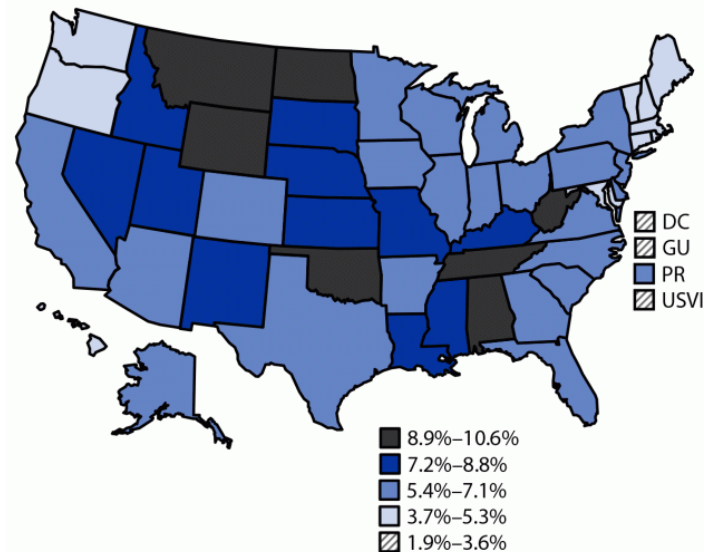
- Up to 10% of adults who have had Covid currently experience Long Covid Symptoms
- 25% with significant activity limitations

Linchflower DG 2023

How Many Cases of Long Covid in US

- Morbidity and Mortality Weekly Report Feb 15, 2023
 - 2022 Behavioral Risk factor surveillance system
 - Self-reported symptoms ≥ 3 mo post infection
- 6.4% non-institutionalized US adults ever experienced Long Covid
- Prevalence varies 1.9% US Virgin Islands to 10.6% West Virginia

FIGURE. Prevalence of reported experience of Long COVID among adults aged ≥ 18 years, by jurisdiction — Behavioral Risk Factor Surveillance System, United States, 2022



Abbreviations: DC = District of Columbia; GU = Guam; PR = Puerto Rico; USVI = U.S. Virgin Islands.

Contains proprietary information.
All rights reserved.



Prevalence

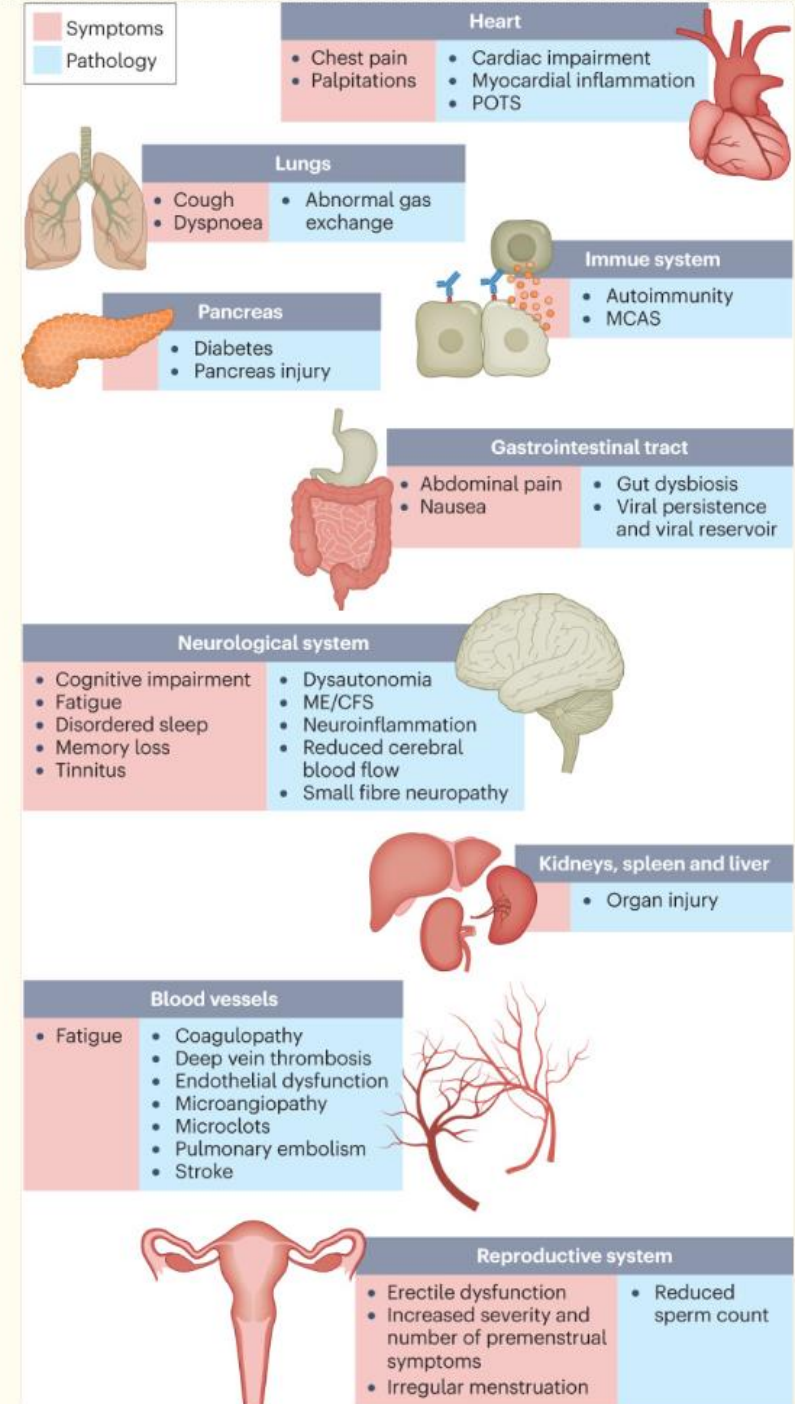
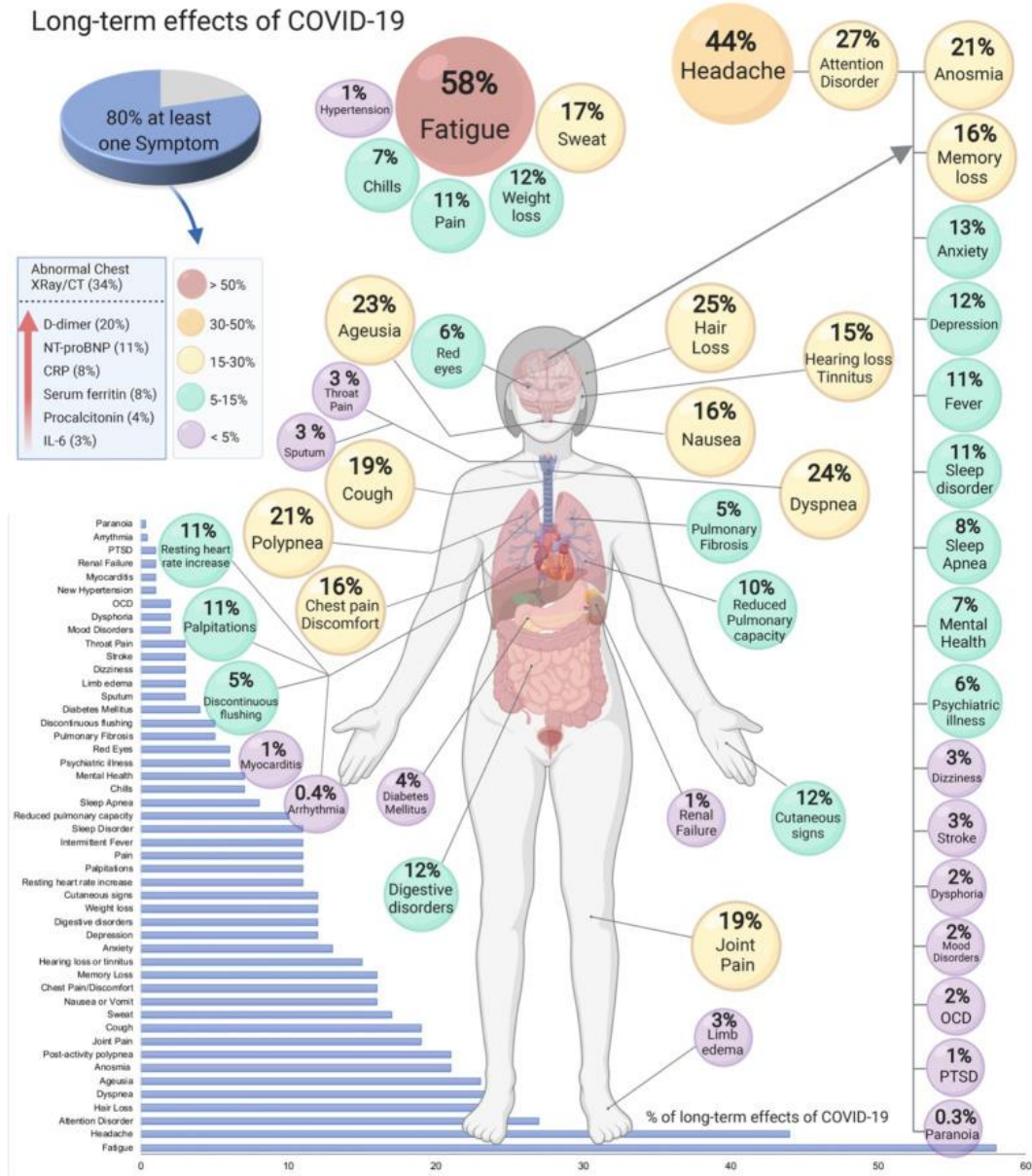
- Idaho 8.3%
- With Population 1.9M then 157,700 Idahoans with Long Covid
- Twice as many cases of Long-Covid in the US vs Coronary artery disease

US News & World Report

Smith-Schoeuwalder Feb 15 2024

What is Long Covid?

Long-term effects of COVID-19



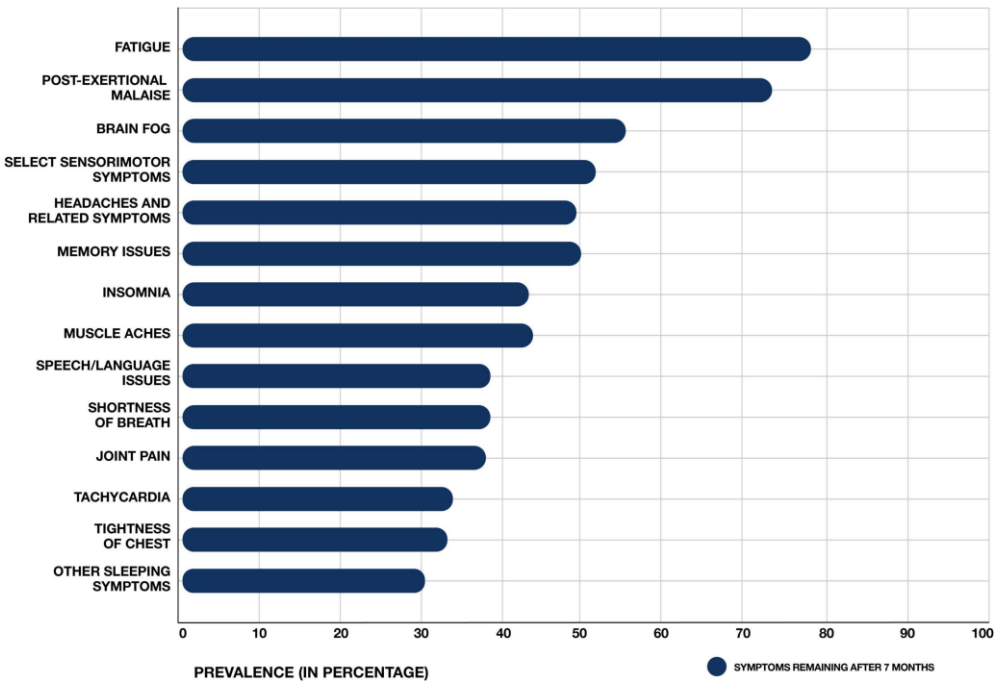
Davis, H.E. 2023 Figure 1



Does Long Covid Get Better?

- Long Covid will likely be a long term disorder for over 1/3 of affected patients
- Long term symptoms persist more for CNS/cognitive symptoms and fatigue (muscle involvement) than respiratory symptoms

REMAINING SYMPTOMS AFTER MONTH 7 (PREVALENCE >30%)

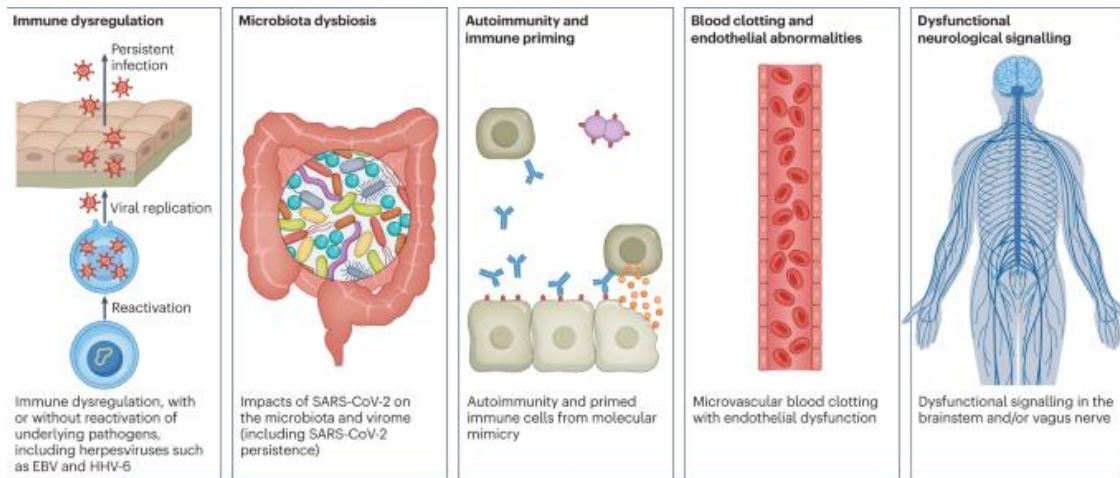


Swank, Zoe

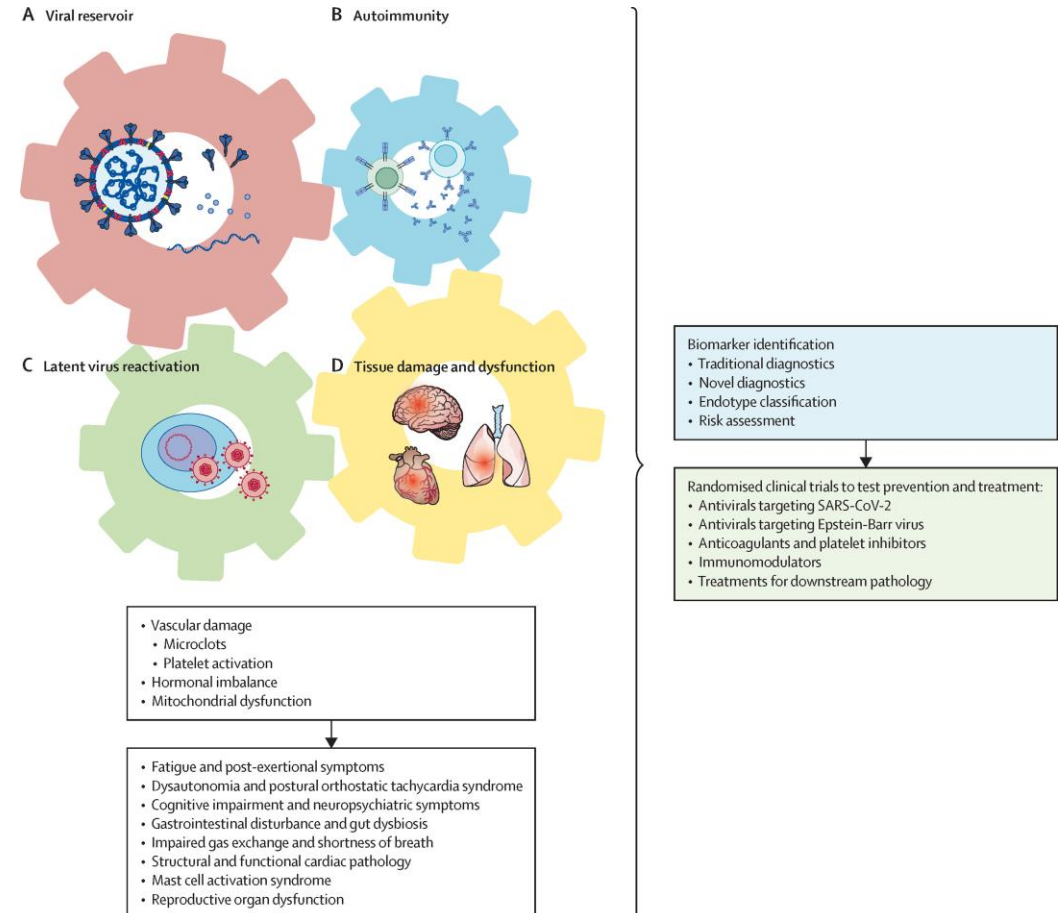
CONFIDENTIAL – Contains proprietary information.
Not intended for external distribution.



What Causes Long Covid - What are the Mechanisms



Davis, H.E. 2021 figure 3



Iwasaki, A 2023 figure

Who is Most at Risk?

- Hospitalized > non-hospitalized
- ICU > non-ICU
- > if loss of taste/smell
- > 5 symptoms during first week of illness
- Age
- Female
- Low socioeconomic status
- Respiratory disease
- Depression
- Comorbidities (Diabetes, cancer, kidney disease, hypertension, neurological disease, obesity CAD)
- Probably some association with asymptomatic acute disease but much less
- Immunologic patterns

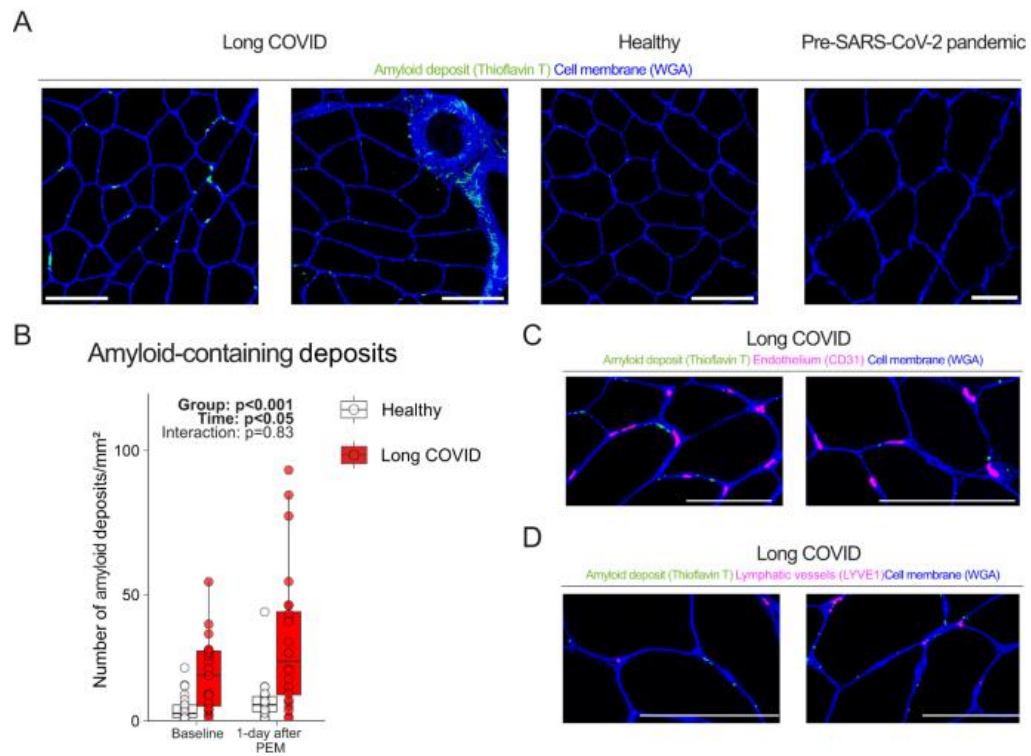
Sudre CH 2021

Hastic CE 2023

Su, Y 2022

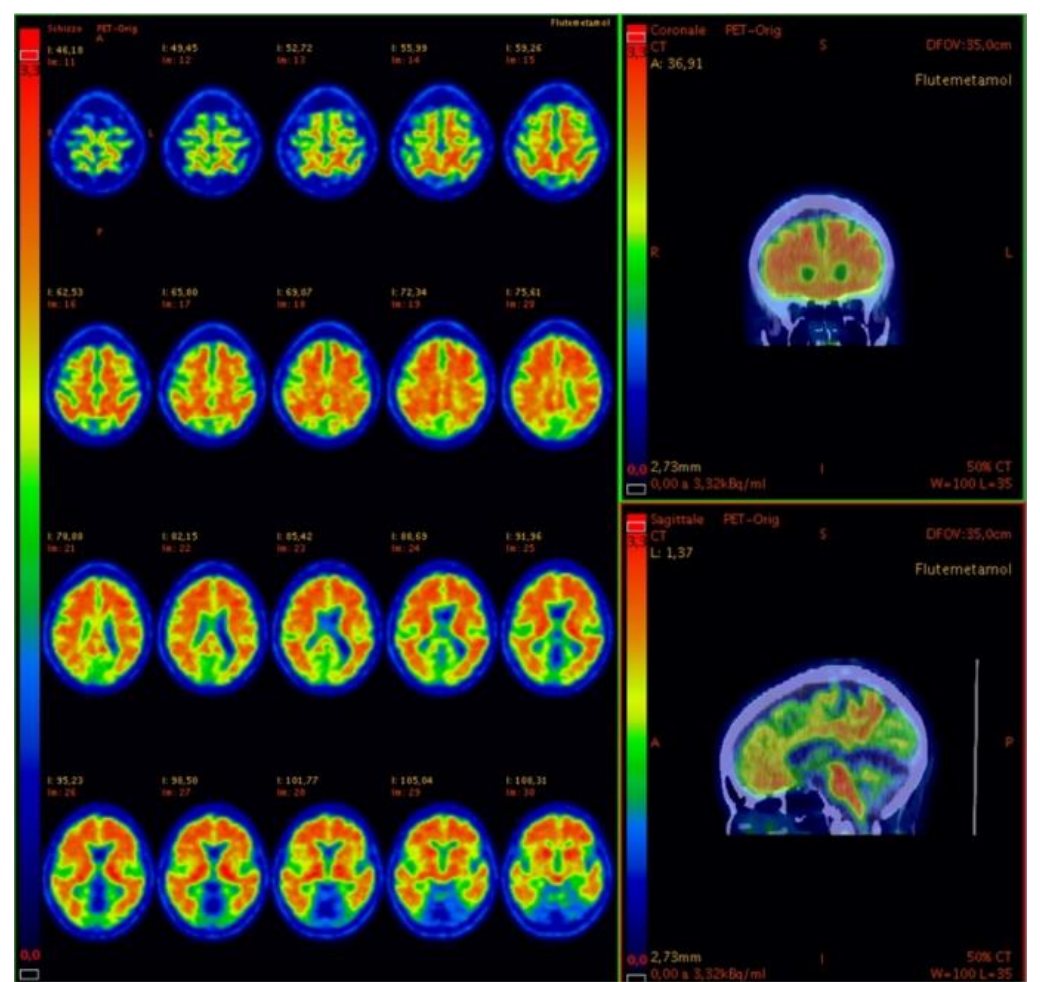
CONFIDENTIAL – Contains proprietary information.
Not intended for external distribution.





Amyloid deposition worsen in muscle after post-exertional malaise

Appelman B 2023



Amyloid deposition in brain

Ferrucci R 2023

In muscle amyloid deposition results from mitochondrial dysfunction – the muscle can't utilize Oxygen and the deposition worsens after exertion re post- exertional malaise

Prevention: The Only Way to Prevent Long Covid is to Prevent Acute Covid

- Do the usual: mask in high risk situations (airplanes), distance, isolate
- JH-1 takes longer exposure, longer time to test positivity, and longer viral shedding
- While disease milder, number of symptoms acutely correlates with risk, re severity of disease acutely predicts probability of Long Covid
- Vaccination has decreased hospitalization by 85% and if disease severity correlates with Long Covid probability (>5 symptoms) then vaccination by decreased acute disease severity should decrease Long-Covid incidence
- Vaccination decreases severity of re-infection, thus lowering the risk of Long Covid

Does Vaccination Lower Risk of Long Covid

- Among health care workers, prevalence of Long Covid decreasing
 - Wave 1 42%
 - Wave 2 36%
 - Wave 3 16.5%
- And prevalence Long Covid decreased by number of vaccines
 - 42% unvaccinated
 - 30% 1 dose
 - 17.4% 2 doses
 - 16% 3 doses

Azzolini E 2022

Why?

- The data is overwhelming: Vaccination significantly decreases Long Covid Risk: even if break through infection by about 70%
- Yet in Idaho only 55% fully vaccinated
- And only 35% of US population age > 65 years

Taquet M 2022, Autonellim 2023, Lundberg-Morris L 2023, Kuodi P 2021

US coronavirus vaccine tracker

Marks P 2024

Other Preventive Measures not as Effective

- Vaccination in presence of Long Covid
 - 54% no change in symptoms
 - 20% improved
 - 20.5% worse
- 82% of patients report continued symptoms

Watauabe A 2023

Hamilton FW 2022

Data on acute treatment of Covid with Paxlovid doesn't suggest benefit in “standard Risk” patients in severity of acute disease or Long Covid Prevention

- EPIC-SR – Pfizer
 - Enrollment ceased due to very low rate of deterioration in standard risk population
 - Outpatients (all comers) with Omicron reduced mortality and hospital admission
 - Decreased 50-85%
 - Metanalysis decrease Omicron outpatient
 - Hospitalization 0.7% vs 1.2%
 - Mortality 0.1% vs 0.2%
- So effect of Paxlovid on outpatients without end – organ disease, comorbidities, immunosuppression minimal
 - Maybe risk of rebound takes precedence (up to 1 in 5 treatment) through also occurs without Paxlovid Rx)

ClinicalTrials.gov 2023

Ledinger SI 2023

Sommer I 2023

Treatment of Long Covid

- Number of Long-Covid Studies
 - Ongoing= 481 studies ClinicalTrials.gov
- Number of FDA approved drugs for Long Covid = 0

Treatment

- Antiviral
 - Paxlovid (Nirmatrelvir/Ritonavir)
 - No benefit for 15 days, ongoing 25 day trial
- Antihistamines
 - Famotidine
- Low dose Naltrexone
 - Blunts immune response
- Anticoagulation
 - No help after hospitalization
- Topical steroids (nasal) & sensitization
 - For decreased taste/smell
- Respiratory symptoms
 - Steroids, bronchodilators
 - Antifibrotic agents for interstitial disease
- Autonomic dysfunction (Increased heart rate, low blood pressure)
 - Cardiac drugs
- Metformin
 - Diabetic drug, affects immune system

Others not likely effective

- Hyperbaric Oxygen
- Supplements, vitamins, probiotics, antioxidants
- Delayed vaccination (in presence of Long-Covid)
 - Some patients improve, some see worse symptoms

What can we do while awaiting more definitive treatment?

- Physical Therapy

- The importance of preventing post-exertional malaise – pacing

- Due to decreased muscle mitochondrial activity
- Deposition of Amyloid

- Pulmonary Rehab

- Patients with abnormal CT, PFT's, hypoxia or dyspnea
- 6 MWT improved by mean 84 meters
- Improved aerobic capacity by cycling or walking
- Improved T-cell function

Aljazeera J 2023

- Vent dependent patients improved dyspnea with exercise training rehabilitation by 42% (cycling, strength training)

- 60-70% Peak Power, gradual increase to 45-60%

Romanet C 2023

Serotonin reuptake inhibitors (SSRI)

- Fluvoxamine may reduce risk for hospitalization in acute Covid – but evidence contradictory
- Sertaline inhibits spike mediated cell-cell fusion
- Fluoxetine inhibits Covid viral replication

Deng J 2023

Chen Y 2021

Dechanmes A 2021

Paucity of data for other drugs for cognitive symptoms, fatigue, PEM, Myalgias

- Possibilities: treat as hypersomnolence in obstructive sleep apnea
 - Modafinil (Provigil) increases dopamine
 - Solriamfetol (Sunosi)- Dopamine/Norepi reuptake inhibitor
 - Lisdexamfetamine (Vyvanase) – amphetamine
 - Methylphenidate (Ritalin) Dopamine/norepi reuptake blocker
 - Dextroamphetamine (Adderall)
- Solriamfetol (Sunosi) Norepi/dopamine reuptake inhibitor more effective in wake-fulness promotion in obstructive sleep apnea patients with residual hyper-somnolence
 - But at > \$700/month insurance never pays in Post-Covid unless also OSA

Other drugs

- Aripiprazole (Abilify)
 - May modulate Post-Covid gene expression Crespo-facorro 2021
 - Nicotine may alter intracellular trafficking Goldense 2021
 - Other second generation antipsychotics decrease IL-1B, IL-6, TNf α , reduce astrocyte and microglia activation Villoutrexa BO 2020
 - Cortisol

The Future

- We are getting Better

Better understanding of Pathogenesis

- Role of Interaction between gut & brain

- chronic cerebral blood vessel damage (amyloid deposition brain)
- Mitochondrial dysfunction in muscle with decreased O_2 uptake (amyloid deposition muscle)
- Importance of gut microbiome alteration with resulting degradation of intestinal barrier & enhanced neurotoxic and neuroinflammatory absorption
- Improved biomarker identification predictive of Long Covid

Masuoka H 2023

Baille K 2023

Better understanding of vaccine effectiveness in prevention of Long Covid

- 590,000 Swedish residents – vaccine before infection

Vaccines	Effectiveness	Incidence
0		
1	21%	
2	59%	
3	73%	1.4%

Register based clinical diagnosis, not just self reported

Lundberg- Morris L 2023

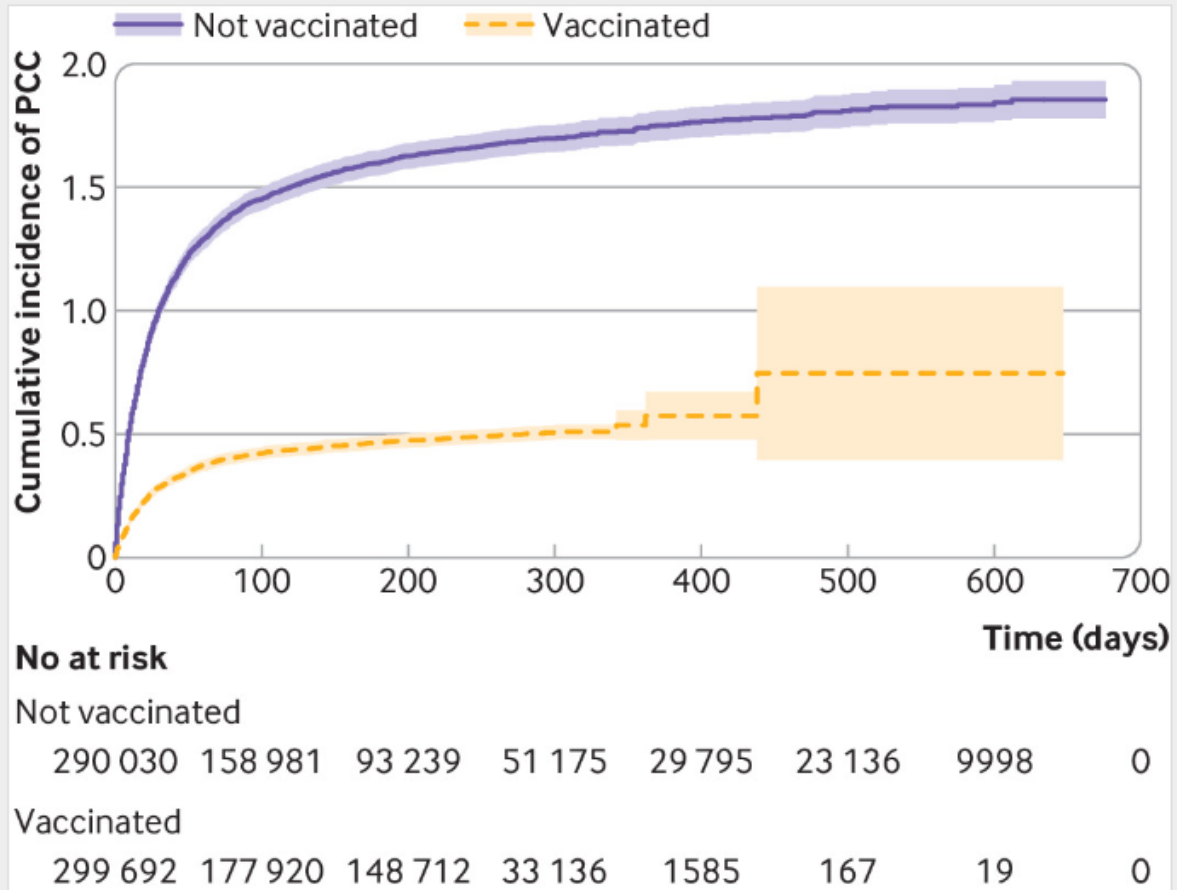


Fig 2
 Cumulative incidence of PCC, using Kaplan-Meier failure function, for individuals vaccinated or not vaccinated against covid-19. Study population included all adult (≥ 18 years) residents in the two largest regions of Sweden with covid-19 first registered during the study inclusion period, 27 December 2020 to 9 February 2022. PCC=post-covid-19 condition

Fig 2 Lundberg Morris L 2023

Better-though still inadequate therapeutic trials

Rehabilitation (168)

- Exercise (51)
- General rehabilitation including telerehabilitation (46)
- Respiratory muscle training (17)
- Cognitive rehabilitation (7)
- Virtual reality rehabilitation (7)
- Breathing and chest mobilization exercises (6)
- Olfactory training (6)
- Yoga rehabilitation (6)
- Heart rate variability biofeedback (2)
- Vocal-based respiratory training (2)
- Activity tracker and a bespoke mobile phone application
- Akili Interactive digital treatment 'AKL-T01'
- Benson's relaxation technique
- BREATHE program for long COVID
- Counterweight-Plus/DIRECT diet weight management program
- Long COVID optimal health program
- Lymphatic drainage massage
- Manual therapy (hand operated technique and breathing exercises)
- Neurofeedback therapy
- NexJ Connected Wellness
- Online singing, breathing and wellbeing program (ENO Breathe)
- PowerBreathe® and Therosold PEP® tools
- Proprioceptive training
- Rehabilitation robot (Luna by EGZOTech ©)
- REMM-HIIT
- Slow-paced breathing
- Sniffin' sticks Duftquartett
- Whole body vibration training

Psychotherapy (12)

- Cognitive behavioral therapy (3)
- Adhera® Digital Health Intervention
- Amygdala and insula retraining program
- HUS internet therapy for bodily stress syndromes
- LISTEN intervention
- Mind body syndrome therapy
- Mindful self-compassion training
- PACS coping and recovery intervention
- Telemedicine mindfulness-based protocol
- Wearable brain sensing wellness device (Muse™-S)

Education (4)

- Cognitive psychoeducation
- Education and strategies intervention
- Medical psychoeducational talks
- Pain and self-management education

Pharmacotherapy (77)

- Clochicine (5)
- Nintedanib (4)
- Pirfenidone (4)
- Ivermectin (2)
- Methylprednisolone (2)
- Mometasone (2)
- Montelukast (2)
- Prednisolone (2)
- Treamid (bisamide derivative of dicarboxylic acid) (2)
- Anhydrous enol-oxaloacetate
- Apixaban
- Atorvastatin
- AXA1125
- Bioarginina C
- Budesonide
- Caffeine
- Cerebrolysin
- Famotidine
- Echinochrome A
- Erythropoietin
- Famotidine
- Fampridine (sustained release)
- Fibrotac
- Gabapentin
- Immulina™ (spirulina)
- ImmunoSEB + ProbioSEB CSC3 (probiotic complex)
- Intranasal Insulin
- Ibudilast
- Ivabradine
- Lactoferrin
- Leronlimab

Pharmacotherapy Cont.

- Loratadine
- LYT-100 (deupirfenidone)
- Metoprolol succinate
- Mycophenolate mofetil
- MYMD1® (Isomyosmine)
- Naltrexone
- Niagen (vitamin B3)
- Omni-Biotic® Pro-Vi 5
- Pentoxifylline
- Pimozide
- Prednisone
- Prospekta
- Remdesivir
- Rivaroxaban
- Rosuvastatin
- RSLV-132
- Ruconest
- S-1226 (8%)
- Sacubitril / Valsartan
- Sodium pyruvate nasal spray
- Somatropin
- Sulodexide
- Taxifolin Aqua
- Temelimumab (formerly GNBAC1)
- Theophylline
- TNX-102
- Vitamin D3
- Vortioxetine
- Xltran Plus™ or Xltran™
- Zofin™ (formerly Organiceal Flow)

Complementary and Alternative Medicine (64)

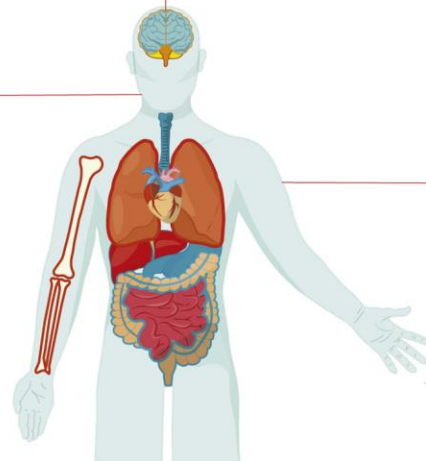
- TCM (25)
- Ayurveda (24)
- Homeopathic medications (4)
- ADAPT-232 (Chisan®)
- Coenzyme Q10
- Cracie bojungikgi-tang extract
- Curcumin/boswellia serrata/ascorbic acid mixture
- Gyeongbang gyeongok-go
- Hanpoong Soonsimhwan
- IMMUNODAA™ botanical ingredient
- Nutraceuticals
- Omega-3 (Eicosapentaenoic acid + docosahexaenoic acid)
- Targeted wellness formula C™
- 5-aminolevulinic acid phosphate

Others (43)

- Transcranial current direct stimulation (9)
- Photobiomodulation (4)
- Transcutaneous auricular vagus nerve stimulation (4)
- Electrical stimulation (2)
- Hyperbaric oxygen (2)
- Allogeneic culture-expanded adipose-derived mesenchymal stem cells
- Allogenic marrow stromal cells
- Bone marrow mesenchymal stem cell derived extracellular vesicles
- CIMAvax-EGF®
- Cold knee casts
- Cranial electrotherapy stimulation
- High tone power therapy
- Hope Biosciences adipose-derived mesenchymal stem cells – allogenic (HB-adMSCs)
- Human immunoglobulin G
- Hydrogen-oxygen generator with nebulizer
- Inogen One® G4 (portable oxygen concentrator)
- Intraoperative use of PEEP - Fixed and individualized
- Lactobacillus plantarum 299v in fermented oat drink
- Microcannula harvest adipose derived tissue stromal vascular fraction (tSVF)
- MON002 (autologous monocytes)
- Personalized multidisciplinary day-hospital intervention
- Plasma exchange
- Platelet rich plasma
- Pulsed ultrasound
- Resistive capacitive monopolar radio frequency at 448 kHz (INDIBA®)
- Stellate ganglion block
- Whole-body cryotherapy

Symbols next to each intervention represent the targeted system:

- Pulmonary system: 🫁
- Cardiovascular system: ❤️
- Non-system specific: 🧑
- Mental health: 🧠
- Musculoskeletal system: 🦴
- Nervous system: 🧠
- Gastrointestinal system: 🍌

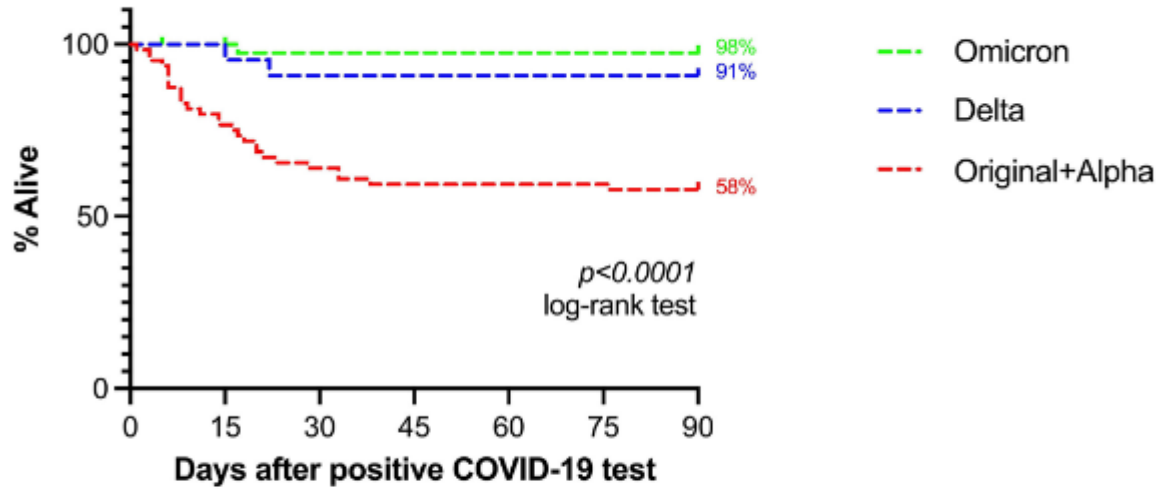


NIH RECOVER Initiative Phase 2 trials

- RECOVER VITAL
 - Longer dose regimen of Paxlovid (nirmatrelvir/ritonavir) – 25 days
- Recover - Neuro
 - Cognitive dysfunction
 - Brain HQ (brain training program)
 - PASC-cognitive recovery (web based)
 - Home based transcranial direct current stimulation
- RECOVER - SLEEP
 - Hypersomnia
 - Test 2 wakefulness-promoting drugs not yet identified
- RECOVER – AUTONOMIC
 - IVIG
 - Ivabradine

With decreased severity decreasing Post Covid Cases

(A) 90-Day Mortality (COVID-19-Related)

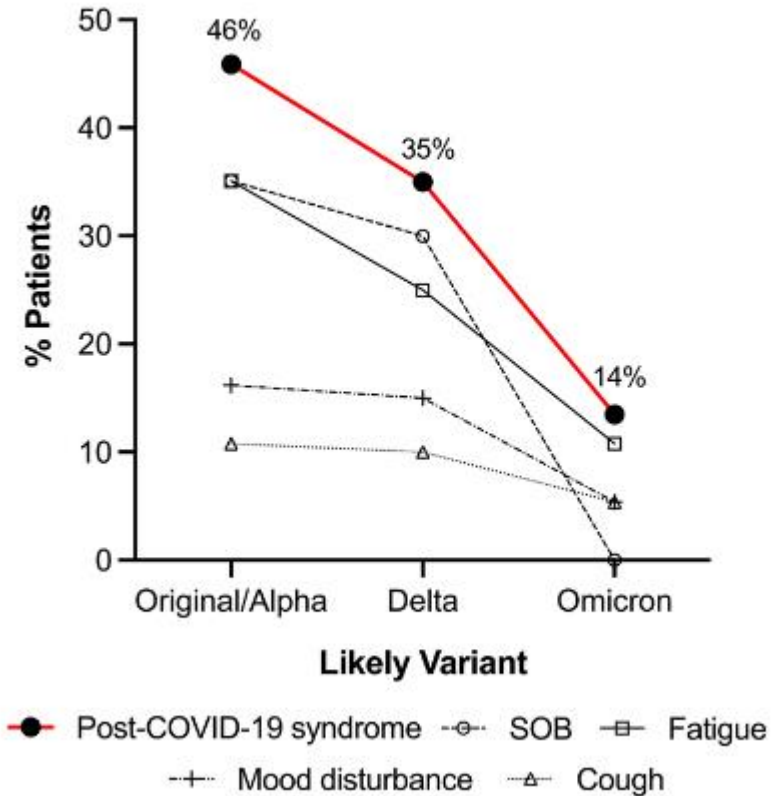


Number of patients at risk

—	42	42	41	41	41	41	41
—	22	21	20	20	20	20	20
—	64	51	42	39	39	39	37

(B)

Post-COVID-19 symptoms



In the end what sustains us,
and what we will remember about
having survived this madness, are the
remarkable people who endured this with
us, the best of humanity - all of us - who
demonstrated the best of our calling. We
endured this together, and supported each other.
We saved lives and lost lives, and we did both with
compassion and competence. We will not forget this.

Krell