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

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EIRMC

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)

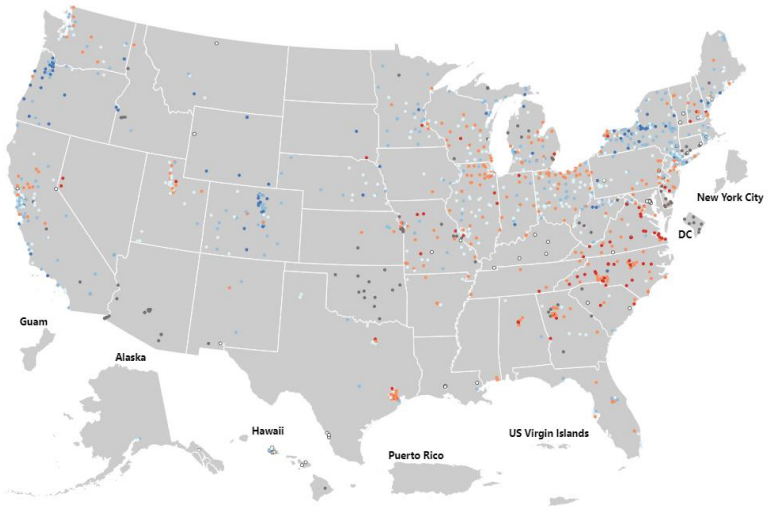
Trend in % COVID-19 Deaths

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

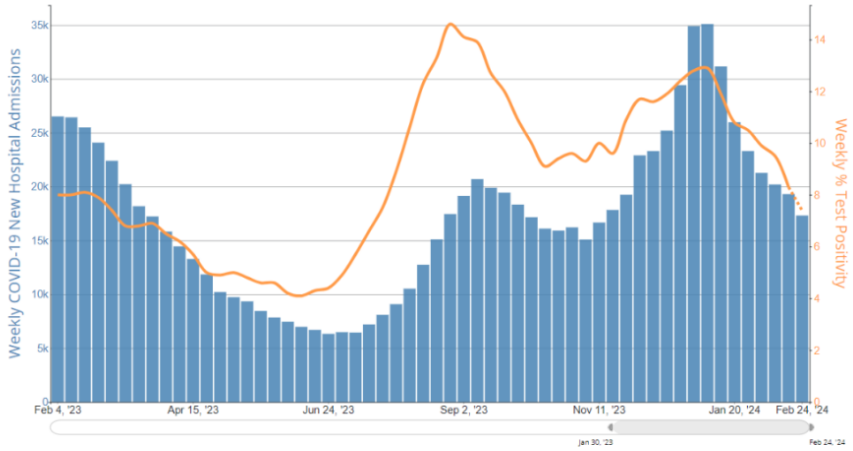
Total number of wastewater sampling sites: 1406

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.

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The Sick Times
IRMC

- 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

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JN.1 Variant

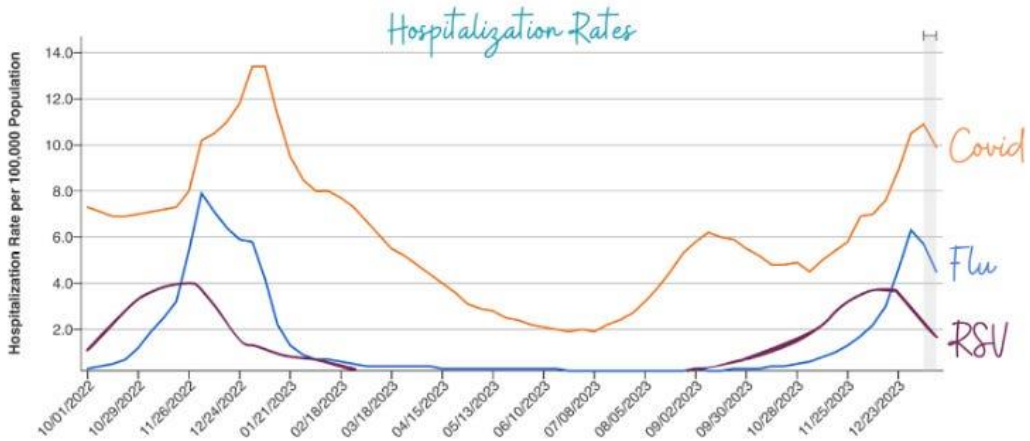
- Evolved from BA.2.86
- Omicron descendent
- Good fit for current vaccine (boosts virus neutralizing antibodies against JN.1 though not specifically targeted)
- Highly contagious, more than other Omicron variants

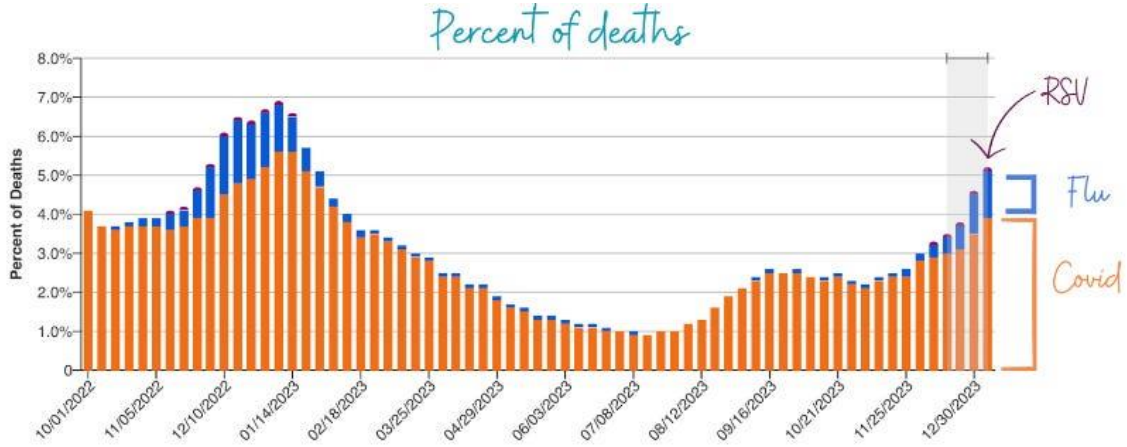
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Good and Bad News

- 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

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Jetelina, K 2023

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Still Abysmal Vaccine rates US

- 41% over age 65 vs 75% flu vaccine

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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

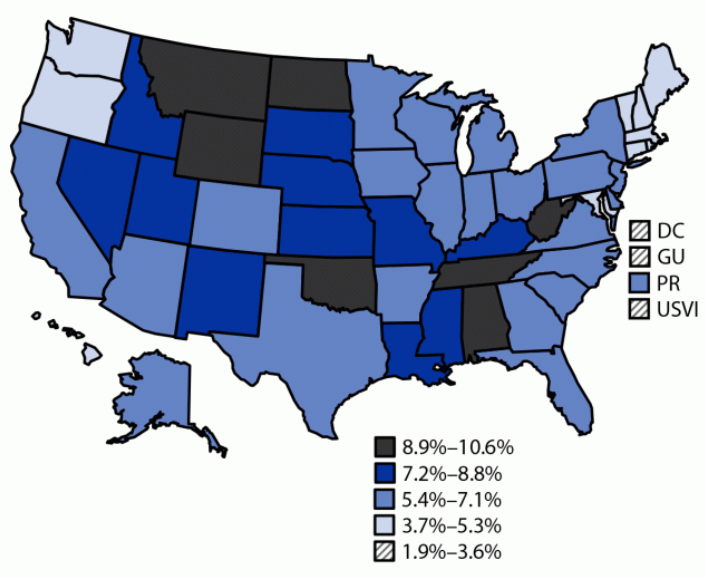
Linchflower DG 2023

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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.

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Prevalence

- Idaho 8.3%

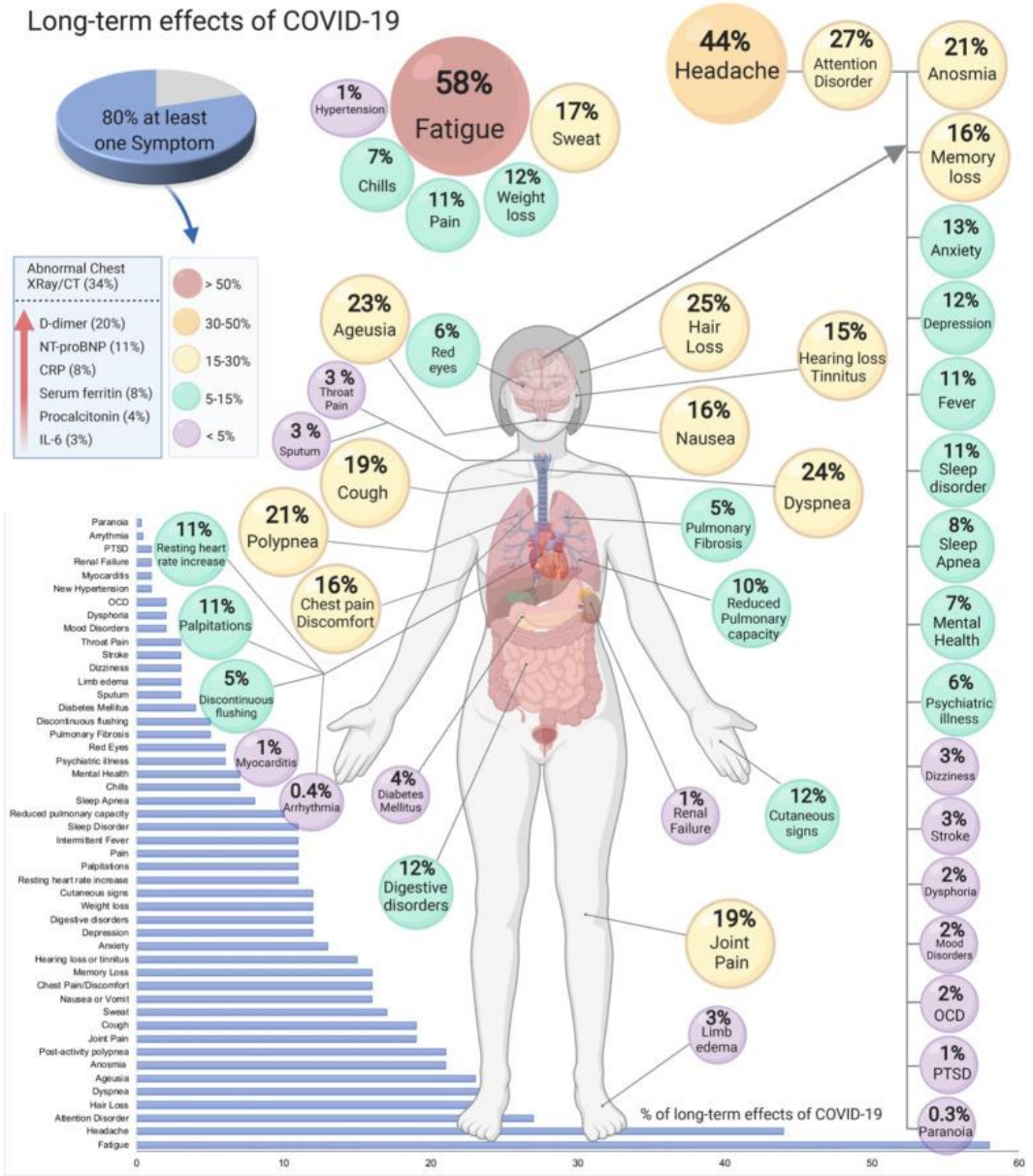
US News & World Report

Smith-Schoeuwalder Feb 15 2024

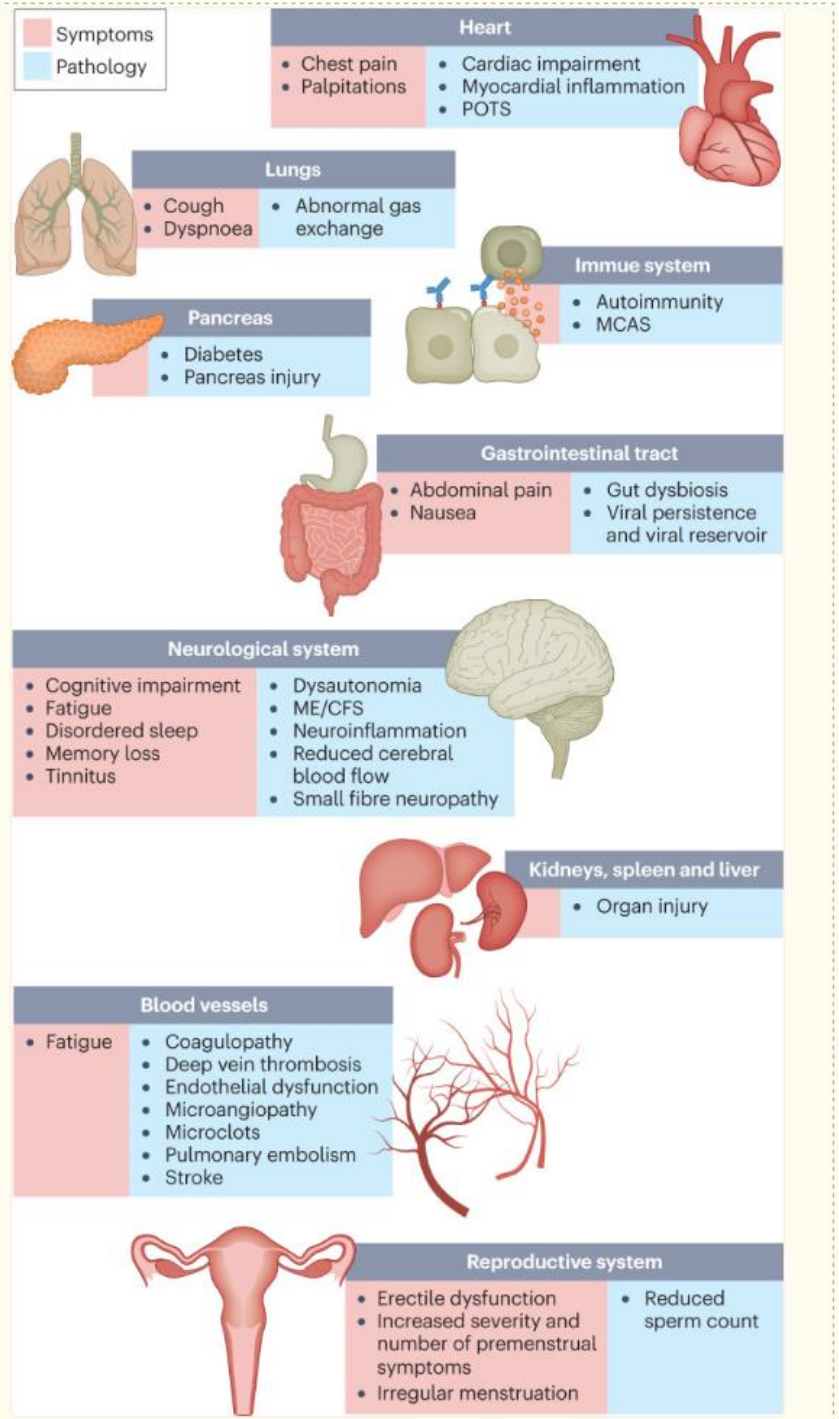
- With Population 1.9M then 157,700 Idahoans with Long Covid
- Twice as many cases of Long-Covid in the US vs Coronary artery disease

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What is Long Covid?



Lopez-Leon S, 2021 Figure 2

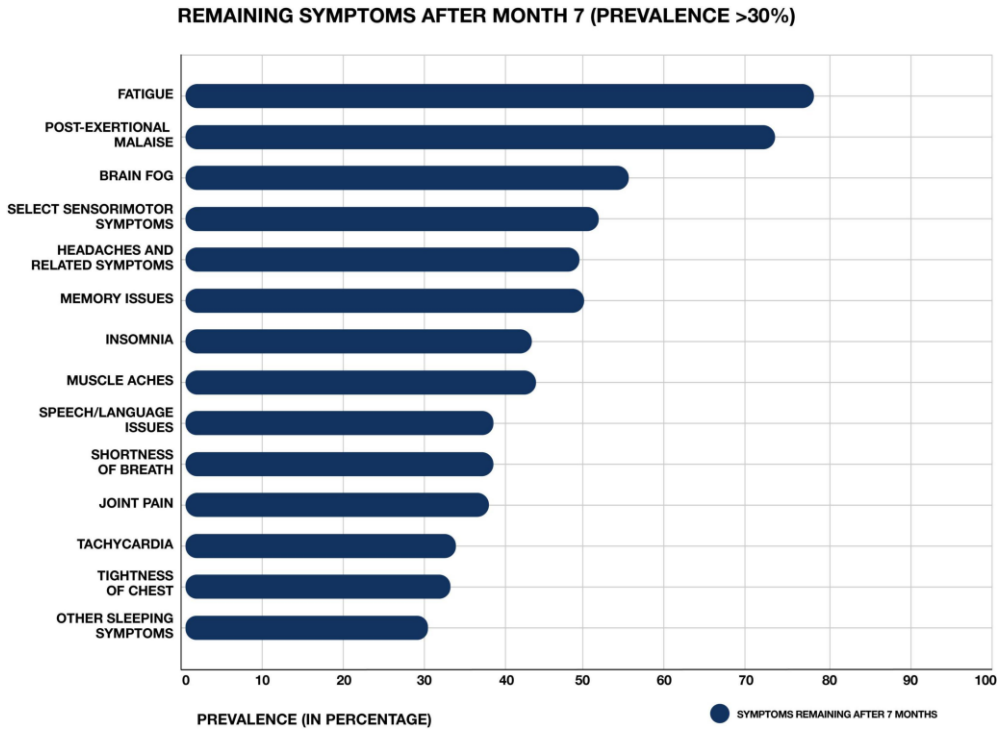


Davis, H.E. 2023 Figure 1

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Does Long Covid Get Better?

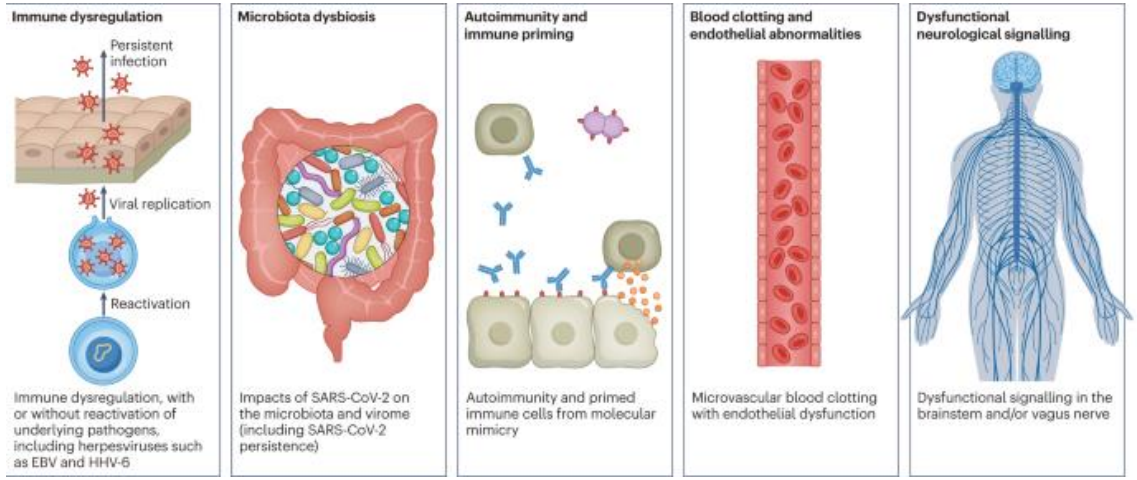
- Long Covid will likely be a long term disorder for over 1/3 of affected patients
- Long term symptoms persist more for CNS/cognitive symptoms and fatigue (muscle involvement) than respiratory symptoms



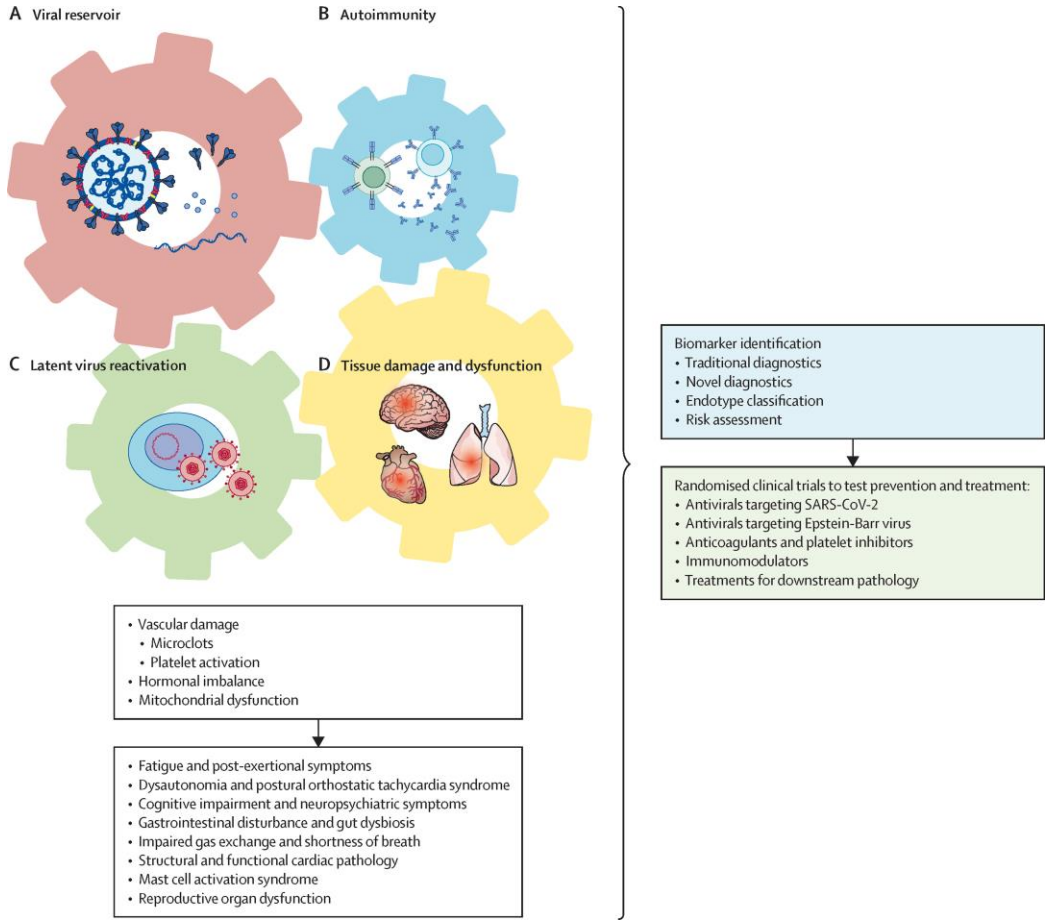
Swank, Zoe

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What Causes Long Covid - What are the Mechanisms



Davis, H.E. 2021 figure 3



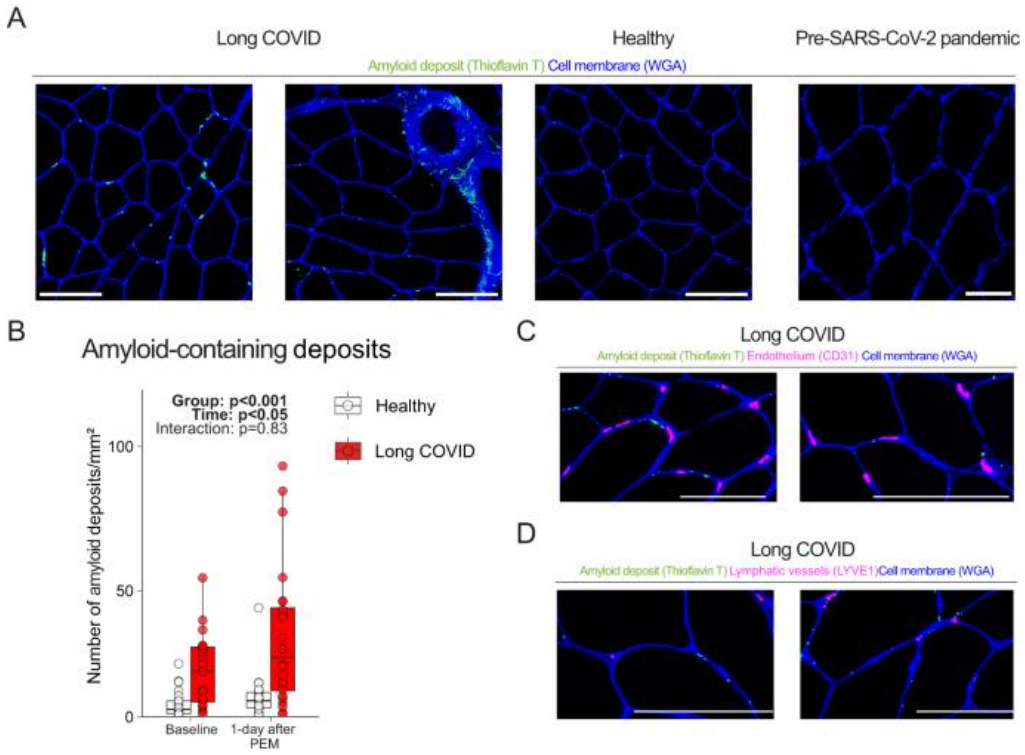
Iwasaki, A 2023 figure

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Who is Most at Risk?

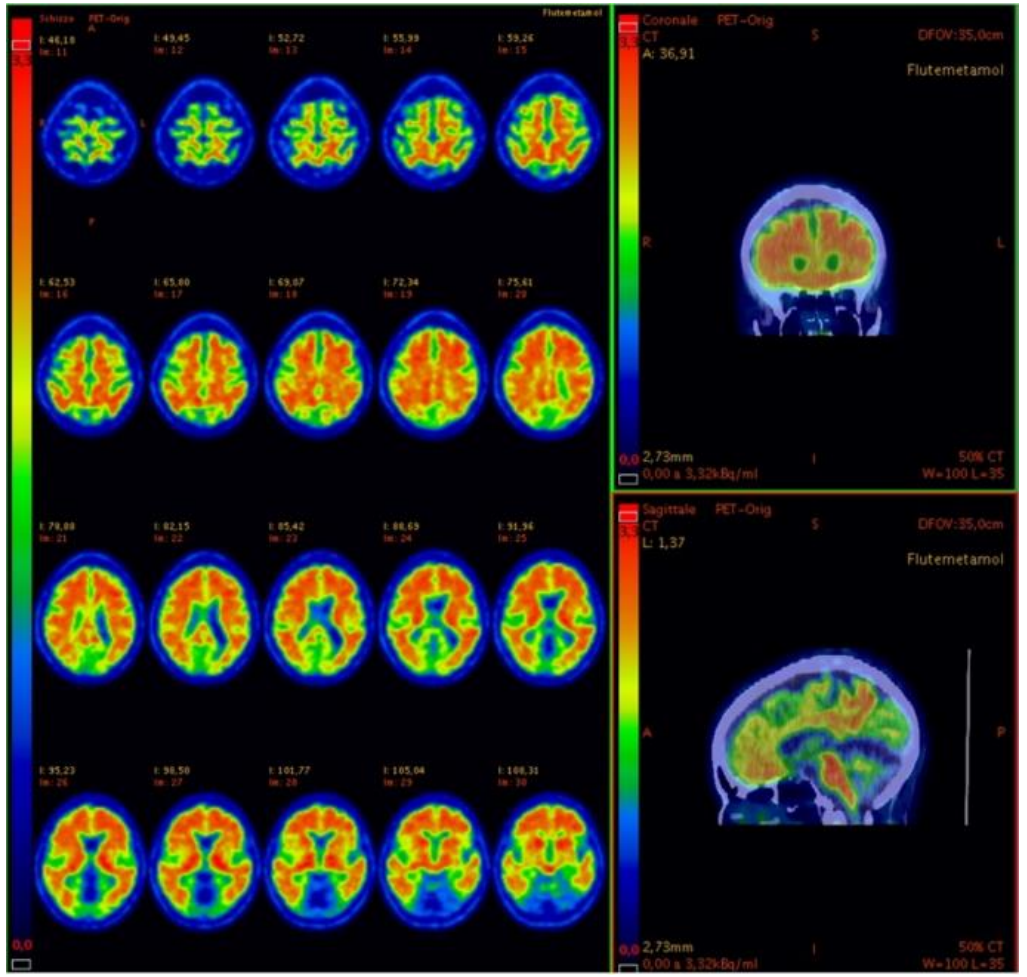
- Hospitalized > non-hospitalized
- ICU > non-ICU
- > if loss of taste/smell
- > 5 symptoms during first week of illness Sudre CH 2021
- Age
- Female
- Low socioeconomic status
- Respiratory disease
- Depression
- Comorbidities (Diabetes, cancer, kidney disease, hypertension, neurological disease, obesity CAD Hastic CE 2023
- Probably some association with asymptomatic acute disease but much less
- Immunologic patterns Su, Y 2022

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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

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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

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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

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Why?

- The data is overwhelming: Vaccination significantly decreases Long Covid Risk: even if break through infection by about 70%

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

- Yet in Idaho only 55% fully vaccinated

US coronavirus vaccine tracker

- And only 35% of US population age > 65 years

Marks P 2024

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Other Preventive Measures not as Effective

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

Watauabe A 2023

- 82% of patients report continued symptoms

Hamilton FW 2022

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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

    ClinicalTrails.gov 2023
  - Outpatients (all comers) with Omicron reduced mortality and hospital admission
    - Decreased 50-85%

      Ledinger SI 2023
  - Metanalysis decrease Omicron outpatient
    - Hospitalization 0.7% vs 1.2%
    - Mortality 0.1% vs 0.2%

      Sommer I 2023
- So effect of Paxlovid on outpatients without end – organ disease, comorbidities, immunosurpression minimal
  - Maybe risk of rebound takes precedence (up to 1 in 5 treatment) through also occurs without Paxlovid Rx)

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Treatment of Long Covid

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

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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

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Others not likely effective

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

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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 Aljazeeri J 2023
    - Improved aerobic capacity by cycling or walking
    - Improved T-cell function
    - 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

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Serotonin reuptake inhibitors (SSRI)

- Fluvoxamine may reduce risk for hospitalization in acute Covid – but evidence contradictory Deng J 2023
- Sertaline inhibits spike mediated cell-cell fusion Chen Y 2021
- Fluoxetine inhibits Covid viral replication Dechanmes A 2021

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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

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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, TNfα, reduce astrocyte and microglia activation — Villoutrexia BO 2020
  - Cortisol

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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 Masuoka H 2023
    - Improved biomarker identification predictive of Long Covid Baille K 2023

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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

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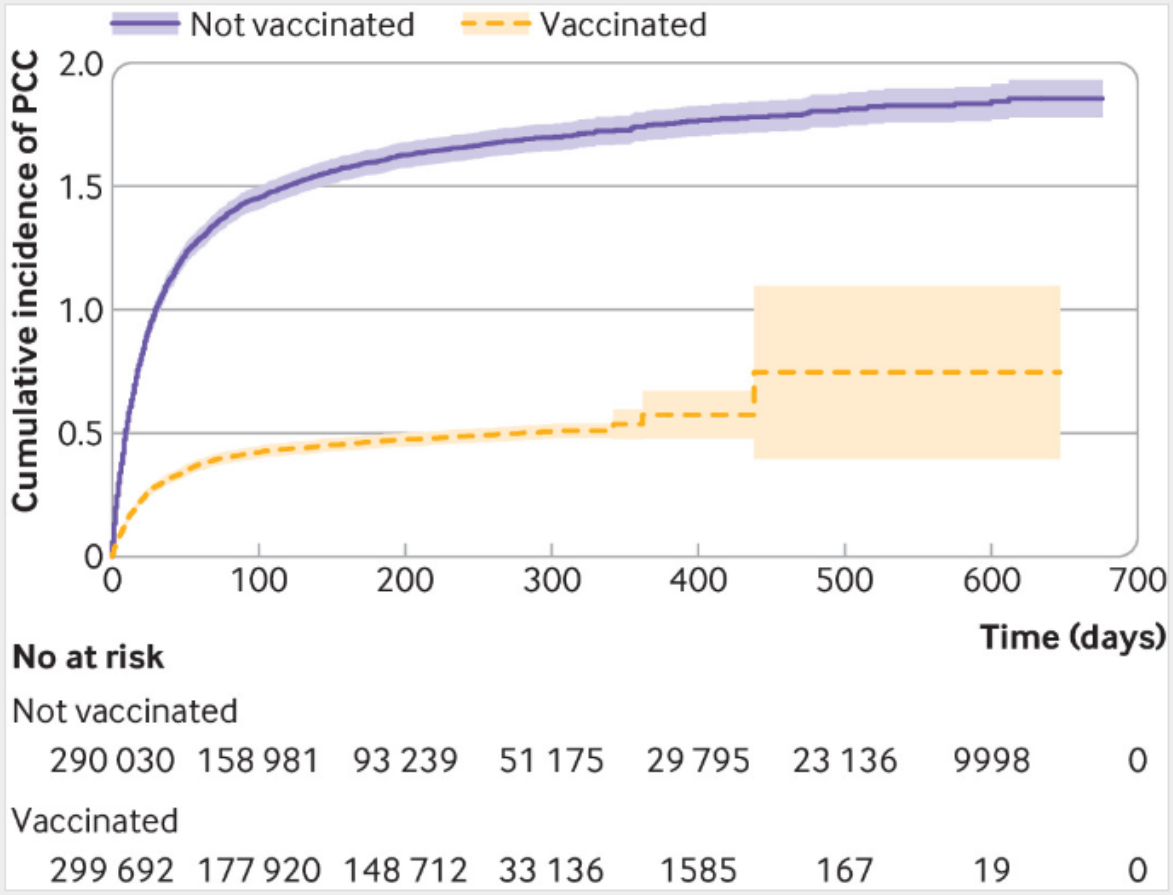


Fig 2

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

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Better-though still inadequate therapeutic trials

Rehabilitation (168)
- Exercise (51)
- General rehabilitation including telerehabilation (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

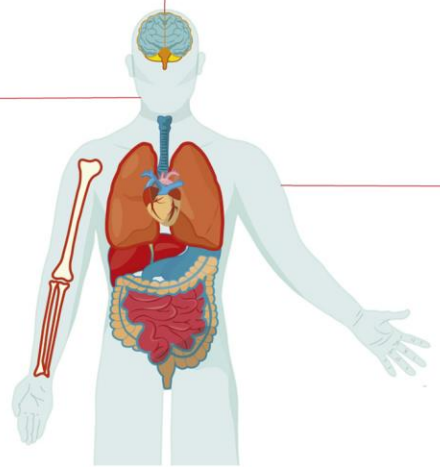
Pharmacotherapy (77)
- Clochicine (5)
- Nintedanib (4)
- Pirfenidone (4)
- Ivermectin (2)
- Methylprednisolone (2)
- Mometasone (2)
- Montelukast (2)
- Prednisolone (2)
- Treamid (bisamide derivative of dicarboxylic acid) (2)
- Anhydrous enol-oxaloacetate
- Apixaban
- Atorvastatin
- AXA1125
- Bioarginina C
- Budesonide
- Caffeine
- Cerebrolysin
- Donepezil
- 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
- Pentoxifyinlline
- Pimozide
- Prednisone
- Prospekta
- Remdesivir
- Rivaroxaban
- Rosuvastatin
- RSLV-132
- Ruconest
- S-1226 (8%)
- Sacubitril / Valsarta
- Sodium pyruvate nasal spray
- Somatropin
- Sulodexide
- Taxifolin Aqua
- Temelimab (formerly GNbAC1)
- Theophylline
- TNX-102
- Vitamin D3
- Vortioxetine
- Xltran Plus™ or Xltran™
- Zofin™ (formerly Organicell Flow)

Complementary and Alternative Medcine (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
- IMMUNODAAT™ botanical ingredient
- Nutraceuticals
- Omega-3 (Eicosapentaenoic acid + docosahexaenoic acid)
- Targeted wellness formula C™
- 5-aminolevulinic acid phosphate

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



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 – allogeneic (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:

Fawzy, Nader A 2023 figure 2

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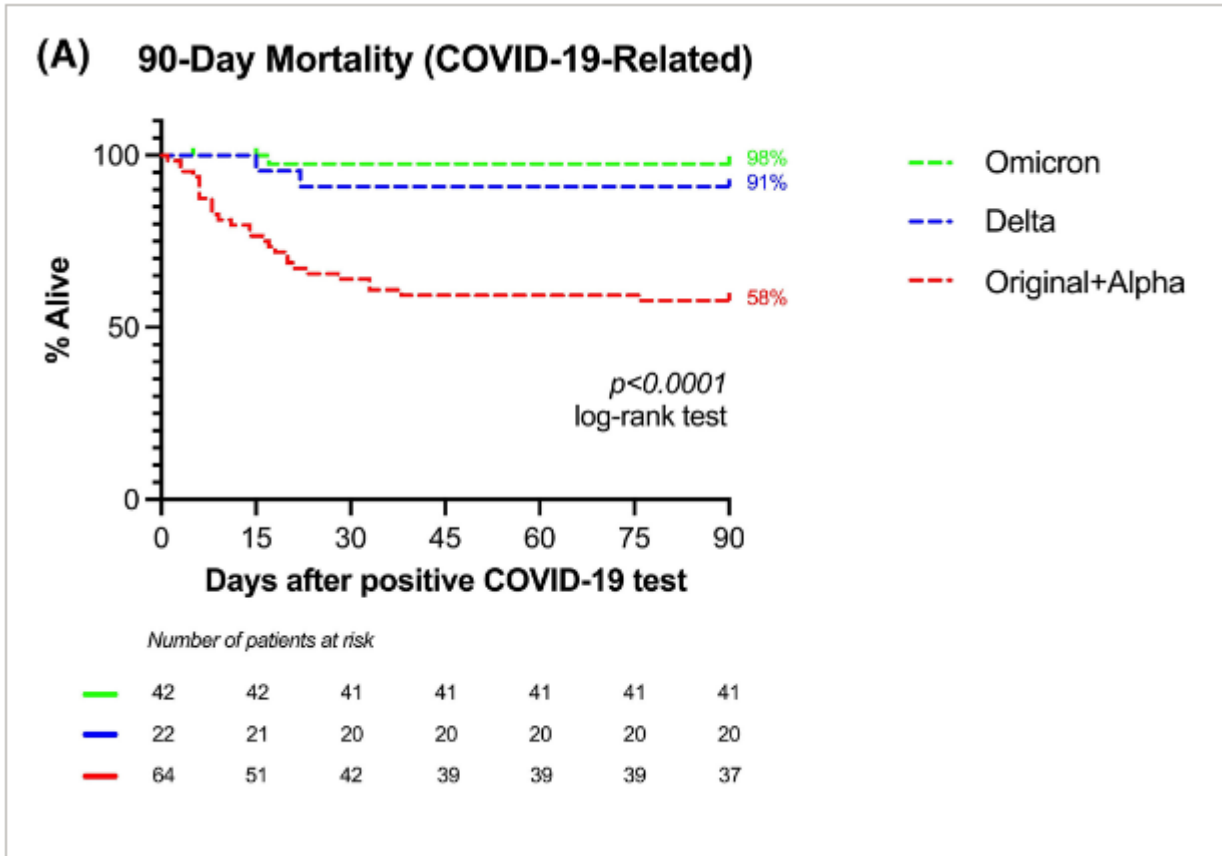
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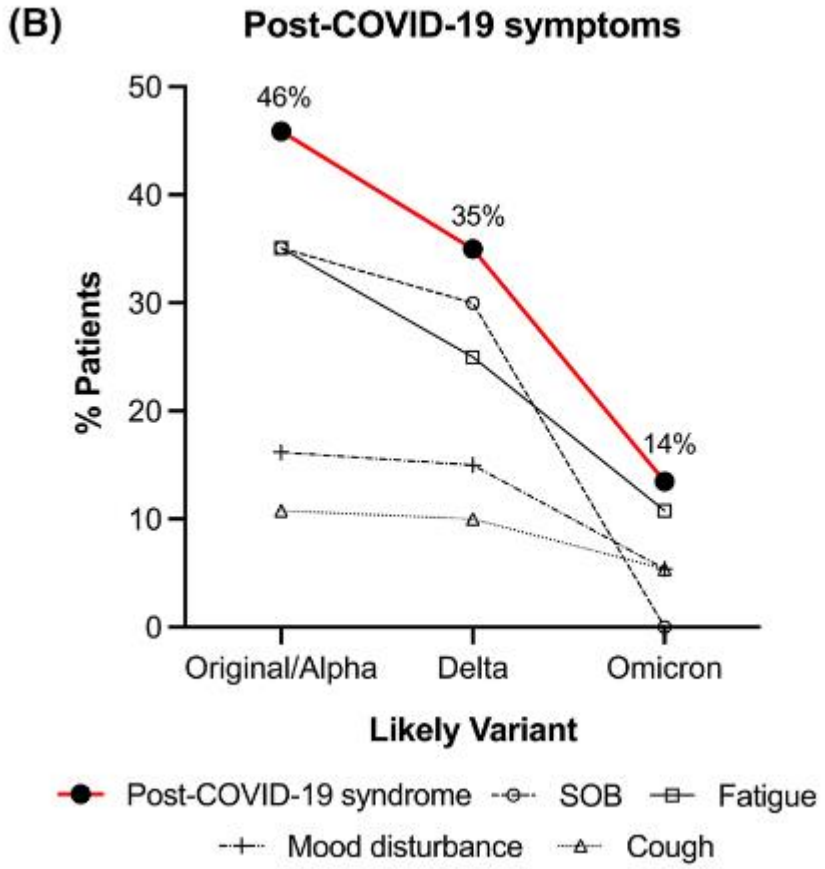
NIH RECOVER Initiative Phase 2 trials

- 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

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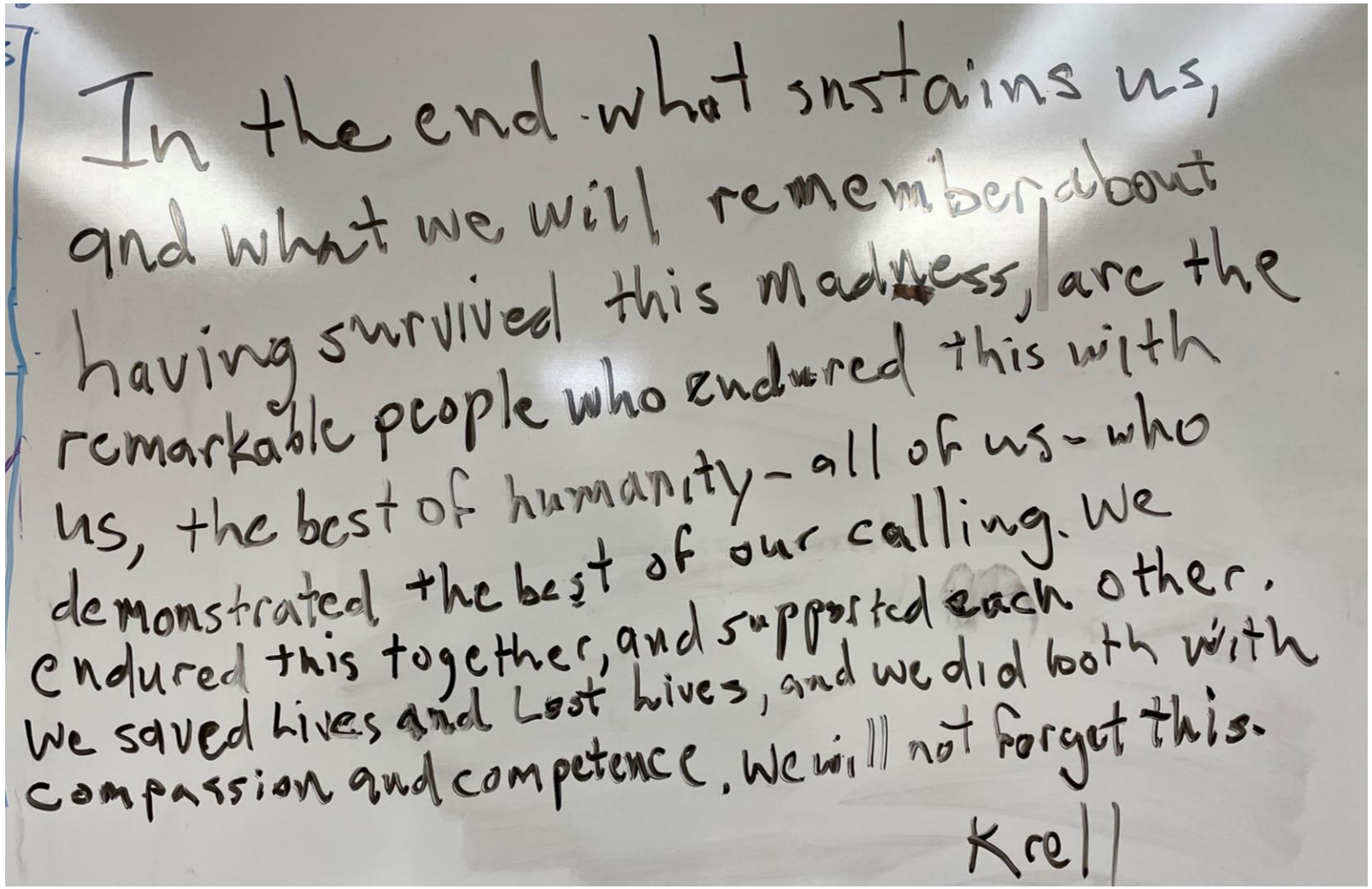
With decreased severity decreasing Post Covid Cases





Willan J 2023

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