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”

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March 28th, 2024
Current State of Covid

COVID-19 Update for the United States

**Early Indicators**
- **Test Positivity**
  - % Test Positivity: 6.5%
  - Trend in % Test Positivity: -19% in most recent week
- **Emergency Department Visits**
  - % Diagnosed as COVID-19: 1.2%
  - Trend in % Emergency Department Visits: -21.2% in most recent week

**Severity Indicators**
- **Hospitalizations**
  - 15,141
  - Trend in Hospital Admissions: -13.6% in most recent week
- **Deaths**
  - % of All Deaths in U.S. Due to COVID-19: 2.2%
  - Trend in COVID-19 Deaths: No change in most recent week

The Sick Times
• 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

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

CDC
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
  o Wastewater levels 27% higher & Positive COVID test 17% higher than 1 year ago
  o But ER visits down 21%
  o Deaths decreased from 5.2% all US deaths to 3.67% for week 12/30/23
    ▪ 839 vs 3658 deaths
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
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
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
What is Long Covid?

Long-term effects of COVID-19

- Fatigue (58%)
- Headache (44%)
- Memory loss (27%)
- Anosmia (21%)
- Sweating (17%)
- Chills (16%)
- Sweats (12%)

Common symptoms:
- Cough (25%)
- Haemoptysis (23%)
- Diaphoresis (21%)
- Fever (19%)
- Nausea (16%)
- Dysphagia (15%)

Less common symptoms:
- Loss of smell (13%)
- Anxiety (12%)
- Depression (8%)

Symptoms by organ:
- Heart:
  - Chest pain
  - Palpitations
  - Cardiac impairment
  - Myocardial inflammation
  - POTS
- Lungs:
  - Cough
  - Dyspnoea
  - Abnormal gas exchange
- Immune system:
  - Autoimmunity
  - MCAS
- Gastrointestinal tract:
  - Abdominal pain
  - Nausea
  - Gut dysbiosis
  - Viral persistence and viral reservoir
- Neurological system:
  - Cognitive impairment
  - Fatigue
  - Disordered sleep
  - Memory loss
  - Tinnitus
  - Dysesthesia
  - ME/CFS
  - Neuroinflammation
  - Reduced cerebral blood flow
  - Small fibre neuropathy
- Kidneys, spleen and liver:
  - Organ injury
- Blood vessels:
  - Fatigue
  - Coagulopathy
  - Deep vein thrombosis
  - Endothelial dysfunction
  - Microangiopathy
  - Microclots
  - Pulmonary embolism
  - Stroke
- Reproductive system:
  - Erectile dysfunction
  - Increased severity and number of premenstrual symptoms
  - Irregular menstruation
  - Reduced sperm count

Lopez-Leon S, 2021 Figure 2

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
What Causes Long Covid - What are the Mechanisms

- Immune dysregulation, with or without reactivation of underlying pathogens, including happenings such as EBV and HHV-6
- Microbiota dysbiosis
- Autoimmunity and immune priming
- Blood clotting and endothelial abnormalities
- Dysfunctional neuroendocrine signaling

Impacts of SARS-CoV-2 on the microbiota and virome (excluding SARS-CoV-2 persistence)
Autoimmunity and primed immune cells from molecular memory
Microvascular blood clotting with endothelial dysfunction
Dysfunctional signaling in the brainstem and/or vagus nerve

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
Amyloid deposition worsen in muscle after post-exertional malaise

Appelman B 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

Ferrucci R 2023
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%

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

• Yet in Idaho only 55% fully vaccinated

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

  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

Watuabe 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% (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)
Treatment of Long Covid

• Number of Long-Covid Studies
  - Ongoing = 481 studies

• 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
  o The importance of preventing post-exertional malaise – pacing
    ▪ Due to decreased muscle mitochondrial activity
    ▪ Deposition of Amyloid
  o 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
    ▪ Vent dependent patients improved dyspnea with exercise training rehabilitation by 42% (cycling, strength training)
      – 60-70% Peak Power, gradual increase to 45-60%
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
- Fluroxetine inhibits Covid viral replication  
  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

• Ariprazole (Abilify)
  o May modulate Post-Covid gene expression
  o Nicotine may alter intracellular trafficking  
  o Other second generation antipsychotics decrease IL-1β, IL-6, TNFα, reduce astrocyte and microglia activation
  o Cortisol

Crespo-facorro 2021
Goldense 2021
Villoutrexia BO 2020
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
Better understanding of vaccine effectiveness in prevention of Long Covid

- 590,000 Swedish residents – vaccine before infection

<table>
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<tr>
<th>Vaccines</th>
<th>Effectiveness</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td>73%</td>
<td>1.4%</td>
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Register based clinical diagnosis, not just self reported

Lundberg- Morris L 2023
Fig 2 Lundberg Morris L 2023

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.
Better-though still inadequate therapeutic trials

Pharmacotherapy (77)
- Clofibrate (11)
- Nateglinide (11)
- Perindopril (11)
- Insulin (11)
- Hydroxyethylcellulose (11)
- Montecane (11)
- Montefeltro (11)
- Penicillin (11)
- Tranil (206) derivative of dicarboxylic acid (11)
- Arginine-endo-vasculone (11)
- Aminophylline (11)
- Nortox + (11)
- AV211 (11)
- Butenafine (11)
- Caffeine (11)
- Clofibrate (11)
- Cetirizine (11)
- Desoprop (11)
- Echinacea (11)
- Enteric (11)
- Fenofibrate (11)
- Fumarudine (11)
- Meprobamate (11)
- Gentamicin (11)
- Intestinal (11) (opiod)
- Immunodef (11) (probiotic complex) (11)
- Intramuscular (11)
- Ivermectin (11)
- Lactoferrin (11)
- Levamisole (11)

Pharmacotherapy Cont.
- Lutostane (11)
- LDT-109 (deprerinamide) (11)
- Memiperone (11)
- Moxipredose (11)
- MXM91* (vasopressin) (11)
- Nalbuphine (11)
- Nifedipine (11)
- Pentoxifylline (11)
- Pimobendan (11)
- Prednisone (11)
- Prospect (11)
- Rendomine (11)
- Rosuvastatin (11)
- Rouvanal (11)
- RXD-132 (11)
- Rimocion (11)
- S-1270 (11)
- Sacubitril (11)
- Sodium nitrite (11)
- Sotalol (11)
- Sulindac (11)
- Targelitin (11) (GHBAC1) (11)
- Theophylline (11)
- TXN 1012 (11)
- Vitamin D (11)
- Wartecose (11)
- Xhurni Plus (11)
- Zolite* (formerly Organon Plus)

Complementary and Alternative Medicine (64)
- TCM (11)
- Ayaevale (11)
- Fencinatic (11)
- ADAPT 323 (Chast17) (11)
- Ceneye (11)
- Cencrul (11)
- Curcuma (11)
- Echinacea (11) (tartaric)
- Flaxseed (11)
- IMFL/gn000* (botanical ingredient) (11)
- Nutrocar (11)
- Omega-3 (11) (Eicosapentanoic acid + docosahexanoic acid)
- TargetedTissueFormulas (11)
- Synoptomic acid (11)
- Synoptomic acid (11)
- Synoptomic acid (11)

Other (65)
- Transcranial current direct stimulation (11)
- Phototherapy (11)
- Transcutaneous auricular nerve stimulation (11)
- Electrical stimulation (11)
- Hypoxic oxygen (11)
- Allergic culture-expanded adipose-derived mesenchymal stem cells (11)
- Allergic tissue (11)
- Bone marrow mesenchymal stem cell derived extracellular vesicles (11)
- CBMA (11)
- Cold laser (11)
- Cranial electrotherapy stimulation (11)
- High dose therapy (11)
- Hope Bioscience adipose-derived mesenchymal stem cells - all-inclusive (11)
- Human: minimoglobin (11)
- Hydrochloric acid generator with nebulizer (11)
- Inogen One G4 (portable oxygen concentrator) (11)
- Intravenous use of PEPP (11)
- Nalbuphine plasmin (29m-spermatic duct drink) (11)
- Microbiome harvest adipose-derived tissue stromal vascular fraction (11)
- MNS02 (11) (autologous mesenchymal stem cells)
- Personalized multidisciplinary day hospital intervention (11)
- Plasma exchange (11)
- Platelet rich plasma (11)
- Pulsed ultrasound (11)
- Resovix sensitive incarminated neumom eye radiosity at 440 kHz (11)
- Sulfate gelatin block (11)
- Whole body cryotherapy (11)

Symbols next to each intervention represent the targeted system:
- Pulmonary system
- Musculoskeletal system
- Cardiovascular system
- Nervous system
- Non-system specific
- Mental health

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Fawzy, Nader A 2023 figure 2

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NIH RECOVER Initiative Phase 2 trials

• RECOVER VITAL
  o Longer dose regimen of Paxlovid (nirmatrelvir/ritonavir) – 25 days

• Recover - Neuro
  o Cognitive dysfunction
  o Brain HQ (brain training program)
  o PASC-cognitive recovery (web based)
  o Home based transcranial direct current stimulation

• RECOVER - SLEEP
  o Hypersomnia
  o Test 2 wakefulness-promoting drugs not yet identified

• RECOVER – AUTONOMIC
  o IVIG
  o Ivabradine
With decreased severity decreasing Post Covid Cases

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

- Omicron
- Delta
- Original+Alpha

% Alive

Days after positive COVID-19 test

p<0.0001
log-rank test

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

% Patients

Likely Variant

- Post-COVID-19 syndrome
- SOB
- Fatigue
- Mood disturbance
- Cough

Willan J 2023
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