

Long-COVID post-viral syndrome: Lessons from the Russian Flu of 1889 for the COVID pandemic

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"While the so-called Spanish influenza of 1918–19 is frequently invoked as an analogue for COVID-19, the Russian influenza might be a better cultural parallel." Mark Honigsbaum

The English medical historian and journalist Mark Honigsbaum offers an interesting anecdote on the impact of the 1889–90 Russian flu in a recent article on the COVID-19 pandemic published in the *Lancet*. The Russian flu pandemic of 1889–1890 had killed around one million worldwide. Several waves of the epidemic recurred over the intervening years from 1891 to 1895.

The English feminist and campaigner for women's suffrage, Josephine Butler, wrote in January of 1892 to her son, "I don't think I ever remember being so weak, not even after the malaria fever at Genoa. I am so weak that if I read or write for half an hour, I become so tired and faint that I have to lie down." (Honigsbaum & Krishnan, 2020)

During the Christmas season of 1891, she was stricken with the Russian influenza and left weak with conjunctivitis and pneumonia for several days. Though her fevers had subsided, she recounted that there had been little improvement in her overall condition three months later.

A post-epidemic analysis conducted in 1957 using blood obtained from people still alive from the period noted that they had antibodies to H2N2, which may have originated from the Russian flu. Four decades later, a seroarcheological study then asserted the strain was most likely an H3N8 subtype instead. However, more recent studies led by Belgian biologist Leen Vijgen indicated that the contagion could have been a coronavirus, specifically the HCoV-OC43.

The "Asiatic" or "Russian" flu originated in central Asia, where it smoldered regionally throughout Siberia and northern India for a period of six months from May to October of 1889. Once it landed in St. Petersburg in November 1889, the pandemic accelerated westward, spreading, in a matter of weeks, into Europe, followed by the United States, and, then, the rest of the Americas, Australia, and coastal Africa, completing its circumnavigation of the globe by the fall of 1890.

The Russian Influenza has been characterized as the prototype of the modern era of a pandemic for the rapidity of its spread within an increasingly interconnected world.

In a scientific report published in PNAS in 2010 on the 1889 influenza pandemic, the authors wrote, "At that time, the 19 largest European countries, including Russia, had 202,887 kilometers of railroads, which is more than now. Transatlantic travel by boat took less than six days at that time, instead of less than one day now (which is not a substantial difference, given the time scale of the global spread of the pandemic.)"

In their support of the Russian flu pandemic's coronavirus theory, Vijgen and his team explained that in the second half of the 19th century, cattle herds were being affected by a deadly contagious respiratory disease. They hypothesized that the bovine coronavirus might have been

the inciting agent in the sickened animals that underwent a zoonotic transfer into humans from 1870 to 1890 when industrialized nations were engaged in massive culling operations to stem the infections in the livestock industry when handlers could have quickly become infected.

The authors determined through a molecular clock technique, which uses the mutation rate of biomolecules to deduce the time in prehistory when two or more life forms diverged, that a common ancestor of the current Bovine coronavirus and HCoV-OC43 dated back to 1890, circa the Russian flu pandemic.

Additionally, they noted that the pronounced neurological symptoms that distinguished the Russian influenza from other influenza outbreaks speaks to coronavirus as a likely candidate.

Other findings indicated that men and the elderly appeared to be more susceptible to the virus. The reproduction number (R0) was 2.1, with a case fatality rate between 0.1 to 0.28 percent.

Infection symptoms included high fevers, crippling fatigue, and central nervous system disorders.

A Dublin physician named John Moore provided an account from a patient who fell ill on December 20, 1889. The female patient wrote, "Then my face and head got very hot and uncomfortable, and pains began in my arms, shoulders, and legs. All night the pains were very bad, sometimes so sharp across the back of my chest that I could have cried out."

A report authored by Mark Honigsbaum, titled "The 'Russian' influenza in the UK: lessons learned, opportunities missed," explains that after the first case was identified in December 1889, the virus began to kill thousands of people over several weeks. "The disease had already sickened the British Prime Minister, Lord Salisbury, and sparked mass absenteeism in the General Post Office's Telegraphic Department, the center of communications of the British Empire."

Perhaps the most famous case was the death of Queen Victoria's grandson, Prince Albert Victor, which changed the line of succession. Russia's czar, the king of Belgium, and Germany's emperor had taken ill but survived their infection.

Honigsbaum notes that the excess deaths from respiratory failure and the pattern of deaths impacting the middle age ranges "should have aided the public health response, but British health authorities preferred to advocate cautious preventive measures that did little to alleviate the pandemic's impact." The medical community was consumed by a now obsolete miasmatic theory that held the disease was caused by a noxious form of bad air.

The pandemic returned a year later, killing twice as many people. From 1890 until 1892, it has been estimated that 110,000 died from the infection in England.

In a study mapping the deaths from influenza in Paris in 1889 and 1890,

the authors highlighted excerpts from a French newspaper *La Lanterne* that reported a single-day high of 450 burials on December 31, 1890 as comparable to the present situation in France in its second COVID-19 surge. The high daily deaths in Paris persisted throughout January 1891. (Kimmerly, Mehroud, & Marin, 2014)

In the context of the present pandemic, specifically considering the post-COVID-19 viral syndrome known better as Long-COVID, Ms. Butler's words quoted at the beginning strike a dreadful chord.

An untold number of people who have recovered from their infection continue their struggles facing chronic ailments with no end in sight and no help from an incredulous health community that has often attributed their complaints to "being in their heads." (Yerramilli, 2020) The post-viral syndrome associated with COVID-19 has only recently been gaining coverage in the media.

In a study that is still to be peer-reviewed, out of 4,182 cases of COVID, 558 (13.3 percent) patients noted symptoms beyond four weeks, 189 (4.5 percent) beyond eight weeks, and 95 (2.3 percent) beyond 12 weeks. These symptoms include extreme fatigue, persistent headaches, shortness of breath, and the loss of smell, affecting disproportionately females, older people, and those of higher weight.

In an online survey of self-reported symptoms from patients from Renown Health System in Reno, Nevada, out of 233 COVID-19 positive cases, 43.4 percent had symptoms lasting more than 30 days, and 24.1 percent had at least one symptom 90 days out from their positive results. These symptoms include chest pain, heart palpitations and tachycardia, poor concentration, shortness of breath, memory loss, confusion, headaches, and dizziness. Those with shortness of breath are at higher risk of developing chronic symptoms.

A European study from the Netherlands found that one-third of 1,837 non-hospitalized patients were dependent on caregivers.

Though these patients do not require intensive medical care, those who have joined social media support groups recount how debilitated their condition has made them, complaining of "rolling waves of symptoms" and "brain fog." As one New Jersey-based administrator for the COVID-19 Slack group poignantly stated, "We're not dead, but we're not living."

One of the most insidious aspects of the chronic effect of COVID-19 infection is the incapacitating exhaustion and ill-feeling. Thousands of those affected report struggling with just getting out of bed, let alone working for more than a few minutes at one time. A small study from Italy of 143 people discharged from a Rome hospital indicated that 53 percent had fatigue, and 43 percent had shortness of breath two months later. (Carfi, Bernabei, & Landi, 2020)

As with the Russian influenza, post-viral syndromes have been frequently reported with viral illnesses. Even with the Spanish flu of 1918, which was caused by the H1N1 influenza virus and killed an estimated 24.7 million to 50 million people, journals kept by treating physicians noted that many of those who survived never fully recovered.

After the Severe Acute Respiratory Syndrome (SARS) pandemic of 2003 that infected over 8,000 individuals and killed close to 800, many of those who survived were followed to assess their health outcomes. In a study of survivors one year out from their infection, 18 percent continued to have decreased walking tolerance while 17 percent had still not returned to work. More than 60 percent had persistent fatigue. Forty-three percent were being evaluated for mental health disorders. Sleep disturbances were common. Caregivers of many of those severely impacted noted a considerable decline in their patients' cognitive capacities. (Tansey & Herridge, 2007)

In a pooled analysis of 28 studies in patients with documented SARS and Middle East Respiratory Syndrome (MERS) infections, six months after discharge, 27 percent had impaired lung functions and reduced exercise tolerance. More than one-third of these patients suffered from

post-traumatic stress disorder and depression compounded by anxiety.

During the early phase of the pandemic, in a letter penned in June to the editors of the journal *Medical Hypotheses*, the lead author Dr. Raymond Perrin, a neuroscientist and specialist in Chronic Fatigue Syndrome from the School of Medicine and Manchester Academic Health Sciences, warned about the potential for a post-viral syndrome that could manifest in patients recovering from a COVID-19 infection, similar to that in SARS patients.

"After the acute SARS episode some patients, many of whom were healthcare workers, went on to develop a Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)-like illness which nearly 20 months on prevented them returning to work. We propose that once an acute COVID-19 infection has been overcome, a subgroup of remitted patients are likely to experience a long-term adverse effect resembling CFS/ME symptomatology such as persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep."

CFS/ME is a complex, fatiguing, long-term medical condition distinguished by lengthy exacerbations after mental or physical activity, significantly diminished capacity to accomplish tasks that had been routine previous to their illness, and unrefreshing sleep or insomnia. The proposed mechanism is a byproduct of the immune response to the infection that traverses the blood-brain barrier via the olfactory pathway into the hypothalamus.

The "pro-inflammatory cytokines" that pass through the blood-brain barriers cause inflammation in the central nervous system leading to "autonomic dysfunction," which manifest "acutely in high fevers and in the long term to dysregulation of the sleep/wake cycle, cognitive dysfunction and profound unremitting anergia (lack of energy)."

There have been over 50 million cases of COVID-19, and by all accounts, the present surge is a massive tsunami of cases that have placed every health system in the Northern Hemisphere on notice. Millions are expected to die. However, millions more, especially within the working class who have lost their jobs, will face an uncertain future of disabling conditions and chronic unemployment unless immediate efforts are made to bring the pandemic under control. Early intervention and supportive care will be necessary to mitigate the long-term consequences for millions. Medical bills and the cost of treatments must be waived.

According to a *Wall Street Journal* report, Tricia Sales, a 41-year-old who fell ill with COVID-19 in March and is experiencing unremitting symptoms of nausea, dizziness, and numbness in her hands and feet, owes more than \$100,000 in medical expenses. Many people are forgoing treatment due to concerns over high deductibles, attempting to live on their savings as they are still too ill to return to work.

The City University of New York Public School of Health estimated that if 20 percent of the US population contracts COVID-19, one-year post-hospitalization costs would be more than \$50 billion, without considering the long-term care post-acute recovery. According to the Kaiser Family Foundation, many insurance companies are raising 2021 premiums to account for expected COVID-19 costs.

Though a paramount concern, death is not the only indicator of importance concerning the health crisis caused by the SARS-CoV-2 virus. Experience with post-viral syndromes has a long history in medical journals. The literature on SARS and MERS should have informed public health policies and provided guidance early during the pandemic in the post-treatment management and care of these patients.

It will be critical to developing rehabilitation programs in this context to address the multidimensional aspect of this disease. It has been predicted that 45 percent of discharged patients will require health and social care, while another 4 percent may need continued inpatient treatment. The health impact on all national health systems will be considerable.

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