

Long COVID: A New Disease Caused by a New Pathogen

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ABSTRACT

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Long COVID refers to persistent health issues following SARS-CoV2 infection, lasting three months or longer. Multiple symptoms pertaining to several organ systems have been described. It is therefore a constellation of conditions, rather than a singular disease entity. Studies from India and elsewhere have revealed similar observations. A substantial number of people who suffer from Long COVID will not show up on official medical records because their symptoms might get attributed to other known conditions. In addition, some individuals might not seek medical attention due to the insidious nature of symptoms. With an incidence of at least 5% with prevailing variants, the socio-economic impact of this condition is huge, yet under-recognised. Four years since the pandemic's arrival, COVID-19's individual severity may have decreased, yet Long COVID remains a perplexing problem with no clear solution.

Keywords: Long COVID, Brain Fog, Post-acute Sequelae of SARS-CoV-2 Infection, Post COVID Condition, Persistent Symptoms, COVID-19 Aftermath, Chronic Illness, Vaccination, Lingering Effects, Viral Persistence, Immune Response

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The identification and description of Long COVID marks a milestone in the history of medicine. It is not often that the world of science is confronted with a novel pathogen which has repeatedly infected millions of individuals in a short span of time, taking the lives of many in the process and leaving several others with sequelae. Most of the initial attention was focused on deaths and acute severe disease, hence Long COVID was overlooked in the early part of the pandemic.

Long COVID is an umbrella term used to describe multiple symptoms that last for longer than three months after recovery of COVID-19, without other explanation.^{1,2} Unlike post polio paralysis which is a well-defined clinical entity, Long COVID comprises a wide spectrum of illnesses pertaining to several organ systems of the body, singly or in combination, brought about by an extended and dysregulated immune response.³ Although estimates of incidence vary depending on study methodology and inclusion criteria, it is generally observed that 10% of symptomatic SARS-CoV2 virus infections lead on to long term symptoms of assorted nature.¹

While it is true that viral infections such as influenza can lead to post recovery fatigue lasting for a few days, the

occurrence of new symptoms such as brain fog and the extended duration of the illness makes Long COVID distinct. Within the spectrum of Long Covid, there are subcategories. In the early part of the pandemic, before the advent of vaccination, COVID-19 caused severe disease in a large number of individuals, and several among those who survived had symptoms resulting from organ damage. Their physical health deteriorated directly as a result of COVID-19, leading to persistent ill health.

More remarkable is the early or delayed appearance of symptoms that are completely new. These pertain to multiple organ systems including skin, endocrine, cardiovascular, musculoskeletal and central nervous systems. A common symptom associated with Long COVID is brain fog, a colloquial term used to describe a state of mild confusion, difficulty remembering tasks, and general slowing of the intellect. Other symptoms include easy fatigability - where even the mildest form of exercise brings on a level of exhaustion that is far out of proportion to the effort made. Numerous other symptoms are listed under the umbrella of Long COVID including muscle and joint pain, chest pain, palpitations, headache and insomnia. A recent

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paper from India by Ghoshal et al. described new onset functional gastrointestinal disorders following COVID.⁴ In a study of people with Long COVID from Spain, neuropsychological assessment revealed cognitive impairment. This included difficulty in concentration (87.85%), word-finding difficulties during speech (86.44%), speed of processing and remembering recent events (76.16%), multitasking (75.23%), and reading comprehension. The striking finding was that the severity of impairment was greater among younger adults.⁵ Symptoms are known to fluctuate in intensity. Long COVID could occur even following a mild bout of COVID. It is either absent or extremely uncommon following asymptomatic SARS-CoV2 infection.⁶

Many people with Long COVID remain undiagnosed. This is due to the insidious, heterogeneous nature of its presentation, lack of awareness and absence of specific diagnostic markers. People with less severe symptoms continue with their daily activity at a level they can tolerate, essentially learning to live with the new impairment. Those who seek medical attention might receive an alternative and more common diagnosis that is compatible with their symptoms. Unlike outcomes such as deaths and hospitalisation that are readily noticed, Long COVID burden in a population is less conspicuous.

The diversity in symptoms and definitions in Long COVID and variation in research methodology lead to a wide range in reported incidence. From India, during the pre omicron era, Sarda et al. from AIIMS Delhi reported a 28% incidence of Long COVID at 28 days among non-hospitalised COVID patients, while Arjun et al. from AIIMS Bhubaneswar reported a 9.2% incidence on longer term follow up of 6 months.^{7,8}

The socioeconomic impact of a new long-term health condition affecting a large section of the population requires greater attention. Research from a Long COVID clinic at Calicut, Kerala, India, by Anuradha et al. reveals that 62% of those who became unemployed due to illness were unable to restart employment even after 10 months.⁹ The authors found greater functional impairment among people with greater severity of initial infection.

The loss of quality of life and diminished economic productivity resulting from the physical and intellectual impairment of Long COVID are substantial. These factors, along with the cost of additional healthcare are estimated to cost \$3.7 trillion for the US (over 5 years), 2.5 billion GBP per year (UK) and 3.5 billion euros for Germany.^{10,11}

With the arrival of Omicron, the frequency of Long COVID after each infection has decreased. This is likely due to the relatively lower severity of the initial infection. However, newer variants spread to greater numbers of people. Thus, even though a smaller percentage of people may develop long COVID, the large number of cases overall is still a cause for concern compared to the period before Omicron.

Karyakarte et.al from BJ Medical College Pune demonstrated that the frequency of Long COVID decreased from 12% during the delta era to 5% after the arrival of Omicron and its sub lineages.⁶ A study from Malaysia has reported 11% incidence of Long COVID following Omicron infection.¹²

The October 2023 US census Household survey revealed that 14.3% of all Americans had ever experienced Long COVID, with the percentage remaining constant over three years.¹³ The prevalence of Long COVID among US adults was 7.5% in June 2022 and 6% in June 2023.³⁴ Among children, 1.3% had ever had Long COVID in 2022, while 0.5% were currently having it. Among children, girls of age 12-17 are the most affected.¹⁴

The ability of the virus to continuously evolve and cause repeated infections in the same individual means that it could also cause a setback among those who had recovered from Long COVID.^{15,16} A significant proportion of Long COVID patients have symptoms lasting beyond two years.^{17,18}

Several terms are in use to describe persistent health issues following COVID recovery. Among them, PASC (Post-Acute Sequelae of COVID-19), and PCC (Post COVID Condition)

are noteworthy. According to the World Health Organisation, Long COVID or PCC represents persistent symptoms lasting greater than three months. Since September 2023, the US CDC has used the term PCC for symptoms extending beyond four weeks.¹⁹

HISTORY

The history of Long COVID is unique in that it was first identified not by doctors, but patients themselves. Several of them wrote about their own experiences, facing considerable amounts of scepticism and disbelief in the process, as is expected for a new disease that has just been described. Patients formed their own support groups, also publishing papers describing their

symptomatology.²⁰ One of the drawbacks of relying solely on the description of Long COVID sufferers is that there are no controls against whom the numbers and the percentages can be compared with. Researchers overcame this problem by including control groups. Thus, people with Long COVID were compared with COVID-recovered individuals who did not have Long COVID, and the outcomes were compared.

After initial reluctance and scepticism, the existence of Long COVID was accepted by the world of science, which has since seen significant research output. In July 2021, Long COVID was added as a recognized condition that could result in a disability under the Americans with Disabilities Act.²¹

Pathogenesis

While 9 out of 10 people symptomatically infected with currently circulating variants recover without any sequelae, that is not the case for 10% or 1 out of 10 people. The root cause of Long COVID is believed to be immune dysregulation that occurs only in this subset of people, regardless of their underlying health status.²² The exact reason and nature of immune dysregulation is unknown. It is more commonly described among women of age 35-49, and is considerably rarer among children.¹⁴

It is possible that such individuals have a prolonged immune response which does not wind down or self regulate itself to a state of normalcy. Another possibility is of the immune system responding to the virus or parts of the virus persisting in areas located far away from the initial site of infection, which is the upper respiratory tract. For instance, the virus has been identified from the gut, which, by itself, has significant immune-related function. The similarity of certain Long COVID symptoms to those of meningoencephalitis has been noted. Reactivation of Epstein Barr virus and CMV infections have been proposed as mechanisms.

Autoimmunity was proposed particularly in the early part of the pandemic, but whether the autoantibodies found were the cause or the effect of the process is debated.^{23,24} Recent research has linked persistent activation of complement with long COVID, the resolution of which has correlated with symptom resolution.²⁵ Complement is a series of proteins which are part of the human innate immune response. When activated, they can inflict non-specific damage to pathogens and human tissue.

Fatigue is the commonest symptom of long COVID patients. There are several postulates that attempt to

explain this symptom. Initial theories of blood clots blocking the microcirculation have given way to mitochondrial dysfunction where muscle cells have difficulty extracting energy currency from mitochondria, which are the powerhouses of the cell.²⁶

Long COVID and vaccination

Although there are rare reports of Long COVID occurring after COVID vaccination,^{27,28} it is unlikely that vaccination is a major contributor because the condition was described well before vaccine rollout. Besides, some studies have shown a decrease in the incidence of Long COVID following the initial bout of COVID among previously vaccinated individuals.²⁹ This is likely from lower severity of the initial infection. However, the apparent protection did not apply to subsequent infections.¹⁵ Dipu TS et al. from AIMS Kochi, India showed that 10.1% of breakthrough infections among previously vaccinated individuals led to Long COVID.³⁰

As Long COVID is attributed to a persistent inflammatory process, a pertinent question is whether vaccination soon after recovering from COVID will increase the risk of Long COVID. Chakrabarti et al from BHU Varanasi reported a nearly 3-times higher risk of post-COVID persistent health issues in individuals who received the vaccine after COVID, compared to those who received the vaccine before getting the infection.³¹

Despite early anecdotal reports of Long COVID improving following COVID vaccination, a systematic review failed to reveal consistent benefit, with some studies showing deterioration.³²

A common thread among published studies is that Long COVID occurs in a finite proportion of people who have symptomatic COVID, and its severity generally correlates with that of the initial infection.

TREATMENT CONSIDERATIONS

There is a false notion that there is no treatment for Long COVID. While it is true that there is no single drug of choice, there are viable therapeutic options for subsets of these patients, especially those with autonomic dysfunction. Beta blockers have been effective for POTS or Postural orthostatic tachycardia syndrome.¹ For selected patients, treatment with SSRI (Selective Serotonin Reuptake Inhibitors) is beneficial.³³ Exercise is not recommended as treatment for symptoms such as post-exertional fatigue that gets worse after even minor physical or mental exertion.

The chief barrier to treatment is lack of recognition of the condition both on the patient's as well as the caregiver's side. Once the syndrome is recognised, patients need acknowledgement and empathy that their symptoms are indeed real. Many patients who suffered from long COVID, especially in the first year of the pandemic were ridiculed by people in good health, claiming that this was an imaginary condition and that the symptoms were all in their mind. The perception at that time was that COVID-19 was an acute illness rather than a trigger for chronic health problems. Although it is true that several viral and bacterial illnesses infections can lead to long-term sequelae, long COVID stands out for the enormous numbers of affected individuals, and the appearance of new symptoms after several months of apparent full recovery from infection.

PREVENTION

Unfortunately there are no specific preventive measures for Long COVID, apart from avoiding SARS-CoV2 virus infection. It was initially postulated that vaccination could prevent it, but studies have revealed only minimal to modest effect at best.

Antiviral agents such as Nirmatrelvir /ritonavir have been used in high-risk individuals with acute COVID, and it was speculated that the use of these agents might reduce the incidence of Long COVID. However, a recent paper has revealed no preventive benefit from use of this drug.³⁵ The apparent lack of benefit could be because the drug is started only after the infection has already set in. The WHO states that the best way to avoid Long COVID is to avoid getting COVID.³⁶

END NOTE

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