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Will SARS-CoV-2 Continue to Evolve in Such a Way That One Day the Risk of Persistent COVID May Become Insignificant?

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Editorial

Will SARS-CoV-2 continue to evolve in such a way that the risk of long COVID may one day become negligible? Theoretically, it's possible, but based on what we've seen so far, it's quite doubtful.

Long COVID is a debilitating and persistent illness that affects people in multiple and dynamic ways. It occurs after a SARS-CoV-2 infection and manifests as a continuous, relapsing-remitting, or progressive disease state affecting one or more organ systems. It can occur after an asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may or may not have been diagnosed. It can be continuous from the time of acute SARS-CoV-2 infection or have a late onset for weeks or months after what appeared to be a full recovery from the acute infection. It can affect children and adults, regardless of their health, disability, socioeconomic status, age, sex, sexual orientation, race, ethnicity, or geographic location. It can exacerbate pre-existing health conditions or present as new conditions. It can range from mild to severe and may resolve within months or persist for months or years. It can impair patients' ability to work, attend school, care for their families, and care for themselves, resulting in profound emotional and physical effects on patients, their families, and their caregivers [1,2].

Post viral symptoms have been documented in diseases ranging from SARS to dengue, but remain understudied. Dengue patients are fatigued for several weeks after infection, and chikungunya patients may be in pain for months [3]. Patients with long COVID join millions of people already suffering from chronic illnesses associated with infections (e.g., myalgic encephalomyelitis-chronic fatigue syndrome, post-treatment Lyme disease, and multiple sclerosis, among others). These illnesses had been identified for decades before a pandemic brought specific attention to their situation [1]. In any case, it is astonishing to think that long COVID has lasted almost half a decade and that some patients who contracted it early on are still suffering from severe symptoms. But the good news is that some research shows that early strains of COVID-19 and earlier variants like Delta appeared to produce more severe forms of long COVID than later strains. Newer cases are milder than those caused by earlier strains. However, there are still some new cases of long COVID that are severe [4–6].

A very small proportion of people who contract COVID-19 will develop immune dysfunction and long COVID. The risk of developing long COVID has decreased significantly since the beginning of the pandemic (from the pre-Delta to Omicron eras), and this decrease is due to changes in SARS variants and COVID-19 vaccines. At the beginning of the pandemic, approximately 2–10% of people who suffered COVID-19 infections developed long COVID. Currently, the risk of developing long COVID has decreased to approximately 0.2–3.5% among vaccinated individuals [7–9].

It is acknowledged that around 70% of the decrease was attributable to vaccination. There are several reasons why vaccines may prevent long COVID: First, vaccines reduce the

risk of severe acute infections, which are linked to a higher risk of long COVID. Vaccines also help the body's immune system clear the virus more quickly, reducing the likelihood of persistent viral particles remaining. Viral persistence is one of researchers' multiple hypotheses regarding the drivers of long COVID. This means that maintaining vaccination rates is likely a major driver in keeping long COVID under control. The remaining 30% was related to changes in viral characteristics. In other words, as SARS-CoV-2 evolved, it changed in ways that may have made people less susceptible to developing long COVID [10–11].

From a clinical perspective, long COVID is not a homogeneous disease. It should be considered a multisystem syndrome, making its differentiation from other conditions very difficult. The clinical picture is as markedly heterogeneous and multisystemic as in the acute phase. Furthermore, its appearance is not related to the severity of the initial infection, so it can affect both mild, even asymptomatic, patients and severely ill patients who have required hospitalization. Although it can affect people of any age, it is more common in middle-aged women [12]. Long COVID manifests in multiple ways, exhibiting various phenotypes or disease subtypes: sensory symptoms such as loss of taste and smell, fatigue symptoms related to extreme physical exhaustion and mental confusion, and cardiovascular or respiratory symptoms [4]. It is important to note that despite coordinated efforts to refine the definitions of Long COVID, due to the novelty and diversity of manifestations of this condition, several terms and definitions have been proposed, but none has gained widespread acceptance and support from patients, physicians, researchers, or government agencies [1].

Five years after the initial identification of Long COVID, the greatest obstacle to understanding the epidemiology and treatment of patients with this condition remains the discovery of a biomarker that allows for its diagnosis. In other words, it is a disease undetectable by biological tests [13]. Without a clear tool to confirm positive diagnoses in patients, pharmaceutical companies are hesitant to fund clinical trials. The findings from 2023 revealed that certain biomarkers can identify long COVID with 80% accuracy. Researchers found that long COVID was associated with immune system inflammation in proteins such as C3, C4, and C5. However, since then, no definitive biomarker has been identified [14].

A wide range of biological mechanisms are involved in the underlying mechanisms of long COVID, including the persistence of the original virus in the body, disruption of the normal immune response, and microscopic blood clotting, even in some people who only had mild initial infections [15]. Scientists have deepened their understanding of the mechanism of long COVID and how it causes severe illness in patients. Several mechanisms can cause this condition, and some of them may overlap. The cause of long COVID is viral reservoirs: residual viral fragments that remain in the blood or body tissues after the acute phase of infection. Symptoms persist because patients never completely eradicate the infection. Other research has shown that the virus alters the composition of the gut microbiome, which, in turn, causes symptoms. Another mechanism of the disease is the virus's impact on mitochondria, the cell's energy source [4].

The SARS-CoV-2 virus is a positive-sense, single-stranded RNA virus with a low mutation rate (estimated at $1.3 \times 10^{-6} \pm 0.2 \times 10^{-6}$ per base per infection cycle) but greater replication and transmissibility in new variants. The presence of eight billion previously uninfected individuals led to the rapid generation of different variants such as alpha, beta, gamma, and delta [16–18]. Acquired immunity is insufficient to provide the desired protection against new SARS-CoV-2 variants such as BQ and XBB, omicron subvariants [19]. However, vaccines have been successful in reducing hospitalization and mortality rates [20,21].

It is inevitable to live without an epidemic outbreak and, therefore, without a pandemic with an increasing population density, as predicted by Kermack and McKendrick in 1927 [22]. The spread of the SARS-CoV-2 virus simply requires the presence of infected and vulnerable individuals, as well as the overlap of time and space for its transmission. Once these conditions are met, a new infection can occur. COVID-19 is establishing itself as an 'all-terrain' virus, which explains the resurgence of coronavirus cases in recent months. SARS-CoV-2 is now circulating year-round, but the combination of elements of the original strain and vaccination prevents "immune escapes." At this point, few can say they "haven't caught COVID." The perception that the virus is still among us is supported by the data, which likely underestimate cases since in many countries, such as Spain, they are estimated using a sentinel network [23,24].

And why hasn't the virus disappeared, and why are there still cases (including an increase in cases detected at least in Europe during the summer and autumn of 2025)? [25]. The SARS-CoV-2 virus circulates year-round, unlike the flu or RSV, which may only see a few isolated cases during the summer months. It cannot be said that the pathogen has found a temporary niche or that it is seasonal like the flu. This is a somewhat different virus, and therefore it is necessary to monitor how it evolves. The SARS-CoV-2 virus has only been with us for five years. This encourages us to continue studying its behavior, which is still not fully understood. And immunization is not 100% effective. So far, the new variants have novel elements, but they retain some older ones. This connection to the ancestral lineages that were circulating is what protects us against what may appear. The changes that give rise to the virus variants are a pure biological necessity for survival. The pathogen seeks mechanisms that better facilitate its circulation and spread. Therefore, at the moment, an immune escape is not expected [25].

In summary, 1) given the existence of the triad or ecological/epidemiological chain: causal agent (with less aggressive, but perhaps more contagious, variants), route of transmission/environmental or contextual factors, and susceptible hosts (despite hybrid immunity—infection and vaccination), cases of COVID-19 and long COVID will continue to occur. And 2) considering that the number and variety of epidemic outbreaks have increased in recent decades and have demonstrated the difficulty of controlling high-incidence epidemics, as well as the vulnerability of our societies and healthcare systems to these phenomena (the SARS, H1N1, MERS, Ebola, and especially COVID-19 pandemics), it can be concluded that cases of long COVID will continue to exist. In this scenario, regardless of the diagnostic and therapeutic challenges of long COVID, contextual factors appear to be of greater importance due to the significant physical, emotional, and economic impacts that long COVID has on individuals, their families, and society in general. In short, it is quite doubtful that SARS-CoV-2 will continue to evolve in such a way that the risk of persistent COVID could one day become negligible.

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