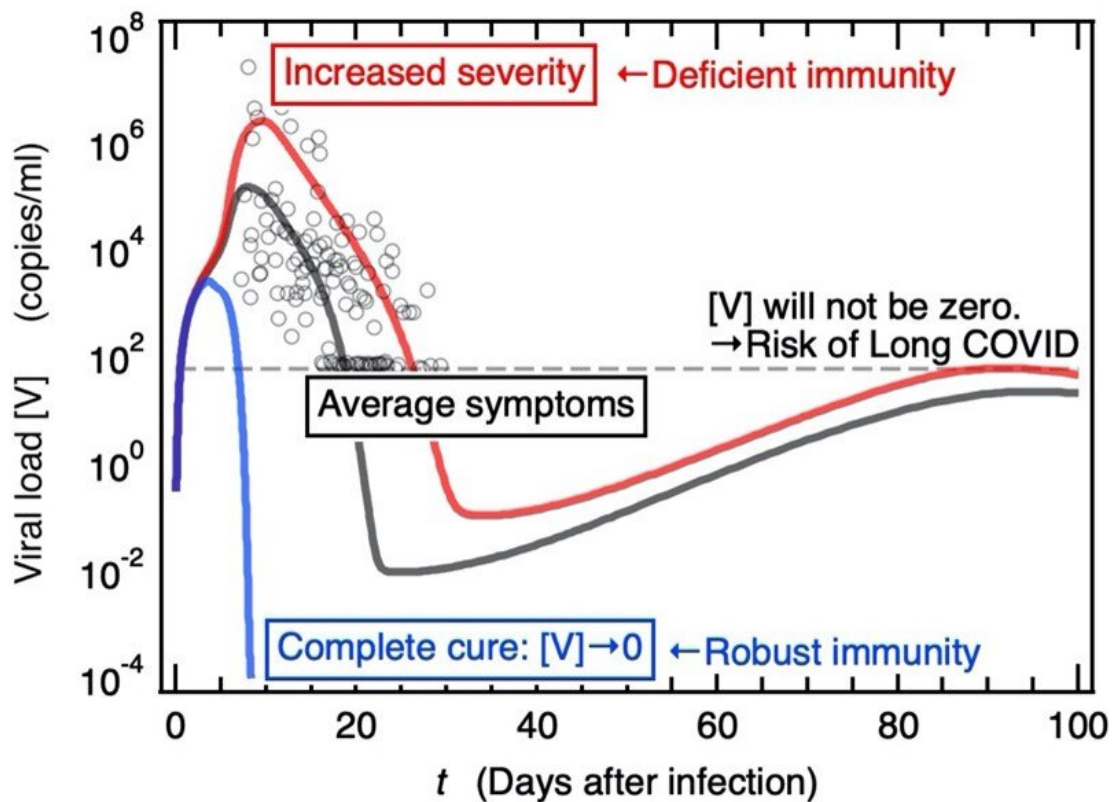


# Are persistent infections of novel coronavirus the cause of sequelae in infected hosts?

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“Average symptoms” shows the results derived from a baseline model when applying a mathematical model to clinical data. Results show “Increased severity” based on “deficient” immunity bearing in mind age-related risk factors. Conversely, the results show a “Complete cure” based on “robust” immunity. Aside from “Increased severity”, even with “Average symptoms,” the viral load [V] tends to retain a finite value rather than decreasing to zero, as the virus is not completely eradicated from the host. However, “Complete cure” indicates that

the virus has effectively been completely eliminated from the infected host.  
Credit: Toyohashi University of Technology.

A research team, comprised of Associate Professor Tomonari Sumi of the Research Institute for Interdisciplinary Science at Okayama University and Associate Professor Kouji Harada of the Center for IT-based Education (CITE) at Toyohashi University of Technology, has developed a mathematical model of the immune response within infected hosts that considers systemic infection of a novel coronavirus (SARS-CoV-2), and demonstrated by conducting experimental computer simulations that persistent viral infections within hosts potentially cause long COVID or post-acute sequelae of COVID-19.

The research team has also revealed that the systemic nature of the [infection](#) is a factor that enables persistent infection within infected hosts.

## Details

This novel coronavirus continues to mutate into new strains during repeated waves of infection, dimming the prospects to quell this pandemic. As a result, the number of patients suffering from what has been termed "long COVID" has significantly increased, and is now deemed a major social issue.

However, the mechanism underlying this long COVID has yet to be clarified, with several different possibilities proposed. One of these is "persistent infection within infected hosts" whereby the virus remains within the body for a prolonged period after infection. The research team sought to clarify whether such persistent infections within infected hosts actually occur, and if so, to identify the causative factors.

In order to consider these questions, the research team developed a [mathematical model](#) that describes the process of persistent novel coronavirus infections within infected hosts as a non-linear simultaneous ordinary differential equation, and conducted simulated viral infection experiments on a computer using models whose parameters had been adjusted based on [clinical data](#) from patients diagnosed with the novel coronavirus.

The results clarified that the virus is not completely eliminated from the body and causes persistent infection, even in the baseline model that produces an average viral load (see Fig. 1: Average symptoms). This persistent infection is attributable—in the case of this novel coronavirus, which is systemic—to the enduring presence of sufficient [host](#) cells, such that infection sites can readily be found. Mathematically, a complete cure—wherein the viral load is reduced to zero—is represented by an unstable equilibrium point, implying that a complete cure is difficult to achieve.

Next, the research team investigated the influence of age-related immunity levels on disease severity. They demonstrated that factors known to be common risks associated with aging—namely (1) Decreased activity by antigen-presenting cells, and (2) Inhibition of interferon signaling by Type I interferon autoantibodies—significantly increased viral production within the body, leading to severe infections (see Fig. 1: Severe infection).

Conversely, they demonstrated that sufficiently robust activity by [antigen-presenting cells](#) and/or antibody production by [plasma cells](#) would result in a complete cure by effectively ridding the infected host of the virus (see Fig. 1: Complete cure). Thus, it can be surmised that enhanced immunity is crucial to avoid persistent infection.

In addition, it was reported that the number of dendritic [cells](#) remained

significantly depressed even some seven months after onset, regardless of the severity experienced by novel coronavirus patients, but the reason was unclear.

This deficiency in [dendritic cells](#) has also been noted in the rare Multisystem Inflammatory Syndrome, which is very similar to Kawasaki disease, and which very occasionally afflicts children infected with this novel coronavirus.

The research team's experimental computer simulations demonstrated that dendritic cell numbers remained significantly depressed, and failed to recover even seven months after infection, being consistent with the long-term clinical observations. The main cause is perceived to be the persistent infection by residual virus within the infected host.

## **Future outlook**

Given that some 540 million people out of the global population of eight billion have been infected so far, it is forecast that long COVID will become an increasingly critical issue. Thus, it is desirable to consider effective therapies for novel coronavirus sequelae, bearing in mind the possibility of [persistent infection](#) within hosts.

This research presents results concerning unvaccinated people who become infected, but little is known about the effect of vaccination-derived immunological memory on persistent infections within hosts. Research that utilizes mathematical models based on clinical data should play a critical role in future in addressing these issues.

## **Sequelae of novel coronavirus (Long COVID)**

Even after recovering from the novel coronavirus, various symptoms

(sequelae) may be observed in some cases, which WHO defines as, "Symptoms of infection with the novel coronavirus that last a minimum of two months, and cannot be explained by an alternative diagnosis."

Reports indicate that 72.5% of patients complain of some residual symptoms two months after being diagnosed with COVID-19, or one month after discharge from hospital, and 54% remain afflicted six months after diagnosis or discharge from hospital.

Symptoms include coughing, fatigue, diminished sense of taste and smell, cognitive dysfunction (brain fog), etc., with some patients complaining of multiple symptoms.

**More information:** Tomonari Sumi et al, Immune response to SARS-CoV-2 in severe disease and long COVID-19, *iScience* (2022). [DOI: 10.1016/j.isci.2022.104723](https://doi.org/10.1016/j.isci.2022.104723)

Provided by Toyohashi University of Technology

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