

# Long COVID Puzzle Pieces Are Falling Into Place—The Picture Is Unsettling

By Ziyad Al-Aly

Since 2020, the condition known as long COVID-19 has become a widespread disability affecting the health and quality of life of millions of people across the globe and costing economies billions of dollars in reduced productivity of employees and an overall drop in the work force (Espinosa).

The intense scientific effort that long COVID sparked has resulted in more than 24,000 scientific publications, making it the most researched health condition in any four years of recorded human history.

Long COVID is a term that describes the constellation of long-term health effects (Yale) caused by infection with the SARS-CoV-2 virus. These range from persistent respiratory symptoms, such as shortness of breath, to debilitating fatigue or brain fog that limits people's ability to work, and conditions such as heart failure and diabetes, which are known to last a lifetime.

I am a physician scientist, and I have been deeply immersed in studying long COVID since the early days of the pandemic. I have testified before the U.S. Senate as an expert witness on long COVID, have published extensively on it and was named as one of Time's 100 most influential people in health in 2024 for my research in this area.

Over the first half of 2024, a flurry of reports and scientific papers on long COVID added clarity to this complex condition. These include, in particular, insights into how COVID-19 can still wreak havoc in many organs years after the initial viral infection, as well as emerging evidence on viral persistence and immune dysfunction that last for months or years after initial infection.

## How Long COVID Affects the Body

A new study that my colleagues and I published in the New England Journal

of Medicine on July 17, 2024, shows that the risk of long COVID declined (Xie, *NEJM* 2024) over the course of the pandemic. In 2020, when the ancestral strain of SARS-CoV-2 was dominant and vaccines were not available, about 10.4% of adults who got COVID-19 developed long COVID. By early 2022, when the omicron family of variants predominated, that rate declined to 7.7% among unvaccinated adults and 3.5% of vaccinated adults. In other words, unvaccinated people were more than twice as likely to develop long COVID.

While researchers like me do not yet have concrete numbers for the current rate in mid-2024 due to the time it takes for long COVID cases to be reflected in the data, the flow of new patients into long COVID clinics has been on par with 2022.

We found that the decline was the result of two key drivers: availability of vaccines and changes in the characteristics of the virus—which made the virus less prone to cause severe acute infections and may have reduced its ability to persist in the human body long enough to cause chronic disease.

Despite the decline in risk of developing long COVID, even a 3.5% risk is substantial. New and repeat COVID-19 infections translate into millions of new long COVID cases that add to an already staggering number of people suffering from this condition.

Estimates for the first year of the pandemic suggest that at least 65 million people (Davis) globally have had long COVID. Along with a group of other leading scientists, my team will soon publish updated estimates of the global burden of long COVID and its impact on the global economy through 2023.

In addition, a major new report by the National Academies of Sciences Engineering and Medicine details all the health effects that constitute long COVID (National Academies). The report was commissioned by the Social Security Administration to understand the implications of long COVID on its disability benefits.

It concludes that long COVID is a complex chronic condition that can result in more than 200 health effects across multiple body systems. These include new onset or worsening:

- Heart disease (Xie, Xu 2022)
- Neurologic problems (Xu, 2022) such as cognitive impairment, strokes and dysautonomia. This is a category of disorders that affect the body's autonomic nervous system—nerves that regulate most of the body's vital mechanisms such as blood pressure, heart rate and temperature.
- Post-exertional malaise, a state of severe exhaustion that may happen after even minor activity—often leaving the patient unable to function for hours, days or weeks
- Gastrointestinal disorders (Xu, 2022)
- Kidney disease (Bowe)
- Metabolic disorders such as diabetes (Xie, Al-Aly 2022) and hyperlipidemia (Xu, 2023), or a rise in bad cholesterol
- Immune dysfunction (Yin)

Long COVID can affect people across the lifespan from children to older adults and across race and ethnicity and baseline health status. Importantly, more than 90% of people with long COVID (Al-Aly) had mild COVID-19 infections.

The National Academies report also concluded that long COVID can result in the inability to return to work or school; poor quality of life; diminished ability to perform activities of daily living; and decreased physical and cognitive function for months or years after the initial infection.

The report points out that many health effects of long COVID, such as post-exertional malaise and chronic fatigue, cognitive impairment and autonomic dysfunction, are not currently captured in the Social Security Administration's Listing of Impairments (SSA), yet may

See *LONG COVID*, next page

Ziyad Al-Aly is Chief of Research and Development, VA St. Louis Health Care System. Clinical Epidemiologist, Washington University in St. Louis. This article is published under a creative commons license from *The Conversation*.

*LONG COVID, from page 79*

significantly affect an individual's ability to participate in work or school.

### A Long Road Ahead

What's more, health problems resulting from COVID-19 can last years after the initial infection.

A large study published in early 2024 showed that even people who had a mild SARS-CoV-2 infection still experienced new health problems (Cai) related to COVID-19 in the third year after the initial infection.

Such findings parallel other research showing that the virus persists (Zuo) in various organ systems for months or years after COVID-19 infection. And research is showing that immune responses to the infection are still evident two to three years (Peluso) after a mild infection. Together, these studies may explain why a SARS-CoV-2 infection years ago could still cause new health problems long after the initial infection.

Important progress is also being made in understanding the pathways by which long COVID wreaks havoc on the body. Two preliminary studies from the U.S. (Santos Guedes de Sa) and the Netherlands (Chen) show that when researchers transfer auto-antibodies—antibodies generated by a person's immune system that are directed at their own tissues and organs—from people with long COVID into healthy mice, the animals start to experience long COVID-like symptoms such as muscle weakness and poor balance.

These studies suggest that an abnormal immune response thought to be responsible for the generation of these auto-antibodies may underlie long COVID and that removing these auto-antibodies may hold promise as potential treatments.

### An Ongoing Threat

Despite overwhelming evidence of the wide-ranging risks of COVID-19, a great deal of messaging suggests that it is no longer a threat to the public. Although there is no empirical evidence to back this up, this misinformation has permeated the public narrative.

The data, however, tells a different story.

COVID-19 infections continue to outnumber flu cases and lead to more

hospitalization and death (Xie, *JAMA*, 2024) than the flu. COVID-19 also leads to more serious long-term health problems (Xie, *Lancet*, 2023). Trivializing COVID-19 as an inconsequential cold or equating it with the flu does not align with reality.

### References

- Al-Aly, Ziyad & Eric Topol, Solving the puzzle of Long Covid. *Science* 383, 830–832 (2024). DOI:10.1126/science.adl0867
- Bowe, Benjamin; Xie, Yan Xu, Evan; Al-Aly, Ziyad. *Kidney Outcomes in Long COVID*. *JASN* 32(11):p 2851–2862, November 2021. | DOI: 10.1681/ASN.2021060734
- Cai, M., Xie, Y., Topol, E.J. *et al.* Three-year outcomes of post-acute sequelae of COVID-19. *Nat Med* 30, 1564–1573 (2024). <https://doi.org/10.1038/s41591-024-02987-8>
- Chen, Hung-Jen *et al.* Transfer of IgG from Long COVID patients induces symptomology in mice. *bioRxiv* 2024.05.30.596590; doi: <https://doi.org/10.1101/2024.05.30.596590>
- Davis, H.E., McCorkell, L., Vogel, J.M. *et al.* Author Correction: Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 21, 408 (2023). <https://doi.org/10.1038/s41579-023-00896-0>
- Espinosa Gonzalez, A. and E. Suzuki (2024), "The impacts of long COVID across OECD countries", *OECD Health Working Papers*, No. 167, OECD Publishing, Paris, <https://doi.org/10.1787/8bd08383-en>.
- National Academies of Sciences, Engineering, and Medicine. 2024. *Long-Term Health*

*Effects of COVID-19: Disability and Function Following SARS-CoV-2 Infection*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/27756>

Peluso, Michael J. *et al.* Tissue-based T cell activation and viral RNA persist for up to 2 years after SARS-CoV-2 infection. *Sci. Transl. Med.* 16, eadk3295(2024). DOI:10.1126/scitranslmed.adk3295

Santos Guedes de Sa, Keyla, *et al.* A causal link between autoantibodies and neurological symptoms in long COVID. *medRxiv* 2024.06.18.24309100; doi: <https://doi.org/10.1101/2024.06.18.24309100>

SSA Disability Evaluation Under Social Security. <https://www.ssa.gov/disability/professionals/bluebook/AdultListings.htm>

Xie, Yan; Taeyoung Choi, M.S., and Ziyad Al-Aly, M.D. Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras. July 17, 2024. *N Engl J Med* 2024;391:515-525. DOI: 10.1056/NEJMoa2403211

Xie Y, Choi T, Al-Aly Z. Mortality in Patients Hospitalized for COVID-19 vs Influenza in Fall-Winter 2023-2024. *JAMA*. 2024;331(22):1963–1965. doi:10.1001/jama.2024.7395

Xie, Y., Xu, E., Bowe, B. *et al.* Long-term cardiovascular outcomes of COVID-19. *Nat Med* 28, 583–590 (2022). <https://doi.org/10.1038/s41591-022-01689-3>

Xie Y, Choi T, Al-Aly Z. Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study. *Lancet: Infectious Diseases*. December 14, 2023. DOI: 10.1016/S1473-3099(23)00684-9

Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 28, 2406–2415 (2022). <https://doi.org/10.1038/s41591-022-02001-z>

Xu, E. & Al-Aly, Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet: Diabetes & Endocrinology* (May 2022). DOI: 10.1016/S2213-8587(22)00044-4

Xu, E., Xie, Y. & Al-Aly, Z. Risks and burdens of incident dyslipidaemia in long COVID: a cohort study. *Lancet: Diabetes & Endocrinology* (January 6, 2023). DOI: 10.1016/S2213-8587(22)00355-2

Yale Medicine Fact Sheets: Long COVID (Post-COVID Conditions, PCC). <https://www.yalemedicine.org/conditions/long-covid-post-covid-conditions-pcc>

Yin, K., Peluso, M.J., Luo, X. *et al.* Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2. *Nat Immunol* 25, 218–225 (2024). <https://doi.org/10.1038/s41590-023-01724-6>

Zuo, Wenting *et al.* The persistence of SARS-CoV-2 in tissues and its association with long COVID symptoms: a cross-sectional cohort study in China. *The Lancet Infectious Diseases*, Volume 24, Issue 8, 845–855. DOI: 10.1016/S1473-3099(24)00171-3

## Correctional Health Care Report Is Online

Current and back issues of *Correctional Health Care Report* are available to subscribers from the Civic Research Institute website. To access CHCR Online, go to the CHCR web catalog page [www.civresearchinstitute.com/chcr.html](http://www.civresearchinstitute.com/chcr.html) and click on the yellow Access Online Edition link. Subscribers can search, read, download, and save articles and entire issues dating back to 2000. If you need help accessing the material, call CRI subscriber services at 609-683-4450 and we'll be happy to help you.