Going Long: Viruses Linger With Lasting Impact

Herpes, HIV, Epstein-Barr and other viruses hang around, causing potential long-term health woes. Should long COVID surprise us?

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Some viruses, like the common cold, are a flash in the pan. They infect us, our bodies fight back — which is what makes us sick — and then they're gone, until the next variant rolls along.

Other viruses linger.

Once HIV gains a foothold in a person's body it never leaves, except for the few individuals who've been cured by bone marrow transplant; people with HIV must continually take antiretroviral drugs to stay healthy and not develop AIDS.

HSV1 and 2 — the viruses responsible for genital herpes and cold sores — flare and fade throughout a person's life. And another herpes virus, varicella-zoster, first presents as chickenpox, then hides for years, even decades, until it reactivates as shingles. Human papilloma virus, or HPV, can trigger cervical, head and neck, anal, vulvar and other cancers. And norovirus recently was identified as a potential driver of Crohn's disease.

From Epstein-Barr to Zika, the list of virus-associated chronic ailments goes on.

Millions of Americans infected by the new coronavirus, SARS-CoV-2, are now dealing with its post-acute sequelae, or PASC, mostly known as long COVID, the latest long-term condition to stem from a virus.

We know they're common; we know they're annoying, and we know that when it comes to the immunocompromised or the unlucky, they can be deadly. But three years after COVID-19 rocked the world, are we now learning viruses are more of a threat than we imagined? Do they all "go long"?

"We're beginning to realize increasingly the long-term impacts of viruses, the infections that they cause and the damage that our immune system can wreak on us as a result of those infections," said Jim Boonyaratanakornkit, MD, PhD, a physician and infectious disease researcher at Fred Hutchinson Cancer Center in Seattle. "As we continue in research, we're finding more and more

examples of the impact of these viruses on long-term health."

Viral warfare

Epstein-Barr virus, also known as EBV or human herpesvirus 4, may be the longest lingerer of all. Although it's not a *malingerer*. It keeps quite busy, infecting about 95% of humans, although most don't realize it because it's often asymptomatic.

In some, EBV drives the so-called "kissing disease," infectious mononucleosis, as can other viruses. In others, particularly in sub-Saharan Africa, Epstein-Barr virus can trigger the cancer Burkitt lymphoma.

Named for the scientists who discovered it, EBV was the first known virus to cause cancer. In addition to Burkitt, it's also been linked to Hodgkin lymphoma, to nasopharyngeal carcinomas and to certain gastric cancers. Last year, researchers tied the virus to multiple sclerosis — at least in individuals with a certain genetic mutation. Some believe EBV or other viruses may be responsible for myalgic encephalomyelitis or chronic fatigue syndrome, often referred to as ME/CFS.

"Another long-term complication debated in the field is RSV [respiratory syncytial virus] infection early in life," said Boonyaratanakornkit. "Some believe it predisposes you to asthma or wheezing later on. That's another area that illustrates how viral infections can have a lasting impact on us long after the virus is gone. There are so many examples."

Boonyaratanakornkit said people have taken viruses "for granted" for years, some even believing contracting and recovering ASAP is the best way to handle them.

Remember chickenpox parties?

"People would bring their kids to get chickenpox so they'd get immunity, which is true," he said. "But potentially they got shingles, too [from the latent varicella-zoster virus]. Sometimes, you get an infection and you don't think about the long-term complication decades from now."

Enter long COVID

While some of the associations between viruses and long-term chronic conditions have been known for years, others, like the link between EBV and MS, are just coming to light.

And just as COVID-19's high death and hospitalization rate among the most vulnerable spotlighted the country's longtime health disparities, long COVID may be shining a light on viruses' propensity to linger once they latch onto us.

And researchers are moving on it.

"There's most definitely a lot to be learned about viruses still," Boonyaratanakornkit said. "The hottest areas of research are EBV and long COVID."

NIH scientists are currently examining the similarities between long COVID and other post-viral fatigue ailments such as long-neglected ME/CFS.

Fred Hutch infectious disease expert Steve Pergam, MD, MPH, called the long-term consequences of infections "a really intriguing space."

"I would argue that it's not just viruses," he said, pointing to a recent review of unexplained post-acute infection syndromes by Yale immunologist Akiko Iwasaki, PhD, and colleagues.

Published in the journal Nature, the authors said (emphasis added), "the relatively similar symptom profiles of individual post-acute infection syndromes, *irrespective of the infectious agent*, as well as the overlap of clinical features with ME/CFS, suggest the potential involvement of a *common etiopathogenesis*."

In other words, it's not just COVID that goes long.

"It may be a number of different pathways to infection in general that can lead to chronic complications," Pergam said. "A classic example is something like the gastrointestinal bacteria campylobacter which has been associated with rheumatologic problems. These infections can set off a pathway toward autoimmunity and other complications. It depends on the illness and the severity of the illness on whether it lingers or there's ongoing issues."

Some of it, Pergam said, is related to our immunity and how we respond to organisms. And some of it is the pathogen itself.

"Some have a stronger predilection to causing long-term sequalae," he said. "There's a lot of space within viruses. You have RNA acute viruses like HIV and most respiratory viruses, and then you have DNA viruses which are different. Some infections can be latent, with consequences over time. And sometimes the long-term consequences from a virus can be MS or cancer."

Persistent vs. transient

Fred Hutch infectious disease expert Rachel Bender Ignacio, MD, MPH, medical director of Fred Hutch's COVID-19 Clinical Research Center, or CCRC, said most clinicians divvy viruses into two camps: persistent and transient.

Transient viruses, she said, are here and gone. Examples include influenza, cold viruses and hepatitis A. Persistent viruses hang around.

"A persistent virus either takes a very long time to clear or it doesn't clear at all," she said. "Herpes, chicken pox, EBV, HIV, HSV, Hepatitis B, roseola — once you have it, it never leaves."

Most coronaviruses, like the kind that drive the common cold, go into the transient box, she said. Same for rhinoviruses.

"These linger longer in immunocompromised patients — they can have a cold for months — but usually, they come and go," Bender Ignacio said.

Many experts assumed SARS-CoV-2 was in the transient box, she said, “because its brethren are in the transient box.”

It’s one reason why there was such initial confusion over long COVID, she said.

“People will test negative from their blood, from their nose, everywhere you look for evidence of ongoing protein production of the virus,” she said. “So, it becomes a question of whether there’s a sanctuary site, a place that the virus is hiding.”

So far, there’s minimal evidence of that, although clinical trials are looking at the phenomenon of viral persistence in long COVID.

“This is why a lot of doctors at the beginning thought people [with long COVID symptoms] didn’t really have anything going on,” Bender Ignacio said. “It’s why they were gaslit. Doctors considered it a transient infection."

Now, it’s apparent long COVID is a thing.

“We have clear evidence in the research setting that people don’t have a normal immune system after or during long COVID,” she said. “We may not have an answer as to how to help them, but the time is long over that people should be dismissive of long COVID.”

Pergam said people who were sickened by mosquito-borne West Nile virus in 1999 had similar symptoms as long COVID patients: fatigue, brain fog, inability to do normal activities.

“Lots of people were profoundly affected by West Nile and many of them weren’t that sick initially — just a fever,” he said. As with long COVID, Pergam said “many also felt left out by the medical community because there weren’t enough resources to support them.”

Bender Ignacio pointed to Lyme disease, a bacterial infection, as having similarly persistent symptoms despite the infection being long gone.

“Also, the Zika virus,” she said. “It should be a transient virus but people end up with inflammatory arthritis and fatigue. In the case of Zika, we think it’s a post-viral syndrome. We think that’s what happening with Lyme, too. The infection is gone but because of the molecular mimicry happening, it’s causing your body to attack the heart, the joints and other things.”

Is it the virus or is it the host? (that’s us)

One reason there’s such a variance in how people respond to infections is that immune systems are all different.

“Some people have robust immune responses,” Pergam said. “If somebody gets a cytokine storm from a COVID-19 infection and has to go to the ICU, some of that is related to the virus, but some of it is the patient’s own immune system. There are some host issues we don’t quite understand. There are just so many viruses and so many pathogens out there.”

And we all respond to them a little differently.

“If my wife and I develop a respiratory virus, she’ll recover with no complications and I’ll develop a chronic cough,” said Pergam, who is immunosuppressed himself after a kidney transplant and cancer treatment. “Is it related to a more severe infection? Being immunosuppressed? Some lower tract disease? There are variances in how people respond to different infections.”

Clinicians, in fact, often see widely different responses to both disease and treatments.

“Think about chemotherapy,” he said. “Many people lose their hair but some people lose it forever and we don’t know why. There’s always going to be nuances in a large genetic pool with people at each end of the spectrum that are not going to fit the mold.”

When it comes to viruses and human beings, we should all be prepared for three potential outcomes, he said.

“Sometimes the immune system gets rid of the virus,” he said. “Sometimes the virus wins. And sometimes our immune system is turned on in a way that isn’t valuable to us. This goes beyond respiratory viruses, too. There are people who never recover from their chemotherapy or who develop long-term consequences from taking certain antibiotics.”

Luckily, the majority of the time, our immune system is right on target, he said, “but occasionally, there’s an aberrant response because of the virus or our genetics.”

In the case of COVID-19, Bender Ignacio thinks it’s mainly the immune response.

“It’s probably how this virus interacts with our immune system,” she said. “In the vast majority of people, it comes and leaves.”

Still, some people develop long COVID and others can develop autoimmune conditions including thyroid disease, adrenal disease and inflammatory joint conditions. And scientists still don’t know if the virus *itself* is lingering or if it’s left a lingering “aftertaste” in our body’s systems.

“It’s not clear whether people with long COVID still have virus hiding in their body or if the virus is long gone but it’s tipped off an inflammatory cascade that doesn’t end when the virus goes away. Science is divided on this,” Bender Ignacio said. “We can’t rule out that there’s some persistent amount of virus in some people, but the vast majority who have long COVID, there isn’t virus. COVID-19 flipped the switch and left the building.”

Predicting who might “go long” is difficult, she said, although data have shown people with diabetes and HIV are more at risk for long COVID. Same for women.

“We think it might be related to different immunology,” she said. “Women tend more toward autoimmunity. There are a lot of unknowns but women have a ‘hotter’ immune response. Sometimes that can turn the forces against yourself. Your immune system starts recognizing your

own antigens and attacking yourself."

Those with compromised immunity are also more at risk — for infection itself and for prolonged sequalae of infection. That's because HIV and some other viral infections, including hepatitis C, cause what Bender Ignacio calls "immune exhaustion."

"Exhausted cells, they're not good at killing viruses," she said. "They're pooped out; their T cells have immune exhaustion. They've been running on a treadmill all day – they can't sprint, which is what they need to do when a new infection comes along."

Just like West Nile virus, though, long COVID doesn't just target those with tuckered-out T cells.

"We have plenty of scenarios of young healthy people with no comorbidities who have long COVID and people who are very medically complicated who don't," Bender Ignacio said.

In other words, long COVID continues to be consistently inconsistent.

Boonyaratanakornkit said some research has shown the more severe your symptoms, the more likely you'll have long COVID, but added that some patients with mild COVID-19 also develop long COVID symptoms like persistent fatigue and brain fog.

"It's not necessarily black and white," he said. "It's not just the sickest patients who develop it."

Prevention, research and understanding

Is there an upside to any of this? Pergam points to a flurry of interest in viral research and the body's immune system as a silver lining.

"Long COVID has provided us with a really robust opportunity to better understand this space," he said. "There's a lot more focus, energy and research dollars going toward studying it. There are no pattens yet; no clear distinctions about who develops it and who doesn't. But that's the purpose of doing studies. They can help us better understand these post-viral complications that occur in some people."

The National Institutes of Health's RECOVER Initiative (Researching COVID to Enhance Recovery) has a number of long COVID studies running; Fred Hutch's CCRC is also researching long COVID therapies.

In the meantime, Boonyaratanakornkit said the tendency of viruses to linger makes infection prevention and control even more crucial.

"We have to protect our cancer patients and our vulnerable populations from developing these complications," he said. "They can be debilitating and can incur high health care costs."

And prevention efforts can be relatively simple (and cheap!). Soap and water destroy most viruses, at least those with a lipid (fat) membrane like the coronaviruses, Hep B and C, HIV, HSV,

Ebola, Zika, dengue and others. They also kill bacteria that can wreak havoc with our gut and respiratory tracts.

And as we learned with COVID-19, social distancing, masking and of course, staying up to date on vaccines — if they are available — can keep us fairly safe from infection.

Currently, there are no vaccines for HIV or HSV, although Fred Hutch scientists have been working toward developing protection against these stubborn viruses for years. But there *are* effective vaccines for many viruses — HPV, polio, influenza, measles, mumps and more — and researchers at Fred Hutch are quite close to creating an Epstein-Barr virus vaccine. Two new RSV vaccines appear to be well on their way to FDA approval, as well.

COVID-19, of course, has incredibly effective vaccines, but uptake for them has waned.

“People have become much more educated about COVID-19 and vaccines, but there’s a subset of the population who are distrustful of science or of vaccines for different reasons,” Boonyaratanakornkit said.

“Not all viruses cause long-term complications and not all hosts get long-term complications. But with the right host, there’s a potential that even a rhinovirus could cause long term damage,” he said. “We have transplant patients with long-term lung damage that was potentially caused by a common cold or RSV. We don’t know.”

What we definitely do know is that viruses have been around millions of years longer than us. And over these millennia, some of them have developed a powerful one-two punch.

“Pathogens can modify our immune system so we attack ourselves,” Boonyaratanakornkit said. “It’s human nature to become complacent, but then we get reminded. Nature is reminding us now with this pandemic. We’re not quite sure yet what the specific mechanisms of long COVID are — that’s still to be determined. But it’s a good reminder to public health and funding authorities that viruses that don’t have a vaccine — like EBV — could be linked to long-term conditions. There’s significant room for improvement to develop vaccines and treatments for viruses that we take for granted.”

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Long COVID Updates
Where are we with long COVID these days?

- There are currently more than 300 clinical trials of therapeutic modalities for long COVID in the works, including 169 rehabilitation trials; 76 trials looking at pharmacological agents and 64 trials exploring traditional Chinese medicine, Ayurveda, homeopathic medications, naturopathic

medications, vitamins, dietary supplements and botanicals.

- There are also two promising prevention options. Paxlovid may prevent long COVID (as well as more severe COVID-19) if taken early. And a recent Lancet preprint shared results from a large randomized controlled trial of metformin, which reduced long COVID risk by 42% compared to placebo (and by 63% when taken within four days of symptoms).
- Cases of long COVID are also dwindling, as are cases of COVID-19 related multisystem inflammatory syndrome in children.
- Long COVID specialty clinics are now in every state save South Dakota and Kansas, including in Washington state through the UW's Post-COVID Rehabilitation Clinic.
- Some repurposed medications have shown promise as therapies, particularly the drug cocktail guanfacine plus N-acetylcysteine (NAC), prescribed off-label for brain fog, and low-dose naltrexone or LDN, an addiction drug, prescribed off-label for its anti-inflammatory properties.
- Research by the NIH's RECOVER Initiative (Researching COVID to Enhance Recovery) recently clustered long COVID symptoms into four categories — *Type 1:* Heart, kidney and circulatory problems; *Type 2:* Lung conditions, sleep disorders and anxiety; *Type 3:* Muscle pain, connective tissue disorders and nervous system disorders; and *Type 4:* Digestive and respiratory problems — which should help clinicians diagnose and potentially treat the condition.
- Science is also closing in on long COVID biomarkers. In a recent systematic review, researchers identified significant associations between 113 blood biomarkers and long COVID symptoms. Three were found to be a potential core set of long COVID biomarkers.
- Understanding and acceptance of long COVID — and perhaps other chronic conditions driven by viruses — has also improved. There's now an International Long COVID Awareness Day. And patients themselves have become vociferous advocates, many posting videos of their struggles; forming or joining support groups such as Body Politic, Survivor Corps, Long COVID Alliance, Long COVID Support, Facebook's Long COVID Support Group, or becoming involved in research through alliances like the Long COVID Research Initiative and/or the Patient-Led Research Collaborative.

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