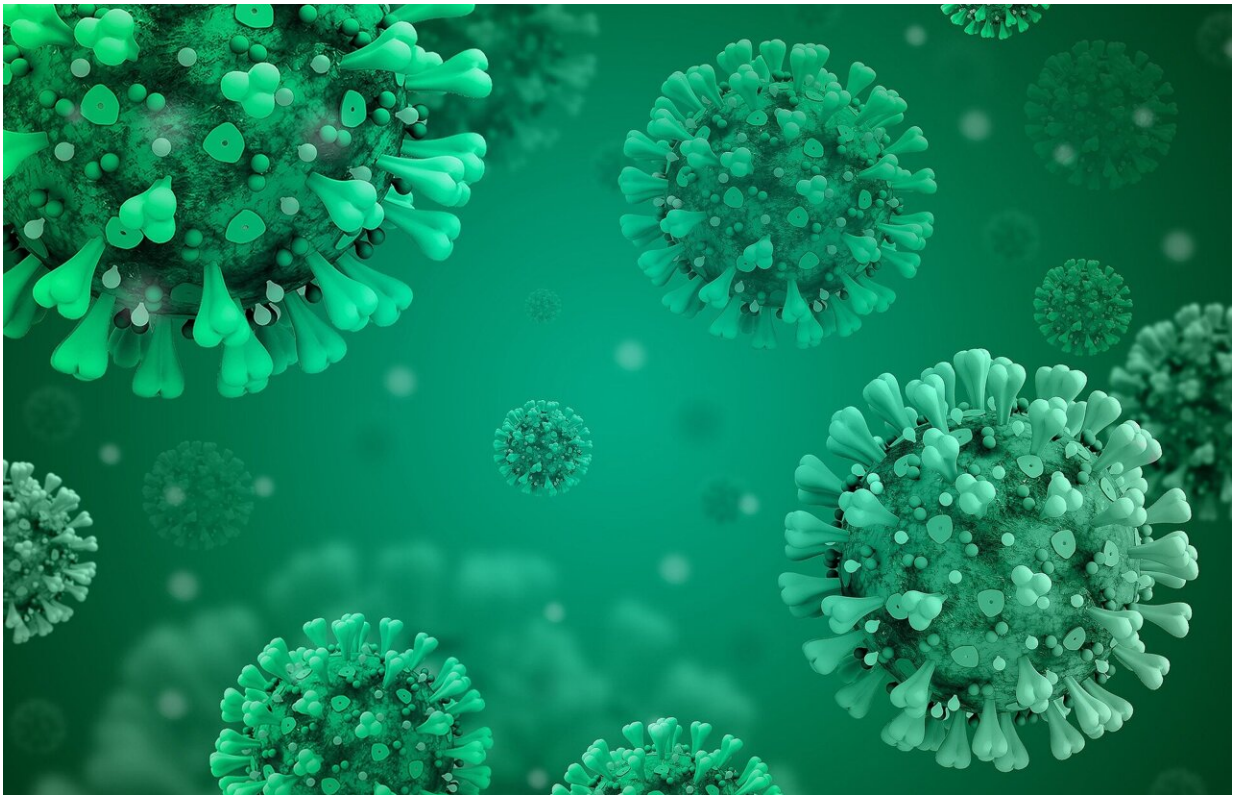


Experts discuss the knowns and unknowns of long COVID

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As the vast majority of the world's population continues to encounter SARS-CoV-2 virus and become infected, one question looms ever larger: What will be the long-term physiological repercussions of having had COVID?

Experts from the Harvard Medical School-led Massachusetts Consortium on Pathogen Readiness discuss the emerging science, latest knowledge, and critical unknowns of the novel syndrome known as long COVID:

- Nahid Bhadelia, founding director, Boston University Center for Emerging Infectious Diseases Policy and Research; associate professor of infectious diseases, Boston University School of Medicine; visiting fellow, the White House Office of Science & Technology Policy; long COVID research group co-lead for MassCPR
- Bruce Levy, HMS Parker B. Francis Professor of Medicine and division chief of pulmonary and [critical care medicine](#) at Brigham and Women's Hospital; long COVID research group co-lead for MassCPR
- Linda Sprague Martinez, associate professor, Boston University School of Social Work; co-director, Community Engagement Program, BU Clinical & Translational Science Institute; long COVID research group health disparities lead for MassCPR
- Jake Lemieux, instructor in medicine, Harvard Medical School, infectious disease specialist at Mass General; viral variants program co-lead for MassCPR

Harvard Medicine News: Set the stage for us and give us the big-picture view on long COVID.

Bhadelia: First, it is important to keep in mind that aside from long COVID, there are many other post-acute infectious syndromes, so the notion that infections can cause long-term post-acute symptoms is not new.

Some of these syndromes develop after [viral infections](#) like Ebola,

Epstein-Barr, polio, dengue, H1N1 flu, and others, while others develop after infection with a bacterial pathogen. We do not understand many of these syndromes, and their scope is not well defined. For many of these, our understanding is limited by research capacity and clinical infrastructure and our ability to capture good, quality data in order to understand the biological phenomena that underpin them.

Levy: Long COVID is such a novel entity that even its definitions vary. The World Health Organization and the Centers for Disease Control and Prevention define it slightly differently, but, broadly speaking, long COVID involves a constellation of symptoms that develop in the aftermath of acute infection—hence the term post-acute sequelae of SARS-CoV-2 infection, or PASC. The WHO says long COVID starts three months from the onset of COVID with symptoms, that these symptoms last at least two months and are not explained by alternative diagnoses. The CDC starts the clock earlier, at four weeks after original infection. Important to note, as of July 1, 2021, post-COVID conditions can be considered a disability under the Americans with Disabilities Act.

HMNews: What is the current profile of long COVID in terms of prevalence and symptoms?

Levy: Keeping in mind that our knowledge is evolving, and this is a moving target, here's what we know so far. Overall, the current CDC estimate is that one in five adults over the age of 18 may have a condition related to COVID, but the estimate is uncertain. According to the CDC, 13 percent of people diagnosed with COVID meet the definition of long COVID one month after infection, and this number drops to 2.5 percent three months after infection.

Among those hospitalized with COVID, more than 30 percent have symptoms suggestive of long COVID six months after infection.

Hospitalization does appear to drive risk for long COVID. It appears the condition is more common in women, with at least 60 percent of long COVID diagnoses occurring among women, but this could also be a factor of who is more likely to seek care.

Fatigue is the most prevalent symptom, with two-thirds of patients reporting it as part of their symptom constellation. Yet, there is a very wide variety of symptoms associated with this condition—neurologic, neurocognitive, respiratory, sleep disturbances, [mental health](#), cardiovascular, rheumatologic, digestive, and more. The long-term effect of long COVID remains to be seen over time. Long-term, will long COVID lead to more vascular illness, atherosclerosis, heart failure? These are all questions that remain to be answered.

HMNews: How much do we know about what drives the development of long COVID? What is known and unknown about its pathophysiology?

Bhadelia: One of the overarching questions in this unfolding mystery is whether these symptoms and conditions are truly caused by COVID itself or are being picked up more just because patients are coming to seek care who weren't before their SARS-CoV-2 diagnoses, and their preexisting conditions are coming to attention. It's very difficult to tease apart. If we don't know biological mechanisms are causing people to be sick, then it's hard to tease apart what's attributable to the virus itself versus other factors.

Another challenge in gleaning answers is the heterogenous nature of studies of long COVID, how differently they are designed, which makes it tricky to compare patient populations across studies. Another complicating factor is that there are many different phenotypes of long COVID, meaning that some people will develop more neurocognitive

symptoms, while others more pulmonary symptoms. Underpinning these phenotypes are potential clues, none of which are slam dunk, but just different angles through which researchers are approaching figuring out the pathophysiology of long COVID.

Some of the hypotheses about what drives long COVID include the presence of persistent reservoirs of SARS-CoV-2 in the body—we've seen this in other infections: reactivation of other dormant viruses such as Epstein-Barr; the presence of predisposing conditions such as diabetes and obesity; the development of a maladaptive autoimmune response against the body's own tissues; chronic inflammation that fails to go away after the infection; blood vessel inflammation and damage; and direct organ injury from the initial severe disease.

In terms of who's at risk: So far, according to CDC data, it looks like the highest risk groups for developing long COVID include those who are not vaccinated, people with medical comorbidities, those with severe initial infections, those who developed multi-system inflammatory syndrome, either adult or pediatric. Ultimately, we want to know enough to create a uniform understanding of what long COVID is by taking away all the confounding factors. But it is important to note that regardless of the cause, there are many people who are suffering and need care, and we need to address that as a health care system.

HMNews: In addition to the science and the research that are so fundamental to understanding long COVID, what are some of the broader health care, policy, and societal implications of long COVID?

Sprague Martinez: Health inequities were pervasive pre-COVID and amplified with the pandemic. Some of the highest infection rates in Massachusetts occurred among [immigrant communities](#), working class

residents, and families of color.

As in COVID, health equity in long COVID is of paramount concern. People of color will likely be disproportionately impacted by long COVID. Long COVID has the potential to further widen existing gaps in health and getting ahead of it is critical.

The MassCPR long COVID research group includes a health equity core of investigators that span disciplines and are embedded at hospitals that conduct clinical trials as part of the NIH Recover Initiative. Our goal is to define the impact of long COVID on diverse communities in Massachusetts and to identify barriers to proper diagnosis and care of long COVID for those communities. We want to increase both awareness of and access to long COVID treatment both among those communities and the primary care providers serving them.

We are also interested in influencing relevant policies at the local, state, and national levels. Right now, we are focused on Black and Latinx communities, but plan to expand and engage other people of color and other marginalized groups in the state. Some of the key elements in advancing health equity will involve direct community engagement to increase diversity and representation in clinical trials that study long COVID and support of community health centers and community health workers. Other elements include engaging the primary care providers to ensure they are getting the latest research and engaging their patients in meaningful conversations that go beyond symptoms to understand the social factors impacting their health and referrals to job retraining programs for patients who cannot continue to do their work because of long COVID symptoms.

Also important will be policies related to eviction moratoriums, many of which have sunset, rental assistance, unemployment insurance, and more. Factors that lead and sustain inequities are caused by racialized policies

that create inequitable living conditions. Tackling inequity will require an understanding of the structural determinants of health.

HMNews: Where are we on the treatment front for long COVID?

Lemieux: First a word on prevention and minimizing risk: Early data suggest that whatever we can do to limit the severity of acute disease will pay dividends on the other side in limiting the incidence of long COVID. That still needs to be explored further, and some therapies will be better than others. We have seen from just about every angle that vaccination limits the severity of disease, and since the risk of long COVID is linked to the severity of acute infection, we believe that vaccination will be partly, but not completely, protective.

Once a patient develops long COVID, that's a very different story. Right now, we are in a situation of having to treat and manage a complicated clinical syndrome that affects multiple systems in different ways. Every patient is different, every patient's symptoms will be different, and potentially the treatment of every patient will be different. That's hard on so many levels—it's hard to establish which treatments are best for which patients and, of course, it's hard for patients.

We are going to be in a period—an unenviable position, frankly—of having to feel our way, of having to treat patients symptomatically and having to conduct [clinical trials](#) and investigations to get at therapies that are safe and effective and reverse the mechanisms of disease to the extent that this is possible, while recognizing we don't yet know the mechanisms of disease for many manifestations of long COVID.

Sprague Martinez: That question of diagnosis and treatment is even more complicated among marginalized communities. For many people it's a

privilege to take the day off from work and to seek care and treatment, especially in the context of employment instability which continues to impact industries such as service, which was very hard hit during the pandemic.

Then there's the question of awareness. Have people heard of Paxlovid? Are they aware it's out there? I can say that many people are not aware. How do we get the word out about it? Then there's testing. Access to at-home testing is not equitable. Many people may not even know they have COVID. We can't assume access to health information or care.

HMNews: Where does the pandemic stand in Massachusetts?

Lemieux: Things are getting better, but transmission of SARS-CoV-2 is still quite high if you look at both at the percentage of positivity and at the absolute case counts. The wastewater RNA levels are high. Although we are probably past the peak of the BA.2.12.1 wave, we are starting to see BA.4 and BA.5 variants starting to show up in a few percentage points of our sequenced cases here in the region. They are more transmissible and likely to cause some surge in cases. So, while we are dealing with the effects of post-acute COVID, we are also likely going to be seeing a lot of ongoing acute COVID into the summer, and there may be a resurgence in the fall.

Provided by Harvard Medical School

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