

Could long COVID be the next wave of the crisis?

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Credit: Pixabay

In late April 2020 Dr. Freya Jephcott developed a persistently high fever. When she went to hospital three weeks later, she tested negative for COVID-19. A scan (an extra precaution, given her risky day-job) revealed inflammation in her body but couldn't point to anything concrete. After two months of fevers she developed painfully swollen ribs and stabbing chest pains. Again, doctors couldn't find a cause.

Things settled but then months later she started experiencing a new range of symptoms: loss of balance, poor coordination, and constant tinnitus—alongside constant fatigue and breathlessness.

I first interviewed Jephcott—a researcher in the University's Department of Veterinary Medicine—last April for our "Tackling COVID-19" series. She is well aware of the devastation an infectious disease can cause in unprepared populations, having worked with Médecins Sans Frontières on outbreaks in some of the poorest regions of the world.

Jephcott, 33, has managed to emerge unscathed from developing countries fighting outbreaks of [infectious diseases](#) like Ebola and TB. But—despite the negative test result—she believes she contracted the [coronavirus](#) in Cambridge. When we meet online in December 2020 she looks exhausted, and apologizes in advance in case her words don't come out in the right order.

"The last week has been hellish," she says. "I don't know if depressive symptoms are part of long COVID or if it's just how long it's gone on. Essentially I get sick, I start to get better, I think I'm over it and then I'll get hit by another wave of symptoms—sometimes quite distinct from what I had before."

"I can't read any more—my language ability just disappeared overnight," she says. "I've started kitchen fires because I keep forgetting things when I'm trying to cook. During the last flare-up I managed to hit my head on a door-frame courtesy of the poor coordination, and ended up getting a handful of stiches. This illness is completely debilitating. It's so disheartening to see people, including doctors, on social media or in the press suggesting it's psychosomatic or simply the stress of lockdown."

Jephcott isn't just frustrated by not knowing when all this will end. She's frustrated because doctors don't know what's happening to her, and they

don't know how to treat her. And she's not alone. Oona Lagercrantz, 19, an undergraduate student at the University, has had suspected long COVID since March last year. As she describes her symptoms, which include a tight chest, fatigue, headaches, muscle twitches and a racing heart, it is again the sense of not-knowing that seems the most difficult aspect for her to deal with.

"When it started in spring I was scared—I didn't know what was happening to me," says Lagercrantz. "Now I'm more used to it, and my GP thinks it's long COVID, although my antibody test was negative so the official diagnosis is 'post-viral fatigue after a viral-infection.'" No-one can tell me what to do to get better. I don't know if I should try to exercise, or if I should rest. It's a mental challenge."

Is it real?

One of the problems facing GPs is that there's no test available to diagnose long COVID. Many people who got ill early in the pandemic could not access a COVID-19 test, and testing them now gives negative results. It's the same with the antibody test—too much time has elapsed since the suspected time of infection. Despite this, a [Facebook support group for long COVID sufferers](#) in the UK currently has around 33,000 members. Is long COVID a real condition?

"A lot of clinicians are skeptical of long COVID in people who haven't had severe COVID, because of the experience with Chronic Fatigue Syndrome (CFS)," says Dr. Nyarie Sithole, an infectious disease consultant and researcher in the University's Department of Medicine. There has been much disagreement in the medical community over CFS—from its causes, diagnosis and treatment, to whether it's even real.

"Many patients who suspect they have long COVID say they feel dismissed by their GPs—some are even being told it's psychosomatic,"

says Sithole, "but from my experience, a good number of them really did have COVID."

In May 2020, Sithole set up a clinic in the Department of Infectious Diseases at Addenbrooke's Hospital to assess patients, referred by their GPs, who suspected they had had COVID-19 and were still experiencing ongoing symptoms.

From blood samples, Sithole looks at whether patients' T-cells—essential cells of the immune system—recognize and react against any elements of the SARS-CoV-2 virus. If the T-cells respond well, patients are highly likely to have been infected with COVID despite having no remaining trace of the virus in their body and a negative antibody test. It's a much more complex procedure than the other COVID-19 tests, but it works.

"By looking at the T-cell immune response, in combination with clinical symptoms and their timing, we can retrospectively make a diagnosis of COVID-19 with a good degree of confidence," says Sithole. And his patients thank him. "Even though we don't have any drugs to treat them yet, it's making a difference to patients to have this diagnosis rather than not know what's happening. I've found a lot of people feel great relief that they're finally being listened to."

It is becoming clear that COVID-19 doesn't just affect the lungs and respiratory system, although this has necessarily been the focus of clinicians fighting to keep severely affected patients alive. Not all patients develop long COVID: some make a good recovery, even from severe illness. But others don't.

COVID-19: A complicated disease

Professor John Bradley, an Honorary Professor at the University of Cambridge, set up the COVID-19 cohort of the National Institute for

Health Research (NIHR) BioResource at Addenbrooke's Hospital early in the pandemic, to enable studies involving large numbers of people. So far, detailed information has been collected from over 6,000 people who want to be involved in COVID research, including 500 who have tested positive for the disease—many of whom are healthcare workers who were asymptomatic but tested positive in routine screening.

"We need large-scale studies to be able to make reliable conclusions," says Bradley. "We're pre-screening people with a questionnaire before seeing them in clinic, so they can be triaged to the right clinicians according to their symptoms. We're finding a wide range of longer-term problems including disorders of mood and brain function, respiratory symptoms, joint problems, fatigue, and issues relating to smell and taste." Depending on their symptoms, patients can be recruited to various research studies for more detailed assessment.

Scrutinizing the immune system

Professor Ken Smith, Head of the Department of Medicine, has just completed the first phase of what he believes to be the largest detailed study in the world of the immune response in COVID-19 patients over three months from the time of their initial diagnosis, monitoring 200 patients.

"The number of people involved in the COVID-19 BioResource has enabled Ken's study to look right across the spectrum, from those who have had the disease with no symptoms at all, to those who were on ventilators in intensive care," says Bradley.

Smith's results indicate that almost all patients who experienced the disease, at all levels of severity, had cleared the coronavirus from their nasopharynx (the upper part of the throat behind the nose) by three weeks after infection. Symptoms after this time appear to be driven by

persistent inflammation.

When our body is infected by a virus, our immune system responds by triggering inflammation to try and kill it. A certain level of inflammation is needed for the body to protect itself. But for some reason, in some COVID-19 patients the inflammation doesn't go away. Smith says that the nature of the inflammation persisting in these patients appears to change over time, and may be related to the long-term features of the disease. Unraveling these details may shed light on why the virus affects people in such different ways.

The term 'long COVID' does not sit well with Smith. He says it's "spectacularly imprecise," as it refers to many quite distinct clinical problems that can follow COVID-19. These range from chronic lung or neurological problems that persist in patients who have required prolonged intensive care for COVID-19, though to persistent fatigue—which may sometimes be attributed to COVID-19 even without evidence of infection. He thinks the latter is likely to be related to other 'post-viral' chronic fatigue syndromes.

"These very different problems need different solutions, and lumping them together under the banner of 'long COVID' may make that more difficult to achieve," says Smith. "Our research needs to focus on well-defined clinical problems that follow COVID-19 if we are to find solutions to help patients."

Scrutinizing the brain

Elsewhere on the Cambridge Biomedical Campus, Professor David Menon is working with colleagues in the NeuroCOVID group to undertake brain imaging and other investigations in participants from the COVID-19 BioResource. He is trying to pinpoint 'modifiable mechanisms' underlying long COVID: changes in the body, after the

acute phase of the disease has passed, that can be targeted with treatments. His focus is on patients who have suffered serious COVID-19 and then developed long-term complications.

"We're running a follow-up clinic for COVID patients who have been in intensive care. After six months, about 20% of them have depression or anxiety, and 30% have problems with memory and concentration. A lot have severe fatigue," he says. "While these symptoms are expected in people who have had an episode of critical illness, they seem a lot more serious in COVID patients."

Taking advantage of the Wolfson Brain Imaging Centre's position right next to Addenbrooke's Intensive Care Unit (ICU), Menon's team in the Department of Medicine has been able to scan the brains of even the sickest patients from the ICU to look for structural changes. They are also testing these patients' cognitive abilities six months after their acute illness. Early results indicate that [brain function](#) is not as good as in healthy people of the same age.

Accumulating information, raising awareness

Bradley is coordinating with a range of other long-COVID studies across England, building on the value of the growing COVID-19 BioResource. Participants are invited to join a national post-hospitalization study of the long-term effects of COVID-19 (called PHOSP-COVID) led by the University of Leicester, which aims to recruit 10,000 patients. And many will be involved in a national study of the long-term neurological and psychological effects of COVID-19 (called COVID-CNS) led by the University of Liverpool and King's College London—Menon is one of Cambridge's lead investigators.

"Just why long COVID symptoms occur after people have apparently cleared the virus from their system is unknown," says Bradley. "In

chronic fatigue syndrome we don't know the cause, although it's thought that infection can be a trigger. In long COVID we know people have had a specific infection."

Professor Clare Bryant, an expert in immunity in the Departments of Medicine and Veterinary Medicine, spoke about long COVID on The Naked Scientists podcast in April 2020, when most people didn't believe it existed. Now it is accepted as a disease, she says, the next challenge is to develop treatments.

"Over the next year we won't just be dealing with consequences of severe COVID, we'll be dealing with the consequences of long COVID—that's the real second wave of this crisis," says Bryant.

"If we don't block the spread of the coronavirus by vaccination, there's the potential for long COVID to go on for years."

Bryant is passionate about getting long COVID on the agenda, and raising awareness that it affects younger people too—including children. Along with Professor David Rowitch in the University's Department of Pediatrics, she is on an Expert Advisory Group for COVID-19 in children with the charity Action Medical Research.

As with everything about this new virus, there is still a lot to learn—and the longest anyone has endured long COVID so far is ten months, making longer-term outcomes very difficult to predict. Jephcott was eventually diagnosed with long-COVID in September, and admitted to University College London Hospital's long COVID clinic for treatment. Lagercrantz received the same diagnosis in January 2021, and is recovering—slowly.

"I think everyone has misunderstood how disabling long COVID is," says Jephcott, adding, "I will definitely get the vaccine—it's not worth getting

COVID a second time."

All the researchers I spoke to agree that long COVID is going to be a major problem. But they are also hopeful that through science they will come to understand it, and find ways to treat it. "If last year's search for a vaccine has proved one thing," says Bryant, "it's that when the scientific community is called on for help, it can deliver."

Provided by University of Cambridge

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