Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
The argument for naturally obtained herd immunity as a solution to the coronavirus pandemic has made a return in recent weeks. But letting the virus spread among younger people, who are less likely to die from covid-19, could lead to devastating consequences. Estimates suggest that there could already be millions of people around the world living with “long covid” – what appears to be a debilitating syndrome that follows a coronavirus infection.

As personal stories of long-term problems accumulate, researchers and health bodies are learning more about what might cause these long-lasting symptoms, and how best to treat them.

**Dismissed by doctors**

“I’m not sure how I caught the virus,” says Heather-Elizabeth Brown, a 36-year-old corporate trainer in Michigan who has severe symptoms six months after her initial diagnosis. “I was social distancing, staying out of crowds and wearing a mask.”

Still, Brown became unwell at the start of April. After initially being dismissed by doctors, and testing negative for the coronavirus twice, Brown was admitted to hospital in mid-April, when she finally tested positive.

By then, she was feverish and struggling to breathe, and chest X-rays revealed signs of pneumonia. Within a couple of days of her hospitalisation, Brown was put on a ventilator and placed in a medically induced coma for a month, she says. During that time, she developed blood clots in her legs and her brain. “It’s a miracle I survived,” she says. She isn’t out of the woods yet.

There isn’t yet an official clinical definition of long covid, but a growing number of people are reporting symptoms that can last for months. Prolonged chest pains, shortness of breath and fatigue are often mentioned. Some people experience lasting damage to their heart and lungs, and blood clots that can cause painful swelling or strokes.

“Everyone has fatigue and headache – that’s virtually universal,” says Tim Spector at King’s College London.

**“People are getting rashes, fevers, hair loss, pins and needles, muscle pains, diarrhoea”**

He has been analysing the symptoms reported through the Covid Symptom Study app, which has more than 4 million users – including people who are healthy and have yet to test positive for covid-19 – based in the UK, US and Sweden.

Shortness of breath and loss of smell and taste are also among the most commonly seen long-term symptoms among the app users, although many others have been reported. “People are getting rashes, fevers, hair loss, pins and needles, muscle pains, diarrhoea... everything on our list,” says Spector.

Brown still gets debilitating fatigue and shortness of breath, struggling to talk for more than 20 minutes or walk up a flight of stairs. She has also started to experience “brain fog”.

“I’ve always had a phenomenal memory, but sometimes I forget things... there’s a certain word that I just can’t seem to find,” she says. “It’s really frustrating.”

She has been hospitalised twice for complications related to her blood clots. She has had physical...
and speech therapy and mental-health support, and says she is taking 15 different medications to manage her covid-19 symptoms and their complications.

The symptoms can temporarily resolve before making a return, and can develop in people whose initial disease was mild, as well as in people recovering from more severe cases of covid-19. Because there is such a wide range of symptoms, it isn’t yet clear if long covid is a single syndrome or many conditions (see “Could long covid be several syndromes?”, page 12).

A couple of recent reports by the US Centers for Disease Control and Prevention (CDC) suggest that some adults develop a multisystem inflammatory syndrome, for example. This rare outcome of covid-19 has already been observed in children. Not all of the adults who develop this syndrome had pre-existing health conditions, and many go on to test negative for covid-19 before they develop symptoms.

“There are the symptoms of not feeling well and not being able to do things, and then there’s the organ damage... a scan shows cardiac inflammation or lung damage, for example,” says Nisreen Alwan at the University of Southampton, UK, who still has symptoms herself months after the onset of covid-19. “Sometimes these are happening in the same people, and sometimes they’re not. There’s a wide range.”

Betty Raman at the University of Oxford and her colleagues have examined 58 people with moderate or severe covid-19. MRI scans revealed tissue abnormalities in the lungs of 60 per cent of these people, in the kidneys of 29 per cent, in the hearts of 26 per cent and in the livers of 10 per cent. Persistent breathlessness was a feature for 64 per cent of people, and 55 per cent had significant fatigue (medRxiv, doi.org/ffjz).

**Millions of cases**

Although we don’t yet know how many people are affected by long covid, a handful of studies suggest that it could be common among those who contract covid-19.

One study in Italy found that, of 143 people who had been hospitalised with covid-19, only 12 per cent reported no symptoms 60 days after the onset of the disease. More than half of the participants were still experiencing fatigue at that point, and many reported shortness of breath and chest pain. (JAMA, doi.org/gg4hvp).

A similar study in France also found that most people who had been hospitalised with covid-19 still felt effects months later. Some 110 days after the onset of their first symptoms, 55 per cent of a group of 120 individuals had fatigue. Around a third were also reporting memory loss (Journal of Infection, doi.org/ghdhzf).

These figures align with other post-viral syndromes. About 80 per cent of people who recover from Ebola are left with problems a year later, for example, says Janet Scott at the University of Glasgow, UK. “They have muscle aches and pains, ocular problems, headaches and a long list of other symptoms.”

One long-term study of people who were hospitalised with SARS following the 2003 outbreak found that about 40 per cent said they still experienced chronic fatigue almost four years after hospital discharge (JAMA Internal Medicine, doi.org/c7xcvp).

Most studies conducted so far have focused on people who were hospitalised with covid-19, largely because these individuals would have had a test result confirming they had the virus, and would be easier to recruit for research. As a result, we still don’t know much about how long covid might develop after a milder infection.

A July report by the CDC found that about one-fifth of those who test positive for the coronavirus will have symptoms two to three weeks later. Spector and his colleagues running the Covid Symptom Study app have been looking at longer-term outcomes.

They have found about 4000 people who have logged symptoms for more than a month – some of whom have had symptoms for two or three months so far. These individuals were healthy when they first started using the app, and all went on to develop symptoms and get a positive test result for the coronavirus, says Spector. Not all of them received hospital treatment.

“That has given us these rough estimates that 1 in 10 [still have symptoms] at one month,” says Spector. Information collected from app users also suggests that 1 in 20 people will have symptoms two months after the onset of illness, and 1 in 50 will have symptoms three months later.

The UK government reports that, as of 25 October, 873,800 had tested positive for the coronavirus, and 58,164 had died. It is possible that at least 75,000 people who contracted covid-19 will still have symptoms a month later, and more than 14,000 will have symptoms three months after their initial infection in the UK alone. Of the 37.8 million confirmed global cases, we might expect at least 3.8 million people to have experienced long covid symptoms already.
It is impossible to know for sure, because the Covid Symptom Study app data comes from people in countries that weren’t testing all those with symptoms during the first wave of infections in March. There is no way of knowing how many people who weren’t hospitalised had the virus. And people were reporting their symptoms through lockdown and furlough, both of which can exacerbate health issues, says Louise Sigfrid at the University of Oxford.

There are other issues with the app data, too. Users are asked to enter information every day about how they are feeling, and select items from a drop-down menu of 20 symptoms. Spector says most users don’t do this daily. Some with long covid say they get bored of listing the same symptoms for weeks or months. Others say they don’t bother typing in their symptoms if they aren’t already included on the app’s list. Spector’s team is currently working to extend the list.

We don’t know whether people who originally had asymptomatic infections might later develop lasting symptoms, but at least one report suggests that this might happen. When Valentina Puntmann at University Hospital Frankfurt in Germany and her colleagues assessed heart inflammation in 100 people who had recently recovered from acute covid-19, they found that 78 individuals showed signs of heart inflammation and damage, including those who had only mild symptoms (JAMA Cardiology, doi.org/gg8n87).

An MRI scan of one man’s heart, for example, showed “severe abnormalities” 67 days after his official diagnosis, despite the fact that he had only experienced a loss of smell and taste and a mild fever for two days.

Who is at risk?

“We’re not sure what the longer-term implications of that inflammation will be,” says Jennifer Ross at the University of Washington in Seattle.

We also don’t yet know who is at risk of developing long covid. The studies that have focused on people who were hospitalised with covid-19 suggest that lasting symptoms are more common in those who had a more severe initial illness, particularly those who required treatment in an intensive care unit.

But there are many anecdotal reports of people who recovered well from severe disease, and others who developed lasting illness after much milder cases.

“Whether you get long covid may be due to pre-existing conditions, lifestyle influences or genetics”

“There’s a lot of individual variation,” says Louise Wain at the University of Leicester, UK, who is co-leading a study into the long-term health outcomes of people hospitalised with covid-19. “It could be due to pre-existing conditions they had or the influence of their lifestyle, it could be related to the treatment they had, or it could be related to their genetics,” she says.

Information from the Covid Symptom Study app suggests that long covid can occur in anyone over the age of 18, says Spector. His team has noticed that lasting symptoms seem to be more likely to affect older individuals, but long covid can also affect young, healthy people.

“We see a lot of reports of people who used to be very physically active reporting it,” says Alwan. We don’t yet know if there is a reason for this, or whether young people who are less likely to develop severe cases of acute covid-19 are more prone to long covid. “It could be that older people are more likely to have died,” says Scott. It is also possible that younger,
healthier people notice their symptoms more because “they really can’t do any of the stuff they used to be able to do”, says Alwan. “But we still really don’t know at all who’s vulnerable.”

Inadvertent damage

The causes of long covid remain a mystery, but several hypotheses are being put to the test. “I think of it in two ways,” says Wain. “There’s the direct damage that the virus can do, and then there’s the inadvertent damage that the body can do when it responds to the virus,” she says. “It’s possibly a combination of those two.”

Prolonged shortness of breath and chest pains could be the result of lung or heart damage, for example.

A man who recovered from covid-19 in physical therapy in Spain

It is possible that the virus could hide away in some body tissues, causing a “grumbling” immune reaction that continually reactivates, says Spector. “Some parts of the body are protected from most of our immune system,” says Scott. The central nervous system, eyes and prostate could all provide a safe haven for the virus to survive in the body, for example.

Scott, Sigfrid and their colleagues are one of several teams that are starting to look for signs of this immune response in blood samples taken from people who are recovering from covid-19. So far, their ISARIC study has recruited more than 100,000 participants from 42 countries. The team will look for immune cells, antibodies and other markers of inflammation, and see how their levels change over time. Sigfrid hopes that blood tests for such things might eventually help identify people who are at risk of developing long covid.

In the meantime, there is plenty that can be done to support people who already have long covid. For a start, doctors and health professionals need to recognise that the condition is real, and not just “in a person’s head”, which is a common complaint from people who have long covid, says Alwan.

To that end, England’s National Institute of Health and Care Excellence, along with a Scottish health body and a group that represents family doctors, is working on a definition of long covid and guidelines on how to identify and treat the various symptoms. “I hope they come up with something broad,” says Alwan. “You need a case definition for it to be measured and for it to be recognised, but it needs to be able to evolve with time. It’s really tricky.”

The definition shouldn’t be based on having had a positive covid-19 test result, says Alwan. Many people who have long covid won’t have been tested during their acute coronavirus infection, or may have received an incorrect result. And antibody tests don’t definitively clarify whether a person has had the coronavirus in the past.

The National Health Service in England has also launched a website offering advice on how to manage various symptoms, and plans to set up treatment centres that address the multiple symptoms of long covid.

At the same time, employers need to be made aware of the impact of long covid, says Sigfrid. Brown feels lucky that her employer was understanding and supportive. As a corporate trainer, much of her work involves talking, which she still finds difficult to do for an extended period of time. Her employer has enabled her to adapt her training to make it easier to carry on doing, and understands when she needs time to rest.

Alwan has found that getting enough rest has helped her. “I’ve learned not to push myself as hard as I used to,” she says.

Ross hopes that our growing understanding of long covid will put another nail in the coffin of the idea that infection-induced herd immunity is the way out of this pandemic. “There’s potential for harm even in folks who don’t have an initially severe infection,” she says. “It’s a cautionary message to all of us to do what we can to prevent infection.”

1 in 3
Proportion of people hospitalised with covid-19 in one study who reported memory loss 110 days after first onset of symptoms

3.8m
People who may already have had symptoms of long covid