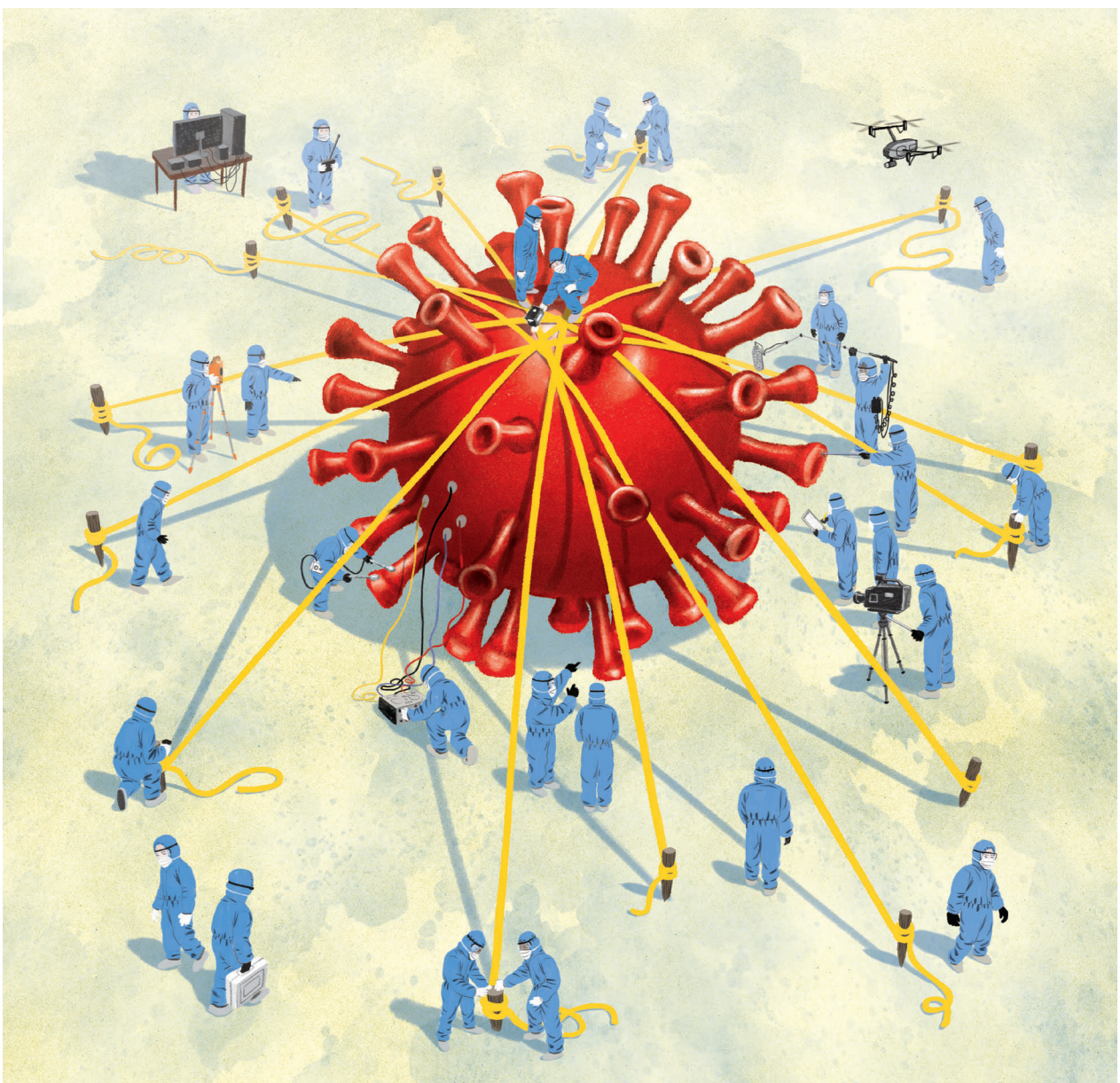
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Taking down COVID-19

Thousands of people are searching for coronavirus treatments. Which are most promising and when will we have them, asks **Carrie Arnold**



JASON RAISH

EYES tight with worry above white surgical masks, more than 300 people slowly boarded the waiting 747 cargo planes at Tokyo's Haneda airport. It was 17 February, and after weeks in quarantine aboard the Diamond Princess anchored off the coast of Japan, they were heading home to the US. Fourteen had tested positive for covid-19.

On arrival, one of the 14 was given an experimental antiviral drug called remdesivir, as part of a global clinical trial. By the time this article went to press, hundreds of covid-19 patients around the world had taken the drug as part of ongoing trials.

Remdesivir was first developed in the mid-2010s to fight Ebola. Although it was found to be ineffective against that virus, it showed promise in early trials against coronaviruses such as the one that causes SARS. That's why many hope it will work against the new coronavirus, SARS-CoV-2. The demand is already so high that its manufacturer, Gilead Sciences, recently had to stop providing access for people outside of trials seeking the drug under compassionate-use schemes for untested medicines.

But we still don't know if remdesivir, or any other drug, works against the new coronavirus. And while 80 per cent of people who catch covid-19 don't require hospital treatment, those who do get admitted desperately need effective drugs, which may still be several months away.

The good news is, we know where to look, and which strategies are most likely to work. At least 60 different compounds are now being investigated, including existing drugs and therapies being designed from scratch, and in record time.

To figure out how to help people fight off covid-19, we first need to understand how it causes harm. Since the covid-19 virus grabbed the world's attention in late December, doctors and researchers have been able to pin down quite a lot about what it does to our bodies. When the coronavirus infects someone, it enters their cells, hijacks their protein-making machinery and begins making copies of itself. These viruses enter neighbouring cells, and the cycle repeats itself. This viral invasion doesn't go unnoticed. Dying cells display fragments of the virus to alert the immune system that a pathogen is present.

Once patrolling immune cells recognise the attack, they sound the alarm by secreting chemicals called cytokines to recruit more disease-fighting cells. From this point, it is a race between the virus and the immune system to see which can respond more quickly. According to a US Centers for Disease Control and Prevention analysis of Chinese reports, in four out of five people, the immune system triumphs easily. These people either have no symptoms or experience something akin to cold or flu. The others, though, become more severely ill, often developing life-threatening pneumonia and struggling to breathe.

> **"At least 60 old and new drugs are being investigated"**

One potential reason for such severe illness is the collateral damage caused by the immune system's attempts to fight off the virus. To prevent it from spreading, the immune system tells infected cells to commit suicide. It is effective, but comes at a high cost due to the large number of dead and dying cells. And as levels of cytokines surge, they can trigger excess inflammation. In extreme cases, this causes a cytokine storm, in which fluids and vast numbers of immune cells can flood the lungs. "It's a severe over-activation of the immune system, which has been finely tuned to know when to switch off," says Jessica Manson, a rheumatologist at University College London Hospital. "The very inflammatory cytokines needed to fight infection start to cause severe damage to the host."

When the immune system spins out of control, that damage can lead to a deadly condition known as acute respiratory distress syndrome as well as sepsis, which can cause multi-organ failure. Millions of years of evolution have created a complicated feedback system that lets the immune system balance its own brakes and accelerator. In a cytokine storm, the immune system has put the pedal to the metal and the brakes no longer work.

Three-pronged attack

For now, the treatments we have for people who get covid-19 and need hospital care are supportive therapies: fluids, painkillers and fever reducers, and antibiotics to treat opportunistic bacterial infections. Those with seriously impaired lung function will rely on ventilators to breathe for them. All of these measures buy time to keep a person alive until their immune system can fight off the virus. But if a cytokine storm becomes part of the problem, doctors have few good options.

To give our bodies a better chance, drug researchers are pursuing three main strategies. The first is to use antiviral medications to stop or slow the virus's ability to make copies of itself and tip the balance in favour of the immune system. A 19 March study of people admitted to a hospital in Nanchang, China, with covid-19 found that those with milder illness had less of the virus in their bodies. This suggests that reducing the amount of virus ›

could make symptoms less severe. The second strategy is to identify antibodies – the proteins our immune systems produce in response to an infection – that work against the virus and deploy them against it. And the final one is to stop the immune system spinning out of control. The goal, says Manson, isn't to switch it off, which would leave a person unable to fight off the virus, but to dial it down a bit.

These are the main aims of the dozens of drugs under investigation, many of which have already been approved by the US Food and Drug Administration for treating other conditions, which gives them a leg up in terms of how quickly they would be available to people with covid-19. But novel, custom-designed therapies have the advantage of working specifically against this viral infection, which could make them more effective.

Not going viral

We don't have many antivirals ready to pull off the shelf. More than 90 have been approved since 1963, when idoxuridine was authorised for the treatment of herpes simplex, but most are only effective against a single type of virus, making it hard to repurpose them against something new. In addition, because viruses rely on their host for most of their functions, it is challenging to create drugs that kill the invaders without harming us too.

To address both these issues, in 2010, the US National Institute of Allergy and Infectious Diseases (NIAID) began investing in the development of more broad-spectrum antivirals. As with broad-spectrum antibiotics, which are effective against a range of bacteria, the aim was to create antivirals that could work against many different viruses. One company the NIAID collaborated with was Gilead, which led to the development of remdesivir.

Preliminary trials against Ebola yielded promising results, and in 2018 Gilead tested the drug in a large-scale clinical trial during an Ebola outbreak in the Democratic Republic of the Congo. When this showed that remdesivir didn't prevent deaths as well as other treatments, it was shelved.

> **"Nations have been brought down by this itty-bitty virus. And we have nothing"**

Earlier in the drug's development, however, researchers had tested remdesivir against the coronaviruses that cause SARS and MERS, another respiratory disease. Studies both in cells and in mice showed that the drug could prevent the viruses replicating – driving hopes that it could work against the new coronavirus too. These findings, plus the fact that the drug has already passed safety trials as part of its testing against Ebola, have rapidly made it the front runner in the race for covid-19 therapeutics. Four large clinical trials evaluating remdesivir are getting under way in the US and these, combined with trials in China, should give preliminary results as soon as the end of this month.

In late February, Bruce Aylward, assistant director-general of the World Health Organization, spoke plainly: "There's only one drug right now that we think may have real efficacy," he said. "And that's remdesivir."

Yet he and other public health officials on the front lines of this pandemic still stress the need for due process. "We're trying to strike a balance between making something with a potential of an effect to the American people available, at the same time that we do it under the auspices of a protocol that would give us information to determine if it's truly safe and truly effective," said Anthony Fauci, head of the NIAID, on 20 March.

As well as other efforts to test antivirals, including drugs once used against HIV, many groups are now evaluating the use of long-standing malaria drug chloroquine and its close cousin hydroxychloroquine. Although the drugs are no longer used in parts of the world because the malaria parasite has become highly resistant to them, in early February a study led by researchers at the Wuhan Institute of Virology in China showed that they demonstrate some antiviral activity in human cells. More recently, French doctors shared results of a trial in which 26 people with covid-19 were given hydroxychloroquine three times a day, in some cases alongside the antibiotic azithromycin. After 10 days, those who received the treatment reportedly had less virus in their blood than 16 people not given the medicines.

That small study prompted US President Donald Trump to tweet about the regimen's promise, much to the chagrin of Fauci, who soon after stressed that the findings were "anecdotal", because the study was small and not rigorously designed. There has already been at least one report of an overdose by someone who attempted to self-medicate with the drug.

Now several clinical trials of hydroxychloroquine are in the works, including one that began on 24 March in New York, in which the drug will be evaluated in combination with azithromycin. Should its efficacy be proven, the low cost and ready availability of hydroxychloroquine should make it easy to mass produce for widespread use. Yet some are wary of heaping too much hope onto this one solution – Trump's enthusiasm notwithstanding. At this point, the hype around hydroxychloroquine says more about our desperation than its genuine promise, says Harold Smith, a molecular biologist at the University of Rochester in New York and founder of a company also developing an antiviral treatment against the new coronavirus with NIAID funding. "Nations have been brought down by this itty-bitty

LUKAS KABON/ANADOLU AGENCY VIA GETTY IMAGES

Some of the drugs being developed are based on antibodies produced by people who have beaten covid-19

TOMOHIRO OHSUMI/GETTY IMAGES

After weeks in quarantine, cruise ship passengers were among the first participants in clinical trials of antiviral drugs

virus, and we have nothing," he says.

Another way to fight the virus, apart from stopping it replicating, is to follow our immune system's lead and look to antibodies. Biotech start-up AbCellera, based in Vancouver, began this process by rapidly identifying all the antibodies in a blood sample taken from someone who had recovered from covid-19. The company then tested them for their activity against the new coronavirus. Within a week of receiving the sample, AbCellera had identified 500 promising antibodies among the millions, or even billions, in the sample, says Ester Falconer, the company's head of research and development. It is now working with Indiana-based drugs firm Eli Lilly to develop an antibody-based therapy for covid-19 and have it ready for testing with a faster-than-ever turnaround. "In four months, we can do something that normally takes five to 10 years," says Falconer.

The same approach is being taken by the New York drug company Regeneron, which says it hopes to start mass producing the most potent antibodies it has identified by mid-April. From there, however, it is still a long road of testing to see if the treatments are safe and can reduce the severity or duration of covid-19.

There is a more old-fashioned way of giving people a dose of added antibodies: collecting them directly from people who have beaten the infection. Pathogen-fighting antibodies continue to circulate at high levels in the blood of recovering patients. Since the 1930s, doctors have given antibody-rich blood serum to boost the defences of people desperately ill with the same infection. The strategy has saved lives during polio and Ebola epidemics, measles outbreaks and even during the SARS epidemic in 2003. Several hundred people have reportedly been treated this way for covid-19 in China already, but the findings haven't yet been published.

Arturo Casadevall at the Johns Hopkins School of Public Health in Maryland says that the antibodies in the serum sop up viruses much like how a sponge sucks up a spill. He is now ramping up a four-site clinical trial to evaluate the strategy within weeks. He also envisions a coronavirus-specific plasma bank in which recovering individuals can provide antibodies to those who are still ailing, something he says could be off the ground in a few months. "One survivor can donate enough plasma to help two sick people," he says.

Calm the storm

The third major approach for covid-19 drugs is one that aims to thwart our immune system's dangerous, hyperactive response. Here, too, the strategies are a mixture of old and new. Recognising that many patients experience symptoms of a cytokine storm shortly before death, Swiss pharmaceutical giant Roche began investigating whether its rheumatoid arthritis drug tocilizumab could interrupt this process. The drug works by inactivating the cytokine interleukin-6, which acts as an accelerator for the immune system. The company will begin enrolling people with pneumonia induced by covid-19 in a large clinical trial this month. Another anti-interleukin-6 drug, sarilumab, is also being tested. "This is the perfect moment to do randomised control trials on existing drugs. We can get them up and running very quickly," says Manson. However, she does worry about using these drugs in large groups of people with little evidence.

Once we have a good idea of what works, the hard part will be actually getting it to people. "The rate-limiting step will be manufacturing capability, not science. We want these drugs to be widely available, which means producing hundreds of millions of doses," says Jeff Chertack, a spokesperson at the Bill & Melinda Gates Foundation. Last month, the organisation launched an endeavour called the Covid-19 Therapeutics Accelerator, which will contribute up to $125 million to speed up drug development from its earliest stages through to manufacturing and distribution. Chertack says its emphasis on all steps in the process is a deliberate strategy to ensure drugs are priced so that people who need them will be able to get them, regardless of income.

If trials show that the repurposed therapies are effective, in principle, they could be available for people with covid-19 just weeks later, as long as they can be manufactured in adequate amounts, says Clifford Lane, deputy director for clinical research at NIAID. Novel treatments could requires months of testing before they are ready for humans. It is a lengthy process, but it also helps to ensure that the massive investment of time and resources to get drugs to patients will pay off in the end. "We need to focus on what will bring the greatest benefit to the largest number of patients," says Lane.

Cost and production are critical concerns, but even more important is having confidence that our drugs will work – and will do no harm. As this article went to press, the global death toll from the new coronavirus was approaching 40,000. People are desperate for effective treatments as soon as possible. But we can't act in haste, says Lane. "In an outbreak like this, it's crucial to find out which interventions are truly of benefit and implement them widely," he says. Just as important, though, is to "eliminate those interventions that aren't and get them out of the way". ▮

Carrie Arnold is a science writer based in Virginia. Follow her @edbites