ZYDUS CADILA

ZyCoV-D is the first DNA vaccine for people to be approved anywhere in the world.

INDIA'S DNA COVID VACCINE IS A FIRST — MORE ARE COMING

The ZyCoV-D vaccine heralds a wave of DNA vaccines for various diseases that are undergoing clinical trials.

By Smriti Mallapaty

India has approved a COVID-19 vaccine that uses circular strands of DNA to prime the immune system against the coronavirus SARS-CoV-2. Researchers have welcomed news of the first DNA vaccine for people that has received approval anywhere, and say many others might soon be hot on its heels.

ZyCoV-D, which is administered into the skin without an injection, has been found to be 67% protective against symptomatic COVID-19 in clinical trials, and will probably start to be administered in India this month. Although the efficacy is not high compared with that of many other COVID-19 vaccines, the fact that it is a DNA vaccine is significant, say researchers.

It is proof of the principle that DNA vaccines work and can help in controlling the pandemic, says Peter Richmond, a paediatric immunologist at the University of Western Australia in Perth. "This is a really important step forward in the fight to defeat COVID-19 globally, because it demonstrates that we have another class of vaccines that we can use."

Close to a dozen DNA vaccines against COVID-19 are in clinical trials globally, and at least as many again are in earlier stages of development. DNA vaccines are also being developed for many other diseases.

"If DNA vaccines prove to be successful, this is really the future of vaccinology" because they are easy to manufacture, says Shahid Jameel, a virologist at Ashoka University in Sonipat, India.

The urgency of combating COVID-19 has fast-tracked vaccines that use genetic technology, such as messenger RNA and DNA vaccines, says David Weiner, director of the Vaccine & Immunotherapy Center at the Wistar Institute in Philadelphia, Pennsylvania.

Fast-tracked development

RNA vaccines were quicker to show strong immune responses in clinical trials; they have now been delivered to hundreds of millions of people around the world. But DNA vaccines have a number of benefits, because they are easy to produce and the finished products are more stable than mRNA vaccines, which typically require storage at very low temperatures.

ZyCoV-D was developed by Indian pharmaceutical firm Zydus Cadila, headquartered in Ahmedabad. On 20 August, India's drug regulator authorized the vaccine for people aged 12 and over. The efficacy figure of 67% came from trials involving more than 28,000 participants, which saw 21 symptomatic cases of COVID-19 in the vaccinated group and 60 among people who received a placebo.

ZyCoV-D contains circular strands of DNA known as plasmids, which encode the spike protein of SARS-CoV-2, together with a promoter sequence for turning the gene on. Once the plasmids enter the nuclei of cells, they are converted into mRNA, which travels to the main body of the cell, the cytoplasm, and is translated into the spike protein itself. The body's immune system then mounts a response against the protein, and produces tailored immune cells that can clear future infections. Plasmids typically degrade within weeks to months, but the immunity remains.

Both DNA and mRNA vaccines have been under development since the 1990s, says Weiner. The challenge for DNA vaccines is that they need to make it all the way to the cell nucleus, unlike mRNA vaccines, which just need to get to the cytoplasm, says Jameel. So, for a long time, DNA vaccines struggled to induce potent immune responses in clinical trials, which is why they had been approved for use as vaccines only in animals, such as horses, until now.

Injection-free vaccine

To solve this problem, ZyCoV-D is deposited under the skin, as opposed to deep in muscle tissue. The area under the skin is rich in immune cells that gobble up foreign objects, such as vaccine particles, and process them. "This helps capture the DNA far more efficiently than in the muscle," Jameel says. Unusually, the vaccine is delivered using a needle-free device pressed against the skin, which creates a fine, high-pressure stream of fluid that punctures the surface and is less painful than an injection.

But despite being more potent than previous DNA vaccines, ZyCoV-D requires a minimum of three doses to achieve its initial efficacy. This is likely to add to the logistical challenge of administering the vaccine during the current pandemic, says Jameel.

Although ZyCoV-D's efficacy seems to be lower than the 90% or higher achieved by some mRNA vaccines, the figures are not comparable, says Jameel. The ZyCoV-D trials in India earlier this year were conducted while the Delta variant of SARS-CoV-2 was the dominant variant in circulation, whereas earlier mRNA vaccine trials were conducted when less transmissible variants were circulating. "The efficacy is essentially against the Delta variant, so that is pretty good," he says.

Some researchers have criticized a lack of transparency in the approval process, because no late-stage trial results have yet been published. Zydus Cadila says the trial is still underway and it will submit the full analysis for publication shortly. The company says the first doses will start to be administered in India in September, and it plans to produce up to

50 million doses by early next year.

Several other DNA vaccines are being developed against COVID-19, using a variety of antigens and delivery mechanisms. Two have entered late-stage trials: one by Japanese company AnGes, based in Osaka; the other, which Weiner helped to develop, by Inovio Pharmaceuticals in Plymouth Meeting, Pennsylvania.

More than half a dozen DNA vaccines for COVID-19 are in early-stage trials, including one by the South Korean biotech company GeneOne Life Science in Seoul, and another that Richmond is involved in, developed by the Thai firm BioNet in Bangkok.

But Richmond expects many more to emerge, targeting diseases for which there are currently no vaccines — from cytomegalovirus, which can be passed to babies during pregnancy, to respiratory syncytial virus. DNA vaccines are also being trialled or developed for influenza, human papillomavirus, HIV and Zika.

DNA vaccines can store lots of information, which means they can encode large proteins or even multiple proteins. Weiner says that gives them promise as anticancer vaccines, which he is exploring in his own research.

"It's a very exciting time for genetic technologies," he says.

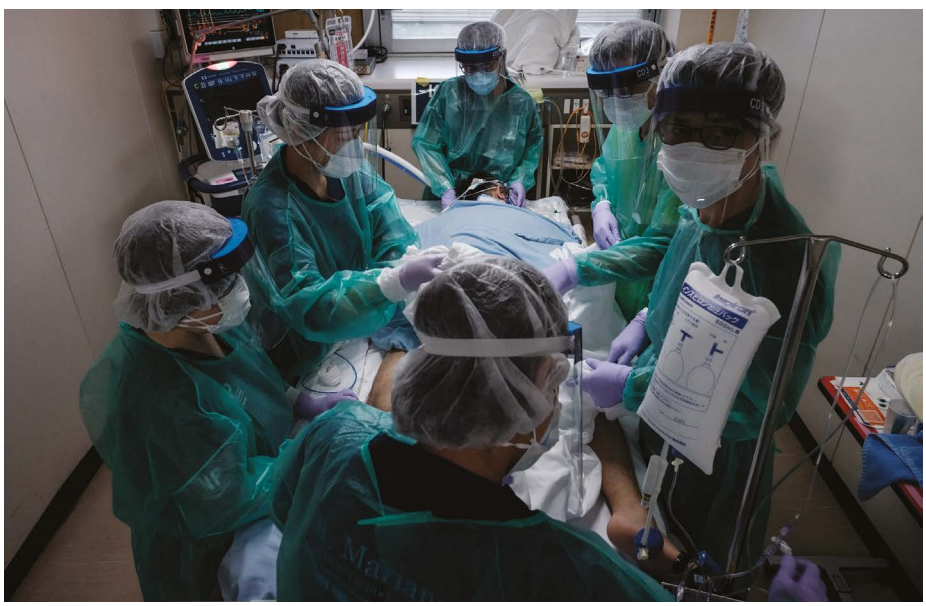
ROGUE ANTIBODIES LINKED TO DEATHS FROM SEVERE COVID

The self-targeting 'autoantibodies' attack blood proteins that play a key part in fighting infection.

By Diana Kwon

Antibodies that turn against elements of our own immune defences are a key driver of severe illness and death following SARS-CoV-2 infection in some people, according to a large international study. These rogue antibodies, known as autoantibodies, are also present in a small proportion of healthy, uninfected individuals — and their prevalence increases with age, which might help to explain why older people are at higher risk of severe COVID-19.

The findings, published on 19 August in *Science Immunology*[1], provide robust evidence to support an observation made by the same research team last October. Led by immunologist Jean-Laurent Casanova at the Rockefeller University in New York City, the researchers found that around 10% of people with severe COVID-19 had autoantibodies that attack and block high levels of type 1 interferons, protein molecules in the blood that have a crucial role in fighting off viral infections[2].



Physicians treat a person with COVID-19 at a hospital in Japan.

YASUYOSHI CHIBA/AFP VIA GETTY

"The initial report from last year was probably one of the most important papers in the pandemic," says Aaron Ring, an immunologist at the Yale School of Medicine in New Haven, Connecticut. "What they've done in this new study is really dig down to see just how common these antibodies are across the general population — and it turns out they're astonishingly prevalent."

The research team focused on detecting autoantibodies that could neutralize more physiologically relevant concentrations of interferons. They studied 3,595 people with severe COVID-19 from 38 countries. Overall, 13.6% of these people possessed autoantibodies, with the proportion ranging from 9.6% of those below the age of 40, up to 21% of those over 80. Autoantibodies were also present in 18% of people who had died of the disease.

Casanova and his colleagues suspected that these devious antibodies were a cause, rather than a consequence, of severe COVID-19. There were hints that this might be the case — the group had previously found that autoantibodies were present in around 4 in 1,000 healthy people whose samples had been collected before the pandemic[2]. The team also found that individuals with genetic mutations that disrupt the activity of type 1 interferons are at higher risk of life-threatening disease[3,4].

To examine this link further, the researchers hunted for autoantibodies in a massive collection of blood samples taken from almost 35,000 healthy people before the pandemic. They found that 0.18% of those aged between 18 and 69 had existing autoantibodies against type 1 interferon, and that this proportion increased with age: autoantibodies were present in around 1.1% of 70- to 79-year-olds, and 3.4% of those over the age of 80.

"There is a massive increase in prevalence" with age, Casanova says. "This largely explains the high risk of severe COVID in people in the elderly population." He adds that these findings have clear clinical implications, and suggests that hospitals should be checking patients for these autoantibodies, as well as mutations implicated in blocking type 1 interferons.

A sample of more than 30,000 people is "too big to ignore", according to Ring. He adds that researchers should now consider whether autoantibodies play a part in driving other infectious diseases. Ring's team has found evidence[5] of autoantibodies against various immune-system components in people with COVID-19, and he and his colleagues are now investigating further. "I suspect that we've just started scratching the surface," Ring says.

1. Bastard, P. *et al. Science Immunol.* **6**, eabl4340 (2021).
2. Bastard, P. *et al. Science* **370**, eabd4585 (2020).
3. Asano, T. *et al. Sci. Immunol.* **6**, eabl4348 (2021).
4. Zhang, Q. *et al. Science* **370**, eabd4570 (2020).
5. Wang, E. Y. *et al. Nature* **595**, 283–288 (2021).