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How soon will we have a coronavirus vaccine? The race against covid-19

The hope is that we will have a coronavirus vaccine in 12-18 months, but for that to happen we may have to rely on untested techniques - and that comes with its own risks.

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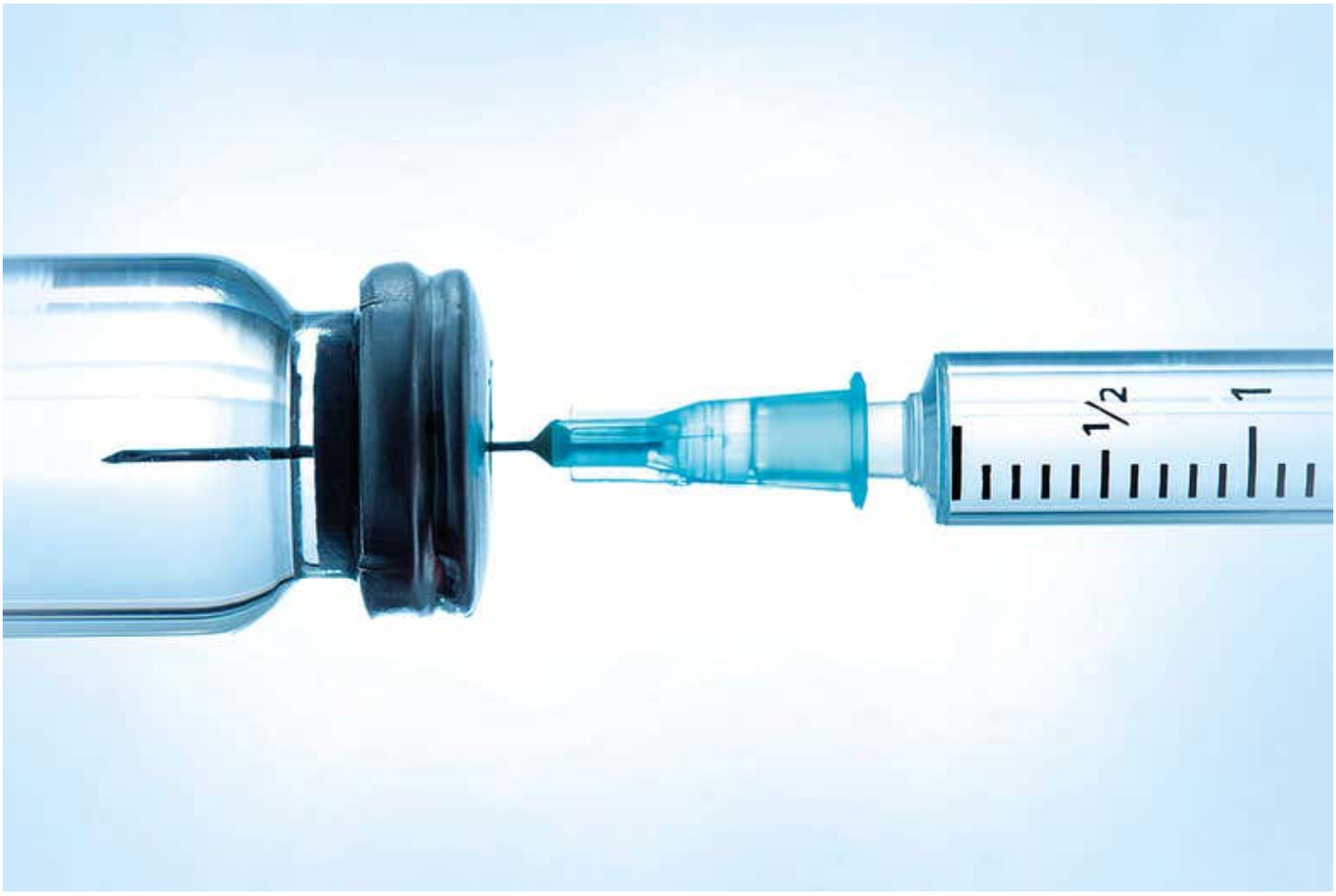
By **Carrie Arnold**



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POTTERING around her kitchen on the morning of 31 December, Kate Broderick scrolled through the headlines while she waited for her tea to brew. One story caught her eye: a mysterious outbreak of severe pneumonia in Wuhan, China. Nearly overnight, the number of cases seemed to explode. "I knew we didn't have time to wait," she says.

A molecular geneticist at Inovio Pharmaceuticals in California, Broderick was poised for what came next. When Chinese officials published the genetic sequence of the new SARS-CoV-2 coronavirus causing the illness just two weeks after the first cases were reported to the World Health Organization, Broderick got to work. Within 3 hours, her team had a prototype vaccine ready for initial testing. It was an unprecedented turnaround, but a moment Broderick and many others had long seen coming.

Making vaccines usually takes a decade or more between development, safety testing and manufacturing, says Seth Berkley, head of Gavi, an international group that promotes vaccine use around the world. With global confirmed cases of the new disease, covid-19, surging past 180,000 at the time of writing, time is of the essence.

To speed things up, scientists are turning to untested classes of vaccines, and rethinking every part of how they are designed, evaluated and manufactured. If the approach works, we will, for the first time, have identified a new disease and developed a vaccine against it while the initial outbreak is still ongoing.

But speed can come with downsides. "We could have a vaccine in three weeks, but we can't guarantee its safety or efficacy," says Gary Kobinger, a virologist at Laval University in Canada.

The hope is to have at least 1 million doses of coronavirus vaccine available to the public in 12 to 18 months, according to Melanie Saville. She is head of vaccine development and research at the Coalition for Epidemic Preparedness Innovations (CEPI), set up in 2017 with funding from the Bill & Melinda Gates Foundation, the Wellcome Trust and several governments. Until now, the fastest we have ever cranked out a vaccine in response to an outbreak was with Ebola – and that took five years, says Berkley. Eighteen months to make a new vaccine widely available is "naively optimistic", says Kobinger. It isn't impossible, but it may mean ripping up the rule book.

All vaccines work by tricking the body into believing it has been exposed to a pathogen. This causes the immune system to respond with antibodies and T-cells to neutralise or kill the invader. Afterwards, some of these remain in circulation, ready for action in case you are exposed to the actual infection. In other words, your immune system is primed.

The more closely a vaccine mimics the disease, the more protection it will provide. We currently have four main strategies for pulling off this trick. Live-attenuated vaccines use actual viruses or bacteria that have been altered to prompt an immune response but not full-blown illness. Inactivated vaccines are exactly what they sound like: they are made by growing huge amounts of the pathogen in vats, which is then inactivated – or killed – with heat or chemicals. Both these strategies are used with flu vaccines, for instance.

The third variety, toxoid vaccines, are used against bacteria that cause disease indirectly, by producing a toxin, as is the case with tetanus, diphtheria and botulism. They contain a piece of the toxin that readies your body's response to the full thing. Lastly, subunit vaccines contain just the small pieces of a pathogen that activate the immune system, which can be polysaccharides (sugars), proteins or a combination of these, called a conjugate. These subunits are made by producing the right sugars and proteins in large vats using engineered bacteria or yeast, then painstakingly removing impurities.

These key vaccine types have been around for decades and have an established safety record, but it can still take up to 15 years to go from prototype to general use, says Berkley (see "How to make a vaccine, step by step"). Two main factors are behind long development times: historically, scientists have spent years studying how a pathogen interacts with the body and the immune system before developing a vaccine; and fewer than one in four candidate vaccines that start clinical trials make it through the whole process and get licensed for use, he says.

A head start

In principle, the tried and tested nature of these approaches should give them an advantage in the sprint to develop a vaccine against the new coronavirus, says Maria Bottazzi at Baylor College of Medicine in Texas. While these vaccine types typically take years to develop, their established safety profile could mean fewer, shorter trials in people.

And getting out of the starting blocks has become easier. New approaches to vaccine development allow us to dramatically shorten the first step in the process. For the new coronavirus, researchers like Annie De Groot, co-founder of the biotech company EpiVax in Rhode Island, used computational models that can jump directly from the genetic sequence to a potential vaccine by zooming in on those parts of the virus that would be good vaccine targets. As soon as SARS-CoV-2 was sequenced, researchers at labs around the world were able to jump in and get to work figuring out what made it tick and how to fight it, says Florian Krammer, an infectious disease and vaccine specialist at Mount Sinai School of Medicine in New York. Like Inovio, many had mock-ups of prototypes ready within hours. Such advances have been a long time coming. "It took us 21 years of work to be able to develop a vaccine in 3 hours," says De Groot.

Matthew McKay at Hong Kong University of Science and Technology is one of those taking advantage of such leaps. He and his team looked at genetic similarities between the new virus and another, earlier coronavirus that shares up to 90 per cent of its DNA: SARS-CoV, the one that caused a SARS outbreak in 2003. Their work on SARS showed that the human immune system responded most strongly to the protein spikes that form the crown, or corona, surrounding the virus and to the proteins that envelop its nucleus. McKay's team also found that one in five of the sites that the immune system could recognise, known as epitopes, were identical between the new coronavirus and the earlier SARS one. His team published that work in February. "This says these appear to be important targets for a vaccine," says McKay. An independent lab published similar findings last week.

> **"It took us 21 years of work to be able to develop a vaccine in 3 hours"**

This initial flurry of work has yielded at least 35 candidate vaccines, six backed by CEPI. In the wake of earlier epidemics such as Ebola, MERS and SARS, CEPI was created to help us respond better – and faster – by having rapid response systems at the ready.

Many of these use the well-established vaccine types, but hope to accelerate the usual timelines by streamlining each step in the process, most notably prototype development. For example, CEPI is funding a collaboration between EpiVax and the University of Georgia to use the results of the company's computer modelling to genetically engineer a segment of the virus into a subunit vaccine, like the one used for hepatitis B worldwide. Bottazzi's team at Baylor is developing a similar vaccine.

Janssen, a pharmaceutical company owned by Johnson & Johnson, has begun work on a possible vaccine using a harmless, genetically engineered adenovirus. That is the same strategy the firm used for Ebola.

Another CEPI-funded initiative uses technology developed by researchers at the University of Queensland in Australia to stabilise the coronavirus protein subunit that would be used in a vaccine and so improve its ability to generate an immune response. The university already has its vaccine in animal trials, according to Saville.

But the tried-and-tested vaccine types aren't the only game in town this time. Inovio, for example, aims to use nucleic acids like RNA or DNA in its vaccine. Although neither DNA nor messenger RNA (mRNA, which helps the body translate genes into protein) create an immune response directly, these vaccines get cells to make the proteins that will create a response.

"Instead of producing viral proteins in a factory, we're injecting RNA and letting your cells be the factory," says Joe Payne, head of Arcturus Therapeutics, one of the companies using this approach.

Once the DNA or mRNA enters a cell, the person's own protein-making machinery takes over. DNA vaccines must be converted by cells into mRNA first, whereas mRNA allows you to skip this stage. Depending on the genetic code used, the resulting viral protein made in the body can be secreted from muscle or skin cells, displayed on the cell's membrane, or be embedded in the membrane itself. These strategies trick the immune system into thinking the body has been invaded by a pathogen, which leads to the creation of T-cells and antibodies – or so the theory goes. So far, no such vaccines have been approved.

Efforts are underway to produce a vaccine against the covid-19 coronavirus adapted from another for infectious bronchitis virus.
JALAA MAREY/AFP via Getty Images

A major hurdle with these vaccines is getting the DNA or RNA into cells, as our blood is filled with enzymes that can chop these substances into bits within seconds. Each company pursuing this approach has developed its own technology to circumvent this problem. Arcturus and a Massachusetts-based biotech firm called Moderna are enveloping the vaccine's genetic material in a protective core, while Inovio is administering a tiny electrical current at the injection site to encourage nearby cells to swallow DNA whole. All three have said they will be able to rapidly scale up production. Moderna has already recruited people in Seattle for an early-stage clinical trial to test for safety. The trial, which will include 45 healthy volunteers, began on 16 March.

"It's a crazy, awesome speed, beyond what we saw with Ebola," says Kobinger.

The safety and efficacy of these new types of vaccines remain unknown, and there are concerns that DNA-based vaccines might affect our own genes or somehow spur harmful immune reactions. As of 17 March, none of the companies had released detailed data about the immune

responses generated in animal models or any potential adverse events.

Moderna is also taking its RNA-based vaccine, mRNA-1273, directly to human trials before completing standard toxicological testing in animals. The firm is relying on safety testing already completed for its other mRNA vaccines in development.

Yet with any new vaccine, there are concerns about something called "immune enhancement". This can happen when a prior vaccination or infection inadvertently facilitates a virus's ability to enter cells and make copies of itself. It means that instead of protecting you, the vaccine could make you vulnerable to more severe infection. Harmful immune enhancement was seen in early animal trials of SARS vaccine and in human trials of a vaccine for a respiratory virus called RSV.

These types of concerns, and the track record of very few vaccines making it from clinical testing through to approval for use in humans, are what make lengthy clinical trials so necessary, says Johan Van Hoof, head of infectious diseases and vaccines for Janssen. Older vaccine technologies have an advantage as they have already been vetted. "It gives a certain level of comfort that you can use these [older] vaccines in an emergency and you already have a solid safety database," he says.

Striking the balance between speed and safety is always going to be a challenge. If a vaccine takes too long to develop, the initial outbreak may be over, which creates its own set of problems. For example, by the time clinical trials of an Ebola vaccine were under way during a large outbreak that began in West Africa in 2014, disease transmission had slowed so much that researchers couldn't treat enough people to gather the robust data needed for regulatory approval. Only after a larger outbreak and a bigger trial was there enough evidence to prove safety and efficacy, says Kobinger, who worked on that vaccine, called Ervebo. It was finally approved by the European Medicines Agency in November 2019.

Left in limbo

None of the other vaccine candidates for Ebola made it as far. The rest, says Greg Poland at the Mayo Clinic in Minnesota, were stored in freezers, unable to find funding quickly enough to even begin testing. No SARS vaccine made it beyond phase I safety trials before the disease vanished and funding dried up.
Money is also critical to vaccine development. "Scientists need to be assured of research funding. Science is not a spigot you can turn on and off," says Poland.

In part, it was the stark realisation during the West African Ebola outbreak that Big Pharma could no longer be relied upon to solely underwrite expensive vaccine research – especially for diseases with little chance of recouping the outlay – that prompted governments and NGOs to seek an alternative. "The formation of CEPI has been a paradigm shift," says Broderick. "Before that, everything was completely reactive."

CEPI's strength isn't only funding research, but also pairing small, innovative biotech firms with the might of established drugs companies. The coalition has funded efforts to develop vaccines against Lassa fever, Zika and Nipah, and even to prepare for "Disease X", the World Health Organization name for any unknown infection that may yet emerge – precisely the situation that arrived with the new coronavirus. CEPI-funded scientists also worked on vaccines against MERS, a coronavirus spotted in 2013 and closely related to SARS, both of which can cause pneumonia.

So when the first reports of severe pneumonia caused by the new coronavirus began trickling out of China, CEPI was ready for action. But it, too, needs a steady supply of funds. Saville estimates that $350 million will be required in just the next few months to meet the accelerated timeline of creating a vaccine for covid-19 within 12 to 18 months.

Given the all-consuming nature of the current pandemic, there is good reason to believe CEPI will get the money it needs. From there, it is a matter of seeing which vaccine options make it through the many steps to eventual regulatory approval. When one does, then the final challenge will be to rapidly scale up manufacturing to produce millions of doses to exacting medical standards.

All these steps are hard enough when there isn't an outbreak, says De Groot, and no one can say how the pandemic will affect supply chains and labour pools related to vaccine development. It is also possible that, by the time a vaccine is ready for late-stage clinical trials, there won't be enough virus circulating to provide firm answers about its efficacy.

So how realistic is the 12 to 18-month timeline? "It's still fairly aspirational," says Saville. It is based on everything going well and faster-than-ever progress through each step in the process. In other words, it is a long shot.

The teams making vaccine candidates know every minute counts. Broderick says the rising number of cases and deaths rattle through her head from the moment she wakes up.

She and others have no doubt that we will eventually have a vaccine against covid-19. It is just too early to say which candidate will be ready first, or what problems we may hit along the way. It could be a bumpy ride, says Poland. "We're building the plane as we're flying."

How to make a vaccine, step by step

It is a race against time to develop a vaccine amid a pandemic. Each step, detailed below, usually takes months to years. An Ebola vaccine broke records by being ready in five years. The hope is to develop one for the new coronavirus in an unprecedented 12 to 18 months.

Develop a prototype
This usually takes years, depending on the technique used. With the current coronavirus outbreak, companies had prototypes within hours thanks to new technologies that can identify which bits of a virus might be used in a vaccine.

Animal trials
These are primarily to demonstrate safety and to test the immune response generated by a vaccine. In some cases, this stage can be skipped altogether, but there may be safety trade-offs.

Phase I human trials
These are the first tests in people, usually involving 20 to 80 individuals and are used to demonstrate safety and ensure any side effects aren't too severe.

Phase II human trials
This requires larger groups of people and is used to test efficacy. Some vaccines can skip from here to regulatory approval when there is urgent need.

Phase III human trials
At this stage, a new vaccine is tested on hundreds to thousands of people, to clearly evaluate both efficacy and safety.

Regulatory approval
After examining clinical trial evidence, regulatory bodies determine whether the vaccine can be licensed for public use. This may come with the requirement that follow-up safety data be gathered.

Mass production
At this point, manufacturing of a vaccine is ramped up under strict quality control and consistency standards.

Public access
When the new vaccine becomes available, governments and public health authorities have to determine which groups of people get it first.

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