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.

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US PRESIDENT Donald Trump is considering allowing the usual procedures to be bypassed so an experimental coronavirus vaccine can be made available to the public in time for the US election in November, according to a report in the Financial Times. AstraZeneca, the drug company developing the vaccine in partnership with the University of Oxford, has said there have been no talks with the US government about fast-tracking the vaccine.

But the race to develop a coronavirus vaccine is speeding up. On 11 August, president Vladimir Putin announced that Russia had approved a vaccine called Sputnik V for widespread use after only two months of small-scale trials, before the usual longer, large-scale trials. China has also allowed volunteers to be given a vaccine although human trials are still running.

These decisions have led to concern that too many shortcuts are being taken in the rush to roll out coronavirus vaccines.

“As long as there are no new, untested components in a vaccine, the need for animal tests is arguable”

“There is no possible room for movement on the highest safety standards,” says Danny Altmann at Imperial College London. “The [covid-19] vaccines will be given to billions in the biggest ever medical endeavour on planet Earth. This needs to be effective and safe. Imagine even in 1000 serious adverse events in a vaccine given to a billion people.”

Vaccines typically take a decade or more to go through the development and testing phases required to ensure a safe and effective dosage that most people will tolerate. The first step is to make a potential vaccine, a process that can take many years. As of 20 August, 139 potential coronavirus vaccines are in this initial stage, according to the World Health Organization. A further 30 are already being tested in people (see “How vaccines get to the front line”, right).

“The Russia vaccine approval was definitely rushed,” says Ayfer Ali at the University of Warwick in the UK. “It had only been tested in people (see “How vaccines get to the front line”, right).

“The research world is focusing on covid-19 with an intensity the likes of which we have not seen before,” says Michael Head at the University of Southampton, UK. “With these resources available, and the urgency of the pandemic, research is happening much faster than in normal times.”

The necessary technologies have also advanced greatly in recent decades. Genetic sequencing is now fast, routine and cheap, for instance. The full sequence of the coronavirus was made public by researchers in China on 10 January, just weeks after the first cases emerged.

A volunteer in Soweto, South Africa, taking part in the Oxford vaccine trial

Thanks to studies of other coronaviruses, including the ones that cause SARS and MERS, researchers knew which part of the genome coded for the so-called spike protein that protrudes from the outside of the virus. This is the part our immune system learns to recognise and the key target of most coronavirus vaccines.

So how is the development of coronavirus vaccines proceeding so much faster than normal if researchers really are taking all the usual precautions? One reason is the unprecedented effort being made. When the pandemic began, thousands of researchers around the world dropped what they were doing and concentrated on the coronavirus instead.

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protein, it pretty much had its candidate coronavirus vaccine, with a bit of tweaking to ensure the protein has the right structure.

Several other potential vaccines, including Sputnik V and the Oxford vaccine, work in much the same way, but use the shell of a cold-causing virus called an adenovirus to deliver the gene for the spike protein to human cells. Again, once these groups had the spike protein gene, they could create vaccines extremely quickly.

What is happening after candidate vaccines have been created is more debatable. Normally, a potential vaccine would be tested in animals and there would then be a pause while the results are assessed. It can take months or years for funders, regulators and ethics boards to give the go-ahead for the next step.

That step is to test a candidate vaccine in a small number of people, usually fewer than 100, to check there are no serious adverse reactions. This is called a phase I trial.

**Bridging the gaps**

There would then be another pause before phase II, when the vaccine is given to more people – perhaps several hundred – and their immune responses studied to work out the most effective dosage, and how many doses are required.

Another gap then comes before phase III trials, in which typically thousands of people are given either the vaccine or a placebo to see whether the vaccine really can prevent infection.

But most groups developing coronavirus vaccines aren’t pausing between stages. Instead, they are overlapping them.

“As soon as they get a good safety signal from phase I, they are going to phase II,” says Eleanor Riley at the University of Edinburgh, UK. “Essentially, the funders have said: ‘Keep going, the money will be there.’”

For instance, Moderna did hardly any animal tests before giving its experimental vaccine to the first volunteer on 16 March. The company didn’t respond when asked to comment on this.

By contrast, there was extensive testing of the Sputnik V vaccine in rats, mice, hamsters, guinea pigs, rabbits and monkeys, said Alexander Gintsburg at the Gamaleya Research Institute of Epidemiology and Microbiology in Moscow, during a press briefing on 20 August.

However, Riley thinks skipping animal tests may be justifiable because we have enough experience of using RNA vaccines to know that they are fairly safe, she says. “As long as there are no new, untested components in the Moderna vaccine cocktail, then the need for animal safety tests is arguable.”

The question is, are vaccine groups taking risks by moving to the next stage so fast? “I guess you could say that they possibly have not fully analysed phase I, but I’m not sure there’s any evidence for that,” says Riley.

If there is any extra risk, it is to the volunteers in trials.

### How vaccines get to the front line

**Moving a vaccine candidate through the standard phases of development can take more than a decade. Due to the urgency of the pandemic, researchers and regulatory bodies are trying to eliminate delays and teams are running some phases concurrently in the hope of making a coronavirus vaccine in just 12 to 18 months.**

**THE STEPS TO MAKING A VACCINE**

**Prototype development** This usually takes years, depending on the technique used. For the current coronavirus, researchers had prototypes within hours due to new technologies that identify the bits of a virus a vaccine might use.

**Animal trials** These primarily test safety and the immune response generated by a vaccine. Skipping this stage can speed things up, but there may be safety trade-offs.

**Phase I human trials** The first tests in people usually involve 20 to 80 individuals and are used to demonstrate safety and ensure any side effects aren’t too severe.

**Phase II human trials** Tests on larger groups of people reveal a vaccine’s efficacy. Some vaccines can jump from here to regulatory approval if there is urgent need. Russia’s vaccine is moving into use for high-risk populations while testing continues in the next phase.

**Phase III human trials** A new vaccine is tested on hundreds to thousands of people to clearly evaluate both efficacy and long-term safety.

**Regulatory approval** Based on human trial data, regulatory bodies determine whether the vaccine can be licensed for public use. Follow-up safety testing may also be required.

**Mass production** Vaccine manufacturing is ramped up under strict quality control and consistency standards.

**Public access** Once a vaccine is available, governments and public health authorities must determine which groups of people get it first.

38 people received the Sputnik V vaccine before it was approved

“Once you’ve done your phase I and you’re pretty sure the vaccine delivery and the few weeks after it is safe, then any other consequences tend to be rare and they don’t rear their heads until you’ve vaccinated thousands of people,” says Riley.

So, as long as large studies are done and the results are judged by the usual standards, coronavirus vaccines should be as safe as any other newly approved vaccine. Testing each one on large numbers of people matters more than time when it comes to spotting rare adverse events, says Riley.

However, it is unclear whether the usual standards are always being applied right now. Putin’s announcement, for instance, suggested that Russia was going to skip phase III trials. That isn’t quite the case, according to Gintsburg. He said that only people in high-risk groups will be given the vaccine straight away. At the same time, a trial involving 40,000 people will be carried out, ahead of the vaccine’s mass deployment in October.

Regulators in most other countries haven’t said what will be needed for a coronavirus vaccine to get approval, but in the US, the Food and Drug Administration has said it would only need to protect 50 per cent of people, and perhaps even just 30 per cent.
“That is unusually low protective efficacy for an approved vaccine,” says Jonathan Kimmelman at McGill University in Canada. With vaccines, it is all about the risk-benefit ratio, he says.

The big danger with approving a vaccine that only protects some people is that all recipients may assume they are shielded from covid-19 and engage in more risky behaviour than they would otherwise.

On the positive side, these vaccines may get far more scrutiny than is typical because of the immense interest in them and there being greater transparency than usual. Many vaccine groups are publishing their results as they go along, which are making headlines around the world.

“Clinical trial data is not usually available to the public, it is mostly the regulators that see it,” says Ali.

There has been unprecedented openness and this needs to continue, says Derek Lowe, a drug discovery chemist based in Massachusetts. “The phase II and III data have to be out on the table, so everyone can see how we’re making the decisions about which candidates are better or worse than others,” he says. “Secrecy would be a disaster.”

Multiple vaccines

Furthermore, never before have so many vaccines for the same disease been developed simultaneously. “A unique situation we have is that we’ll likely have multiple vaccines,” says Harald Schmidt at the University of Pennsylvania.

So even if the first vaccines to get approval are only partially effective, they may soon be replaced by better ones. After all, it is going to take years to vaccinate everyone on the planet.

“But nobody is yet through the big, difficult bottleneck of successful, safe phase III trials, so let’s not count any chickens,” says Altmann.

The duration of immunity given by a vaccine will also not be clear after early trials. “Given hopes to have a vaccine by year end and where we are with trials, by necessity, we’ll only know that they protect for three months,” says Schmidt.

People in the phase III trials are told to take all the usual precautions to avoid infection, not least because half of them were given a placebo rather than the vaccine. So it could take many months for it become clear whether a vaccine works – especially in countries where case numbers are low – and far longer to know how long protection lasts.

But there is a big shortcut we could take: human challenge studies. With one of these, researchers would give people a vaccine and then deliberately infect them with the coronavirus to see if it works. Tens of thousands of people have already expressed a desire to volunteer. However, so far it has been regarded as too risky to try, given that there is no treatment that can guarantee survival from covid-19.

Assuming at least some vaccines do prove effective, the next challenge is churning out billions of doses. And even after any vaccines are rolled out to the public, monitoring will continue, in what is sometimes called phase IV. Many of the approvals are likely to initially be so-called conditional emergency use authorisations, with full approval coming later.

“It is still possible that some extremely rare events will not be captured in trials – that is true of any drug or vaccine – but after phase III trials, this is a minuscule risk,” says Ali. “I expect scrutiny after approval will be immense for covid-19 vaccines, as it has been so far for covid-19 scientific research.”

It is unusual for serious adverse events to emerge after vaccines are rolled out, says Riley, but it does happen occasionally. For instance, a vaccine against H1N1 swine flu was linked with cases of narcolepsy, though this finding remains controversial. There was also a rise in narcolepsy in China, where the vaccine wasn’t used, probably due to the virus itself.

Even if any vaccine did turn out to cause a rare adverse effect, people might still be better off being given it. Keith Neal at the University of Nottingham in the UK points out how deadly the coronavirus can be, especially in those aged 60 or above. “I doubt if the vaccines have anywhere near that risk,” he says. “We are in a public health emergency.”

“A rushed, unsafe vaccine for coronavirus could risk extending the pandemic by months or years”

It is also possible that coronavirus vaccines might turn out to have unexpected benefits, like some other vaccines. For instance, the HPV vaccine intended to prevent cervical cancer has also reduced the number of premature births.

Overall, Kimmelman thinks there are some increased risks from the shortening of the usual vaccine development process. But this is being offset by the far greater resources and scrutiny.

“How that balances out is anybody’s guess,” he says.

Kimmelman also worries that politics and nationalism could influence the approval process, as seems to have happened in Russia.

Altmann echoes these concerns. “I have lost sleep that the knock-on from the Sputnik V announcement could lead to a cold war space race between populist politicians seeking to strong-arm regulatory bodies into rushed approvals,” he says. So far, there is no sign of this, he says.

The stakes couldn’t be higher.

“A rushed, unsafe vaccine could undermine public confidence, feeding directly into the rhetoric of anti-vaccine activists, and add fire to their existing body of lies and misinformation,” says Head.

“That could risk extending the pandemic by months or years.”

**Number of vaccines being tested in human trials as of 20 August**

![A researcher at Moderna, a Massachusetts-based firm working on a vaccine](image)