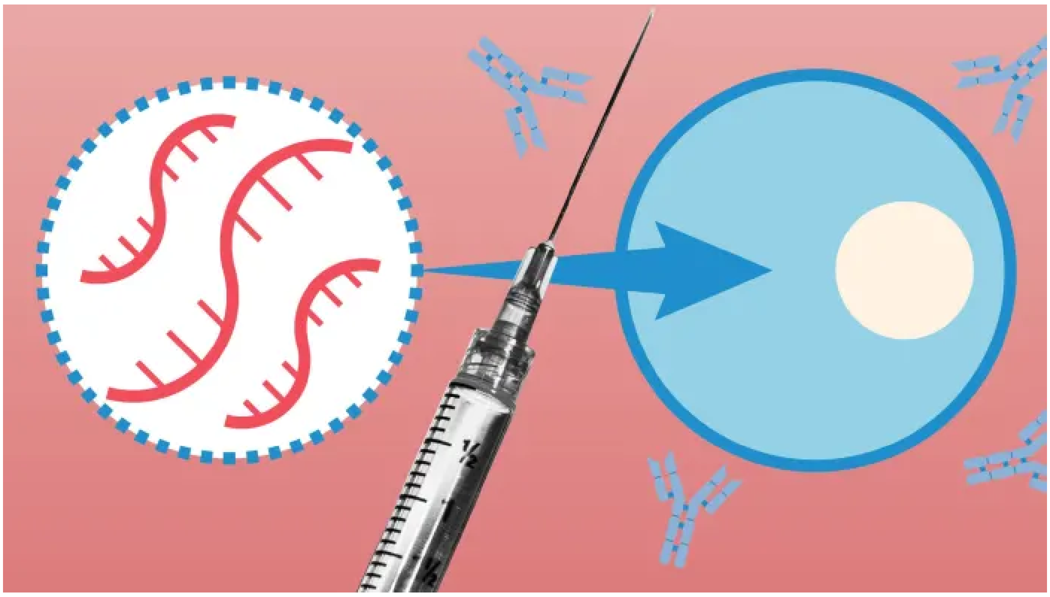
Coronavirus treatment

# Secret ingredients behind the breakthrough Covid vaccines

Moderna and BioNTech-Pfizer's shots use same mRNA technology but with key differences



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**Clive Cookson** in London 4 HOURS AGO

Two breakthrough vaccines that use the same revolutionary technology have been shown to be highly effective in preventing Covid-19, but differences in the way the shots are designed affect how quickly production can be increased and how they are distributed.

The vaccines — one produced by US company Moderna and the other through a partnership between Pfizer and Germany's BioNTech — both recorded efficacy rates higher than 94 per cent in clinical trials, raising global hopes they can provide a route out of the pandemic.

At the heart of both shots is a strand of messenger ribonucleic acid or mRNA — a sequence of around 2,000 biochemical letters of genetic code that carry instructions to the recipient's immune system to recognise and fight coronavirus infection. The technology has never been used in a vaccine before.

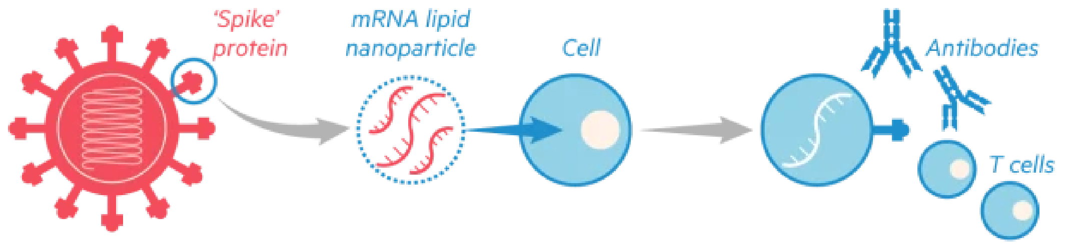
Moderna's vaccine uses 100 micrograms of RNA per dose, while Pfizer-BioNTech's shot uses only 30 micrograms making it easier to produce and less expensive, explained Zoltán Kis, a researcher at Imperial College London's Future Vaccine Manufacturing Hub.

That should enable Pfizer-BioNTech to increase production of their vaccine more quickly than their US competitor. Immunologists added that it was not yet clear why Moderna's shot needed the larger dose of RNA.

"It is notoriously difficult for outsiders to find out exactly what's inside a vaccine," said Alexander Edwards, associate professor of biomedical technology at Reading university. "But how it is put together can have a big effect on how it works." Although the RNA in each is essentially the same, there may be tiny differences in the genetic sequence which make Pfizer-BioNTech more effective at smaller doses.

## How mRNA vaccines work

Genetic instructions are given to the immune system to recognise the virus




Scientists focus on the genetic sequence for the virus's 'spike' protein. This is used to synthesise an mRNA sequence – instructions that cells can use to make the 'spike' protein

The synthetic mRNA is packaged in a lipid nanoparticle that delivers the instructions to a cell

Once inside the cell, its cellular machinery follows the mRNA instructions to produce the viral protein. This is displayed on the surface of the cell and stimulates an immune system response

Source: Pfizer


"The RNA for mRNA vaccines is produced by a chemical process rather than the biological processes used to produce other vaccines, which involve growing cell cultures," said Prof Edwards. It is altered slightly from the "wild type" RNA naturally present in the virus, to make it more stable and more easily read by human cells, he said.

In both the Moderna and Pfizer-BioNTech vaccines the RNA is encapsulated in "lipid nanoparticles". These microscopic droplets of oily liquid — about 0.1 micron in diameter — enclose and protect the fragile genetic instructions as they are manufactured, transported and finally injected into people. The composition of the lipid nanoparticles is slightly different in the two vaccines, scientists said, with a number of implications.

"These nanoparticles can give a magic kick to the formulation," said Prof Edwards. "You might have a list of ingredients but you don't know how they are combined to produce particles with the best size and shape. There are strong parallels with food production — you may know the ingredients for Heinz Ketchup but you can't make it."

Pfizer and BioNTech obtain their nanoparticles from Acuitas, a specialist Canadian company, while Moderna has developed its own lipid technology.

"The art and challenge of developing nanoparticles is to combine lipids with different physical characteristics in a way that stabilises the RNA as effectively as possible," said Mike Watson, a former head of vaccines at Moderna.

In both cases, cold storage is needed to keep the nanoparticles in good shape and to stop the mRNA degrading. But while Moderna's vaccine is stable enough to survive storage for six months at -20C, the temperature of a standard domestic or medical freezer, the Pfizer/BioNTech vaccine needs to be stored and transported at -70C.

As a result, once approved by the regulatory authorities, Moderna's vaccine can be distributed "more easily and at lower cost", said Imperial's Dr Kis.

Pfizer and BioNTech have had to design special “thermal shippers” that can maintain the product for up to 15 days at that temperature when regularly refilled with dry ice. Each package has a thermometer linked to GPS, which tracks its temperature and location across Pfizer’s distribution network. Even so, the temperature requirement will make it harder to distribute the vaccine in countries without sufficient cold chain storage capacity like many in Africa and Asia.

In contrast, adenovirus vaccines under development such as the one produced by Oxford university and AstraZeneca, can be stored for many months without freezing. Rather than using mRNA, the Oxford vaccine attaches the coronavirus spike protein genes used to provoke the immune response to a harmless adenovirus, which carries them into human cells. Sarah Gilbert, a leader of the Oxford team, said its vaccine was stable at ordinary fridge temperatures of between 2C-8C.

Differences in the way Pfizer-BioNTech and Moderna’s lipids are formulated are also likely to affect the way each shot works. “The lipid nanoparticles have some adjuvant activity, providing a little inflammation with the vaccination that helps the immune system to make antibodies and T-cells that target the Sars-Cov-2 virus,” said Brian Ferguson, an immunology researcher at Cambridge university.

Another approach, under development by Imperial College and in early clinical testing, is a self-amplifying RNA vaccine which makes more copies of itself after injection into human cells. That approach could ultimately reduce the amount of RNA needed to as little as 1 microgram per dose, Dr Kis said.