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The company says its vaccine is 90 per cent effective. What does this really mean and what do we still need to know? Graham Lawton reports

US DRUG-MAKER Pfizer and its German partner BioNTech released some positive-looking results on 9 November from a clinical trial of their experimental covid-19 vaccine BNT162b2.

The headline figure is “90 per cent effective”. While the results are an important step towards a coronavirus vaccine, the news may not be quite as good as it first seems.

What did Pfizer and BioNTech find?
The results are from a phase III clinical trial, the final stage of testing whether a vaccine or drug is both safe and effective. The companies gave the vaccine or a placebo to 43,538 participants in a double-blinded study, meaning that about half the people were dosed with the real thing and half with the placebo, but nobody knows who got what. They then waited until there were 94 confirmed cases of covid-19. As of 8 November, 38,955 participants had received two doses.

An independent committee then “unblinded” the study and found that about 90 per cent of the cases were in the placebo group. The raw numbers haven’t been released, but back-of-the-envelope calculations suggest that 85 cases were in the placebo group and nine were in the vaccine group.

Does this mean we are on the brink of a successful vaccine? Not yet. It is an interim verdict, not a final one. And the “end point” of this trial – the criterion against which success or failure is judged – is almost the bare minimum. It merely looks at whether people are protected from being infected by the virus, not whether the vaccine prevents severe illness or death.

Of course, people who don’t catch the virus cannot get very ill or die from it. But if 10 per cent of vaccinated people remain vulnerable, that may still add up to a lot of illness and death. The trial isn’t big enough to pick that up.

“The studies do not have adequate numbers of patients in them to be able to reliably tell us if they prevent severe disease,” says Susanne Hodgson at the University of Oxford’s Jenner Institute, which researches vaccines, who spoke to New Scientist about covid-19 vaccine trials in general, not about Pfizer’s specifically. “We will need to give these vaccines to much larger populations in order to collect that kind of data.”

Hodgson has been working on the UK clinical trials of the SARS-CoV-2 candidate vaccine being developed by the University of Oxford and AstraZeneca but has no links to the Pfizer/BioNTech vaccine.

Another thing to bear in mind, says Hodgson, is that vaccine effectiveness in the real world can be lower than that seen in clinical trials. This may be because vaccines don’t work very well in older people, and are usually tested in younger ones. Pfizer and BioNTech haven’t released specific details of the age profile of their study.

So we still have to wait for the final result?
Yes. The trial will go on until there have been 164 confirmed infections, with another interim assessment after 120 infections. The chances of the result flipping are vanishingly small.

A bit like vote counting in the US presidential election, the case numbers in the placebo group have already reached a level that cannot be surpassed by the vaccine group, and are approaching the threshold needed to “win”, at least according to criteria laid out by the World Health Organization (WHO) in its official assessment of what would constitute a safe and effective covid-19 vaccine.

That threshold is 50 per cent reduction of relative risk, which in this trial would mean no more than 54 cases in the vaccine group from a total of 164 cases across both groups.

When might we reach that end point?
Extrapolating from the study so far, quite soon. The trial began on 27 July and racked up 94 cases in around three months. It needs just 70 more to get to the magic number of 164. With cases...
soaring in many parts of the world – the trial is global with many volunteers in the US – that could happen before Christmas.

What happens then?

If the numbers are still good, the companies could decide to apply to a regulator such as the US Food and Drug Administration (FDA) for approval, or what is technically called “licensure”. The FDA has said it won’t cut any corners. It hasn’t put an estimated timescale on the approval process, but says that it will adhere to standard procedure: review the data itself, seek advice from the Vaccines and Related Biological Products Advisory Committee, and initiate a period of public comment. It may ask for further data from the companies.

According to the World Economic Forum, vaccine approval usually takes one or two years. But the FDA has also said it will expedite the process without shortcutting it. “The FDA will not authorize or approve any COVID-19 vaccine before it has met the agency’s rigorous expectations for safety and effectiveness,” said FDA commissioner Stephen Hahn in a statement on 29 September.

And then we are home and dry?

No. Even if a regulator says yes, there are hurdles to overcome, not least a limited supply. “We expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses in 2021,” the companies said in a press release announcing the result. About 14 billion doses are required to vaccinate everyone, allowing for inevitable wastage and the fact that each person would need two doses.

Vaccines also require careful post-licensure evaluation, often called phase IV trials, because adverse reactions may be too rare to be picked up in clinical trials but serious enough to make the vaccine unsuitable for widespread use, says Hodgson. Some adverse reactions may take months or even years to be detected, she says. No serious safety concerns have been seen in the present trial, the companies said. But the vaccine is of a type that has never been approved before – it is an RNA vaccine that uses messenger RNA from the virus to elicit an immune response, rather than the usual attenuated virus or viral proteins – so there may yet be surprises. The companies said that trial participants will be monitored for two years after receiving their second dose.

What about approval for emergency use?

That is a distinct possibility. The FDA has a procedure called emergency use authorisation (EUA), which can grant temporary approval to unproven medicines in an emergency situation. Pfizer and BioNTech said they intend to apply for one for their vaccine but don’t yet have enough safety data. They are gathering that information and could have enough in the third week of November. The FDA has already issued a number of EUAs, but one has since been revoked. The WHO also has emergency use listing criteria, but Pfizer and BioNTech haven’t announced plans to go through the WHO’s process.

Are there any other negatives?

Yes. This vaccine requires two doses, which the WHO regards as less than ideal. Single-shot vaccines are better because you need to make fewer doses and there is no requirement for a booster shot that people might end up missing.

Another downside is that the results exclude people who have been infected with the virus before. A successful vaccine will inevitably be given to people who have had the disease, so we need to know its effect on them too. Again, the companies say they have data on this and will continue to investigate it as the trial runs on.

Then there is the fact that the results were released by press release, not in a scientific paper, so the fine details are hard for scientists to evaluate. Pfizer and BioNTech said they will submit the data to a peer-reviewed journal. We also don’t know at this stage how long any protection from the vaccine would last.

If the vaccine succeeds, is it likely to produce herd immunity?

Again, we don’t know for sure, but it looks reasonably promising if enough people get vaccinated. If the vaccine stops 90 per cent of people who receive it from getting infected, as appears to be the case in the trial, then those people are a dead end for the virus. In theory, they cannot catch or transmit it, although the data released by the companies doesn’t confirm this beyond doubt.

Given that the herd immunity threshold for SARS-CoV-2 is estimated to be about 70 per cent, a vaccination rate of about 78 per cent of the population could then produce herd immunity. But with vaccine hesitancy hovering at around 25 per cent in many countries, that might be a stretch. We also don’t know if the vaccine works in older people or children under 12, which might push the threshold higher.

What is the state of play with other vaccines?

According to the WHO, there are currently 46 other candidate vaccines in clinical trials, seven of them in phase III.

But overall this is good news, right?

Yes. “Even a partially efficacious vaccine could have a really significant impact on the course of the pandemic,” says Hodgson.