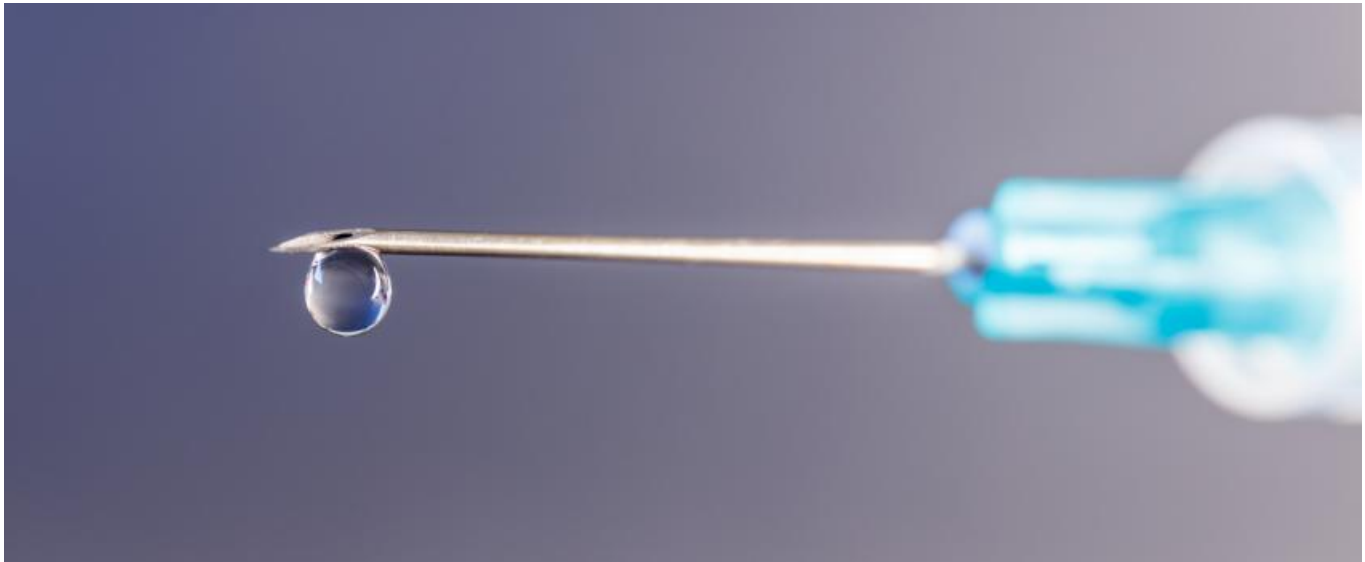


Astrazeneca's vaccine looks increasingly like an also-ran



[Elizabeth Cairns](#)



Yesterday's analysis of data on Astra's Covid-19 vaccine suggests it might remain a non-Western option.

Of the five questions about Astrazeneca's Covid-19 vaccine project *Evaluate Vantage* posed last month, three remain unanswered after [publication of a fuller analysis](#) of interim phase III data yesterday. And the answers that have been provided make for uneasy reading.

For a start the headline-grabbing efficacy figure of 90% among patients who received a half-strength priming dose is still unexplained, with the researchers conceding that it is possible that chance might have played a part in this "intriguingly high" number. And data on older patients is still conspicuous by its absence – one of several holes that leave the jab's chances of approval and labelling hard to judge.

With reference to *Vantage's* [earlier piece looking at outstanding questions](#) over AZD1222, here is a look at what we know now.

Why might a lower priming dose work better, and is this a real effect?

The researchers posited several possible explanations for the higher efficacy in the low-dose/standard-dose regimen, including lower levels of anti-vector immunity with the lower first dose, or differential antibody functionality or cellular immunity. No definitive reason was forthcoming, with Andrew Pollard, the director of the Oxford vaccine group, saying on a webcast that this seemed to be "something to do with that half dose priming the immune system in a different way".

Also on the webcast, Astra's head of biopharmaceuticals R&D, Sir Mene Pangalos, said that the company had not yet decided whether to do another trial investigating this dose, or what such a study might look like. So for now it is hard to know whether this odd finding will ever be proven. The more robust efficacy figure for the standard dose regimen was confirmed as 62%.

For which dose(s) will Astra be seeking approval?

Astra is dodging responsibility for this one. Professor Pollard said the focus of the regulatory review would be the two full doses, but added that the entire data package discussed in the paper, which covers the UK-based COV002 trial and the Brazilian COV003, had already been handed over to regulators. Therefore "it is entirely up to the regulators to look at the data and decide exactly what they think their label should say".

Can Astra use these data to file for US emergency use authorisation?

Finally a concrete answer: almost certainly not. Astra's base case assumption, according to its chief executive, Pascal Soriot, is that the US FDA will require US data, "but of course it's for them to decide". Oxford University's Sarah Gilbert added that because readout depended on events the researchers do not know when the US trial data might become available.

Moreover, aside from the FDA's unwillingness to approve products with no US patient data, the standard dose regimen is not good enough. In the UK trial the efficacy figure in those receiving two standard doses was 60.3%, but the lower bound of the confidence interval was 28%, falling beneath [the FDA's criterion of 30%](#).

The Brazilian data just about meet this threshold, with efficacy of 64.2% and a lower CI bound of 30.7%. US approval would therefore hinge on the FDA deciding that this, along with the better efficacy figures for the low-dose/standard-dose regimen in the UK trial, is good enough, but the chances of that seem slim.

What about safety?

The big news here is that investigators have finally admitted a case of transverse myelitis as being "possibly related to vaccination". This occurred 14 days after the booster shot, and an independent neurological committee considered the most likely diagnosis to be of an idiopathic, short segment, spinal cord demyelination.

The neurological experts judged two other cases of this condition as unlikely to be related to the vaccine. Of these two probably unrelated cases, one was in a patient with previously unrecognised multiple sclerosis, and the other occurred in the control group.

There was one other potentially vaccine-related serious adverse event: a patient had a fever higher than 40°C, though they recovered rapidly and were not admitted to hospital. This subject remains masked to group allocation, so they might not have even received AZD1222. The subject continues in the trial, and received a second dose of either Astra's vaccine or the control without a similar reaction.

It should be noted that the protocols for several of the AZD1222 trials, including COV002 and 003, call for at least some of the patients to be given prophylactic paracetamol to help guard against pain, fever, chills, muscle aches, headaches, and malaise.

This safety record is not exactly terrible, but is notably worse than anything that has been seen in the trials of the mRNA vaccines developed by Pfizer/Biontech and Moderna. Still, the reports of allergic reactions to the Pfizer jab that emerged in the UK today raise the spectre of post-approval events, which could occur with any vaccine candidate.

How did AZD1222 perform in older patients?

This is still a mystery. The low-dose/standard-dose regimen was not given to any patients aged over 55, and of those participants given two standard doses the proportion aged over 55 was just 21% in the UK trial and 11% in Brazil. In all, only five cases of Covid-19 included in the primary analysis occurred in subjects older than 55 years of age – too few to calculate efficacy in this population.

This answer might come after more cases have accrued; if not, it will once more be a case of waiting for the US data. More than 20% of the 40,000-odd enrollees in the US study are aged over 60, Mr Pangalos said, a much larger older population than in the UK and Brazil trials, which enrolled just 1,006 and 412 over-55s respectively.

In the meantime, Astra pointed to the [data it released three weeks ago](#) showing similar antibody levels in older and younger patients. Based on this, Mr Pangalos said that Astra does not believe there will be a difference in efficacy across age groups, but the absence of concrete infection numbers in older patients is glaring.

If AZD1222 does score approval based on these data it will not be in the US and might not be in over-55s. It's cheap and it's easy to transport – but compared with trial data on the mRNA vaccines, neither AZD1222's efficacy or safety impresses.

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