Evaluate Vantage

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Moderna's Covid-19 vaccine shows promise

Madeleine Armstrong

But the trade-off between efficacy and tolerability could limit mRNA-1273's use to those who need it least.

Detailed data with Moderna's Covid-19 vaccine are finally in, and were seized upon by a market thirsty for good news in the fight against coronavirus. While the results are very early they contain promise: all 45 healthy volunteers in the study showed neutralising antibodies after receiving two doses of mRNA-1273.

The downside was an adverse event profile that suggests the project might not be the magic bullet that many are hoping for. And the fact that, to be effective, any Covid-19 vaccine might need to be dosed yearly – or more regularly – makes Moderna's vaccine look even more unpalatable.

Otherwise healthy people might accept side-effects like fever and chills, but these could be an issue in older and sicker patients – the populations that need protection from coronavirus the most.

These potential issues did not appear to concern investors: Moderna's share price climbed 12% this morning, giving the company a staggering $31bn market cap. The company has certainly made the most of enthusiasm – or desperation – for a Covid-19 vaccine. After dribbling out data from the phase I NIAID-sponsored trial in May, a $1.3bn public offering swiftly followed (*Moderna reminds the markets of biotech's dual purpose, May 19, 2020*).

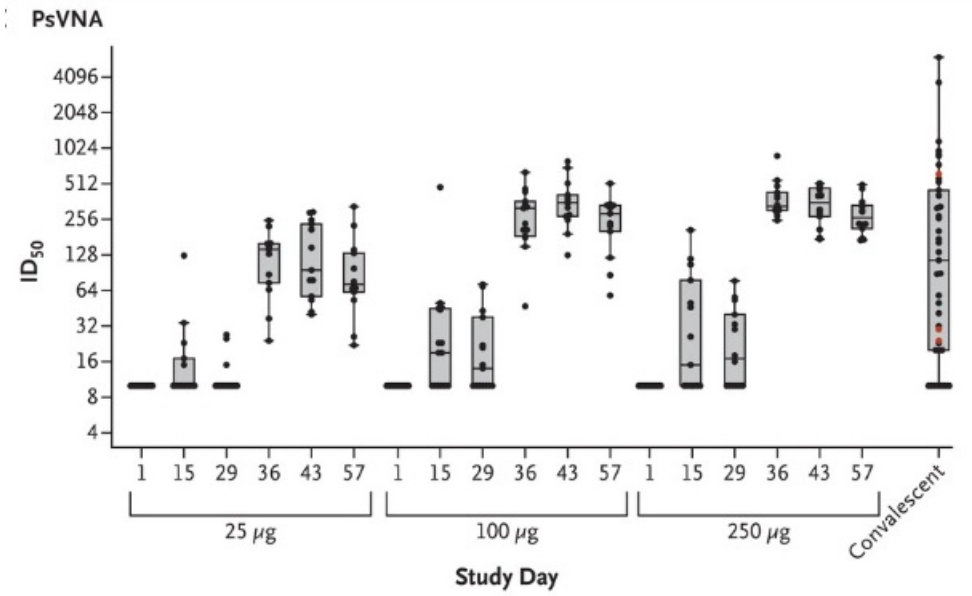
Neutralising antibodies

At the time, there was scant detail about mRNA-1273's ability to elicit neutralising antibodies, which are thought to be an indicator of a vaccine's ability to provide protection against the coronavirus.

Some of the blanks were filled in yesterday with the publication of full results from the same study in the *New England Journal of Medicine*. Promisingly, the mean levels of neutralising antibodies were similar to or above those seen in patients recovering from Covid-19.

The 100µg dose is the most relevant – this is the one that Moderna has selected to take into phase III.

Neutralising antibody levels with mRNA-1273 (PsVNA assay)



Source: NEJM article.

However, there are still many unanswered questions. For one, it is still unclear whether neutralising antibodies will translate into protection against Covid-19.

Durability is another big unknown, and there are reasons for caution: the chart above shows neutralising antibody levels peaking at day 43 before falling at day 57, the latest time point studied.

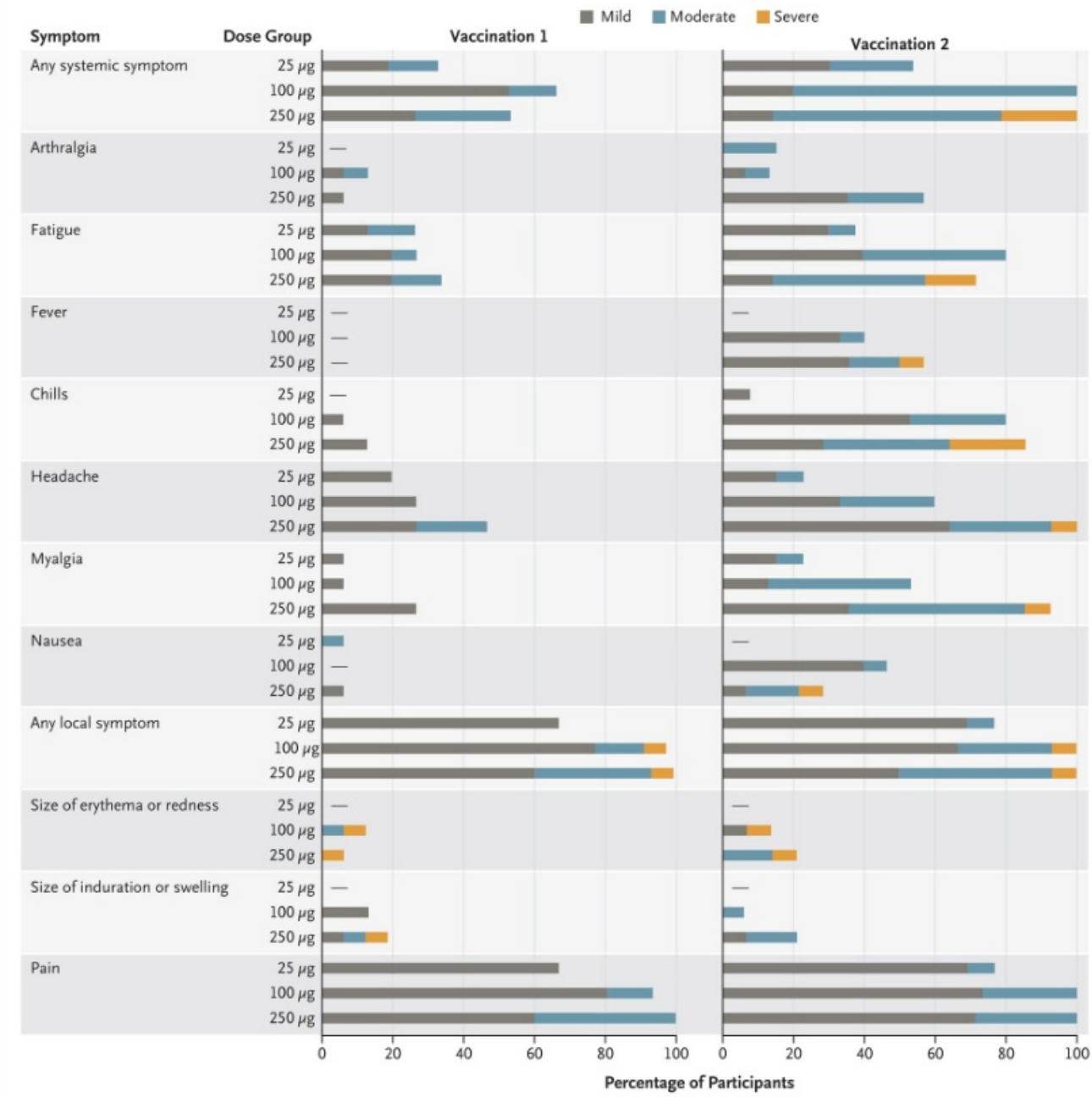
Similar to Biontech?

Still, the results look in line with those recently seen with Biontech and Pfizer's rival mRNA Covid-19 vaccine candidate, BNT162b1 (*Covid-19 vaccines remain hot – in spite of Inovio, July 1, 2020*). The studies are difficult to compare, however, given the different assays that were used to measure neutralising antibody levels.

Cross-trial comparison of neutralising antibody levels with mRNA-1273 and BNT162b1				
	Geometric mean titres			
mRNA-1273*				
	Convalescent sera	**25µg**	**100µg**	**250µg**
Day 57	109	81	232	270
BNT162b1				
	Convalescent sera	**10µg**	**30µg**	
Day 28	94	168	267	
**Using pseudovirus neutralization assay, PsVNA. Data from last available time point with each vaccine. Source: Moderna press release July 15, 2020; BNT162b1 trial preprint.*				

With so few patients studied so far, it is hard to say which project has a better chance of succeeding. But the adverse event profile of mRNA-1273 should give investors reason for pause. It is clear now why Moderna dropped the 250µg dose, with cases of severe fever and chills seen in this cohort.

Adverse events with mRNA-1273



Source: NEJM article.

Another big caveat to interpreting these results is that this part of the trial only enrolled those aged 55 and younger. An accompanying editorial in the NEJM raised the potential difficulty of finding a therapeutic window in older people. Older patients' weakened immune systems mean they might need a higher dose of vaccine to elicit a response; however, this would be the population least able to tolerate adverse events.

Older adults are being studied in other cohorts of the phase I trial, which will hopefully shed some light on mRNA-1273's risk-benefit profile in this key population.

In the meantime, Moderna is pushing on and plans to enrol the first patients into a placebo-controlled phase III trial by the end of the month. The Cove study, in 30,000 participants, has a primary endpoint of prevention of symptomatic Covid-19.

The speed at which the company has acted has been impressive. But it will be important not to sacrifice safety in the rush to get a vaccine to market.