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Merck’s Covid-19 vaccines head for the scrapheap

Madeleine Armstrong

Merck & Co’s move illustrates how hard it will be for the second wave of Covid-19 vaccine candidates to succeed.

After the stunning performance of mRNA-based vaccines against Covid-19 it was always going to be tough for the second wave of vaccine developers. Merck & Co has become the first company to bite the bullet and discontinue its projects following disappointing early efficacy data.

Others might soon be forced to follow suit – not only because of questions over the strength of their data, but also because they might simply be too late to the game. Notably, a big question mark hangs over Sanofi and Glaxosmithkline’s contender, while Curevac has given up on the US entirely, at least for now.

Late last year Sanofi and Glaxo reported lacklustre neutralising antibody levels in older adults in a phase I/II trial. Merck has seen something similar with its candidates, V590, which it was developing alongside the International AIDS Vaccine Initiative (Iavi), and V591, which it gained through the acquisition of Themis.

While Sanofi and Glaxo hope to reformulate their vaccine to improve efficacy, Merck has canned its projects entirely.

Giving up

The US company said that, in phase I studies, both vaccines were well tolerated, but the immune responses triggered were lower than those seen in people who had had Covid-19, and below those reported with other vaccines. Full data will be submitted for publication, and these will no doubt be pored over for clues about what went wrong.

V590 and V591 both work differently from the mRNA vaccines already on the market and from Astrazeneca’s AZD1222, which uses a chimp adenoviral vector. V590 employs a recombinant vesicular stomatitis virus (rVSV) – the same vector used in Merck’s approved Ebola vaccine Ervebo – while V591 uses an attenuated measles virus.

There might still be legs in the rVSV approach, Iavi believes: the non-profit organisation said it and Merck would continue to evaluate this technology to see if changes in the route of administration, viral vector or spike protein might lead to improved immune responses.

However, with no such projects in the clinic, any vaccines coming out of this research would likely be too late

to make a mark on the current pandemic.

Next wave

Even companies with mid-stage assets could find it hard to gain a foothold. Recruiting subjects into pivotal trials could be problematic, given that people might not want to run the risk of receiving either placebo or a vaccine that could turn out to be less effective than Pfizer/Biontech's Comirnaty or Moderna's mRNA-1273.

Sanofi and Glaxo's candidate might become another casualty: the groups had hoped to start pivotal trials by December, but now say a phase IIb study will begin in February, comparing their candidate with an authorised Covid-19 vaccine. A global phase III trial is slated for the second quarter.

The project is an adjuvanted recombinant protein-based vaccine, a more traditional approach than the products already on the market. But tradition has not counted for much during the pandemic: Merck, Sanofi and Glaxo all have more experience in the vaccines space than many of the frontrunners.

The most advanced recombinant protein candidate is Novavax's NVX-CoV2373, which should yield pivotal data imminently. Also expected very soon are phase III results with a single injection of Johnson & Johnson's adenoviral vector-based project JNJ-78436735 (*J&J provides early hope for single-dose Covid-19 vaccine, January 14, 2021*).

The ability to protect against Covid-19 with a single injection could provide a unique selling point, but J&J is hedging its bets here, starting a pivotal study of a two-jab regimen in November. If the single-shot data disappoint, JNJ-78436735 too could end up being an also ran.

Even some mRNA vaccine developers are finding it tough going. Germany's Curevac has told *Evaluate Vantage* that it has, for now, ruled out the US market, which a spokesperson described as "saturated in terms of pre-purchased vaccine doses as well as clinical trial centre occupancy". However, the company still sees potential in the post-pandemic phase in the US.

Moderna is not relaxing its grip any time soon, though. The company said today that it would start phase I development of an emerging variant booster candidate, mRNA-1273.351, against the B.1.351 variant first identified in South Africa.

As for Merck, its press release made no mention of further work on rVSV vaccines, but instead said the company would now focus on two potential Covid-19 therapies: MK-7110, previously known as CD24Fc, originated by Oncoimmune and which had promising interim phase III data in November; and MK-4482 or molnupiravir, an antiviral being developed in collaboration with Ridgeback Biotherapeutics. MK-4482 is in phase II/III studies in hospital and outpatient settings, with data due this quarter.

This story has been updated to include the involvement of Ridgeback with MK-4482.