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Does FDA's plasma nod set a dangerous precedent?

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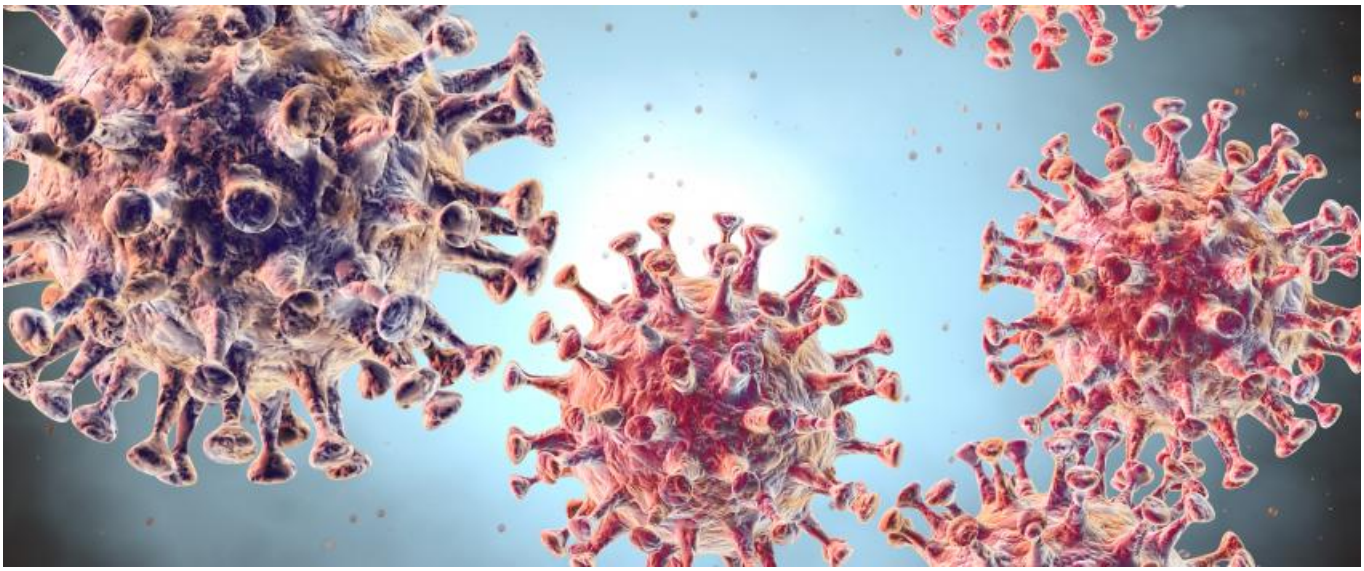

The FDA's emergency use authorisation for plasma for Covid-19 looks questionable. If this presages an early vaccine nod, we should be very afraid.

Last night's announcement that the US FDA had granted emergency use authorisation for convalescent plasma for Covid-19 caused shockwaves. The inaccurate claims that the FDA has made about the data used to support plasma's use, and the timing of the announcement – just a day after President Trump criticised the FDA – raise questions about the agency's credibility.

In reality, fast-tracking plasma – which is already being used for Covid-19 – is unlikely to make a huge difference in terms of usage, although it will make recruiting into robust studies harder. Much more worrying is the precedent that the EUA could set for Covid-19 vaccines in development.

Safety worries

If a coronavirus vaccine gets rushed onto the market in a similar way, this would prompt an even fiercer backlash from the scientific community. The main concern is that any small study used as the basis for an EUA might not uncover a safety signal that would be detected in a larger trial – not a trivial consideration for a vaccine destined for millions of people worldwide.

Many already harbour worries that coronavirus vaccines are being developed too quickly, potentially at the cost of safety. There have been hints that a vaccine might be available as early as this winter, but a more realistic – and still optimistic – scenario is an available vaccine by winter 2021.

Still, this is not fast enough for some. The Financial Times reported last night that the FDA is considering an EUA for Astrazeneca and the University of Oxford's Covid vaccine candidate, AZD1222, ahead of the US presidential election in November.

Astra made clear it had nothing to do with the idea, with a spokesperson telling *Vantage* that the company "has not discussed emergency use authorisation with the US government and it would be premature to speculate on that possibility".

The spokesperson added that the company does not anticipate phase II/III efficacy data until later this year. AZD1222 is currently in a 30,000-patient phase III study, although the FT reported that an EUA could be based on a 10,000-patient UK trial that will yield results sooner.

Interesting timing

The FT report came just a day after President Trump accused “the deep state, or whoever, over at the FDA” of making it difficult for drug companies to test vaccines and therapeutics. He claimed the agency was hoping to delay projects until after the presidential election.

That tweet also came the day before the EUA for convalescent plasma, which was announced during a press conference by President Trump yesterday.

The timing of the plasma EUA is undoubtedly odd: just a week ago, the go-ahead was reportedly put on hold after NIH officials raised concerns about the data, a move that was criticised by the president.

Yesterday’s announcement did little to clear up confusion about the data in question. Both President Trump and FDA commissioner Stephen Hahn claimed that convalescent plasma had been shown to reduce mortality by 35% in a study carried out by the Mayo Clinic.

Crucially, no randomised, placebo-controlled trials have so far been carried out with convalescent plasma, which uses plasma from donors who have recovered from Covid-19. The main data so far come from a preprint of an observational trial based on the Mayo Clinic’s expanded access programme. This reported a seven-day mortality rate of 8.7% in patients treated with plasma within three days of Covid-19 diagnosis, versus 11.9% in patients treated four days or more after diagnosis.

It is unclear where the 35% figure came from. An FDA spokesperson highlighted a 37% reduction in mortality in patients treated with high titre versus low titre plasma – but this is a subgroup analysis of a subgroup analysis, using an arbitrary titre cutoff, making its relevance highly questionable and leading to widespread condemnation of the agency.

> Convalescent plasma has shown to be beneficial for 35% of patients. This risk reduction figure - shown in chart below - is from @MayoClinic data from expanded access program that was analyzed by FDAA for the emergency use authorization announced today. pic.twitter.com/UNAWrhHa3p
>
> — Emily J. Miller - FDA (@FDASpox) August 24, 2020

Perhaps there would not have been such outrage if the convalescent plasma decision looked apolitical. It makes sense that standards are lower for EUAs than for full approvals – the former are designed to fast track projects intended for emergencies where nothing or little else is available.

However the latest decision will make it harder to generate definitive evidence of convalescent plasma’s benefit, or lack of, given that it will stymie recruitment into randomised trials in the US.

The UK Recovery trial, which uncovered dexamethasone's benefit, could provide an answer here – it treated its first patient in its convalescent plasma arm in June. That cohort has enrolled 350 patients so far and data are expected in late 2020, a spokesperson told *Vantage,* although “this depends on the scale of the epidemic in the UK over the coming months”.

Ultimately, the EUA might make little difference to the uptake of convalescent plasma, which has already been used to treat around 70,000 US patients and, in any case, will be limited by the availability of donors.

But the way the FDA’s announcement was made – and the way the agency doubled down on questionable data – raise serious doubts about whether rigorous standards will be upheld in Covid vaccine decisions.

This story has been updated to include details on the Recovery trial's enrolment and timings.