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The COVID-19 pandemic has exacerbated a fringe anti-vaccine movement, previously limited to niche communities, either skeptical about vaccine benefit, or suspicious of vaccination motives. Unfortunately, today it is no longer surprising to meet even physician colleagues who consider COVID-19 vaccination to have been either a mistake or even an unholy nexus between politics, pharma, academia, and industry. In this background, it is not surprising that recently, a rare life-threatening post-vaccination complication named ‘thrombosis with thrombocytopenia syndrome’ (TTS), was the topic of well-circulated disinformation on social media.

The trigger for this was a court submission by Astra Zeneca that its COVID vaccine, ChAdOx1-nCoV19, manufactured as Covishield by Serum Institute in India, can in rare cases cause clots due to TTS. Many people mistakenly saw this as new information that to their mind explained the recent increase in heart attacks and strokes, among the youth, when this is old information about a rare side-effect that occurs in just a few people out of every million recipients. As far back as March 2021, after tens of millions of doses had been administered, countries in Europe and UK reported cases of TTS, a week to a month after receiving ChAdOx1-nCoV-19, with remarkably extensive thrombosis.

**Risk vs benefit**

In some nations, with other available highly effective options, recombinant DNA vaccines were paused. In India and other nations, a risk-benefit analysis, and consideration of alternatives, favoured continuation. Unfortunately, with elections around the corner, this story has become politicised and has been used to imply irreparable harm to our health, alluding to an increase in heart attacks and strokes. It was also used to cast aspersions on the Serum Institute and vaccine advocacy. Nothing could be further from the truth, as illustrated by objectively considering the risk, benefit, and alternatives that guided India’s vaccine policy during the pandemic.

First, risk. TTS was found to occur most commonly in fit, healthy, young women around thirty years of age at a very low frequency of around one to two per lakh (100,000). At a general population level, it was estimated to occur at only about two to three cases per million people vaccinated. To put these numbers in perspective, the Ministry of Road Transport and Highways estimates annual deaths in road accidents at about ten per lakh. Thus, the highest estimated risk of TTS is still much lower than the annual risk of dying in a road accident. While we should strive to improve on both numbers, since every death that can be avoided matters, there is absolutely no reason for fear; not then, not now a couple of years after.

Second, benefit. Covishield was associated with over 80% protection against severe COVID-19 and over 90% protection against death in multiple studies, including during the severe Delta wave. For a 50% chance of contracting COVID-19 and 0.1% risk of death, this corresponds to a mortality benefit of around 40 in 100,000 - that outweighs the risk by far. The true benefit is much more than this, however. Reducing disease severity is important for minimising immediate suffering and stress on healthcare systems, as well as minimising long-term disability and risk of premature heart attacks and strokes. While we do not have sufficient Indian data for Covishield, it is clear from global data that COVID-19 increased the risk of subsequent thrombotic events, including heart attacks and strokes by three-four fold, even after the infection was fully resolved. This risk was observed very early in the pandemic, even before vaccines were developed, and was found to be reduced by vaccination. The current disinformation about vaccines and young heart attacks ignores this important data from large studies.

Last, but not the least, alternatives. European nations, UK, USA, and Australia stopped the use of ChAdOx1-nCoV19 / Covishield after TTS reports, despite benefits outweighing risks. They had sufficient doses of mRNA vaccines that were more immunogenic and not associated with TTS although cases of non-fatal myocarditis had been observed. Given this alternative, it was a sensible decision. For India, given the extremely large number of doses required and slow production of Covaxin, which requires culture and inactivation of the virus, it made more sense to continue.

Can we predict or prevent vaccine induced TTS?It seems that this is a rare side effect of the current recombinant DNA platform technology, since a similar vaccine used in America, developed by Johnson and Johnson, also increased TTS risk. Antibodies to platelet activating factor (PF4) are seen in most patients, similar to another drug-induced TTS – heparin-induced thrombosis and thrombocytopenia. Overall, it seems that the same powerful induction of immune response that makes DNA vaccines effective also carries a small risk of inducing auto-immune responses that lead to side effects. People who benefit the most from vaccines – older people and those with diabetes – seem to also be least likely to develop such aberrant responses. A similar pattern has been seen with mRNA vaccines and autoimmune myocarditis, where young healthy males were most at risk. Killed virus vaccines appear to be safer but induce lower levels of immune response, conferring lower levels of protection against severe disease and death. This was importantly seen in elderly deaths during the 2022 Omicron wave in Hong Kong.

**No perfect choice**

As in much of medicine, there is no perfect choice. Further research is essential to maximise benefits, minimise risks, and increase alternative options. However, at any given point of time, a decision must ultimately be made within available options, given available knowledge. In my own family, fully aware of the TTS reports from Europe and UK, I chose to go ahead with Covishield for high-risk older adults, as soon as possible. My low-risk daughters received Covaxin. Sensibly, Covishield was not used to vaccinate children. The risk-benefit analysis was unfavourable, with risk of severe infection and death in children being ten to hundred-fold lower than in adults. There were some missteps also. First and foremost, we have a data problem. Despite having given nearly a billion doses of Covishield, almost all our knowledge of critical side effects like TTS comes from outside India. The new digital India can do better. Second, while it is acceptable to choose an imperfect best option, we need to be nimbler in creating alternatives. For example, protein-subunit vaccines like Covovax (also made by Serum Institute) could have replaced Covishield for boosters. I do note that the risk of TTS was much lower in subsequent doses and the older population that received boosters was at the least risk.

A question that comes up repeatedly is whether there has been a recent increase in thrombotic events like heart attacks and strokes in otherwise healthy young people. Indian data is unfortunately lacking, but western data confirms a large increase in young heart attacks and strokes after COVID-19. As mentioned previously, this risk was highest in the unvaccinated and increased after every surge in infections. SARS-CoV2 never quite left. It keeps circulating and evolving to escape immunity, periodically giving rise to infection surges that are mostly ignored due to milder symptoms in a partially immune population. For example, based on viral load in sewage and sequencing of wastewater, we had a silent surge of undiagnosed JN.1 SARS-CoV2 infections in January this year. Whether these undetected COVID-19 infections are increasing clotting risks is not established, but it is far more likely than the concerns about a vaccine given more than two years ago doing so. Unfortunately, we have not been able to develop an adequate vaccine for preventing infection so far, at least over a long period. I fear that with anti-vaccine disinformation reaching new heights, enthusiasm for vaccine research will decline. That would be the real tragedy.

To conclude, vaccines are some of the most effective public health interventions against infectious diseases. We need to stop the fear-mongering and celebrate the great Indian COVID-19 vaccination drive that saved innumerable lives. If at all I had a wish, it would be that more of us received them sooner.