COMMENTARY / HEALTH

Like Icarus, are we flying too close to the sun with a DNA vaccine against COVID-19?

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Prime Minister Narendra Modi visited the Zydus Biotech Park in Ahmedabad to review the development of the COVID-19 vaccine on 28 November 2020. PTI

COVID-19

On 18 August 2021, Joe Biden, the president of the United States of America, announced that people who had received the Pfizer and Moderna vaccines for COVID-19 would need a third dose eight months after their second doses. He later updated it to a five-month gap between the second and third doses. Israel, one of the countries with the highest vaccination coverage, is now preparing for a fourth dose of vaccines for its population. Meanwhile, in India has hastily approved a DNA vaccine without fully considering possible long-term consequences.

The world over, governments have hurriedly given emergency-use authorisation for COVID-19 vaccines, relying on the preliminary data of efficacy from phase III trials. The duration of protection offered by vaccines and the catalogue of serious adverse effects will be known only after two years, once all the data from the phase III trials is available. In India, we have gone one step further and have permitted the use of vaccines with no published phase III data. This is unnecessarily risky.

Biden's decisions about the booster doses seem to have been announced in panic, even before the US Food and Drug Administration had evaluated the need for the extra dose. Ostensibly, this decision was taken to stymie the spread of the highly contagious Delta variant of the novel coronavirus. Rochelle Walensky, the director of the US Centers for Disease Control and Prevention, or CDC, was more forthcoming when she said in a press briefing that vaccine protection was waning. She said that data from Israel showed an increased risk of severe disease among those vaccinated early.

The severe disease in the vaccinated is reminiscent of what happened with a dengue vaccine a few years ago. Initially, Dengvaxia, which was made by Sanofi and launched in the Philippines in 2016, seemed to evoke a good antibody response in recipients. However, when exposed to the virus in the next dengue season, the vaccinated suffered more serious symptoms than the unvaccinated. This fiasco resulted in criminal charges against the vaccine makers in the Philippines.

The antibodies against viruses are of various types and generally act as protective agents. Most of the antibodies are usually what are called neutralising antibodies. However, some antibodies, called facilitating antibodies, paradoxically help the virus and make the condition of the patient more serious. Another type of antibodies, called binding antibodies, can cause further problems. Binding antibodies cannot eliminate the virus but they activate the "panic button" of the immune system. They stimulate cytokines in the body, which are proteins that act mediating agents in the growth and activity of cells in the immune system. If levels of neutralising antibodies fall, which they tend to do over time, the binding antibodies may cause unregulated production of such mediators and cause a cytokine storm that overwhelms the body, and result in multi-organ dysfunction and even death. The mechanism of such antibodies causing more severe disease is called antibody-dependent enhancement or ADE.

This may be the elephant in the room for mass vaccinations. The waning of protective neutralising antibodies that the CDC noted, and the increased severity of disease in the vaccinated, suggests that the mechanism of antibody-dependent enhancement is in play with the coronavirus infections. An article in the *Journal of Infection* in August 2021, describes how this is especially a problem with the Delta variant of COVID-19, where vaccine-derived neutralising antibodies have a decreased affinity for the spike protein of this new variant, and facilitating antibodies (that facilitate infection) have an increased affinity. The spike protein is a protrusion on the surface of the coronavirus membrane and the site where it attaches to host cells to penetrate and infect them. The authors suggest that the Delta variant may cause ADE in people who have received vaccines that were designed on the spike sequence of the original Wuhan strain.

The Biden administration and advocates of booster shots hope that booster doses will increase the levels of neutralising antibodies and dampen ADE. There is, however, no empirical evidence that this strategy will work or how many such boosters will be needed throughout life—like riding the proverbial tiger that one is afraid to dismount. The Biden announcement has, predictably, led to confusion and widespread disquiet. Warp-speed does not work well for science where lives are at stake.

Unknown to many people, India has already patented and granted emergency-use approval to a vaccine which is a presumed solution to the problem of waning antibodies. On 24 August, the Drugs Controller General of India granted emergency-use authorisation, or EUA, to the world's first DNA vaccine for use in humans. The Indian company Zydus Cadila developed the vaccine called ZyCoV-D, with help from the National Biopharma Mission, the National Institute of Virology and the Indian Council of Medical Research. The innovation involves injecting a formulation that contains a bit of the DNA of the virus—in this case, the genes to produce the spike protein—into the recipient. This DNA enters the nucleus of the host cell and the inserted genes direct the cell to make the antigen, that is, the spike protein. This spike protein stimulates the body to produce antibodies against itself, and hence grants protection from the viral infection.

In a press release on 1 July, the manufacturer Zydus Cadila claimed that unlike conventional vaccines made of a killed or attenuated virus, or even the latest mRNA vaccines, this DNA vaccine will not allow antibody levels to wane over time. However, there is no empirical evidence yet in the public domain to back up this claim. The DCGI granted this EUA without the company publishing data from any phase III trials that independent scientists can evaluate.

One is constrained to say this is reckless adventurism at best, and unnecessarily risks the lives of people. Once inserted into the nucleus, there is no way to switch off this process of production of alien protein in the body. The WHO has listed some risks associated with DNA-based vaccines. There is a concern, for example, that the continued expression of a foreign antigen can result in unwanted immunopathological effects such as immunosuppression and inflammation. So, anti-DNA antibodies—antibodies that recognise and bind to DNA—may precipitate diseases like systemic lupus erythematosus, or SLE. Among the risks anticipated by the WHO, the most alarming is that the vaccine DNA may integrate with the host chromosome and change a person's genome. If this occurs in reproductive cells, it can affect fertility and result in perinatal toxicity—a risk to the pregnant mother and her baby. Furthermore, the spike protein produced by the vaccine can result in abnormal clotting of blood or even death. The extent of all these risks will take years to evaluate. The granting of EUA to this vaccine, without adequate long-term testing, is deeply disturbing.

ZyCoV-D is the second indigenously developed vaccine for use in humans. The DCGI granted emergency approval to Covaxin, the first indigenous vaccine, on 3 January 2021, without the manufacturer even releasing its phase III trialdata. But Covaxin's approval by the Indian regulator has been called into question by the more rigorous scrutiny of foreign regulators. On 30 March, Anvisa, the Brazilian drug regulator, conducted an on-site evaluation of Covaxin because the country had plans to place an order for it. Anvisa noted serious problems with the manufacturing process. They were not sure that the SARS-CoV-2 virus was completely killed and that the vaccine was free of microbial contamination. This suggests a risk of getting COVID-19 from the vaccine itself and developing bacterial sepsis. Furthermore, Anvisa noted that there was no standardisation of vaccine potency from dose to dose. There were also allegations of corruption and bribing. Eventually, the Brazil government decided to drop its plans to buy 20 million doses of Covaxin.

Science, CRISPR technology—Clustered Regularly Interspaced Short Palindromic Repeats used for gene editing—and disease prevention with vaccines have made huge strides in recent years. A certain amount of pride in human progress is justified. But we have swung to the side of hubris. Processes and procedures have been compromised. Like Icarus with wings of feathers and wax, we can fly too close to the sun where the wax will melt and we will fall into the sea. One hopes it is not already too late to learn from Icarus.

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KEYWORDS: COVID-19 | Covid-19 vaccine | coronavirus | pandemic | drugs controller general of India | Bharat Biotech | covaxin | Zydus Cadila

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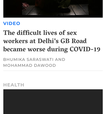

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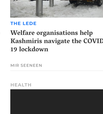

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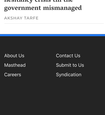

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