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HOW THE COVID-19 PANDEMIC ALTERED THE VACCINE STORY IN INDIA

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Last week, Twitter temporarily blocked a post by Florida's surgeon general Joseph A. Ladapo. He had advised against the use of mRNA COVID-19 vaccines on young men, who he said could be at a greater risk of developing cardiac-related issues. Ladapo received a vociferous blowback from the medical community. Indeed, the coronavirus vaccine story is far from over, still making headlines with great regularity.

These vaccines may not be a panacea, and Indian scientists and regulators, as in other countries, will have to wait for years before a complete understanding of the vaccines' effects on the body is possible. But the COVID-19 pandemic did something unprecedented for vaccine development, which has influenced the way other diseases are approached: it compressed the time it takes to unveil a suitable vaccine from decades to months.

Within just nine months of the pandemic being declared, Pfizer brought out the first protective vaccine against COVID-19: 12 billion doses of vaccines, by a clutch of manufacturers, have been administered the world over to date. Back home, since January 2021, 219 crore vaccines have been administered, largely produced by the Pune-based Serum Institute of India (Covishield), and Hyderabad-based Bharat Biotech Ltd. (Covaxin).

The pandemic changed the way Indian vaccine manufacturers and regulators conceived, tested and evaluated vaccines, emboldening them to apply emerging technologies to old diseases and experiment with new ways to inoculate. Pre-pandemic industry estimates suggest India's vaccine production accounted for 60% of global production.

"Indian science has benefited as a lot of technology has become accessible, research papers have been published; with mRNA vaccines proving successful against coronavirus, they can at least be tried in others," says Anurag Agrawal, Dean, BioSciences and Health Research, Trivedi School of Biosciences, Ashoka University, Haryana.

The story of dengue, which infects 400 million every year, is a particularly complex one. The dengue virus, transmitted to people by the *Aedes aegypti* mosquito, has four variants. Being infected by one doesn't immunise against the other three. In fact, someone infected for the second time may actually be at greater risk of a severe infection thanks to a phenomenon called antibody dependent enhancement, where antibodies produced during the first infection can — instead of being protective — exacerbate a later infection. As much as 80% of infections are mild according to WHO, and some 1% can be fatal.

Because of how the virus behaves in the body, developing a vaccine has been confounding.

"Scientists have tried several approaches to develop a potential dengue vaccine: from using a killed version of the virus to using modified versions of the virus and they haven't really worked," says Swetha Raghavan, a scientist at the National Centre for Biological Sciences, Bengaluru. But COVID-19 has opened up a new opportunity with the development of mRNA vaccines.

"We started this work during the pandemic and the success of mRNA in COVID-19 vaccines influenced me greatly to choose this platform," she says. Raghavan and her group have tested a potential vaccine against dengue in small animals such as rodents. The focus of their research

now is studying how the immune system of these animals respond to the mRNA vaccine. Typically it can take decades to create a new molecule, and longer to test them.

“Using mRNA, or even DNA, we can evaluate which parts of the virus are antigenic, or eliciting a response from the immune system. In the traditional approach, you usually need the whole virus,” says Raghavan. “The next step is testing it on primates and facilities for that are limited in India. So, we still have a long way ahead.”

A major advantage to these vaccines is that they can be produced quickly unlike the traditional methods using a virus that needs special containment facilities. “Now, the typical development cycle of a vaccine — that mRNA and DNA technologies have shown — can be compressed. You don’t need a whole virus, but just parts of it and this reduces the risk of handling it. This cuts costs and encourages newer players to test new vaccine approaches,” says Taslimarif Saiyed, CEO of Centre for Cellular and Molecular Platforms, Bengaluru, which helps biotechnology startups — including that of Raghavan’s — research and develop therapeutic products.

As head of a government committee to examine new vaccines, Govindarajan Padmanabhan, formerly the director of the Indian Institute of Science, Bengaluru, is optimistic about the future of mRNA. “You can start a production cycle in the morning and by evening have enough for tests. You can eliminate all the bioreactors and costs associated with storage facilities. You can create new vaccines updated to evolving strains of the virus,” he says.

mRNA vaccines however aren’t the only game in town. The Gujarat based Zydus Cadila developed a different type of DNA-based vaccine, called Zycov D, against COVID-19, the first such anywhere in the world approved for human use. Such DNA vaccines, older in provenance than mRNA vaccines, involve inserting DNA for an antigen — or the part of the virus that stimulates the immune system — into a special kind of circular DNA called plasmids that are usually only found in bacteria. These plasmids work as mules that can carry the antigen-code into the body’s cells and produce antigen that the immune system can recognise.

Like mRNA vaccines the advantages lie in being able to make vaccines in sufficient quantities quickly and safely. The challenge with DNA vaccines, says Raghavan, is that making the DNA cross into the nucleus was difficult and the trusty syringe wasn’t always the best choice. Zycov D uses a PharmaJet needle-free system that, akin to a hydraulic jet, propels the vaccine into the cells through the arm.

The holy grail of modern vaccine development is to minimise adverse reactions and the contemporary approach to this end is to use as little of the virus, or expose only those parts of the virus that are absolutely necessary for training the immune system.

Prior to the pandemic, the Serum Institute of India and Bharat Biotech developed vaccines for multiple disease largely relying on the traditional approach, which is harvesting a disease-causing virus, rendering them incapable of multiplying in the body, and creating formulations that can be safely injected to elicit protective antibodies from an individual’s immune system. But during COVID-19, both companies took divergent turns. Bharat Biotech stuck to the tried and tested approach whereas the Serum Institute of India relied on a relatively newer approach, called vector vaccine, successfully tested by scientists at the Oxford University.

Rather than use a whole virus, they wrapped DNA in a harmless, dead virus called an adenovirus, a kind of virus that sickens chimpanzees but not people. Once injected into the body, the DNA specifically codes only for a part of a coronavirus called the spike protein, that it uses to infect healthy cells. The many such spike proteins produced coax the immune system to make protective antibodies.

COVID-19 vaccines also spurred companies in India to experiment with newer devices to administer vaccines.

Bharat Biotech unveiled iNCOVACC, which is a COVID-19 vaccine that can be administered nasally, much like the way polio drops are given to children. Similar to Covishield, the formulation contains the spike protein that's ensconced in a harmless adenovirus; the objective being to get the body to produce antibodies immediately, when the coronavirus enters the nose. This should ideally prevent even the mildest form of illness that a coronavirus infection can cause along with preventing the person-to-person spread. This is a step above what injection-administered COVID-19 vaccines can do.

While the company has conducted the three mandatory stages of human trials, they are yet to publish results that demonstrate if two doses of iNCOVACC are indeed more effective in preventing mild coronavirus infection.

The Serum Institute of India recently announced a quadrivalent vaccine, meaning it protects against four types of the virus that causes cervical cancer in women. CERVAVAC introduces 'virus like particles' , again doing away with introducing an actual virus, to stimulate an immune response from the body. The 'virus like particles' approach is being employed in several other therapies and vaccines and Serum's breakthrough involved being able to devise an efficient low-cost process to make these particles while keeping costs to a fraction of what these vaccines now cost in India.

While mRNA offered the advantages of not requiring biological processes, the technology is complex, evolving and needing a number of components, enzymes and raw materials, brought in from various sources, says Soumya Swaminathan, Chief Scientist, WHO. "Many of the tried and tested vaccines work well and do the job they are meant to do. Only in instances where there are gaps or disadvantages with existing technology, would there be a need to shift to mRNA," she says.

Meanwhile, tuberculosis, which claims 400,000 Indian lives annually, is unlikely to be reined in by an mRNA or DNA vaccine. "Tuberculosis is a master at evading the immune system. Vaccines can work for diseases where the immune system, once exposed, can learn to build a defence. This doesn't work for tuberculosis and neither mRNA or DNA is likely to solve that," says Agrawal.

For instance, designing a tuberculosis vaccine depended not on the platform-technology employed but identifying an optimal combination of antigens that elicit the best protective immune response. "Using an mRNA platform will not solve that problem, though it offers a possibility for rapid development and testing of new tuberculosis vaccines. It is an exciting time for R&D in this space and Indian institutions and companies are well placed to take advantage of these technological developments as well as the existing supportive ecosystem," Swaminathan says.

While it is unlikely that India's vaccine companies will fully switch to newer vaccine technologies any time soon Agrawal believes that in the decades ahead, there may be entirely new ways to deliver vaccines. "Traditional vaccines won't go away anywhere soon but I would imagine that it would become easier to synthesise proteins and have nano-bots deliver the required medicine right into specific cells. We are at a stage where technology is changing at an exponential rate and, who knows, two or three decades from now the way we administer vaccines may be unrecognisably different."

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