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INSIDE THE MAKING OF INDIA'S FIRST HPV VACCINE

Serum Institute of India's Cervavac can be a game changer in the fight against cervical cancer

Clockwise: Adar C. Poonawalla, CEO of Serum Institute of India; a demo vial of Cervavac; a technician at the vial inspection station at SII's campus in Pune. JIGNESH MISTRY/MINT

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PUNE

A six-minute drive from the old campus of Serum Institute of India Pvt Ltd (SII), at Hadapsar in Pune, takes you to its new campus, the Poonawalla Bio-Tech Park. While the old campus resembles a public research institution with its dichromatic, two-storey buildings flanked by numerous palm trees, the Bio-Tech Park is the opposite. It has a distinctive corporate feel, with shiny high rises and new factories. The park is still a work in progress, though. There are cranes at work and scaffolding around several buildings.

The world's largest manufacturer of vaccines had planned to inaugurate the park with the production of the human papillomavirus (HPV) vaccine, India's first indigenously made one, months ago. HPV infections are among the most common sexually transmitted diseases and such vaccines can prevent many related cancers such as cervical cancer.

But then, covid-19 changed its course. Part of the facility was used to make covid vaccines.

The pandemic has ebbed and now, the focus is back on the HPV jab that promises to slash the prices of similar vaccines from foreign manufacturers. The vaccine, called Cervavac, was launched on 1 September and will be released soon.

The jab was part of a grand vision Adar Poonawalla, the chief executive officer (CEO) of SII, set for himself and the company. That vision included building world-class capacity and products around critical diseases such as cervical cancer, malaria and tuberculosis among others—products with a potential for global impact.

Cervical cancer is the second most common cancer among women in India, which causes over 75,000 deaths every year, according to a 2020 estimate published in *The Lancet*. At roughly 120,000, India accounts for one-fifth—and the largest proportion—of total cases in the world. Over 80% of cervical cancer cases in India, and around 70% of cases worldwide, are attributed to two high-risk types of HPV: 16 and 18. According to the National Cancer Institute, the US government's principal agency for cancer research and training, HPV is a group of more than 200 related viruses and there are about 14 high-risk HPV types.

While regular cervical screening (pap test) is a preventive strategy, the transmission of the disease can only be contained through widespread vaccination, making it the primary prevention measure. But the current vaccines aren't a mass market phenomenon. Their uptake in India, thus far, has been low.

There are two vaccines available in the Indian market: Gardasil and Gardasil 9, manufactured by MSD (Merck & Co. in the US). Gardasil is effective against four types (6, 11, 16 and 18) and comes with a price tag of roughly ₹3,500. At around ₹10,000, Gardasil 9 is a recent one; it is effective against nine HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58).

"Cost is the major factor that has limited the introduction of HPV vaccines in low- and middle-income countries," says Dr Gagandeep Kang, professor of gastrointestinal sciences at Christian Medical College, Vellore. She agrees that a cheap, easily available HPV vaccine can "control and reduce" cervical cancer.

It is here that SII's Cervavac can be a game changer. It has proven to be as effective as Gardasil against HPV types 6, 11, 16 and 18 during trials, says Dr Hitt Sharma, a scientist at the company. And it would be available at almost one-third the price of Gardasil in the private market and at one-tenth for the government.

"The vaccine will first be available in the private market in April-May, at a price of ₹1,000-1,500 per dose," says Poonawalla. Four-five million doses are expected to be supplied in 2023. SII will boost the capacity to 60-70 million doses thereafter. The annual production is eventually expected to stabilize around 140 million doses. "We may begin exporting from 2025 onwards," Poonawalla adds.

> The phase 2 trials were conducted among about 600 subjects across 10 sites in India in October 2018. It was successfully concluded by January 2020.

THE SCIENCE

The breakneck speed at which covid vaccines were readied gave a false impression about the process of vaccine development. Vaccines usually have a gestation period of 10-15 years.

After Harald zur Hausen discovered the strains of cervical cancer-causing virus during 1980-84, which won him a Nobel Prize in medicine in 2008, it took another seven years to make a breakthrough leading to HPV vaccines. Researchers Ian Frazer and Jian Zhou replicated a part of the virus into virus-like-particles (VLPs), the building block for the HPV vaccine. It took roughly a decade for Merck & Co. to come up with a commercial vaccine since it acquired the licences in 1995. GSK plc., a British multinational pharmaceutical company, soon followed suit.

Unlike drugs, vaccines do not have their "generics" per se. So, even though SII arrived in the HPV vaccine space several years later than MSD and GSK, there was no readymade recipe available for it to copy and mass produce. The company had to develop its own processes.

In 2011, SII imported 'platforms' (clones of yeast) from Germany and kicked off the process. The yeast platform is where VLPs for different HPV types are expressed and separated. But that involves a number of steps whose conditions had to be figured out by SII scientists through trial and error, over many years.

The first step is fermentation (a biochemical process), where the cellular culture (yeast) is grown. In one batch of production, a tiny vial of 1.5 millilitres containing cellular material is converted into a broth of 120 litres over several days. The pH conditions, dissolved gases content, etc., are optimized here to get the accurate yield.

The scientists then separate the VLPs from this broth over a couple of days, and further purify them. The purified material, which is now just three to eight litres, is tested for its physical and chemical properties and finally poured in polypropylene bottles.

There are four different bottles of VLPs corresponding to four different types of HPV, which need blending. Before that can happen, additional components (excipients) to enhance the immune response and stability of the vaccine are added. This process is called 'formulation', one of the most critical steps in vaccine making. Scientists at SII found the correct components and conditions for formulation after a lot of tinkering. Once the mixtures of different types have blended well, and shown enough stability, they are passed on to automated filling stations.

Thanks to abundant labour and advanced infrastructure, SII produces vaccines at a scale its western rivals cannot. This brings down the cost. However, that alone does not explain the lower cost. SII's vials often contain multiple doses—it went up to 10 doses for Covishield, the covid-19 jab—which reduces the cost of manufacturing, packaging, storage and distribution.

That is not just a matter of business practice but of correct scientific formulation. As vaccines are easily susceptible to microbial contamination, preservatives need to be added to allow multiple withdrawal from a single vial. And the search for the right combination of preservatives took some time and effort.

mint SHORT STORY

WHAT

SII launched Cervavac, India's first indigenously made HPV vaccine on 1 September. It will be released at almost one-third the price of its competition in the private market.

AND

Cervavac's affordability could allow it to be part of government vaccination programmes, not just in India but worldwide. India may include it in its Universal Immunization Programme.

NOW

Four-five million doses are expected to be supplied in 2023. SII will eventually boost the annual production to around 140 million doses. It plans to export from 2025 onwards.

THE TRIALS

It took two-three years for SII to finalize the correct recipe for HPV vaccines and advance to pre-clinical studies, which were conducted in the labs of Syngene International Ltd (a subsidiary of Biocon) and Eurofins Advinus Pvt Ltd, in Bengaluru in 2014-15.

A set of tests were initially done on rats and rabbits. "As the HPV vaccine will be administered on girls and women of child-bearing potential, its reproductive toxicity (effects on fertility) was also demonstrated, in addition to the effects of acute and repeat doses," explains Dr Sharma.

SII then submitted the relevant reports to the Central Drugs Standard Control Organization (CDSCO), the regulatory body, and sought permissions for human trials, which began in 2017.

The first human trial was on healthy adult population of 18-45 years of age, not on the target population (adolescent girls and boys, for instance, are part of the target population for HPV vaccine). It was conducted by Syngene among 20-30 volunteers, who were followed up for 30 days. Their blood samples were also drawn to study the biochemical parameters. The volunteers are monitored for any serious adverse events. "One or two women reported blood in their urine, but that turned out to be remnants of their period blood," says Dr Sharma. The investigator ruled that the vaccine is safe, he adds.

The SII team then filed a request to conduct phase 2 and 3 trials, to expedite the process. This can be done in cases where the makers are certain about the safety of the vaccine. The phase 2 trials were conducted among about 600 subjects across 10 sites in India in October 2018. It was successfully concluded by January 2020, which showed that the efficacy of Cervavac was similar to that of Gardasil.

HPV vaccines' efficacy is measured in terms of the response of the body's immune system. And multiple studies have shown 98-100% of seropositivity (presence of antibodies in the blood sample) for Gardasil even after several years of vaccination.

The third trial was delayed due to the pandemic, and SII had to enrol fresh subjects due to attrition. In total, 1,700 subjects participated across 12 sites in India. The study concluded in March 2022 without any major complaints—no side effects, beyond mild pain and fever were reported.

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SII's vaccine was cleared for marketing by the CDSCO on 12 July. Two doses at a gap of six months are recommended for those 9-14 age group. Three doses are recommended for those between 15 and 26 years. The second and the third are to be administered after two and six months of the first dose, respectively.

SII received support from the Biotechnology Industry Research Assistance Council (BIRAC), set up by India's department of biotechnology (DBT), the Bill and Melinda Gates Foundation (BMGF) and the International Agency for Research on Cancer, World Health Organization. It received funding support up to $9 million from DBT and BMGF. The project cost around $100 million.

THE ROLLOUT

In the past, older HPV vaccines in India have been mired in controversies. Seven deaths were reported during a study among 23,000 girls in Andhra Pradesh and Gujarat in 2007-10. While the study and the vaccines received a lot of bad press, and were suspended in 2010, a government investigation found no link between the deaths and the vaccination.

"On deeper investigation, it was found that the deaths were unrelated to the vaccination (for example, drowning), but the issues were with the way the study was conducted even though the vaccine was safe and licensed," says Dr Kang.

This episode created a lot of suspicion among people, which both SII and the government may have to reckon with once the new vaccine is rolled out.

But one thing is certain—Cervavac's affordability could allow it to be part of government vaccination programmes, not just in India but worldwide. As initial volumes will be small, the Indian government may defer the implementation under the Universal Immunization Programme (UIP) by six months or so. Under UIP, immunization is provided free of cost against 12 vaccine preventable diseases. The price for the government procurement will start at ₹300-400, and may even go below ₹300 once the demand goes up, says Poonawalla.

Barring covid, tetanus and adult diphtheria (Td) vaccines, all vaccines that are administered under government programmes are for children. An adult vaccine under the UIP is not common in India. Will girls and women come forward?

"Pediatric vaccination programmes are a success because women, especially when they wear their mother's hat, make sure their children receive the shot," says Poonawalla. "I'm confident that once the information is out, women will take the decision that it's good for their girls, boys and themselves," he adds.

Boys and men can also take also take HPV vaccine to prevent themselves from genital warts and anal, penile and oropharyngeal (head and neck) cancers.

As a bulk of the target population would be the young, SII is open to exploring channels such as social media to reach out. Perhaps, bring a celebrity on board to build awareness. "We already have that in mind, but we do not want to disclose that just now. You will hear a lot about it when the time comes," Poonawalla says, with a smile.