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Covid-19: India is at centre of global vaccine manufacturing, but opacity threatens public trust

With the second largest population and one of the biggest pharmaceutical manufacturing capacities in the world, India has a central role in the covid-19 vaccination effort. But hurried approval of its own vaccine threatens to undermine domestic trust, writes Kamala Thiagarajan

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On 3 January, India's top drug regulator issued emergency approval for two vaccines for restricted use against covid-19, even though phase III clinical trials for Covishield and Covaxin are still ongoing in India.[1]

In a nation with the second highest number of infections in the world and more than 150 000 covid-19 deaths, the panic driven by news of new virus variants fuelled approval. At a press conference on 3 January, VG Somani, the drugs controller general of India, said he was approving the vaccines as an "abundant precaution" against the spread of the highly transmissible variant found in the United Kingdom.

But a lack of transparency, particularly around Covaxin, India's first home produced vaccine, threatens to shatter trust at a time when the country is planning one of the largest and most difficult vaccination efforts in the world, while deploying its pharmaceutical production expertise to supply vaccine stocks to countries desperately in need of them.

A tale of two vaccines

Of the two vaccines approved, Covishield is the better known. It's a version of the Oxford University-AstraZeneca vaccine that was found to have an average efficacy of 70.4% in a peer reviewed study. Covishield is an Indian version made by the world's largest vaccines manufacturer, the Serum Institute of India, and phase III trials on an Indian cohort have begun, with 1600 people enrolled in November.

Covaxin is India's first home produced vaccine against covid-19. It was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research and the National Institute of Virology, and 25 800 people have been registered for trials across the country. On 21 January, *The Lancet* published Covaxin's phase I trial data, giving it a green light for safety and stating that it generates adequate immune response, but said further efficacy trials were warranted.[2]

Both vaccines require two doses and work by priming the immune system with a SARS-CoV-2 spike protein. Covishield uses a weakened version of adenovirus, while Covaxin uses an inactivated SARS-CoV-2 virus extracted from an asymptomatic patient.

The emergency approval of the vaccines does not mean that safety was compromised in any way, says Samiran Panda, chief of epidemiology and communicable diseases at the Indian Council of Medical Research.

"We will continue to assess and monitor efficacy data, which should be made public once phase 3 and 4 of the trials is complete, but allowing the vaccine for use in prioritized groups now could mean preventing fresh infections, saving people from suffering the crippling effects of long covid and even death," he told *The BMJ*. Potential vaccine recipients will be given an information fact sheet, asked to provide informed consent, and monitored over a longer period of time. In the case of any adverse event, compensation would be offered, Panda says.

But K Srinath Reddy, president of the non-profit Public Health Foundation of India, believes that something so important demands a better standard of transparency. "From a purely scientific perspective, Covaxin [manufacturers] should ideally have provided the regulator with efficacy data before seeking approval," he says. "Did the context alter the decision-making process? It appears to be so."

The All India People's Science Network, representing multiple scientists' organisations, has described the approval of Covaxin as hasty. "This achievement will be hailed as a major Indian scientific achievement once efficacy data are released—but by this hasty approval, the government has shot itself in the foot," the network said in a statement.

Covaxin question marks

Beyond the hurried approval, activists from the central Indian city of Bhopal are questioning the way in which Covaxin's phase III clinical trials have been conducted.

Rachna Dhingra is a social activist working with the survivors and families of the victims of India's Union Carbide accident, a chemical leak in Bhopal in 1984, one of the worst industrial disasters in Indian history. In early December 2020, she says, People's University, a privately run medical college and hospital, sent their staff to the areas behind the abandoned Union Carbide factory. At least 700 people were recruited for the Covaxin trial and paid Rs750 (£7.5; €8.4; $10.3), but there is no record of informed consent, despite audiovisual recording of consent from people who cannot read or write being mandatory since 2013.

This was not followed up, says Dhingra. "Many did not understand that they were participants in a trial. They thought the jab was protection against covid."

Follow-up on their symptoms was inadequate and further hindered by the fact that they could not make a written record of their reactions to the vaccine. Many family members shared one phone and not everyone was available for such monitoring.

The controversy has been widely covered in the Indian media.[3] On 21 December, one trial participant, a 42 year old man, died; he had received a first dose of Covaxin on 12 December. Autopsy listed the cause of death as cardiorespiratory failure as a result of poisoning. Bharat Biotech said in a statement that it could not confirm whether the participant received the placebo or the vaccine, because it was a double blind study, but the adverse event had been investigated and found to be unrelated to the vaccine.[4]

It followed reports in November of a participant in the Covishield trials in Chennai demanding compensation after he was diagnosed with acute neuroencephalopathy, which he claimed was because of the vaccine.[5] The Serum Institute of India said in a statement that the medical condition had no link to the vaccine.

Neither of these unfortunate incidents seems to be vaccine related, but Anant Bhan, an adjunct professor at Yenepoya University in Mangaluru, says confusion arose because of the lack of transparency surrounding the trials, and the failure to communicate the rationale behind the emergency authorisation of the vaccine.

"As the number of participants in a trial increases, there's a higher chance you will catch adverse events, which would be relatively rarer in smaller groups," he says. "This is why efficacy data is important to know—safety is an ongoing process even in phase 4, as you market the vaccine.

"It's concerning, because all this could have an impact on public trust in the vaccine, undermining such a critical public health intervention."

India's vaccine drive

India's huge immunisation drive began on 16 January 2021. The health ministry is aiming to vaccinate four priority groups: healthcare workers, people over 50, public workers, and those under 50 with comorbidities—with the former two groups to be inoculated first in an initial rollout to 30 million people

As of 19 January, 1.5 million people had been vaccinated, although there were initial reports of scepticism among medical workers, with less than 30% of New Delhi health workers across six government hospitals accepting vaccinations.[6]

The vaccines are being provided free to frontline workers—with no choice as to which one recipients receive. They are paid for by the Indian government, which says that the two approved vaccines cost them a quarter of the price on the global market, making them the cheapest in the world. Covishield is priced at Rs200 and Bharat Biotech's Covaxin will cost Rs295 for a single dose. Furthermore, Bharat Biotech is providing the government with 1.65 million free doses of Covaxin, reducing costs further.

But when the vaccines reach the private market, prices are expected to be much higher. Covishield will likely be around five times higher,[7] at Rs1000 per dose, and at the time of writing there are no measures in place to keep them affordable for those who need it. The health ministry's vaccine campaign is aiming for 300 million people to be vaccinated in its initial phase.

With the world's second largest population, at 1.36 billion, that's a huge potential market. There are media reports of the government allowing the import of other vaccine brands without any restrictions on pricing to ensure speedy clearance and delivery.[8] Pfizer, manufacturer of the world's first approved vaccine, is interested, though it has been asked by the government to undertake local trials.[9]

With one of the largest pharmaceutical manufacturing capacities in the world, India seems well placed to deal as both importer and exporter.

On 22 December, US pharmaceutical company Ocugen signed a letter of intent to codevelop Bharat Biotech's vaccine for the American market. And in the wake of mixed efficacy results for the Chinese Sinovac vaccine, Brazil has looked to India for both Covaxin and Covishield stocks. On 23 January, two million doses of Covishield, requested by the Brazilian president, had already been delivered,[10] and a memorandum has been signed by private Brazilian clinics for five million doses of Covaxin to be delivered by March.[11] Meanwhile, India is donating 800 000 doses of Covishield to be divided between Bangladesh, Bhutan, Myanmar, Nepal, the Philippines, and Seychelles as a goodwill gesture, with Afghanistan, Sri Lanka, and Mauritius also in line for donations.[12]

India's biotech companies are also expected to produce 300 million doses of Russia's Sputnik V vaccine. Sputnik V also cleared Indian safety trials in mid-January,[13] paving the way for phase III clinical trials and possible local rollout. This may prove crucial as the powdered version of the vaccine can be stored at refrigerator temperatures, making it more suitable for India's climate.

It puts India in a prime position to both benefit from the world's vaccine need and provide for its own citizens.

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