

How Developing Countries Can Make mRNA Covid Vaccines

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Across the developing world, hundreds of millions of people are unable to get a vaccine to protect themselves from the ravages of Covid-19, and millions of them have already become infected and died.

Depending on wealthy nations to donate billions of doses is not working, public health experts say. The solution, many now believe, is for the countries to do something that the big American mRNA vaccine makers say is not feasible: Manufacture the gold-standard mRNA shots themselves.

Despite mounting pressure, the chief executives of Moderna and Pfizer have declined to license their mRNA technology in developing countries, arguing it makes no sense to do so. They say that the process is too complex, that it would be too time- and labor- intensive to establish facilities that could do it, and that they cannot spare the staff because of the urgent need to maximize production at their own network of facilities.

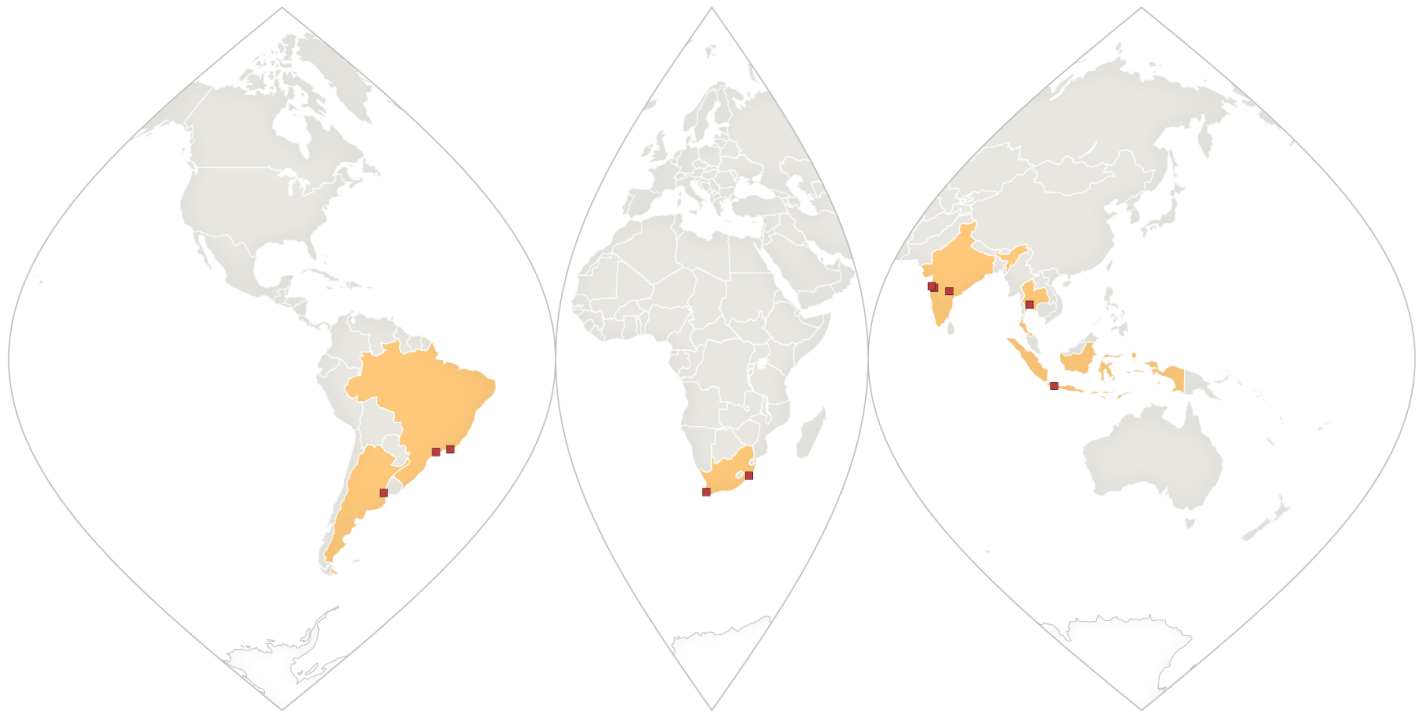
"You cannot go hire people who know how to make mRNA: Those people don't exist," the chief executive of Moderna, Stéphane Bancel, told analysts.

But public health experts in both rich and poor countries argue that expanding production to the regions most in need is not only possible, it is essential for safeguarding the world against dangerous variants of the virus and ending the pandemic.

Setting up mRNA manufacturing operations in other countries should start immediately, said Tom Frieden, the former director of the Centers for Disease Control and Prevention in the United States, adding: "They are our insurance policy against variants and production failure" and "absolutely can be produced in a variety of settings."

The vaccine needs of poorer countries were supposed to be met through Covax, a multinational body meant to facilitate global vaccine distribution — but donations have been slow and limited. Wealthier countries have locked up supply. Just 4 percent of people in low-income countries are fully vaccinated.

Experts in both the development and production of vaccines say the mRNA vaccines involve fewer steps, fewer ingredients and less physical capacity than traditional vaccines. Companies in Africa, South America and parts of Asia already have much of what they would need to make them, they say; the technology specific to the mRNA production process can be delivered as a ready-to-use modular kit.



Ten Candidates for mRNA Production

The Times assessed 10 companies around the world that are strong candidates to manufacture mRNA vaccines.

Most estimates put the cost of setting up production at \$100 million to \$200 million. A few large pharmaceutical producers in developing countries have these funds at hand; others would need loans or investors. The U.S. International Development Finance Corporation and the International Finance Corporation both have billions of dollars in funding available for this kind of project, as low-interest loans or a share of equity.

The New York Times interviewed dozens of executives and scientists at vaccine, drug and biotechnology companies across the developing world and from those conversations, found 10 strong candidates to produce mRNA Covid vaccines in six countries on three continents. The key criteria include existing facilities, human capital, the regulatory system for medicines and the political and economic climate.

Which Companies Could Produce mRNA Vaccines?

The Times assessed leading companies based on suitable production facilities and the availability of skilled workers, the country's history of drug regulation and certification for drug export, and other political and economic factors that affect research and trade.

The Serum Institute of India, the world's largest vaccine maker, has huge capacity and extensive supply chains. It already produces Covid vaccines for Oxford-AstraZeneca and Novavax, as well as other vaccines for the W.H.O. and Unicef, and is investing in mRNA production. The Indian government barred exports of its Covid vaccines for months this year.

Based in Hyderabad, **Biological E** is a large and experienced company that has its own protein subunit Covid vaccine in Phase 3 trials. The Indian company has a contract to bottle the Johnson & Johnson Covid vaccine. It says it could make 100 million mRNA doses a month. It has W.H.O. prequalification for seven products.

Based in Rio de Janeiro, **Bio-Manguinhos** already produces more than 120 million doses of vaccine each year and has W.H.O.-prequalified products. As a public institution, it can't access funding from bodies such as the U.S. International Development Finance Corporation, but it has solid support from Brazil's government.

Instituto Butantan, a renowned scientific research institute in São Paulo, produces two-thirds of Brazil's vaccines and has strong government support. Butantan is already producing China's Sinovac vaccine, and is testing its own Covid vaccine.

Gennova Biopharmaceuticals in Pune is testing its own Phase 2/3 mRNA Covid vaccine. The CEO worked on vaccines at the U.S. National Institutes of Health. The company developed new mRNA technology with HDT Bio of Seattle. Gennova has limited manufacturing capacity of its own but its parent is a large generics maker, and it has strong Indian government support.

Based in Bangkok, **BioNet-Asia** is a growing private vaccine maker currently testing a Phase 2 Covid vaccine candidate invented at Chulalongkorn University. It uses mRNA encapsulation technology developed with the University of Pennsylvania.

Durban-based **Aspen Pharmacare** bottles the Johnson & Johnson vaccine and says it could produce a billion mRNA vaccine doses within a year with a \$100 million investment and a partner for the drug substance. Aspen has strong facilities and a footprint across Africa; constraints include the country's smaller pool of experienced biotech personnel and infrastructure challenges in South Africa.

Cape Town's **Biovac Institute** has a contract to bottle the Pfizer-BioNTech vaccine. Biovac is a partner in the W.H.O. mRNA tech transfer hub, and has solid government backing. Cape Town has a strong clinical trials infrastructure.

Based in Argentina, **Singerium Biotech** was selected by the W.H.O. as an mRNA development center. The company bottles vaccines, but does not produce drug substance. The country is politically and economically fragile.

BioFarma is a large state-owned company in Indonesia which currently bottles China's Sinovac vaccine. It has W.H.O. prequalification. Its halal production process makes its vaccines suitable for use across the Muslim world.

The candidates include companies that are already making other Covid vaccines, such as the Serum Institute of India, the world's largest vaccine maker; public institutions that are already testing their own mRNA vaccines for the coronavirus; and firms tapped by the World Health Organization to be regional centers for mRNA development.

Two companies in Asia are already making their own mRNA vaccines against Covid.

Genova Biopharmaceuticals in Pune, India, has one in Phase 2 and 3 clinical trials. Genova says that unlike the mRNA shots currently in use, its vaccine can be stored at the temperature of a standard medical refrigerator.

Genova's manufacturing site in Pune, India Karan Deep Singh/The New York Times

Genova is headed by Sanjay Singh, a biochemist who worked on malaria vaccines at the National Institutes of Health in the United States for six years before returning to India. The company is negotiating with contract manufacturers to make its vaccine while also working to expand its existing production capacity from 100 million to one billion doses a year, and it could be in production with its Covid shot within months, Dr. Singh said.

BioNet-Asia, a Thai drug maker, is producing test batches of a Covid mRNA vaccine developed at Chula Vaccine Research Center in Bangkok that is in Phase 2 trials.

If results continue to be positive, the vaccine could go to Thailand's drug regulator by March, and BioNet would be ready for commercial production on approval, said Kiat Ruxrungtham, who heads the research team making the ChulaCov19 vaccine.

"Having this capability and capacity of this technology platform within the country — the goal is when you have a new variant spreading or you have the next pandemic, you can start things very quickly instead of waiting to buy vaccines like we have been doing so far," Dr. Ruxrungtham said.

Other drug companies would like to license one of the existing mRNA vaccines — pay a fee to receive the formulation and instructions, then share a royalty on each dose they sell — and start making it as quickly as possible. Stephen Saad, chief executive of Aspen Pharmacare in Durban, South Africa, said that with an investment he estimated at \$100 million, his firm could be producing a billion doses of mRNA vaccine within a year — more than enough to supply all of Africa, across which Aspen already has a distribution network.

Bio-Manguinhos, the immunobiology arm of a venerated Brazilian public health research organization, will soon start clinical trials of an RNA-based Covid vaccine, said Sotiris Missailidis, deputy director of technology development for the research center.

This year, Bio-Manguinhos nearly doubled its production capacity — to 215 million doses — of other vaccines, including AstraZeneca's Covid shot, which it produces under contract. Brazil has a medical regulatory agency that maintains the same standards as the U.S. Food and Drug Administration and the European Medicines Agency.

A range of factors has restricted access to vaccines in developing countries, including supply chain and shipping bottlenecks, and politics: the Serum Institute was supposed to supply Covax, but India's government banned exports at the height of that country's second wave. Aspen in South Africa won a contract to bottle the Johnson & Johnson vaccine, but it had to export many of the shots right back to Europe and to Canada until activists created a public outcry.

"What we've learned through this pandemic is that it really does matter where the doses are coming off the production line," said Andrea Taylor, who tracks vaccine production for the Duke Global Health Innovation Center.

Making mRNA vaccine shots differs in significant ways from traditional vaccine production. It is an enzymatic process, not a biological one that involves live cells, and in many ways is closer to the work of making drugs, said Zoltan Kis, a chemical engineer who analyzed mRNA production capacity for the Future Vaccine Manufacturing Research Hub at Imperial College in London.

In fact, when BioNTech was ready to start production of its vaccine, it went not to a vaccine maker but to a cancer drug plant in Germany. Moderna's contract manufacturer in Switzerland employed former food scientists from Nestle, enlisted to transfer their chemistry skills.

"It's a game changer because you don't have to deal with the same stakeholders anymore," said Alain alSahani, a vaccines expert with Doctors Without Borders' access-to-medicines campaign.

Moderna's contract manufacturers use a modular production kit that can make 100 million doses — some in the business compare the concept to an Ikea kitchen.

The Covid mRNA vaccines have already earned more in a single year than any previous product in pharmaceutical history and are on track to bring in more than \$53 billion in revenue this year alone. The longer Pfizer and Moderna have a proprietary lock on the technology to make them, the greater the edge they will have on any future vaccine for cancer or other diseases, said Zain Rizvi, an expert on access to medicines with the advocacy organization Public Citizen. When a company has a functioning production line, it is a straightforward process to swap the mRNA content and make vaccines for a different pathogen, such as malaria or H.I.V.

This argument over manufacturing Covid mRNA vaccines echoes one that was made two decades ago about treatments for H.I.V. Hundreds of thousands of people died of AIDS in Africa long after antiretroviral drugs were widely available in wealthy nations, because the patented medications were being sold at a price far too high for governments in the worst-affected countries to purchase.

Treatment access advocates staged a global campaign demanding that the drug makers license low-cost producers or release the rights to their intellectual property to allow someone to fill the gap.

Although major Western pharmaceutical companies insisted there was no way to make the drugs more cheaply, Indian, Brazilian, Thai and South African drug makers said they could do it. Indian generic companies reverse-engineered many of the formulas, and today, the bulk of the world's AIDS drugs are made in these countries.

Now, the W.H.O. has taken on a similar challenge. Because efforts to win licensing deals or other cooperation from Pfizer and Moderna have been unsuccessful to date, the organization is backing an effort to reverse-engineer Moderna's vaccine at a technology transfer hub in South Africa, said Martin Friede, who runs the Initiative for Vaccine Research at the W.H.O. The biotechnology company Afrigen Biologics will make the mRNA and the Biovac Institute will manufacture the vaccines.

Patrick Tippoo, head scientist at Biovac, which has a contract to bottle the Pfizer Covid vaccine, said the institute would prefer to own the technology to make an mRNA vaccine. But the fastest route to production would be a partnership with the maker of one of the existing mRNA vaccines. If Biovac had access to the "recipe" and instruction from people who have made the vaccine, and were to purchase modular production suites, the company could make the vaccines in 12 to 18 months, he said.

Instead of sharing its recipe, Moderna announced earlier this month that it would spend up to \$500 million to build its own vaccine plant in Africa. (The company did not specify which of the 54 countries it planned to build in or how long it would take.) And BioNTech, the inventor of Pfizer's mRNA process, has announced plans to build plants in Africa in the next four years.

The Western pharmaceutical industry, and some supply chain and health experts, says — the fastest route to closing the Covid vaccine gap is to focus on a more equitable distribution of vaccines made by the existing players.

"No enforced technology transfer would do more to address equity than what's already lined up," said Thomas Cueni, director of the International Federation of Pharmaceutical Manufacturers and Associations, an industry lobby group in Geneva.

Intent on spreading production capacity across the developing world, the W.H.O. is also working on a second track that will seek partnerships with institutions such as Dr. Ruxrungtham's research center in Bangkok, with their own mRNA vaccines. These vaccines would potentially be cheaper to produce and, critically, could be heat stable — not requiring ultra cold storage — and thus far more appropriate for use in low resource settings, Dr. Friede said.

Some of the efforts are producing innovations that could benefit their regions far beyond the current pandemic.

Genova in India has worked with a Seattle startup called HDT Bio to develop a new method to deliver mRNA with a lipid nanoparticle, one that does not require extreme cold storage. "We wanted to solve the problem of the scalability issue, and the temperature issue," Dr. Singh, the chief executive of Genova, said. "If we can solve these problems, we are building a solution not just for India but also a global solution."

Genova received seed funding from the government of India, and it plans to use internal resources, and a potential partnership it is negotiating with a large multilateral agency, to take its vaccine forward, Dr. Singh said.

While Genova has the technology, other producers such as the Brazilian and Argentine vaccine makers would need infrastructure — such as the kits Moderna used to set up production with its contractor in Switzerland.

For the producers not yet working with mRNA, the fastest way to start making Covid shots would be a partnership with Pfizer or Moderna, but the technology transfer process would involve hundreds of steps, said Prashant Yadav, a supply chain expert with the Center for Global Development.

"Can you do it for mRNA just by sending the transfer document blueprints and having a few Zoom calls, or a team to visit for a few days? In most cases, probably not," he said. An experienced team that stayed onsite for a period of time would be crucial.

Dr. Yadav estimated it would take one of the producers in South Africa or Brazil up to 18 months to have an mRNA vaccine ready to go in arms, with a recipe-share. There would also need to be a parallel process of boosting the capacity of national regulatory agencies which will be critical to maintaining quality.

Dr. Kis said that any manufacturer that had a site at the standard set by the U.S. Food and Drug Administration-governed system of best practice for pharmaceutical manufacturing could switch to mRNA production in six months, using the pop-up production kits.

"We will build facilities in these regions to enable them to respond to this current pandemic — or maybe the pandemic will be over — but this time the world has seen what the cost of not being prepared is, so hopefully this time we've got the political will," Dr. Friede of the W.H.O. said. "Richer countries are going to have to put their hands in their pockets and contribute to the construction and maintenance of these facilities. Because in a pandemic, you're not safe until your neighbor is safe."

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She joined The Times in 2021. Previously she was a foreign correspondent for the Globe and Mail in South Asia, Africa and Latin America. She also reported from the Middle East, and covered the wars in Iraq and Afghanistan. A Canadian, she is an eight-time winner of the country's National Newspaper Award.

She is the author of several books, including "28 Stories of AIDS in Africa" and "Promised the Moon: The Untold Story of the First Women in the Space Race."

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