Engineering 15 (2022) 3–5

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

News & Highlights

Access Issues Spur Local Vaccine Efforts in Developing World

Chris Palmer

Senior Technology Writer

After more than a year of struggling to obtain supplies of the breakthrough messenger ribonucleic acid (mRNA) vaccines for the coronavirus disease 2019 (COVID-19), some low- and middle-income nations are taking steps towards producing these vaccines on their own soil. While it is possible that the global COVID-19 vaccine supply may soon outstrip demand, these efforts could help put these countries on paths to create the homegrown research and manufacturing infrastructure needed to better safeguard themselves against future global outbreaks of COVID-19 variants and other diseases.

"The Global South must never again be this dependent on the Global North," said Olusoji Adeyi, president of Resilient Health Systems, a policy analysis and consulting firm in Washington, DC, USA.

Just months into the global pandemic, Pfizer (New York City, NY, USA), working with BioNTech (Mainz, Germany), and Moderna (Cambridge, MA, USA) had independently—with funding from the German and US governments, respectively—developed, tested, and gained emergency approval for COVID-19 mRNA vaccines [1]. Created with unprecedented speed [1], these groundbreaking vaccines rely on the mRNA they contain to direct cells to produce the spike protein found on the surface of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). The immune system identifies the protein as foreign, generating an immune response that attacks the virus itself and cells it has infected.

The two currently available mRNA-based vaccines both elicit impressive immune responses with minimal side effects. However, due to their high price and their need for storage at extremely low temperatures, few people in developing countries have had access to them. Indeed, more than 70% of Moderna and Pfizer/BioNTech's doses have shipped to wealthy nations [2]. Overall, as of May 2022, less than 16% of people in low-income countries have received at least one dose of any COVID-19 vaccine, compared with more than 65% in high-income countries [3].

"The fact that the countries of the Global South could not readily access the mRNA vaccines was a serious eye opener," said Adeyi, who previously served as director of the Health, Nutrition and Population Global Practice at the World Bank. "That realization is a good thing, though, showing it is in the best interest of low- and middle-income countries to build out their own research and development capacity, their own manufacturing infrastructure, and their own logistics and supply chain systems that are not dependent upon funding or approval of high-income countries."

Beyond directing most mRNA doses to wealthy countries, Moderna and Pfizer/BioNTech have refused pleas to share or license their intellectual property (IP), which would allow manufacturers in poorer countries to produce the shots. And while more than 100 nations have pushed for a waiver on IP for COVID-19 vaccines that was first proposed by India and South Africa at a World Trade Organization meeting in October 2020, action has stalled as the European Union, Switzerland, and the United Kingdom remain opposed [2].

"If we look at historical trends, this kind of hoarding has happened before, so it was not particularly surprising. But it is shortsighted," said Amyn Malik, a postdoctoral researcher at Yale Institute for Global Health. Withholding effective vaccines from the developing world makes the entire globe more vulnerable to new variants, Malik said. "As the word 'pandemic' describes, we are talking about a global event. It is not restricted to any one place. Until most of the world population has been vaccinated, we will not be able to end the pandemic."

The reasons the companies cite for withholding their IP include concerns over quality control and the time required to bring Global South manufacturers up to speed [2]. However, independent investigations by *The New York Times* [4] and *Nature* [5] identified 10 and 100 manufacturers, respectively, in the Global South capable of producing the mRNA vaccines. "Moderna and Pfizer have repeatedly said for the last three years that no one else can do what they do, and we all knew that was not the case. The ability is there," said Tahir Amin, co-founder of the New York-based non-profit organization Initiative for Medicines, Access and Knowledge.

Lacking access to mRNA COVID-19 vaccines, many developing nations have instead relied primarily on inactivated vaccines, like the Chinese CoronaVac and Sinopharm vaccines, which use killed SARS-CoV-2, or viral-vector shots, like Russia's Sputnik V vaccine and the one made by Johnson & Johnson (New Brunswick, NJ, USA), which use a modified, non-virulent version of the virus to deliver immunogenic viral proteins. But the viral-vector shots, produced by growing adenoviruses in living mammalian cells, are harder to make than the mRNA vaccines and have been reported as less effective, spurring some low- and middle-income countries to search for ways to manufacture the mRNA vaccines on their home soil [2] (though a new report suggests the Johnson & Johnson shot, at least, may be as effective at preventing infections, hospitalizations, and deaths as the mRNA vaccines [6]).

https://doi.org/10.1016/j.eng.2022.06.001

One of the more prominent efforts toward increasing the Global South's access to mRNA vaccines has been a World Health Organization (WHO)-led technology-transfer hub. In partnership with Afrigen Biologics and Vaccines (Cape Town, South Africa), the WHO tech-transfer hub is reverse engineering Moderna's mRNA vaccine. The WHO hub, which launched in South Africa in June 2021, replicated Moderna's shot because there is more public information on its development compared to the Pfizer–BioNTech vaccine; Moderna additionally has stated that it will not enforce its COVID-19 patents during the pandemic [7].

The initial steps the WHO and Afrigen researchers took beginning in September 2021 included making a deoxyribonucleic acid molecule to serve as a template to synthesize the mRNA, and encapsulating the genetic material in a generic, nonproprietary lipid sheath. Their next step is to recreate the mixture of lipid nanoparticles that Moderna uses to encapsulate the mRNA [6], though Adeyi says those plans may change due to the emergence of lawsuits claiming Moderna's lipid nanoparticle recipe infringes on IP from a trio of biotechnology companies [8,9].

So far, Afrigen has made only microliters of the vaccine and making more will require additional innovation. The WHO expects a replica of the Moderna vaccine to be ready for clinical trials by the end of November 2022 [7]. Subsequent phases of the project will involve Afrigen teaching companies in South Africa, Tunisia, Nigeria, Egypt, and Senegal to produce their own batches [10]. "This is a very concrete, promising way of establishing viable manufacturing capacities in those countries," Adeyi said.

In another development announced in February 2022, BioNTech said it will be sending modular factories to Africa to make its mRNA vaccine from start to finish, apart from the last fill-finish step [11]. The modular factories, dubbed BioNTainers, consist of one drug substance module and one formulation module, each stuffed into six standard shipping containers (Fig. 1). BioNTech claims each complete setup can produce about 50 million doses a year at a cost far less than building a traditional factory [11].

BioNTech plans to begin setting up its modular factories in mid-2022 in Senegal, Rwanda, and potentially South Africa, with manufacturing beginning roughly 12 months later. BioNTech will staff and operate the facilities for the first 2–3 years, after which time the BioNTainers will run independently [11]. Moderna also recently announced that it will build a factory in Kenya capable of producing 500 million mRNA doses per year [12].

In addition to the Moderna and Pfizer/BioNTech related efforts, some Global South-based companies are working to create their own mRNA vaccines. More than a dozen new mRNA vaccines are currently under development in ten countries, including China, India, Vietnam, and Thailand. Compared to the Moderna and Pfizer/BioNTech's shots, some of these vaccines would be easier to store, and many would be cheaper. The furthest along is one under development by Walvax Biotechnology in Kunming, China [13]. Instead of using mRNA that encodes the entire spike protein, the Walvax shot, which could be stored in a standard refrigerator, encodes only the receptor binding domain, a key portion of the spike protein. In July 2021, the company started a placebo-controlled phase 3 trial in China, Indonesia, Mexico, and Nepal that will enroll 28 000 people; the company anticipates being able to manufacture 400 million doses a year [13].

Fig. 1. BioNTech's modular factory for manufacturing the mRNA vaccine it developed with Pfizer consists of a drug substance module and a formulation module. Dubbed the BioNTainer, the factories are designed to produce up to 50 million doses a year at a cost far less expensive than building a traditional factory. Credit: BioNTech (public domain).

While not an mRNA vaccine, another vaccine that could benefit low-income countries has been developed by Novavax (Gaithersburg, MD, USA). The shot, called Nuvaxovid, relies on more traditional vaccine development technology already in place in many developing countries [14]—inducing animal cells (in Nuvaxovid's case, moth cells) to produce a protein subunit that closely resembles a key protein from the virus (in this case, the SARS-CoV-2 spike protein) plus an immune-boosting adjuvant to help provoke an immune response. The vaccine, which generates antibody responses comparable to currently available competitors, has now been approved for use in 28 countries [15]. And because the vaccine is protein-based, like those used to prevent shingles and influenza, Novavax hopes it will appeal to people skeptical of the gene-based mRNA vaccines.

Researchers are also looking to boost access with novel ways to deliver COVID-19 vaccines, including the use of microneedle array patches, grids of tens to thousands of sub-millimeters projections dry-coated with vaccine. These needle-free, room temperature stable patches may sidestep the need to ship and store under cold chain conditions and could possibly enable self-administration [15]. One such array just entering clinical trials is being developed by Cambridge, Massachusetts-based Vaxxas and will deliver the HexaPro vaccine developed at the University of Texas at Austin [16].

All this innovation may be for naught, though, with respect to the COVID-19 pandemic. Demand for COVID-19 vaccines is now waning while supply is increasing. The African Union and COVID-19 Vaccines Global Access (COVAX), the WHO-backed group aimed at ensuring equitable global access to COVID-19 vaccines, have recently decided not to obtain hundreds of millions of mRNA vaccines as developing nations have struggled to turn supplies into inoculations due to a lack of funds, vaccine hesitancy, supply-chain obstacles, and other factors that have hampered distribution. More than nine billion doses could be produced globally in 2022, but demand could decline to 2.2 billion to 4.4 billion doses a year by 2023, with Pfizer/BioNTech alone capable of producing that many [17].

In any case, an additional upside of developing nations building their own mRNA vaccine manufacturing factories is that these could, in theory, be quickly repurposed to create vaccines for new COVID-19 variants and pathogens that cause other diseases. BioNTech, for example, is working on mRNA vaccines for malaria and tuberculosis [11] and Moderna launched a clinical trial in the United States in March 2022 to evaluate an mRNA-based human immunodeficiency virus (HIV) vaccine [18].

"Research and manufacturing need to be globalized," Amin said. "We've seen from this pandemic that we cannot rely on just a few pharmaceutical actors to supply the globe."

References

[1] Welsh J. Coronavirus variants—will new mRNA vaccines meet the challenge? Engineering 2021;7(6):712–4.
[2] Maxmen A. The fight to manufacture COVID vaccines in lower-income countries [Internet]. London: Nature; 2021 Sep 15 [cited 2022 Apr 24]. Available from: https://www.nature.com/articles/d41586-021-02383-z.

[3] Coronavirus (COVID-19) vaccinations [Internet]. London: Our World in Data; 2022 Jun 1 [cited 2022 Jun 1]. Available from: https://ourworldindata.org/covid-vaccinations#what-share-of-the-population-has-received-at-least-one-dose-and-completed-the-initial-vaccination-protocol.
[4] Nolen S. Here's why developing countries can make mRNA COVID vaccines [Internet]. New York City: The New York Times; 2021 Oct 22 [cited 2022 Apr 24]. Available from: https://www.nytimes.com/interactive/2021/10/22/science/developing-country-covid-vaccines.html.
[5] Prabhala A, Alsalhani A. Developing countries can make the mRNA vaccines they need. Nat Hum Behav 2022;6(2):167.
[6] Mandavilli A. As virus data mounts, the J&J vaccine holds its own [Internet]. New York City: The New York Times; 2022 Mar 15 [cited 2022 Apr 24]. Available from: https://www.nytimes.com/2022/03/15/health/covid-johnson-vaccine.html.
[7] Maxmen A. South African scientists copy Moderna's COVID vaccine [Internet]. London: Nature; 2022 Feb 3 [cited 2022 Apr 24]. Available from: https://www.nature.com/articles/d41586-022-00293-2.
[8] Abutaleb Y, Rowland C. Moderna faces new lawsuit over lucrative coronavirus vaccine [Internet]. Washington, DC: Washington Post; 2022 Feb 28 [cited 2022 Apr 24]. Available from: https://www.washingtonpost.com/health/2022/02/28/moderna-arbutus-patent-infringement-lawsuit/.
[9] Cross R. Alnylam sues Moderna and Pfizer over key COVID vaccine ingredient [Internet]. Boston: Boston Globe; 2022 Mar 22 [cited 2022 Apr 24]. Available from: https://www.bostonglobe.com/2022/03/22/business/alnylam-sues-moderna-pfizer-over-key-covid-vaccine-ingredient/.
[10] WHO announces first technology recipients of mRNA vaccine hub with strong support from African and European partners [Internet]. Geneva: World Health Organization; 2022 Feb 18 [cited 2022 Apr 24]. Available from: https://www.who.int/news/item/18-02-2022-who-announces-first-technology-recipients-of-mrna-vaccine-hub-with-strong-support-from-african-and-european-partners.
[11] Kansteiner F. BioNTech to ship modular mRNA factories to Africa starting this year [Internet]. New York City: Fierce Pharma; 2021 Sep 16 [cited 2022 Apr 24]. Available from: https://www.fiercepharma.com/manufacturing/biontech-plots-first-modular-mrna-factory-africa-by-middle-2022.
[12] Keenan J. Moderna taps Kenya as site for $500M mRNA manufacturing facility [Internet]. New York City: Fierce Pharma; 2022 Mar 7 [cited 2022 Apr 24]. Available from: https://www.fiercepharma.com/manufacturing/moderna-taps-kenya-site-500m-mrna-manufacturing-facility.
[13] Cohen J. New crop of COVID-19 mRNA vaccines could be easier to store, cheaper to use [Internet]. Washington, DC: Science; 2022 Apr 5 [cited 2022 Apr 24]. Available from: https://www.science.org/content/article/new-crop-covid-19-mrna-vaccines-could-be-easier-store-cheaper-use.
[14] Healy M. With old-school technology, can Novavax win over COVID vaccine skeptics? [Internet]. Los Angeles: Los Angeles Times; 2022 May 16 [cited 2022 May 19]. Available from: https://www.latimes.com/science/story/2022-05-16/novavax-covid-vaccine-skeptics.
[15] Weiss P. Microneedle makers seek to engineer a better shot. Engineering 2021;7(12):1661–4.
[16] Taylor NP. Vaxxas strikes deal to tee up trial of COVID-19 vaccine patch [Internet]. New York City: Fierce Pharma; 2022 Mar 29 [cited 2022 May 19]. Available from: https://www.fiercepharma.com/pharma/vaxxas-strikes-deal-tee-trial-covid-19-vaccine-patch.
[17] Paton J. Moderna COVID shots turned down by buyers on delivery woes [Internet]. New York City: Bloomberg News; 2022 Apr 5 [cited 2022 Apr 24]. Available from: https://www.bloomberg.com/news/articles/2022-04-05/buyers-turn-down-moderna-covid-vaccine-as-pandemic-demand-wanes.
[18] Rogers J. NIH launches clinical trial of three mRNA HIV vaccines [Internet]. Bethesda: National Institutes of Health; 2022 Mar 14 [cited 2022 Apr 24]. Available from: https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trial-three-mrna-hiv-vaccines.