Pandemics and the illumination of "hidden things"

Lessons from South Africa on the global response to Covid-19

P. Terblanche & M. Makhoana

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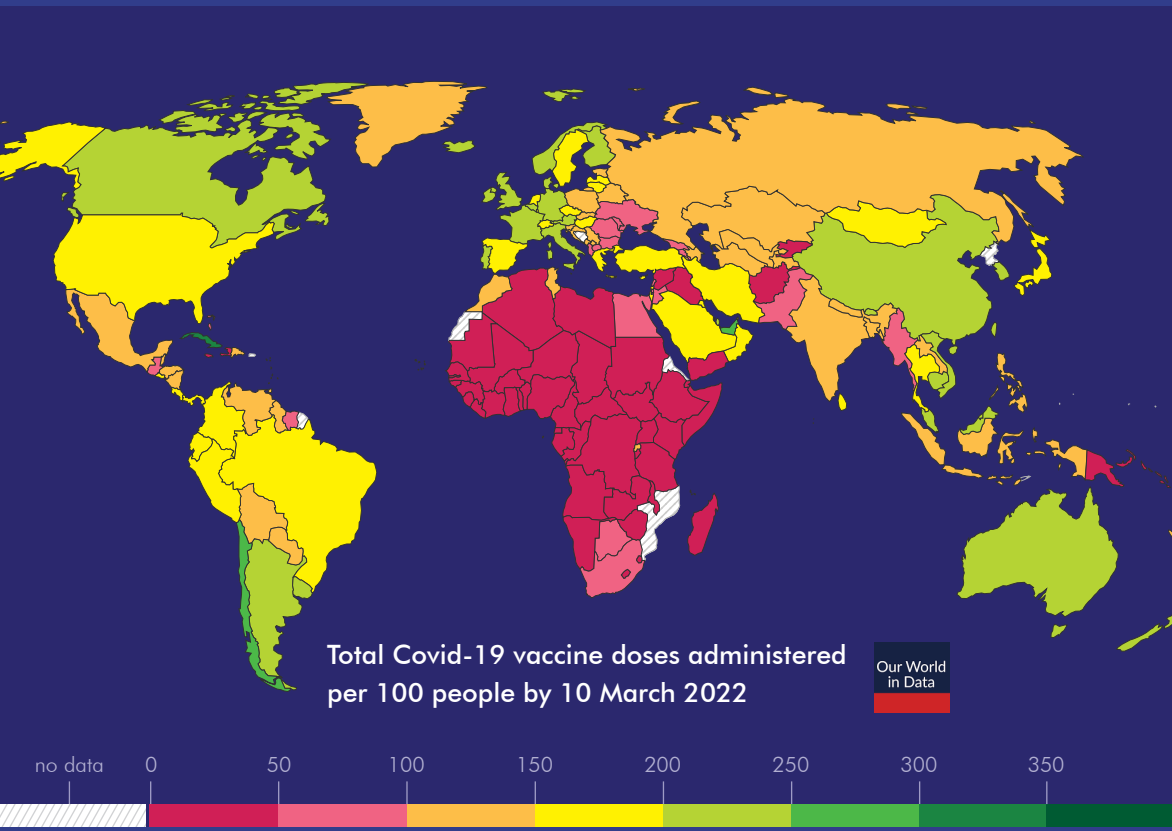

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Adaption of *World in Data*. Image shows Total Covid-19 vaccine doses administered per 100 people, as of 11 March 2022 (two years since the WHO declared Covid-19 a "pandemic").

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Reflections from the mRNA Hub in SA: Successes, challenges, lessons and future opportunities

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Never before has a disease outbreak underscored the gross inequity in access to vaccines than the Covid-19 pandemic. It confirmed, as many chapters in this collection show, once again, that low and middle-income countries are highly vulnerable to inequitable access to new immunisations and other health technologies, in part because manufacturing capacity remains concentrated in a small number of high-income countries.

A more globally distributed manufacturing capacity for vaccines and other health technologies would reduce the gap in making future vaccines timeously and equitably available and accelerate the collective effort to control outbreaks.

"A key moment for increasing vaccine capacity"

By mid-July 2021, high-income countries had administered more

than one billion doses of Covid-19 vaccines. Low and middle-income countries, in contrast, had given out almost 600 million despite being home to more than 75% of the world's population (Mathieu, 2021).

In the midst of this startling inequality came the 21 June 2021 WHO statement announcing the creation of an "mRNA Hub". It would be dedicated to making mRNA vaccine manufacturing technology available to low and middle-income countries to enable them to, one day, produce immunisations and build future pandemic preparedness (WHO, 2021).

"Today's announcement is a great step forward for SA, and for the world," WHO DG, Tedros Adhanom Ghebreyesus, said of the launch shortly after (UN News 2021). "I hope this will be a key moment for increasing production capacity in Africa for Covid-19 vaccines, but also for future vaccines."

Partners would provide training and funding to support production, quality control, production regulation and — where needed — assist with necessary licences. The mRNA Hub, meanwhile, would develop mRNA technology as a public good, sharing it with local producers from around the world to enable them to make affordable, locally produced mRNA vaccines in the future.

Afrigen Biologics and Vaccines (Afrigen), in SA, was selected by the WHO to host the mRNA Hub and establish mRNA vaccine production. The South African Medical Research Council (SAMRC) would provide the research and the partly state-owned bio-pharmaceutical company, Biovac, would become the first "spoke" — a recipient of the technology that would eventually join others from low and middle-income countries.

That the WHO selected Afrigen Biologics and Vaccines, a small, start-up biotech company in the Southern tip of Africa to house the mRNA Hub, raised eyebrows.

Many must have wondered: Could a small, unknown African biotech firm deliver on the goals of such an ambitious programme?

However, the addition of Biovac — one of Africa's foremost vaccine suppliers — to the consortium reduced that scepticism. Biovac's addition would fast-track market access for the mRNA

Hub's home-grown mRNA Covid-19 vaccine, following a technology transfer from Afrigen.

Although decades in the making, mRNA vaccine technology had become especially alluring for low and middle-income countries during Covid-19 and ahead of the mRNA Hub's creation. This is, in part, because established producers had been able to use modular solutions or repurpose existing plants relatively quickly to scale up mRNA Covid-19 vaccine production in a matter of months. Today, many experts also believe the technology holds promise beyond Covid-19 and could, one day, unlock vaccines aimed at HIV and TB, for instance. For reasons such as these, expanding mRNA technology in Africa had been a feature of discussion at the African Union aimed at increasing local production as part of pandemic preparedness from as early as 2021.

But for the mRNA Hub, only one question remained unanswered.

Where would the mRNA vaccine technology come from?

This question became the single biggest driver of implementation and partnership strategies. It also fuelled a determination to succeed.

Early successes: Incremental steps, phenomenal support

No existing Covid-19 mRNA vaccine producer was willing to partner with the mRNA Hub to share its technology.

In the absence of an established mRNA vaccine partner, its ultimate success would clearly lie in small scientific and technological steps coupled with unparalleled funding and technical support from the WHO, civil society organisations, the United Nations, governments and the MPP. The MPP is a United Nations-backed organisation working to increase access to life-saving medicines. As part of its innovative model, MPP negotiates licensing agreements with patent holders to allow broader, more affordable versions of medicines to be produced for low and middle-income countries.

The first technological milestone came within three months of the mRNA Hub's inception, when scientists at the University of the Witwatersrand and Afrigen successfully produced a mRNA vaccine

candidate at lab scale. In laboratory testing, the immunisation elicited high levels of immune response and demonstrated an ability to neutralise SARS-CoV-2 comparable with relevant international benchmarks. It also demonstrated a good tolerance and safety profile in early studies.

Although there was a misconception that SA's first, home-grown mRNA vaccine was a "copy" of existing mRNA Covid-19 vaccines, this is untrue. Instead, SA scientists combined scant information from patent applications with years of their own research in the field of mRNA — some of which was dedicated to, one day, producing treatments for neglected, tropical diseases affecting the continent.

Subsequently, the Afrigen team demonstrated its ability to scale up laboratory processes and has supplied material for further preclinical studies of the mRNA Hub's first mRNA vaccine. At the time of writing, the SAMRC was expected to begin early human clinical trials of the vaccine by mid-2023.

The candidate vaccine's name is AfriVac 2121, in honour of the date the mRNA Hub was announced by the WHO.

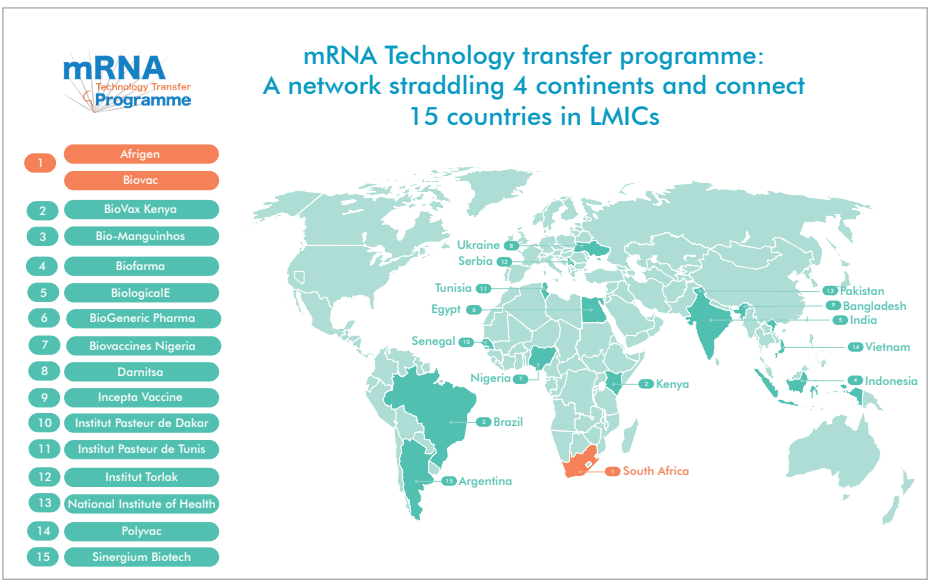

Figure 4: The 15 local producers selected as initial spokes for the Hub. Together these producers span four continents.

In parallel with the Hub's mRNA technology platform development and soon after the first laboratory-scale product was developed, Afrigen started transferring knowledge to the 15 low and middle-income country "spokes" that form the mRNA Hub's initial network (see Figure 4).

By the end of 2022, Afrigen had trained nine out of 15 spokes in introductory mRNA vaccine production. Biovac integrated well with the programme and is assisting with the development of quality control assays and support to ensure Afrigen processes meet stringent regulatory standards. Biovac will be taking Afrigen's good manufacturing practice production process, currently used for laboratory testing, and developing it for commercial use.

Conscious of the challenge to ensure the sustainability of the programme, the mRNA Hub engaged early with partners to address three challenges:

1. Operating in a complex intellectual property landscape;
2. Ensuring mRNA vaccines produced by the mRNA Hub would be fit-for-purpose: heat-stable and without the need for ultra-cold storage, for example, not available in existing, lowand middle-income country supply chains; and
3. Achieving production cost efficiencies to ensure affordability of next generation vaccines.

These goals led the mRNA Hub to collaborate with the US's NIH, mRNA production specialists Quantoom Biosciences, and mRNA immunotherapies experts eTheRNA. Many more strategic partnerships are expected in 2023.

Complex and ever-evolving intellectual property issues remain a challenge to manage and will require partnerships — and policy changes — in the near future.

Early challenges yield unexpected opportunities

It is evident that the mRNA Hub's challenges and successes have been intertwined.

For example, in the absence of a willing technology transfer partner, the mRNA Hub was forced to innovate, expanding its own

knowledge base. This resulted in the creation of an mRNA vaccine development platform (not just a product) that now carries the opportunity for vaccine innovation, multi-product production capabilities and new technology partnerships.

As more low and middle-income countries receive this platform technology, it will create a network of new vaccine producers that will contribute to vaccine production and innovation, complementing rather than disrupting existing global supply.

Still, the absence of a product-specific technology transfer partner did result in significant challenges in quality and regulatory systems that had to be developed in-house and from scratch. The time needed to develop these systems delayed original timelines for a turnkey technology transfer project. However, it allowed for significant capacity building and learning as well as the design of a facility and systems that lend themselves to different economies of scale. mRNA Hub-created systems that can accommodate a wide range of production volumes provide an opportunity to de-risk investment in multiple, smaller production units. We believe the mRNA Hub will show that even at smaller scales, mRNA vaccine production can be done with sustainable operating costs, which is important as countries ramp up production or perhaps choose to keep lower levels of manufacturing at the ready as part of pandemic preparedness units.

For decades, many vaccine producers in low and middle-income countries have been relegated to the final "fill and finish" steps of vaccine production — simply filling vials and finishing vaccines received from established producers. This has meant that emerging firms have been overly reliant on producers in high-income countries for vaccines.

As mentioned above, the mRNA Hub programme has already created and capacitated a network of vaccine producers. Some spokes are established vaccine producers and their participation in the mRNA Hub has enabled them to diversify existing production platforms to include mRNA. This has allowed some producers to — for the first time — establish drug product manufacturing capabilities to go beyond fill and finish.

Others, of course, will establish wholly new manufacturing capabilities to produce and supply mRNA vaccines.

Ultimately, the impact of this programme will reach far beyond the Covid-19 pandemic.

The collective knowledge and innovation capacity of the mRNA Hub and its spokes will usher in a new era of mRNA vaccines designed, developed and produced in low and middle-income countries and relevant for their burden of diseases. In this way, the programme could radically begin to shift the vaccine landscape, fostering greater equity and capacity in previously vulnerable and disadvantaged regions of the world.

We must build the complete vaccine production ecosystems that empower low and middle-income countries to address local needs effectively.

In 2021, the African Centres for Disease Control and Prevention launched the Partnerships for African Vaccine Manufacturing (PAVM) as part of a larger strategy to build a continental approach and capacity for vaccine production. This approach is the way forward and needs to be implemented effectively. The mRNA Hub and partners will strive to support the continent's ambition to self-supply 60% of its essential vaccines by 2040 by providing access to mRNA vaccine production technology alongside training and support.

This will be done through providing access to mRNA vaccine production technology, developing a portfolio of mRNA vaccines, training and building capacity to ensure that vaccine innovation platforms, integrated with GMP facilities for production of clinical material, are available to support supply and security.

Covid-19's most important lesson is that countries and regions that cannot locally produce significant volumes of vaccines and other health products have no guarantee of timely access to the tools they need to respond to epidemics or pandemics. This lesson need not be re-learned.

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Dr Morena Makhoana is the chief executive officer of Biovac. Previously, he served as the company's medical affairs director and then deputy chief executive officer. He serves on several committees within the vaccine industry and as a board member of other healthcare and non-healthcare companies.

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