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White Paper

Spotlight on Biovac

Building Local Biomanufacturing Capacity in South Africa

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Introduction

Currently, African producers make only one per cent of the vaccines used in Africa.[2] That is one tenth of one per cent of the global supply of vaccines.[3] The COVID-19 pandemic underscored Africa's need for quality vaccine manufacturing capacity across the continent so that every nation could respond effectively to health crises.

The industry can build on the existing capabilities of over a dozen companies across the continent – companies with experience in filling and finishing products, producing drug substances, and conducting research and development (R&D).[4]

African political leaders have prioritized manufacturing capacity building. Leaders are aware that, to sustain biomanufacturing operations between crises, biomanufacturers must produce other health products, such as routine vaccinations. Capacity that is left idle cannot be quickly brought back into action when the next crisis hits.

This case study on the Biologicals and Vaccines institute of Southern Africa (the Biovac Institute, hereafter simply, Biovac) – a South African biopharmaceutical company – traces Biovac's strategic evolution from a vaccine supplier to a vaccine manufacturer and biopharmaceutical innovator.[5] It highlights the process, partnerships, and technology transfers that have underpinned the company's progress over time.

The steady and deliberate transformation of Biovac serves as a blueprint for sustainably expanding the manufacturing capacity of biologics in the pharmaceutical value chain in Africa and other developing regions.

At a time when global, regional, and national policymakers and funders are heavily invested in extending biomanufacturing capacity, Biovac's experience provides insights into the public policies and other factors that support capacity building and that leaders of such initiatives ought to put in place. Throughout, this case study presents the lessons learned.

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African vaccine manufacturing: A sense of urgency

During the COVID-19 pandemic, African nations and lower income countries in other regions endeavored to get personal protective equipment, diagnostics, vaccines, and treatments for their people, as richer countries locked down and held on to excess supply.[6]

As the virus spread, vaccine producers in China, India, the European Union, and the United States were ready to respond: their facilities already produced vaccines and other biologics daily. With capacity, trained workers, quality controls and regulatory systems on hand, they could divert resources to, and rapidly scale up, the production of COVID-19 vaccines.

African political leaders lamented that Africa was "last in line" during the pandemic. To prepare for the next health crisis, they decided to build out the continent's capacity for producing quality vaccines, starting with cultivating a sustainable vaccine manufacturing ecosystem.

"Merck KGaA, Darmstadt, Germany is playing a key role in building sustainable manufacturing capacity in Africa," said Josephine Cheng, Senior Modality Expert. "Our work with African partners is rooted in our long-held tradition of thinking from the customer's perspective. We engage in deep conversations to understand their challenges and propose collaborative approaches that create win-win situations, fostering long-term relationships built on trust and shared success."

Partnering for the goal

In April 2021, the African Union (AU) and the Africa Centers for Disease Control and Prevention (AfricaCDC) jumped on the opportunity to expand pharmaceutical manufacturing capacity on the continent. Together they formed the Partnership for African Vaccine Manufacturing (PAVM).[7]

Today PAVM has the mandate to develop and oversee execution of a framework for action so that the African manufacturers can produce the targeted 60 per cent of vaccines that Africa needs by 2040.[8] Over time, they can apply such capacity to produce the full range of biologics, a category of health products made from living cells that includes vaccines, to meet growing demand.

In September 2022, through the AfricaCDC, the African Union issued a public health order calling for "expanded manufacturing of vaccines, diagnostics and therapeutics."[9] Among its five action items for Member States was "expanding local manufacturing of health products" by:

- Coordinating with the AfricaCDC, the AU Commission and the African Continental Free Trade Area (AfCFTA) Secretariat to build capacity and increase demand;
- Calling on GAVI (formerly, the Global Alliance for Vaccination and Immunization) and other so-called *vaccine purchasing mechanisms* such as the Revolving Fund for Access to Vaccines of the Pan American Health Organization (PAHO), to buy 30 per cent of their vaccines from African manufacturers; and
- Advocating for removal of trade and other barriers to achieving these goals.

Generating demand

United Nations agencies such as UNICEF and its alliance partners such as GAVI use vaccine purchasing mechanisms that specialize in (1) procuring safe and effective vaccines in bulk from the international market and (2) supplying them at low cost to countries in need. In some cases, they also help manufacturers to secure long-term contracts called *advance market commitments* (AMCs). Such commitments not only help fledgling regional manufacturers to raise money for expanding their facilities but also give purchasing agencies a predictable supply and lower cost products over the period.

A goal of PAVM is to *supply* such bodies as GAVI, WHO, and UNICEF rather than *rely* on them for access to vaccines. That means drumming up demand and securing long-term demand commitments and other financing tools for African producers so that they can invest in and scale up their operations.[10] This demand generation is critical, as countries across the continent expand their own capacity and depend less on GAVI and others that buy from manufacturers elsewhere in the world. With predictable demand, manufacturers can invest and scale their operations, thereby becoming cost competitive over the longer term.

For its part, GAVI – the most important procurement agency for African vaccines – committed to help Africa grow its vaccine production capacity. In December 2022, the GAVI board approved "a plan to support the development of a regionally diversified vaccine manufacturing ecosystem," including "supply security" as a procurement condition alongside elements like price.[11] A year later, GAVI announced a new fund – the African Vaccine Market Accelerator (AVMA) – to raise as much as one billion US dollars over the next ten years, for African suppliers to offset the initial higher costs of their products.[12]

To meet this demand, experienced producers like the Holding Company for Biological Products and Vaccines (Vacsera) in Egypt, Biovac in South Africa, and the Institute Pasteur Senegal across the continent are expected to catalyze local biologics manufacturing in Africa.[13] Equally significant, these efforts can inform local vaccine manufacturing policies and programs across regions for raising funds, building capacity, training the workforce, assuring quality, complying with regulations, managing demand, and securing AMCs from international organizations and national governments.

Table 1.

Vaccines supplied by Biovac in 2023.

Vaccine	Pathogen
Hepatitis B	Hepatitis B (Hep B) virus
Measles	Measles virus
Pneumococcal conjugate	Streptococcus pneumoniae bacterium
Bacillus Calmette-Guérin	Mycobacterium tuberculosis
Tetanus toxoid	Clostridium tetani bacterium
Hexavalent containing	
– Diphtheria	– Corynebacterium diphtheriae
– Tetanus	– Clostridium tetani bacterium
– Pertussis	– Bordetella pertussis bacterium (whooping cough)
– Poliomyelitis	– Polio virus
– Hib	– Hæmophilus influenza b bacterium
– Hep B	– Hepatitis B virus

Source: Biovac products, as of 10 Feb. 2024, https://www.biovac.co.za/products/.

Today, Biovac manufactures fewer than 10 million vaccines each year, some of these with partners. Biovac's story, which spans two decades, has important lessons for those seeking to extend biomanufacturing networks across developing regions in the service of public health.

Biovac: A new approach to serving citizens

Around the turn of the millennium, the South Africa government was exploring the effectiveness of its *public-private partnerships* (PPP) as a means of developing public infrastructure and delivering essential services. It set up a PPP unit within the National Treasury and enlisted the nonprofit National Business Initiative to train government personnel in working with the private sector.[14]

At the time, a multinational accounting firm was advising the State Vaccine Institute (SVI) on a potential PPP. Founded in 1965, the SVI had produced fetal bovine serum for cell cultures, human growth hormone to stimulate metabolism and growth in children, and vaccines that were largely derived from dead virus cells like those causing rabies and smallpox.[15] In terms of the pharmaceutical value chain (Figure 1), the SVI was delivering across four of the five stages: manufacturing substances, formulating drugs, filling and finishing products, and distributing them to its people.

Such local manufacturing was especially critical during the years of apartheid-related sanctions.[16] But these substances were relatively low tech. Eventually, the cost of importing them fell below the cost of making them. In addition, SVI struggled to keep up with modern good manufacturing practices (GMP) and so it ceased production in 2001.[17]

The Consortium, led by Biovac Holdings, entered into a competitive bidding process to partner with the government in finding private partners for its envisioned PPP. The aim of the PPP was to rebuild vaccine manufacturing capacity while supplying the government's vaccine needs.[18] Original members of the consortium included Biovac Holdings as the consortium lead (South Africa), Heber Biotec (Cuba), VaxIntel (British Virgin Islands), and the Disability Employment Concerns Trust (DECT), set up to make investments on behalf of its approximate 4.8 million beneficiaries.[19] Over the next 15 years, Heber, Vaxintel, and DECT divested their shares, leaving the original Biovac Holdings (renamed Kahma Group) as the sole private shareholder.

Stage 1 →	Stage 2 →	Stage 3 →	Stage 4 →	Stage 5 →
Discover and patent new solutions	**Manufacture substances**	**Formulate products**	**Package and label products**	**Distribute and export products**
– Research and develop new products – Complete pre-clinical/ clinical trials – Secure IP/regulatory approval	– Produce active drug ingredients (e.g., antigens) – Produce inactive drug ingredients (i.e., *excipients*)	– Mix and make drugs	– Fill vials – Finish packaging for shipment	– Source products for wholesale or retail – Warehouse, transport, and distribute products – Manage cold chain logistics
Across value chain				
– Use good manufacturing practices – Meet all quality and regulatory standards		– Meet all health policy and industry objectives – Deliver positive value-for-money		

Value chain adapted from Biovac Institute and Wellcome Trust Emergency Response, "Manufacturers Overview: Biovac," Presentation, Global mRNA Hub, WHO, 20 April 2023, https://cdn.who.int/media/docs/default-source/immunization/mrna-ttp/april-2023/6_biovac.pdf.

Figure 1.

Responsibilities at each stage of the pharmaceutical value chain.

Strategic horizons

In 2003, Biovac emerged as a PPP agreement between the Consortium and the South African government represented by the National Department of Health (DOH). Initially, the government held 40 per cent in the company, but it increased its share to 47.5 per cent when the company needed to raise additional capital in the PPP – which it sourced from an agency linked to the Department of Science and Technology – and the Consortium held the rest.[20] The government granted Biovac use of the facilities of the SVI, but the facilities and its equipment for vaccine manufacturing were out of date, and its remaining two dozen employees needed training on modern standards of vaccine manufacturing.[21]

Through the PPP, the government sought to secure its requisite supply of vaccines at minimum cost and build out its domestic manufacturing capacity over time.[22] Biovac's leadership envisioned a fully integrated vaccine company, one that would ultimately develop its own novel vaccines.

To reach this long-term goal, Biovac put in place a *reverse-integration* strategy with three horizons. It would develop skills and capabilities at the lower end of the value chain, performing packaging and distribution, and fill and finish, then work its way up the value chain, steadily training and attracting talent, upgrading equipment and facilities, and layering on more advanced skills and complex capabilities (Figure 2).

With this approach, Biovac could reinvest earnings from its vaccine procurement and distribution operations into its manufacturing facilities and basic R&D capacity for the domestic market, which would eventually cut the foreign exchange costs of imports. Most important, it would earn the trust of its partners, competitors, regulatory agencies, and nongovernmental organizations around the world. Its source of revenue was solely the DoH's distribution contract, which was insufficient for covering all these activities. Hence, Biovac sought external capital to meet its objectives.

Each horizon hinged on strategic and carefully managed *technology transfers*, whereby Biovac's select partners would pass along the process and product knowledge and techniques that Biovac's employees needed to implement the new technology. The challenge of a technology transfer is simple but not obvious: recipients may not have – and may be unaware of not having – the prerequisite knowledge, skillsets, processes and equipment, to make the most of the technology transferred to them end to end.

For some projects, the originator company was the vaccine tech transfer partner, providing Biovac with information, expertise, and inputs necessary for efficient, quality local production. For others, Biovac called on experts from third parties such as Merck KGaA, Darmstadt, Germany, to facilitate improvements in the development and manufacturing process. The technical experts at Merck KGaA, Darmstadt, Germany specialize in removing the bottlenecks. By leveraging the proven benefits of their SAFC® and Millipore® portfolios to solve processing problems, tech transfer can proceed smoothly. Through collaborations such as these, new products and services can also be co-developed.

Horizon 1, 2003–2008	Horizon 2, 2008–2013	Horizon 3, 2013–present
Import, package, label, and distribute	**Fill, formulate, and manufacture**	**Innovation new processes and products**
– Develop relationships up the value chain – Develop distribution networks – Package and label products – Warehouse, transport and distribute products – Develop cold chain capabilities	– Introduce new equipment and facility – Fill vials, ampoules or syringes, finish products and produce drugs – Expand production expertise for active and inactive drug ingredients (i.e., antigens and excipients) – Expand logistics expertise	– Introduce new R&D labs – Expand bulk production capabilities – Complete pre-clinical/clinical trials – Invest in new technology platforms
Across value chain		
– Attract partners to transfer technology – Attract retain talent with advanced degrees – Use good manufacturing practices – Leverage technology transfers at every stage		– Train, reskill, and upskill employees – Meet all quality and regulatory standards – Meet all health policy and industry objectives – Deliver positive value-for-money

Source: Biovac, "Setting Up Vaccines Human Capital Capacity in South Africa," Presentation, Biovac Institute and Litha Biotech, 30 Nov. 2011, https://www.who.int/phi/Session3B_Retention_local_workforce_Makhoana.pdf.

Figure 2.

Biovac's reverse-integration strategy.

Horizon 1: Vaccine Supply

Central to its PPP agreement, Biovac first had to supply the country's Expanded Program on Immunization (EPI) aimed at the South African children.[24] That meant importing vaccines for:

- diphtheria, tetanus and pertussis (DTP);
- measles;
- inactivated polio (IPV);
- oral polio (OPV);
- bacillus Calmette-Guerin (BCG);
- hepatitis B virus (HBsAg).[25]

Fulfilling that mission required it to recruit experts, cultivate its suppliers and distribution network, implement quality controls, and develop its packaging, labeling, and cold chain storage and transport capabilities – all essential skills to master and demonstrate to potential partners for more advanced assignments up the value chain. Biovac assumed the risk of procuring, storing, and distributing these vaccines for the EPI.[26] Biovac's first chief executive officer, Mr. Selwyn Kahanovitz, expected Biovac to produce a generic tetanus toxoids vaccine within 18 months.[27] He and Biovac's other stakeholders soon realized that building the requisite capability would take much longer and require more financial and human resources.

Seeking partnerships

From the get-go, the Consortium sought partners. It signed a memorandum of understanding (MoU) for manufacturing with the South African AIDS Vaccine Initiative, should it discover an effective HIV/AIDS inoculation.[28] A few years later Biovac struck a similar deal with the Italian National Institute of Health to make material for Italy's HIV vaccine candidate, when it would be ready for clinical testing.[29]

In 2005, amid concerns over the deadly H5N1 virus, the Dutch government gave Biovac and the US National Institute for Communicable Diseases modest funds to study the feasibility of manufacturing a vaccine to prevent an outbreak of bird flu in South Africa.[30] In 2006, the neighboring state of Namibia reported its first outbreak of polio in ten years, with over two dozen cases and seven deaths; Biovac mobilized to send a million doses of the polio vaccine to its neighbor.[31]

In 2007, Biovac invested ZAR 54 million to upgrade and expand its production facility, including cold rooms, in preparation for a bilateral technology transfer from its Cuban partner Heber.[32] After Biovac trained its staff in Cuba, it formulated and filled modest quantities of Heber's hepatitis B vaccine. This foray was Biovac's first in formulating vaccines, and it fell short because of Biovac's inexperience with such a complex challenge. Biovac forged ahead with its packaging and labeling of vaccines.

Shaping the discourse and shifting perceptions

In September 2010, during the International Vaccine Technology Workshop in India, a group of workshop participants from Africa banded together to launch the African Vaccine Manufacturing Initiative (AVMI).[33] They recognized the need to advocate for "sustainable human vaccine manufacturing capacity in Africa," to coordinate their advocacy at a high level, celebrate partnerships, promote a steady and broad-based build out of capacity, and attract financial, political, and human capital for local ventures in the biopharmaceutical value chain.[34]

Biovac's Chief Science and Innovation Officer Patrick Tippoo was among them.[35] A modest man with a long view of the industry, he understood the importance of balancing inspiration and perspiration: grand, audacious visions married with small, achievable goals along the way. As a founding member and executive director of AVMI, he knew what vaccine manufacturers in Africa needed: certainty in demand, procurement set-asides for higher-cost fledgling producers, and a preference for IP sharing on mutually agreed commercial terms as opposed to a compulsory approach, which would chase away tech owners and deprive local manufacturers of high-value projects.[36]

Mr. Tippoo was instrumental in founding AVMI, and Biovac volunteered to host the secretariat. At the time, Biovac was already a member of the Developing Countries Vaccine Manufacturers Network (DCVMN), which the Department of Vaccines and Biologicals of the World Health Organization initiated in 2000. The DCVMN is a voluntary alliance. It serves as a platform for biologics producers in developing-countries to share their manufacturing expertise.[37] As vice president of DCVMN from 2019 to 2022, Mr. Tippoo influenced policy discussions of expanding COVID-19 vaccine manufacturing capacity. His advocacy has been tireless and ongoing.

Another force of change in the biopharmaceutical industry in Africa is Dr. Morena Makhoana, CEO of Biovac and a board member of several companies in and outside the healthcare sector.[38] With his focus on "getting to yes" and building trust, he has crafted win-win agreements with industry collaborators and stakeholders in the public sector. As a leader, he has driven the transformation of Biovac's plant and operations through dedicated teams by mapping equipment upgrades and facility expansions to technology transfer deals.

Together, Dr. Makhoana, Mr. Tippoo, and their peers have shaped the conversation around local vaccine manufacturing. They continue to focus industry members on what is doable or within reach. Drumming up enthusiasm for investments in African companies, countries, and the continent comes with the responsibility of managing expectations and reminding investors that, statistically speaking, many ventures fall short or fail – in Africa as on every other continent – and that the handful of successful enterprises end up driving the industry for decades to come in Africa and beyond.

Horizon 2: Tech Transfer and Vaccine Manufacturing

Biovac's first R&D program in 2004 aimed to produce a widely used pentavalent vaccine locally. Its five-in-one vaccine would protect against diphtheria, tetanus, pertussis (whooping cough), hepatitis B, and hæmophilus influenzae type B (known as Hib, a bacterium that causes meningitis, pneumonia and the ear infection otitis). Biovac worked to develop its own Hib antigen, which was hard to import in bulk, while importing the other four antigens, including whole-cell pertussis. It would then formulate and finish the pentavalent for sale.

The project developed Biovac's conjugate vaccine competency end to end, that is, its capabilities to ferment bacteria and to purify and conjugate a carbohydrate antigen with a protein antigen to strengthen the delivery and effectiveness of the vaccine.[39] It invested in biosafety level 3 (BSL-3) fermentation suites and set up a platform for developing and validating its methods of assessing the stability, potency, and purity of product samples.[40]

But in 2009, the SA Ministry of Health mandated a wholesale shift from whole-cell pertussis (wP) to acellular (aP) in vaccines for children.[41] That meant that Biovac could not sell its five-in-one shots to the EPI, nor could it conduct clinical trials with children in South Africa unless it reformulated its pentavalent with the different pertussis antigen.[42] So, it shuttered the project and focused more on partnering for manufacturing to ensure midterm commercial viability as it worked out its R&D strategy.

Learning and licensing its intellectual property

Not deterred, Biovac decided to license what it had learned in its pentavalent development. That was a shrewd strategic pivot: the market price for a dose of a pentavalent vaccine fell from its peak of $3.65 in 2004 to between $0.69 and $1.15 in 2021, but the value of Biovac's intellectual property held firm.[43] It licensed its Hib technology package to two international vaccine manufacturers, one of which has successfully commercialized a wP based pentavalent vaccine using the package, and the other recently commercialized an aP based pentavalent vaccine.

Biovac also applied its Hib know-how to develop other products within the bacterial fermentation and conjugate space, such as the pneumococcal conjugate vaccine with partners such as PATH and Chengdu Institute for Biological Products, a subsidiary of Sinopharm.

It not only transferred technology packages but delivered training. In its partnerships with the Italians for an HIV/AIDS vaccine and with the Infectious Disease Research Institute for a TB vaccine, Biovac developed capabilities in recombinant vaccine technology.[44]

Finally, in its work with PATH in 2017, Biovac embarked on a technical proof of concept for a novel group B streptococcus (GBS) conjugate vaccine. The South African company wanted to prove that it could start from scratch, develop a pipeline, and take a product all the way to market. Biovac secured initial funding from the Bill & Melinda Gates Foundation and benefitted from the technical expertise of PATH and Merck KGaA, Darmstadt, Germany.[45] So, while Biovac never completed its pentavalent product, it gained significant scientific knowledge that fueled its follow-on successes.

Merck KGaA, Darmstadt, Germany-Biovac Partnership Legacy

Since 2010, Merck KGaA, Darmstadt, Germany has been a key partner to Biovac in its journey to build vaccine capabilities and capacity. Merck KGaA, Darmstadt, Germany prioritized Biovac as a priority partner and supplied the company with raw materials from it's SAFC® portfolio designed for pharma and biopharma manufacturing. In addition, consumables and systems from it's Millipore® portfolio of expert pharm/biopharm products and CTDMO services, were provided. These solutions were supported by teams of technical experts to support process development activities from development of drug substance through formulation and fill-finish.

Merck KGaA, Darmstadt, Germany has delivered both on-site and off-site technical support, including skills development training, to strengthen Biovac's operations. This continued partnership will further be strengthened through the expansion of Biovac's DS to include whole cell oral vaccines as well as mRNA vaccines.

Contracting and expanding

In early 2010, Biovac announced an bold goal: to increase its annual capacity sevenfold in three years. That meant expanding its plant quickly so that, by 2013, it could manufacture 35 million doses a year, with 70 per cent of those earmarked for South Africa.[46]

But how? With neither a robust local venture capital for financing high-risk projects nor a robust local biotech industry to contribute to new product development, Biovac pivoted to a strategy of partnering with large multinationals on technology transfers of leading vaccines. Through tech transfers, Biovac could build capacity faster. It could prove itself as a manufacturer while leveraging its growing expertise to develop novel products.

By contracting with Sanofi Pasteur, Pfizer's Wyeth subsidiary, and others, Biovac was able to secure the ZAR 130 million (~$15.5 million in 2010) it needed for plant expansion from the Industrial Development Corporation (IDC) of South Africa, a local development finance institution.[47] The expanded capacity would help Biovac respond to possible pandemics such as the swine flu (H1N1 virus), which was the biggest pandemic threat at the time.

In 2011, the Western Cape office of the Department of Trade and Industry, Economic Development and Tourism submitted a proposal for a new medical technology park in Pinelands, at the southern tip of the province where Biovac had offices. The Western Cape provincial cabinet approved the use of 14,000 square meters for the park, with an initial investment of ZAR 110 million.[48] The vision was to convert the properties adjacent to Biovac into a health technology park so that a biotechnology ecosystem would grow in and around Biovac.[49]

Transferring models and methods

In mid-2012, Sanofi announced that it would transfer technology for its novel six-in-one vaccine Hexaxim (DTaP-hepB-IPV-Hib) to Biovac for manufacturing in South Africa. The government applauded it as "the world's first fully liquid hexavalent vaccine," protecting children against diphtheria, tetanus, whooping cough, poliomyelitis, hepatitis B and hæmophilus influenza type B.[50] Biovac executives expected the transfer process to take at least three years, starting with training in Cape Town and France, followed by process simulations and testing in Biovac's facility, and concluding with regulatory filings and approvals from SA Health Products Regulatory Authority.

During that time, Biovac honed its technical skills. It further modernized its plant so that it could manufacture four million doses of Hexaxim a year, with room to ramp up significantly as it explored new markets in the surrounding region of Southern Africa Development Community.[51]

All this effort paid off: in November 2015, Biovac signed a second multi-year technology transfer agreement worth $20 million for making the pediatric version of Pfizer's Prevenar-13, a conjugate vaccine that accounted for 40 per cent of the National Department of Health vaccine budget.[52] Infants required three shots for protection from streptococcus pneumoniae. This project further solidified Biovac as a reliable partner for multinationals and brought in the type of high-end equipment and consumables (such as sterile disposable bag systems) that Pfizer, Merck Sharp & Dohme (MSD), and others used in their own facilities.

By the end of 2019, Biovac was producing Sanofi's Hexaxim with a goal of making four million doses.[53] For Pfizer's Prevenar-13, Biovac's executives projected an output of three million doses in the first half of 2021.[54] The deal was Pfizer's first in the region, and it allowed Biovac to implement Pfizer's latest formulation system in manufacturing, a boon to staff skills and knowledge.[55]

Demonstrating higher-value capabilities

According to researchers at the Hague and the Vrije University in the Netherlands, the scarcity of technical facilities for fill-and-finish activities was among the key bottlenecks for scaling up COVID-19 vaccine manufacturing.[56]

In July 2021, Pfizer brought BioNTech to the table, to sign a letter of intent with Biovac to manufacture their breakthrough BNT162b2 COVID-19 vaccine for distribution across the African Union.[57] The deal was an affirmation of Biovac's capabilities: Pfizer and BioNTech selected their contract manufacturers according to the quality of their work, compliance and safety records, technical and project management competencies, available capacity, level of workforce training, positive working relationships, and a strong commitment to working with agility through a fast-paced program.[58]

Satisfied with Biovac's work on Prevenar-13 vaccine, Pfizer made quite a pledge at the South African Investment Conference in March 2022: it would put down ZAR 255 million ($14.7 million) to enhance Biovac's pandemic readiness capabilities, including an ultra-cold storage facility.[59]

The technology transfer included on-site development and equipment installation, after which Biovac joined Pfizer's manufacturing network of 20-plus facilities across three continents. It sourced its drug substances from Europe. In just over a year, Biovac had not only learned to formulate an mRNA vaccine but released its first batch, with a targeted annual output of 100 million doses by 2023 – all for the 55 member states of the African Union.[60]

In March 2023, Biovac and Pfizer unveiled their new "Freezer Farm" in Cape Town. By then, Pfizer had invested a total of ZAR 855 million in Biovac's infrastructure, staff training, and skills development over the two projects.[61] Biovac's work with Sanofi and Pfizer served as its blueprint for manufacturing its own products.

In parallel, Biovac announced its collaboration with nine development partners (Table 2) to raise ZAR 2.3 billion ($150 million) for expanding its manufacturing plant so that it could scale and expand its vaccines manufacturing output.[62]

Table 2.

Biovac's development partners in building plant capacity.

Organization	Acronym	Description
African Development Bank	AfDB	A multilateral development finance institution with headquarters in Abidjan, Ivory Coast
British International Investment	–	UK development finance institution, formerly called the Colonial Development Corporation
European Investment Bank	EIB	Lending arm of the European Union
European Union Delegation to South Africa	–	Unit operating under the European External Action Service
Proparco	–	Established in 1977 and owned by the French Development Agency and private shareholders from developed countries
German Investment and Development Society	DEG	Subsidiary of KfW Development Bank
Industrial Development Corporation of South Africa	IDC	Established in 1940, fully owned by the South African Government
International Finance Corporation	IFC	Member of the World Bank Group
International Development Finance Corporation	DFC	An agency of the US federal government

Horizon 3: Innovation and Biomanufacturing Leadership

At times, nongovernmental organizations (NGOs) have criticized organizations like Biovac for doing "only" fill-and-finish jobs. In the Merck KGaA, Darmstadt, Germany team's experience, that's normal. The starting point for many successful biopharmaceutical manufacturers is fill and finish. Building strong and resilient capacity takes many years of working closely in partnerships and learning through technology transfers. Biovac worked stepwise over time to gain skills, secure relationships, and meet medium-term targets with its partners, thereby building its reputation and technical capacity over time. Its business and technical foundations are strong.

Mastering technology transfers

In June 2021, a consortium of seven organizations (Table 3) including the WHO formed a technology transfer "hub" in South Africa to develop an mRNA vaccine candidate and transfer mRNA technologies to the hub's "spokes," namely, pre-selected research and training institutes and pharmaceutical enterprises looking to increase their vaccine manufacturing capacity and reduce their reliance on imported products and talent.[63]

Here, WHO advocated for the hub model of technology transfer so that its transfers could be *multilateral*: that is, the hub aggregates, integrates, and delivers all the data, research, know-how, access to intellectual property, and training necessary for its spokes to produce. Through their agreements with the hub, spokes have everything they need to implement and validate their own vaccine manufacturing processes.

Technical and commercial teams from Merck KGaA, Darmstadt, Germany worked with Afrigen Biologics Vaccines, host of the mRNA hub, to develop the process.[64] Biovac took on the task of upscaling the technology that it received from the hub. Its mission is critical: it agreed to (1) test the technology in-house for robustness and reproducibility, (2) scale it and develop critical process parameters (CPP), (3) industrialize and optimize the process, and (4) transfer this new industrial manufacturing process, with Afrigen, to the designated spokes.[65]

Senior Regional Account Manager Southern Africa Walter Bronkhorst said, "We understand the critical tempo of each step in the drug development journey. This is how Merck KGaA, Darmstadt, Germany was able to provide seamless service for building a robust and reliable process efficiently and quickly."

Accelerating Tech Transfer via the mRNA Hub

The continued efforts of the local Millipore® Manufacturing Science and Technology (MSAT) and commercial teams demonstrate the strong commitment of Merck KGaA, Darmstadt, Germany to the WHO mRNA Hub's global tech transfer program, building on the company's pre-pandemic relationships with key mRNA Hub participants. The company's involvement includes the provision of technology training, process development, and equipment consultation, all in collaboration with global stakeholders. As part of its on-site and off-site assistance, Merck KGaA, Darmstadt, Germany has deployed process development scientists and facilitated technical seminars and internal programs for global team alignment. Merck KGaA, Darmstadt, Germany has also contributed to scaling up knowledge, skills, and equipment, and supporting single-use assemblies for technical, engineering, and GMP batches. In July 2024, Merck KGaA, Darmstadt, Germany signed a non-binding MOU with Afrigen to develop mRNA platform technology, scale up and help with troubleshooting challenges in mRNA process optimization. The goal of the MOU is to expand access to life-saving therapies in South Africa and low- and middle-income countries (LMICs). This work accelerates the mRNA Hub's technology transfer program and aligns with Merck KGaA, Darmstadt, Germany's broader commitment to enhance vaccine production capacity, improve vaccine equality, and expedite access to the emerging mRNA platform technology globally.

In March 2022, PAHO held its first training at Afrigen's site in Cape Town for a group of scientists from Sinergium Biotech in Argentina and the Bio-Manguinhos Institute of Technology in Brazil, two spokes in the mRNA hub. They studied the manufacturing process, from formulating LNPs and performing data analytics to producing and controlling mRNA vaccines.[66] The training was integral to future process optimization and technology transfer.

Table 3.

Members of mRNA Vaccine Technology Transfer Hub.

Organization	Mandate in hub
World Health Organization	Coordinates resources, monitors implementation
Afrigen Biologics and Vaccines (Avacare Health and IDC)	Establishes mRNA vaccine production process, produces materials for phase 1 clinical trials, and transfers laboratory scale technology to Biovac
South African Medical Research Council	Conducts and delivers research, supports clinical development
Biologicals and Vaccines (Biovac) Institute of South Africa	Receives technology from Afrigen, manufactures vaccine, and transfers industrial scale production back to Afrigen for distribution to the spokes
African Union	Coordinates resources
Africa Centres for Disease Control and Prevention	Provides regional insight, oversight and expertise
Medicines Patent Pool	Drafts agreements, facilitates and monitors their implementation
Access to COVID-19 Tools Accelerator	Fast-tracks the development, production, and equitable access to COVID-19 tests, treatments, and vaccines
South African Government	Ensures government buy-in

Source: PAHO, "Latin American Manufacturers Complete First Training in mRNA Technology in Bid To Improve Regional Vaccine Production," News, Pan American Health Organization, 11 March 2023, https://www.paho.org/en/news/24-3-2022-latin-american-manufacturers-complete-first-training-mrna-technology-bid-improve.

Biovac is involved with a mRNA technology project with Pfizer to carry out fill-and-finish of its COVID-19 vaccine. By the end of 2022, Biovac had run "its first mRNA demonstration batch in its partnership with Pfizer." It was – more quickly than originally anticipated – "on track to get regulatory approval within months" so that it could "start mRNA vaccine production in 2023," according to Mr. Tippoo.[67] Biovac has judiciously managed the IP and know-how exchanged in this separate, as well as a complementary, mRNA technology partnership.

By April 2023, Afrigen had established an mRNA COVID-19 vaccine manufacturing process in the laboratory and began scaling it to make batches of the vaccine for clinical trials to GMP standards. Merck KGaA, Darmstadt, Germany supported process development behind the scenes and contributed raw materials, consumables, and equipment. In parallel, Afrigen organized training programs in anticipation of transferring this technology via the hub to Biovac and other spoke partners.[68] As of this writing, spokes that were poised to benefit from Biovac's contributions to the mRNA hub included BioGeneric Pharma SAE (Egypt), Bio-Manguinhos Institute (Brazil), Biovaccines Nigeria Ltd. (Nigeria), Institut Pasteur de Dakar (Senegal), Institut Pasteur de Tunis (Tunisia), Incepta Vaccine Ltd. (Bangladesh), Biofarma (Indonesia), BiologicalE (India), National Institute of Health (Pakistan), Institut Torlak (Serbia), Sinergerium Biotech (Argentina), Darnitsa (Ukraine), and Polyvac (Viet Nam).[69]

Expanding infrastructure and capability

In November 2022, Biovac signed a licensing and technology transfer agreement with the nonprofit International Vaccine Institute (IVI), to make an oral cholera vaccine (OCV), including the drug substance required for OCV. This is one of the few fully end-to-end production of a vaccine in Africa. Through the partnership, Biovac has an opportunity to set up and scale up the technology in a GMP environment for making drugs for clinical trials and, ultimately, for global distribution, to prevent cholera outbreaks worldwide.[70]

For the first phase of the project, Wellcome Trust and the Bill & Melinda Gates Foundation committed funding to Biovac so that it could expand its facilities across the biopharma value chain.

When Biovac brings its expanded facility on line, it can begin demonstrating its vaccine manufacturing excellence end to end, from innovating to inoculating patients.[71] It will have successfully completed the process of reverse integration in relation to the OCV vaccine. Merck KGaA, Darmstadt, Germany has committed to support in-process robustness locally through its Millipore® Manufacturing Science and Technology (MSAT) team, including but not limited to the filtration, chromatography, and clarification steps, and to assist in optimizing these processes for industrial scale manufacturing. In 2024, the largest Millipore® tangential flow filtration (TFF) system was installed at Biovac in Africa, thus strengthening Biovac's global competitive position.[72] Biovac expects to produce batches for the first clinical trial in 2025 and to get regulatory approval in 2027.

At the time of this writing, Biovac was still supplying about 80 per cent of the routine vaccines for South Africa's children but was anticipating a drop due to competition from importers. In December 2023, the IFC announced that it was loaning Biovac $7 million to cover production of its current vaccine portfolio. IFC also agreed to support Biovac in constructing a new multi-vaccine manufacturing plant, boosting its capacity from 150 million to 560 million doses in Cape Town.[73]

Thanks to many years of collaboration with its global technology transfer partners (Figure 3), Biovac offers the following services today:

- Upstream processing (bacterial fermentation);
- Downstream processing (polysaccharide and protein purification, conjugation);
- Formulation (licensed);
- Filling (licensed);
- Filling (owned – pre-filled syringes);
- Inspection/labeling/packaging (licensed);
- Quality control (licensed).

Stage 1 →	Stage 2 →	Stage 3 →	Stage 4 →	Stage 5 →
Discover and patent solutions (pre-clinical)	**Manufacture substances**	**Formulate products**	**Fill and finish products**	**Package and label products**
– Bill & Melinda Gates Foundation – PATH – Wellcome Trust – International Vaccine Institute – mRNA Hub Programme	– Biovac Hib antigen – Oral cholera vaccine	– Pfizer Prevenar-13	– Sanofi hexavalent – Pfizer Prevenar-13 – Pfizer BioNTech COVID-19	– AJ Vaccines – Centro de Ingeniería Genética y Biotecnología (CIGB)
		– Merck KGaA, Darmstadt, Germany		

Adapted from Biovac Institute and Wellcome Trust Emergency Response, "Manufacturers Overview: Biovac," Presentation, Global mRNA Hub, WHO, 20 April 2023, https://cdn.who.int/media/docs/default-source/immunization/mrna-ttp/april-2023/6_biovac.pdf.

Figure 3.

Technology transfer partners along Biovac's value chain.

World-class workforce

To turn Biovac's manufacturing facilities into a certified world-class plant, Biovac leadership deployed a multi-pronged strategy early on for developing skills locally. First, it cultivated and has maintained strong relationships with local institutions of higher education such as Cape Peninsula University of Technology (CPUT), Stellenbosch University, University of Cape Town (UCT) and University of the Western Cape (UWC); and it regularly welcomes graduate and doctoral students from their departments of science and technology.[74]

Biovac has also deployed interns from CPUT in its R&D, quality control, engineering, and production departments. Stellenbosch and UCT have assisted in product development. Through the LEAP science and math schools, it has granted bursaries to biotech scholars from disadvantaged backgrounds; and it has set up internship and mentorship programs to attract local math and science talent and to engage young scientists in its work.[75]

Second, its training and development program is ongoing, with a portfolio of customized courses, train-the-trainer initiatives, biopharmaceutical manufacturing site visits and audits locally and abroad, technology transfers with its many partners and Merck KGaA, Darmstadt, Germany (e.g., scarce aseptic manufacturing skills), and training from equipment suppliers like Bosch on factory and site acceptance tests (FAT/SAT) and qualification processes (e.g., design, installation, operation, and performance).[76]

Third, Biovac has worked with professional firms such as the African Management Services Company and the German Society for International Cooperation (GIZ) to assist with identifying and recruiting talent with global vaccine manufacturing experience and expertise in operations, engineering and production.[77]

Of Biovac's 350 employees, 94 per cent are black, 53 per cent are women, 40 per cent earned undergraduate or postgraduate degrees and 20 per cent hold diplomas.[78] It has created 8,500 job opportunities through its partnerships and projects, with more jobs to come from recent investments.[79] As a testament to all these efforts, Biovac's female leaders were "highly commended" in the category of health and pharmaceuticals at the 2023 Standard Bank Top Women Awards ceremony.[80] Biovac also earned Level 1 status for its contributions to broad-based black economic empowerment (B-BBEE, Table 4).[81] It is an economic and employment anchor in its community, in addition to its broader contribution to public health in South Africa.

Table 4.

Broad-based Black Economic Empowerment.

Measured entity	
Company name	Biologicals and Vaccines Institute of South Africa (Pty) Ltd.
Trade name	Biovac Institute
Registration number	1998/011727/07
VAT number	4430206161
Certificate number	TBI009991-REV8
B-BBEE scoring	
B-BBEE element	**B-BBEE score**
Equity ownership	25.00
Management control	15.51
Skills development	14.36
Enterprise/supplier development	41.79
Socioeconomic development	5.00
Youth employment service	0.00
Biovac Institute's total	*101.66*
B-BBEE results	
Status	Level 1 contributor
Recognition level	135%
Empowering supplier?	Yes
Black ownership of Biovac Institute	
Voting rights of black people	51.02% flow-through
Voting rights of black women	11.20% flow-through
Economic interest of black people	51.22% flow-through
Economic interest of black women	11.20% flow-through
51% black ownership?	Yes
30% black women ownership?	Not yet
51% black designated group supplier?	Not yet

Flow-through means that auditors traced ownership to natural black persons rather than to black-owned companies.
Sources: Nicholas Erasmus, "Biovac B-BBEE Certificate: Level 1 Contributor," AQRate (Pty.) Ltd., issued 25 May 2023, https://www.biovac.co.za/wp-content/uploads/2023/05/B-BBEE-Certificate-Biovac-TBI009991-REV8.pdf.

Role of public policy

During the COVID-19 pandemic, governments around the world turned to industrial policy as a means of managing the health crisis, subsidizing R&D and vaccine manufacturing, fast-tracking approval processes for new vaccines, treatments and diagnostics, and creating vaccine purchasing mechanisms to provide demand certainty for producers while assuring availability for patients. Post-pandemic, governments across regions are embracing their role in encouraging sustainable local vaccines production, for improved healthcare delivery as well as pandemic preparedness and response.

Policies must effect structural change

But public policy can fail – and has failed in South Africa – when politicians wield policymaking for short-term goals rather than with long-term structural changes in the economy in mind.[82] Here is a case in point. The South Africa Department of Science and Innovation and the Department of Trade, Industry and Competition had both been promoting their country's biopharmaceuticals as solid investments. Their advocacy helped Biovac to attract global technology transfer partners like Sanofi and Pfizer.

Then, in April 2023, Biovac's original shareholder, the Department of Health, surprised Biovac and its investors by deciding to buy pediatric pneumococcal vaccines not from Biovac but rather from the local subsidiary of Cipla, a generic pharmaceutical company in India.[83] The government claimed ZAR 2.4 billion in savings, but this decision potentially jeopardized jobs, good will, and foreign investment in South Africa's biopharmaceutical industry. Biovac disputed the figure quoted, because it reflected the old price of supplying Prevenar13 rather than the price in its bid.

"Manufacturing is largely about economies of scale," said Stavros Nicolaou, former chair of the trade association, Pharmaceuticals Made in South Africa (PHARMISA). In his view, when most of the demand sits in the public sector, then the public's health and economic imperatives must align.[84] Yet, the government's tender system operates on a two-year cycle, which gives local manufacturers little time to project revenues, allocate capital, and scale operations to deliver the product in time.[85] If a manufacturer wins a contract in one cycle but loses it two years later, then its investment goes cold.

Policies must create stability in demand

Policymakers can serve their communities by balancing the face value of the price (short-term savings) and the best value for the money (long-term prosperity). Moreover, procurement policies and practices must align across departments, so that business leaders and investors get a unified message, not mixed messages that put their investments in doubt. Health departments can make longer-term procurement commitments, and their policies can help stimulate demand.

Creating enabling policy environments for the development of strategic sectors, such as healthcare, is a difficult balancing act. In reality, policymakers tend to look at successful companies, and at the characteristics they have in common, then set policies that reinforce those characteristics.[86] Consider vaccine purchasing mechanisms. In general, they procure products at the lowest cost globally and then distribute them to the vaccination programs of developing country at special subsidized prices. Such mechanisms have massively increased the protection of the global population – an outcome to celebrate – but they favor global giants over higher cost local vaccine manufacturers in their home markets.

PHARMISA has advocated for government policies that "balance the trading playing fields." In its view, local policies favor importers that "are subsidized by the export destination." As a result, the South African pharma market is "highly vulnerable to import substitution and displacement."[87] Policymakers must understand how national, regional, and local trade and education policies affect the business cases and tech transfer potential of local manufacturers.

Policies must ensure resilience

Mr. Tippoo suggested introducing "what some call a 'resilience premium', on the vaccines we buy, and invest that premium in the development of vaccine manufacturing infrastructure in Africa. That will give African vaccine manufacturers the chance to become part of the global vaccine supply chain."[88]

The competitive landscape of the vaccine sector is significantly influenced by government policies. Newcomers to the industry often face shifting EPI recommendations, mercurial funding guidelines, and evolving regulatory requirements. Entrepreneurs cringe at regulatory complexity, and investors shy away from regulatory uncertainty. If regulators could coordinate, harmonize, and stabilize their policies, processes, and requirements within and across borders, this could create pathways for local manufacturers to leverage their capabilities in global markets.

An organization such as the African Medicines Agency, with its mandate to develop common standards and harmonize legislation, could supplement the capabilities of regional economic communities and national medicines regulatory authorities.[89] If it proved itself a credible Pan African regulatory collaborator, then it could become a one-stop shop for approval of medicines and other health technologies across the continent.

Finally, Mr. Tippoo recommends asking the right questions. The question is not simply, "How do we bring more manufacturing capacity on line?" The world did that quickly during the COVID-19 pandemic. The question is more like, "How do we keep our capacity ready for action?" Countries cannot flip a switch to bring a factory online in a catastrophe. They must keep it idling, with up-to-date equipment, an up-to-speed workforce, and up-to-code facilities and operations. Therefore, policymakers must adopt a global view of health, of global expertise across the biopharmaceutical value chain, and of global biologics supply and manufacturing capacity, so that they can tap quickly into these resources in a health crisis.

Lessons learned

The following elements contributed to Biovac's success during the past two decades, across a diverse set of projects.

Big-picture strategy front and center
Biovac's leadership kept its reverse-integration strategy top of mind so that it could select and sequence its projects according to the capabilities that each project would help Biovac's staff to master. Having a source of baseline income through procurement, distribution, and fill-and-finish capabilities helped Biovac survive shifts in policy and market dynamics as it built its R&D and manufacturing capacity over many years. Despite challenges over the years, its leaders never lost sight of the big picture.

Strong business case for every project
First, Biovac considered market size and market demand locally and for export. Second, moving into manufacturing, they determined the modality, the molecule type, and the pipeline. Third, they ascertained the human resources necessary to run the facility and talent retention strategies to keep them on staff after training them for a project. Finally, they articulated a bold goal, like eradicating cholera, and identified significant milestones that would stir up enthusiasm and maintain interest in a project over its life cycle.

Partnerships to accelerate capacity building
Biovac's leaders capitalized on its biological and scientific experience to attract further partners and investments. It also capitalized on the deep bench strength, years of front-line experience, and practical wisdom of every partner. The global giants took decades to grow into their present forms. Partnerships and technology transfers shrink the unknowns and minimize the trial and error, accelerating the timeframe for building biomanufacturing and R&D capacity.

Public-private support for workforce development
Its leaders understood that Biovac would not succeed in a biotech space if it lacked qualified people, or if it failed to invest in its people. Attracting highly qualified students to work in local manufacturing requires a shared public-private vision of the local economy's potential. Governments can support five- and ten-year workforce development and retention plans. Vacsera in Egypt, for example, is known for its long-term vision and investments in the country's young people to develop its own R&D capacity for biologics.[90]

Trust as a priority
There must be trust in the expertise of the global partner, trust in the quality of the product and services transferred, and respect for the individuals on each team. Biovac itemized everything critical to the project's success at a commercial scale, including talent, relationships, trust, and respect. Without those, a project could not move forward, and bad attitudes could even contaminate the partnership. Transparency – even when things did not go as planned – remained core to Biovac's brand. With these qualities, significant growth was possible.

Technology transfer on mutually agreed terms
At a higher level, the policies of governments, inter-governmental, and nongovernmental organizations must help developing countries to transition from *procurement* through purchasing mechanisms to *production* through tech transfers and the emergence of local biologics manufacturers. This requires a legally certain and predictable business environment that includes the right trade policies and frameworks for IP protection. Hubs and voluntary bilateral transfers work better than coercion.

"Technology transfer partnerships are the best mechanisms we have to drive accelerated capacity building," said Mr. Tippoo.[91]

Reinforcing Mr. Tippoo's comments, Merck KGaA, Darmstadt, Germany Senior Process Development Engineer EMEA Shajahan Cheriya added, "Our commitment extends beyond providing services to our partners; we are dedicated to empowering them beyond all expectations. We work to ensure they have the tools, knowledge, and support needed to succeed in every endeavor."

What clearly sets Biovac apart as a partner is (1) its proven collaborations with leading biopharmaceutical innovators and influential nongovernmental organizations, (2) its leadership in changing global perceptions of biologics made in Africa, (3) its access to world-class talent at the crossroads of innovation, and (4) its commitment to serving the people of Africa with quality biologics through times of calm and crisis.

Acronyms

AfCFTA, African Continental Free Trade Area

AfDB, African Development Bank

AfricaCDC, Africa Centres for Disease Control and Prevention

AMC, advance market commitment

API, active pharmaceutical ingredient

AU, African Union

AVMA, African Vaccine Market Accelerator

AVMI, African Vaccine Manufacturing Initiative

BCG, Bacillus Calmette–Guérin

CEPI, Coalition for Epidemic Preparedness Innovations

COVAX, COVID-19 Vaccines Global Access[1]

COVID, coronavirus disease

CPP, critical process parameters

CTM, clinical trial material/manufacturer

DCVMN, Developing Countries Vaccine Manufacturers Network

DECT, Disability Employment Concerns Trust

DOH, National Department of Health, South Africa

DTaP, diphtheria, toxoid, and acellular pertussis

DTP, diphtheria, tetanus, and pertussis

DTwP, diphtheria, toxoid and whole-cell pertussis

EPI, Expanded Program on Immunization (for children)

GAVI, formerly Global Alliance for Vaccines and Immunization

GBS, group B streptococcus

GIZ, Gesellschaft für Internationale Zusammenarbeit (Society for International Cooperation)

GMP, good manufacturing practices

HBsAg, hepatitis B virus surface antigen

Hib, hæmophilus influenzae type B

IFC, International Finance Corporation

IP, intellectual property

IPV, inactivated polio vaccine

LNP, lipid nanoparticles

LoI, letter of intent

MoU, memorandum of understanding

mRNA, messenger ribonucleic acid

OPV, oral polio vaccine

PAHO, Pan American Health Organization

PATH, formerly Program for Appropriate Technology in Health

PAVM, Partnership for African Vaccine Manufacturing

pDNA, plasmid deoxyribonucleic acid

PPP, public-private partnership

R&D, research and development

SA, South Africa (used only as an adjective before a noun)

SDG, UN Sustainable Development Goal

SVI, State Vaccine Institute

TB, tuberculosis

UN, United Nations

WHO, World Health Organization

ZAR, South African rand

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