mRNA Technology Transfer Programme

mRNA hub a year later — history, progress to date, potential beyond COVID

Caryn Fenner, Afrigen Biologics (Pty) Ltd

AVAC, HVAD webinar

20 April 2023

AFRIGEN TIMELINE

2014 — Establish local production capacity and capabilities for a TB vaccine

Partnership with Seattle based NPC, Infectious Diseases Research Institute (IDRI) and SA vaccine company Biovac

2017 — Created the first Adjuvant Formulation Centre in Africa

In-licensing adjuvant formulations from IDRI

2018 — Develop vaccines using new generation adjuvants and formulations

Partnership with owners of relevant antigens

2019 — Develop formulation platform for CAMS and pharmaceuticals

Vitamins, Minerals & Nutraceuticals

21 Jun 2021 — Contracted by the WHO under the COVAX initiative to be the mRNA vaccine technology transfer and training Hub for LMICs

Afrigen and partners developing the first mRNA Covid19 vaccine in Africa - Creating capacity and capabilities on the continent.

Aug, 2021 — Vaccine facility construction completed

Nov, 2021 — Training & Knowledge transfer from WITS

Jan, 2022 — Afrigen signs grant agreement with MPP

*WHO announces establishment of **global biomanufacturing training hub in Republic of Korea***

- Re-assignment of space to product innovation & training
- First lab scale mRNA vaccine batch produced

Feb, 2022

WHO DG & Belgium Minister Kitir visit

Mar, 2022 — First spokes training

June 2022 — First indication of AfriVac 2121 immunogenicity

POC 1 mouse study results

July 2022 — Afrigen collaboration with NIH on mRNA vaccine research announced

Nov 2022

100 mL scale achieved

Jan 2023 — Hamster immunogenicity and challenge study

Afrigen Biologics & Vaccines

The South African consortium

AFRIGEN - Hub Establishment and mRNA technology development at R&D scale and technology transfer

BIOVAC - Establishment of the first technology recipient and mRNA technology process scale up and validation

SAMRC - Establishment of a R&D network to develop a 2nd generation mRNA technology applicable to COVID-19 and other diseases

Afrigen Biologics & Vaccines An Avacare Health & IDC Company

BIOVAC

saMRC advancinglife

African Union

AFRICA CDC Centres for Disease Control and Prevention Safeguarding Africa's Health

science & innovation Department: Science and Innovation REPUBLIC OF SOUTH AFRICA

AU, ACDC, DSI - support and funding

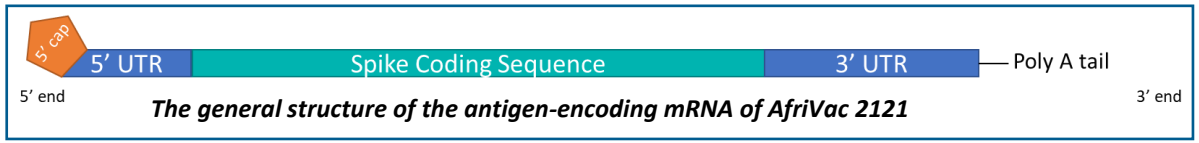
medicines patent pool

World Health Organization

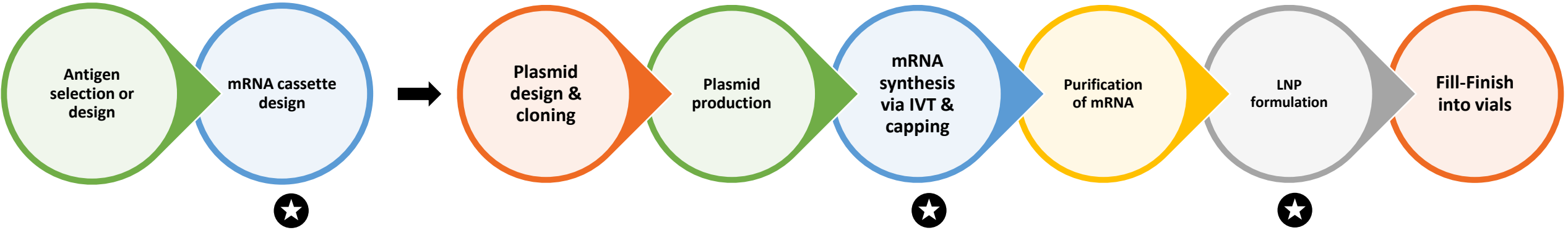
WHO and MPP - co-lead the Programme

mRNA Technology Transfer Hub Programme

High level process flow chart for mRNA vaccine production



mRNA Covid-19 vaccine: Proof of concept product, First generation



Second generation products and technologies that addresses:

- Thermostability
- Reduced cost of goods
- Freedom to operate

saMRC advancinglife SAMVAC

CRADAs

mRNA Technology Transfer Programme

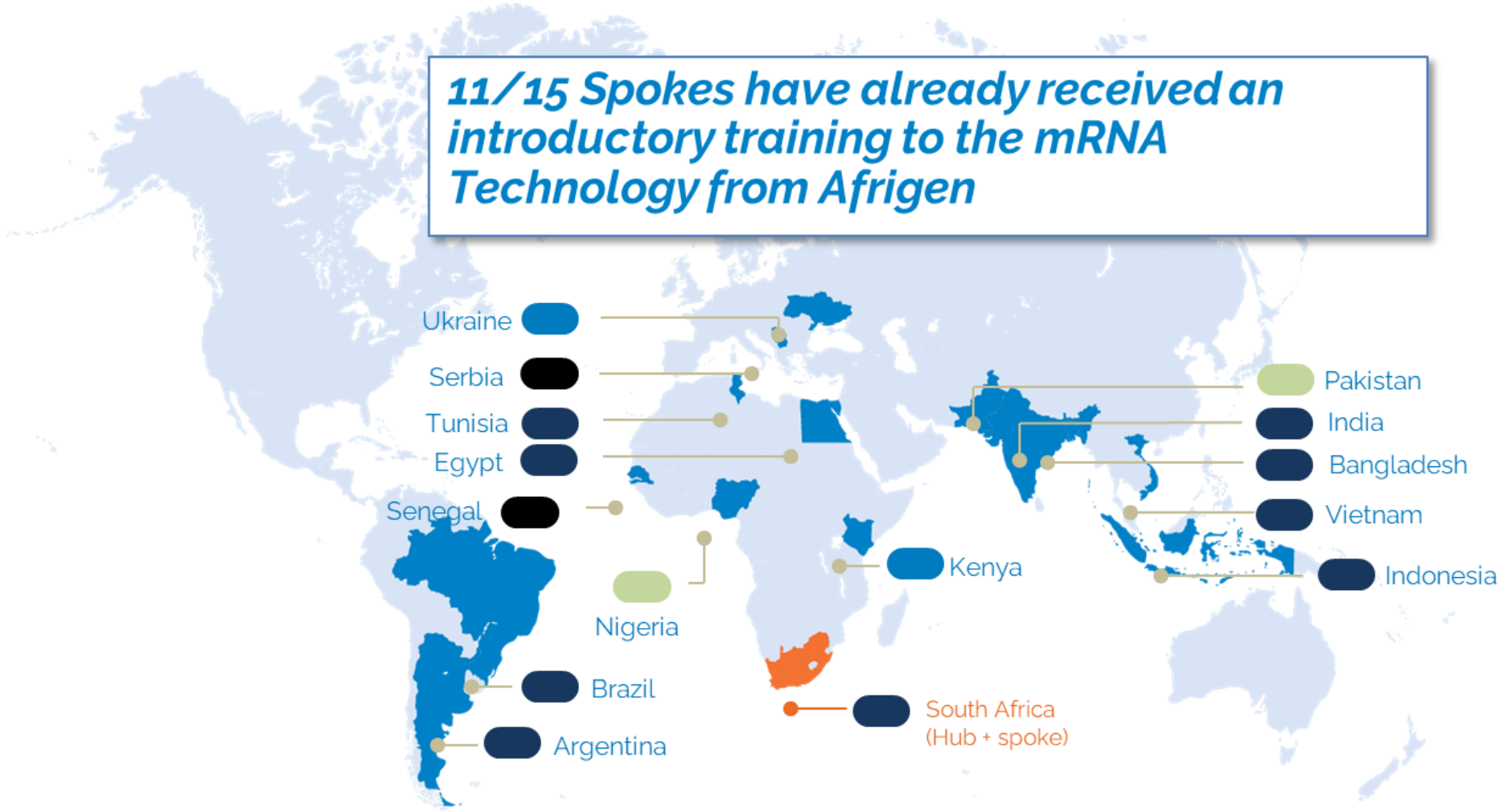
Strategy to Demonstrate Platform Validity

For mRNA Hub technology transfer from Afrigen to partners

Pre-clinical comparability of Afrivac2121 to approved Covid-19 reference mRNA vaccine

Manufacturing and analytical data packages to conclude Afrivac2121 technology transfer to partners

Knowledge transfer to the Partner network



Nigeria: 19-21 June 2023
Pakistan: 17-19 July 2023
Kenya and Ukraine Q3 2023

mRNA Technology Transfer Programme

3 Key elements in preparation for multi-lateral technology transfer which aligns with the access model of this WHO/MPP mRNA technology programme

Hardware : Facilities equipped to enable end-to-end mRNA technology development and manufacturing

Software: Systems development/optimization: QMS conforming to highest regulatory and quality standards, data management and security and mRNA product and process design

Brainware: Investment in relevant integrated rapid skills development training – equip our people

Afrigen End-to-End Research, Development and Manufacturing facility

Semi-Industrial Manufacturing Facility

- +2000 m^2 End-to-end sterile vaccine development facility at Afrigen Biologics
- Plasmid manufacturing/BSL 1/2 microbial cultivation
- mRNA synthesis (IVT)
- Formulation (Knauer installed and operational)
- Fill/Finish 2R-20R multidose vials (3 million vials per annum)
- Visual Inspection, labelling & packaging
- Cold storage

Class B Fill & Finish Area

R&D and Analytical Laboratories

- Cell culture for Potency assay under development

QC Labs

- Includes Isolator for Sterility assay

Stability Room

- Multiple stability chambers
- Fridges/Freezers
- Accelerated – 6 months
- Long term Zone 2 and 4b – 24 to 36 months

ICH Stability Zones

Zone	Type of Climate
Zone I	Temperate zone
Zone II	Mediterranean/subtropical zone
Zone III	Hot dry zone
Zone IV	Hot humid/tropical zone
Zone IVb	ASEAN testing conditions hot/higher humidity

Long Term Testing Conditions

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21ºC ± 2ºC	45% rH ± 5% rH	12 Months
Zone II	25ºC ± 2ºC	60% rH ± 5% rH	12 Months
Zone III	30ºC ± 2ºC	35% rH ± 5% rH	12 Months
Zone IV	30ºC ± 2ºC	65% rH ± 5% rH	12 Months
Zone IVb	30ºC ± 2ºC	75% rH ± 5% rH	12 Months
Refrigerated	5ºC ± 3ºC	No Humidity	12 Months
Frozen	-15ºC ± 5ºC	No Humidity	12 Months

Accelerated and Intermediate Testing Conditions

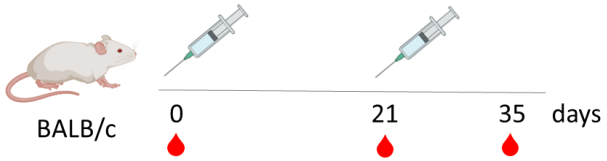
Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40ºC ± 2ºC	75% rH ± 5% rH	6 Months
Accelerated Refrigerated	25ºC ± 2ºC	60% rH ± 5% rH	6 Months
Accelerated Frozen	5ºC ± 3ºC	No Humidity	6 Months
Intermediate	30ºC ± 2ºC	65% rH ± 5% rH	6 Months

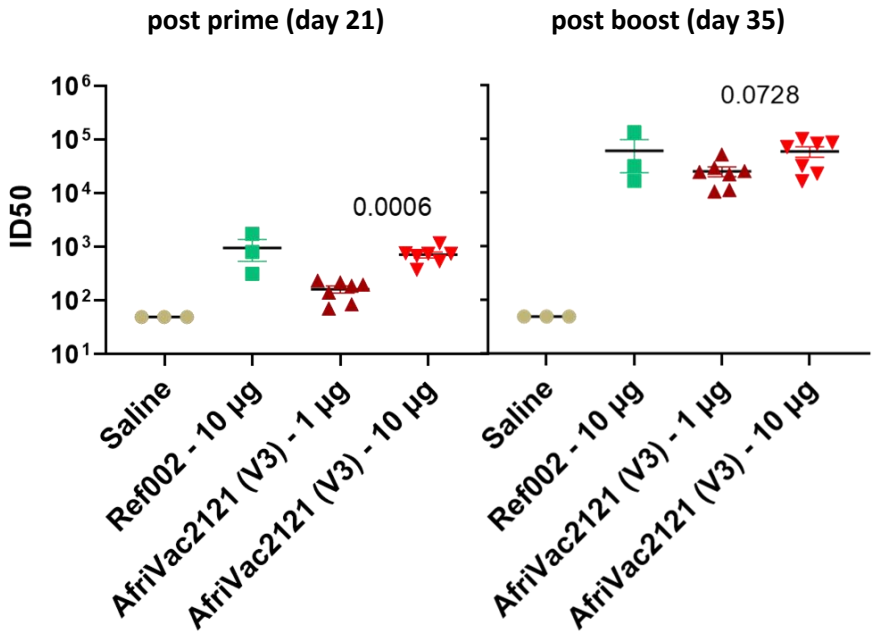
Cryogenic Facility

- Storage of Master and Working Cell Banks

mRNA Technology Transfer Hub Programme

Preliminary results





Mann Whitney U test

Neutralisation against Wuhan (D614G) SARS-CoV-2

- Material prepared at 100 mL IVT scale using representative process
- 1 µg and 10 µg doses of AfriVac2121 neutralize Wuhan variant equally well post boost (day 35).
- AfriVac 2121 is comparable to Ref002 based on neutralisation activity
- Currently being evaluated in Hamster challenge study

Successful attainment of product specification of the development batch prepared at 100 mL scale; the development work progressed to next scale – 1L IVT

Effectiveness of mRNA vaccine boosters against infection with the SARS-CoV-2 omicron (B.1.1.529) variant in Spain: a nationwide cohort study

Susana Monge, Ayelén Rojas-Benedicto, Carmen Olmedo, Clara Mazagatos, María José Sierra, Aurora Limia, Elisa Martín-Merino, Amparo Larrauri, Miguel A Hernán, on behalf of IBERCovid

Summary

Background The omicron (B.1.1.529) variant of SARS-CoV-2 has increased capacity to elude immunity and cause breakthrough infections. The aim of this study was to estimate the effectiveness of mRNA-based vaccine boosters (third dose) against infection with the omicron variant by age, sex, time since complete vaccination, type of primary vaccine, and type of booster.

Methods In this nationwide cohort study, we linked data from three nationwide population registries in Spain (Vaccination Registry, Laboratory Results Registry, and National Health System registry) to select community-dwelling individuals aged 40 years or older, who completed their primary vaccine schedule at least 3 months before the start of follow-up, and had not tested positive for SARS-CoV-2 since the start of the pandemic. On each day between Jan 3, and Feb 6, 2022, we matched individuals who received a booster mRNA vaccine and controls of the same sex, age group, postal code, type of vaccine, time since primary vaccination, and number of previous tests. We estimated risk of laboratory-confirmed SARS-CoV-2 infection using the Kaplan-Meier method and compared groups using risk ratios (RR) and risk differences. Vaccine effectiveness was calculated as one minus RR.

Findings Between Jan 3, and Feb 6, 2022, 3 111 159 matched pairs were included in our study. Overall, the estimated effectiveness from day 7 to 34 after a booster was 51·3% (95% CI 50·2–52·4). Estimated effectiveness was 52·5% (51·3–53·7) for an mRNA-1273 booster and 46·2% (43·5–48·7) for a BNT162b2 booster. Effectiveness was 58·6% (55·5–61·6) if primary vaccination had been with ChAdOx1 nCoV-19 (Oxford–AstraZeneca), 55·3% (52·3–58·2) with mRNA-1273 (Moderna), 49·7% (48·3–51·1) with BNT162b2 (Pfizer–BioNTech), and 48·0%

Lancet Infect Dis 2022; 22: 1313–20
Published Online June 2, 2022 https://doi.org/10.1016/S1473-3099(22)00292-4
See Comment page 1257

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RESEARCH

OPEN ACCESS

Check for updates

Effectiveness of mRNA-1273, BNT162b2, and BBIBP-CorV vaccines against infection and mortality in children in Argentina, during predominance of delta and omicron covid-19 variants: test negative, case-control study

Juan Manuel Castelli,[1] Analia Rearte,[1,2] Santiago Olszevicki,[1] Carla Voto,[1] María Del Valle Juarez,[1] Martina Pesce,[1] Agustina Natalia Iovane,[1] Mercedes Paz,[1] María Eugenia Chaparro,[1] Maria Pia Buyayisqui,[1] María Belén Markiewicz,[1] Mariana Landoni,[1,3] Carlos María Giovacchini,[1,3] Carla Vizzotti[1]

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2022;379:e073070 http://dx.doi.org/10.1136/bmj-2022-073070
Accepted: 02 November 2022

ABSTRACT

OBJECTIVE
To estimate the effectiveness of a two dose vaccine schedule (mRNA-1273, BNT162b2, and BBIBP-CorV) against SARS-CoV-2 infection and covid-19 related death and short term waning of immunity in children (3-11 years old) and adolescents (12-17 years old) during periods of delta and omicron variant predominance in Argentina.

DESIGN
Test negative, case-control study.

SETTING
Database of the National Surveillance System and the Nominalized Federal Vaccination Registry of Argentina.

PARTICIPANTS
844 460 children and adolescents without previous SARS-CoV-2 infection eligible to receive primary

the odds of SARS-CoV-2 infection among two dose vaccinated and unvaccinated participants. Vaccine effectiveness was estimated as (1−odds ratio)×100%.

RESULTS
Estimated vaccine effectiveness against SARS-CoV-2 infection was 61.2% (95% confidence interval 56.4% to 65.5%) in children and 66.8% (63.9% to 69.5%) in adolescents during the delta dominant period and 15.9% (13.2% to 18.6%) and 26.0% (23.2% to 28.8%), respectively, when omicron was dominant. Vaccine effectiveness declined over time, especially during the omicron period, from 37.6% (34.2% to 40.8%) at 15-30 days after vaccination to 2.0% (1.8% to 5.6%) after ≥60 days in children and from 55.8% (52.4% to 59.0%) to 12.4% (8.6% to 16.1%) in adolescents.
Vaccine effectiveness against death related to SARS-CoV-2 infection during omicron predominance was

nature microbiology

Article

https://doi.org/10.1038/s41564-022-01272-z

Comparative effectiveness of third doses of mRNA-based COVID-19 vaccines in US veterans

Received: 28 July 2022

Accepted: 17 October 2022

Published online: 2 January 2023

Check for updates

Barbra A. Dickerman[1,2,9], Hanna Gerlovin[3,9] ✉, Arin L. Madenci[1,2,4], Michael J. Figueroa Muñiz[3,5], Jessica K. Wise[3], Nimish Adhikari[3,5], Brian R. Ferolito[3], Katherine E. Kurgansky[3,6], David R. Gagnon[3,5], Kelly Cho[3,7], Juan P. Casas[3,7] & Miguel A. Hernán[1,2,8]

Vaccination against SARS-CoV-2 has been effective in reducing the burden of severe disease and death from COVID-19. Third doses of mRNA-based

Comparative effectiveness of 3 or 4 doses of mRNA and inactivated whole-virus vaccines against COVID-19 infection, hospitalization and severe outcomes among elderly in Singapore

Check for updates

Celine Y. Tan,[a,] Calvin J. Chiew,[a,b] Vernon J. Lee,[a,c] Benjamin Ong,[a,d] David Chien Lye,[b,d,e,f] and Kelvin Bryan Tan[a,c]*

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The Lancet Regional Health - Western Pacific 2022;29: 100654
Published Online 2 December 2022 https://doi.org/10.1016/j.lanwpc.2022.100654

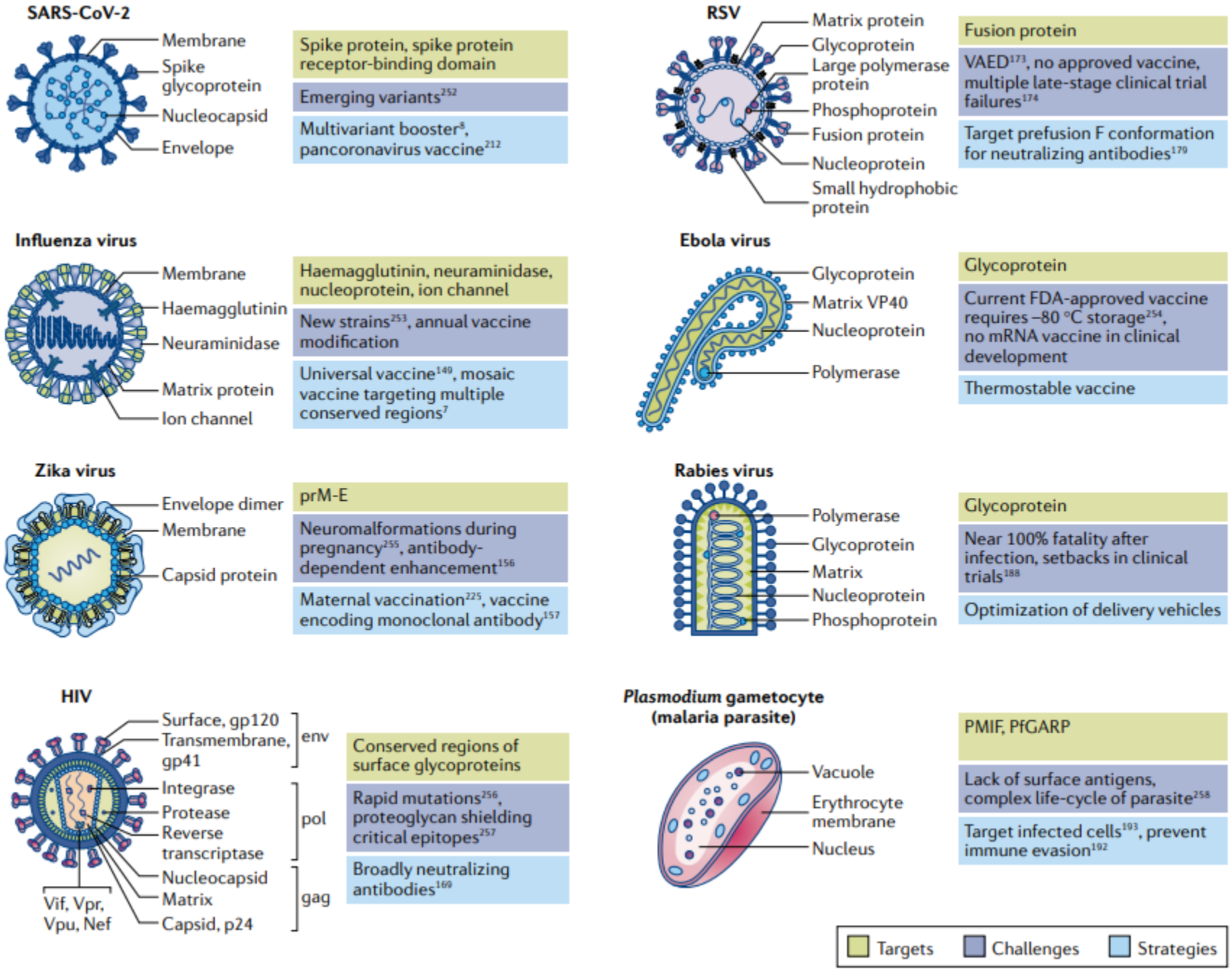
Previous studies have found that two doses of inactivated whole-virus vaccines elicited lower antibody titers and conferred less protection against SARS-CoV-2 infection than two doses of mRNA vaccines.[1,2] To maintain immunity among older persons who are most vulnerable to severe outcomes, a fourth vaccine dose with BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) has been recommended for individuals aged 60 and above in Singapore. CoronaVac (Sinovac) is

to account for the time-varying nature of vaccination status, and an individual could contribute person-time to multiple groups. Poisson regression was used to estimate incidence rate ratios (IRR) of infection, hospitalization, and severe disease, adjusting for age, sex, ethnicity, housing type (as a marker of socioeconomic status) and calendar date (to account for varying force of infection across time). Individuals who received three doses of mRNA vaccine served as the reference group

mRNA vaccines in development protect against array of common pathogens using disease specific targeting strategies

- Surface proteins enabling cell entry (SARS-COV-2, Influenza, Zika and RSV)
- Surface glycoprotein (HIV, Ebola, Rabies)
- Non-surface antigen (Plasmodium)

- Use mRNA vaccines encoding conformation- specific proteins, conserved regions of antigens or monoclonal antibodies



https://www.nature.com/articles/s41573-021-00283-5.pdf

mRNA technology: opportunities and challenges

Opportunities

- Platform manufacturing and testing processes
- Multi-product production facility is feasible
- Small footprint and cost-efficient manufacturing
- Potential application to many vaccine targets
- Versatility for complex antigens/multi-valency
- Safety and efficacy demonstrated in widespread application for Covid-19
- Short lead times to clinical development
- Enables rapid iteration in exploratory medicine trials

Challenges

- Core mRNA immunology is still evolving
- Fundamental structure-function understanding of mRNA architecture still being developed
- Vaccine product (LNP) temperature stability is yet to be adequately addressed
- Capabilities beyond CMC are required for antigen design:
    - Understand host-pathogen interactions for wide variety of infectious diseases
    - Antigen design and vaccinology
    - Preclinical functional assay development
- Durability & breadth of protective immune response (is covid-19 vaccine typical?)
- Intellectual property minefield

Afrigen portfolio - initial assessment process

- Incorporation of analysis by the Partnership for African Vaccine Manufacturing (PAVM)
  - Framework for Action (4/2021, 3/2022)
  - Market Design and Demand Intelligence Workshop (6/2022)
- Review of CEPI, GAVI, BMGF and WHO priority diseases
- Input from key opinion leaders
- Initial assessment of potential for mRNA/LNP application and technical feasibility
- Preliminary, high-level assessment of need in Africa
- Initial prioritization developed for further pressure testing and elaboration

Assessing mRNA utility and development feasibility

Targets in

mRNA/LNP Suitability & Testing

- What is the degree of antigen complexity?
- Is the antigen design space well understood?
- Are there adequate preclinical models of immunity or protection
- Is mRNA likely to induce protective immune response?
- Are research tools and assays accessible

Clinical & Regulatory Development Path

- Does correlate of protection exist?
- Can immunogenicity non-inferiority studies be conducted vs. standard of care?
- What are the access/safety risks for the target population?
- Is there an established regulatory path for approval?
- What is the degree of complexity of the clinical studies?

Additional Criteria

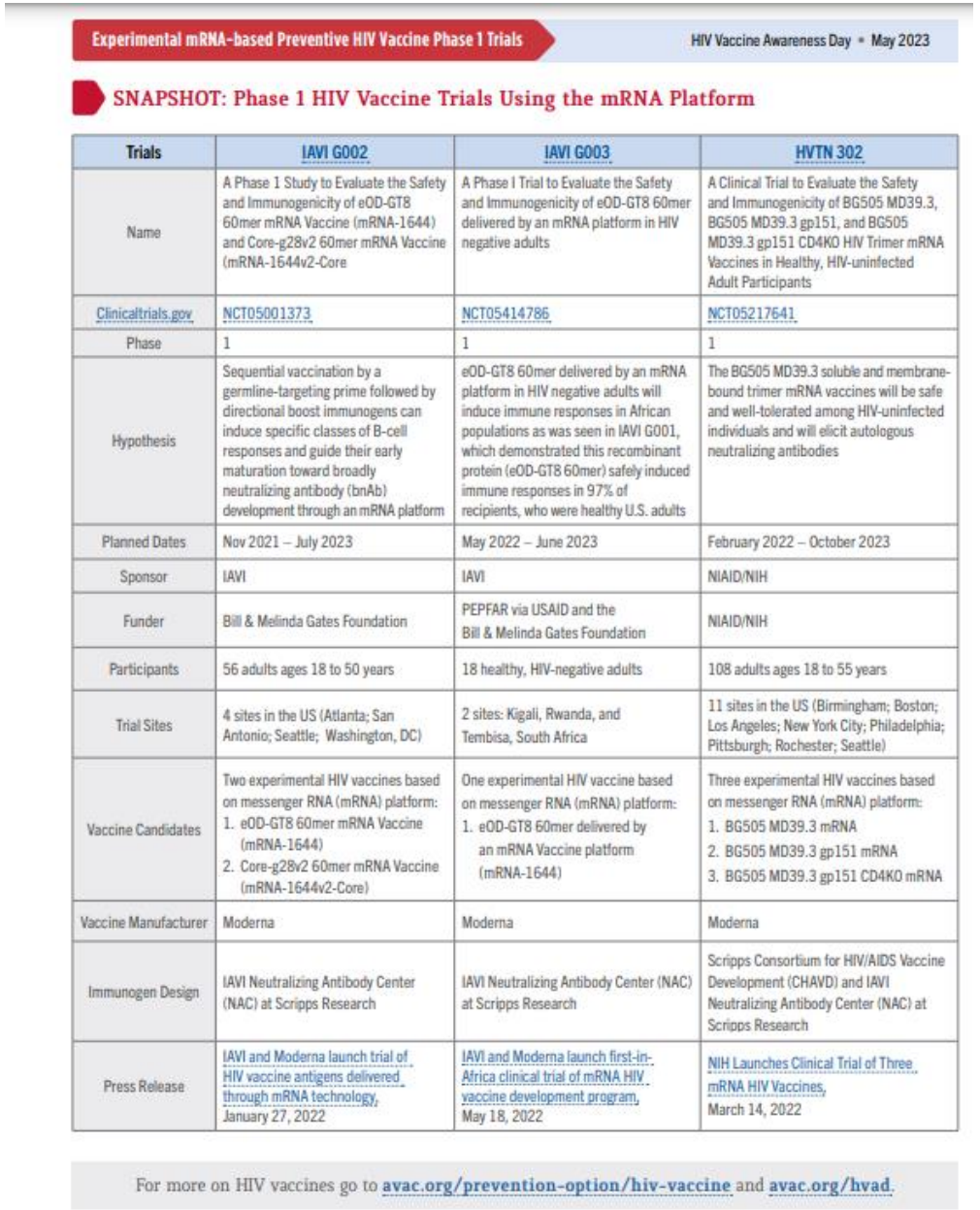
- Are the antigens available?
- How many antigens should be included?
- How important is genetic diversity of the pathogen?
- What is the complexity of the formulation?
- Are existing vaccines accessible?
- Are clinical study participants accessible?
- What is the market potential?
- Is funding available?

Priorities out

mRNA Technology Transfer Hub Programme

Potential for HIV vaccine

- mRNA platform offers a nimble and responsive approach to vaccine design and testing, potentially shaving off years from typical vaccine development timelines
- 3 Phase 1 trials ongoing, completion June/July/October 2023
- Theoretically, a vaccine should be possible. Still doing basic research to advance our understanding of immunity to HIV.
- Hub, SAMVAC project started- development of HIV subtype C mRNA vaccines expressing Env-Gag antigens
- Application to HIV-VISTA programme funded by USAID.



Experimental mRNA-based Preventive HIV Vaccine Phase 1 Trials — HIV Vaccine Awareness Day • May 2023

SNAPSHOT: Phase 1 HIV Vaccine Trials Using the mRNA Platform

Trials	IAVI G002	IAVI G003	HVTN 302
Name	A Phase 1 Study to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer mRNA Vaccine (mRNA-1644) and Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core	A Phase I Trial to Evaluate the Safety and Immunogenicity of eOD-GT8 60mer delivered by an mRNA platform in HIV negative adults	A Clinical Trial to Evaluate the Safety and Immunogenicity of BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO HIV Trimer mRNA Vaccines in Healthy, HIV-uninfected Adult Participants
Clinicaltrials.gov	NCT05001373	NCT05414786	NCT05217641
Phase	1	1	1
Hypothesis	Sequential vaccination by a germline-targeting prime followed by directional boost immunogens can induce specific classes of B-cell responses and guide their early maturation toward broadly neutralizing antibody (bnAb) development through an mRNA platform	eOD-GT8 60mer delivered by an mRNA platform in HIV negative adults will induce immune responses in African populations as was seen in IAVI G001, which demonstrated this recombinant protein (eOD-GT8 60mer) safely induced immune responses in 97% of recipients, who were healthy U.S. adults	The BG505 MD39.3 soluble and membrane-bound trimer mRNA vaccines will be safe and well-tolerated among HIV-uninfected individuals and will elicit autologous neutralizing antibodies
Planned Dates	Nov 2021 – July 2023	May 2022 – June 2023	February 2022 – October 2023
Sponsor	IAVI	IAVI	NIAID/NIH
Funder	Bill & Melinda Gates Foundation	PEPFAR via USAID and the Bill & Melinda Gates Foundation	NIAID/NIH
Participants	56 adults ages 18 to 50 years	18 healthy, HIV-negative adults	108 adults ages 18 to 55 years
Trial Sites	4 sites in the US (Atlanta; San Antonio; Seattle; Washington, DC)	2 sites: Kigali, Rwanda, and Tembisa, South Africa	11 sites in the US (Birmingham; Boston; Los Angeles; New York City; Philadelphia; Pittsburgh; Rochester; Seattle)
Vaccine Candidates	Two experimental HIV vaccines based on messenger RNA (mRNA) platform: 1. eOD-GT8 60mer mRNA Vaccine (mRNA-1644) 2. Core-g28v2 60mer mRNA Vaccine (mRNA-1644v2-Core)	One experimental HIV vaccine based on messenger RNA (mRNA) platform: 1. eOD-GT8 60mer delivered by an mRNA Vaccine platform (mRNA-1644)	Three experimental HIV vaccines based on messenger RNA (mRNA) platform: 1. BG505 MD39.3 mRNA 2. BG505 MD39.3 gp151 mRNA 3. BG505 MD39.3 gp151 CD4KO mRNA
Vaccine Manufacturer	Moderna	Moderna	Moderna
Immunogen Design	IAVI Neutralizing Antibody Center (NAC) at Scripps Research	IAVI Neutralizing Antibody Center (NAC) at Scripps Research	Scripps Consortium for HIV/AIDS Vaccine Development (CHAVD) and IAVI Neutralizing Antibody Center (NAC) at Scripps Research
Press Release	IAVI and Moderna launch trial of HIV vaccine antigens delivered through mRNA technology, January 27, 2022	IAVI and Moderna launch first-in-Africa clinical trial of mRNA HIV vaccine development program, May 18, 2022	NIH Launches Clinical Trial of Three mRNA HIV Vaccines, March 14, 2022

For more on HIV vaccines go to avac.org/prevention-option/hiv-vaccine and avac.org/hvad.

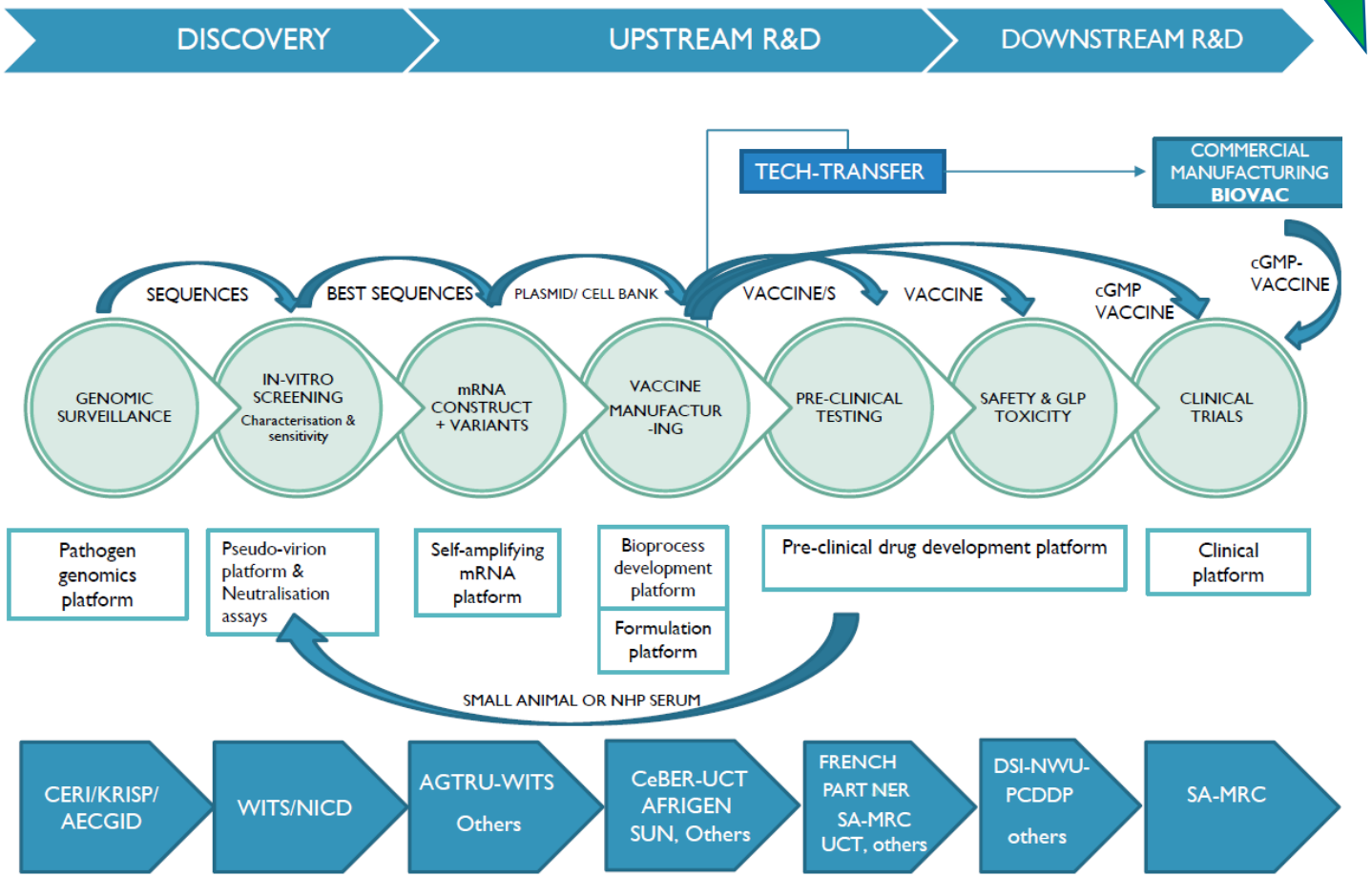
mRNA Program Local Innovation Platform

Omicron, TB and HIV

Build innovation capacity and develop pipeline of homegrown products

SAMVAC – South African mRNA Vaccine Consortium

- Genomics (NGS-SA, CERI)
- Immunology (NICD)
- Vaccine construction (WITS)
- Lipid carriers (WITS)
- Enzyme production (SUN)
- Process development (UCT)
- Process scale-up, GMP manufacturing (Afrigen)
- Preclinical (PUDAC, NWU)



Contribution and Recognition

- WHO
- Medicines Patent Pool(MPP)
- Funders: France, Belgium, Germany, Norway, Canada, Switzerland, South Africa, EC/EU. SA Government DSI
- AU and Africa CDC (PAVM)
- SAMRC
- Biovac
- Civil Society Groups
- mRNA Hub Steering Committee
- mRNA Hub Scientific Advisory Committee
- PATH
- NIH/VRC
- Curapath
- University of the Witwatersrand, NICD, CeBER-UCT, PCDDP, NWU, and other SA Universities
- Afrigen Team and Supporting Stakeholders and Shareholders