David Harrison for TAC Cape Town 2015

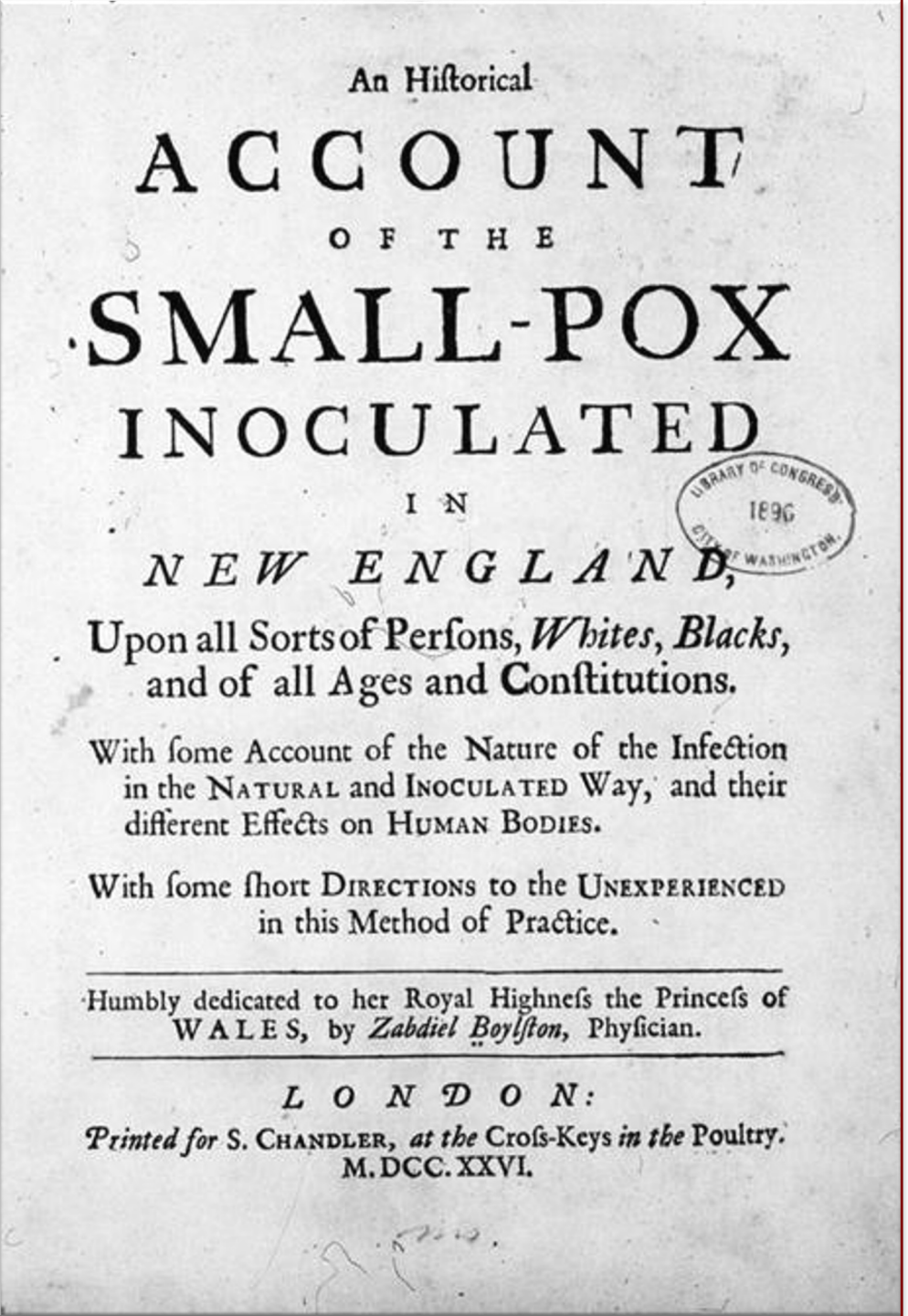
A (TB) advocate's perspective on mRNA vaccines for TB and HIV + local manufacturing

What's All the Buzz About: mRNA, manufacturing, vaccines access

June 1, 2023

Mike Frick
TB Project Co-director

TAG
Treatment Action Group



An Hiſtorical

ACCOUNT

OF THE

SMALL-POX

INOCULATED

IN

NEW ENGLAND,

Upon all Sorts of Perſons, *Whites*, *Blacks*, and of all Ages and Conſtitutions.

With ſome Account of the Nature of the Infection in the NATURAL and INOCULATED Way, and their different Effects on HUMAN BODIES.

With ſome ſhort DIRECTIONS to the UNEXPERIENCED in this Method of Practice.

Humbly dedicated to her Royal Highneſs the Princeſs of WALES, by *Zabdiel Boylſton*, Phyſician.

LONDON:

Printed for S. CHANDLER, *at the* Croſs-Keys *in the* Poultry.
M.DCC.XXVI.

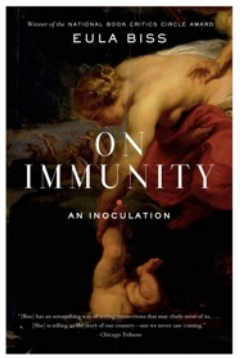
Vaccination: an original *South* → North technology transfer (one made under brutal, unequal conditions)

Onesimus explained that he had *"undergone an Operation, which had given him something of ye Small-Pox, and would forever preserve him from it, adding, That it was often used [. . .] and whoever had ye Courage to use it, was forever free from ye Fear of Contagion."*

Sources:

Eula Biss, *On Immunity,* 2014

WEB Du Bois Research Institute @ Harvard FAS



Work on mRNA for TB and HIV began *before* COVID-19

Press Release

BioNTech Announces New Collaboration to Develop HIV and Tuberculosis Programs

4 September 2019

Press Release in English - PDF

— Bill & Melinda Gates Foundation invests $55 million in an infectious disease collaboration that could reach up to $100 million in total funding —

Mainz, Germany, September 4, 2019 – BioNTech SE, a clinical-stage biotechnology company focused on patient-specific immunotherapies for the treatment of cancer and other serious diseases, announced today that it has signed an agreement with the Bill & Melinda Gates Foundation (the Gates Foundation) to develop HIV and tuberculosis programs, further expanding the Company's infectious disease portfolio. This partnership includes an initial equity investment of $55 million, which is expected to close within the next week. The funds will be used to develop preclinical vaccine and immunotherapy candidates to prevent HIV and tuberculosis infection as well as to lead to durable antiretroviral therapy-free remission of HIV disease. Total funding under the collaboration could reach $100 million through potential future grant funding from the Gates Foundation that would be used to underwrite the evaluation of these candidates in the clinic and support the initiation of new infectious disease projects.

- Initial equity investments by Gates Foundation of $55 million to "develop preclinical vaccine and immunotherapy candidates to prevent HIV and TB…"
- Total funding could reach $100 million through future grant funding to support clinical evaluations.
- BioNTech "will retain rights for commercialization of the vaccine candidates in the developed world, while providing affordable access to the candidates in developing countries."

The COVID-19 pandemic has taught us to ask about what this means, specifically.

And to ask: **are there better ways?**

The mRNA vaccines are coming! (maybe) *for TB*

BIONTECH

Has registered two phase I clinical trials of two investigational vaccines under the name BNT164 (BNT164a1 and BNT164b1).

- NCT05537038 (Germany?)
- NCT05547464 (South Africa)

Each will evaluate safety, reactogenicity, and immunogenicity of three dose levels of the vaccines given in a three-dose schedule.

iavi moderna

April 7, 2022: "[Moderna and IAVI] today announced a new collaboration to employ mRNA technology to meet the challenge of a range of global health threats: HIV/AIDS, tuberculosis, antimicrobial-resistant enteric infections, and COVID-19."

mRNA Technology Transfer Hub Programme

Has started preclinical work on a TB vaccine candidate(s).

Discussed mRNA and TB vaccines on April 21 during the Hub's week-long meeting in Cape Town.

+ others e.g., **PopVax**

Source: TAG 2022 TB Vaccines Pipeline Report

The TB Vax Pipeline

by developers, sponsors, and funders

Phase I	Phase IIa	Phase IIb	Phase III
TB/FLU-05E • RIBSP Kazakhstan, Russian Federation Ministry of Health	**ChAdOx1.85A + MVA85A** • University of Oxford	**H56:IC31** • Staten Serum Institut, Valneva (IC31 adjuvant), IAVI, EDCTP	**MIP (Immuvac)** • ICMR, Cadila Pharmaceuticals
AdHu5Ag85A • McMaster University, CanSino	**AEC/BC02** • Anhui Zhifei Longcom	**DAR901** • Dartmouth College, GHIT Fund	**VPM1002** • Serum Institute of India, VPM, ICMR, NIH/NIAID, EDCTP
BNT164 • BioNTech		**ID93/GLA-SE** • NIAID/NIH **QTP101** • Quratis	**M72/AS01E** • Gates MRI, GSK (AS01E adjuvant), Wellcome Trust (MESA-TB trial)
		RUTI • Archivel Farma	**MTBVAC** • Biofabri, University of Zaragoza, IAVI, TBVI, EDCTP
			GamTBVac • Gamaleya Research Center, Russian Federation Ministry of Health
			BCG (re)vaccination • Gates MRI, ICMR, NIH/NIAID (BCG revaccination) • Henry Jackson Foundation (traveler BCG)

- Sponsor(s) and Major Partner

Protein/adjuvant

Mycobacterial *live attenuated*

Mycobacterial *inactivated*

Viral vector

mRNA

The first trial of an mRNA-based TB vaccine enrolled its first participant last month.

The mRNA vaccines are coming! (maybe) *for HIV*

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

Moderna Moderna Moderna

Source: https://www.avac.org/resource/phase-1-mrna-hiv-vaccine-trials-0

> "mRNA is a necessary tool to iterate to create the vaccine regimen we think will be necessary to coax immunity toward what we think is likely to work."
>
> – Senior HIV vaccine researcher @ mRNA Hub Meeting in April 2023 (paraphrased from notes)

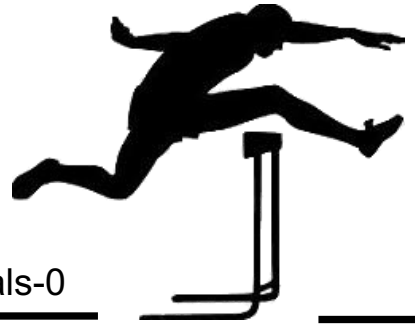
Unpacking the “(maybe)”

- There’s nothing inherently magic about mRNA:

> “mRNA platforms deliver a piece of genetic material that instructs the body to make a protein fragment of a target pathogen (such as HIV), which the immune system will hopefully recognize and mount a defense against.”[1]

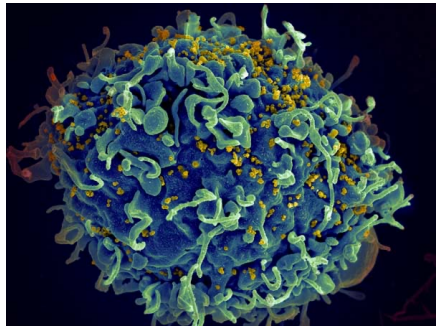
The question is: what to deliver?

Or: what’s the right target? What does protective immunity require and how best to use vaccines to achieve it?



[1] https://www.avac.org/resource/phase-1-mrna-hiv-vaccine-trials-0

mRNA may help answer these questions as part of a larger strategy to develop HIV and TB vaccines. *It won't be easy.*

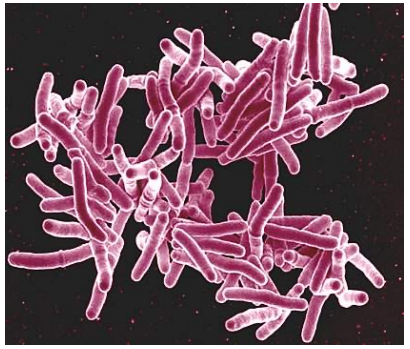


HIV

"The development of an effective HIV-1 vaccine is particularly challenging owing to the exceptional and increasing genetic diversity of the HIV-1 lentivirus, its complex mechanisms of immune evasion and the ability of HIV-1 to integrate into host immune cells to become resistant to host immunity and treatment regimens."

– Haynes et al, Nature Review Immunology, 2022

TB



- "The development of effective TB vaccines is hindered by a lack of knowledge about the mechanisms of protective immunity and the antigens that induce protective responses" […]
- "MTB has a large genome (~4,000 protein-coding genes), so the host T cell repertoire faces the challenge of recognizing many MTB antigens. And TB immunologists face the challenge of identifying which antigens are processed and presented to T cells in humans."

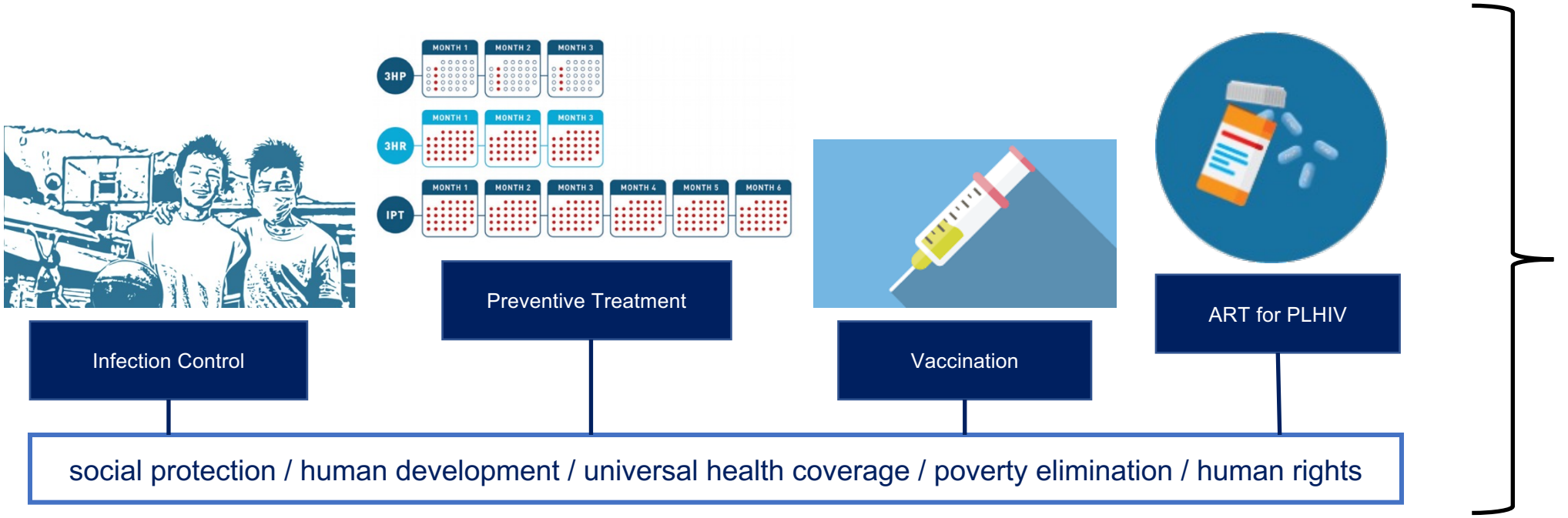
– Ogongo and Ernst commenting on a *Nature Medicine* paper by Musvosvi et al, 2023

"We are not building a product, we are building a platform."[1]

- mRNA is not a panacea or promise, but instead:
  - A tool (but not the only one)
  - deployed within a larger strategy
  - that allows for more early iteration
  - and "de-risks" failure by allowing us to fail faster, earlier, at less cost
  - and to get back to the clinic again more quickly to try something else.

- mRNA is a platform technology on which many applications can be built, but only if it's shared and open to many different developers.
- The mRNA platform is itself evolving and improving, and it will improve faster if many people are working on it.

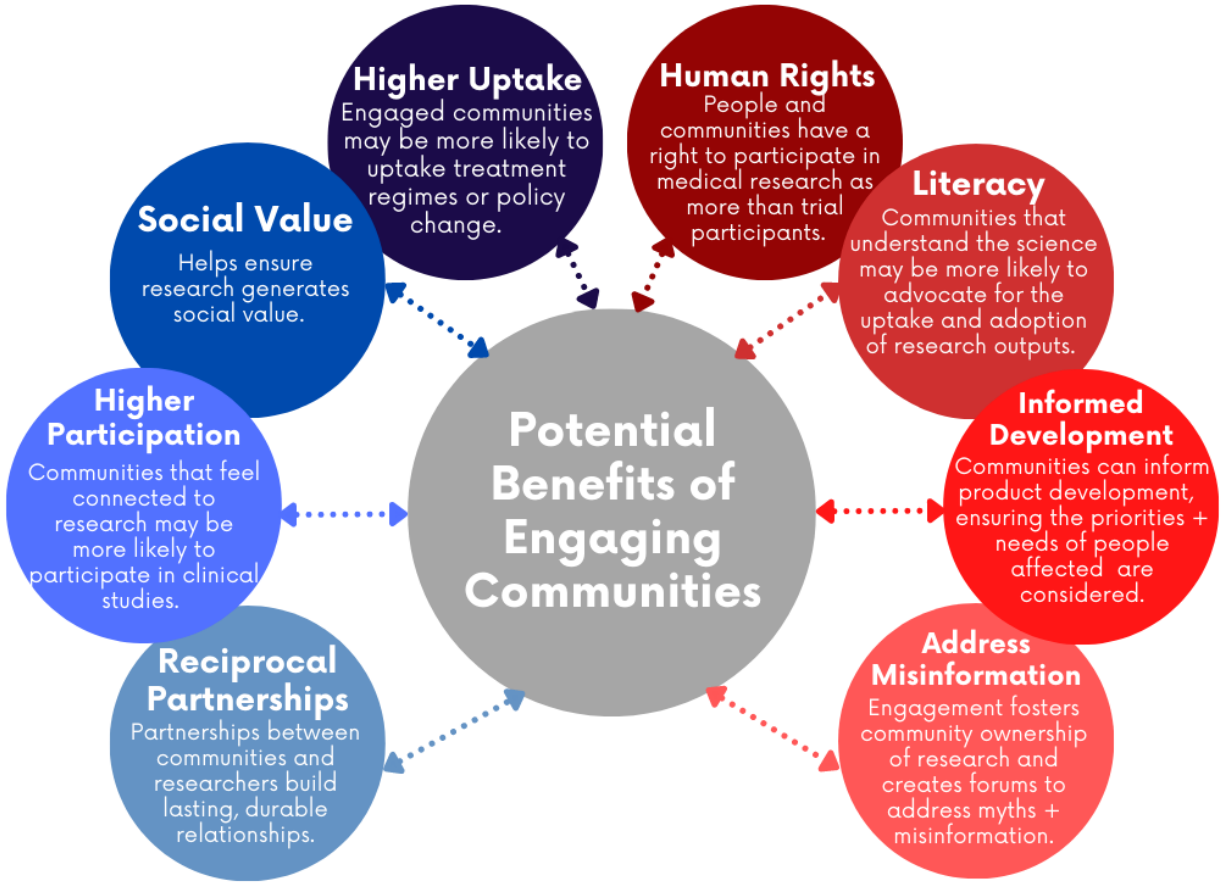
Vaccines – and vaccine platforms – don't exist in a vacuum.



- mRNA vaccines for TB and HIV will be developed alongside other biomedical preventive interventions and against a background of disease risk shaped by the socio-political determinants of health.
- **Community engagement in mRNA vaccine development will be key!**

Images: Delek Hospital; IMPAACT4TB; TAG

The reasons to – and benefits of – engaging communities early, often are manifold



- The mRNA Tech Transfer Hub Programme needs to establish an intentional program of community engagement that engages the diversity of civil society's skillset in:
  - shaping vaccine design
  - informing study protocols
  - promoting inclusive trials
  - determining acceptability
  - addressing (mis)information –
  - creating demand
  - ensuring freedom to operate (IP).

Image: Erin McConnell @ TAG for SMART4TB

“We need good science like we need clean water.”[1]

Everyone has the fundamental human right to enjoy the benefits of scientific progress and its applications, without discrimination.

Access

Development — Invest in research and channel resources to support a “*purposive development*” of science and technology to meet the needs of marginalized and disadvantaged groups.

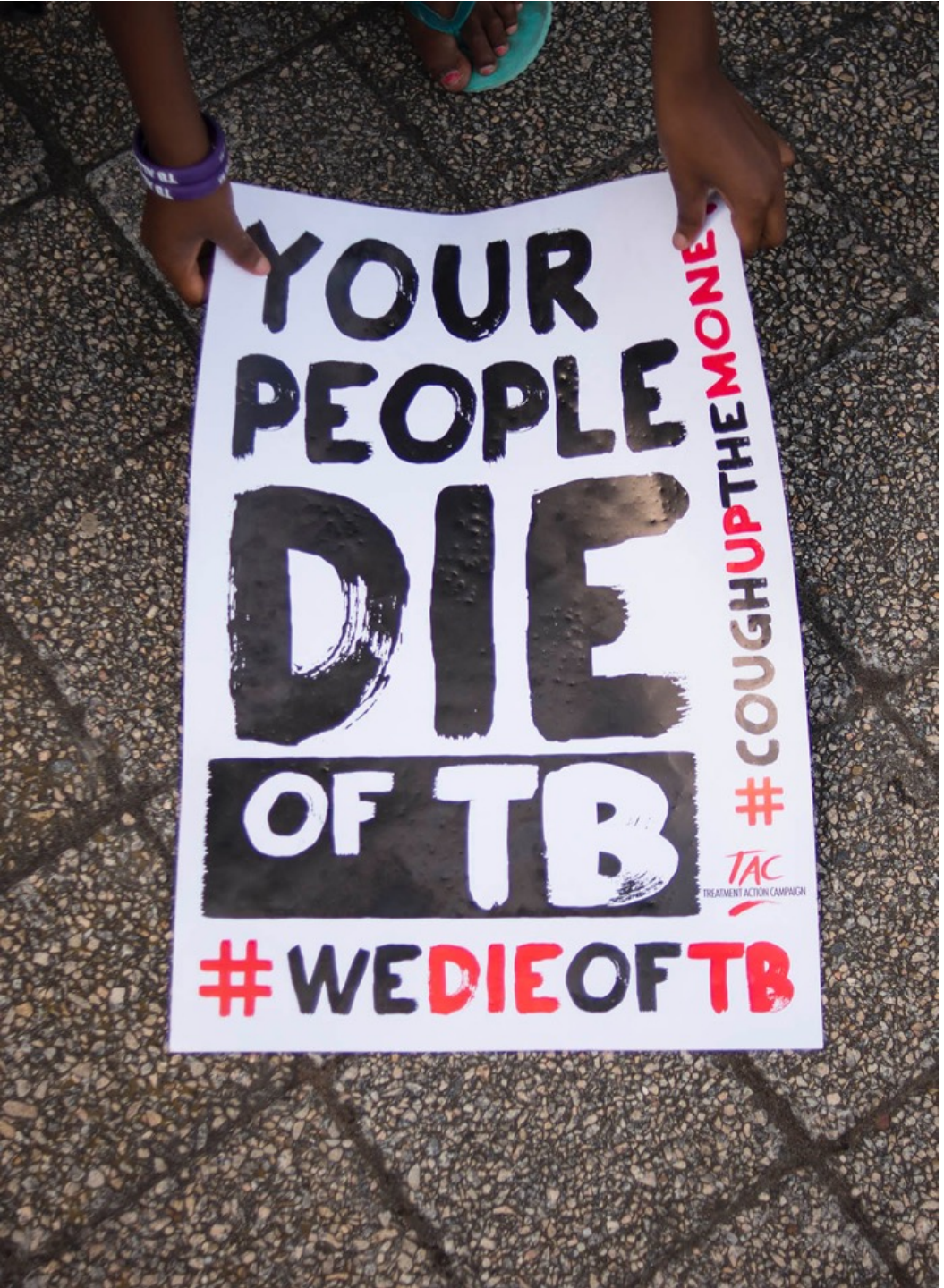
Diffusion — Connect people to the benefits of science (tangible and intangible) in a way that ensures non-discrimination and enables participation.

Conservation — Ensure that the benefits gained through science are lasting—not just for people alive today, but also for future generations; not for a privileged few, but for the many.

mRNA Technology Transfer Hub Programme

We need vaccine development programs that can work on all three dimensions of access, together, simultaneously, as part of the vision – the mRNA Tech Transfer Hub Programme can do that!

[1] Glenda Gray. State of the Field and Future Direction of Research and Development for TB and HIV/AIDS Vaccines. AIDS 2016. Durban, South Africa.



Thank you!

mike.frick@treatmentactiongroup.org