Webinar

TAG
Treatment Action Group

TB Vaccine Development:
The Next Chapter Starts Now

https://www.treatmentactiongroup.org/webinar/tb-vaccine-development-the-next-chapter-starts-now/

Thursday, April 13

8:00 am NYC, 2:00 pm Cape Town/Geneva

5:30 pm New Delhi, 7:00 pm Jakarta

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The TB Vaccine Pipeline

Vaccine Candidates and Clinical Trials Advocates Should Know

Mike Frick

TB project co-director

TAG
Treatment Action Group

Agenda

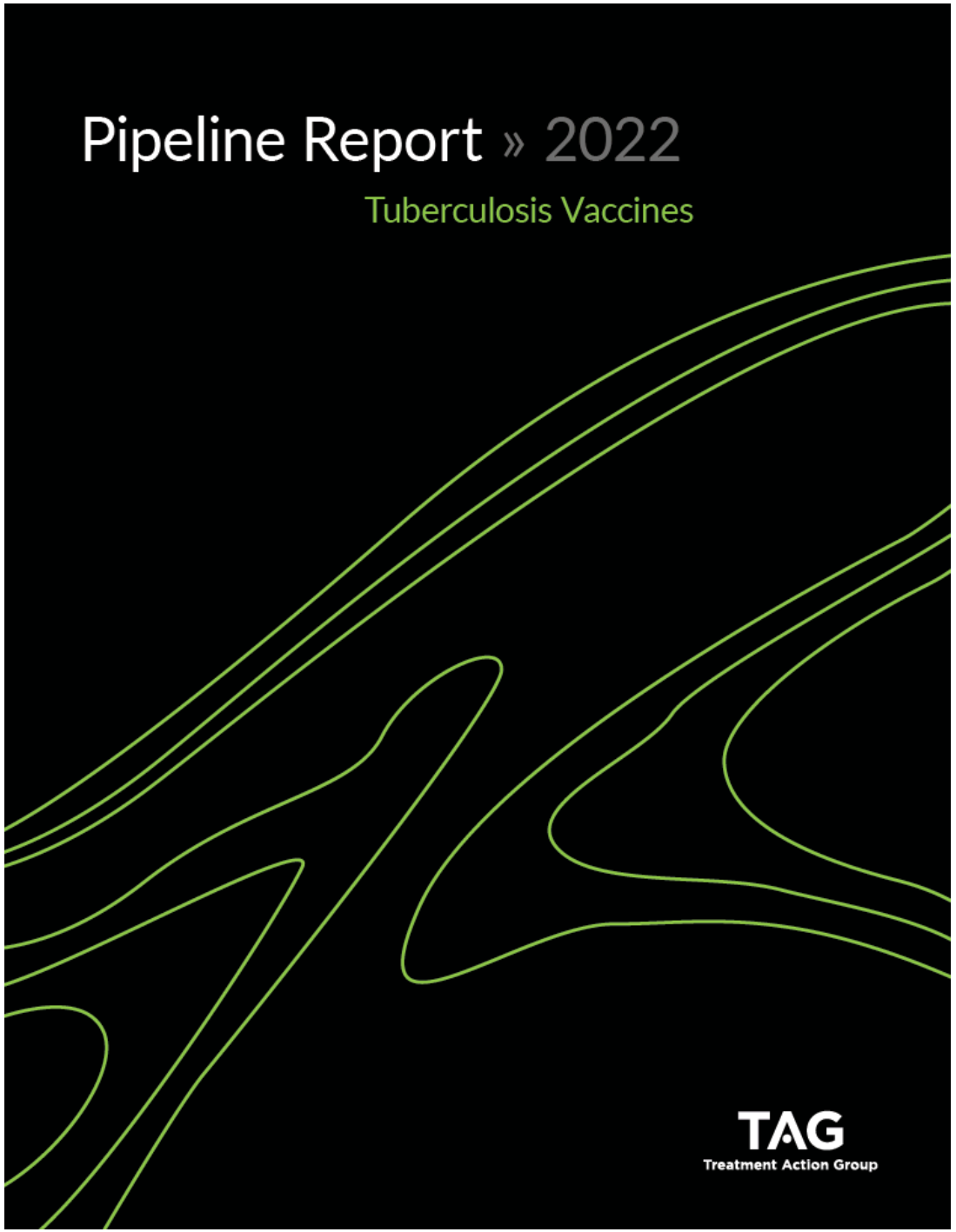
2 opening questions

3 vaccine development strategies

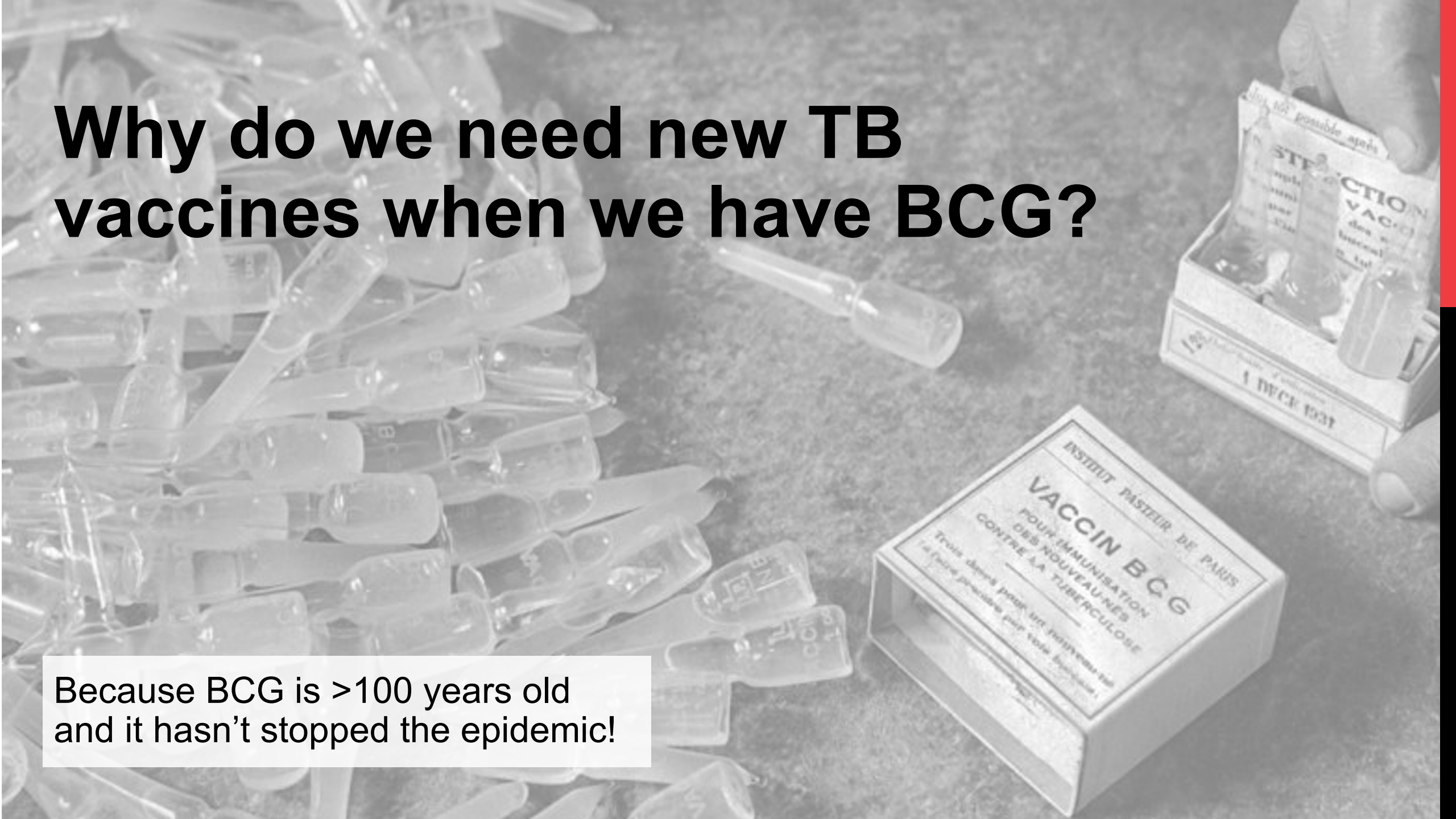
6 views of the pipeline

4 candidate close-ups

https://www.treatmentactiongroup.org/resources/pipeline-report/2022-pipeline-report/



Why do we need new TB vaccines when we have BCG?



Because BCG is >100 years old
and it hasn't stopped the epidemic!

BCG: the only existing vaccine against TB

- Bacillus Calmette–Guérin (BCG): developed by Albert Calmette and Camille Guérin in France in early 1900s (interrupted by WWI).
- First introduced into human use in **1921.**
- BCG is a live attenuated form of *Mycobacterium bovis*, the organism that causes TB in cattle.
- Part of the EPI package and given to infants soon after birth. Believed to be the mostly widely administered vaccine in human history.
- Protects children against severe forms of TB (e.g., TB meningitis, miliary TB, disseminated TB), but offers highly variable protection against pulmonary TB in adolescents and adults, who account for most TB transmission.

THE LANCET
Global Health

Infant BCG vaccination and risk of pulmonary and extrapulmonary TB throughout the life course: a **systematic review** and **individual participant data meta-analysis**

- Analyzed individual-level data from 68,552 TB contacts in 26 case-contact cohort studies from 17 countries (all published within the last 20 years). Found that:
  - infant BCG vaccination was effective in preventing all TB, pulmonary TB, and death, especially among younger children.
  - the overall effectiveness of BCG against all forms of TB was 18%. The protective effect of BCG against TB waned in participants ≥ 5 years.
  - BCG provided >80% protection against death, an effect that lasted through age 14.

"These results suggest that infant BCG vaccination, although important to young children who are at high risk of tuberculosis, does not prevent adult-type cavitary tuberculosis and is therefore insufficient to impede the tuberculosis epidemic, providing further evidence that novel vaccines are urgently needed."

Martinez et al, 2022 10.1016/S2214-109X(22)00283-2

Why is it taking so long to develop new vaccines against TB?

Because we're running the hurdles, not a straightaway sprint. There are multiple obstacles – scientific, political, financial – that we have to jump over, knock down, or clear away.

TB vaccine **strategies**

Currently, there are three overarching strategies guiding TB vaccine development efforts. Each is known by the primary endpoint of interest.

- POI = prevention of infection
- POD = prevention of disease
- POR = prevention of **r**ecurrence (**r**elapse or **r**einfection)

The Pipeline

the bird's eye view

16

The pipeline contains **~16 vaccine candidates** including 6 in or preparing for phase III trials.

>75,000

The field is mounting multiple phase III trials that will together enroll over **75,000 people**. (The most since the middle of the 20th century!)

Dozens

These phase III trials will bring TB vaccine science to **over a dozen countries.**

100,000s

Investigators will collect **hundreds of thousands of participant samples** that will guide next-generation vaccine development and immunology and other basic science research on TB.

∞

Ongoing and planned phase II and III trials will enroll **diverse populations of people at risk of TB**, including PLHIV, children, household contacts of people with TB, people treated for TB disease, and people with MTB infection and those without.

The Pipeline *by name*

Phase I	Phase IIa	Phase IIb	Phase III
TB/FLU-05E *Also TB/FLU-01L & TB/FLU 04L*	ChAdOx1.85A + MVA85A	H56:IC31	MIP (Immuvac)
AdHu5Ag85A	AEC/BC02	DAR901	VPM1002
BNT164		ID93/GLA-SE QTP101	M72/AS01E
		RUTI	MTBVAC
			GamTBVac
			BCG (re)vaccination

Vaccine candidate name

Very little in early phases!

The Pipeline *by type*

Phase I	Phase IIa	Phase IIb	Phase III
TB/FLU-05E *Also TB/FLU-01L and TB/FLU-04L*	ChAdOx1.85A + MVA85A	H56:IC31	MIP (Immuvac)
AdHu5Ag85A	AEC/BC02	DAR901	VPM1002
BNT164		ID93/GLA-SE QTP101	M72/AS01E
		RUTI	MTBVAC
			GamTBVac
			BCG (re)vaccination

- Protein/adjuvant
- Mycobacterial *live attenuated*
- Mycobacterial *inactivated*
- Viral vector
- mRNA

The 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

One candidate, two names, two different sponsors

The Pipeline
by clinical trials

Phase I

TB/FLU-05E
Also TB/FLU-01L and TB/FLU-04L
- Phase I trial TBA

AdHu5Ag85A
- NCT02337270

BNT164
- NCT05537038
- NCT05547464

Phase IIa

ChAdOx1.85A + MVA85A
- NCT03681860

AEC/BC02
- NCT04239313

Phase IIb

H56:IC31
- **NCT03512249 (POR)**

DAR901
- **NCT02712424 (POI)**

ID93/GLA-SE
- A5397/HVTN603 (Rx vax)
- NCT03722472

QTP101
- **Phase IIb/III TBA (POD)**

RUTI
- NCT04919239 (Rx vax)
- NCT05455112 (Rx vax)

Phase III

MIP
- **CTRI/2019/01/017026 (POD)**

VPM1002
- **CTRI/2019/01/017026 (POD)**
- **NCT04351685 (POI)**
- **NCT03152903 (POR)**
- NCT05539989

M72/AS01E
- **Phase III trial TBA (POD)**
- NCT04556981 (PLHIV)
- NCT05190146 (Epi study)

MTBVAC
- **NCT04975178 (POI)**
- Phase I/II in PLHIV TBA
- **Phase III trial in adults & adolescents TBA (POD)**

GamTBVac
- NCT04975737 (POD)

BCG (re)vaccination
- **NCT05330884 (POD)**
- **NCT04151161 (POI)**
- **NCT04453293 (pre-travel)**
- NCT05539989

Protein/adjuvant

Mycobacterial *live attenuated*

Mycobacterial *inactivated*

Viral vector

mRNA

- Clinical trial registry number
  bold = phase III (efficacy endpoint)
- Rx vax = therapeutic vaccines

The Pipeline
by PLHIV inclusion

Phase I

TB/FLU-05E
Also TB/FLU-01L and TB/FLU-04L
- Phase I trial TBA

AdHu5Ag85A
- NCT02337270

BNT164
- NCT05537038
- NCT05547464

Phase IIa

ChAdOx1.85A + MVA85A
- NCT03681860

AEC/BC02
- NCT04239313

Phase IIb

H56:IC31
- NCT03512249 (POR)

DAR901
- **NCT02712424 (POI)**

ID93/GLA-SE
- **A5397/HVTN603 (Rx vax)**
- NCT03722472

QTP101
- Phase IIb/III TBA (POD)

RUTI
- NCT04919239 (Rx vax)
- NCT05455112 (Rx vax)

Phase III

MIP
- CTRI/2019/01/017026 (POD)

VPM1002
- CTRI/2019/01/017026 (POD)
- NCT04351685 (POI)
- NCT03152903 (POR)
- **NCT05539989**

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MTBVAC
- NCT04975178 (POI)
- **Phase I/II in PLHIV TBA**
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- NCT04975737 (POD)

BCG (re)vaccination
- NCT05330884 (POD)
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- NCT04453293 (pre-travel)
- **NCT05539989**

Protein/adjuvant

Mycobacterial *live attenuated*

Mycobacterial *inactivated*

Viral vector

mRNA

Previous, current, or planned studies in PLHIV or that include PLHIV **in bold**

THE LANCET
HIV

Developing tuberculosis vaccines for people with HIV: consensus statements from an international expert panel

Maurine D Miner, Mark Hatherill, Vidya Mave, Glenda E Gray, Sharon Nachman, Sarah W Read, Richard G White, Anneke Hesseling, Frank Cobelens, Sheral Patel, Mike Frick, Theodore Bailey, Robert Seder, Joanne Flynn, Jyothi Rengarajan, Deepak Kaushal, Willem Hanekom, Alexander C Schmidt, Thomas J Scriba, Elisa Nemes, Erica Andersen-Nissen, Alan Landay, Susan E Dorman, Grace Aldrovandi, Lisa M Cranmer, Cheryl L Day, Alberto L Garcia-Basteiro, Andrew Fiore-Gartland, Robin Mogg, James G Kublin, Amita Gupta*, Gavin Churchyard**

New tuberculosis vaccine candidates that are in the development pipeline need to be studied in people with HIV, who are at high risk of acquiring *Mycobacterium tuberculosis* infection and tuberculosis disease and tend to develop less robust vaccine-induced immune responses. To address the gaps in developing tuberculosis vaccines for people with HIV, a series of symposia was held that posed six framing questions to a panel of international experts: What is the use case or rationale for developing tuberculosis vaccines? What is the landscape of tuberculosis vaccines? Which vaccine candidates should be prioritised? What are the tuberculosis vaccine trial design considerations? What is the role of immunological correlates of protection? What are the gaps in preclinical models for studying tuberculosis vaccines? The international expert panel formulated consensus statements to each of the framing questions, with the intention of informing tuberculosis vaccine development and the prioritisation of clinical trials for inclusion of people with HIV.

Lancet HIV 2022; 9: e791–800
Published Online
October 11, 2022
https://doi.org/10.1016/
S2352-3018(22)00255-7

*Contributed equally

Fred Hutchinson Cancer Research Center, Seattle, WA, USA (M D Miner PhD, E Andersen-Nissen PhD, A Fiore-Gartland PhD, J G Kublin MD); **Cape Town HIV**

Panel: Key consensus points

- To inform vaccine strategies among people with HIV across the tuberculosis disease and HIV spectrum, the potential individual-level and population-level effect of novel tuberculosis vaccines targeting people with HIV should be modelled.
- Trials of tuberculosis vaccine candidates should include people with HIV with careful consideration of safety, immunogenicity, and efficacy specific to people with HIV. For people of all ages with HIV, subunit protein or adjuvanted tuberculosis vaccines and inactivated mycobacterial vaccines should be prioritised, followed by non-replicating viral-vectored vaccines.
- As live-attenuated vaccines are being developed for infants, it will be important to know the safety, immunogenicity, and efficacy of these vaccines in infants with HIV on antiretroviral therapy (ART). The evaluation of immunogenicity and safety of novel live-attenuated vaccines early in development, considering the possible risks and benefits for each candidate vaccine (in each age group) in people with HIV on ART, is encouraged. Novel vaccine platforms such as mRNA and DNA should be prioritised for evaluation among people with HIV, including infants and children.
- All people with HIV participating in tuberculosis vaccine trials must be on ART. Eligibility criteria for people with HIV on ART differ depending on CD4 T-cell count and viral load. Tuberculosis vaccine trial participants with HIV should either previously have completed a course of tuberculosis preventive treatment (TPT) before enrolment or be offered TPT during the study. Community stakeholders of people with HIV should be engaged early in the process to provide input into study design, trial conduct, and results dissemination.
- Correlates of protection and other immunogenicity endpoints identified in people without HIV should be applied to and evaluated in people with HIV with immune-bridging studies.
- Non-human primate simian immunodeficiency virus and simian HIV models (with and without ART) should be invested in for tuberculosis vaccine studies.

"Trials of TB vaccine candidates should include people living with HIV . . . "

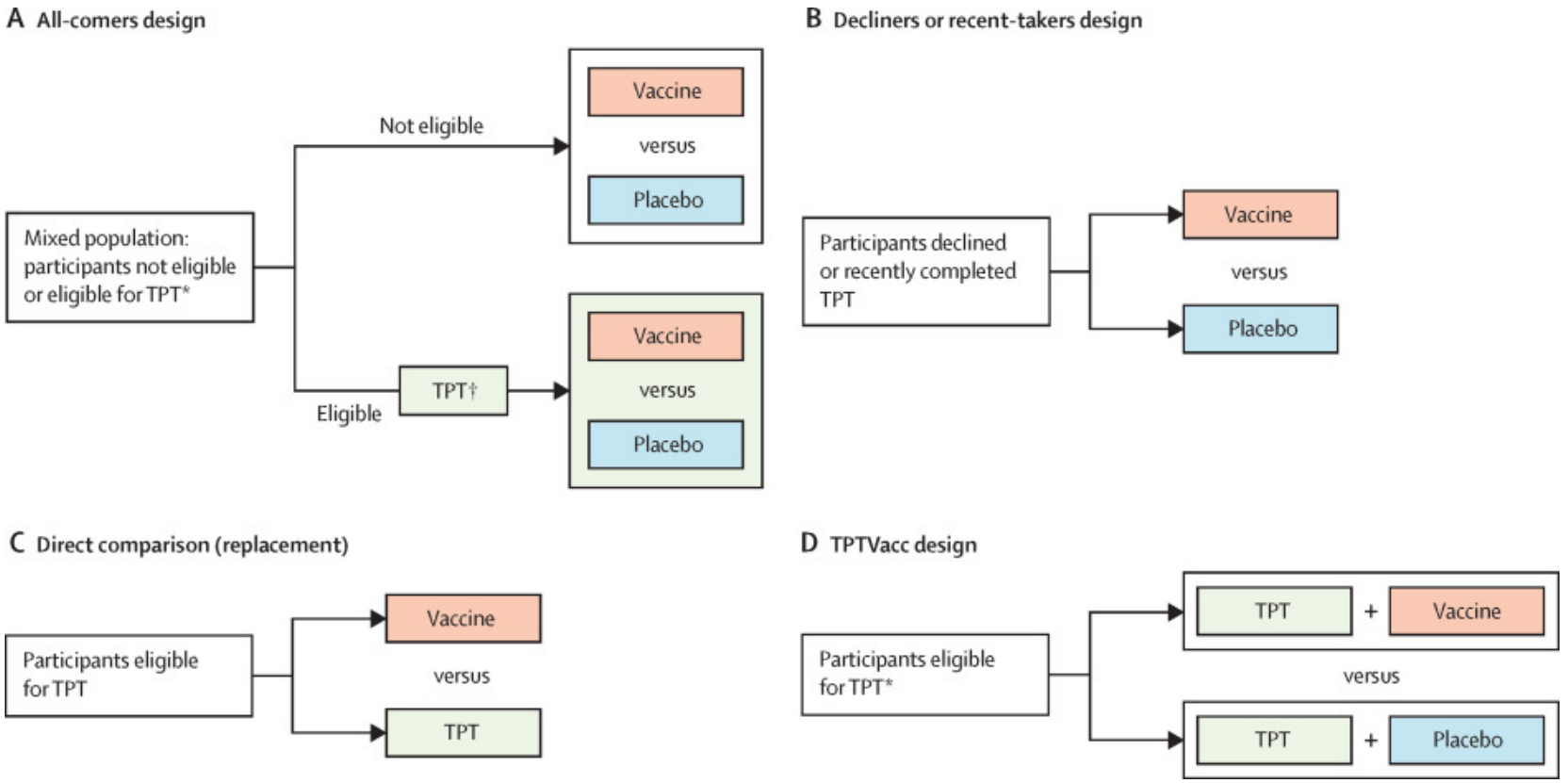
"All people with HIV participating in TB vaccine trials must be on ART."

"TB vaccine trial participants with HIV should either previously have completed TB preventive treatment before enrollment or be offered TPT during the study."

THE LANCET
Respiratory Medicine

Clinical trials of tuberculosis vaccines in the era of increased access to preventive antibiotic treatment

Molebogeng X Rangaka, Mike Frick*, Gavin Churchyard, Alberto L García-Basteiro, Mark Hatherill, Willem Hanekom, Philip C Hill, Yohhei Hamada, Matthew Quaife, Johan Vekemans, Richard G White, Frank Cobelens*



VPM1002

VPM1002
- CTRI/2019/01/017026 (POD)
- NCT04351685 (POI)
- NCT03152903 (POR)
- IMPAACTP2035/HVTN604

- VPM1002 is a live vaccine based on recombinant BCG (i.e., BCG with purposeful genetic modifications to provide better safety and efficacy).
- Developed at the Max Planck Institute in Germany, licensed to Vakzine Projekt Management (VPM), which then provided an exclusive sublicense to the Serum Institute of India (SII).
- Three ongoing phase III trials.

POD	Completed enrollment in a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 and MIP (vs. placebo) in preventing TB disease (pulmonary or extrapulmonary) among 12,721 household contacts (≥6 years old, HIV negative) of people with TB in India (CTRI/2019/01/017026). (Secondary objectives include efficacy evaluation for POI.) Primary completion: 2022.
POI	Undergoing a phase III trial evaluating the efficacy, safety, and immunogenicity of VPM1002 (vs. BCG) in preventing MTB infection among 6,940 newborns (HIV-exposed and uninfected eligible) in Gabon, Kenya, South Africa, Tanzania, and Uganda (NCT04351685). Primary completion: November 2022.
POR	Undergoing a phase II/III trial evaluating efficacy, safety, and immunogenicity of VPM1002 (vs. placebo) in preventing TB disease recurrence (pulmonary or extrapulmonary) in 2,000 HIV-negative adults ages 18–65 years successfully treated for TB in India and Bangladesh (NCT03152903). Primary completion: February 2022.
Other	Planning for a phase I/II safety/immunogenicity study of VPM1002 or BCG revaccination (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents ages 8–14 with and without MTB infection in South Africa (IMPAACTP2035/HVTN604; LEAP).

Results this year?

Results by 2024?

Phase III Trial of **VPM1002** and **MIP**

CTRI/2019/01/017026

>12,700

child, adolescent, and adult participants randomized

1 VPM1002

2 placebo

3 MIP

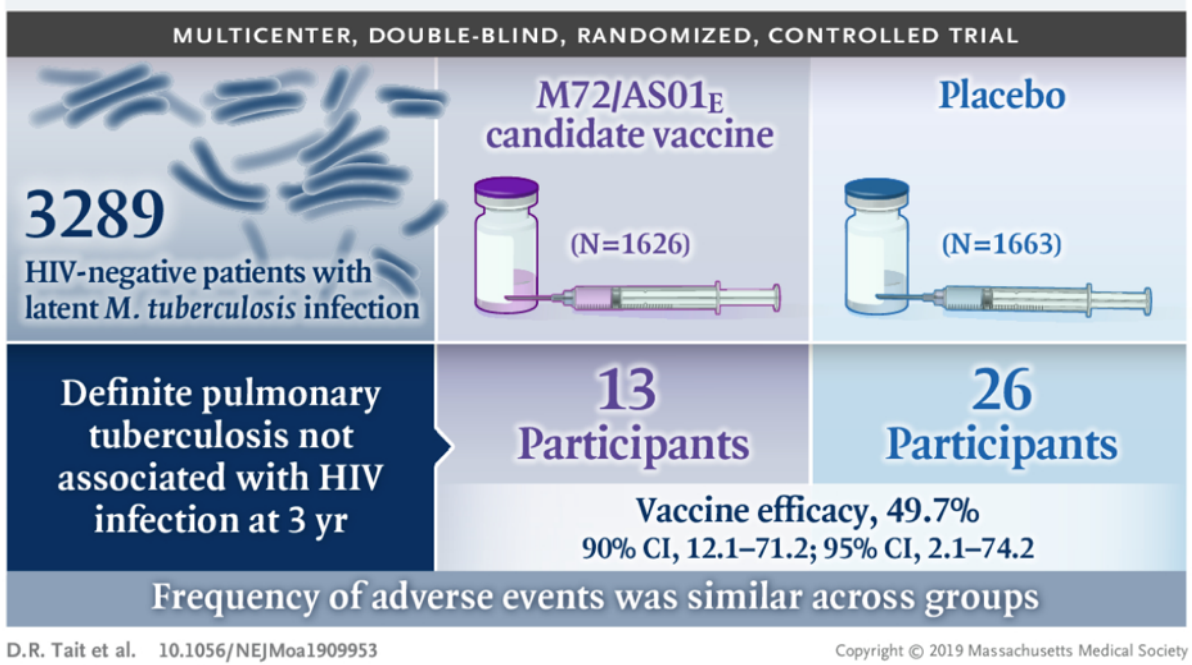
Household contacts
≥6 years
HIV-negative

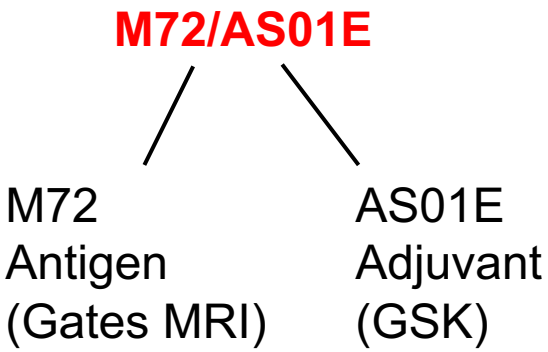
- 3 arm study with two experimental vaccine candidates: VPM1002 and MIP.
- The trial will compare VPM1002 and MIP to placebo.
- Primary outcome: **POD**. “To compare the percentage of confirmed TB cases (PTB and EPTB) in the vaccinated and placebo groups from 2 months after first dose of vaccine till 38 months follow-up period.”
- “Final analysis will be done at the time when 160 incident TB cases are observed in the trial or end of follow up period whichever is earlier.”
- Status: fully enrolled.

M72/AS01E

M72/AS01E
- **Phase III trial TBA (POD)**
- **NCT04556981 (PLHIV)**
- NCT05190146 (Epi study)

- Subunit protein/adjuvant vaccine.
- Initially developed by GSK and now being taken forward by the Gates Medical Research Institute.
- Positive efficacy signal in phase IIb trial in Kenya, South Africa, and Zambia.





49.7% (90% CI: 12.1–71.2) protection against developing bacteriologically confirmed pulmonary TB disease among HIV-negative, MTB-infected adults.

M72/AS01E

- **Phase III** study (next slide).
- **MESA-TB**: Safety/immunogenicity study of M72/AS01E in ~400 PLHIV (16–35 years) in South Africa on ART and who have previously taken TB preventive treatment.
  - Co-funded by Wellcome Trust.
  - Participants must have HIV RNA <200 copies/mL at screening and CD4+ cell counts ≥200 cells/μL.
- **Epidemiology study** to prepare for the phase III trial. The study will assess IGRA positivity and TB incidence near potential trial sites.
  - Will enroll 8,000 participants in Bangladesh, Brazil, DRC, Gambia, India, Indonesia Kenya, Mozambique, Peru, Philippines, South Africa, Uganda, Vietnam, Zambia.
  - Data will be a “global good” available to other vaccine developers and researchers.

Starting soon?

Complete and results expected soon. Will allow PLHIV to enroll in the phase III trial. **NCT04556981**

Epi study to prepare for ph. III trial. **NCT05190146**

Phase III Trial of **M72/AS01E**

To begin soon

26,000

participants to be randomized

1 M72/AS01E

2 placebo

Cohort	N
IGRA+, HIV-	20,000
IGRA-, HIV-	4,000
HIV+	2,000
Total	26,000

- Primary objective: Evaluate vaccine efficacy in the prevention of bacteriologically-confirmed pulmonary TB (**POD**) among participants who are IGRA+ (indicating MTB infection) and HIV-negative.
- Gates MRI hopes to open enrollment in late 2023 or early 2024 and to have results 4–5 years after enrollment begins. **~2028**
- Status: preparing to open. A preparatory epi study is underway in ~11 countries.

Information as reported by Gates MRI in 2022 TAG Pipeline Report

MTBVAC

MTBVAC
- NCT04975178 (POI)
- Phase I/II in PLHIV TBA
- Phase III trial in adults & adolescents TBA (POD)

- MTBVAC = live attenuated MTB (i.e., a weakened version of the TB pathogen itself!) In this case, the attenuation is the deletion of two genes responsible for virulence (phoP and fadD26).
- In 2022, Biofabri reached an agreement with Bharat Biotech “to guarantee the worldwide production and the supply of the future vaccine in more than 70 countries with a high TB incidence.”

POD	Undergoing a phase III trial to evaluate the efficacy, safety, and immunogenicity of MTBVAC (vs. BCG) in 6,960 HIV-unexposed and HIV-exposed, uninfected infants in South Africa, Senegal, and Madagascar (NCT04975178; MTBVACN3). Primary completion: June 2027.
	Plans for advanced clinical efficacy studies of MTBVAC in adults and adolescents are under development (source: IAVI and Biofabri).
Other	Completed a phase IIa dose-defining safety/immunogenicity study of MTBVAC (vs. BCG) in 99 South African infants (NCT03536117). (Informed dose selected for phase POD III trial listed above.) Completion: March 2022.[Y]
	Planning for a phase Ib safety/immunogenicity study of MTBVAC in PLHIV (including a subgroup of people with advanced HIV disease) is underway. Study initiation is targeted for 2023 (registry number and other details forthcoming. Source: IAVI and Biofabri).

Phase III trial of **MTBVAC**

NCT04975178

~7,000

infant participants

- HIV unexposed newborns
- HIV exposed, uninfected newborns

1 MTBVAC

2 BCG

single dose

- Primary outcome: Prevention of TB disease (**POD**) in healthy HIV-uninfected (HU) and HIV-exposed uninfected (HEU) newborns.
- Infants will be followed for a minimum of 24 months to see how many develop TB disease.
- Status: recruiting.

BCG revaccination

BCG (re)vaccination
- NCT05330884 (POD)
- NCT04151161 (POI)
- NCT04453293 (pre-travel)
- IMPAACTP2035/HVTN604

- Earlier phase II study that found BCG revaccination had an estimated vaccine efficacy of 45.4% (95% CI: 6.4–68.1) against sustained IGRA conversion (secondary endpoint).
- Sustained IGRA conversion = an initial conversion from negative to positive (signaling TB infection) and subsequent tests stay positive upon testing three and six months after the initial conversion.

POD	Undergoing a phase III efficacy, safety, immunogenicity study of BCG revaccination (vs. TB preventive treatment) among 9,200 BCG-vaccinated, HIV-negative child and adolescent household contacts ages 6 to 18 years in India (NCT05330884; BRiC). Primary completion: June 2025.
POI	Undergoing a phase IIb study to evaluate the efficacy, safety, and immunogenicity of BCG revaccination (vs. placebo) in 1,820 BCG-vaccinated, MTB-uninfected adolescents aged 10–18 years in South Africa (NCT04152161). Primary completion: April 2023. Undergoing a phase III trial to evaluate the efficacy and safety of pre-travel vaccination with BCG (vs. placebo) among 2,000 BCG-naïve, MTB-uninfected adults aged 18–65 years, either healthcare workers or long-term travelers to high-TB-burden countries from the United States (NCT04453293). Primary completion: May 2024.
Other	Planning for a phase I/II safety/immunogenicity study of BCG revaccination or VPM1002 (vs. placebo) in 480 HIV-positive and HIV-negative pre-adolescents aged 8–14 years with and without MTB infection in South Africa (IMPAACTP2035/HVTN604).

New trial. First study of vaccine vs. preventive treatment.

Fully enrolled.

Phase IIb study of BCG revaccination

NCT04152161

1,820

adolescents randomized

1 BCG

2 placebo

single dose

10–18 years old
BCG-vaccinated
No indication of TB infection (IGRA-)
HIV-negative

- Primary outcome: Number of participants with sustained IGRA conversion from a negative to positive test (**POI**).
- IGRA used is the QuantiFERON®-TB Gold Plus (QFT).
- Sustained Conversion = initial conversion and QFT positive 3 and 6 months later.
- **Status**: fully enrolled.
- Sponsor: Gates MRI.

BCG revaccination: comparing trials

	Before	Now
	BCG revax – Phase IIa trial (previous study)	**BCG revax Phase IIb trial (current study)**
Participant size:	989 adolescents	1820 adolescents
Age:	12–17 years old	10–18 years old
Sites:	Worcester, Western Cape	Across South Africa
TB infection test (IGRA)	QFT Gold	QFT Gold Plus
Primary endpoint	IGRA conversion	Sustained IGRA conversion

What would a positive result mean?

- A positive result from this study could spark a policy change recommending a second dose of BCG in adolescence to protect high-risk people from MTB infection.
- *Or* it could motivate a phase III POD trial among IGRA-negative people to see if BCG revaccination protects against TB disease.

The mRNA vaccines are coming! (maybe)

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).

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

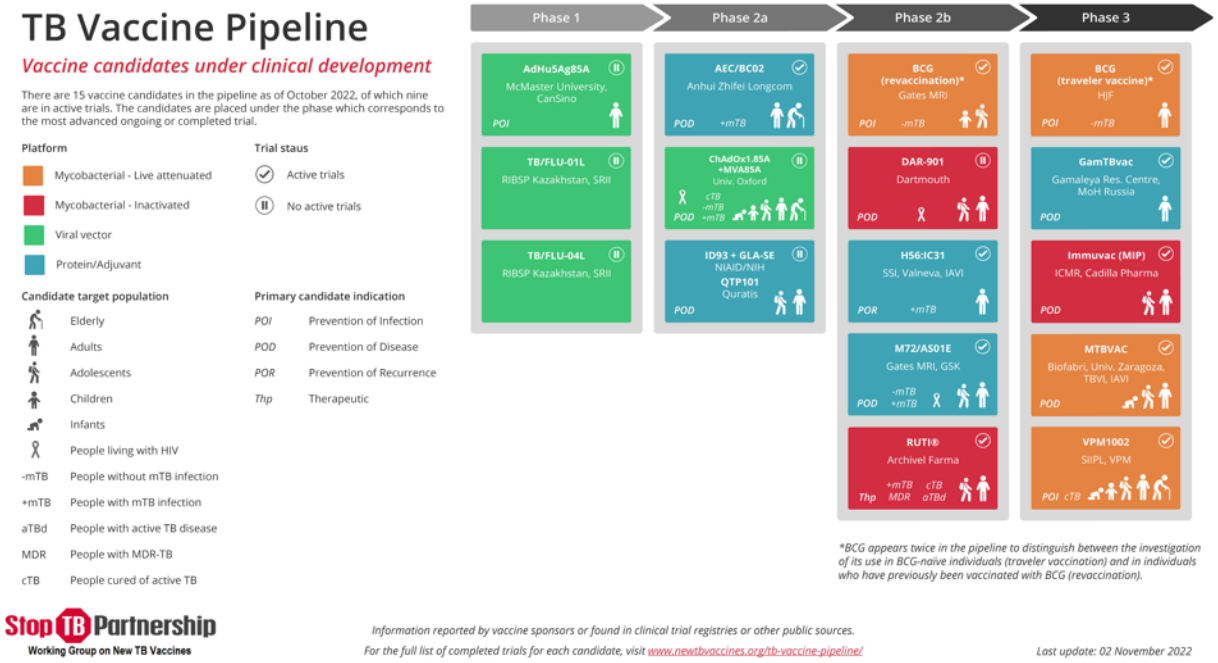
Thank you!

mike.frick@treatmentactiongroup.org

And thanks to the Working Group on New TB Vaccines and partners in the TB Vax ARM coalition.

If you would like to learn more about the TB Vax ARM's activities or join the monthly meetings, email Shaun Palmer at SPalmer@iavi.org.

Want more information from TAG? Join our list here!



POD = prevention of disease

- Most relevant for licensure and scale-up.
- Requires measuring the incidence of clinical – ideally, microbiologically confirmed – TB in the vaccine and placebo/control arms.
- Long, with large sample size, and therefore expensive. Why?
  - Estimated incidence of TB disease in most high-incidence countries is not above 400/100,000 per year, so very large sample sizes are needed in order to measure protective efficacy with sufficient precision.
  - Participants must be followed for several years to see if protection is durable/lasting.
  - These limitations can be (partially) addressed by enrolling participants with TB infection (IGRA+ or TST+) as opposed to people without TB infection.

POI = prevention of infection

- Requires measuring the incidence of infection with MTB in the vaccine and placebo/control arms.
- Not clear if prevention of infection is a licensable endpoint from the perspective of regulators.
- Smaller, cheaper, faster trials. Why?
  - Incidence of TB infection is ~10–20 times higher than incidence of TB disease, so trials can enroll faster and accrue endpoints more quickly than POD trials.
- **HOWEVER**:
  - No easy way to measure infection. TST and IGRAs do not measure infection directly. Sustained IGRA conversion – negative to positive, with no reversion to negative – is the most common POI endpoint.
  - Not clear if POI signals POD. Only 5–10% of people with TB infection progress to TB disease—does a vaccine prevent infection in individuals who would progress otherwise?