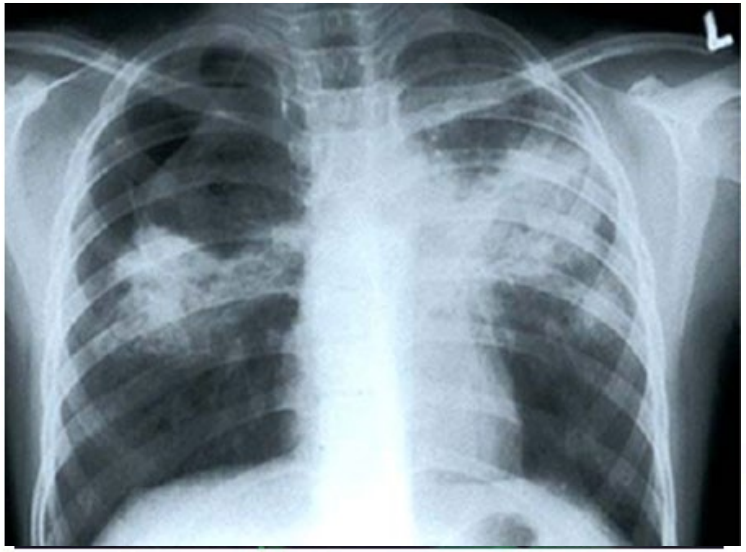
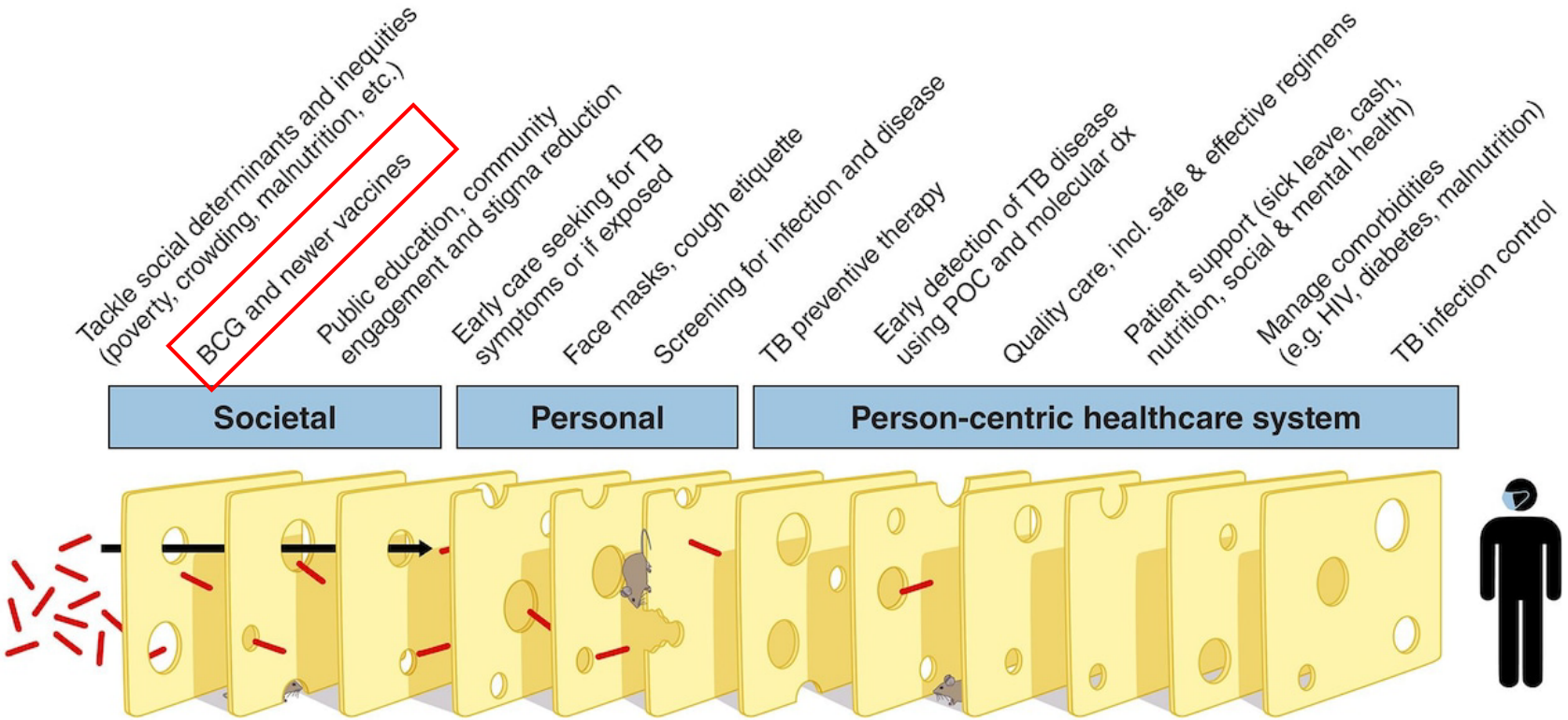
# Prevention is better than Cure:
# Development of More Effective TB Vaccines



Tom Scriba
thomas.scriba@uct.ac.za
Swiss TPH Hybrid Symposium
22 March 2023

# The Swiss Cheese Model for Ending TB




Misinformation mouse

**Each intervention (layer) has imperfections (holes).**
**Multiple layers improve success.**

Adapted for TB by Jen Furin & Madhu Pai (@paimadhu), with permission from Dr Ian Mackay (@mackayIM)
With input from Amrita Daftary, Petra Heitkamp, Joel Klinton, Emily MacLean, Lena Faust, Giorgia Sulis, Sophie Huddart, Anita Svadzian

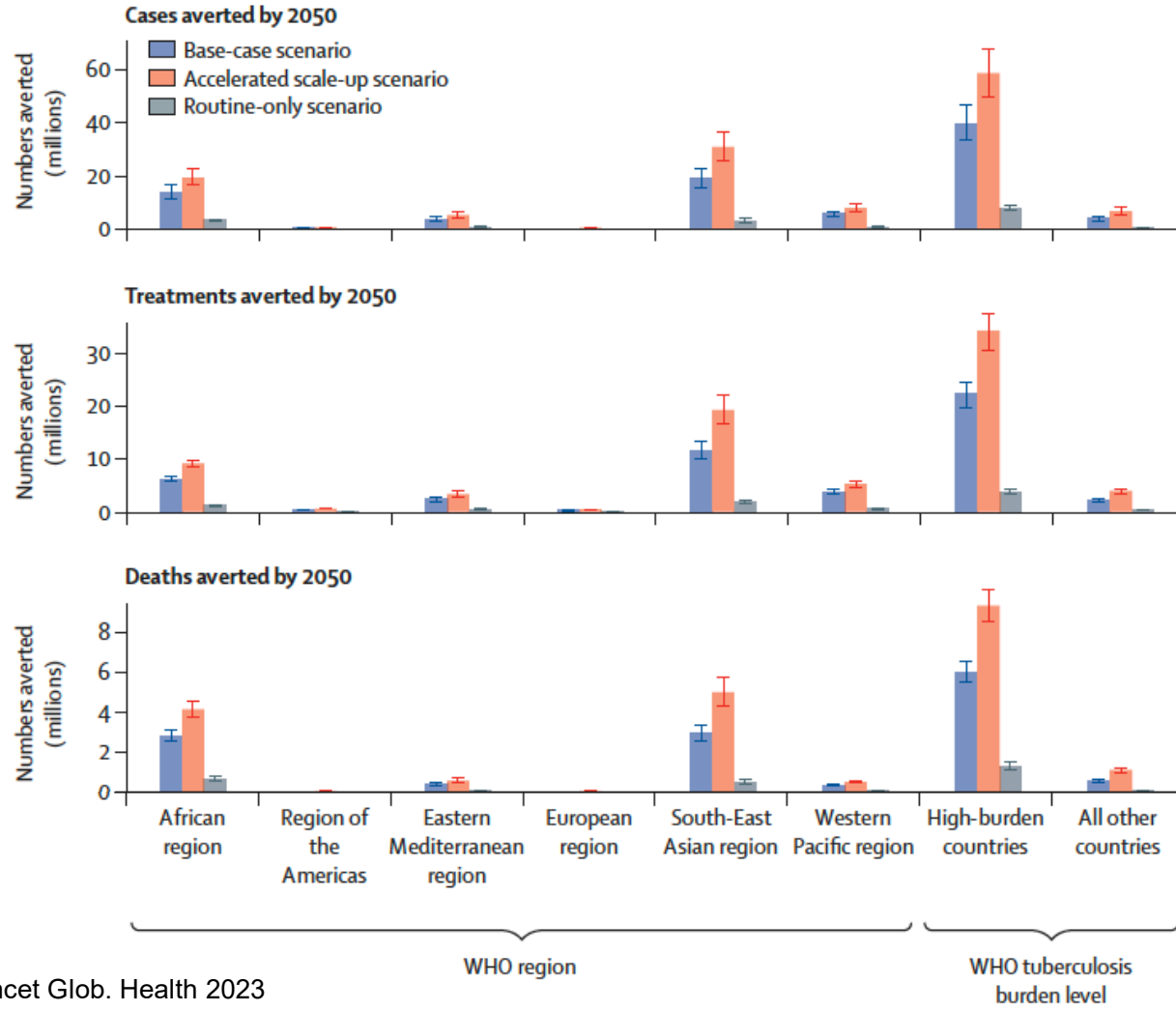
# Impact of TB vaccination

- TB vaccine with 50% efficacy, 10 year duration
- Adolescent and adult vaccine

Routine-only: vaccination of 9 year olds (80% coverage with 5 year-scale up)

Base-case: One-time vaccination campaign for all individuals aged 10 years and older (70% coverage)

Accelerated (instant) scale-up



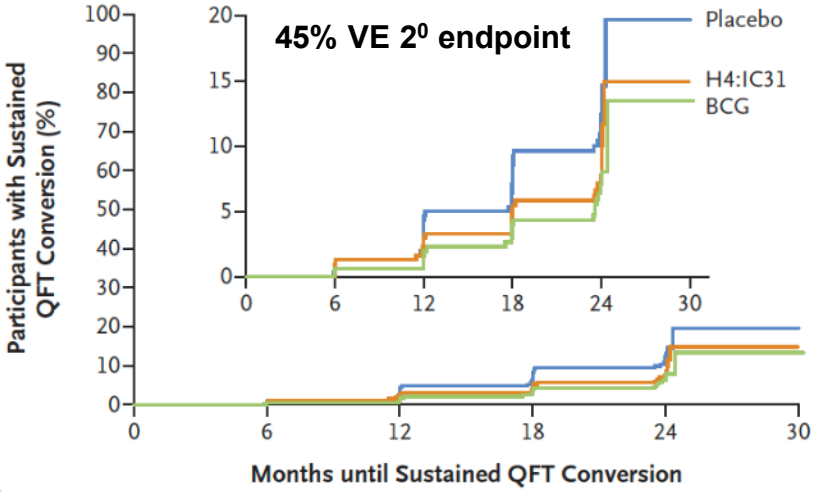

Clark et al., Lancet Glob. Health 2023

# Efficacy signals in well-conducted human clinical trials

ORIGINAL ARTICLE

## Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination

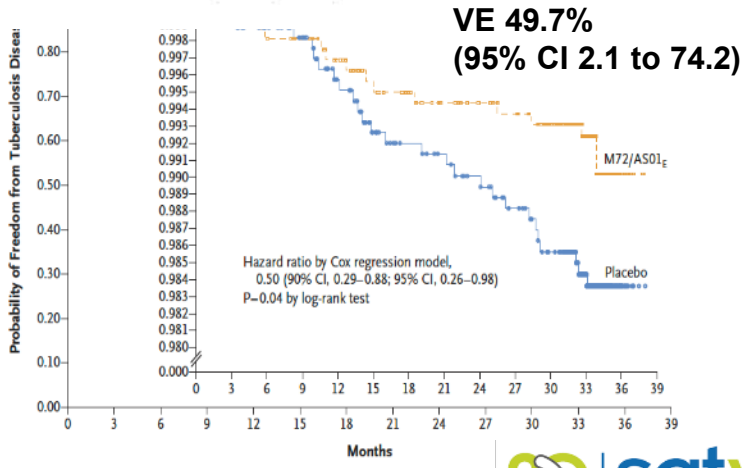
E. Nemes, H. Geldenhuys, V. Rozot, K.T. Rutkowski, F. Ratangee, N. Bilek, S. Mabwe, L. Makhethe, M. Erasmus, A. Toefy, H. Mulenga, W.A. Hanekom, S.G. Self, L.-G. Bekker, R. Ryall,* S. Gurunathan, C.A. DiazGranados, P. Andersen, I. Kromann, T. Evans, R.D. Ellis, B. Landry, D.A. Hokey, R. Hopkins, A.M. Ginsberg, T.J. Scriba, and M. Hatherill, for the C-040-404 Study Team†



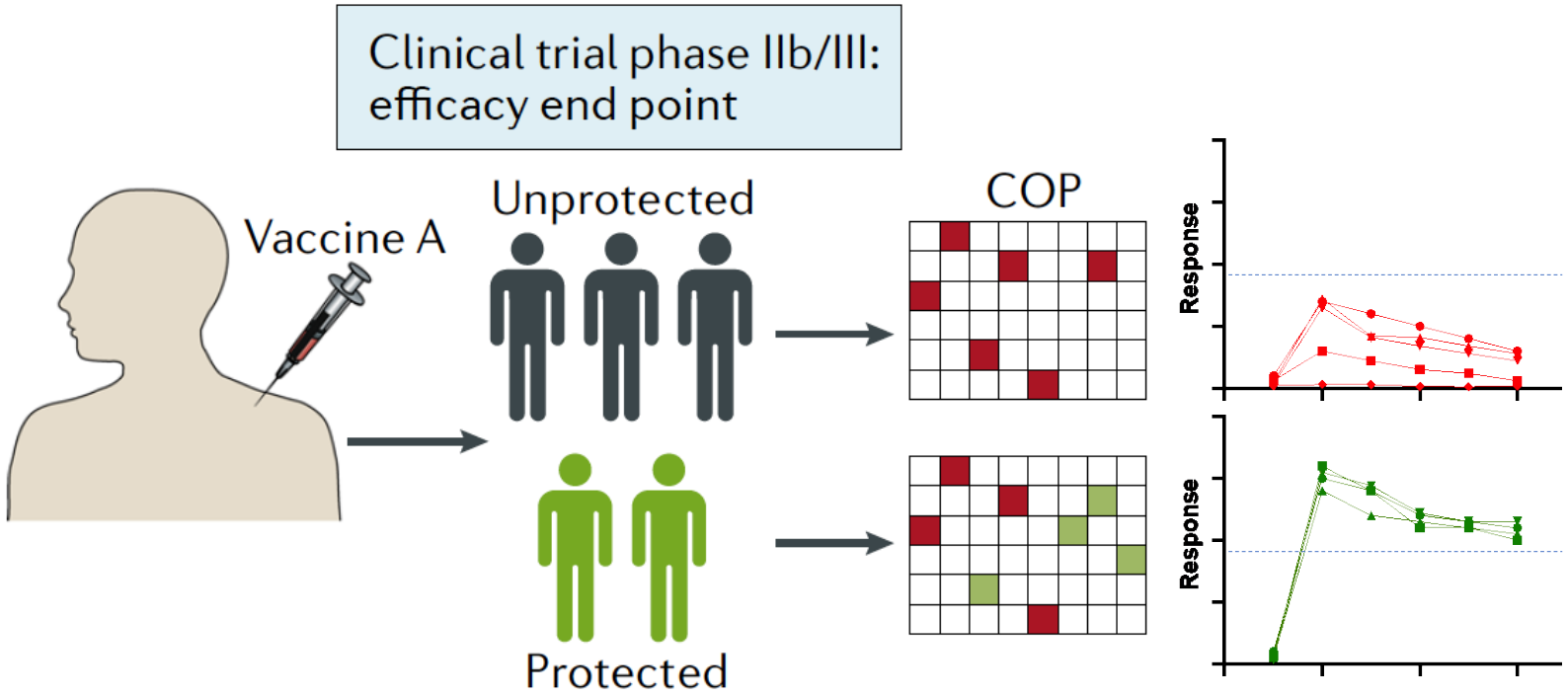

ORIGINAL ARTICLE

## Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

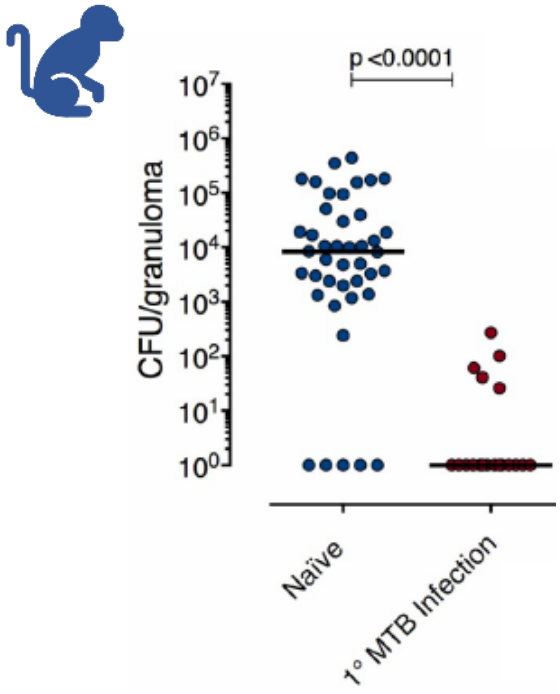


# Vaccine-induced immune responses do not necessarily correlate with protection

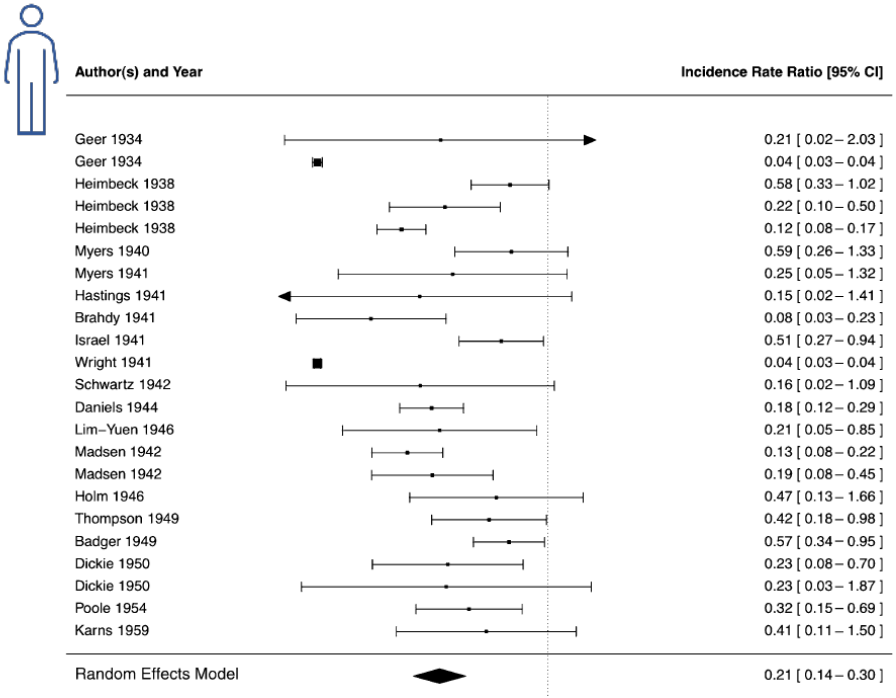



Andersen and Scriba, NRI 2019

# M.tb infection strongly protects against TB upon re-exposure

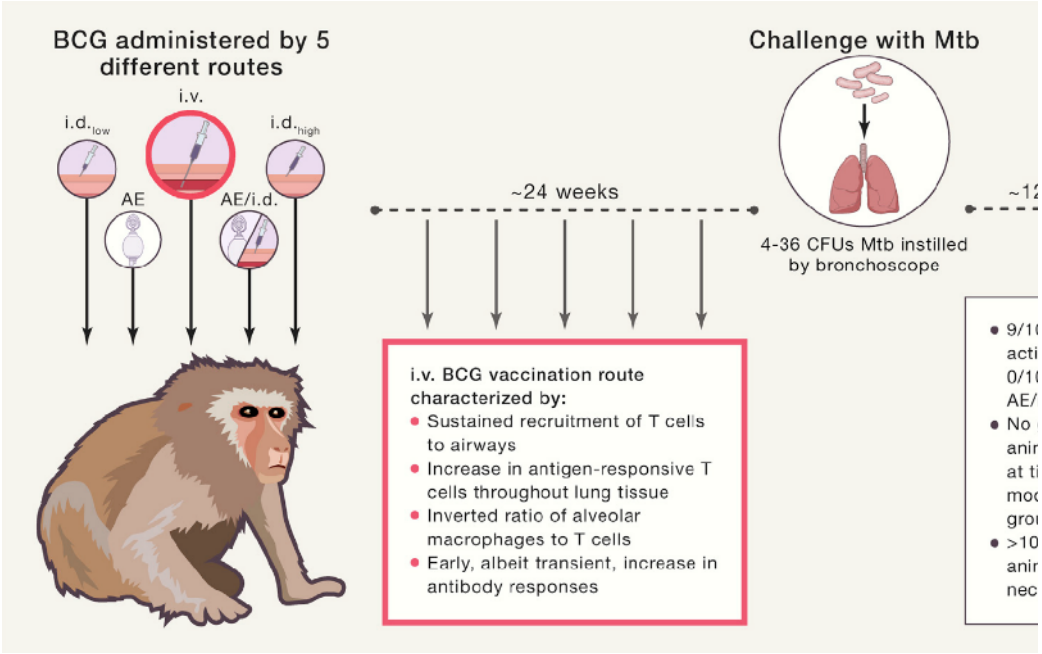


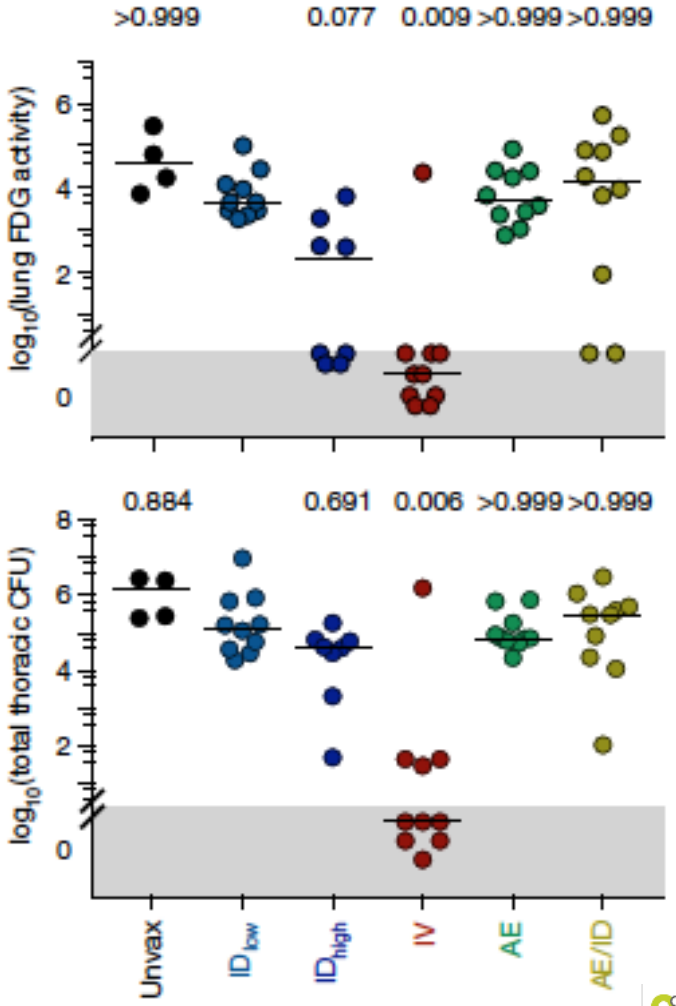

Cadena et al., Plos Path 2019




Andrews et al., CID 2012

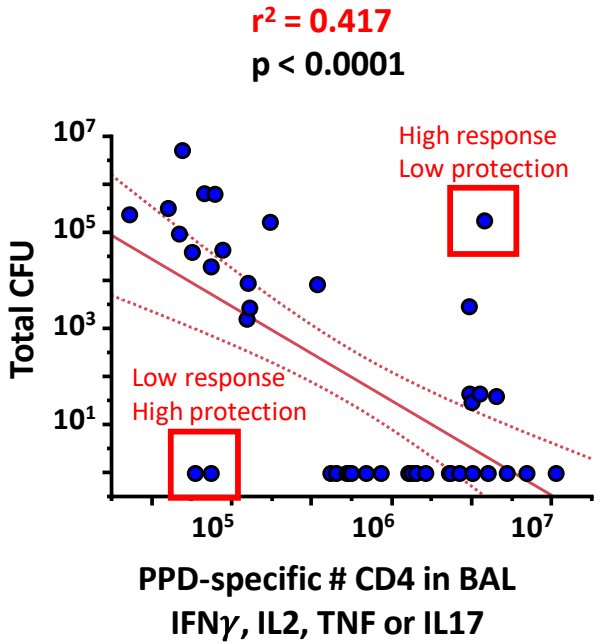
# We can learn about protective immunity from different administration routes




Darrah et al., Nature 2020; commentary by Scriba and Mizrahi., Cell 2020

# Antigen-specific CD4 T cells in BAL associated with protection



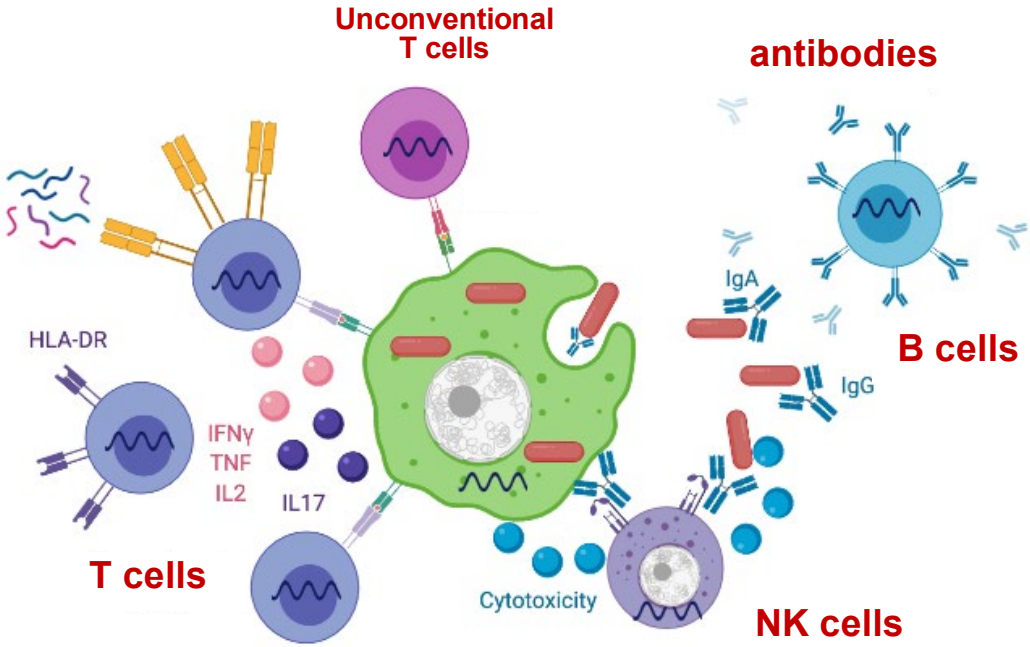

Trishia Darrah, Bob Seder, Joanne Flynn, Edward Irvine, Galit Alter, unpublished

# Identification of **immune correlates of protection** against TB

## The quest for vaccine-induced immune correlates of protection against tuberculosis

Elisa Nemes, Andrew Fiore-Gartland, Cesar Boggiano, Margherita Coccia, Patricia D'Souza, Peter Gilbert, Ann Ginsberg, Ollivier Hyrien, Dominick Laddy, Karen Makar, M. Juliana McElrath, Lakshmi Ramachandra, Alexander C. Schmidt, Solmaz Shotorbani, Justine Sunshine, Georgia Tomaras, Wen-Han Yu, Thomas J. Scriba, Nicole Frahm; the BCG Correlates PIs Study Team & the M72 Correlates PIs Study Team

Vaccine Insights 2022


Nicole Frahm
Elisa Nemes
Leadership team

Scientific Advisory Committee

BMGF
Gates MRI
NIH

17 assays/approaches
12 laboratories

satvi

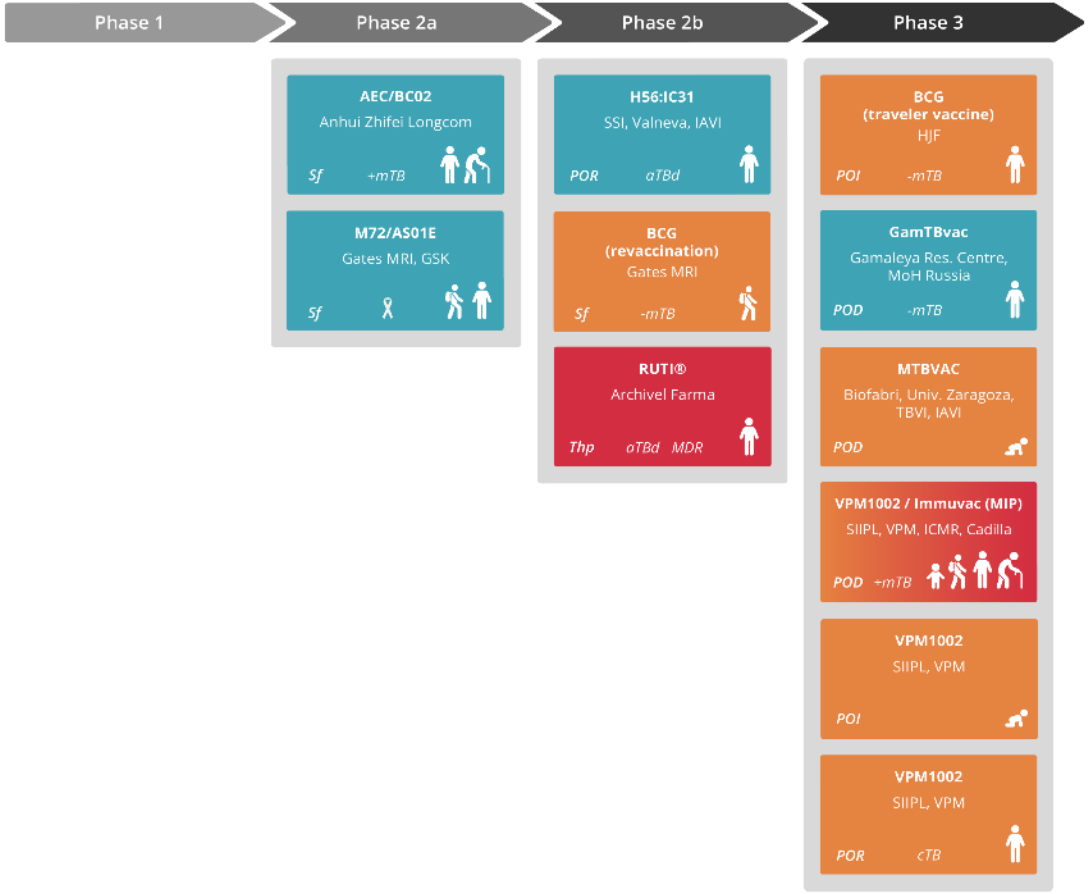
# The meager Candidate TB Vaccine Pipeline 2022: 10 candidates in Phase 2b/3

| PHASE 1 | PHASE 2A | PHASE 2B | PHASE 3 |
|---|---|---|---|
| **AdHu5Ag85A**<br>MCMASTER UNIV, CANSINO<br>Viral Vector | **AEC/BC02**<br>ANHUI ZHIFEI LONGCOM<br>Protein / Adjuvant | **BCG (Revaccination)**<br>GATES MRI<br>Mycobacterial – Live Attenuated | **BCG (Travel vaccine)**<br>HJF<br>Mycobacterial – Live Attenuated |
| **TB/FLU-01L**<br>RIBSP, SRII<br>Viral Vector | **ChAdOx1.85A+MVA85A**<br>UNIV OXFORD<br>Viral Vector | **DAR-901**<br>DARTMOUTH<br>Mycobacterial – Inactivated | **GamTBvac**<br>GAMALEYA RES. CENTRE, MOH RUSSIA<br>Protein / Adjuvant |
| **TB/FLU-04L**<br>RIBSP, SRII<br>Viral Vector | **ID93+GLA-SE (QTP101)**<br>QURATIS (QTP101); NIAID/NIH (ID93+GLA-SE)<br>Protein / Adjuvant | **H56:IC31**<br>SSI, VALNEVA, IAVI<br>Protein / Adjuvant | **Immuvac (MIP)**<br>ICMR, CADILA<br>Mycobacterial – Inactivated |
| | | **M72/AS01E**<br>GATES MRI, GSK<br>Protein / Adjuvant | **MTBVAC**<br>BIOFABRI, UNIV ZARAGOZA, IAVI, TBVI<br>Mycobacterial – Live Attenuated |
| | | **RUTI®**<br>ARCHIVEL FARMA<br>Mycobacterial – Inactivated | **VPM1002**<br>SIIPL, VPM<br>Mycobacterial – Live Attenuated |

# TB Vaccine Pipeline

## *Active clinical trials of TB vaccine candidates*

There are 11 active clinical trials across nine candidates as of October 2022.




**Platform**

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant

**Trial target population**

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -mTB — People without mTB infection
- +mTB — People with mTB infection
- aTBd — People with active TB disease
- MDR — People with MDR-TB
- cTB — People cured of active TB

**Primary trial indication**

- *Sf* — Safety
- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic

Stop TB Partnership
Working Group on New TB Vaccines

*Information reported by vaccine sponsors or found in clinical trial registries or other public sources.*
*For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/*

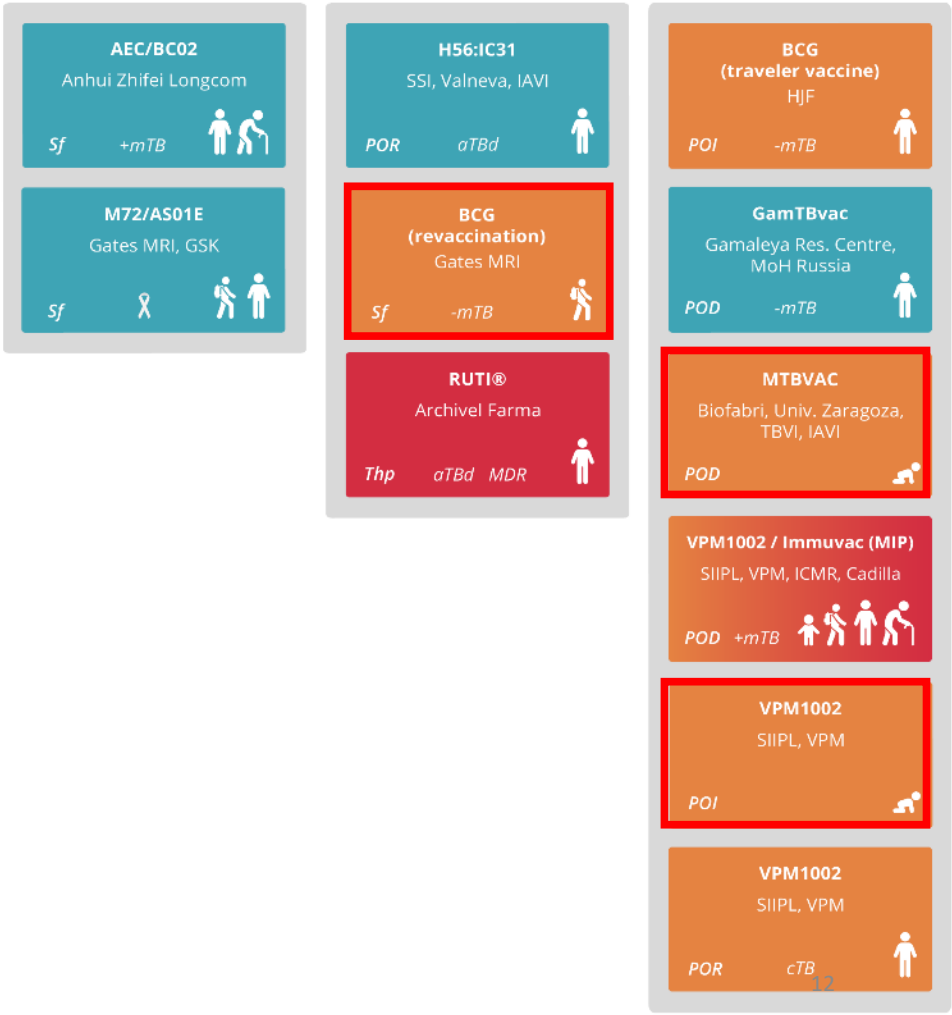
*Last update: 02 February 2023*

# 1. Live mycobacterial vaccines

BCG

VPM1002

MTBVAC



BCG

# BCG REVAX trial (Gates MRI-TBV01-201) Phase 2b, NCT04152161

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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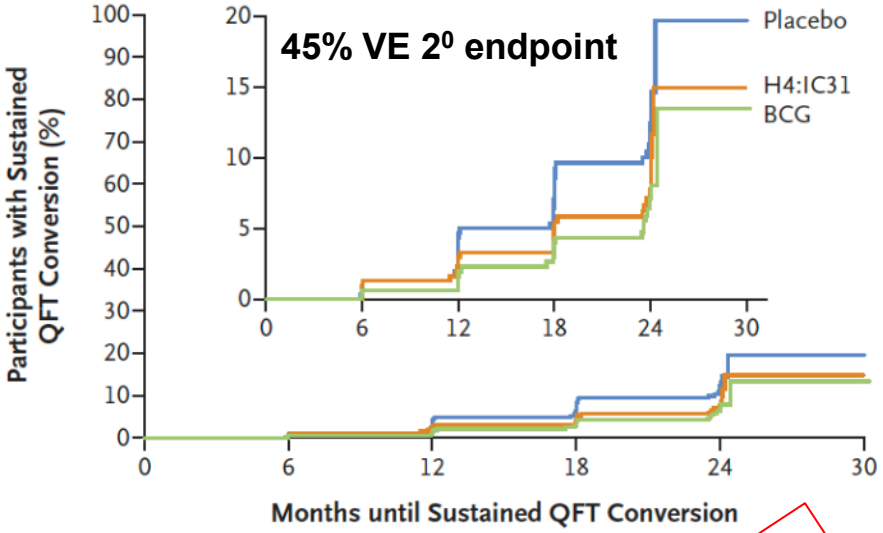



**Ongoing (Gates MRI)**

- 1,800 IGRA- SA adolescents (10-18 yr)
- randomized BCG revaccination or placebo
- 5 sites in South Africa
- follow-up 48 months
- primary endpoint sustained IGRA+ conversion (QFT-Plus) thru 6 months

**Primary analysis expected 2023**

**Need to validate POI findings in POD trial?**

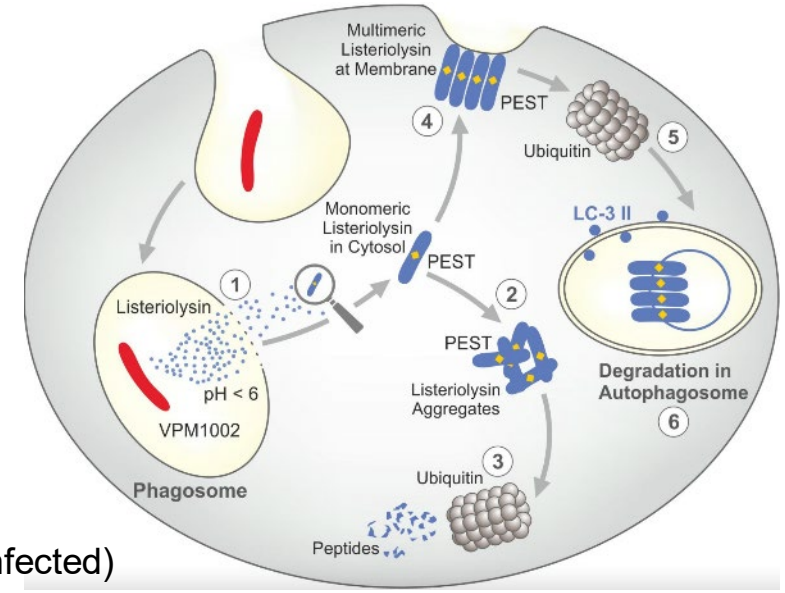
VPM1002

# VPM1002

## Phase 3 PrIMe (NCT04351685)

**Safety and immunogenicity of VPM1002 versus BCG in South African newborn babies: a randomised, phase 2 non-inferiority double-blind controlled trial**

*Mark F Cotton, Shabir A Madhi, Angelique K Luabeya, Michele Tameris, Anneke C Hesseling, Justin Shenje, Elisma Schoeman, Mark Hatherill, Sajjad Desai, Dhananjay Kapse, Sina Brückner, Anthonet Koen, Lisa Jose, Andrew Moultrie, Sutika Bhikha, Gerhard Walzl, Andrea Gutschmidt, Leigh A Kotze, Devon L Allies, Andre G Loxton, Umesh Shaligram, Maria Abraham, Hilary Johnstone, Leander Grode, S H E Kaufmann, Prasad S Kulkarni*




**Ongoing (SII, VPM)**

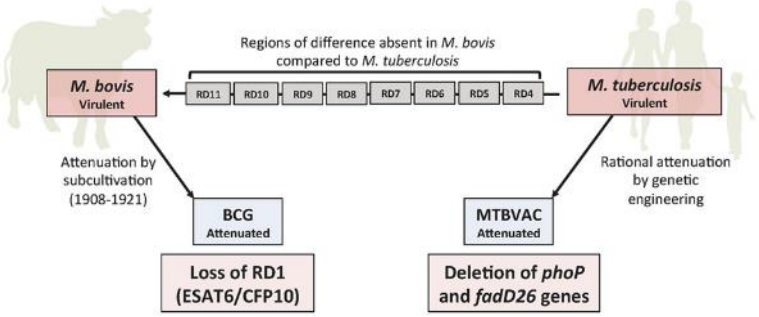
1. 6,940 newborn infants (HIV unexposed and HIV-exposed uninfected)
2. Gabon, Kenya, South Africa, Tanzania, and Uganda,
3. BCG or VPM1002
4. FU 36m (POI, POSI; safety; $2^0$ POD)

Expected 2025

POD (HHC; CTRI/2019/01/017026
POR (NCT 03152903)

MTBVAC

# MTBVAC-203
# Phase 3, NCT04975178




**Live-attenuated *Mycobacterium tuberculosis* vaccine MTBVAC versus BCG in adults and neonates: a randomised controlled, double-blind dose-escalation trial**

*Michele Tameris*, Helen Mearns*, Adam Penn-Nicholson, Yolande Gregg, Nicole Bilek, Simbarashe Mabwe, Hennie Geldenhuys, Justin Shenje, Angelique Kany Kany Luabeya, Ingrid Murillo, Juana Doce, Nacho Aguilo, Dessislava Marinova, Eugenia Puentes, Esteban Rodríguez, Jesús Gonzalo-Asensio, Bernard Fritzell, Jelle Thole, Carlos Martin, Thomas J Scribat, Mark Hatherill†, and the MTBVAC Clinical Trial Team*

*Lancet Respir Med* 2019; 7:757–70

**Started end 2022 (Biofabri, Unizar, SATVI)**

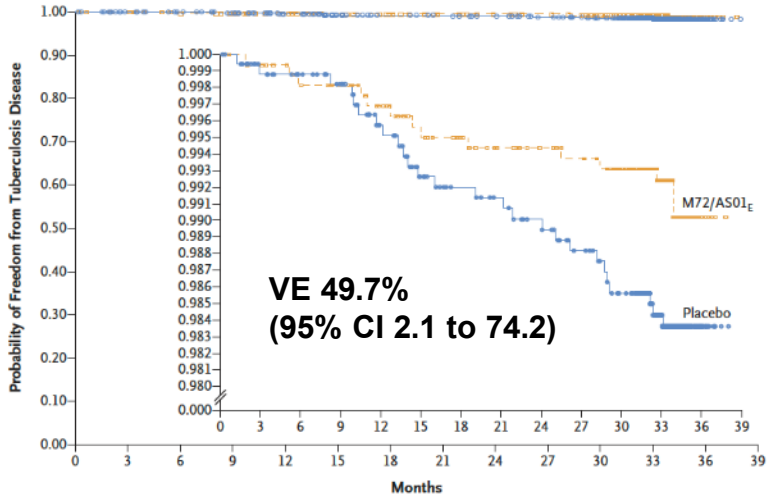
- 7,000 HIV unexposed and HIV-exposed uninfected newborns
- randomized BCG or MTBVAC (dose above)
- 6 sites in South Africa, Senegal and Madagascar
- 72m FU for TB

**Expected 2028/9**

# 2. Protein/adjuvant vaccines

- M72/ASO1$_E$
- GamTBvac
- H56:IC31

# Next steps for M72/AS01$_E$: **Phase 3 POD**




The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

ORIGINAL ARTICLE

## Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

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**Underway:**

- MESA TB trial of M72/ASO1$_E$ in PLHIV
- Epi study 50 sites, 12-15 countries, IGRA prevalence survey (Gates MRI)
- Capacity development for phase 3 trial

**Planned: Phase 3 efficacy, safety, and immunogenicity licensure trial, multiple sites and countries, 2024 (Gates MRI)**

→20,000 adolescents and adults aged 14–44 years, IGRA+(-); include PLHIV

# H56/IC31: **Phase 2b POR trial** (NCT03512249)

Antigens: ESAT-6, Ag85B and Rv2660c

Adjuvant: NH2-KLK5KLK-COOH peptide and TLR9 agonist ODN1a

**Dose Optimization of H56:IC31 Vaccine for Tuberculosis-Endemic Populations**

A Double-Blind, Placebo-controlled, Dose-Selection Trial

Sara Suliman[1,2*], Angelique Kany Kany Luabeya[1,2*], Hennie Geldenhuys[1,2], Michele Tameris[1,2], Soren T. Hoff[3], Zhongkai Shi[4], Dereck Tait[5], Ingrid Kromann[3], Morten Ruhwald[3], Kathryn Tucker Rutkowski[4], Barbara Shepherd[4], David Hokey[4], Ann M. Ginsberg[4], Willem A. Hanekom[1,2], Peter Andersen[3], Thomas J. Scriba[1,2‡], Mark Hatherill[1,2‡], and the H56-035 Trial Group

**Ongoing (SSI, IAVI)**

Phase 2b trial fully enrolled (n = 831)

TB patients with successful treatment completion

6 sites in South Africa and Tanzania

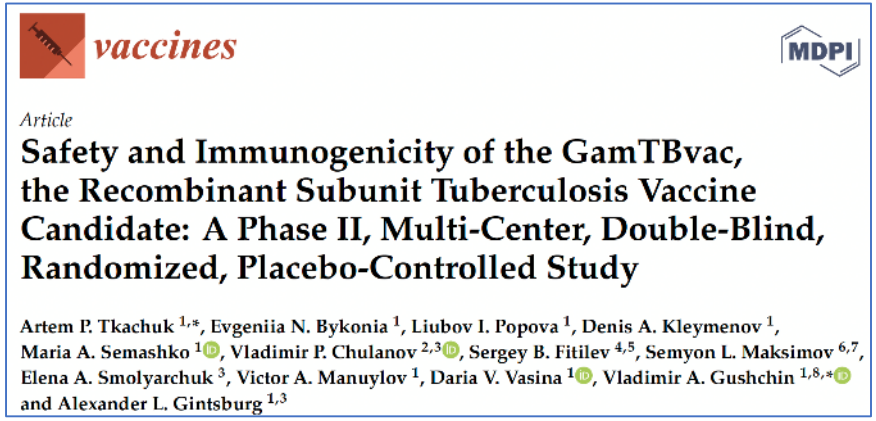
Follow-up virtually completed (target of 23 TB cases exceeded)

Expected 2023

# GamTBvac: **Phase 3 POD**
# NCT04975737

Antigens: ESAT-6, CFP-10 and Ag85A

Adjuvant: DEAE-dextran and CpG



vaccines

MDPI

*Article*

**Safety and Immunogenicity of the GamTBvac, the Recombinant Subunit Tuberculosis Vaccine Candidate: A Phase II, Multi-Center, Double-Blind, Randomized, Placebo-Controlled Study**

Artem P. Tkachuk [1,*], Evgeniia N. Bykonia [1], Liubov I. Popova [1], Denis A. Kleymenov [1], Maria A. Semashko [1], Vladimir P. Chulanov [2,3], Sergey B. Fitilev [4,5], Semyon L. Maksimov [6,7], Elena A. Smolyarchuk [3], Victor A. Manuylov [1], Daria V. Vasina [1], Vladimir A. Gushchin [1,8,*] and Alexander L. Gintsburg [1,3]

**Ongoing:**

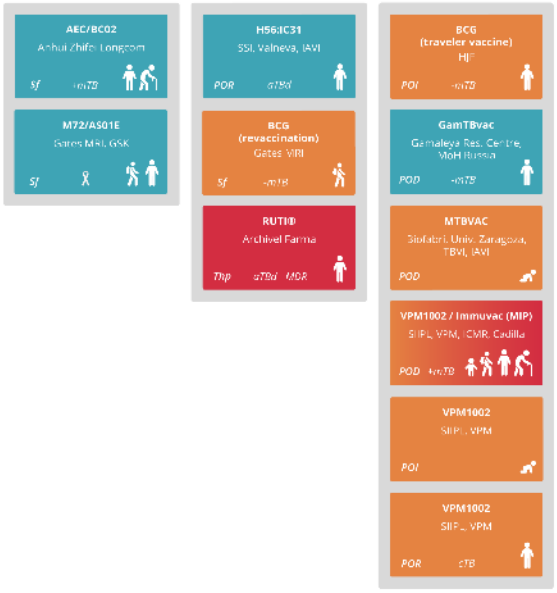
- 7,180 HIV- BCG+ IGRA- adults aged 18–45 years (Russia MoH)
- Follow-up 24 months
- TB disease

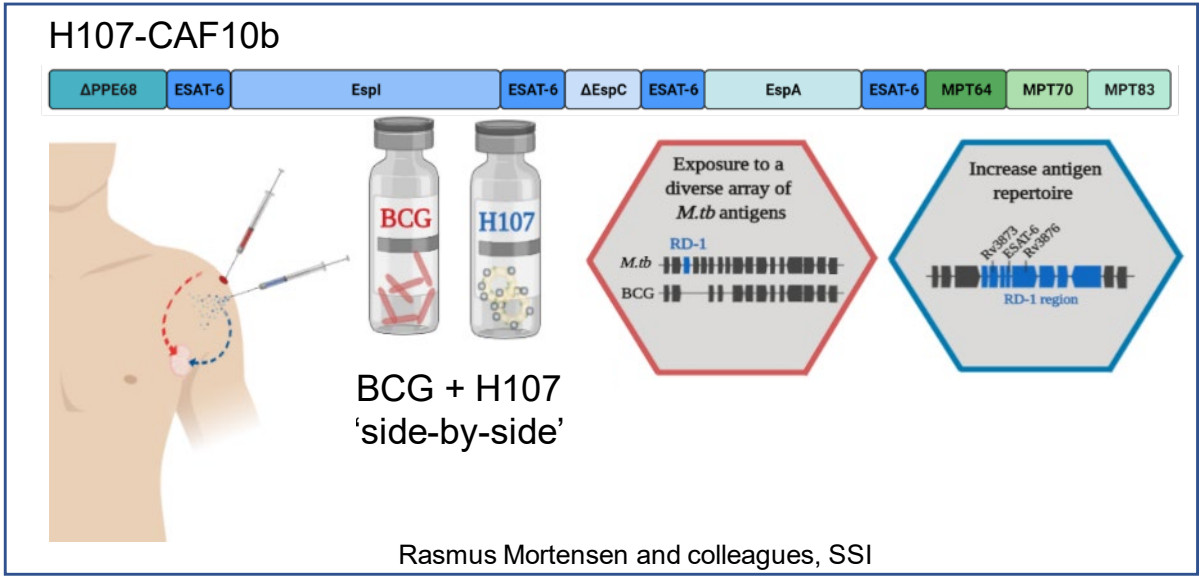
Expected 2025

THE GAMALEYA NATIONAL CENTER OF EPIDEMIOLOGY AND MICROBIOLOGY

20 YEARS OF TB RESEARCH | satvi TOWARDS A WORLD WITHOUT TB

# We should plan for implementation now – we cannot afford to wait and see




The pipeline must be fed with new (improved) products

More rational antigen selection, adjuvant studies to get to higher efficacy estimates

# Take home

- Vaccine protection against TB is possible, plausible and the outlook is positive (but not at warp speed)
- Exciting advances in understanding of correlates of protection against TB in animals & humans are happening
- The clinical pipeline for TB vaccines is meager, but a number of vaccine candidates are in late-stage clinical trials
  - More efficacy results soon
- TB vaccine development deserves much more investment and research

## collaborators

## funders

# Thank you for your attention

Tom Scriba

thomas.scriba@uct.ac.za