Tuberculosis Vaccine R&D

Mark Hatherill

South African Tuberculosis Vaccine Initiative
University of Cape Town, South Africa

WHO Global Tuberculosis Report 2022

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	ChAdOx185A-MVA85A[b,i] University of Oxford	BCG revaccination to prevent infection[d,j] Gates MRI	GamTBvac[e] Ministry of Health, Russian Federation
TB/FLU-01L[b] TB/FLU-04L[b] RIBSP	ID93 + GLA-SE(QTP101)[e] Quratis U.S. NIH/NIAID	DAR-901 booster[f,j] Dartmouth	MIP/Immuvac[f,i,j] ICMR, Cadila Pharmaceuticals
BNT164[c] BioNTech SE	AEC/BC02[e] Anhui Zhifei Longcom	H56: IC31[e] SSI, Valneva, IAVI	MTBVAC[d,h] Biofabri, University of Zaragoza, IAVI, TBVI
		M72/AS01E[e,j] GSK, Gates MRI	VPM1002[d,g,i,j] SIIPL, VPM
		RUTI®[f] Archivel Farma, S.L.	BCG vaccination to prevent infection (TIPI)[d] HJF
Pending: H107 (SSI) first-in-human			BCG revaccination in children and adolescents (BRiC)[d,i,j] ICMR

14 candidates + BCG

3 viral vector
- Ad5Ag85A
- TB/FLU-01/4L
- ChadOx185A

5 subunit
- ID93+GLA-SE / QTP101
- AEC/BC02
- H56:1C31
- M72/AS01$_E$
- GamTBvac

3 inactivated mycobacterial
- 1 *M. obuense* (DAR-901)
- 1 *M. tuberculosis* (RUTI)
- 1 *M. indicus pranii* (Immuvac)

3 live mycobacterial
- 1 *M. tuberculosis* (MTBVAC)
- 1 rBCG (VPM1002)
- BCG revaccination

1 mRNA (BNT164)

Development #1

The TB vaccine pipeline

2012 vs 2022

Phase I	Phase IIa	Phase IIb	Phase III
AdHu5Ag85A[b] McMaster, CanSino	ChAdOx185A-MVA85A[b,i] University of Oxford	BCG revaccination to prevent infection[d,j] Gates MRI	GamTBvac[e] Ministry of Health, Russian Federation
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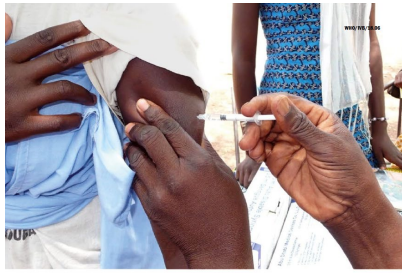
			BCG revaccination in children and adolescents (BRiC)[d,i,j] ICMR

2012
12 candidates
Phase 1 dominant

6 candidates no longer in development
6 candidates 2012 and 2022 (2 static)
8 new candidates

2022
14 candidates + BCG
Phase 2b-3 dominant

WHO Preferred Product Characteristics (PPC) for New TB Vaccines



WHO Preferred Product Characteristics
for New Tuberculosis Vaccines

Adolescents & Adults

50% or greater efficacy

Protect with/post- & without/pre- *Mtb* infection

Protect in diverse geographies

Safe in PLWHIV, elderly, pregnancy

10+ years protection

Infants

Superior efficacy vs BCG*

Superior safety vs BCG

Safe in HIV-infected infants

10+ years protection

*Infant BCG

VE 74% *Colditz, Pediatrics 1995*

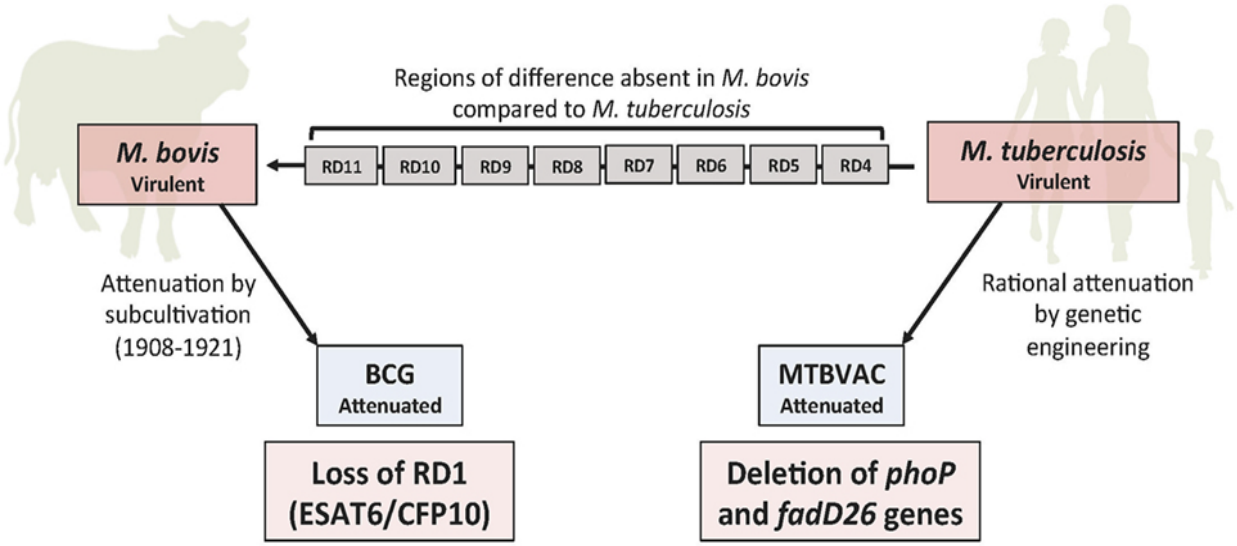
VE 59% *Mangtani, CID 2014*

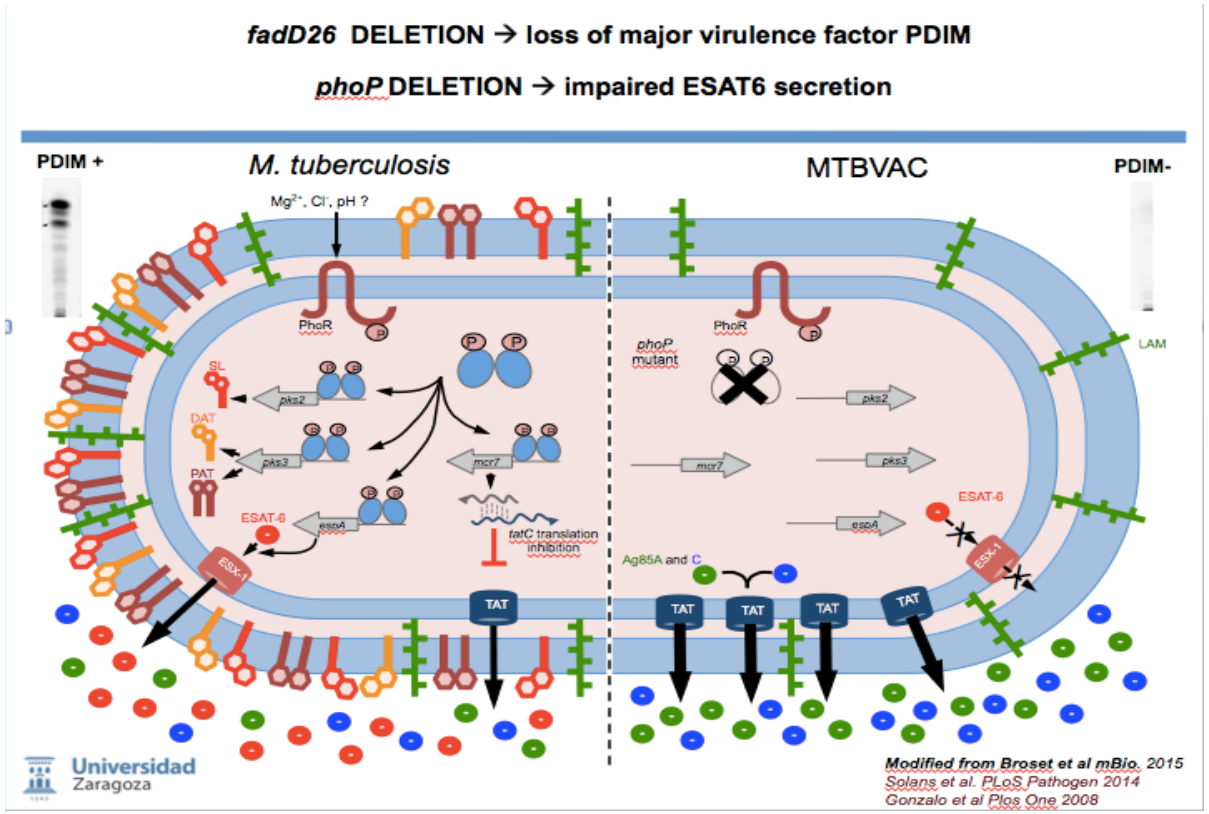
MTBVAC
Phase 3 POD (infants)

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 Scriba†, Mark Hatherill†, and the MTBVAC Clinical Trial Team

Lancet Respir Med 2019; 7:757–70





Started: Randomised, Double-blind Controlled Phase 3 Trial to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC Administered in Healthy HIV unexposed and HIV exposed uninfected Newborns in Tuberculosis Endemic Regions of Sub-Saharan Africa (NCT04975178) >7,000 HIV-unexposed and HIV-exposed uninfected newborns, randomized BCG or MTBVAC, 72m FU for TB disease

ClinicalTrials.gov Identifier: NCT04975178

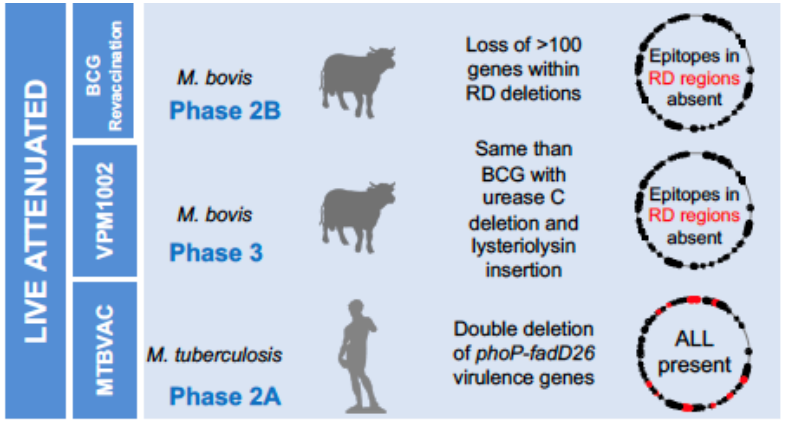
Recruitment Status : Recruiting
First Posted : July 23, 2021
Last Update Posted : October 12, 2022

Planned: Safety & immunogenicity (PLWH on ART)
Phase 3 safety & efficacy (adolescents & adults)

VPM1002

Phase 3 POI (Infants)
POD (Household Contacts >6 years)
POR (Adult TB patients)

VPM1002: recombinant urease C-deficient, listeriolysin-expressing BCG vaccine derived from the BCG Prague strain (minus RD1 and RD2 genes)



Follow-up: A multicenter, phase III, double-blind, randomized, active-controlled study to evaluate the efficacy and safety of VPM1002 in comparison to BCG in prevention of *Mycobacterium tuberculosis* infection in newborn infants (NCT04351685)

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

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

ClinicalTrials.gov Identifier: NCT04351685

Recruitment Status : Recruiting
First Posted : April 17, 2020
Last Update Posted : October 19, 2021

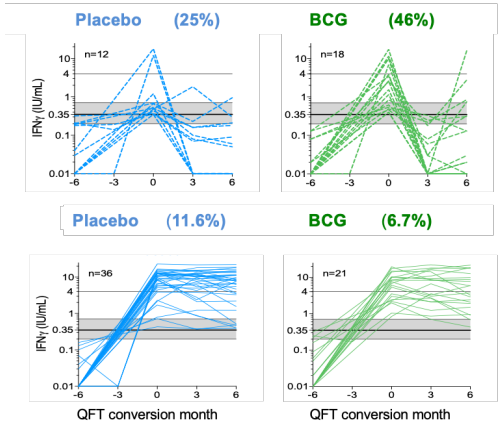
Next Steps…
BCG Revaccination
PO(S)I

The NEW ENGLAND JOURNAL of MEDICINE

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†



BCG 45% efficacy against sustained IGRA+ conversion

Sustained Mtb infection?

Follow-up: A Randomized, Placebo Controlled, Observer-Blind, Phase IIb Study to Evaluate the Efficacy, Safety, and Immunogenicity of BCG Revaccination in Healthy Adolescents for the Prevention of Sustained Infection With Mycobacterium Tuberculosis (BCG REVAX; Gates MRI-TBV01-201) (NCT04152161)

1,800 IGRA- SA adolescents (10-18 yr), randomized BCG revaccination or placebo
FU 48 months; primary endpoint sustained IGRA+ conversion 6 months
Results primary event-driven analysis expected end 2023…

ClinicalTrials.gov Identifier: NCT04152161

Recruitment Status : Active, not recruiting
First Posted : November 5, 2019
Last Update Posted : August 11, 2021

How to validate positive findings?

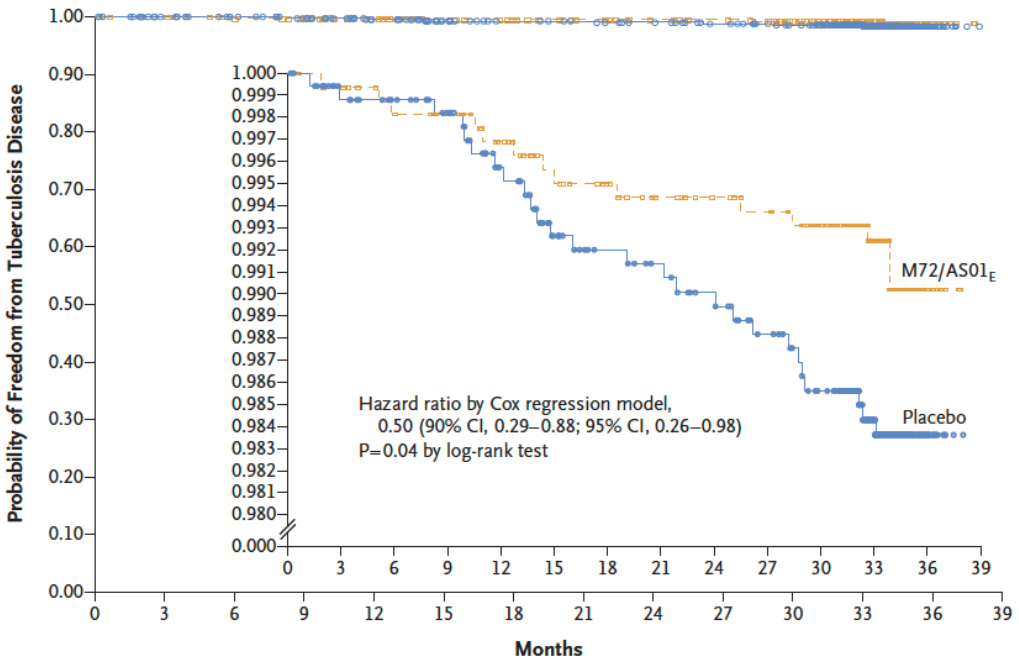
--> POD trial BCG revaccination in IGRA- adolescents
TB incidence IGRA- lower, sample size +/- 60-70,000
Country-level interest in pragmatic trial with passive follow-up?

M72/AS01$_E$
POD (adolescents/adults)

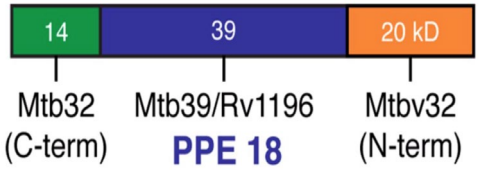
3,575 IGRA+ HIV- adults
Zambia, Kenya, SA

Randomized (1:1)
M72/AS01$_E$ or Placebo
2 doses, 1 month apart

Subclinical TB excluded baseline
3-year follow-up
Micro+ symptomatic TB



Year 1	VE 27.4%	(95% CI −128.8 to 77.0)
Year 2	VE 55.2%	(95% CI −45.3 to 86.2)
Year 3	VE 60.2%	(95% CI−27.0 to 87.5)
Years 1-3	**VE 49.7%**	**(95% CI 2.1 to 74.2)**



Brennan, Infection & Immunity 2017

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

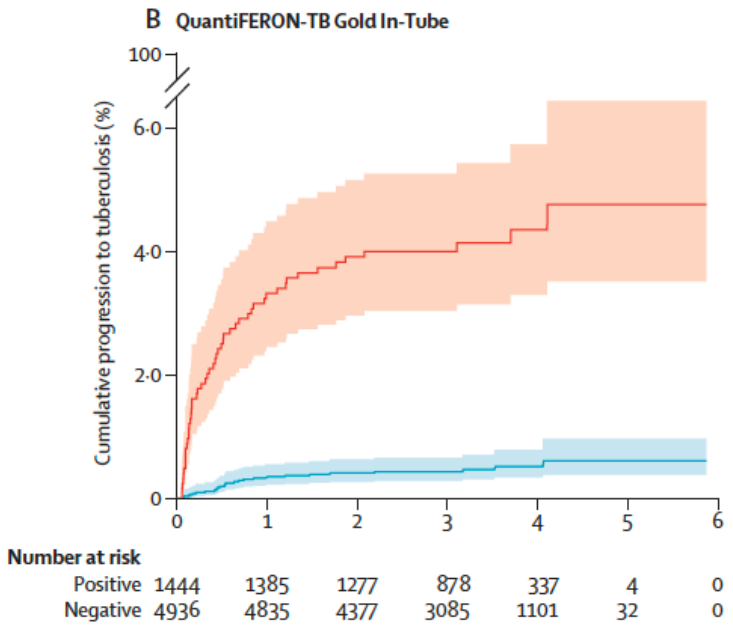
Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

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

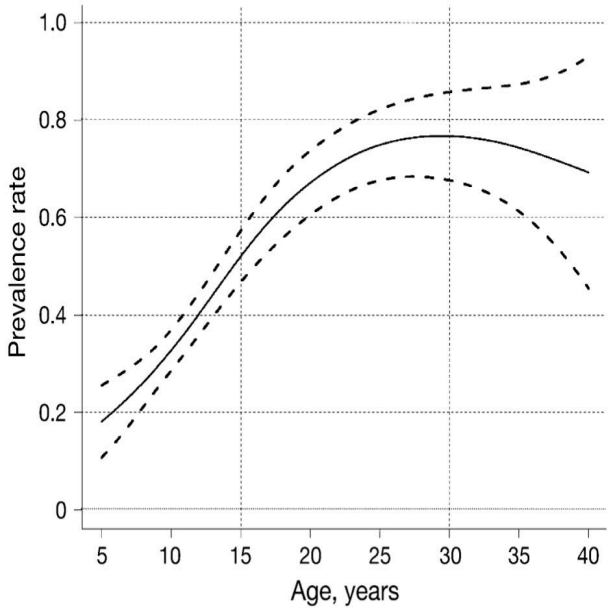
Planned: Phase 3 efficacy, safety, and immunogenicity licensure trial, multiple sites and countries, 2024
26,000 adolescents and adults aged 15-44 years, IGRA+(-); HIV-(+); (POD; 2^0 POI)
Site selection epi study (IGRA+ rates) multiple countries

Vaccinate before (IGRA-) or after (IGRA+) *M. tuberculosis* exposure?

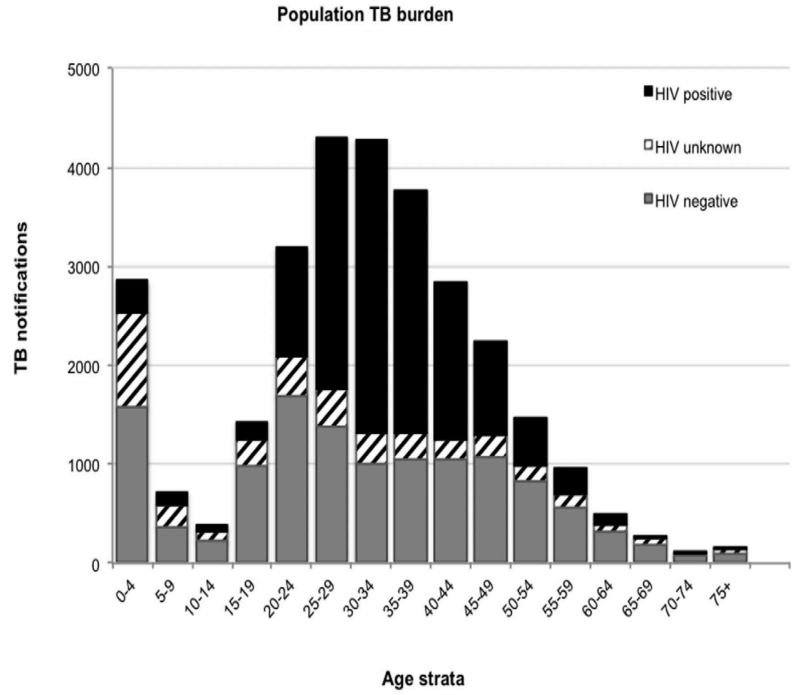
~23% global population (1.7 billion) Mtb-sensitized, ie. 77% not… *Houben, PloS Medicine 2016*



TB disease incidence after Mtb exposure
Abubakar Lancet ID 2018



TST (10mm+) prevalence rate by age
Wood et al, IJTLD 2010



TB Disease notifications (HIV-negative) by age
Wood et al, PLoS ONE 2011

Risk of TB disease highest within 2 years of exposure

***M.tb* infection and TB disease rates increase rapidly through adolescence into young adulthood**

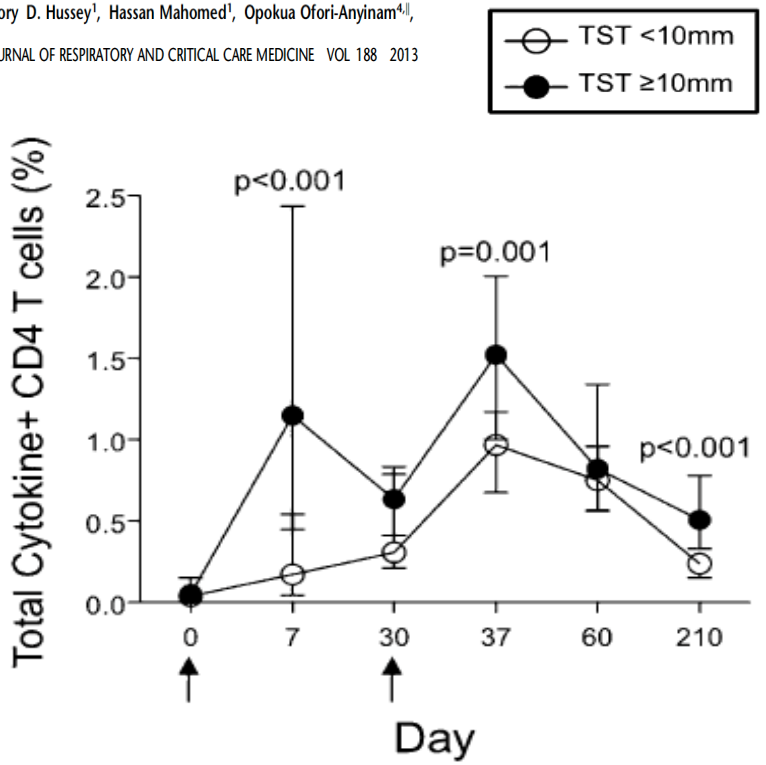
Target IGRA- pre-adolescents or IGRA+ adolescents and adults?

Can M72/AS01$_E$ protect Mtb-unsensitized (TST-/IGRA-) individuals against future exposure, infection, and progression to TB disease?

Induction and Regulation of T-Cell Immunity by the Novel Tuberculosis Vaccine M72/AS01 in South African Adults

Cheryl L. Day[1,2,3,*], Michele Tameris[1,*], Nazma Mansoor[1], Michele van Rooyen[1], Marwou de Kock[1], Hennie Geldenhuys[1], Mzwandile Erasmus[1], Lebohang Makhethe[1], E. Jane Hughes[1], Sebastian Gelderbloem[1,‡], Anne Bollaerts[4], Patricia Bourguignon[4], Joe Cohen[4], Marie-Ange Demoitié[4], Pascal Mettens[4], Philippe Moris[4], Jerald C. Sadoff[5,§], Anthony Hawkridge[1], Gregory D. Hussey[1], Hassan Mahomed[1], Opokua Ofori-Anyinam[4,‖], and Willem A. Hanekom[1,‖]

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 188 2013

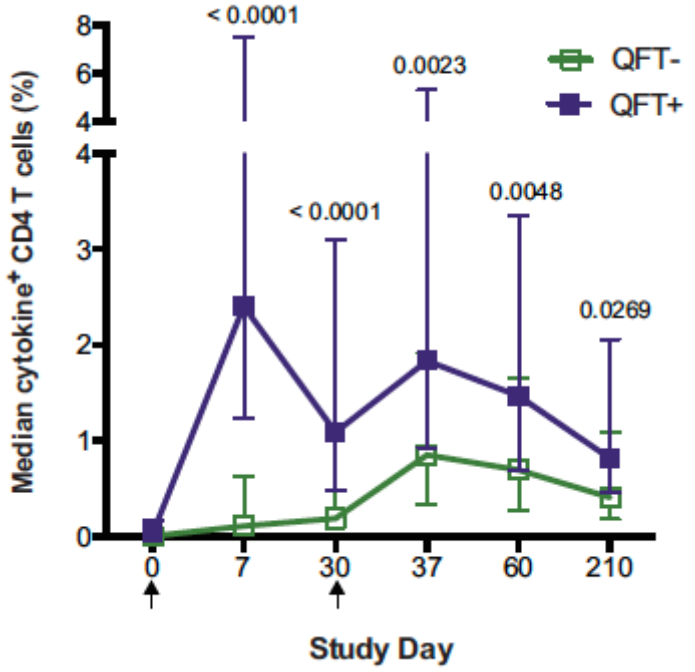


Adults: Total frequencies of M72-specific cytokine+ CD4 T cells were higher in TST+ vs TST-

Contents lists available at ScienceDirect
Vaccine
journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of candidate vaccine M72/AS01$_E$ in adolescents in a TB endemic setting

Adam Penn-Nicholson[a,*,1], Hennie Geldenhuys[a,1], Wivine Burny[b], Robbert van der Most[b], Cheryl L. Day[a,c,d], Erik Jongert[b], Philippe Moris[b], Mark Hatherill[a], Opokua Ofori-Anyinam[b,2], Willem Hanekom[a,2], ıccine Study Team,



Adolescents: M72/AS01$_E$ induced higher median cytokine+ CD4 T cell responses in IGRA+ vs IGRA-

Modelling studies

Vaccine efficacy in IGRA+ populations → greatest reduction in TB incidence by 2050
(IRR 51%, 52%, and 54% in China, South Africa, India)

Vaccine efficacy only in IGRA- populations → moderate reduction in TB incidence by 2050
(IRR 19, 36, and 51% in China, South Africa, India), greater impact in higher-transmission settings

Harris et al, Sci Transl Med 2020
*Assumptions: 10-year, 70% efficacy against disease

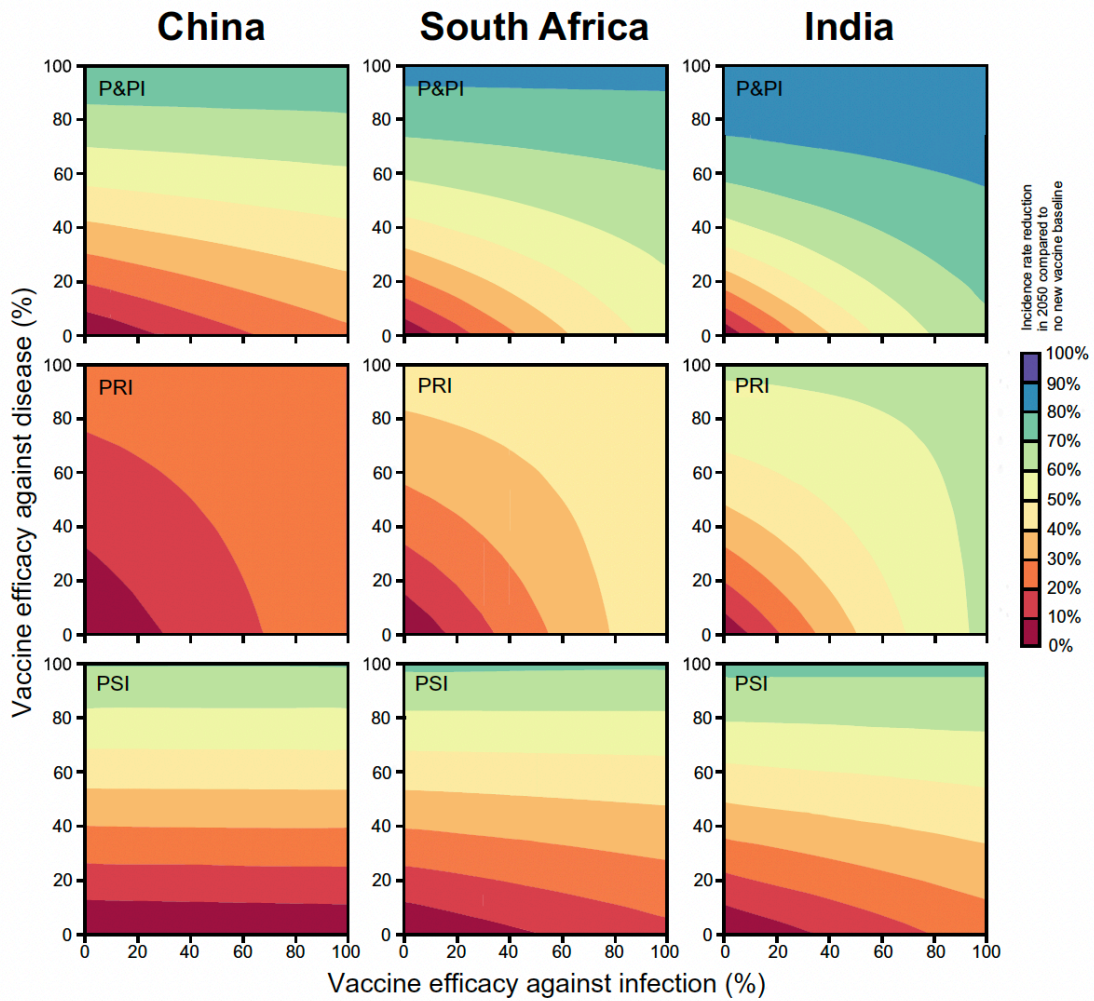


Fig. 3. Vaccine impact by prevention of infection and prevention of disease efficacy. IRR in 2050 by country from a vaccine with 10-year duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (P&PI; top row), pre-infection populations (PRI; middle row), or post-infection populations (PSI; bottom row), assumed safe and efficacious in HIV-positive populations, delivered from 2025 as routine vaccination of 9 year olds and as 10-yearly mass campaigns in China, South Africa, and India.

Optimal strategy?

Vaccine efficacy in both IGRA- and IGRA+

or

Combination pre- and post-exposure approaches

Delays…

Trial duration

Slow growing Mtb pathogen, slowly progressive TB disease, no epidemic waves, no immune correlates of vaccine-induced protection = long efficacy trials (5+ years)

"*TB vaccine development is not a 100-day dash; it is an endurance marathon that requires an altogether different kind of stamina…*" **TAG TB Vaccine Pipeline Report 2022**

Delays…

Trial-to-trial interval

Collective stakeholder inertia / failure to plan for success / lack of appetite for risk

M72/AS01$_E$ Phase 2b trial completed 16th November 2018

Final efficacy results published 29th October 2019

Phase 3 trial expected to start in 2024…

Immune correlates results expected 2025…

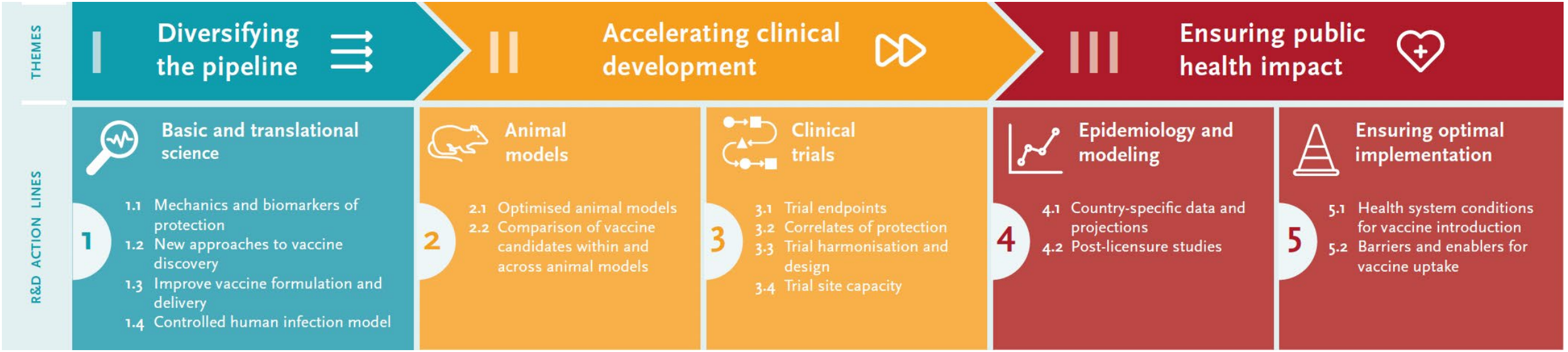
THE GLOBAL TB VACCINE R&D ROADMAP

Accelerating research and development of new vaccines against tuberculosis: a global roadmap

*Frank Cobelens, Rajinder Kumar Suri, Michelle Helinski, Michael Makanga, Ana Lúcia Weinberg, Britta Schaffmeister, Frank Deege, Mark Hatherill, on behalf of the TB Vaccine Roadmap Stakeholder Group**

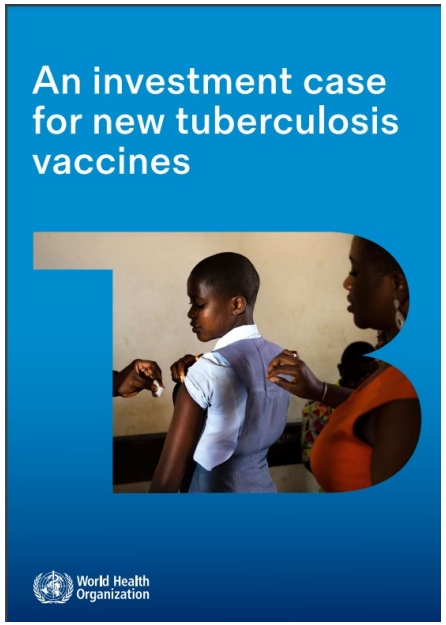
Cobelens et al, Lancet Infect Dis 2022

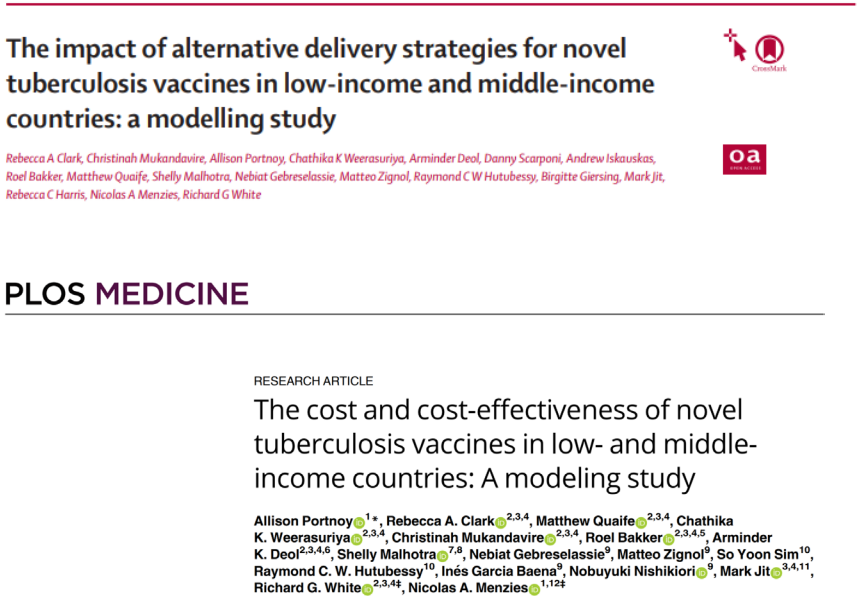
Supported by EDCTP through a grant to the Amsterdam Institute of Global Health and Development in collaboration with WHO



Priorities: diversity of vaccine design and delivery; validated preclinical models; more efficient clinical trials; discovery of immune correlates of protection; understanding of cost-effectiveness, demand and integration into existing programmes

Unleash new funding streams, reduce financial risk





Ongoing

Assessment of full value of new TB vaccines

Development of Evidence Considerations for Vaccine Policy (ECVP)

Development of a Global Framework for Countries to achieve Rapid Introduction and Impact of New TB Vaccines for Adults and Adolescents

Global advocacy efforts

→ drive demand, funding, implementation and uptake of a new, effective TB vaccine

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International AIDS Vaccine Initiative

EDCTP

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TBVI
TuBerculosis Vaccine Initiative

STATENS SERUM INSTITUT

SERUM INSTITUTE OF INDIA
Cyrus Poonawalla Group

IDRI
INFECTIOUS DISEASE RESEARCH INSTITUTE

SANOFI PASTEUR

BIOFABRI

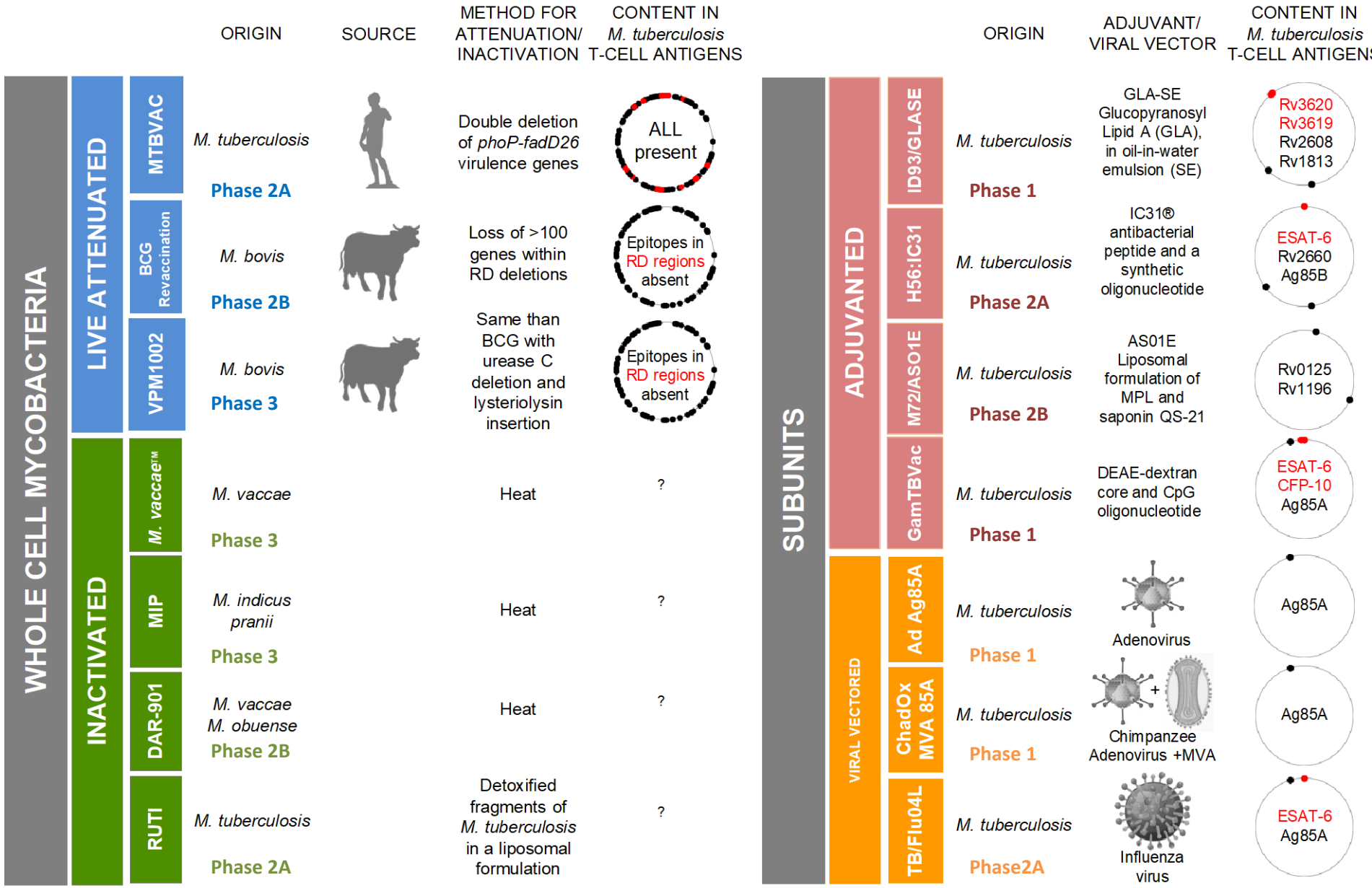
Study participants and their communities
Investigators and study teams
Sponsors and funders
Collaborators

NIH
National Institute of Allergy and Infectious Diseases

satvi SOUTH AFRICAN

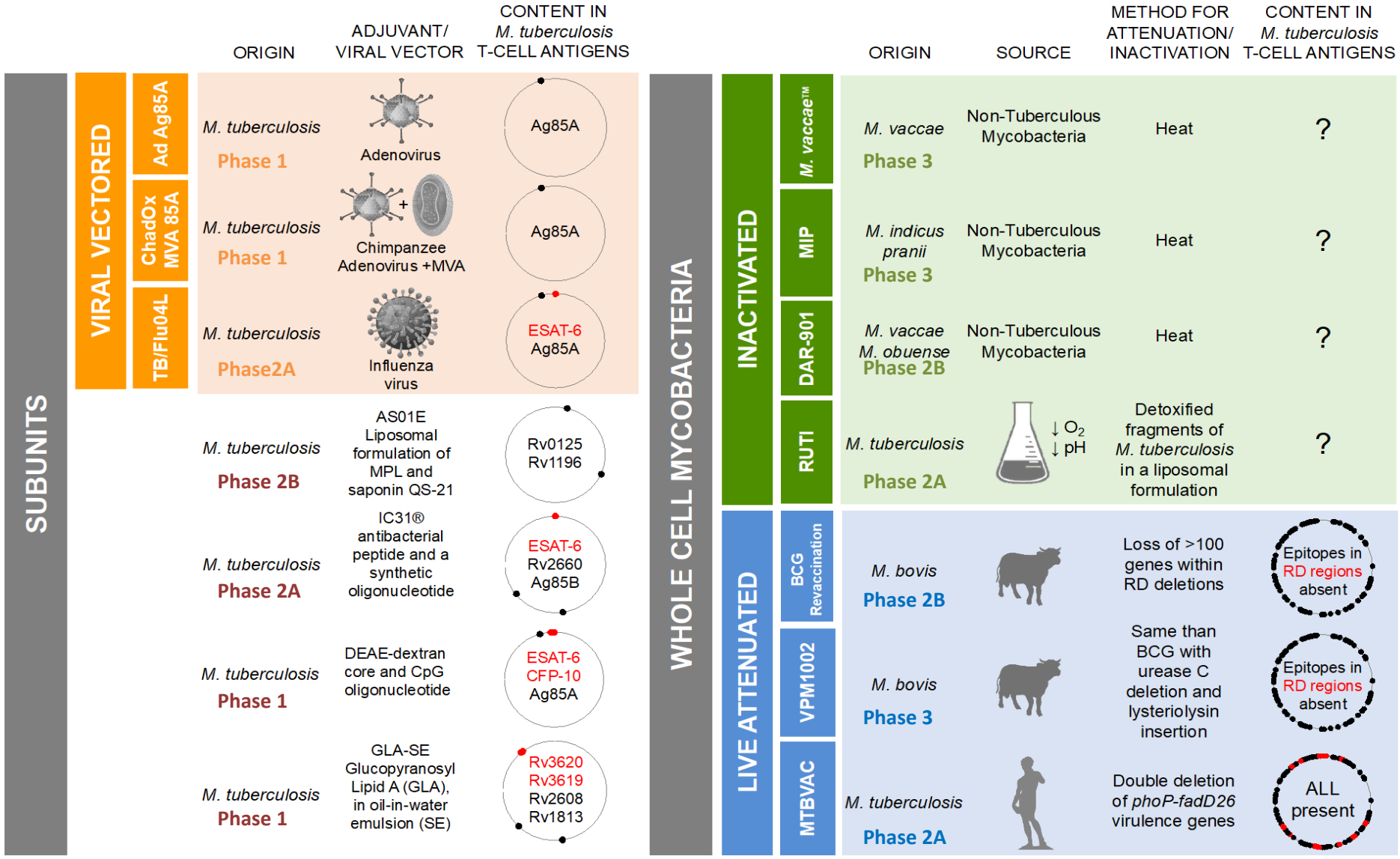
EXTRA SLIDES

DIVERSITY OF THE PIPE LINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS



Slide courtesy Carlos Martin, Update on TB Vaccine Pipeline, Applied Sciences April 2020

DIVERSITY OF CANDIDATES IN CLINICAL TRIALS



Courtesy Carlos Martin
Update on TB Vaccine Pipeline , Applied Sciences 2020