



Tuberculosis Vaccine R&D

Mark Hatherill

South African Tuberculosis Vaccine Initiative
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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} SI IPL, 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
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		M72/AS01E ^{e,j} GSK, Gates MRI	VPM1002 ^{d,g,i,j} SIPL, VPM
		RUTI ^{®f} Archivel Farma, S.L.	BCG vaccination to prevent infection (TIPI) ^d HJF
			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



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

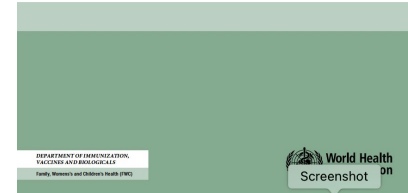
*Infant BCG

VE 74% *Colditz, Pediatrics 1995*

VE 59% *Mangtani, CID 2014*



WHO Preferred Product Characteristics
for New Tuberculosis Vaccines



World Health
Screenshot

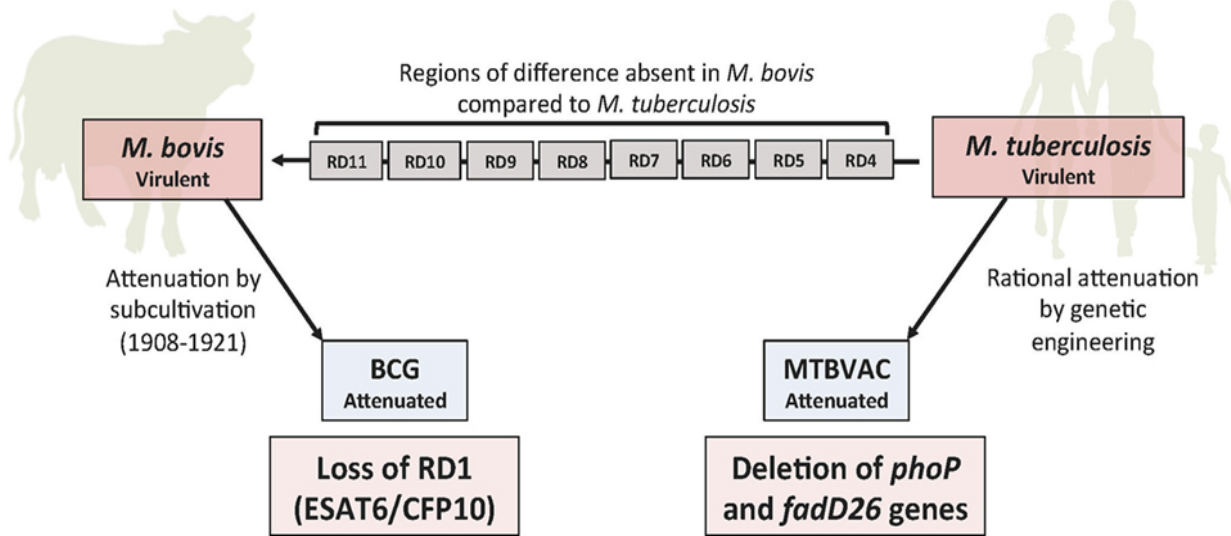
MTBVAC

Phase 3 POD (infants)

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

Michèle Tameris*, Helen Mearns*, Adam Penn-Nicholson, Yolande Gregg, Nicole Bilek, Simbarashe Mabwe, Hennie Geldenhuys, Just in Shenje, Angeliqwe Kany Kany Luabeya, Ingrid Murillo, Juana Doce, Nacho Aguilo, Dessimilava Marinova, Eugenia Puentes, Esteban Rodriguez, Jesús Gonzalo-Asensio, Bernard Fritzel, Jelle Thole, Carlos Martin, Thomas J Scribat, Mark Hatherill†, and the MTBVAC Clinical Trial Team

Lancet Respir Med 2019; 7:757-70

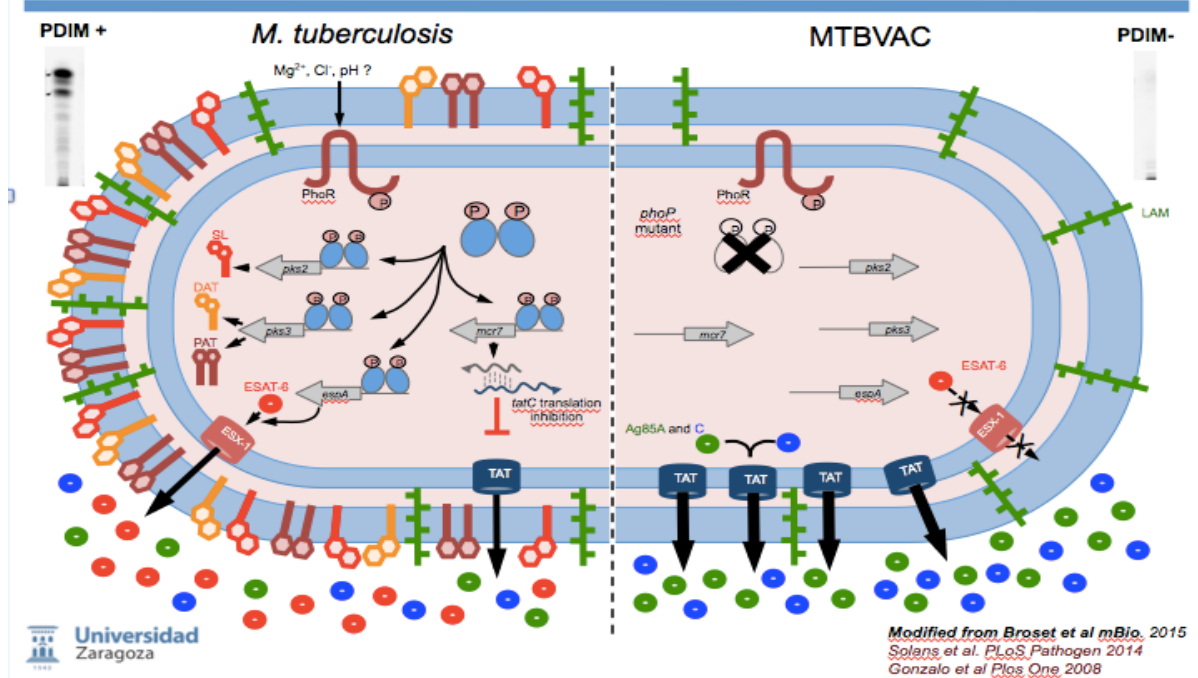


Started: Randomised, Double-blind Controlled Phase 3 Trial to evaluate the Efficacy, Safety and Immunogenicity of MTBVAC Administered in Healthy HIV unexposed and HIV exposed uninfected Newborns in Tuberculosis Endemic Regions of Sub-Saharan Africa (NCT04975178) >7,000 HIV-unexposed and HIV-exposed uninfected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

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

fadD26 DELETION → loss of major virulence factor PDIM

phoP DELETION → impaired ESAT6 secretion



ClinicalTrials.gov Identifier: NCT04975178

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

VPM1002

Phase 3 POI (Infants)

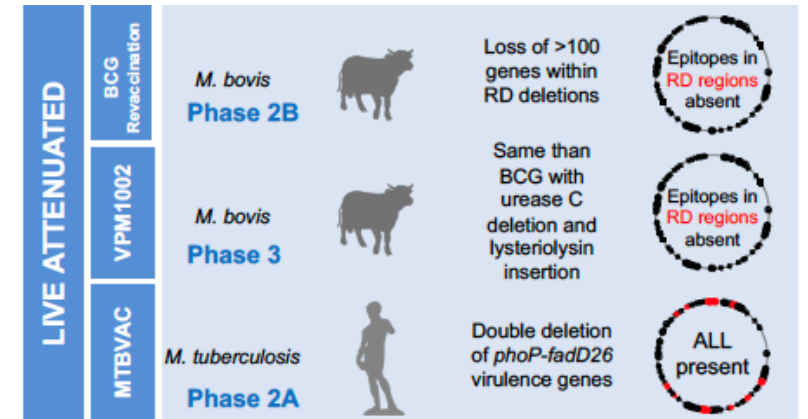
POD (Household Contacts >6 years)

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; 2⁰ 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 Hesselning, 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

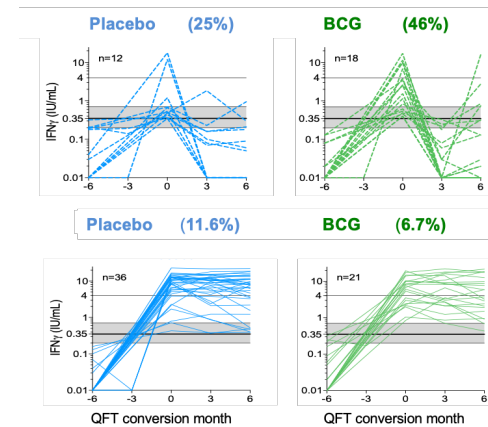
Next Steps... BCG Revaccination PO(S)I

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. Makhetha, 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?

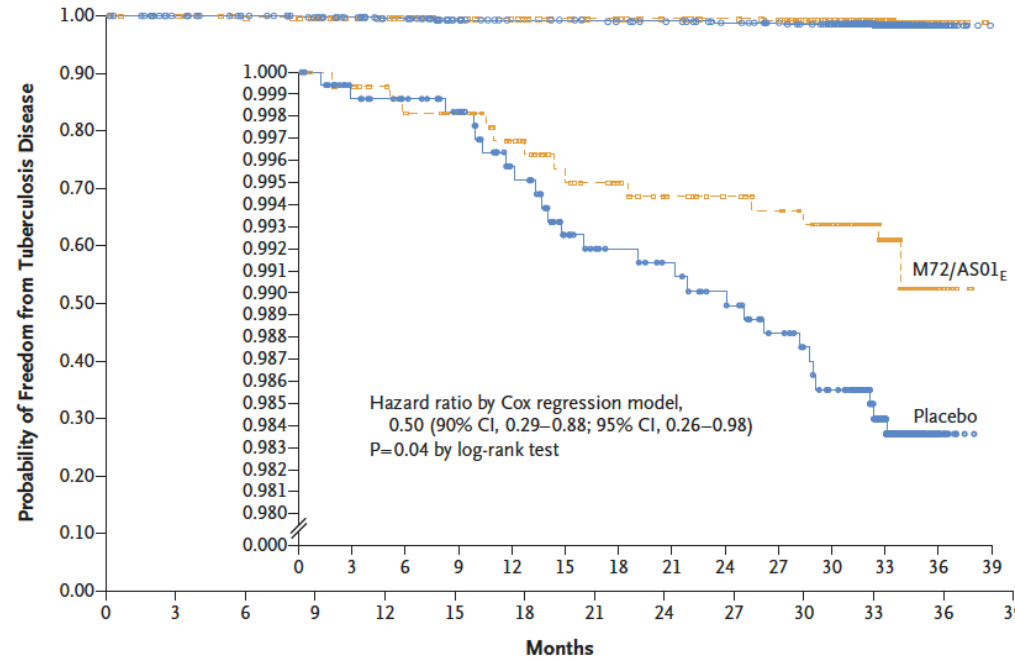
--> POD trial BCG revaccination in IGRA- adolescents
TB incidence IGRA- lower, sample size +/- 60-70,000
Country-level interest in pragmatic trial with passive follow-up?

M72/AS01_E POD (adolescents/adults)

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

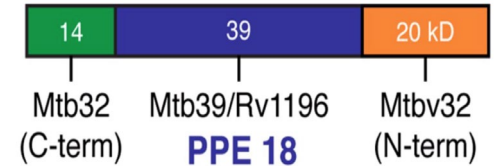
Randomized (1:1)
M72/AS01_E or Placebo
2 doses, 1 month apart

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)

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; 2⁰ POI)
Site selection epi study (IGRA+ rates) multiple countries



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. Demoitie, M. Tameris, M. Malahleha, J.C. Innes, E. Hellstrom, N. Martinson, T. Singh, E.J. Akite, A. Khatoun Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

ORIGINAL ARTICLE

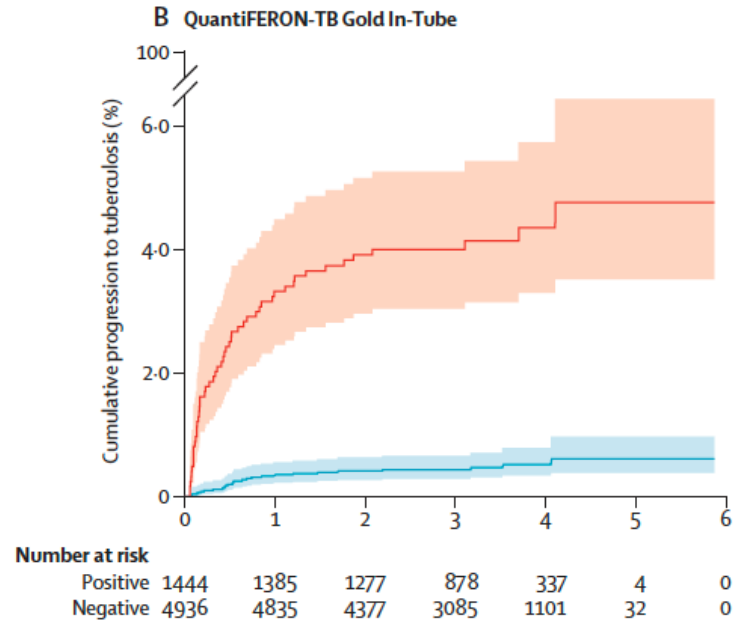
Final Analysis of a Trial of M72/AS01_E Vaccine to Prevent Tuberculosis

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. Demoitie, A. Diacon, T.G. Evans, P. Gillard, E. Hellstrom, 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

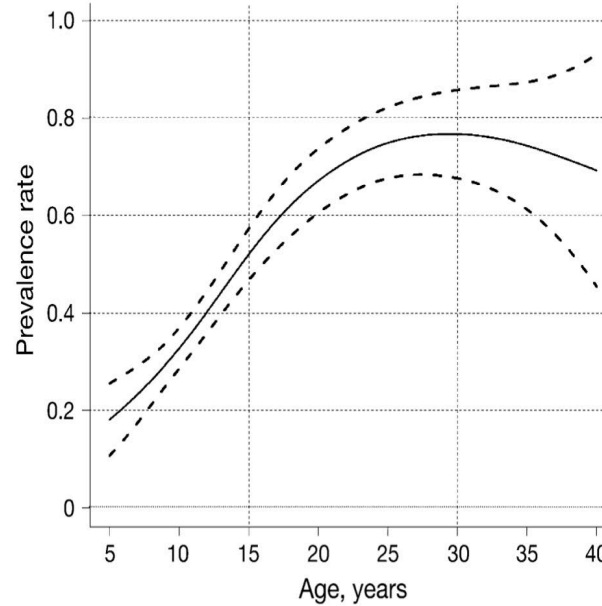
Vaccinate before (IGRA-) or after (IGRA+) *M. tuberculosis* exposure?

~23% global population (1.7 billion) Mtb-sensitized, ie. 77% not...

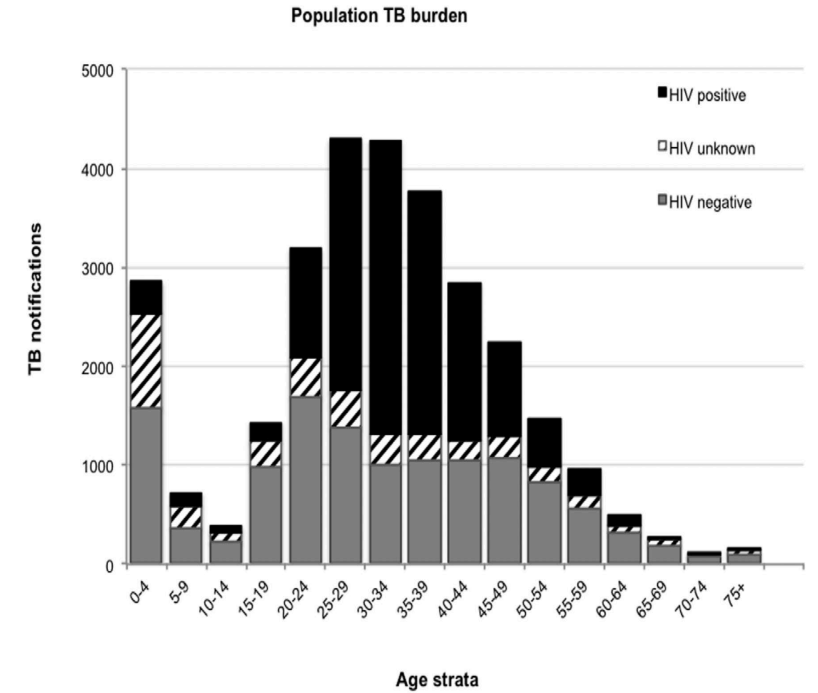
Houben, PLoS Medicine 2016



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

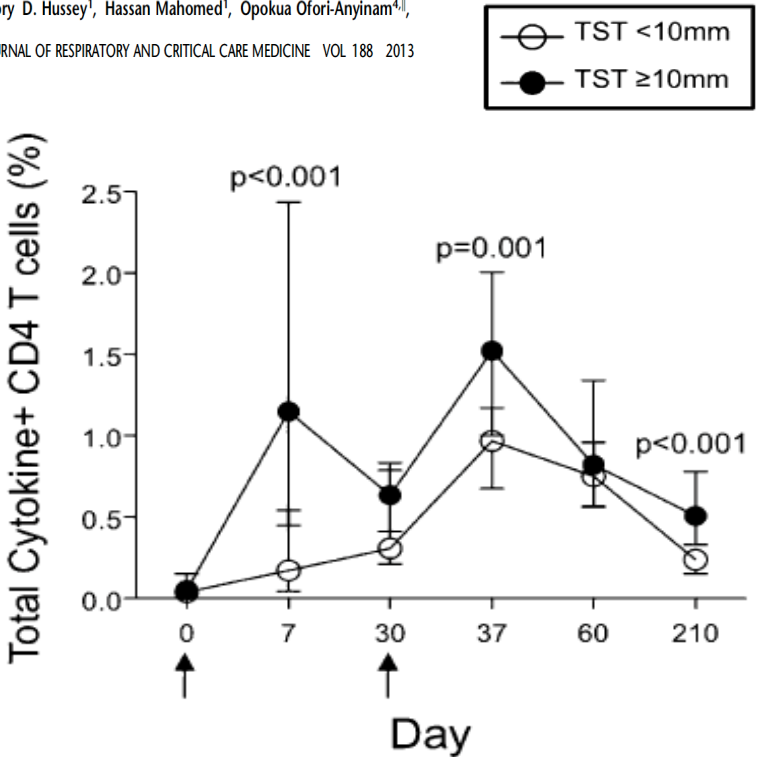
Cheryl L. Day^{1,2,3,*}, Michele Tameris^{1,*}, Nazma Mansoor¹, Michele van Rooyen¹, Marwou de Kock¹, Hennie Geldenhuys¹, Mzwandile Erasmus¹, Lebohang Makhetha¹, E. Jane Hughes¹, Sebastian Gelderbloem^{1,†}, Anne Bollaerts⁴, Patricia Bourguignon⁴, Joe Cohen⁴, Marie-Ange Demoitié⁴, Pascal Mettens⁴, Philippe Moris⁴, Jerald C. Sadoff^{5,§}, Anthony Hawkrigde¹, Gregory D. Hussey¹, Hassan Mahomed¹, Opokua Ofori-Anyinam^{1,||}, and Willem A. Hanekom^{1,||}

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 188 2013

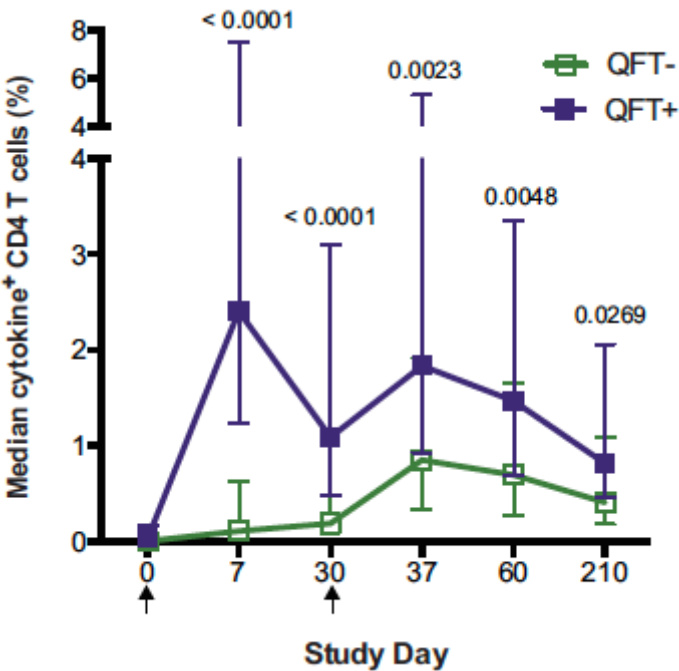


Safety and immunogenicity of candidate vaccine M72/AS01_E in adolescents in a TB endemic setting

Adam Penn-Nicholson^{a,*,1}, Hennie Geldenhuys^{a,1}, Wivine Burny^b, Robert 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}, Vaccine Study Team,



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



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

Optimal strategy?

Vaccine efficacy in both IGRA- and IGRA+

or

Combination pre- and post-exposure approaches

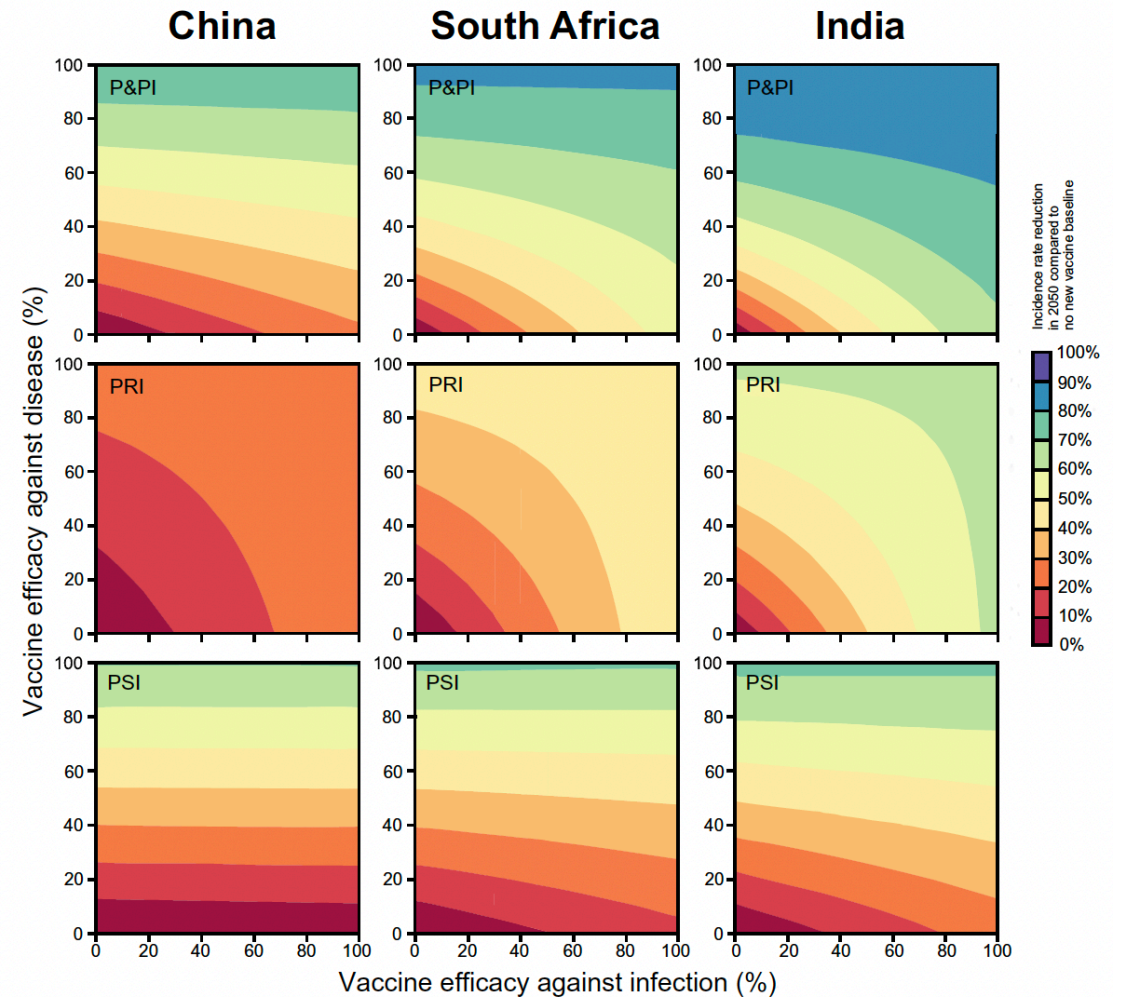


Fig. 3. Vaccine impact by prevention of infection and prevention of disease efficacy. IRR in 2050 by country from a vaccine with 10-year duration of protection for prevention of infection or disease or both, with efficacy in pre- and post-infection populations (P&PI; top row), pre-infection populations (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.

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...

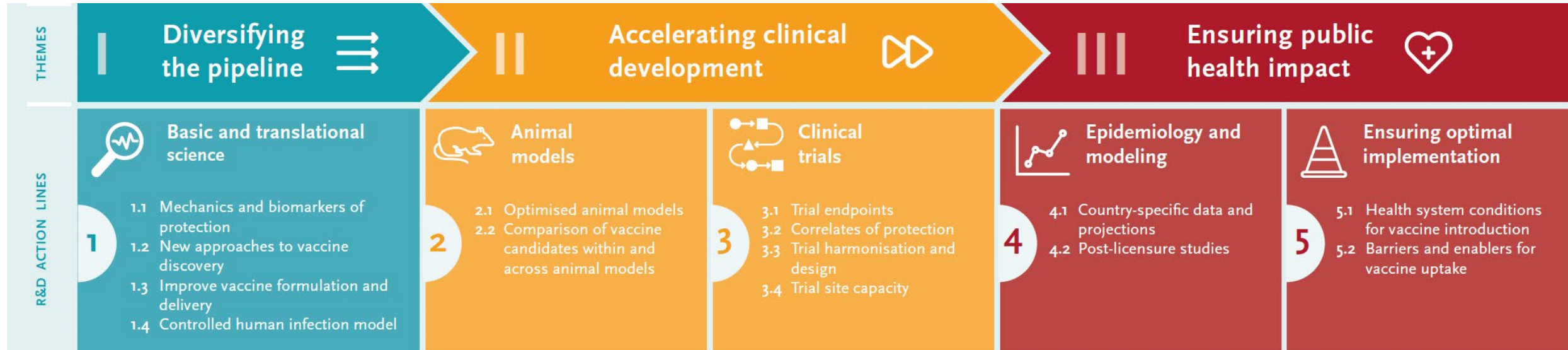
THE GLOBAL TB VACCINE R&D ROADMAP

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

WHO Evidence Considerations for Vaccine Policy Development (ECVP)

Draft document

22 August 2022 | Technical document

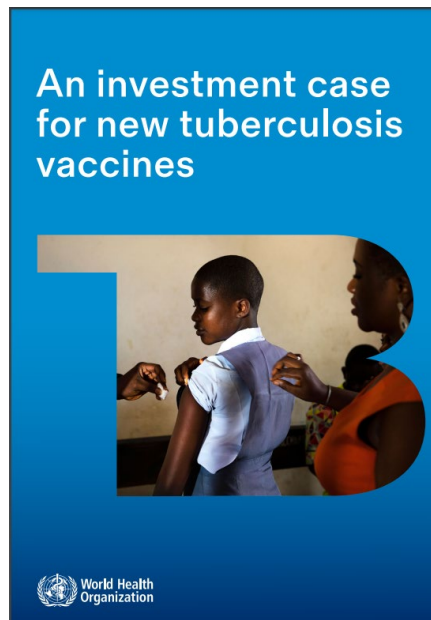


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Overview

WHO's IVB department has developed a novel kind of guidance for vaccine development stakeholders, referred to as Evidence Considerations for Vaccine Policy, or ECVP. The ECVP document aims to provide early information on the data and evidence that is likely to be required to support WHO policy recommendations. The original concept of the ECVP was developed through a global stakeholder meeting (published here), after which both a generic ECVP framework (posted on this page) and subsequently the first ECVP exemplar has been drafted for new Tuberculosis (TB) vaccines intended for adults and adolescents in collaboration with a global expert technical working group. The link to the TB vaccine ECVP can be found here:

Public consultation of ECVP for TB vaccines intended for adults and adolescents.



The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study

Rebecca A Clark, Christinah Mukandavire, Allison Portnoy, Chathika K Weerasuriya, Arminder Deol, Danny Scarponi, Andrew Iskasukas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond C W Hutubessy, Birgitte Giersing, Mark Jit, Rebecca C Harris, Nicolas A Menzies, Richard G White



PLOS MEDICINE

RESEARCH ARTICLE

The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study

Allison Portnoy^{1*}, Rebecca A. Clark^{2,3,4}, Matthew Quaife^{2,3,4}, Chathika K. Weerasuriya^{2,3,4}, Christinah Mukandavire^{2,3,4}, Roel Bakker^{2,3,4,5}, Arminder K. Deol^{2,3,4,6}, Shelly Malhotra^{7,8}, Nebiat Gebreselassie⁹, Matteo Zignol⁹, So Yoon Sim¹⁰, Raymond C. W. Hutubessy¹⁰, Inés Garcia Baena⁹, Nobuyuki Nishikiori⁹, Mark Jit^{3,4,11}, Richard G. White^{2,3,4‡}, Nicolas A. Menzies^{1,12‡}

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



EDCTP

BILL & MELINDA
GATES foundation



TuBerculosis Vaccine Initiative



STATENS
SERUM
INSTITUT



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



National Institute of
Allergy and
Infectious Diseases



EXTRA SLIDES

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

WHOLE CELL MYCOBACTERIA		ORIGIN	SOURCE	METHOD FOR ATTENUATION/ INACTIVATION	CONTENT IN <i>M. tuberculosis</i> T-CELL ANTIGENS	SUBUNITS		ORIGIN	ADJUVANT/ VIRAL VECTOR	CONTENT IN <i>M. tuberculosis</i> T-CELL ANTIGENS		
WHOLE CELL MYCOBACTERIA	LIVE ATTENUATED	MTBVAC	<i>M. tuberculosis</i>	Double deletion of <i>phoP-fadD26</i> virulence genes	ALL present	SUBUNITS	ADJUVANTED	<i>M. tuberculosis</i>	GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)	Rv3620 Rv3619 Rv2608 Rv1813		
		Phase 2A	BCG Revaccination	<i>M. bovis</i>	Loss of >100 genes within RD deletions			Epitopes in RD regions absent	Phase 1	<i>M. tuberculosis</i>	IC31® antibacterial peptide and a synthetic oligonucleotide	ESAT-6 Rv2660 Ag85B
		Phase 2B	VPM1002	<i>M. bovis</i>	Same than BCG with urease C deletion and lysteriolysin insertion			Epitopes in RD regions absent	Phase 2A	<i>M. tuberculosis</i>	AS01E Liposomal formulation of MPL and saponin QS-21	Rv0125 Rv1196
	Phase 3	<i>M. vaccae</i>	Heat	?	?			Phase 2B	<i>M. tuberculosis</i>	DEAE-dextran core and CpG oligonucleotide	ESAT-6 CFP-10 Ag85A	
	INACTIVATED	MIP	<i>M. indicus pranii</i>	Heat	?		?	VIRAL VECTORED	Ad Ag85A	Adenovirus	Ag85A	
		Phase 3	DAR-901	<i>M. vaccae</i> <i>M. obuense</i>	Heat		?		?	ChadOx MVA 85A	Chimpanzee Adenovirus +MVA	Ag85A
		Phase 3	RUTI	<i>M. tuberculosis</i>	Detoxified fragments of <i>M. tuberculosis</i> in a liposomal formulation		?		?	TB/Flu04L	Influenza virus	ESAT-6 Ag85A
		Phase 2B										
		Phase 2A										

DIVERSITY OF CANDIDATES IN CLINICAL TRIALS

		ORIGIN	ADJUVANT/ VIRAL VECTOR	CONTENT IN <i>M. tuberculosis</i> T-CELL ANTIGENS			ORIGIN	SOURCE	METHOD FOR ATTENUATION/ INACTIVATION	CONTENT IN <i>M. tuberculosis</i> T-CELL ANTIGENS	
SUBUNITS	VIRAL VECTORED	<i>M. tuberculosis</i>	Ad Ag85A	Adenovirus	Ag85A	Phase 1	<i>M. tuberculosis</i>	Non-Tuberculous Mycobacteria	Heat	?	
			ChadOx MVA 85A	Chimpanzee Adenovirus + MVA	Ag85A						
			TB/Flu04L	Influenza virus	ESAT-6 Ag85A						
	WHOLE CELL MYCOBACTERIA	INACTIVATED	<i>M. tuberculosis</i>	AS01E Liposomal formulation of MPL and saponin QS-21	Rv0125 Rv1196	Phase 2A	<i>M. tuberculosis</i>	Non-Tuberculous Mycobacteria	Heat	Detoxified fragments of <i>M. tuberculosis</i> in a liposomal formulation	?
				IC31® antibacterial peptide and a synthetic oligonucleotide	ESAT-6 Rv2660 Ag85B						
				DEAE-dextran core and CpG oligonucleotide	ESAT-6 CFP-10 Ag85A						
				GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)	Rv3620 Rv3619 Rv2608 Rv1813						
	WHOLE CELL MYCOBACTERIA	LIVE ATTENUATED	<i>M. tuberculosis</i>			Phase 2A	<i>M. tuberculosis</i>	Non-Tuberculous Mycobacteria	Heat	?	
WHOLE CELL MYCOBACTERIA	LIVE ATTENUATED	<i>M. bovis</i>	BCG Revaccination		Phase 2B	<i>M. bovis</i>	Non-Tuberculous Mycobacteria	Loss of >100 genes within RD deletions	Epitopes in RD regions absent		
			VPM1002								
			MTBVAC								
WHOLE CELL MYCOBACTERIA	LIVE ATTENUATED	<i>M. bovis</i>			Phase 3	<i>M. bovis</i>	Non-Tuberculous Mycobacteria	Same than BCG with urease C deletion and lysteriolysin insertion	Epitopes in RD regions absent		
WHOLE CELL MYCOBACTERIA	LIVE ATTENUATED	<i>M. tuberculosis</i>			Phase 2A	<i>M. tuberculosis</i>	Non-Tuberculous Mycobacteria	Double deletion of <i>phoP-fadD26</i> virulence genes	ALL present		

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