Testing new TB vaccines for people with HIV

Mark Hatherill

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

1. Candidate TB Vaccine Pipeline

2. TB Vaccine R & D Roadmap

3. WHO Preferred Product Characteristics

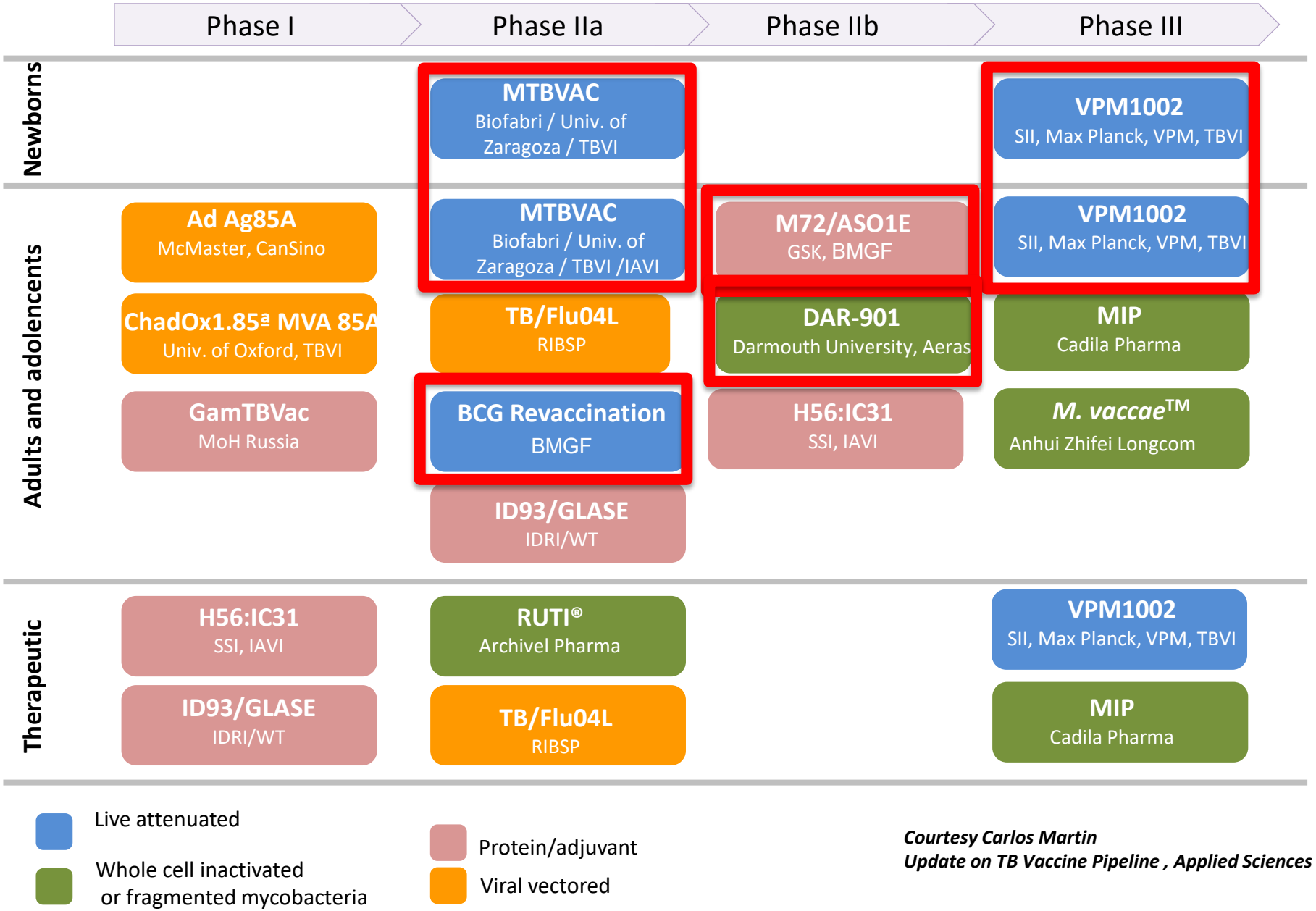
4. Age, Exposure, Infection and Disease – When to vaccinate against HIV-associated TB?

5. Testing candidate TB vaccines for infants and children

6. Testing candidate TB vaccines for adolescents and adults

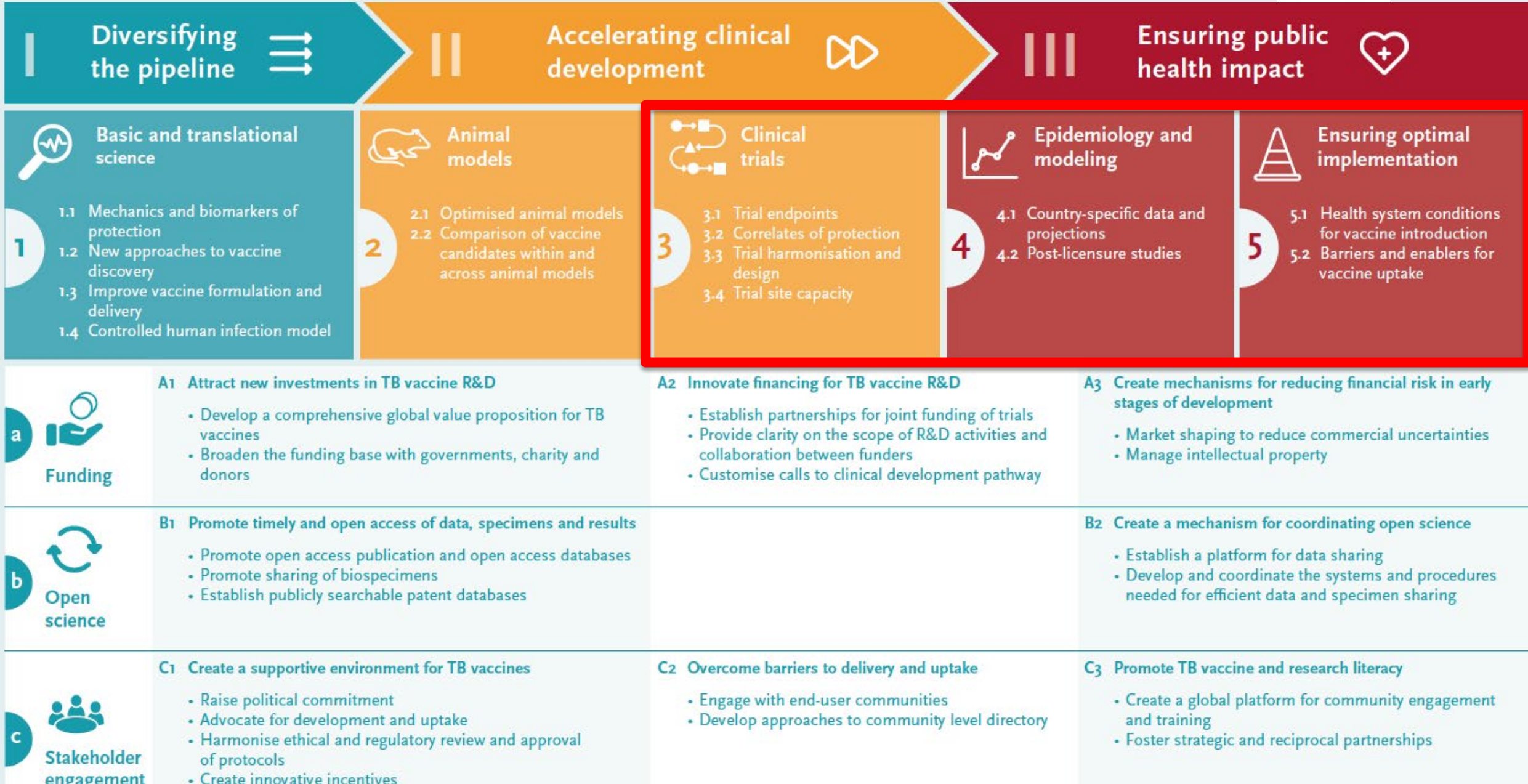
7. Challenges & knowledge gaps

CANDIDATE TB VACCINE PIPELINE

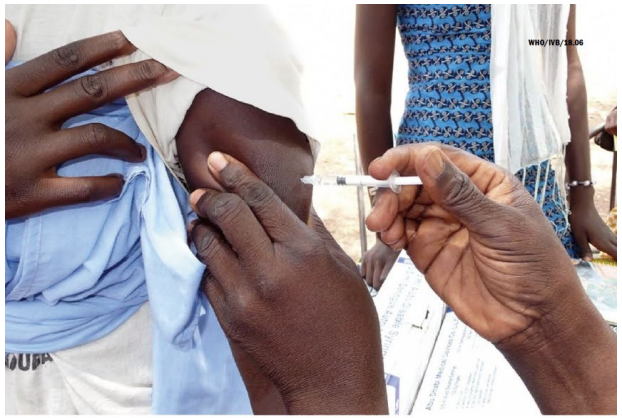


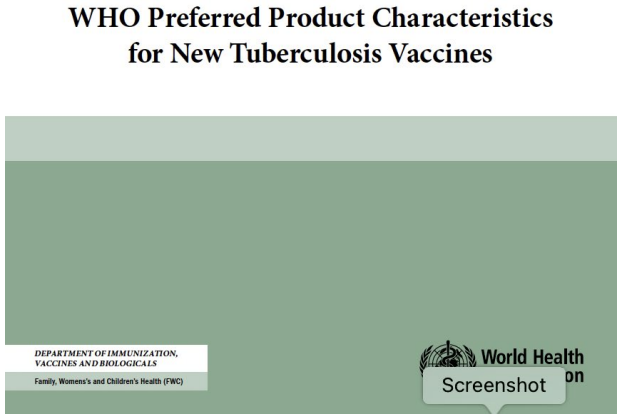
Courtesy Carlos Martin
Update on TB Vaccine Pipeline , Applied Sciences 2020

The TB Vaccine R & D Roadmap



WHO Preferred Product Characteristics (PPC) Strategic Priority #1: New TB Vaccines for Use in Adolescents and Adults

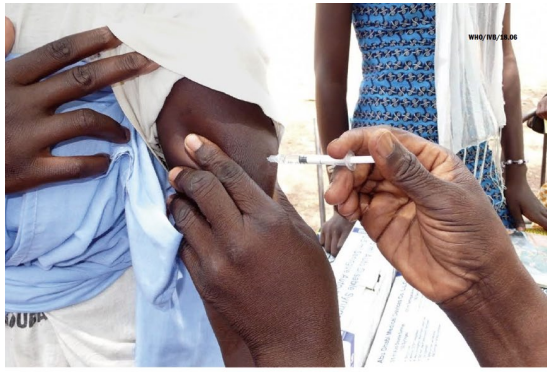


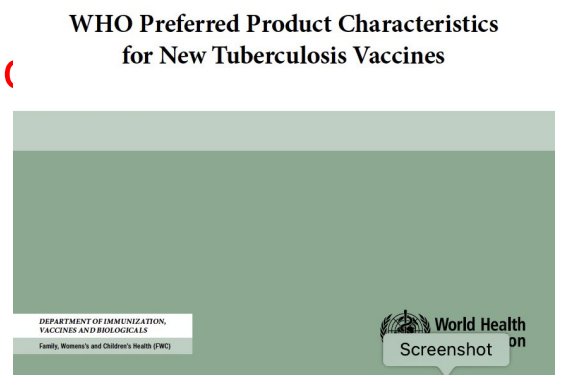


- **OUTCOME MEASURE AND EFFICACY**
  - 50% or greater efficacy in preventing confirmed pulmonary TB
  - Protect both subjects with and without past *Mtb* infection
  - Protective in different geographical regions and latitudes

- **SAFETY**
  - Safety should be favourable in particular risk groups, such as individuals living with HIV/AIDS

WHO Preferred Product Characteristics (PPC) Strategic Priority #2: New TB Vaccines for Use in Neonates and Infants

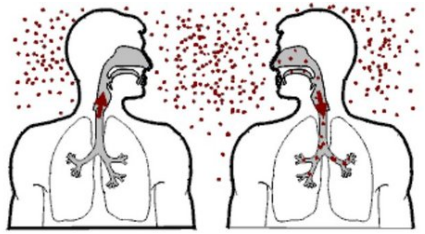


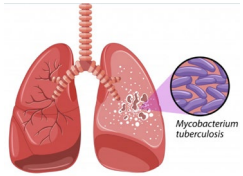


- **OUTCOME MEASURE AND EFFICACY**
  - Equal to or greater than 80% vaccine efficacy as compared to baseline incid or superior efficacy as compared to BCG
- **SAFETY**
  - Improved safety as compared to current BCG
  - Demonstrated safety in HIV infected babies
  - Reduction of injection site swelling, pain, drainage, and scarring, and local lymphadenopathy would represent welcomed improvement over BCG

Age, Exposure, Infection and Disease – When to vaccinate against TB?

TB

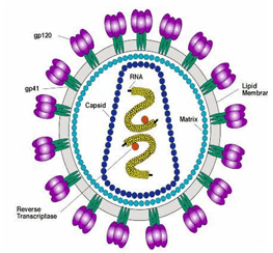


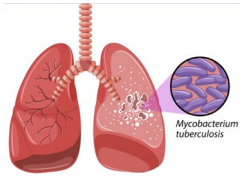


Risk of *M. tuberculosis exposure,* infection & TB disease

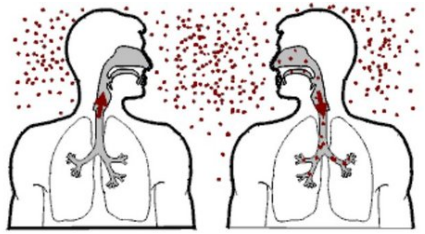
Age, Exposure, Infection and Disease – When to vaccinate against HIV-associated TB?

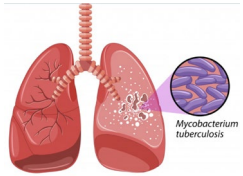
HIV





TB

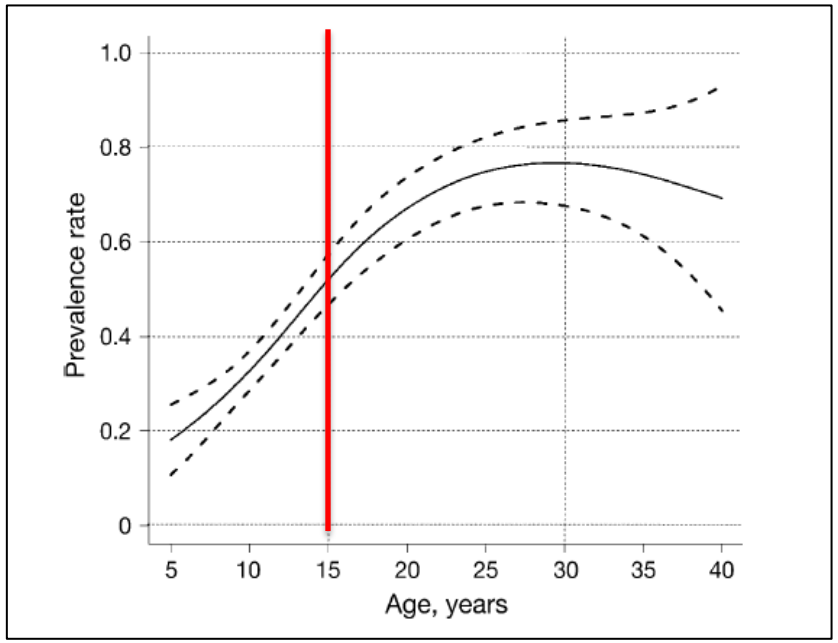




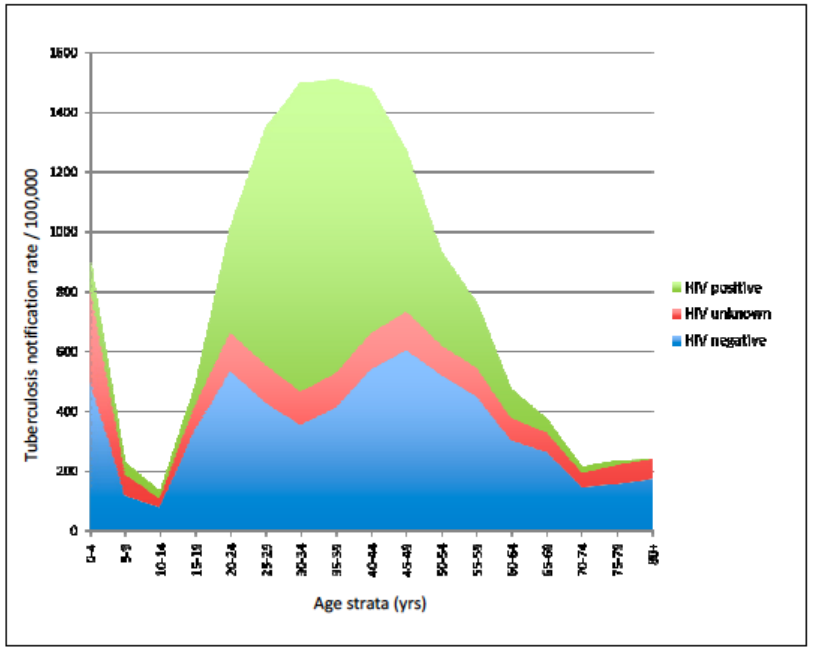
Risk of *M. tuberculosis exposure,* infection & TB disease

Age, Exposure, Infection and Disease – When to vaccinate against HIV-associated TB?

Mtb infection



TB Disease



Cape Town, South Africa

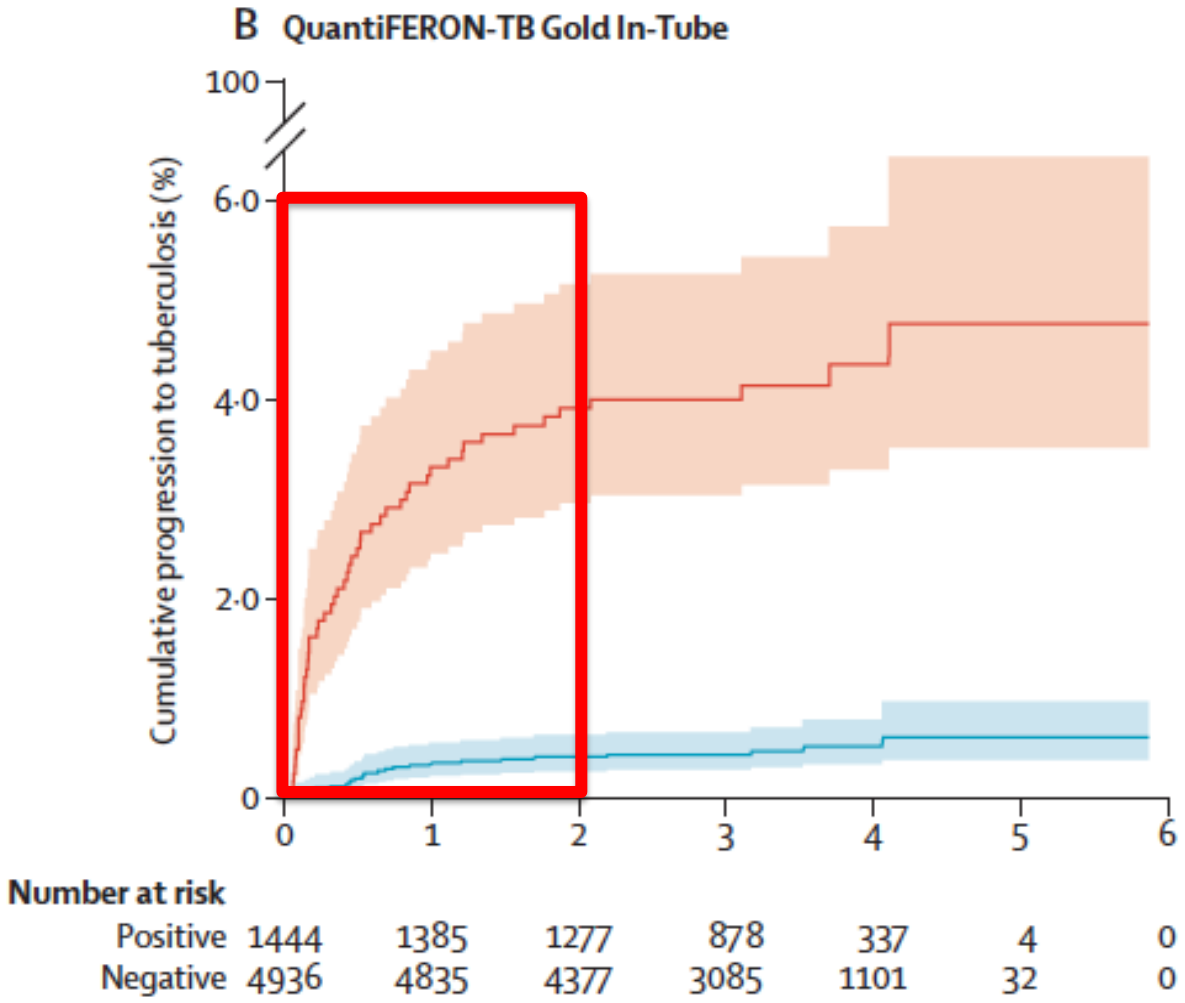
Infants	7%	*Andrews LRM 2017*
Children (5-10 yr)	28%	*Wood (TST) IJTLD 2010*
Adolescents (12-18 yr)	50%	*Mahomed IJTLD 2011*
Adults (25 yr)	75%	*Wood (TST) IJTLD 2010*
Adults (30yr)	88%	*Wood (TST) IJTLD 2010*

Wood SAMJ 2010

2 TB incidence peaks <5 and 15-55 years of age

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Abubakar Lancet ID 2018

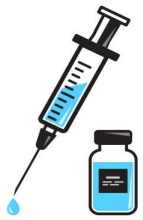
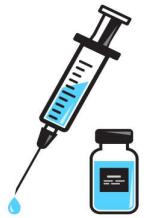
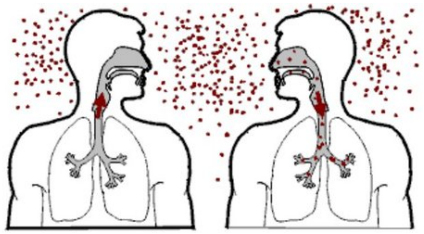


High risk of progression to TB disease
1-2 years after *M.tb* infection
(few people @ any time)

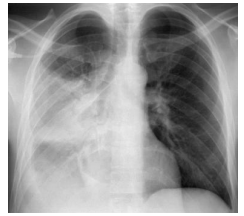
Low risk of progression to TB disease
>2 years after *M.tb* infection
(many people @ any time)

Pre-exposure Approach

Vaccinate
<u>before Mtb infection</u>
to prevent infection and/or TB disease

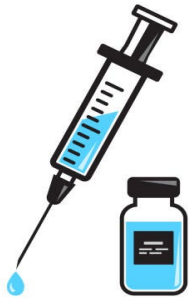
BCG → M.tb infection → TB disease

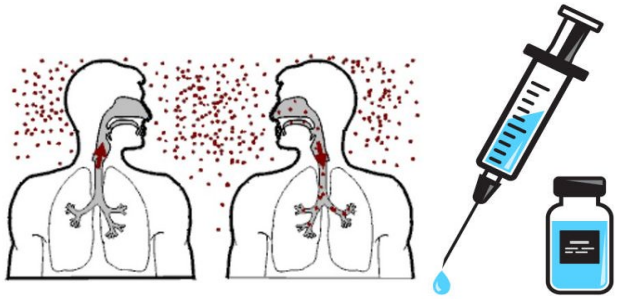


eg. Infant BCG replacement +/- heterologous boost for children, young adolescents

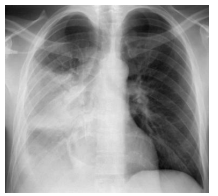
Post-exposure Approach

Vaccinate
<u>after Mtb infection</u>
to prevent TB disease





BCG → M.tb infection → TB disease



eg. subunit/killed vaccine in older adolescents and adults

Testing candidate TB vaccines for infants and children

Testing candidate TB vaccines for (older) adolescents and adults

HIV	IGRA-	IGRA+
	Infants	Adolescents
	Children	Adults

Live mycobacterial vaccines
BCG
VPM1002
MTBVAC

Subunit/killed vaccines
M72/AS01$_E$
Others

Bacille Calmette Guerin (BCG)

Benchmark comparator live mycobacterial vaccines

BCG VACCINATION AGAINST TUBERCULOSIS IN CHICAGO

A Twenty-year Study Statistically Analyzed

Sol Roy Rosenthal, M.D., Ph.D., Erhard Loewinsohn, M.D., Mary L. Graham, M.D., Dorothy Liveright, Margaret G. Thorne, and Violet Johnson, with Statistical Analysis by H. C. Batson, Ph.D.

Institution for Tuberculosis Research of the University of Illinois, the Chicago Municipal Tuberculosis Sanitarium, Research Foundation, and the Cook County Hospital, Chicago

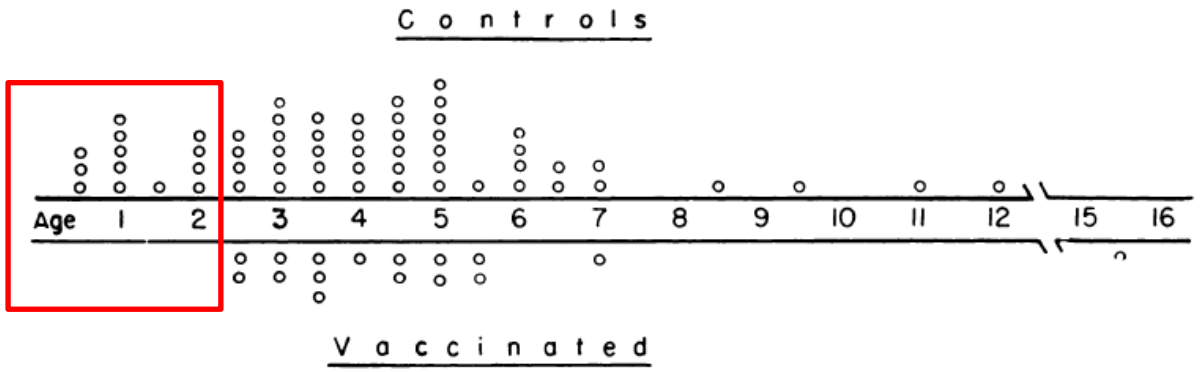
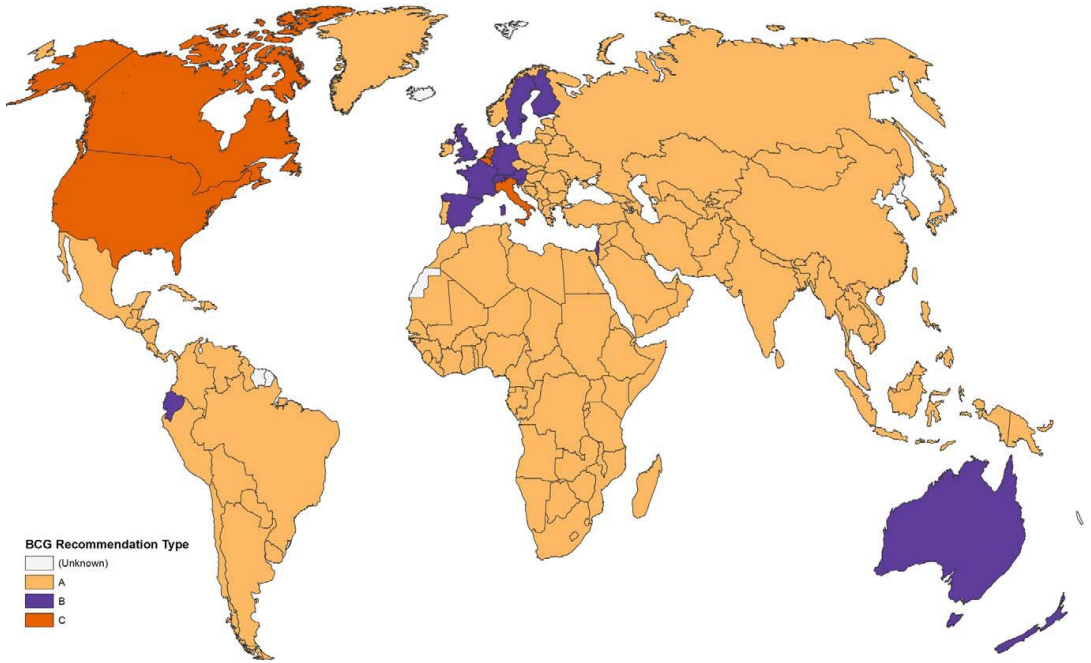


FIG. 1. Comparison of time of development of tuberculosis in the vaccinated and control groups. Each circle represents a case of nonfatal tuberculosis.



Licensed multiple countries

UNICEF cost: 10-28 US cents per dose

64% efficacy TBM

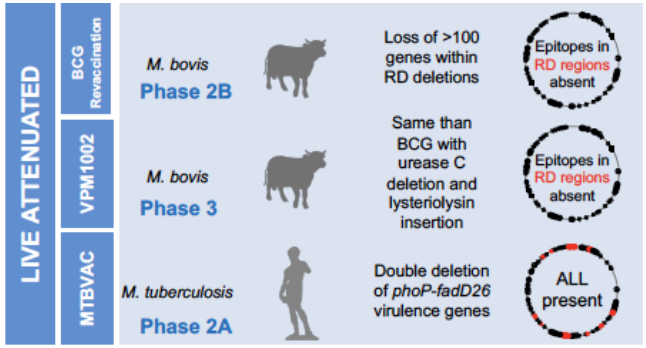
78% efficacy Disseminated TB

Colditz, Pediatrics 1995

Zwerling PLoS Medicine 2011

VPM1002

POR
POI (Infants)
POD (HHC)



Study to Test the Efficacy and Safety of Recombinant BCG Vaccine in Prevention of TB Recurrence in India (vs placebo; 2,000 Rx cured TB patients)

ClinicalTrials.gov Identifier: NCT03152903

Recruitment Status : Recruiting
First Posted : May 15, 2017
Last Update Posted : February 28, 2018

See **Contacts and Locations**

Evaluation of Efficacy and Safety of VPM1002 in Comparison to BCG in Prevention of TB Infection in Infants (vs BCG; 6,940 newborn infants, incl. HEU)

ClinicalTrials.gov Identifier: NCT04351685

Recruitment Status : Not yet recruiting
First Posted : April 17, 2020
Last Update Posted : April 17, 2020

See **Contacts and Locations**

Phase 3 POD trial VPM-1002 (vs MIP vs placebo; 12,000 household contacts >6 yr)

CTRI/2019/01/017026

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical and Vaccine Immunology®

Safety and Immunogenicity of the Recombinant *Mycobacterium bovis* BCG Vaccine VPM1002 in HIV-Unexposed Newborn Infants in South Africa

André G. Loxton,[a] Julia K. Knaul,[b] Leander Grode,[b] Andrea Gutschmidt,[a] Christiane Meller,[b] Bernd Eisele,[b] Hilary Johnstone,[c] Gian van der Spuy,[a] Jeroen Maertzdorf,[d] Stefan H. E. Kaufmann,[d] Anneke C. Hesseling,[e] Gerhard Walzl,[a] Mark F. Cotton,[f] the VPM Study Group

May be less reactogenic vs BCG in infants
Subcutaneous injection site abscess
n=5 (41%) BCG
n=4 (11%) VPM

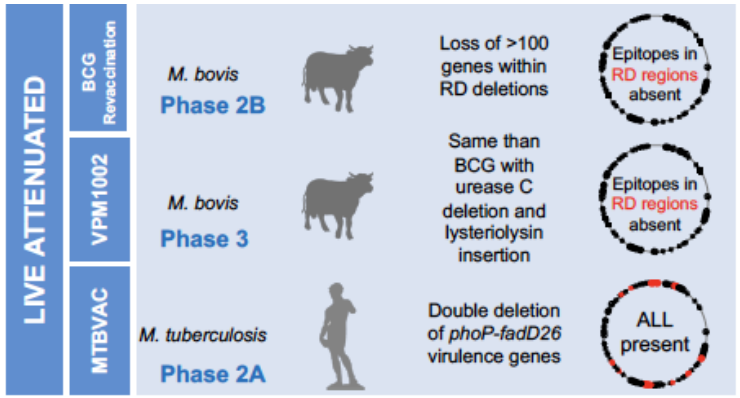
Publication of infant Phase 2 data awaited…

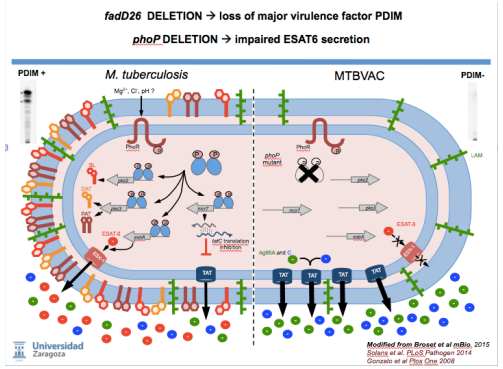
ClinicalTrials.gov Identifier: NCT02391415

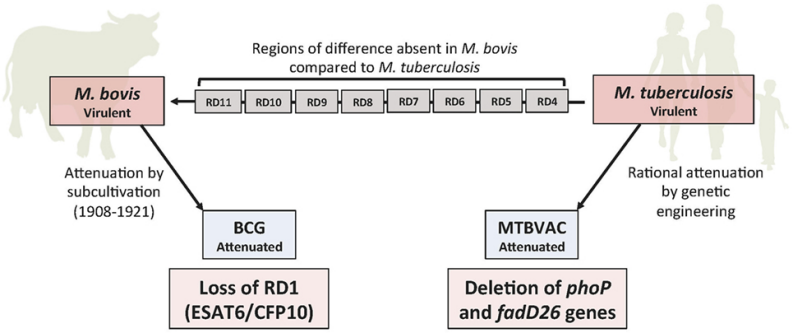
Recruitment Status : Completed
First Posted : March 18, 2015
Last Update Posted : April 18, 2018

MTBVAC

Phase 2 infants
Phase 2 adults







Dose-Defining Safety and Immunogenicity Study of MTBVAC in South African Neonates (3:1 vs BCG; n=99)

MTBVAC Study in Adults With and Without Latent Tuberculosis Infection in South Africa (2:1 vs BCG; n=144 IGRA+ IGRA-)

→ **Phase 3 infant POD trial 2022 (incl. HEU)**

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

Safety, immunogenicity, dose-escalation
18 BCG+ IGRA- adults, 36 BCG- infants
(3:1 MTBVAC vs BCG)
Well-tolerated
Dose-related IGRA conversion/reversion
Diagnosis unconfirmed TB (vs BCG/MTBVAC)

ClinicalTrials.gov Identifier: NCT03536117

Recruitment Status : Recruiting
First Posted : May 24, 2018
Last Update Posted : February 15, 2019

ClinicalTrials.gov Identifier: NCT02933281

Recruitment Status : Recruiting
First Posted : October 14, 2016
Last Update Posted : March 26, 2019

Limitations of BCG vaccine

BCG efficacy is variable
Average RR 0.5 (0.35 – 0.72)

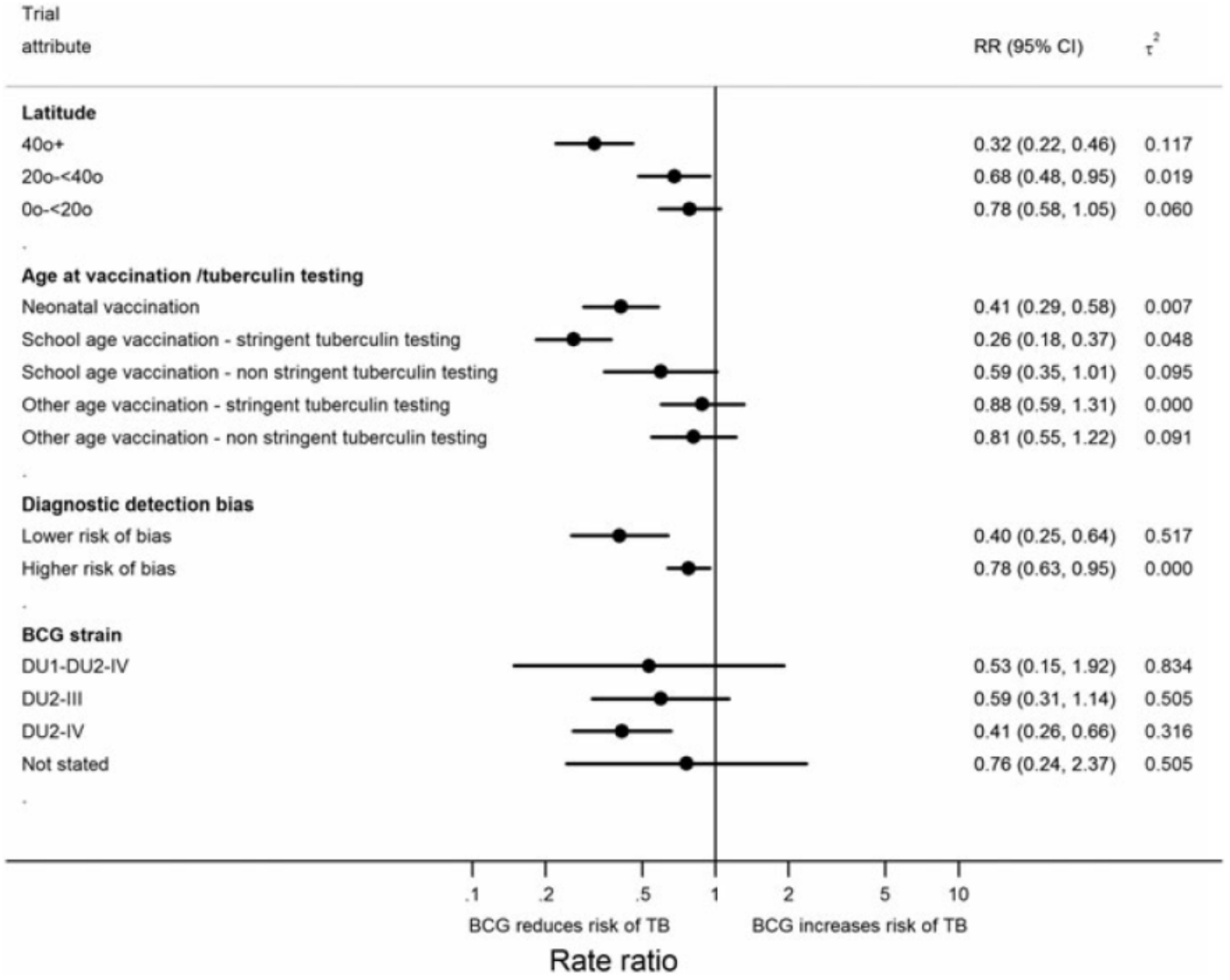
BCG protects against TB disease in infants, and Mtb-uninfected children

No significant protection in Mtb-infected and uninfected adults
Meta-analysis, Mangtani CID 2014

Implications for efficacy of BCG and new live mycobacterial vaccines in high TB burden countries where >40% adolescents/adults are Mtb-infected

Risk of disseminated BCG disease in HIV-infected infants (ART-)

Hesseling, Bulletin WHO 2009



HEALTH TECHNOLOGY ASSESSMENT
VOLUME 17 ISSUE 37 SEPTEMBER 2013
ISSN 1366-5278

BCG vaccination protects against TB for +/- 10 years

Efficacy declines over time in most studies
Some exceptions
Few studies lasted >15 years

Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis

I Abubakar, L Pimpin, C Ariti, R Beynon, P Mangtani, JAC Sterne, PEM Fine, PG Smith, M Lipman, D Elliman, JM Watson, LN Drumright, PF Whiting, E Vynnycky and LC Rodrigues

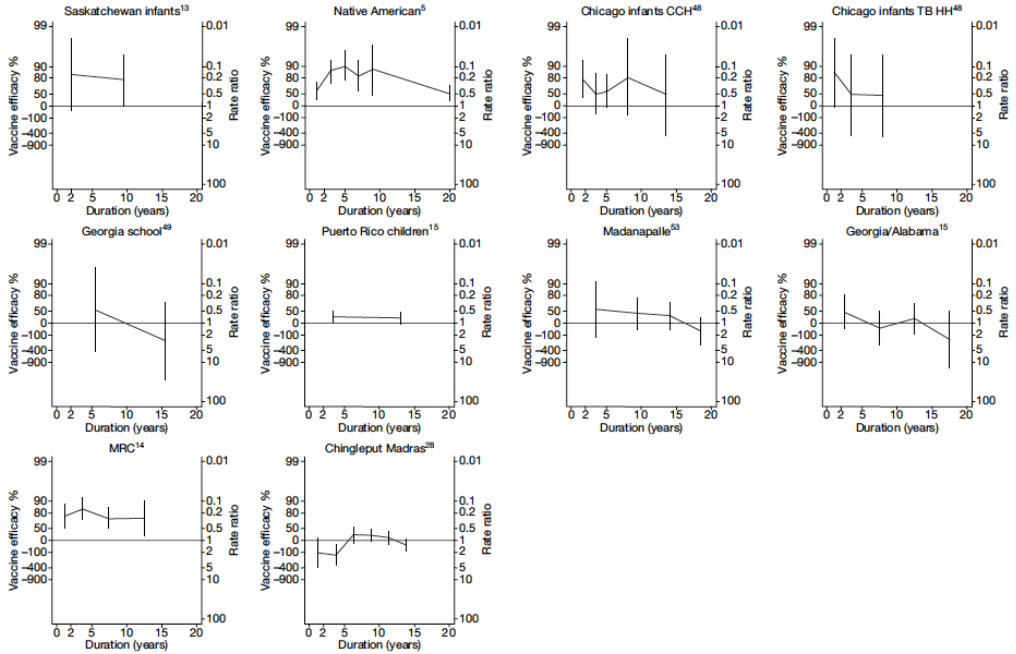
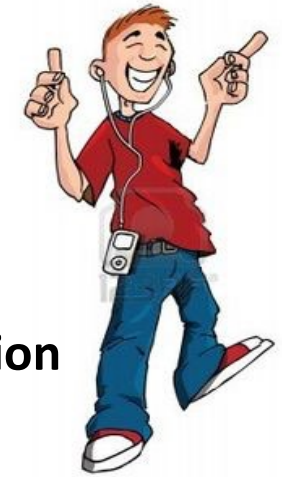


FIGURE 81 Vaccine efficacy and rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, over time. CCH, Cook County Hospital; TB HH, tuberculosis households.

Protection in first 10 years of follow-up

Trial	Rate ratio (95% CI) for effect of BCG vaccination in the first 10 years	VE (95% CI) for effect of BCG vaccination in the first 10 years
Native American[5]	0.19 (0.14 to 0.26)	81 (74 to 86)
Chicago Infants CCH[48]	0.33 (0.18 to 0.59)	67 (41 to 82)
Georgia (School)[49]	0.47 (0.04 to 5.17)	53 (–417 to 96)
Puerto Rico Children[15]	0.69 (0.50 to 0.95)	31 (5 to 50)
Georgia/Alabama[15]	0.83 (0.42 to 1.64)	17 (–64 to 58)
Madanapalle[53]	0.17 (0.04 to 0.77)	83 (23 to 96)
Chingleput[28]	1.03 (0.8 to 1.32)	–3 (–32 to 20)

BCG Revaccination (or heterologous vaccine boost) in adolescence?



THE LANCET

Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi

Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial

Laura C Rodrigues, Susan M Pereira, Sergio S Cunha, Bernd Genser, Maria Yury Ichihara, Silvana C de Brito, Miguel A Hijjar, Ines Dourado, Alvaro A Cruz, Clemax Sant'Anna, Ana Luiza Bierrenbach, Mauricio L Barreto

Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial

Mauricio L. Barreto[a,*], Susan M. Pereira[a], Daniel Pilger[b], Alvaro A. Cruz[c], Sergio S. Cunha[d], Clemax Sant'Anna[e], Maria Y. Ichihara[a], Bernd Genser[a,f], Laura C. Rodrigues[b]

No longer practiced in Eastern Europe

2 large RCT showed no efficacy of BCG revaccination

TST/IGRA status unknown

No efficacy of primary BCG in Karonga, Malawi (*Ponnighaus Lancet 1992*)

33% VE subgroup children <11 years of age in Salvador, Brazil

Can BCG Revaccination prevent TB in children who are Mtb-uninfected at vaccination?

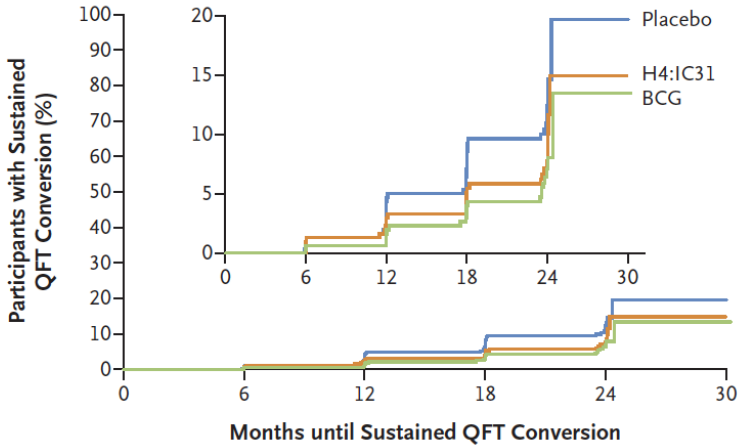
The NEW ENGLAND JOURNAL of MEDICINE

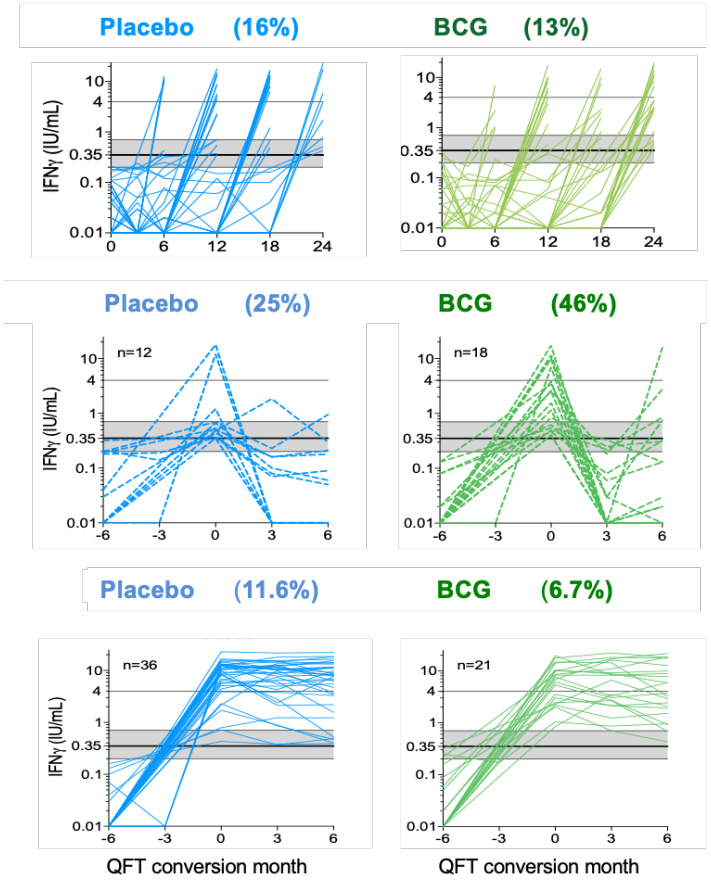
ORIGINAL ARTICLE

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 Revaccination of adolescents
45% efficacy against #2 endpoint
(sustained IGRA+ conversion)





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

N=1,800 IGRA-
Aged 10-18 yr
FU 48 months
Sustained IGRA+ conversion (QFT-Plus)

ClinicalTrials.gov Identifier: NCT04152161

Recruitment Status : Recruiting
First Posted : November 5, 2019
Last Update Posted : January 20, 2021

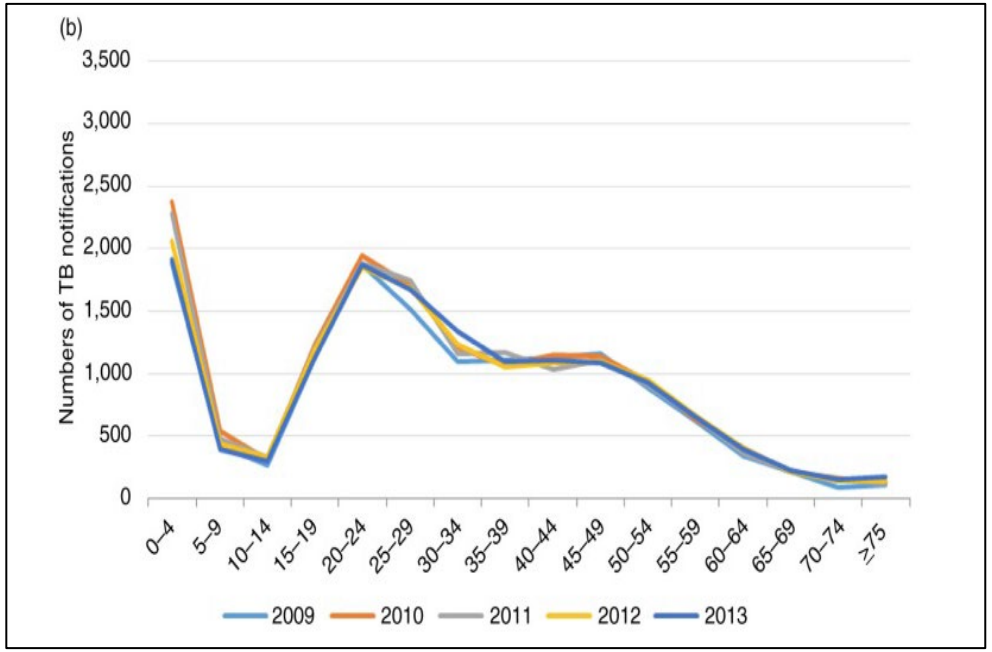
Sufficient evidence POI to test efficacy against TB disease?

Take Home Messages #1

1. **New live mycobacterial vaccines (VPM1002, MTBVAC) entering trials to replace BCG at birth include HEU infants**

2. **Some evidence suggests efficacy of BCG Revaccination against TB disease should be tested in IGRA- adolescents without HIV**
   - Target population pre-teens?
   - Large, long, costly trial
   - Bridging studies – correlate of protection
   - Include other live mycobacterial vaccines (VPM1002, MTBVAC)

3. **Inclusion of IGRA- adolescents with HIV (ART)**
   - Justified on basis of 4X risk vs HIV-
   - Theoretical risk of disseminated vaccine disease
   - Would require safety and immunogenicity data
     - BCG, live mycobacterial vaccines



Hermans and Wood, J Int AIDS Soc 2015

Frigati LJ et al. *Journal of the International AIDS Society* 2021, **24**:e25671
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25671/full | https://doi.org/10.1002/jia2.25671

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Tuberculosis infection and disease in South African adolescents with perinatally acquired HIV on antiretroviral therapy: a cohort study

Lisa J Frigati[1,2,§], Katalin A Wilkinson[3,4], Stanzi leRoux[5], Karryn Brown[5], Sheena Ruzive[3], Leah Githinji[1], Wonita Petersen[1], Sabine Belard[6,7], Mark F Cotton[2], Landon Myer[5] and Heather J Zar[1,8]

Testing candidate TB vaccines for infants and children

Testing candidate TB vaccines for (older) adolescents and adults

HIV	**IGRA-**	**IGRA+**
	Infants	Adolescents
	Children	Adults

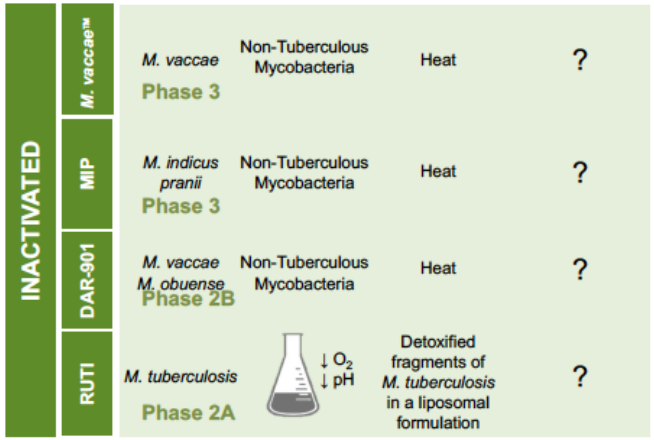
Live mycobacterial vaccines
BCG
VPM1002
MTBVAC

Subunit/killed vaccines
M72/AS01$_E$
Others

M. obuense

(SRL172)

POD



DarDar Trial (Tanzania)

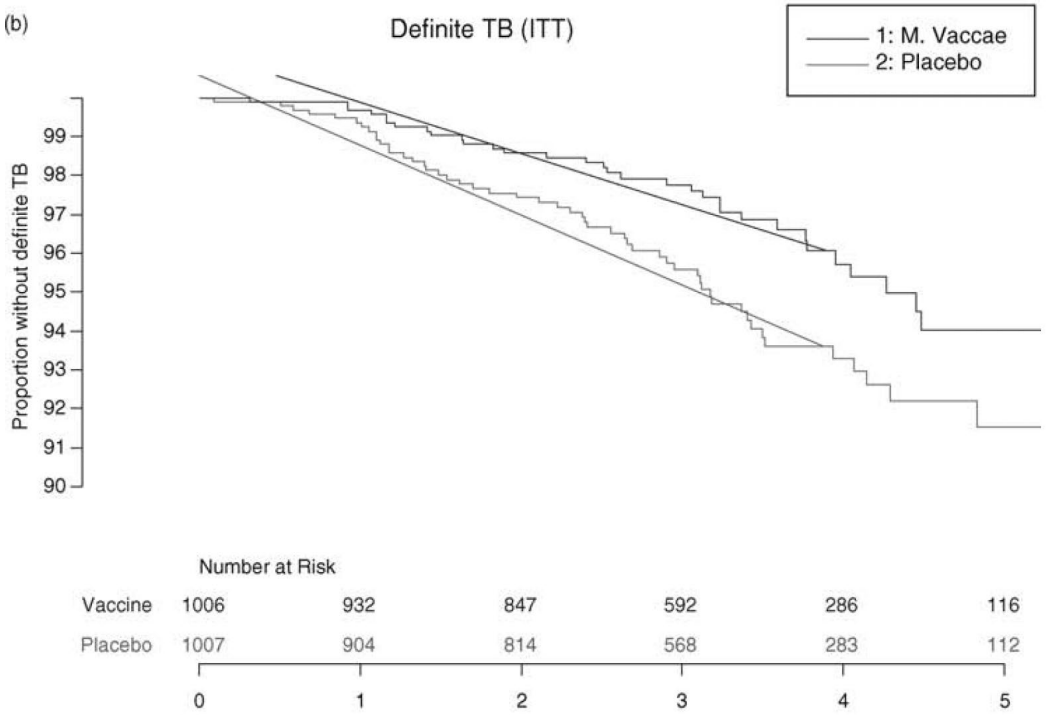
5-dose regimen *M. obuense (vaccae)* 1:1 Placebo
2,013 PLWH CD4 >200 TST+/- 2 → 28% ART
FU median 3 years

Well-tolerated, no effect CD4/VL
No efficacy Disseminated TB (#1 endpoint)
39% efficacy Definite TB (#2 endpoint)

Prevention of tuberculosis in Bacille Calmette–Guérin-primed, HIV-infected adults boosted with an inactivated whole-cell mycobacterial vaccine

Charles F. von Reyn[a], Lillian Mtei[b], Robert D. Arbeit[c], Richard Waddell[a], Bernard Cole[d], Todd Mackenzie[e], Mecky Matee[b], Muhammad Bakari[b], Susan Tvaroha[a], Lisa V. Adams[a], Charles R. Horsburgh[f], Kisali Pallangyo[b], the DarDar Study Group*

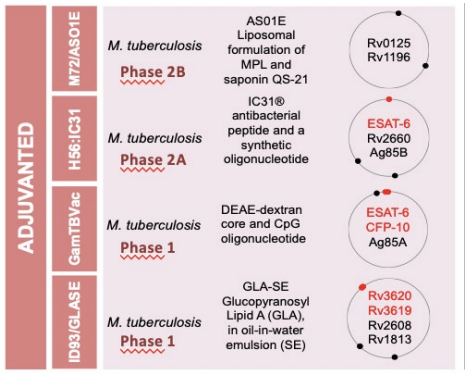
AIDS 2010, **24**:675–685

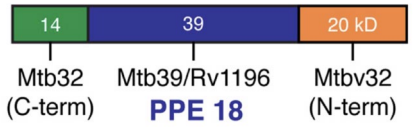


ORIGINAL ARTICLE

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



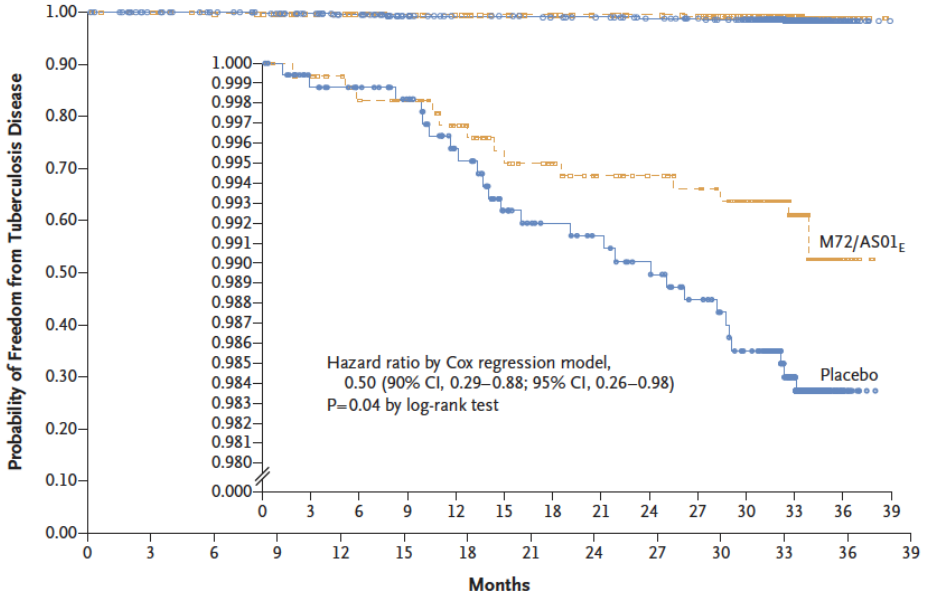


Brennan, Infection & Immunity 2017

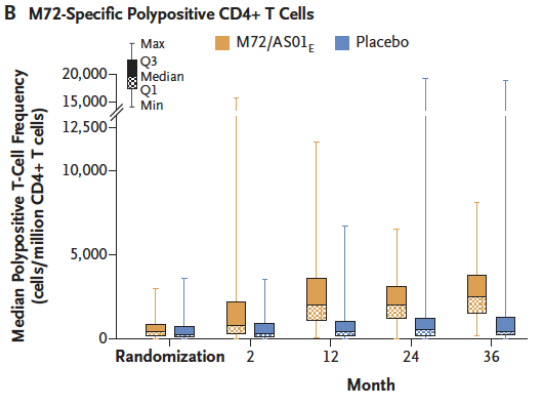
3,575 IGRA+ HIV- adults 18–50 years

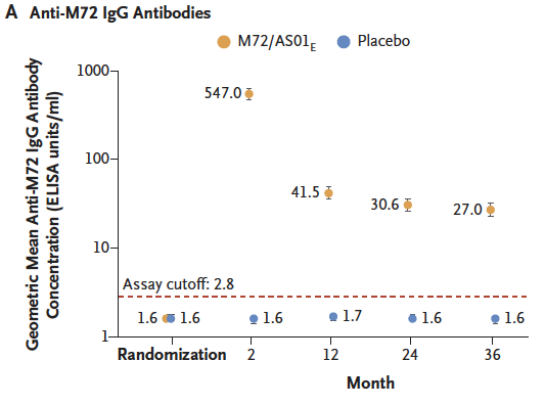
Zambia, Kenya, SA

Randomized (1:1), M72/AS01$_E$ (*M.tb* proteins 32A and 39A) or Placebo, 2 doses, 1 month apart



VE 49.7% **(95% CI 2.1 to 74.2)**





Will M72/AS01$_E$ offer protection against TB in people who are IGRA- at vaccination?

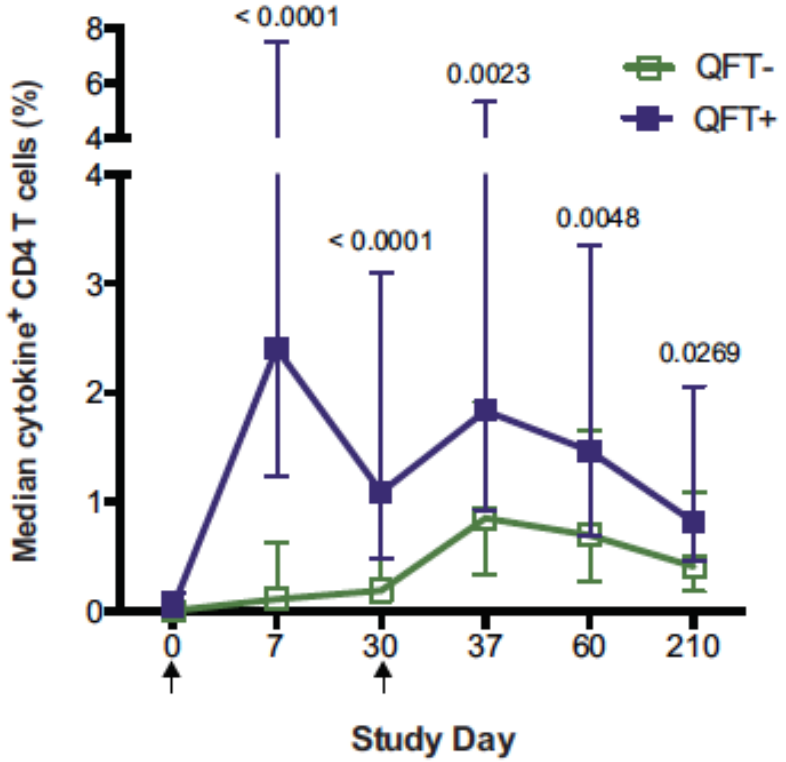
Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

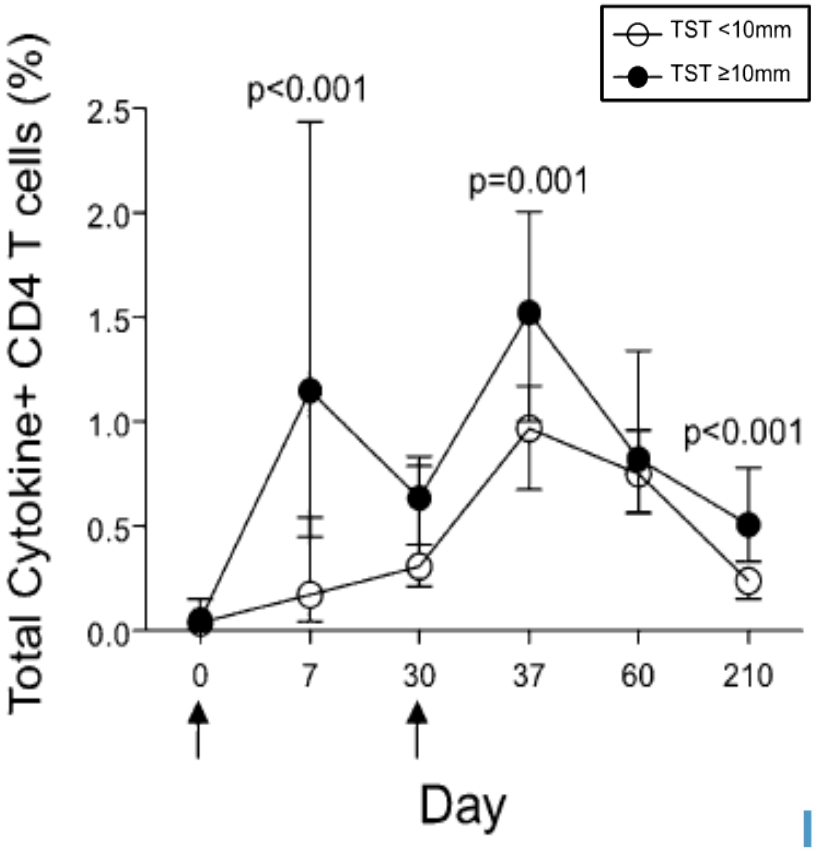
Adam Penn-Nicholson[a,*,1], Hennie Geldenhuys[a,1], Wivine Burny[b], Robbert van der Most[b], Cheryl L. Day[a,c,d], Erik Jongert[b], Philippe Moris[b], Mark Hatherill[a], Opokua Ofori-Anyinam[b,2], Willem Hanekom[a,2], the Vaccine Study Team,



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



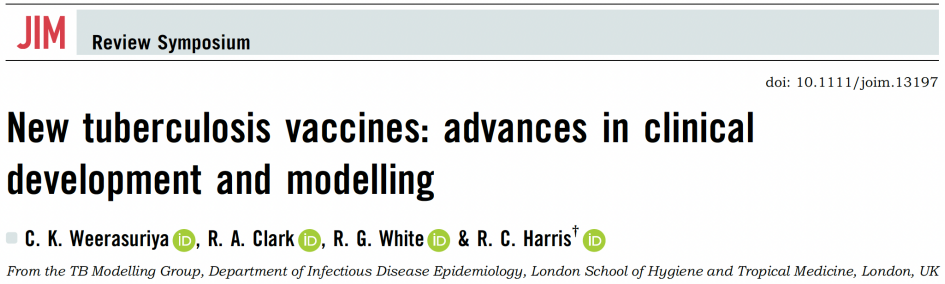
Modelling studies

Assumptions: 10-year, 70% efficacy against disease

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

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

Harris et al, Sci Transl Med 2020


JIM Review Symposium

doi: 10.1111/joim.13197

New tuberculosis vaccines: advances in clinical development and modelling

C. K. Weerasuriya, R. A. Clark, R. G. White & R. C. Harris†

From the TB Modelling Group, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

"In South Africa, where HIV prevalence is high, contraindication in HIV-positive populations was found to substantially reduce the overall epidemiologic impact of TB vaccination."

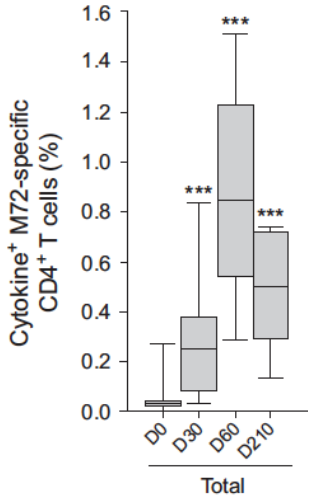
Is M72/AS01$_E$ safe and immunogenic in people with HIV?

Safety and immunogenicity of the M72/AS01 candidate tuberculosis vaccine in HIV-infected adults on combination antiretroviral therapy: a phase I/II, randomized trial

Eleonora G. Thacher[a,*], Matthias Cavassini[b,*], Régine Audran[a], Anne-Christine Thierry[a], Anne Bollaerts[c], Joe Cohen[c], Marie-Ange Demoitié[c], Dawit Ejigu[c], Pascal Mettens[c], Philippe Moris[c], Opokua Ofori-Anyinam[c,†] and François Spertini[a,†]

37 (22) HIV infected adults, Switzerland
Stable on ART, CD4 cell count >200/microL

M72/AS01 well tolerated
Polyfunctional M72-specific CD4+ T-cell response persisted through 210 days
All vaccinees seropositive for anti-M72 IgG after second vaccination to study end



A Randomized, Controlled Safety, and Immunogenicity Trial of the M72/AS01 Candidate Tuberculosis Vaccine in HIV-Positive Indian Adults

Nagalingeswaran Kumarasamy, Selvamuthu Poongulali, Anne Bollaerts, MSc, Philippe Moris, MSc, Faith Esther Beulah, MSc, Leo Njock Ayuk, Marie-Ange Demoitié, PhD, Erik Jongert, PhD and Opokua Ofori-Anyinam, PhD

240 (120) HIV uninfected and HIV infected adults, India
HIV infected cohort, ART-naïve and stable on ART

M72/AS01 well tolerated, no adverse effects on CD4 or VL
Polyfunctional M72-specific CD4+ T-cell responses and M72-specific IgG responses higher in ART-stable vs ART-naïve subjects

ClinicalTrials.gov Identifier: NCT04556981

Recruitment Status : Active, not recruiting
First Posted : September 21, 2020
Last Update Posted : December 22, 2020

ARandomized, Placebo-controlled, Observer-blind, Phase 2 Study to Evaluate Safety and Immunogenicity of the Investigational M72/AS01E Mycobacterium Tuberculosis (Mtb) Vaccine in Virally Suppressed, Antiretroviral-treated Participants With Human Immunodeficiency Virus (MESA-TB)
N=400 PLWH, 16-35 years, ART+, previous TPT+ (ongoing…)

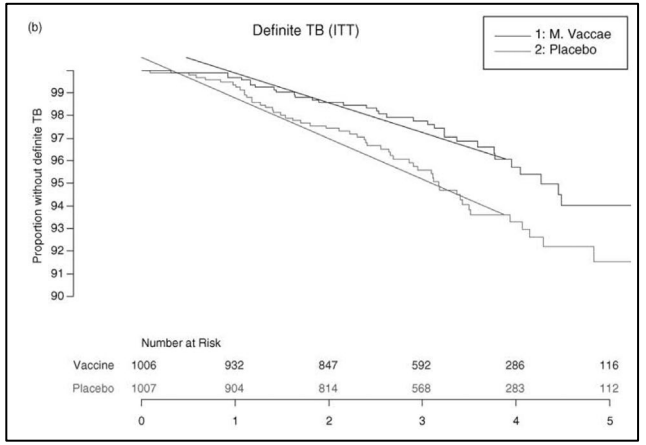
Take Home Messages #2

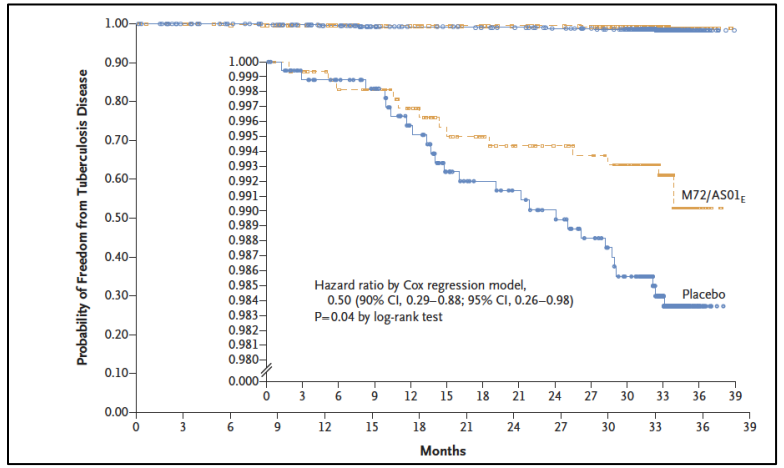
1. **Evidence that a killed/inactivated vaccine (*M. obuense*) offers protection against TB in people with HIV**

2. **Evidence of efficacy of a subunit vaccine (M72/AS01E) against TB in IGRA+ people without HIV**
   - Efficacy in IGRA- unknown
   - Lower immunogenicity (cellular) in IGRA-

3. **M72/AS01$_E$ appears safe in people with HIV**
   - Small studies, more data needed
   - Lower immunogenicity (cellular, humoral) in ART-

4. **Modelling suggests vaccination of IGRA+ populations --> greatest reduction in TB incidence by 2050**
   - Impact of vaccination of IGRA- depends on transmission setting





Challenges

Balance of risk and benefit

Avoidance of risk to children and adults with HIV vs urgent need for protection against HIV-associated TB

Enable inclusion in planned efficacy trials

Test safety, immunogenicity of live attenuated mycobacterial vaccines (rBCG, Mtb)
in infants, children and adolescents with HIV

Mitigate risks

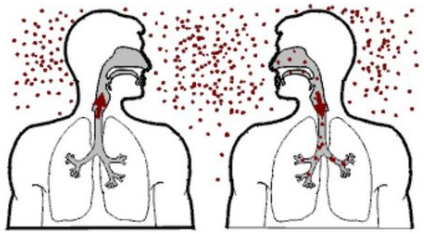
Inclusion of ART-stable - excludes highest risk group for HIV-associated TB

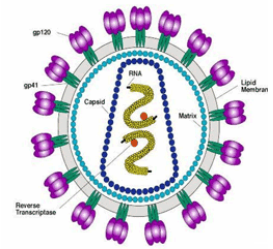
Knowledge Gaps

Model impact of TB vaccination, ART and IPT coverage, against HIV-associated TB

Demonstrate cost-effectiveness in TB/HIV endemic countries → policy

Unknowns




gp120
gp41
RNA
Capsid
Matrix
Lipid Membran
Reverse Transcriptase

Acknowledgements

040 Trial Investigators
018 Trial Investigators
BioFabri, MTBVAC team
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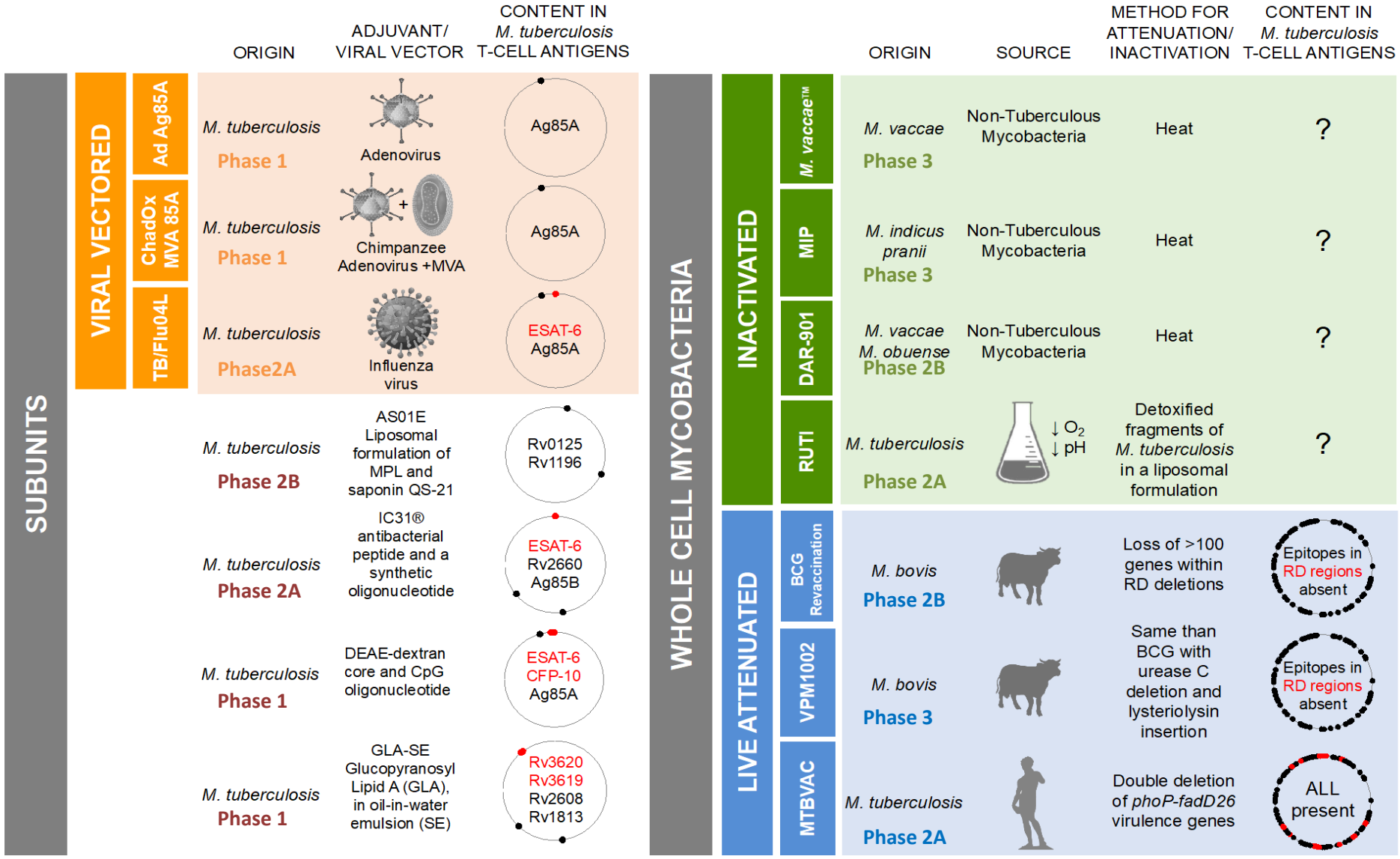
Carlos Martin, University of Zaragoza
Fordham von Reyn, Dartmouth College
Epi, Modelling and Trial Designs RC, CTVD
DAIDS Cross-network TB Vaccine Working Group
Johan Vekemans, WHO New TB Vaccine Working Group
Tom Scriba, Elisa Nemes, SATVI, University of Cape Town

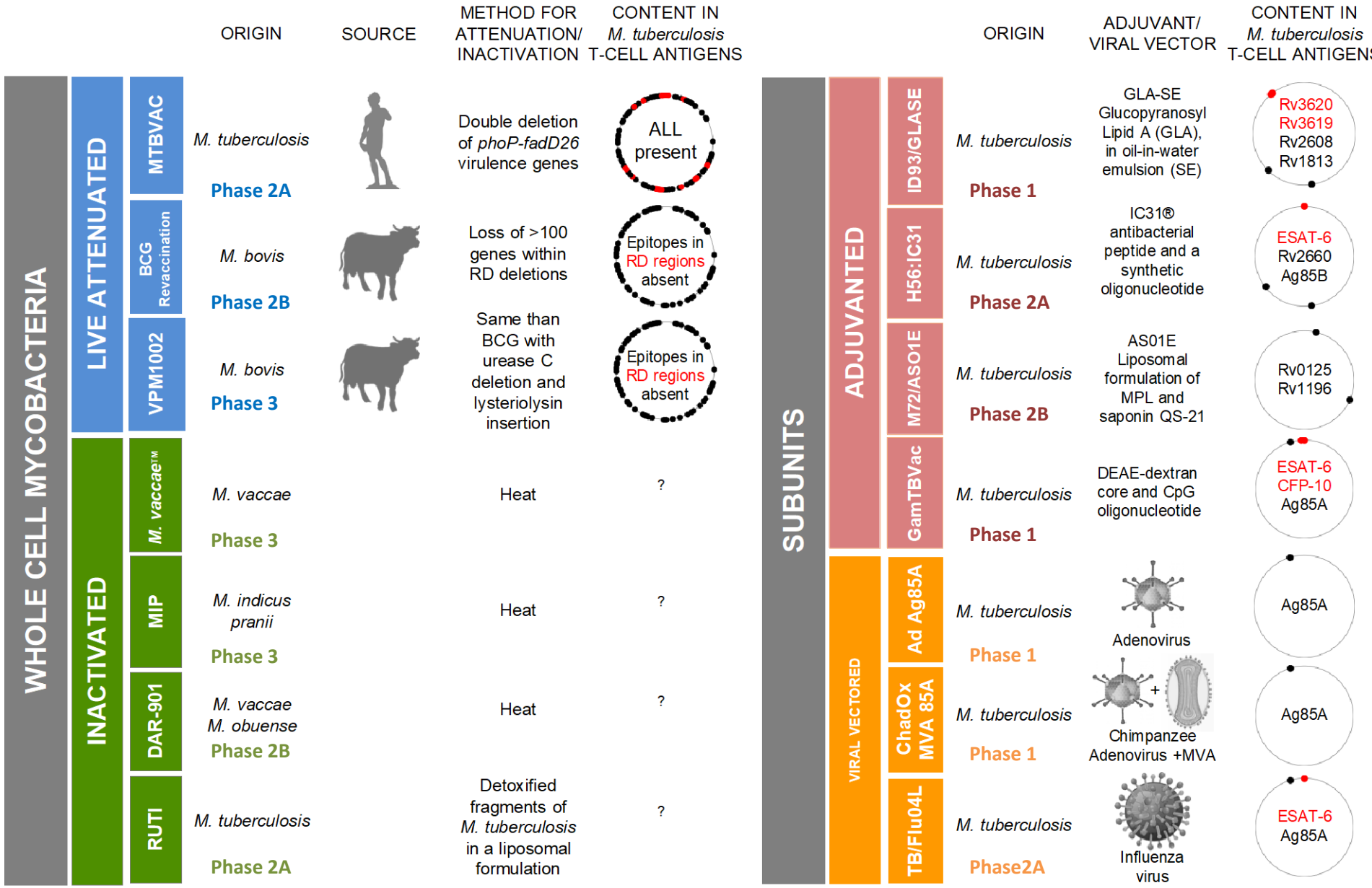
EXTRA SLIDES

DIVERSITY OF CANDIDATES IN CLINICAL TRIALS



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

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



Update on TB Vaccine Pipeline Applied Sciences April 2020