# Leveraging Early Adolescence to Prevent TB (LEAP):

# IMPAACT2035 and beyond

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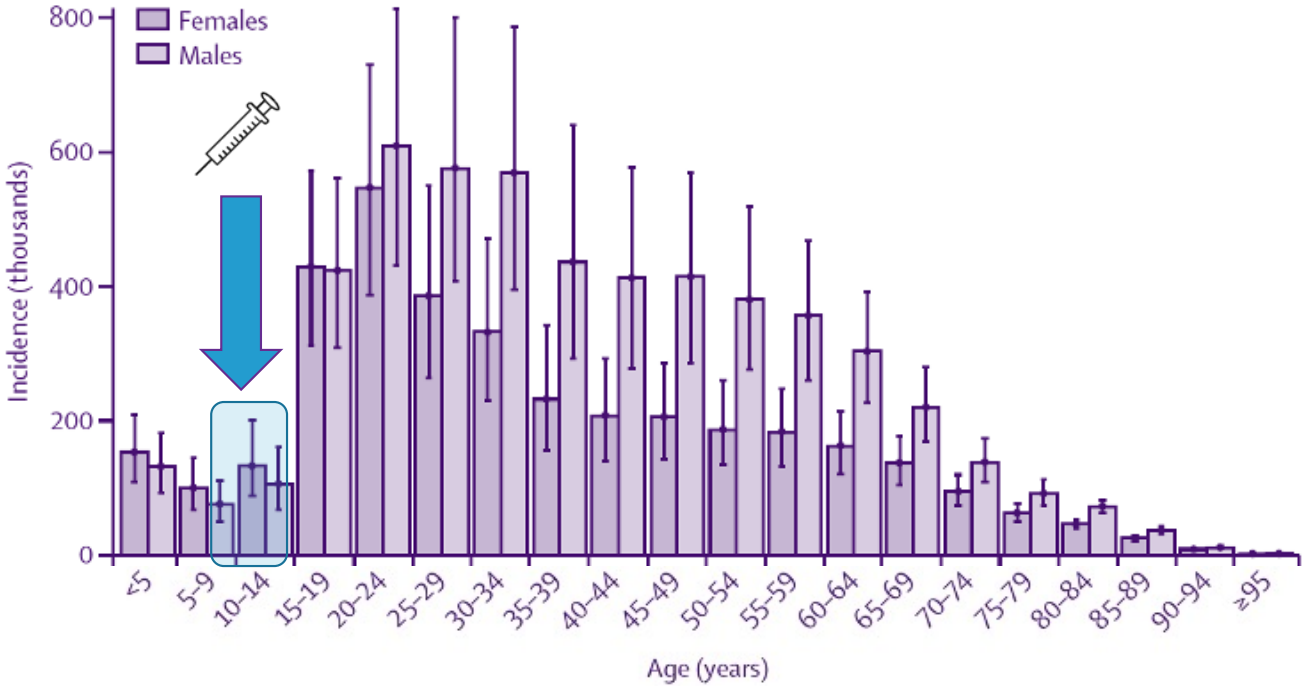
ANNUAL MEETING
2024

# Leveraging Early Adolescence to Prevent TB (LEAP)

**Window of opportunity for TB vaccination prior to ↑ TB incidence**




GBD Tuberculosis Collaborators, *Lancet Infect Dis* 2018

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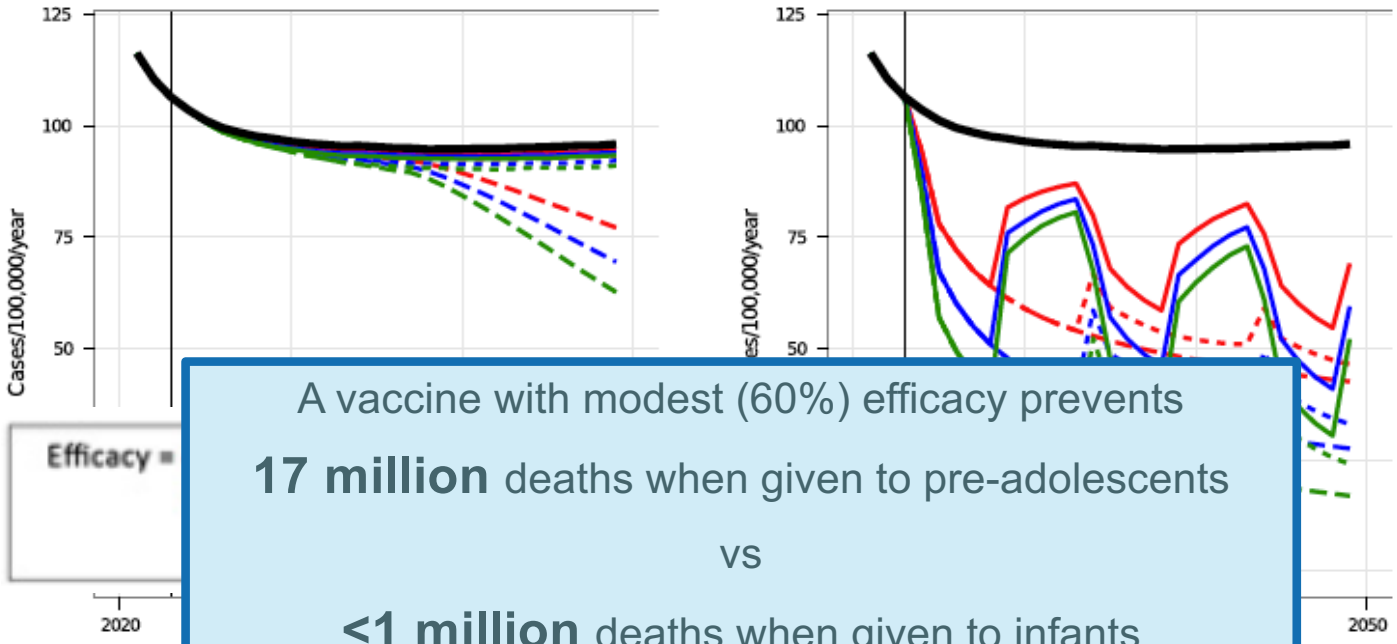
# A TB vaccine targeted to pre-adolescents has the greatest public health impact

Infants

Pre-adolescents 10y (school) +
Adolescents/adults (mass campaigns)




A vaccine with modest (60%) efficacy prevents

**17 million** deaths when given to pre-adolescents

vs

**<1 million** deaths when given to infants

*Knight PNAS 2014*

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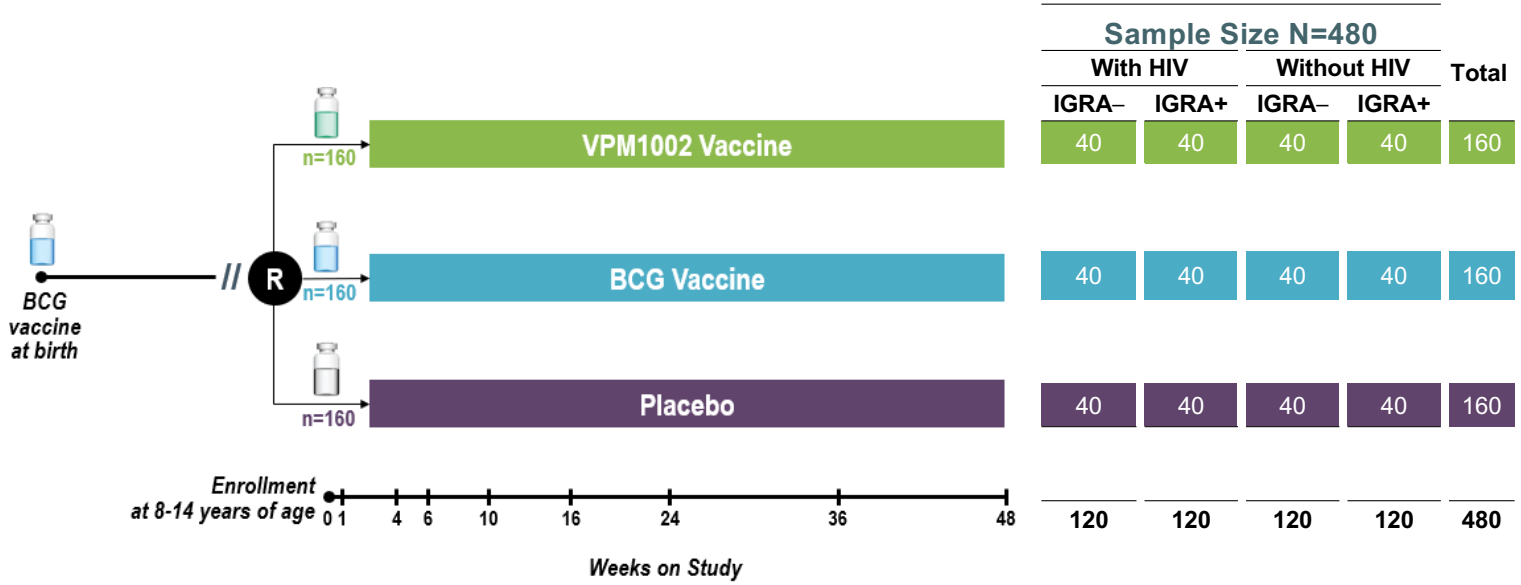
# IMPAACT2035/ HVTN604: LEAP Study

**Primary Objectives:**

1) **Safety** by HIV status
2) **Cellular immunogenicity** by HIV and *M.tb* sensitization status




- Children with HIV: CD4 >200 & virologically suppressed on ART
- 5 IMPAACT & 4 HVTN sites in South Africa

HIV VACCINE TRIALS NETWORK

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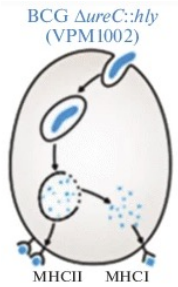
# VPM1002

- Live recombinant BCG
  - rBCGΔureC::hly
  - Listeriolysin O disrupts phagosome
  - ↑ MHC I presentation, inflammasome
- Preclinical studies:
  - Improved survival SCID mice[1]
  - No dissemination[2]
- Rapid scalability (VPM & SII)



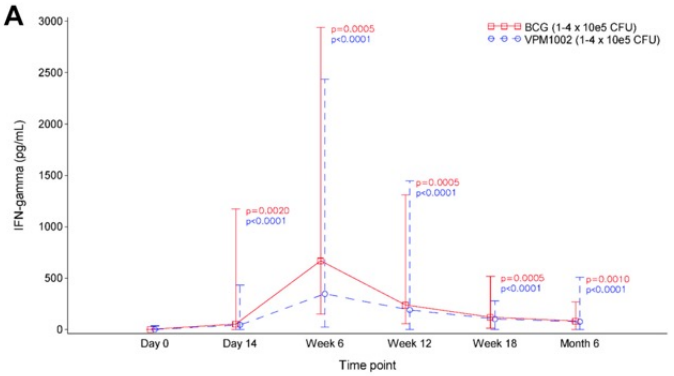

VPM
Vakzine Projekt Management GmbH

SERUM INSTITUTE OF INDIA PVT. LTD.
Cyrus Poonawalla Group

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**

- Phase 1 HIV-, IGRA- South Africa
- Newborns (no maternal HIV exposure)
- N=36 VPM vs N=12 BCG
- 2011-2012 (Sponsor VPM)




- Similar CD4 and CD8 IFN$\gamma$+ immunogenicity
- Higher magnitude IL-17 VPM vs BCG
- Lower abscess VPM (11.7%) vs BCG (47.1%)

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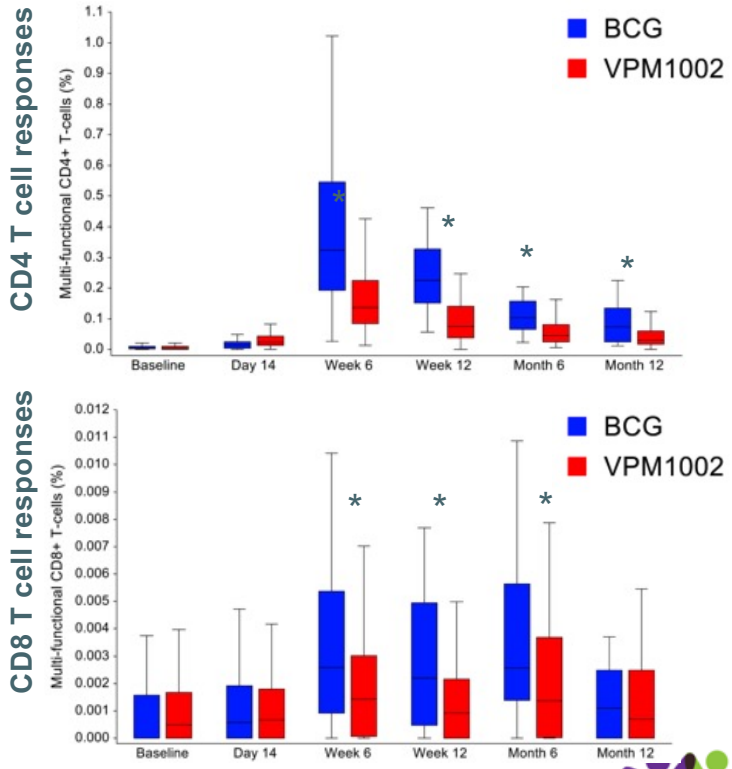
[1]Grode JI 2005; Kaufmann Exp Rev Vaccines 2104; [2]Nadolinskaia App Biochem Microbiology 2020

# VPM1002 lower reactogenicity + immunogenicity vs BCG

- Phase IIb, South African HIV-exposed and HIV-unexposed newborns (N=416 )
- VPM1002 noninferior safety vs BCG
  - ↓ grade 3-4 (*lymphadenopathy 2% vs 33%)*
- VPM1002 less reactogenic vs BCG
  - ↓ scarring *(21% vs 74%)*
  - ↓ ulceration *(1.6% vs 22%)*
  - ↓ abscess *(<1% vs 14%)*
- VPM1002 lower CD4 and CD8 immunogenicity vs BCG




Multifunctional ≥2+ IFNγ, TNF, or IL-2

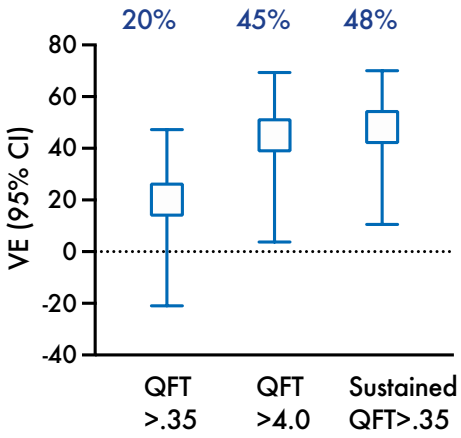
*Cotton et al. Lancet ID 2022*

# BCG Revaccination

ORIGINAL ARTICLE

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

- Phase 2 HIV-, IGRA- South Africa
- Age 12-17 years
- N=330/arm, partially-blinded
- 2014-2017 (Aeras)




sQFT>0.35: BCG (6.7%) vs. Placebo (11.6%)

KEYSTONE SYMPOSIA

**Tuberculosis: The Host-Pathogen Interface**

March 24-27, 2024 | Keystone Resort, Keystone, CO, United States
Scientific Organizers: Marcel A. Behr, Lalita Ramakrishnan and Kevin B. Urdahl

- Phase 2b HIV-, IGRA- South Africa
- Age 10-18 years
- N=900/arm, observer-blinded
- 2019-2025 (Gates MRI)

BCG revaccination did not prevent sustained QFT conversion compared to placebo over 42 weeks follow-up (7.1 vs 6.9%)

*Nemes NEJM 2018;*
*Schmidt Keystone Symposia 2024*

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# Trial Timeline

**Delayed legal negotiations**

CAP555 Submitted MAR2020 → TBSC APR2020 → SLG/EMT SEP 2020 → Approved Protocol Dev JAN 2021 → CTA Initiated APR 2021 → Protocol v1 JUL 2022 → SAHPRA Approved DEC 2022 → GMO Approved MAR 2023 → CTA Signed MAY 2024

3-year CTA delay
- indemnification
- clinical trial insurance

## Shift in Scientific Landscape

- MAR 2024: BCG Revaccination Results Presented
- MAY 2024: DAIDS recommends removal of BCG arm
- JUNE 2024: HVTN EMT recommends awaiting efficacy in VPM1002 POD/POR trials
- JULY 2024: Study closed given uncertainty of BCG/VPM1002 pathway to licensure

**Delayed Sponsor Results**

| VPM1002 Study | Start/End | Publish |
|---|---|---|
| Phase 2 infant VPM1002 vs BCG (N=48) | 2011–2012 | 2017 |
| Phase 2a infant VPM1002 vs BCG (N=416) | 2015–2017 | 2022 |
| Phase 2b/3 POI/POD infant VPM1002 vs BCG (N=6,940) | 2020–2025* (?) | |
| Phase 2b POR adults 18-65y (N=2,000) | 2017–2023 | |
| Phase 3 POD HHC 6-99 years (N=9,200) | 2019–01/2024 | |

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# *M. bovis* whole cell vaccines: a story to unfold

## BCG Revax

**POI ≠ POD**

- Phase 3 POD, India
- Household contacts, age 6-18y
- N=9,200 (BCG vs TPT)
- 2024-2027 (SII)

*NCT05330884*

- Programmatic Roll-out, India
- High-risk individuals
  - *>50 years*
  - *Underweight*
  - *Diabetes*
  - *EtOH/smoking*
- February 2024 – present (NIRT)

## VPM1002

7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

Driving innovation from discovery to access

Phase 2b POR, India
Adults 18-65y
N=2,000 (VPM1002 vs Placebo)
2019 – 2023 (SII)

*NCT03152903*

Phase 3 POD, India
Household contacts, age 6-99y
N=9,200 (VPM1002 vs MIP)
2019 – 2023 (ICMR)

*CTRI/2019/01/017026*

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# Learning from the past: whole cell vaccine efficacy modified by prior mycobacterial exposure

↓ NTM exposure/ ↓ age ↑ VE

BCG ReVAC Cluster RCT, 9y FU


**Overall VE 12% (-2-24%)**

+Prior BCG[1]:
Age <11 Salvador (↓ NTM) POD VE 33% (3-54%)
No prior BCG[2]: POD VE 25% (3-43%)

[1]Baretto Vaccine 2011; [2]Pereira Lancet ID 2012

# What other TB vaccine candidates can we evaluate?

| | | |
|---|---|---|
| Whole cell | **MTBVAC** | *(Biofabri) → await HVTN605 study pause* |
| | ~~DAR-901~~ | *No POI → not likely to move forward* |
| | ~~MIP~~ | *Pending efficacy signal for POD trial* |
| | ~~RUTI~~ | *Rx vaccine, low enthusiasm* |
| Protein Subunit | **ID93/GLA-SE** | *Study product available via DAIDS* |
| | ~~M72/AS01$_E$~~ | *(Gates): No access to study product* |
| | ~~H107/CAF10b~~ | *(SSI): pending Phase1a/1b ~2026* |
| | ~~H56/IC31~~ | *No POR; SSI halted development* |
| | ~~AEC/BC02~~ | *Unlikely study product access (China)* |
| | ~~GamTBvac~~ | *Unlikely study product access (Russia)* |
| Viral vector | ~~ChAdOx1 85A +MVA85A~~ | *Low enthusiasm* |
| mRNA | ~~BNT164a1~~ | *(BioNTech):* |
| | ~~BNT164b1~~ | *pending Phase 1~2026* |

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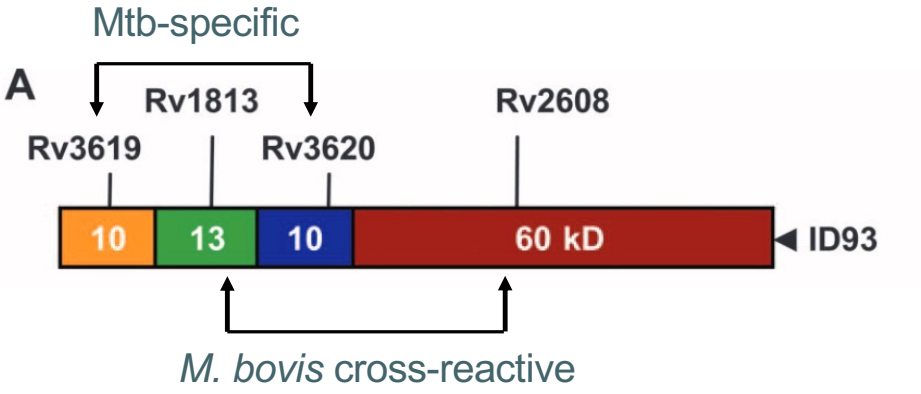
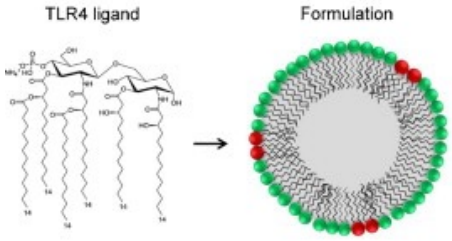
# ID93 and GLA-SE

- ID93: Four Mtb antigens
  - Virulence (3) Rv3619, Rv3620, Rv2608
  - Latency (1) Rv1813
- Synthetic oil-in-water emulson
  - **G**lucopyranosyl **L**ipid **A** **S**table **E**mulsion
  - TLR4 agonist
- Dominant Th1 response
  - ↓ Mtb CFUs after NHP challenge




Bertholet Sci Trans Med 2010; Misquith Colloids and Surfaces 2014

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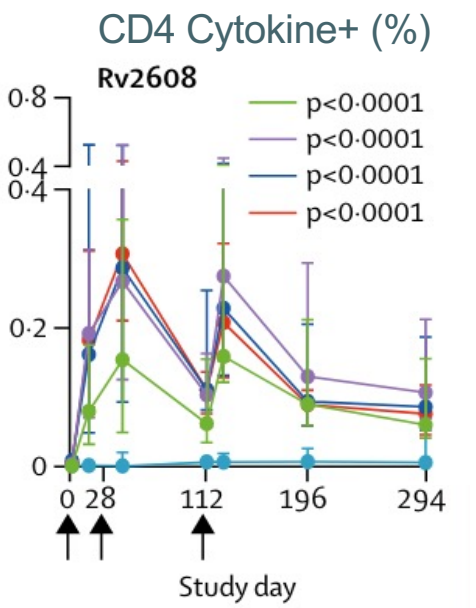
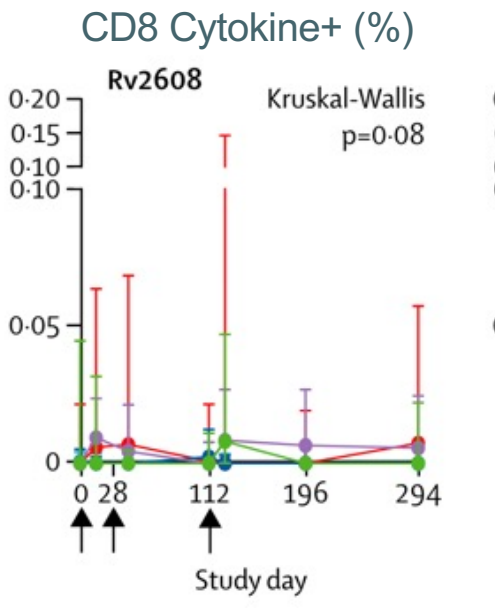
# ID93/GLA-SE is safe and elicits robust CD4 immunogenicity after 2 doses

- Phase 1 HIV-, IGRA-/+ South Africa
- Age 18-50 years
- N=66 (15/vaccine arm) Vaccine: placebo 5:1
- 3 IM doses (d0, d28, d112)
  - Dose finding x 4 cohorts
- Overall AEs Mild
- Higher injection site pain in IGRA+
  100% vs 60%, p=0..02
- Milk flu-like symptoms more frequent in IGRA+ vs IGRA-
- Robust CD4 immunogenicity, poor induction of CD8 responses
  - Peak CD4 immunogenicity by dose 2
- Higher polyfunctional CD4 responses in IGRA+ vs IGRA-

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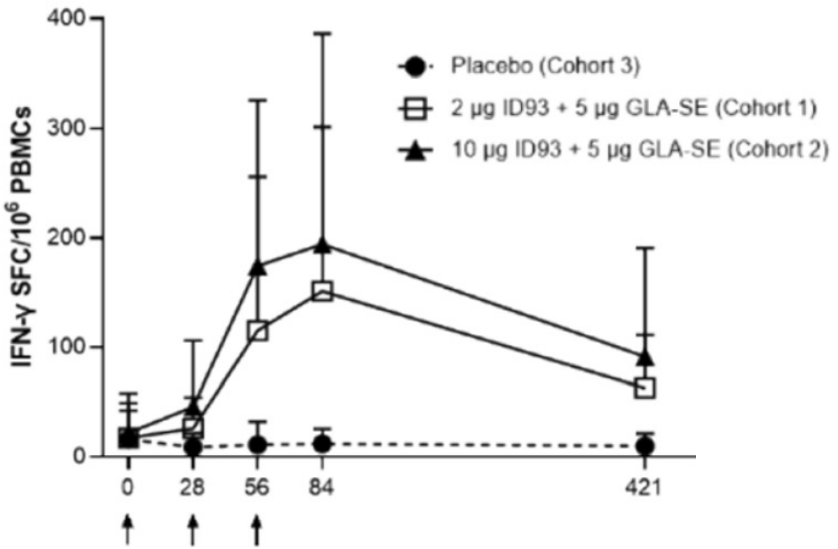
# ID93/GLA-SE peak immunogenicity after 3 doses in South Korea

- Phase 2a, South Korea
- Age 19-64 years, HIV-/IGRA- healthcare workers
- N=107
- 3 IM doses (d0, d28, d56)

- All AEs 51/91 (48%), most mild
- Severe AEs 3/107 (3%), all unrelated
- Vaccine-related:
  - AEs 26/107 (24%)
  - SAEs: 0/107 (0%)
    - Dyspepsia 4/107 (4%)
    - Nasopharyngitis 3/107 (3%)
    - Headache 2/107 (2%)

Phase 2b/3, SE Asia (Quratis) QTP101
Age 14-45 years (3 doses)
N=9,000
2025 – 2029 (?)




Choi Infect Dis Ther 2023

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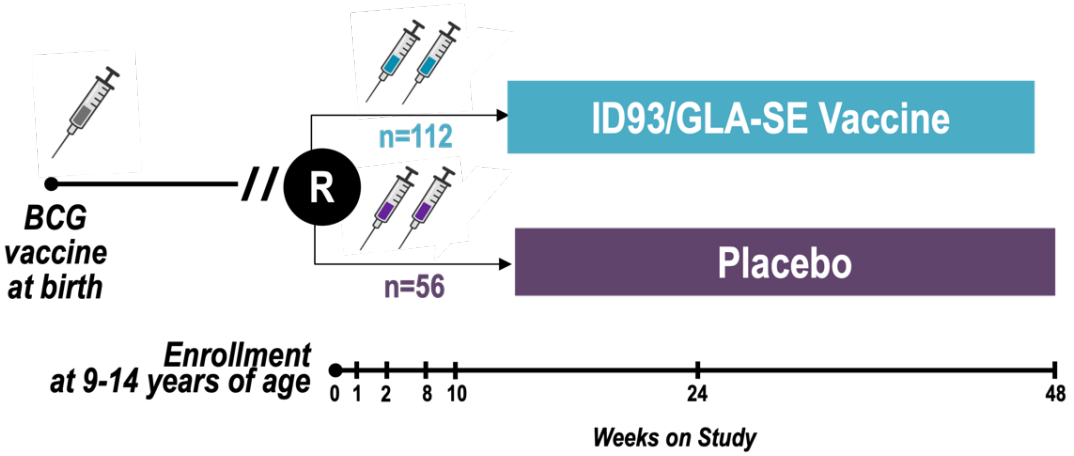
# LEAP-2: Proposed Study Design




| Study Product | Living with HIV | | Living Without HIV | |
|---|---|---|---|---|
| | IGRA+ | IGRA- | IGRA+ | IGRA- |
| ID93/GLA-SE | 28 | 28 | 28 | 28 |
| Placebo | 14 | 14 | 14 | 14 |

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# Proposed Study Objectives

**Primary Objectives:**

**1) Safety** (overall)

**2) Cellular immunogenicity (wk 10)**
by HIV and *M.tb* sensitization

**Secondary Objectives:**

**1) Cellular immunogenicity (wk 48)**
by HIV and *M.tb* sensitization

**2) Humoral immunogenicity**
by HIV and M.tb sensitization

**3) Safety** by HIV+/- and M.tb sensitization +/-

| Vaccine Arm | Placebo Arm | Placebo Arm Adverse Event Rate | 80% Power | |
|---|---|---|---|---|
| | | | Minimum Detectable Adverse Event Rate Vaccine Arm | Minimum Detectable Difference (Vaccine − Placebo) |
| 28 | 14 | 1.0% | 37.2% | 36.2% |
| | | 2.5% | 41.3% | 38.8% |
| | | 5.0% | 46.8% | 41.8% |
| | | 7.5% | 50.7% | 43.2% |
| | | 10.0% | 54.0% | 44.0% |
| 56 | 28 | **1.0%** | **22.9%** | **21.9%** |
| | | 2.5% | 26.2% | 23.7% |
| | | 5.0% | 30.8% | 25.8% |
| | | 7.5% | 35.3% | 27.8% |
| | | 10.0% | 39.2% | 29.2% |
| 112 | 56 | **1.0%** | **13.2%** | **12.2%** |
| | | 2.5% | 16.7% | 14.2% |
| | | 5.0% | 21.3% | 16.3% |
| | | 7.5% | 25.4% | 17.9% |
| | | 10.0% | 29.0% | 19.0% |

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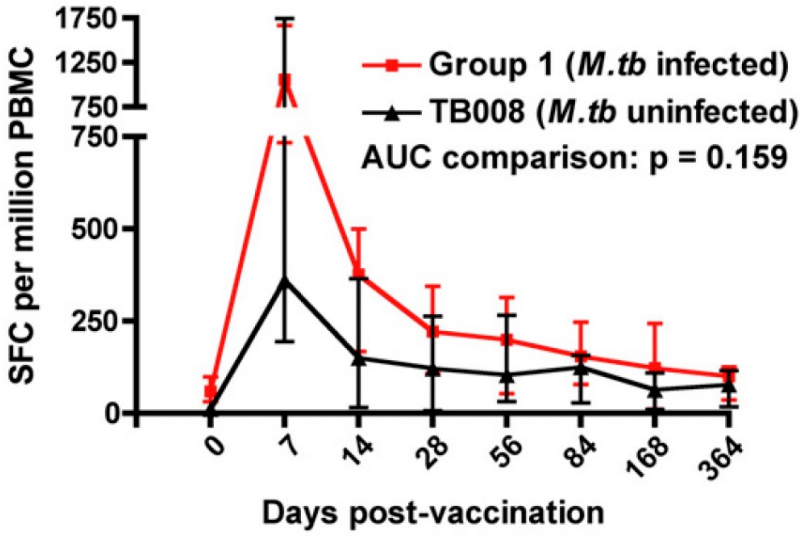
# Differences in Immunogenicity by IGRA status

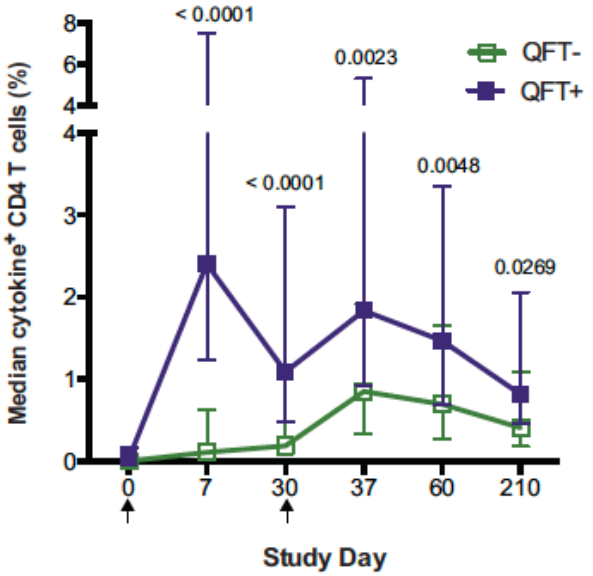
**A Phase IIa Trial of the New Tuberculosis Vaccine, MVA85A, in HIV- and/or *Mycobacterium tuberculosis*–infected Adults**

Thomas J. Scriba[1*], Michele Tameris[1*], Erica Smit[1], Linda van der Merwe[1], E. Jane Hughes[1], Blessing Kadira[1], Katya Mauff[2], Sizulu Moyo[1], Nathaniel Brittain[3], Alison Lawrie[3], Humphrey Mulenga[1], Marwou de Kock[1], Lebohang Makhethe[1], Esme Janse van Rensburg[1], Sebastian Gelderbloem[4], Ashley Veldsman[1], Mark Hatherill[1], Hendrik Geldenhuys[1], Adrian V. S. Hill[3], Anthony Hawkridge[1], Gregory D. Hussey[1], Willem A. Hanekom[1], Helen McShane[3†], and Hassan Mahomed[1†]




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,

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# Differences in Immunogenicity by HIV status

**Long-term safety and immunogenicity of the M72/AS01$_E$ candidate tuberculosis vaccine in HIV-positive and -negative Indian adults**

**Results from a phase II randomized controlled trial**

Nagalingeswaran Kumarasamy, MBBS, PhD[a], Selvamuthu Poongulali, MBBS, DGO[a], Faith Esther Beulah, MSc[a], Elaine Jacqueline Akite, MSc[b], Leo Njock Ayuk, MD[b], Anne Bollaerts, MSc[b], Marie-Ange Demoitié, MSc[b], Erik Jongert, PhD[b], Opokua Ofori-Anyinam, PhD[b], Olivier Van Der Meeren, MD[b,*]

- Overall sustained M72-specific polyfunctional CD4 immunogenicity over 3 years follow-up
- Lower CD4 immunogenicity in ART-naïve vs HIV+ART+

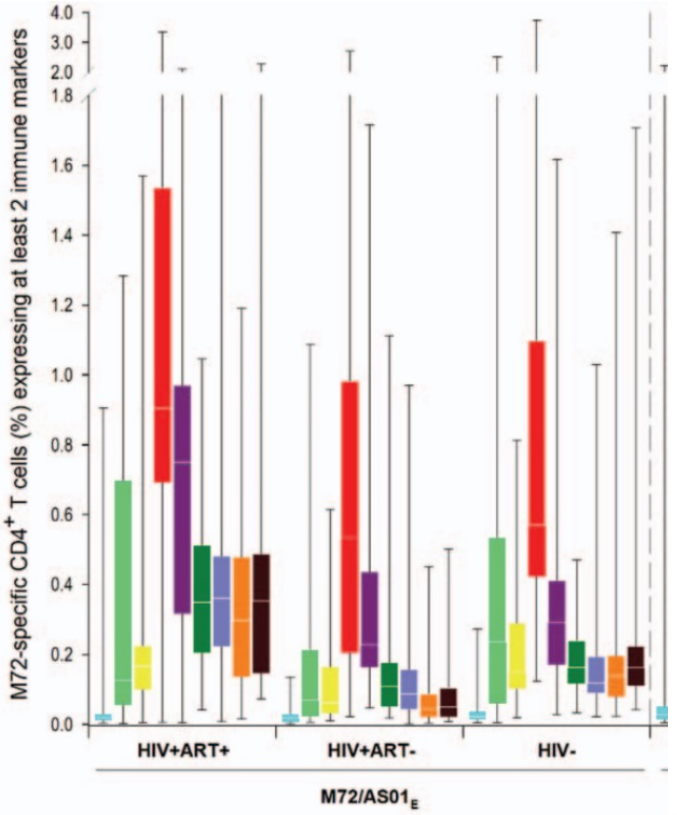
Await immunogenicity findings by HIV status:

**MESA Trial (M72)**

- No difference M72-specific IgG/CD4 HIV+ vs HIV-

*(Kahn IUATLD 2023)*

**HVTN605 (MTBVAC)**




| | Wilcoxon rank-sum test p-value | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | D7 | D30 | D37 | D60 | M7 | Y1 | Y2 | Y3 |
| HIV+ART+ vs HIV+ART- | 0.233 | 0.096 | 0.012 | 0.015 | 0.004 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| HIV+ART+ vs HIV- | 0.744 | 0.615 | 0.911 | 0.119 | 0.002 | <0.0001 | 0.001 | 0.002 | 0.001 |
| HIV+ART- vs HIV- | 0.169 | 0.036 | 0.015 | 0.340 | 0.761 | 0.036 | 0.025 | 0.000 | <0.0001 |

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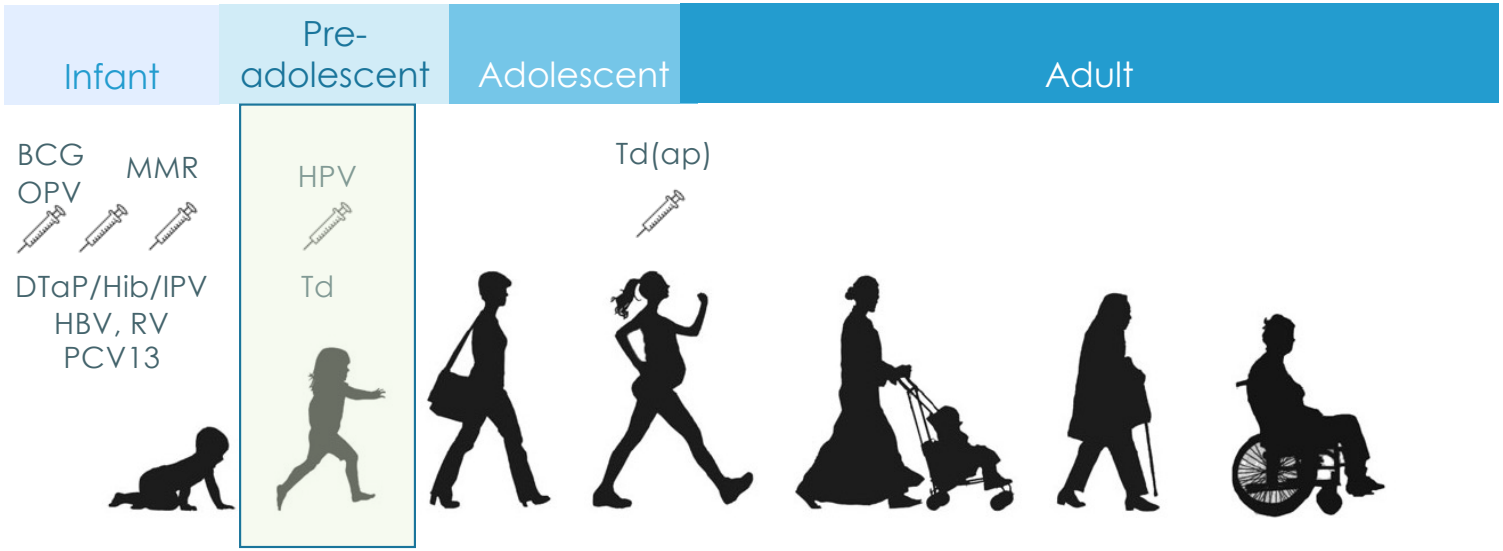
# Optimizing Timing of TB Vaccine for **Roll-Out**




9-14 years

**GAP**: No other trials include this age group with sufficient sample size to assess safety/immunogenicity (overall), or by HIV/IGRA status

HVTN605
Age 12-14
N=26

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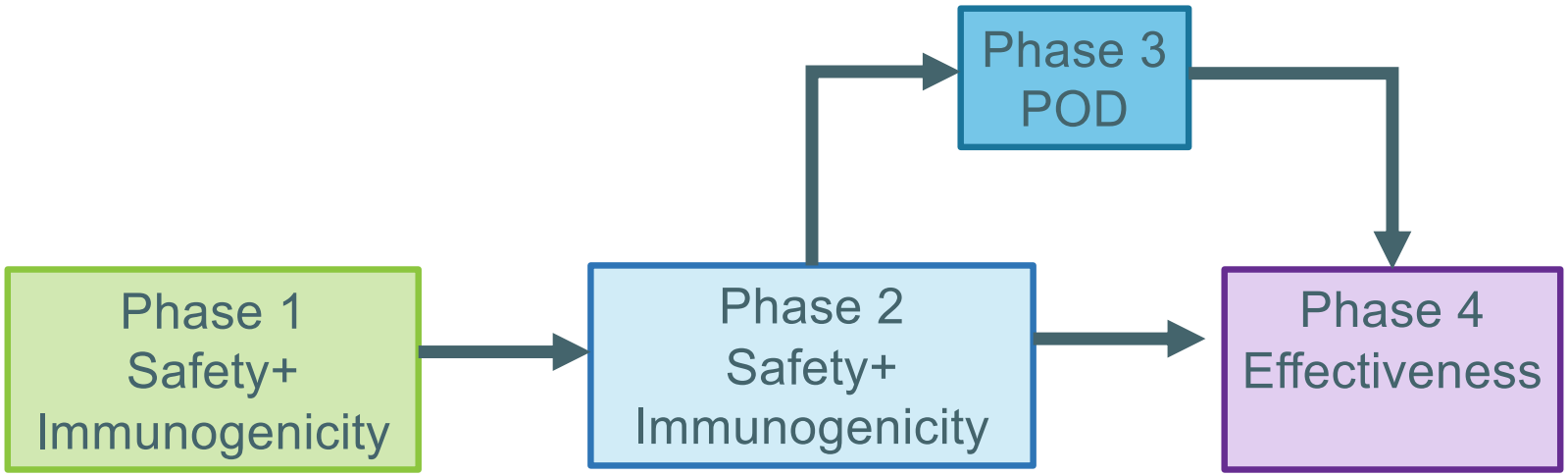
# Pre-licensure phase 2 studies are critical to avoid delayed vaccine roll-out in school age children




Licensure/policy gatekeeper: what N is enough?

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# Accelerating **impact** of new TB Vaccines for Children and PLWP with HIV




Concurrent Phase 2a Candidates in Phase 2b/3

Advance Phase 1→ 2 Candidates

(Sponsor-dependent)

# Thank You

The **ENTIRE**
IMPAACT2035/HVTN604 Study Team

EMORY • Children's • GT
Pediatric Research Alliance

EMORY UNIVERSITY SCHOOL OF MEDICINE

EMORY VACCINE CENTER
Where Science Meets Hope

National Institute of Allergy and Infectious Diseases
K23AI143479

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development
K12HD000850

HIV VACCINE TRIALS NETWORK

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CCIV
Center for Childhood Infections & Vaccines

CFAR

Georgia CTSA

PeRSEVERE Grant
UL1-TR002378

DORIS DUKE CHARITABLE FOUNDATION

# Thank You


*Photo credit: PATH*

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National Institute of Child Health & Human Development

K23AI143479

K12HD000850

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# Additional Reference Slides



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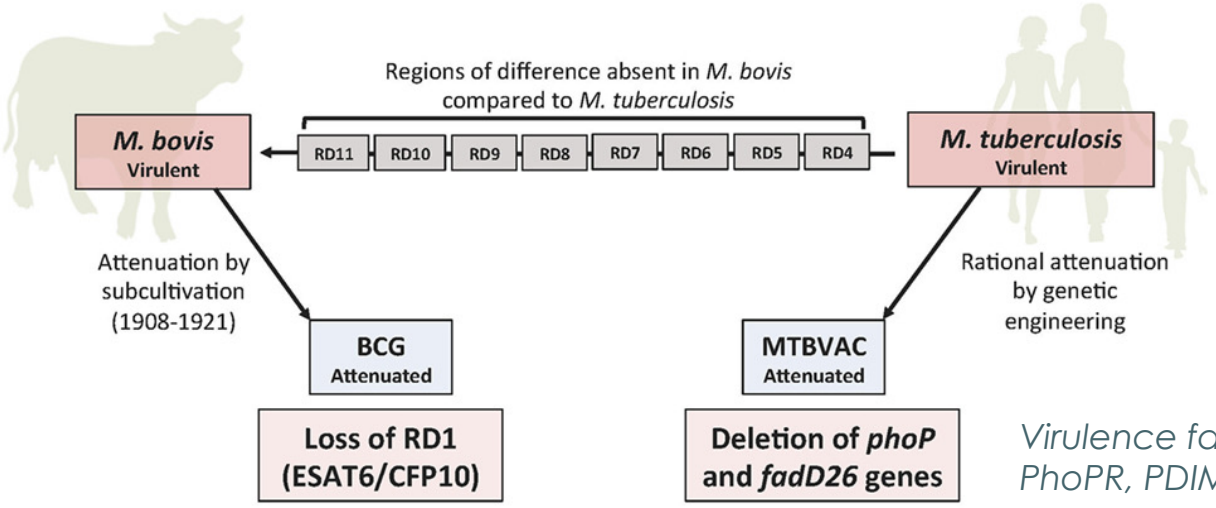
# MTBVAC




*Virulence factors: PhoPR, PDIM*

- MTBVAC retains ~25% Mtb T cell epitopes absent in BCG
- Preclinical mouse studies: survival in SCID; ↑ protection vs BCG

BIOFABRI Universidad Zaragoza

*Arbues Vaccine 2013* *Gonzalo-Asensio Front Immunol 2017*

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# MTBVAC safe and elicits high CD4 responses in infants

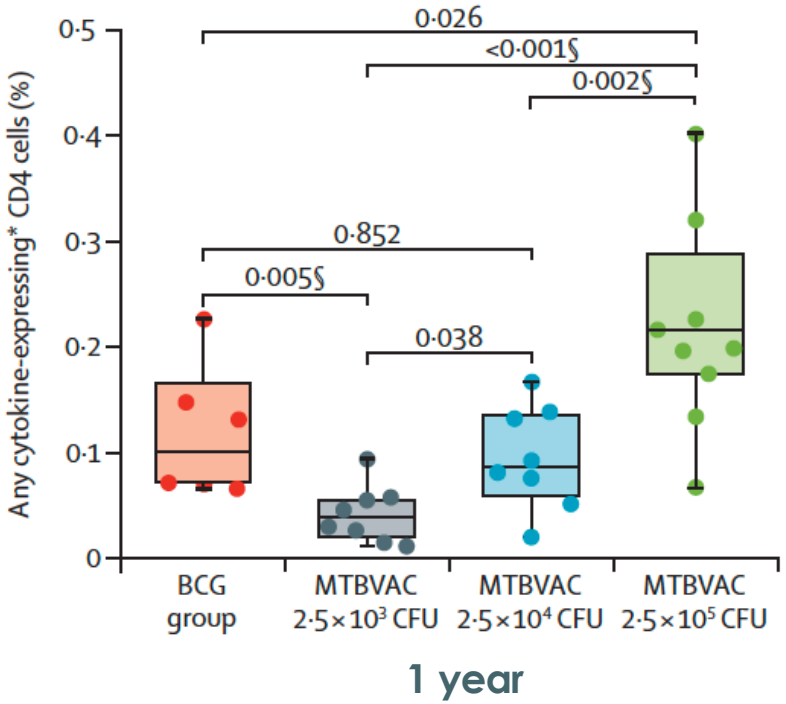
- Phase I South African infants (N=36)

- No related SAEs (1 death MTBVAC)
- Similar reactogenicity MTBVAC vs BCG
- Higher CD4 responses up to 1 year MTBVAC vs BCG
- IGRA conversion in MTBVAC recipients
  - dose-related *[7/9 (78%) high-dose]*

- Phase 3 POD(Biofabri)
- N=7,120 infants, South Africa
- 2022 - 2029 *(NCT04975178)*

- Phase 2a (DAIDS, HVTN605)
- Age 12-45
- N=276 HIV+/-, IGRA+/- , South Africa
- 2024-2025 *(NCT05947890)*

- Phase 2b/3 (Biofabri/IAVI)
- Age 14-45, IGRA+
- N=4,300 HIV-, IGRA+
- 2025 (?)-2028 *(NCT06272812)*




*Tameris & Mearns et al, Lancet Respir Med 2019*

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