

The TB Vaccine Landscape: *Accelerating Impact*

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IMPAACT

International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

ANNUAL MEETING
2024

Roadmap



Describe the current TB vaccine landscape

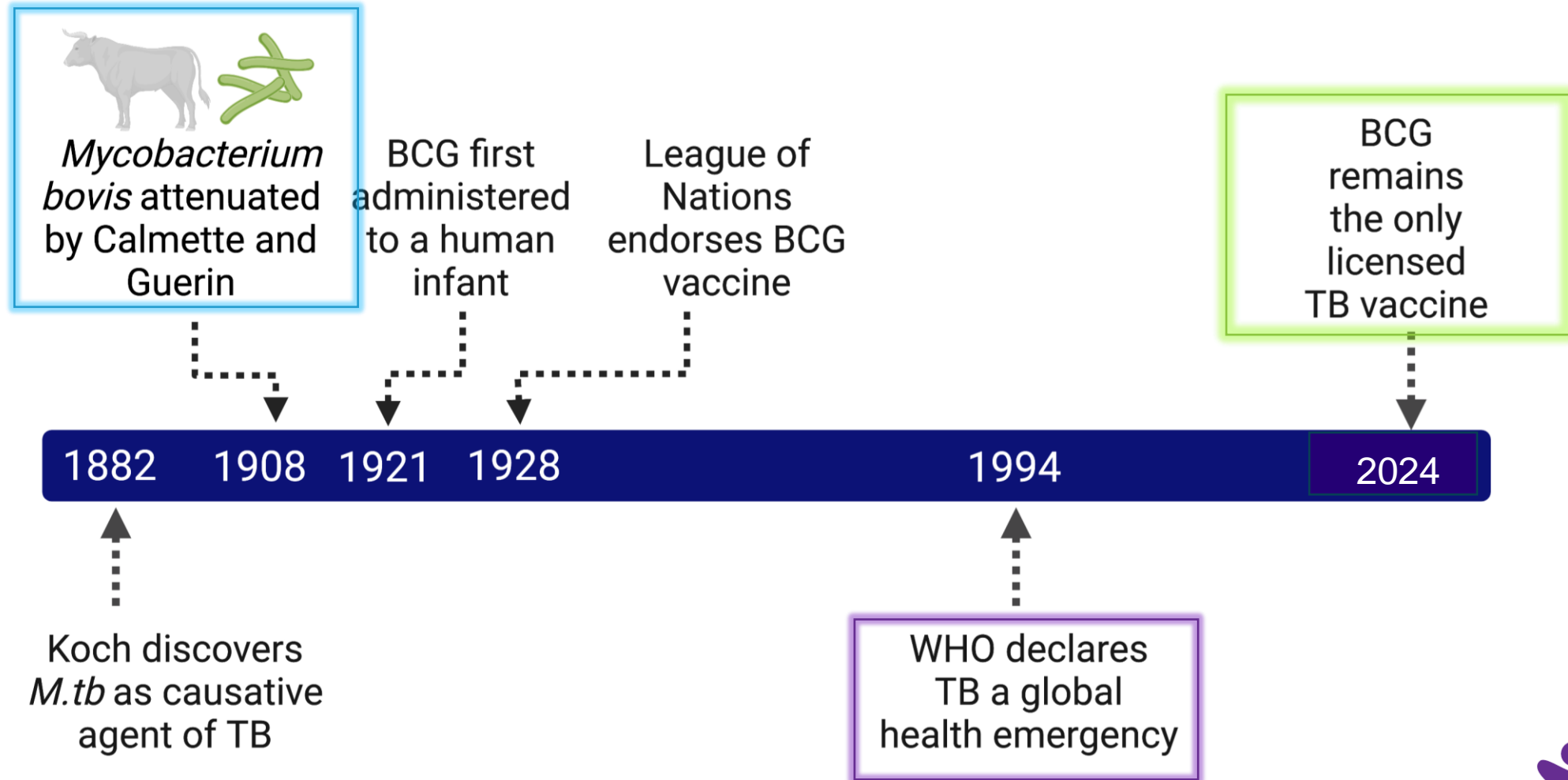


Define challenges of TB vaccine development



Design strategically to accelerate impact

The first >100 years of TB vaccination



Ongoing TB mortality despite BCG

>1 million deaths/year



#1 Cause of death
PLWHIV

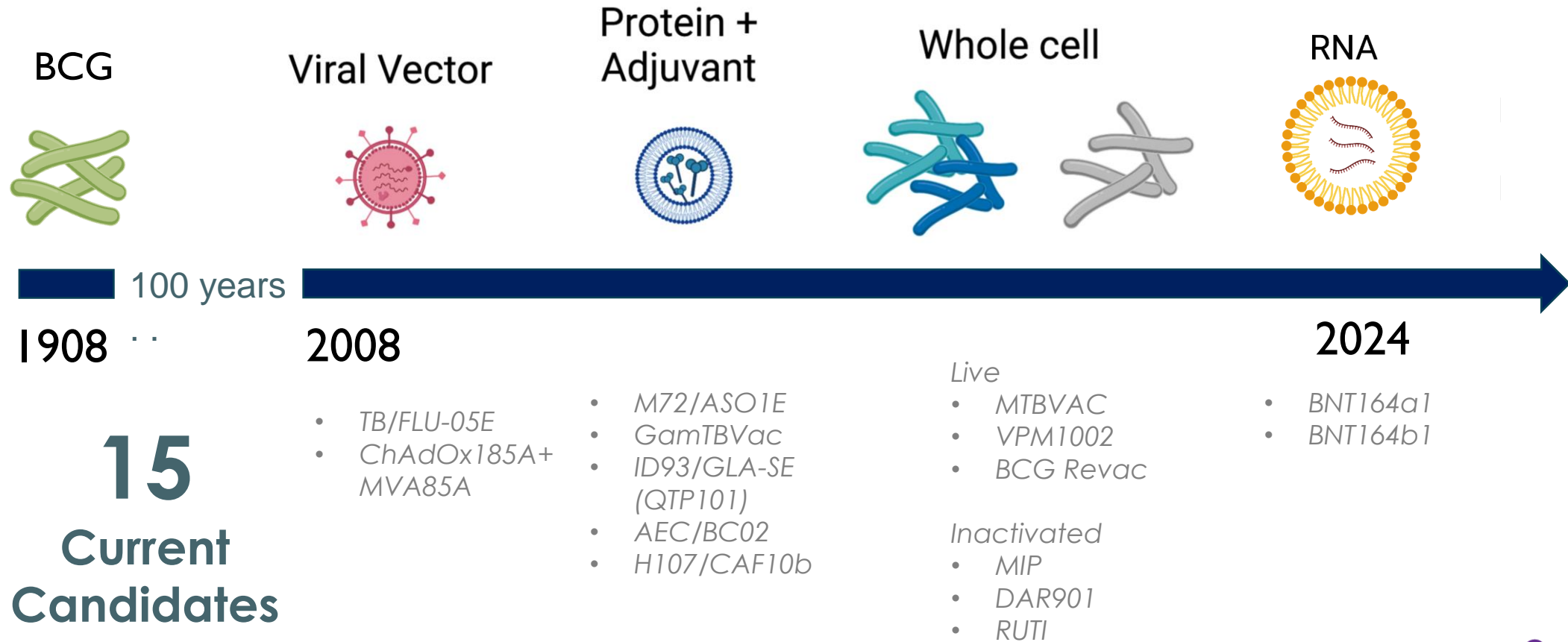


Children and adolescents
~25% TB deaths



Pregnancy
4-fold ↑ maternal
and perinatal
death

Introduction of new TB vaccine candidates



TB Vaccine Indications and Endpoints

6

Prophylactic

Post-exposure

Therapeutic

No *Mtb* infection
(IGRA-)



Prevent *Mtb* infection
(POI)

Prevent TB disease
(POD)

- *Mtb* infection (IGRA+)
- Household contacts



Prevent TB Disease
(PoD)

- TB disease



Shorten Treatment (Rx)
Prevent Recurrence (PoR)

WHO TB Vaccine Target Populations

7

PRIORITY



World Health
Organization

**WHO Evidence
Considerations
for Vaccine Policy
Development
for Tuberculosis
Vaccines Intended
for Adults and
Adolescents**

Adolescents



Adults

Safe, effective (>50% POD)
and affordable

TB Vaccine Candidates in Late-Stage Development



- M72/AS01_E
- ID93+GLA-SE

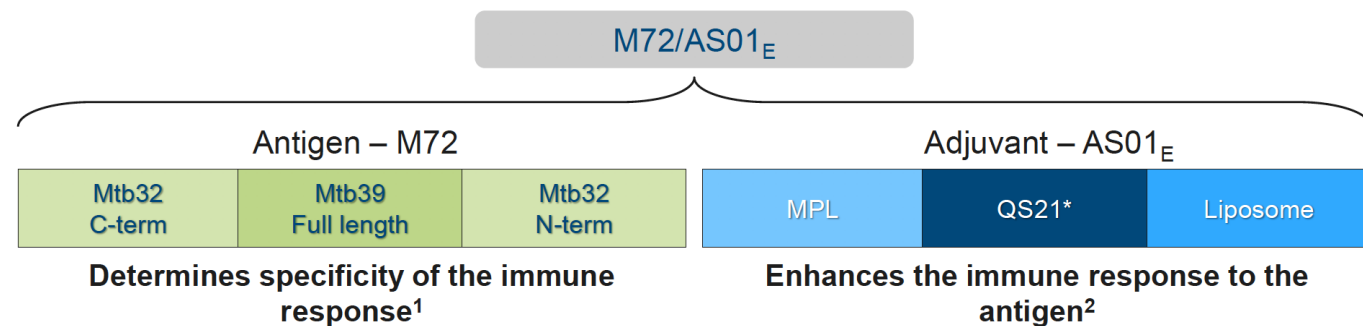


- BCG Revax
- VPM1002
- MTBVAC



M72/AS01_E

- M72: Two Mtb antigens
 - Mtb39a
 - Mtb 32a
- Adjuvant AS01_E
 - **M**onophosphoryl **L**ipid **A** (MPL)
 - *Q*uillaja *s*aponaria (QS-21)
- 2 doses, 1 month apart

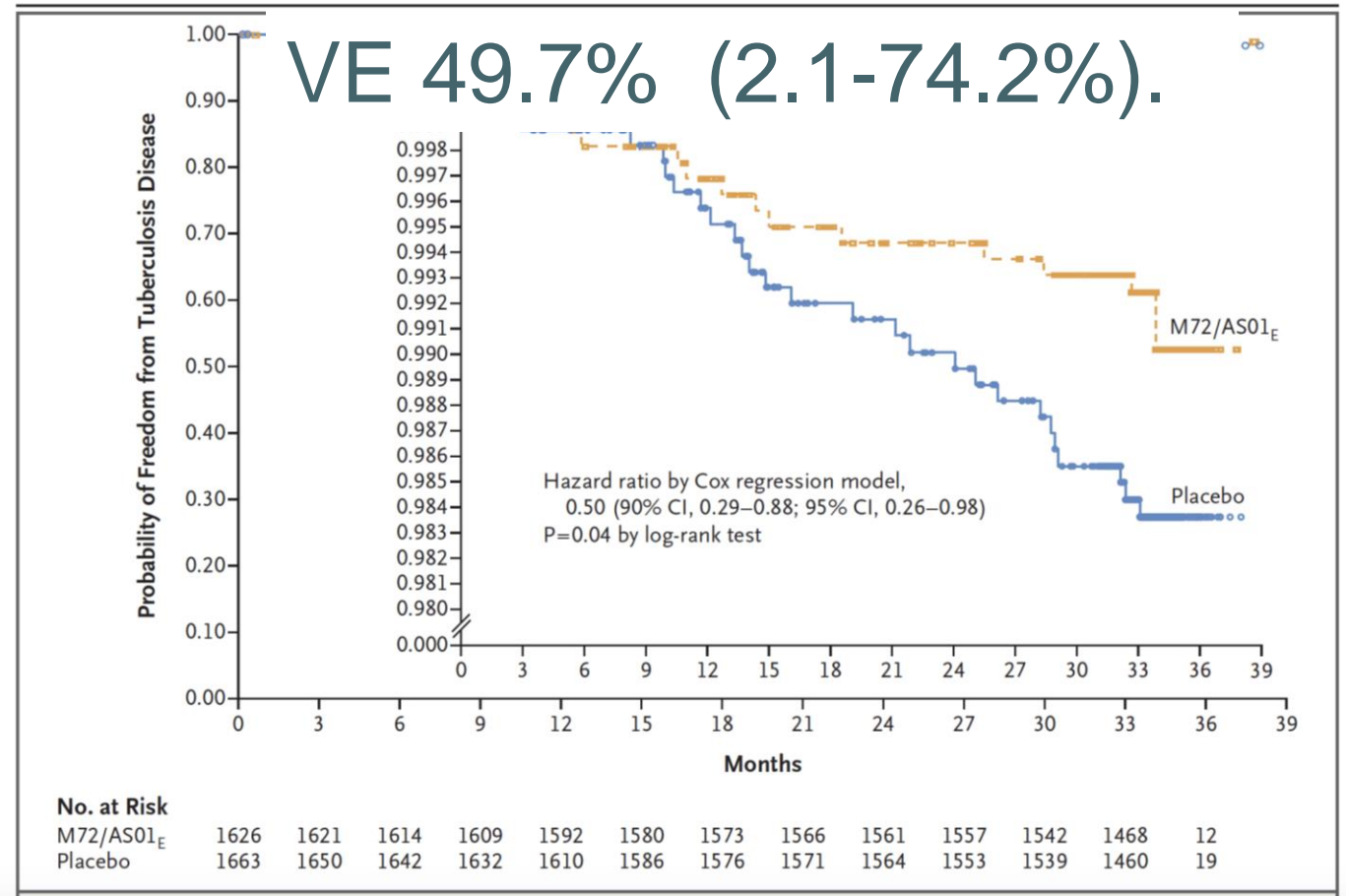




M72/AS01_E prevents TB in IGRA+ adults

- Phase 2b, Africa
- Age 18-50 years, HIV-, IGRA+
- N=3,575

- Phase 3, Africa + SE Asia
- Age. 15-44 years, HIV-/+, IGRA-/+
- N=26,000
- 2024-2028 (Gates) (NCT06062238)

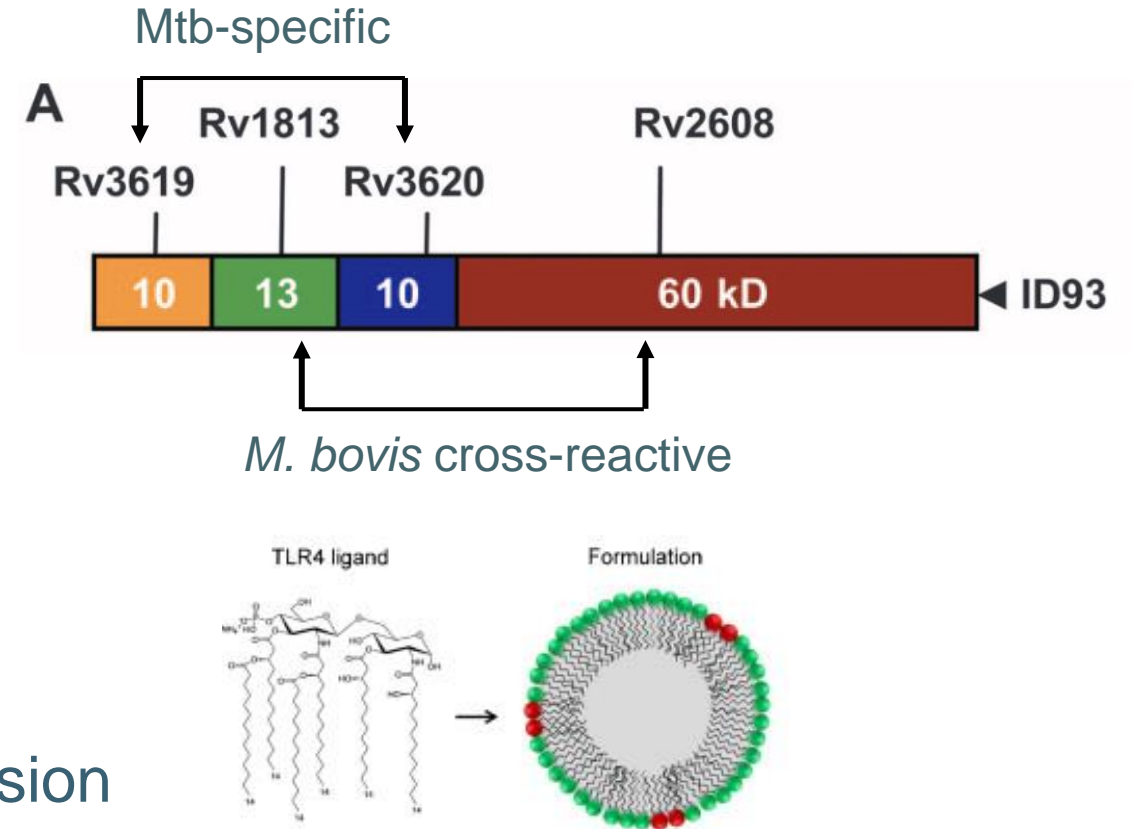


Van der Meeren NEJM 2018; Tait NEJM 2019



ID93 and GLA-SE

- ID93: Four Mtb antigens
 - Virulence (3) Rv3619, Rv3620, Rv2608
 - Latency (1) Rv1813
- Synthetic Adjuvant
 - **G**lucopyranosyl **L**ipid **A** **S**table **E**mulsion
 - TLR4 agonist in oil-in-water emulsion

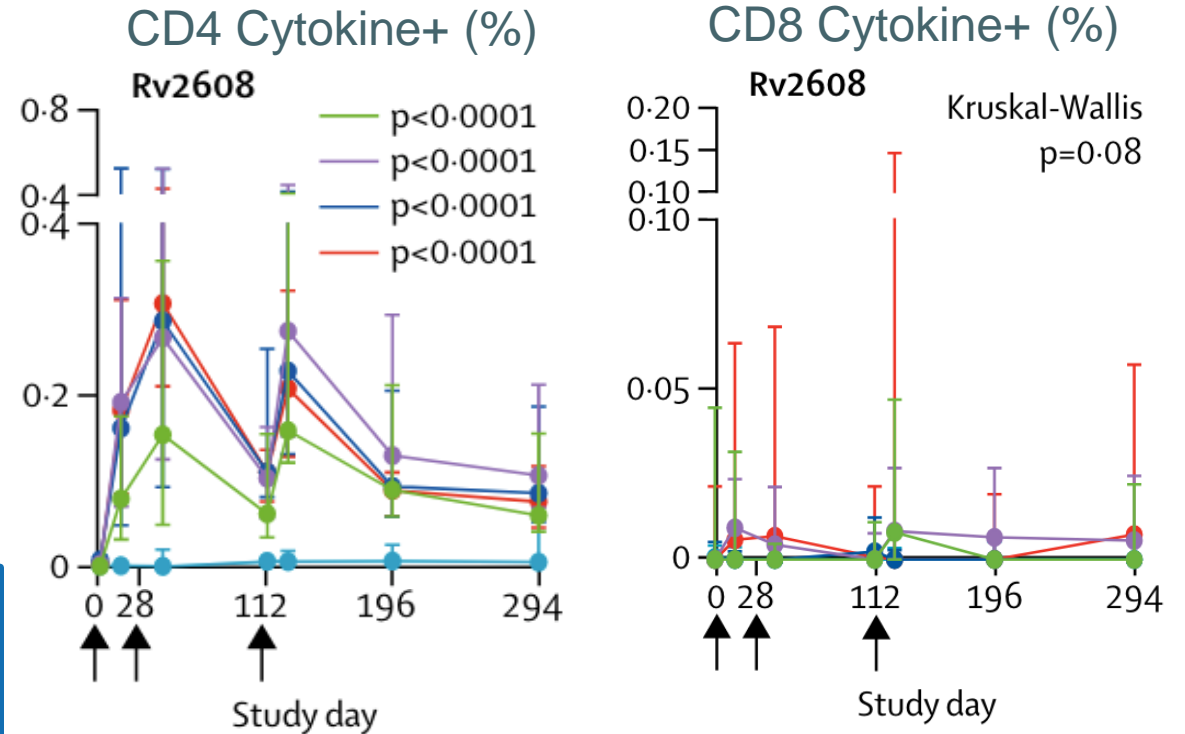




ID93/GLA-SE is safe and elicits robust CD4 immunogenicity after 2 doses

- Phase 1, South Africa
- Age 18-50 years, HIV- ,IGRA-/+
- N=66
- 3 IM doses (d0, d28, d112)
- Higher AE frequency IGRA+
 - Injection site pain 100% vs 60%, $p=0.02$
 - Mild flu-like symptoms

- Phase 2b/3, SE Asia
- Age. 14-45 years, HIV-, IGRA-/+
- N=>9,000
- 2024-2029 (?) (Quratis)



Dosing: ID93+GLA-SE

- Cohort 1: 10ug/2ug (IGRA-)
- Cohort 2: 2ug/2ug
- Cohort 3: 10ug/2ug
- Cohort 4: 10ug/5ug

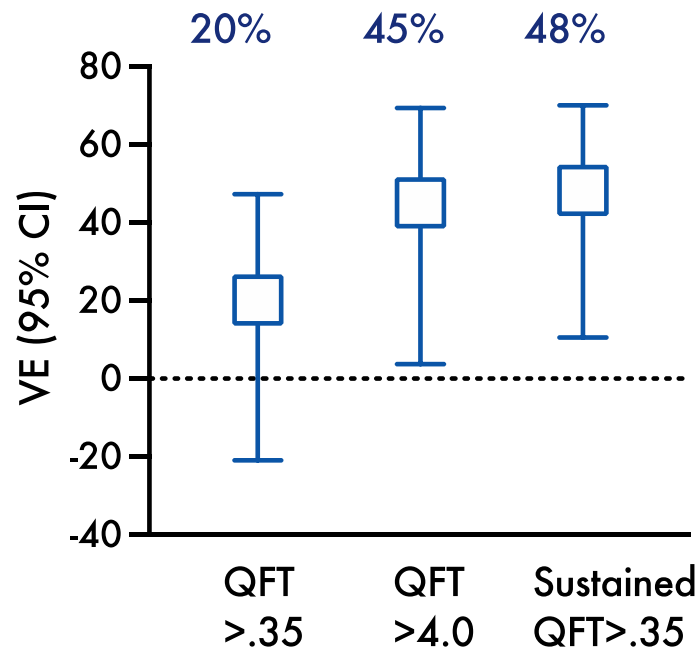


BCG Revaccination prevents sustained Mtb infection

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 (Aeras)



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
- 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

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



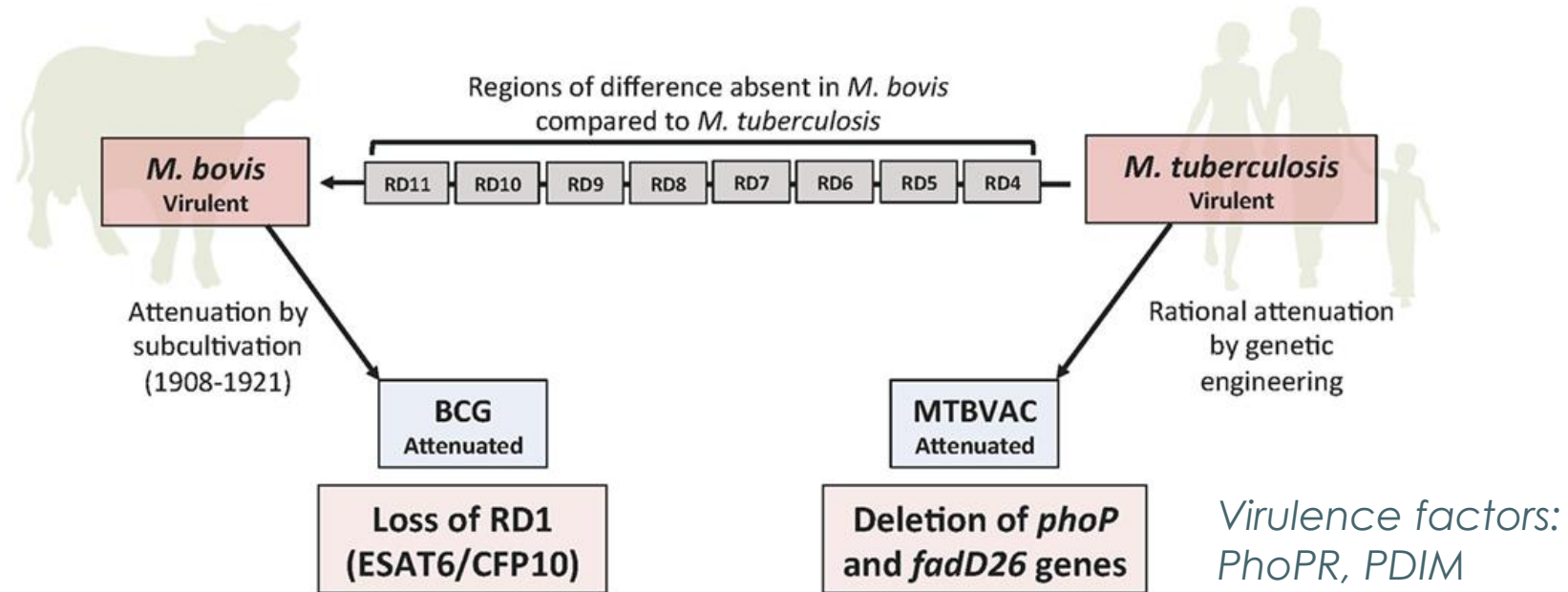
Phase 2b POR, India
Adults 18-65y
N=2,000 (VPM1002 vs Placebo)
2019 – 2023 (SII)

NCT03152903

Phase 3 POD, India
Household contacts, age 6-99y
N= 12,721 (VPM1002 vs MIP)
2019 – 2023 (ICMR)

CTRI/2019/01/017026

MTBVAC

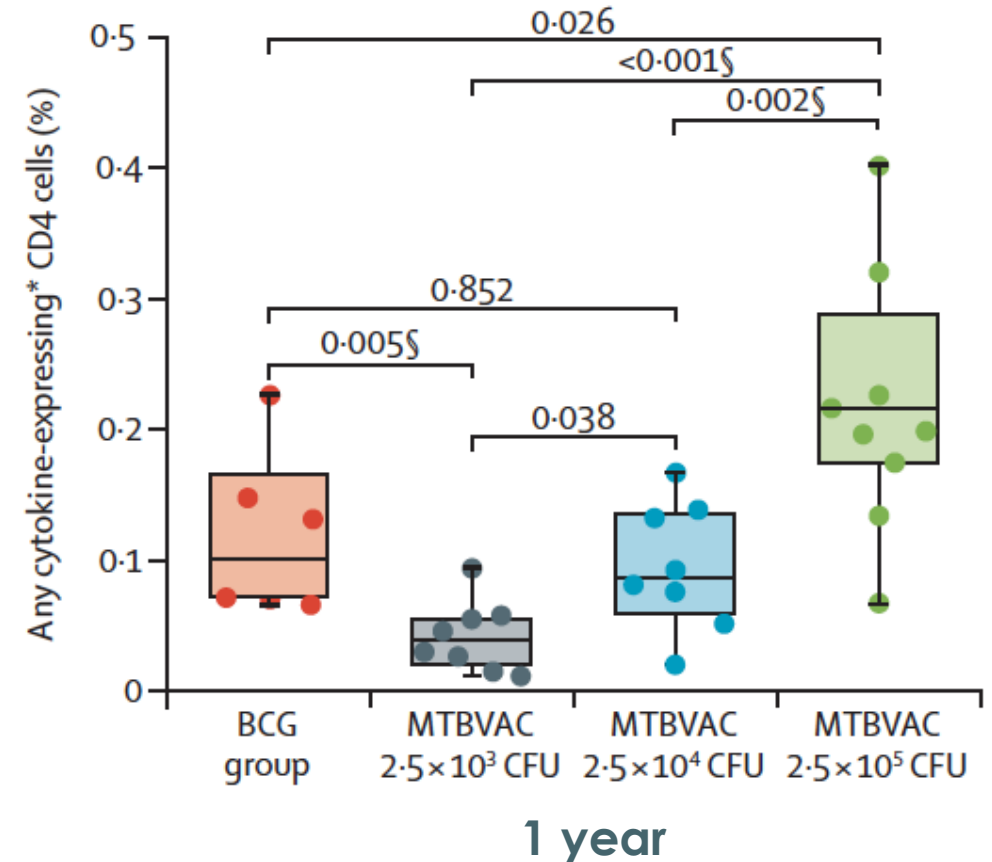


- MTBVAC retains ~25% Mtb T cell epitopes absent in BCG
- Preclinical mouse studies: survival in SCID; ↑ protection vs BCG

MTBVAC safe and elicits high CD4 responses in infants

- Phase I South African infants (N=36)
- No related SAEs
- 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] 2.5×10^5 CFU

- Phase 3 POD
- N=7120 infants, South Africa
- 2022 - 2029 (Biofabri) (NCT04975178)
- Phase 2b POD
- 14-45 years HIV-, IGRA+
- N= 4,300
- 2025-2029 (Biofabri/IAVI)



Tameris & Mearns et al, Lancet Respir Med 2019

Roadmap



Describe the current TB vaccine landscape

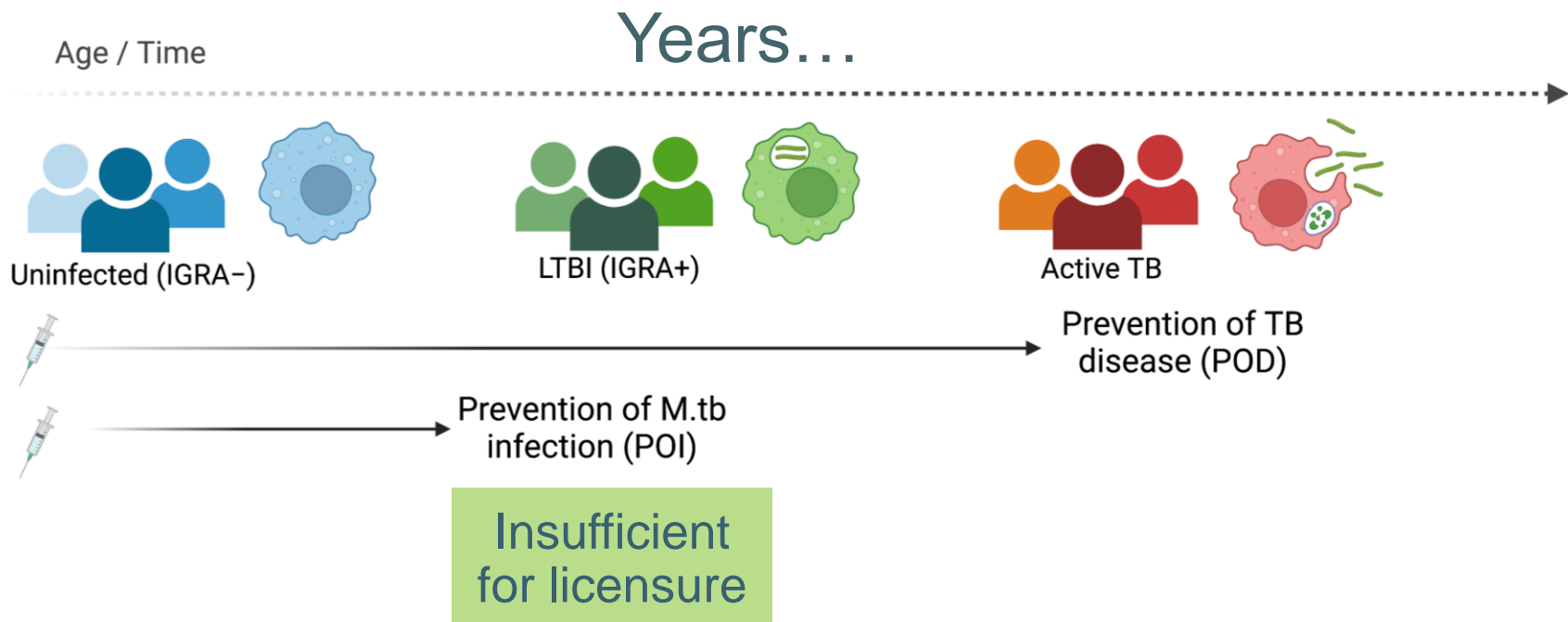


Define challenges of TB vaccine development



Design strategically to accelerate impact

Prolonged time to endpoints

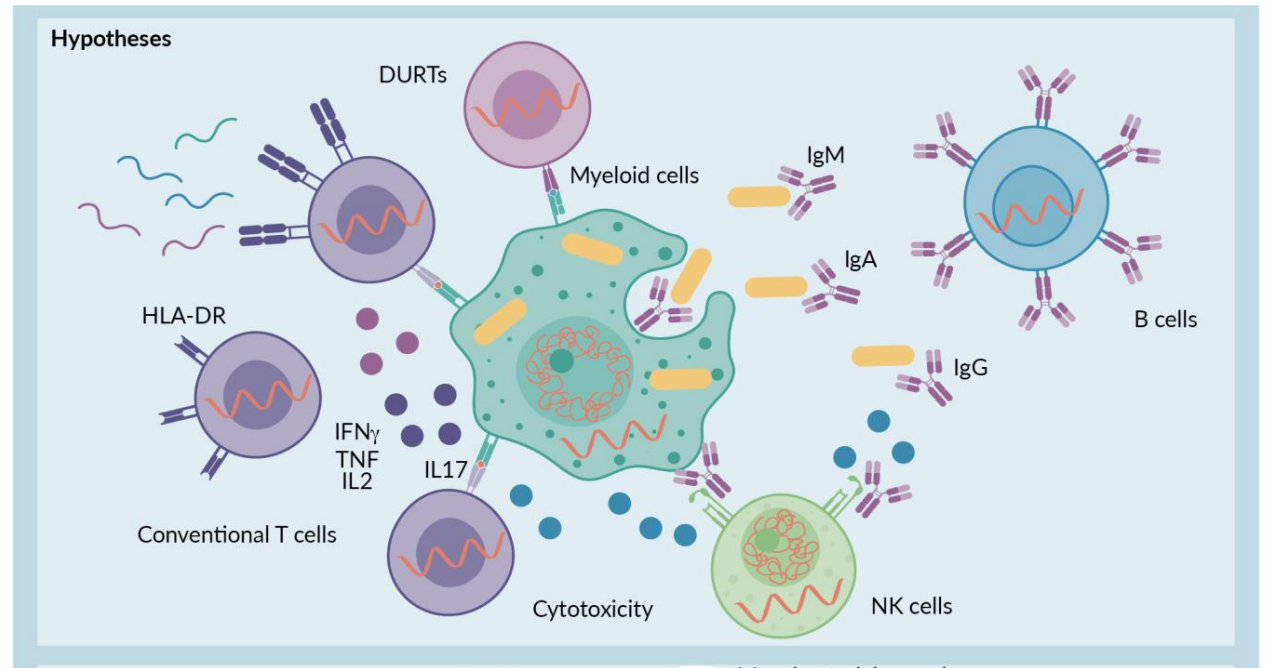


Immune correlates of protection unknown

EXPERT INSIGHT

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

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



Mtb infection:

- BCG REVAX

TB disease:

- M72/ASO1_E 2b

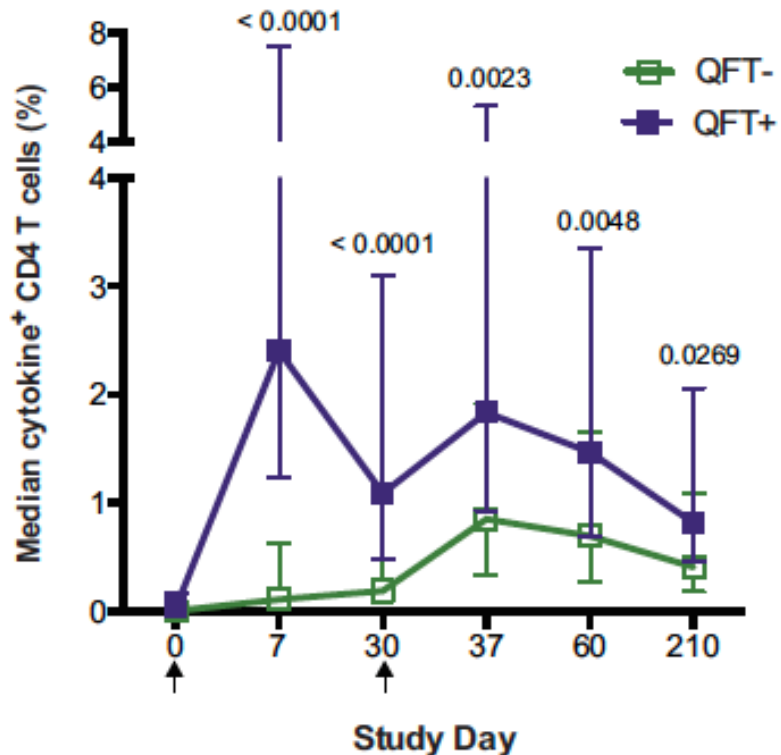
Biobanking samples is critical for future immune correlate discovery and immunobridging to special populations

Prior immunity modifies vaccine response; differential effect by vaccine type



Subunit vaccines

IGRA+ ↑ immunogenicity



Whole cell vaccines

↑ NTM exposure, age ↓ VE

BCG ReVAC Cluster RCT, 9y FU



Overall VE 12% (-2-24%)

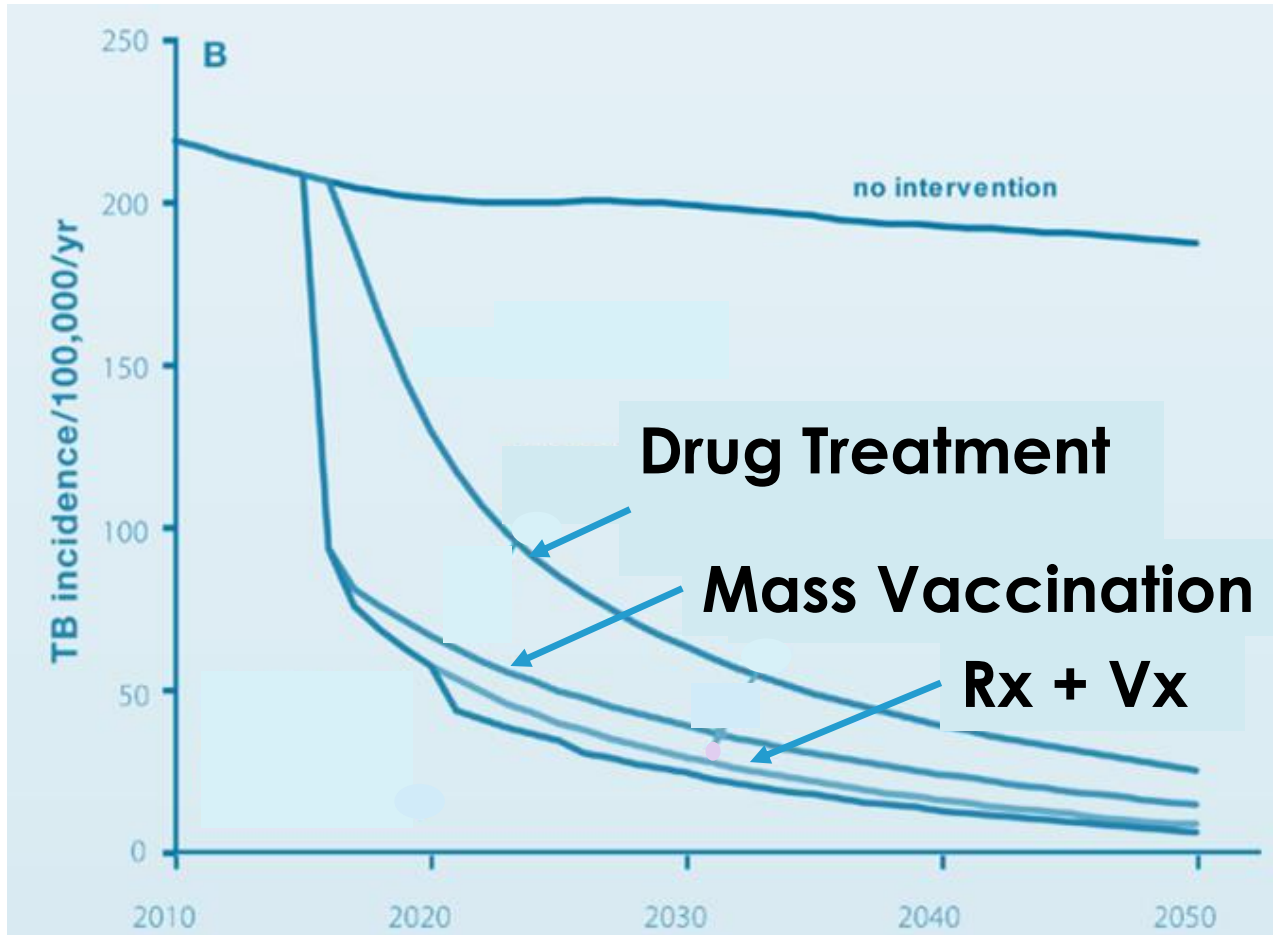
+Prior BCG:

Age <11 Salvador (↓ NTM) POD VE 33% (3-54%)

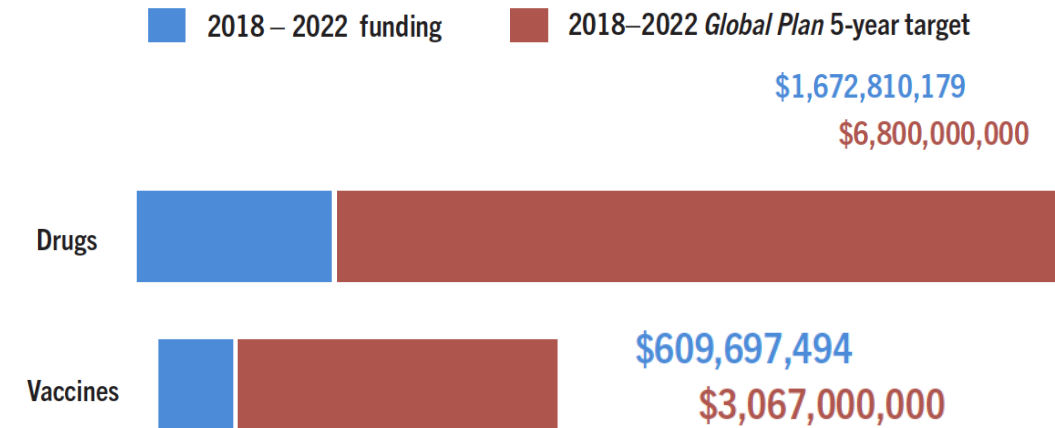
No prior BCG: POD VE 25% (3-43%)

Global TB vaccine funding is inadequate

TB Vaccination is Essential to End TB



Therapeutics are prioritized



Vx vs Rx:
~1/3

Roadmap



Describe the current TB vaccine landscape



Define challenges of TB vaccine development



Design strategically to accelerate impact

Apply Lessons Learned from COVID: Streamline



OPERATION WARP SPEED ACCELERATED VACCINE PROCESS

■ R&D + Preclinical Trials Vaccine Candidate/s Identified
■ Phase I Clinical Trials

■ Phase II Clinical Trials
■ Phase III Clinical Trials

■ Manufacturing
■ Distribution



- Adaptive clinical trial design
 - Overlapping phases
 - Phase 1-3 single protocol (Pfizer)
 - Flexibility: ongoing case detections post unblinding

Eliminate inequities in evidence

INSUFFICIENT DATA

Age 12-14
Pre-adolescents
PLWHIV

Adolescents



Adults



EXCLUDED

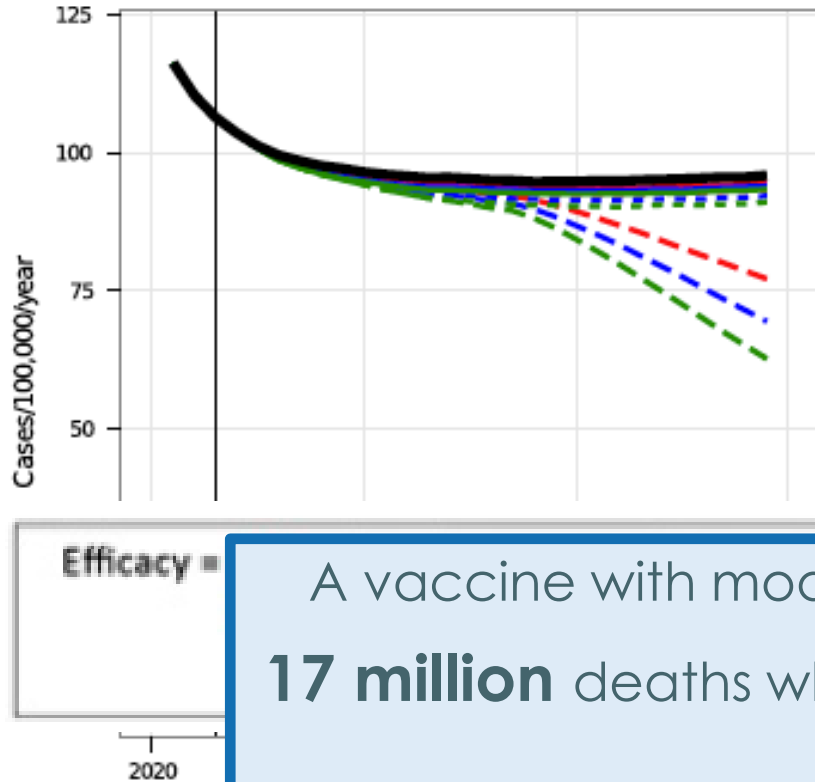
from all current
TB vaccine trials

Pregnant Lactating

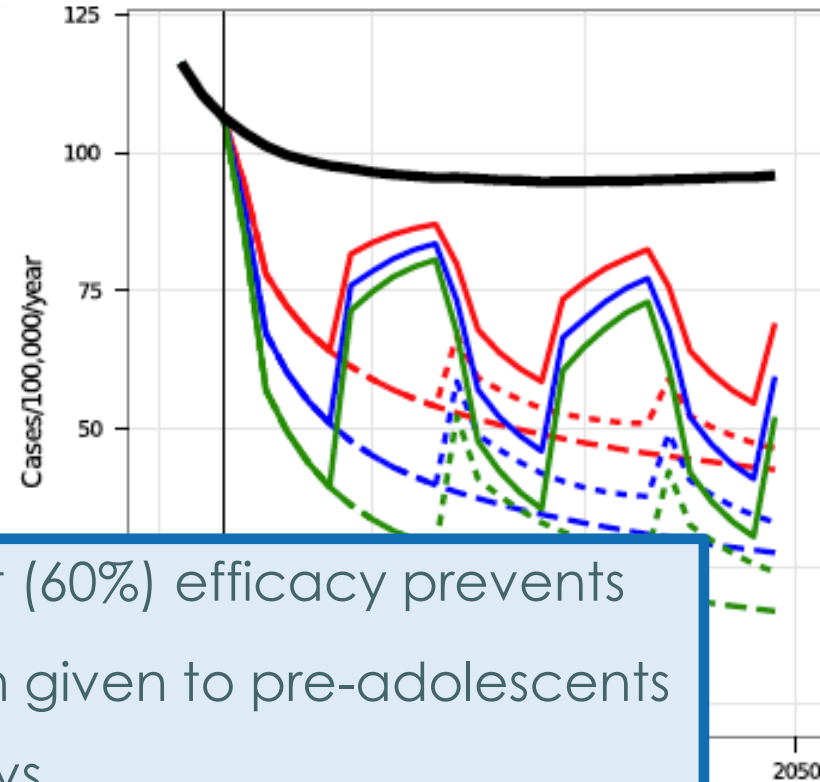


Align Evidence with Public Health Impact

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

Leverage Existing Health Care Systems

“Vaccines don’t save lives.
Vaccinations save lives.”
-Walter Orenstein



Well Child Care



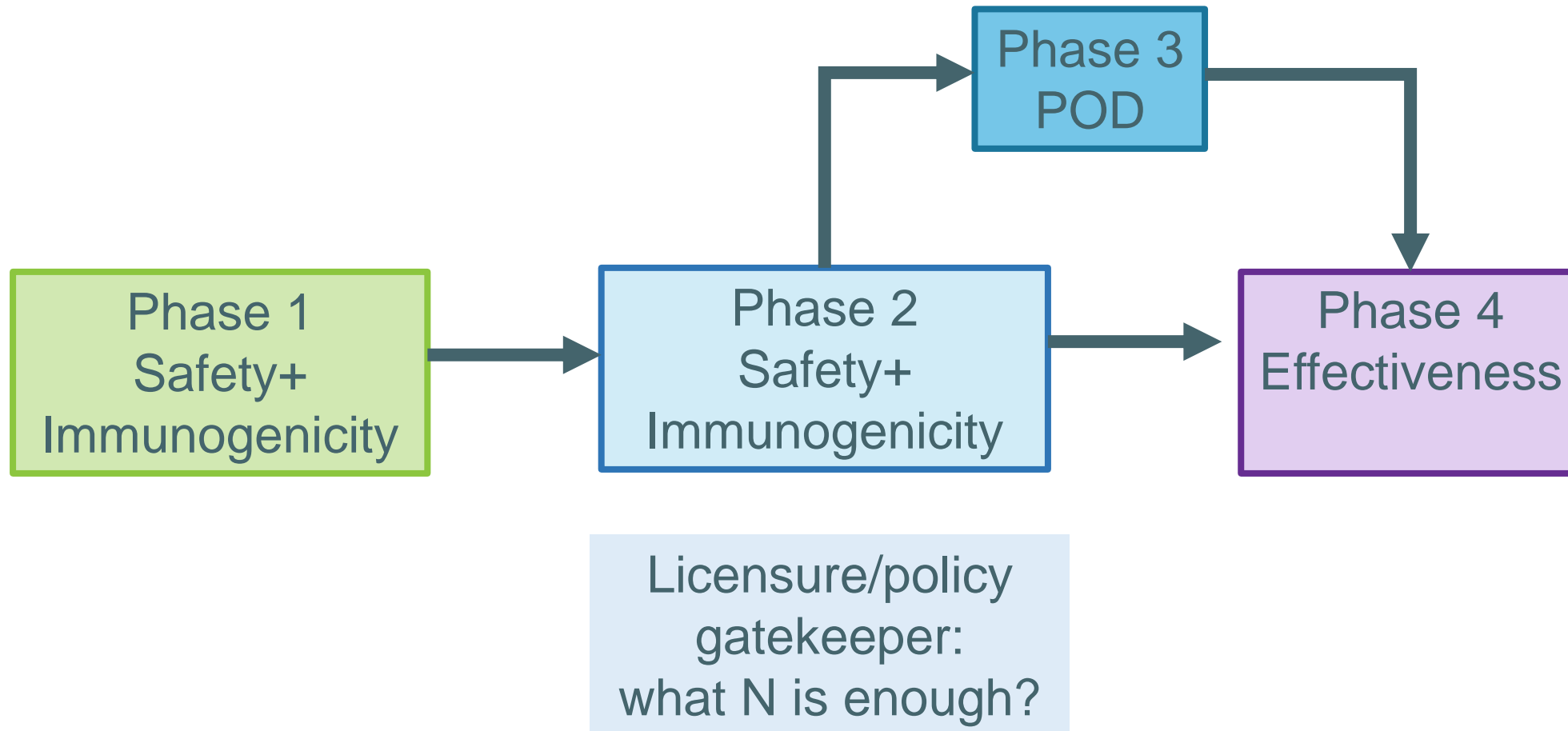
EPI: Td+HPV



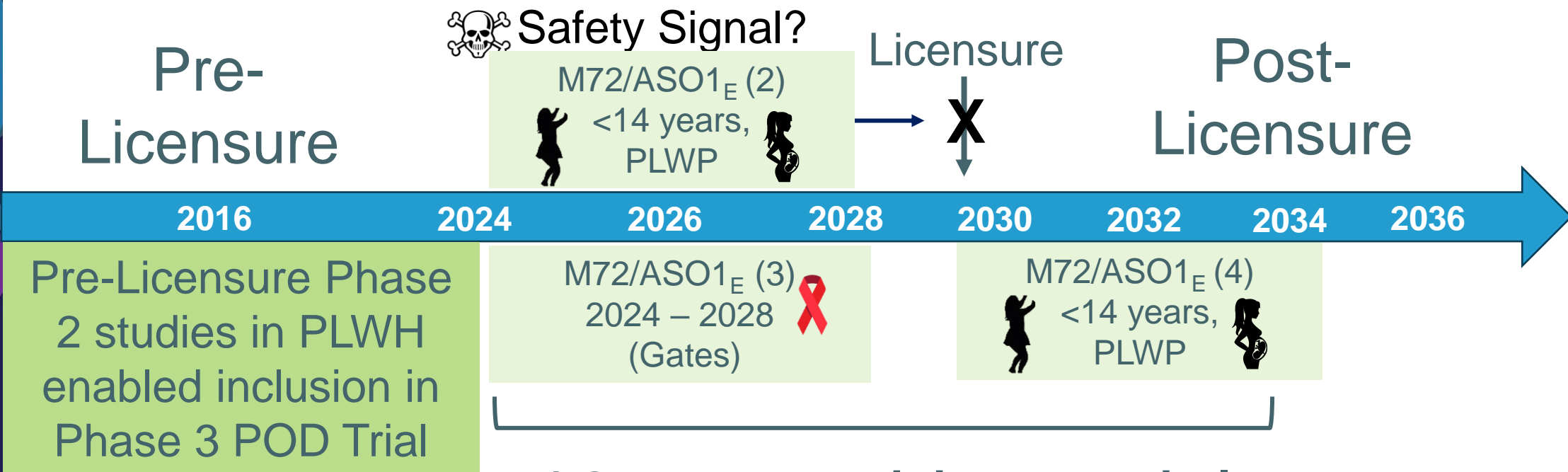
Antenatal Care + Delivery






Pre-licensure phase 2 studies are critical to avoid delayed vaccine roll-out in target populations



Risk Tolerance: Pre- vs Post-Licensure inclusion of special populations



-  Pregnant and Lactating Women and People (PLWP)
-  Children <14 years
-  People living with HIV (PLWH)

~10-year evidence delay

BCG Revac (1)
2013-2015
(HVTN602)

H4:IC31 (1)
2013-2016
(P1113)

**VPM1002
BCG
Revac (2)
(IMPAACT
2035/604)

ID93/GLA-SE (2b POR)
2024-2029
(HVTN603/
A5397)

MTBVAC (2a)
2024-2025
(HVTN605)

**VPM1002/
MIP (3)
2017-2024
(SII)

M72/ASO1E (3)
2024 - 2028
(Gates)

GamTBVac (3)
2022 - 2025
(Russian Govt)

MTBVAC (2b)
2025 - 2029
(Biofabri/IAVI)

ID93/GLA-SE (2b/3)
2025 - 2029 (?)
(Quratis)

**BCG Revacc (3)
2024-2027
(ICMR)



**Children <14 years



People living with HIV (PLWH)



HIV VACCINE TRIALS NETWORK

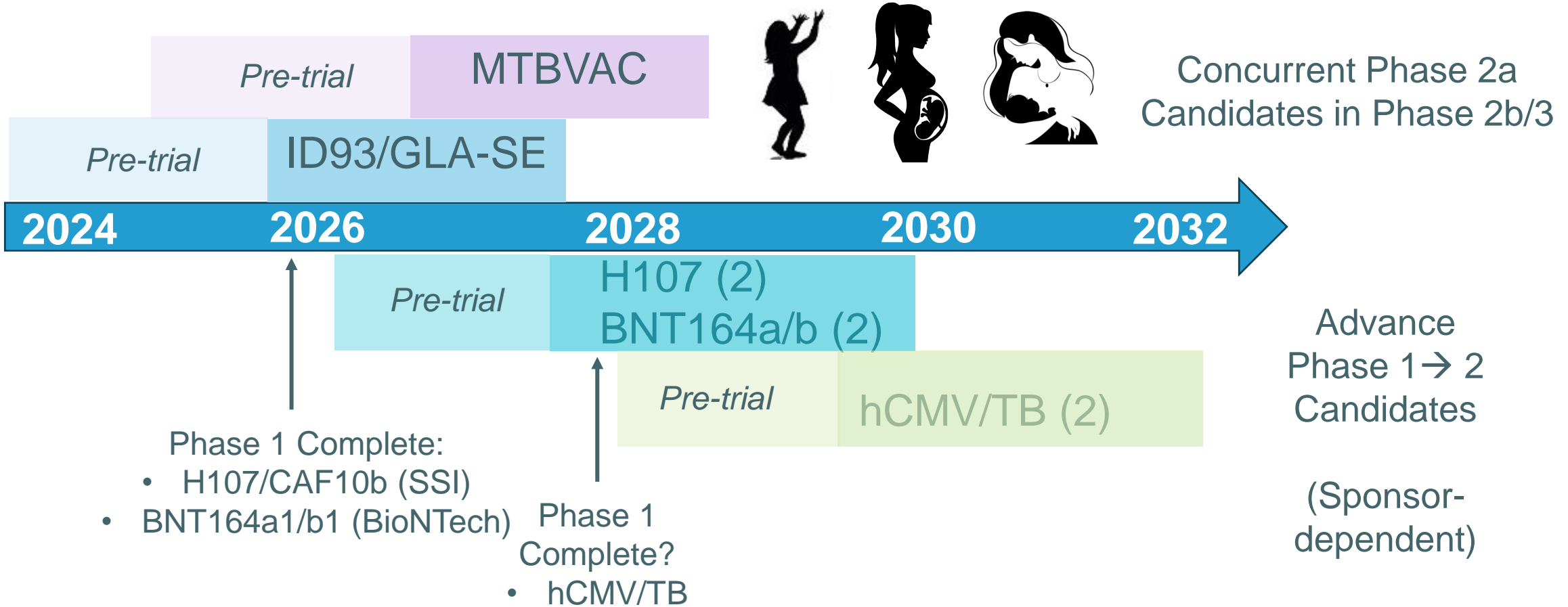


DAIDS-Network Precedent: Advance Phase 1-2 TB vaccine studies for PLWH

Complementary with Industry/Nonprofit- sponsored TB vaccine POD Trials



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



Landscaping TB Vaccines: Designing the Future



- **Adaptive clinical trial design**
- **Eliminate inequity in evidence**
- **Align evidence with public health impact**

Thank You



The entire IMPAACT2035/HVTN604 Study Team



Photo credit: PATH

EMORY • Children's • GT
Pediatric Research Alliance



K23AI143479

K12HD000850



HIV VACCINE
TRIALS NETWORK



IMPAACT
International Maternal Pediatric Adolescent
AIDS Clinical Trials Network



PerSEVERE Grant
UL1-TR002378



Additional Slides

Table 1: Current Phase 2b/3 Whole Cell TB Vaccine Trials					
Trial/Sponsor	Phase/ Outcome	Other arm(s)	Study Population	N	Timeline
MTBVAC					
NCT04975178 <u>Biofabri/IAVI</u>	3 POD	BCG	Newborns HIV-/HIV-exposed South Africa	7,120	09/2022 - 09/2029
NCT06272812 <u>Biofabri/IAVI</u>	2b POD	Placebo	14-45 years *HIV-, IGRA+ South Africa, TBD	4,300	09/2024 - 03/2028
VPM1002					
NCT03152903 SII	2b POR	Placebo	18-65 years HIV-, <u>Hx TB</u>	2,000	02/2017 - 02/2024 <i>Results expected 2024</i>
CTRI/2019/01/01 7026 ICMR	3 POD	MIP	HHC age >6 years HIV- India	12,721	01/2019 - 2023 <i>Results expected 2024</i>
NCT04351685 SII	3 POI	BCG	Newborns HIV-/HIV-exposed Multi-center Africa	6,940	11/2020 - 11/2025 [*2028?]
BCG					
NCT05330884 ICMR	3 POD	TPT	HHC age 6-18 yrs <u>HIV- India</u>	9,200	07/2024 - 06/2027
POD= Prevention of Disease; POI=Prevention of Infection; POR=Prevention of Recurrence; HHC=Household contact; TPT=Tuberculosis preventive therapy; *Need to clarify with trial sponsor					

VPM1002/MIP (3)
2017 - 2024
6-99 years
India, HIV- HHC
N=12,721
(SII)

GamTBVac (3)
2022 - 2025
18-45 years
Russia, HIV-
N=7,180

M72/ASO1E (3)
2024 – 2028
15-44 years
SSA, SE Asia
N=26,000
(Gates)

ID93/GLA-SE (2b/3)
2025 – 2029 (?)
14-45 years
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N=9,000
(Quratis)

BCG Revacc (3)
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India, HIV- HHC
N=9,200
(ICMR)

MTBVAC (2b)
2025 - 2029
14-45 years
SA, HIV-, IGRA+
N=4,300
(Biofabri/IAVI)

Safety: TB Vaccination during Lactation



No theoretical safety concerns

- Case report of intravesicular BCG during lactation, no AEs *Barbur Immunother 2022*
- Preclinical studies demonstrate safety of BCG in lactation *Williams Heliyon 2022*
- Infants immunized with BCG at birth
- No licensed vaccines (live/inactivated) contraindicated during lactation*

*Except YFV



Enhance Infant Mucosal Immunity (?)

- Mtb-specific IgA
 - Inhibit epithelial cell Mtb infection *in vitro* *Zimmerman EMBO Mol Med. 2016*
 - Protect from Mtb infection + TB disease in NHP *; Dijkman Nat Med 2019*

Cranmer (PI) K23AI143479 BM Humoral Mtb CoP in progress

17 Nov
10:05

TBS-EP05-08 Breast milk is enriched with functional anti-mycobacterial antibodies that decline over time

Lisa Marie Cranmer

05m • Salle Maillot 5