# TB vaccines at PDVAC

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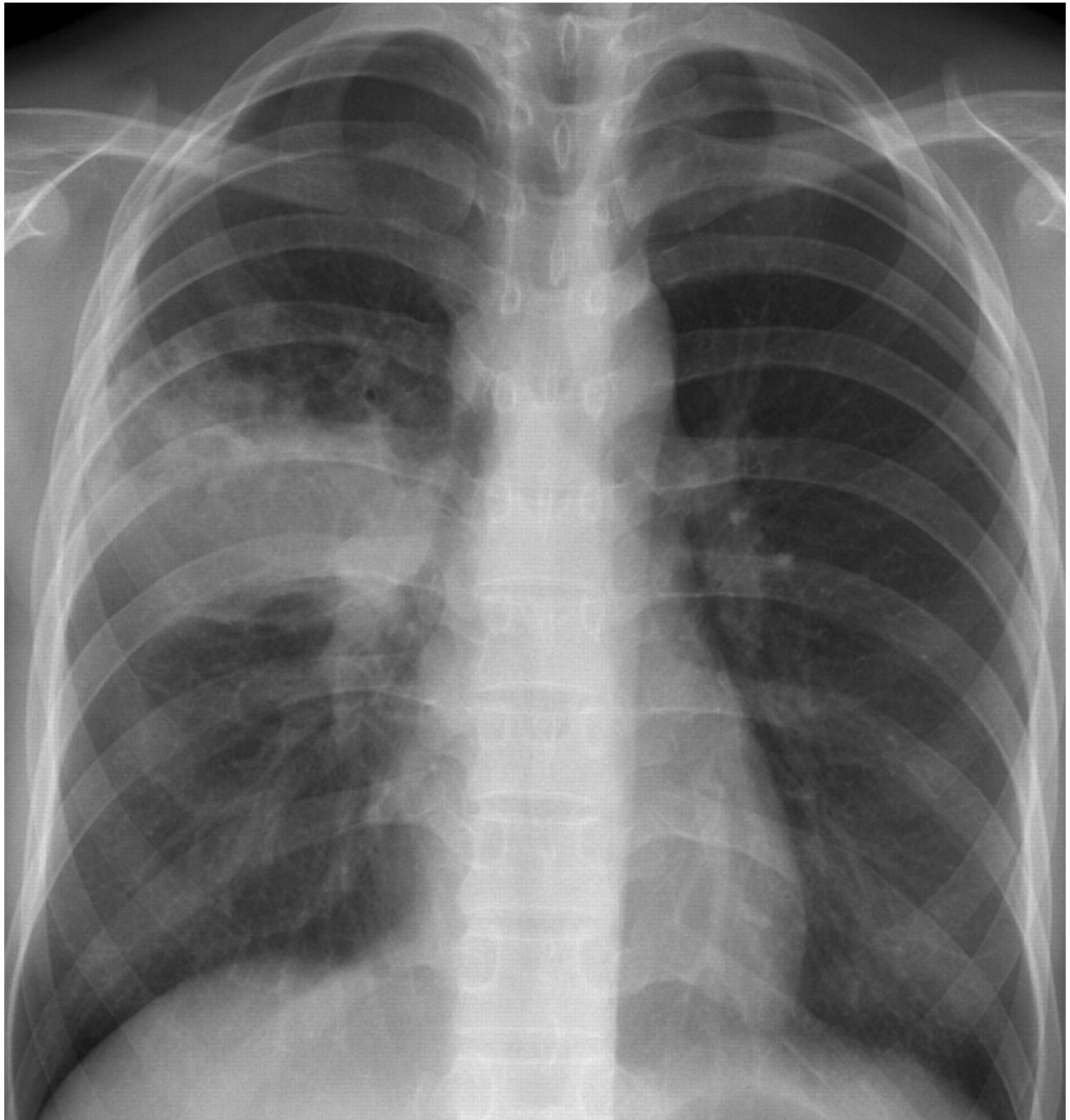
# TB most commonly manifests as lung disease.



https://ajronline.org/doi/full/10.2214/ajr.07.3896

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# TB symptoms.

SA NDoH.

Stuck, et al. Lancet ID 2024; 24:726.

**But! >50% of persons with TB disease may be asymptomatic!**

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# Persons with asymptomatic TB: the unknowns.

1. Exactly how many?
2. What proportion transmits the pathogen?
3. What proportion self-cures?
4. What proportion progresses to symptomatic disease?
5. How do we find and diagnose them?
6. How should they be treated?
7. Do novel vaccines prevent this form of disease?

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# Number of persons with new TB disease in 2023.

**10.8M**

**270K**

95% CI 10.1M-11.7M and 168K-395K, respectively.
WHO Global TB Report 2024.

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# 1.25M people died from TB globally in 2023, including 56,000 South Africans.

95% CI 1.13M-1.37M. WHO Global TB Report 2024.

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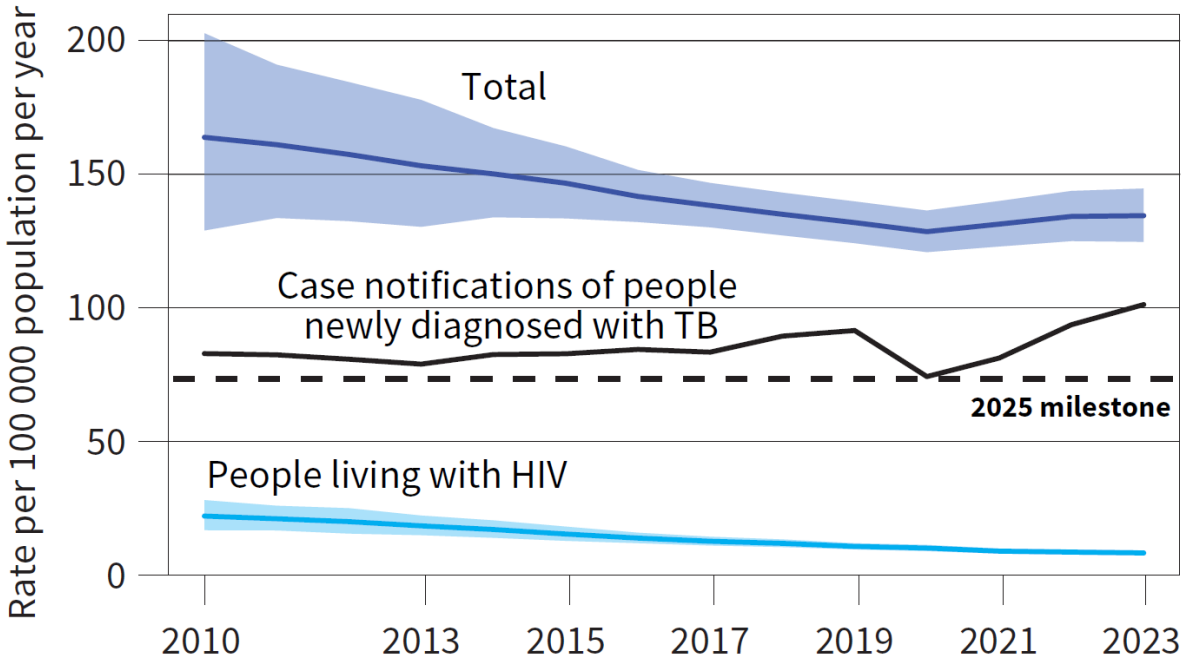
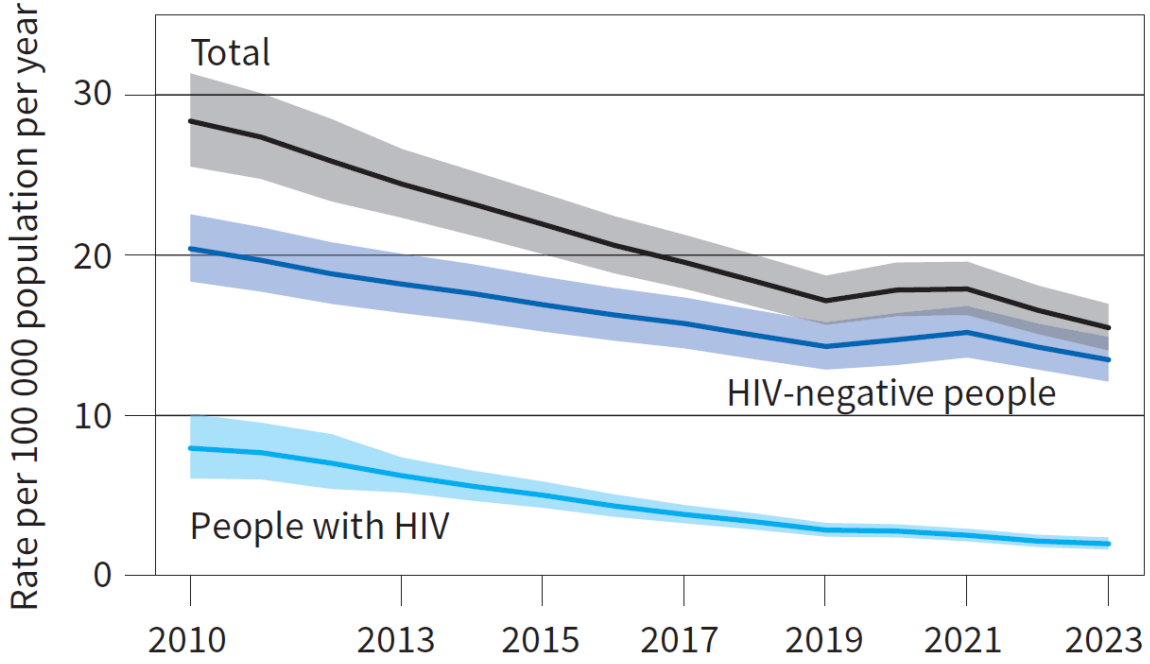
# Global TB (non-)control.

## Incidence.




## Death rate.




WHO Global TB Report 2024.

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# The impact of social protection and poverty elimination on global tuberculosis incidence: a statistical modelling analysis of Sustainable Development Goal 1

Daniel J Carter, Philippe Glaziou, Knut Lönnroth, Andrew Siroka, Katherine Floyd, Diana Weil, Mario Raviglione, Rein M G J Houben*, Delia Boccia*

| | *Reduction in global TB incidence 2015-2035* |
|---|---|
| Ending extreme poverty | 33.4% |
| Expanding social protection coverage | 76.1% |
| Both | 84.3% |

95% CI for each: 15.5-44.5, 45.2-89.9 and 54.7-94.9, respectively.
Carter, et al. Lancet Glob Health 2018;6:e514.

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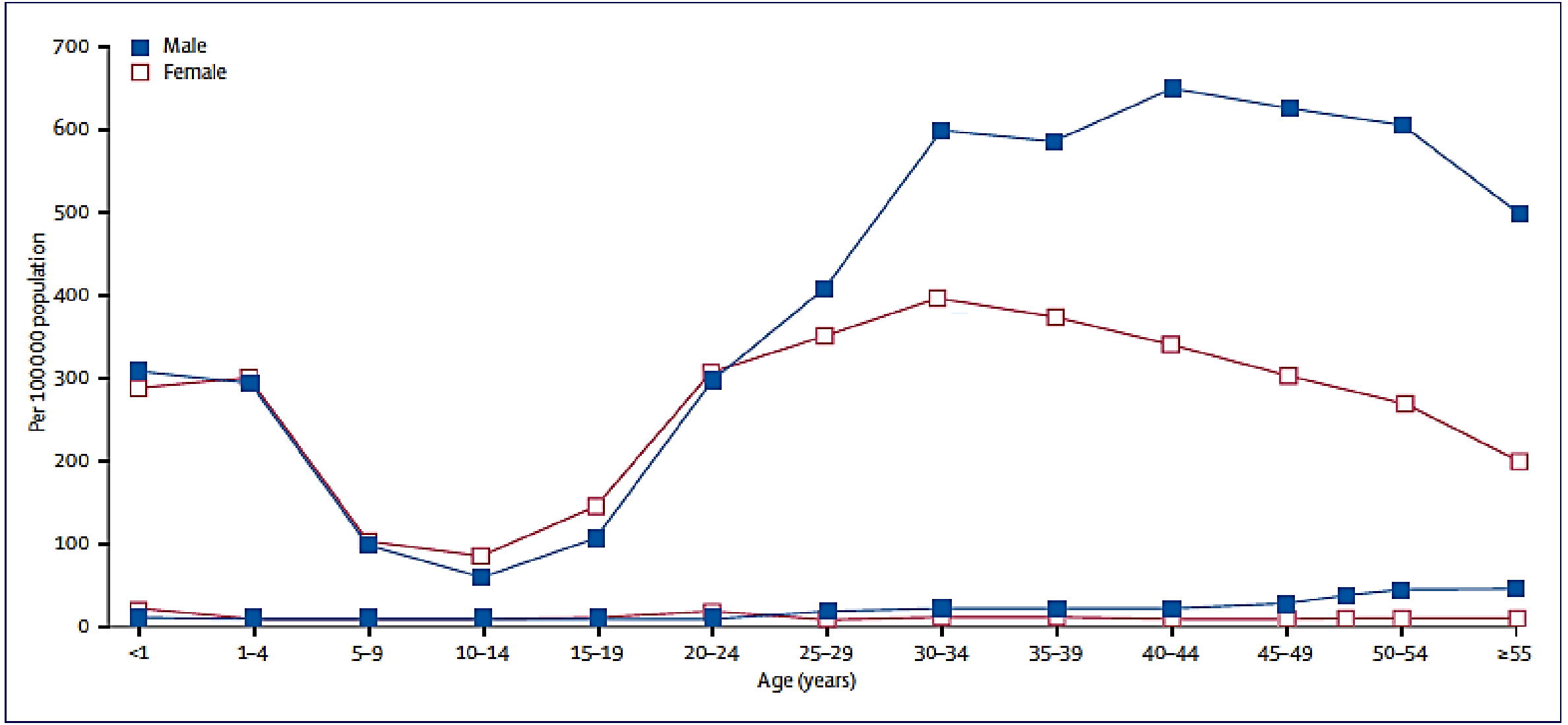
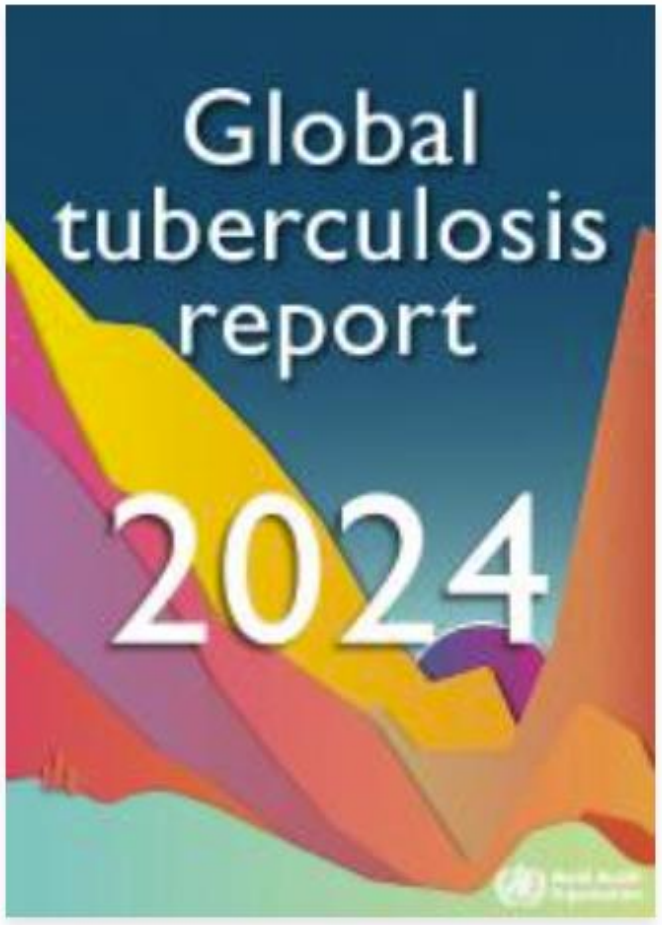
# For impact on the TB epidemic, vaccinate adolescents and adults.

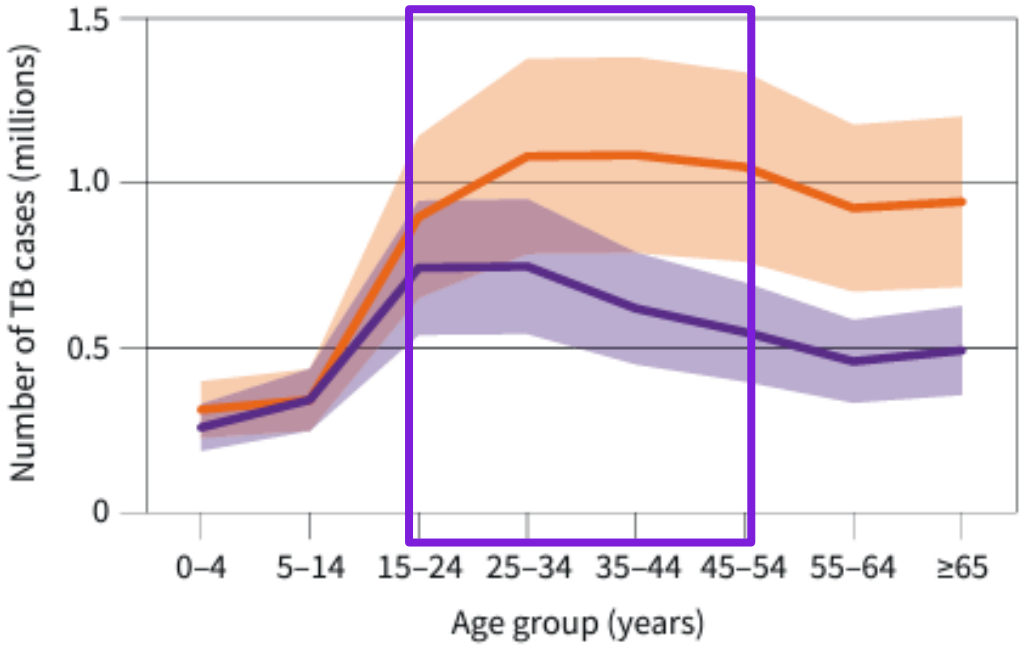



Donald, et al. IJTLD 2004;8:621.

# TB is once again causing more deaths than any other pathogen

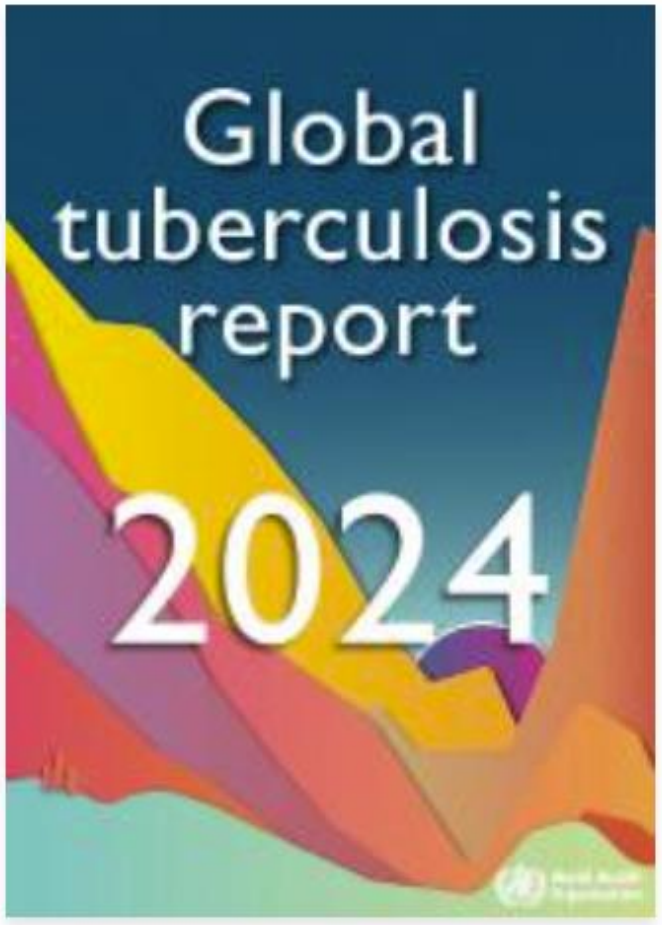



**Global estimates of TB incidence disaggregated by age group and sex (female in purple; male in orange), 2023**




***Adolescents and younger adults have the most cases and are the main source of TB transmission, and therefore are the highest priority target population for TB vaccines***

# TB is once again causing more deaths than any other pathogen

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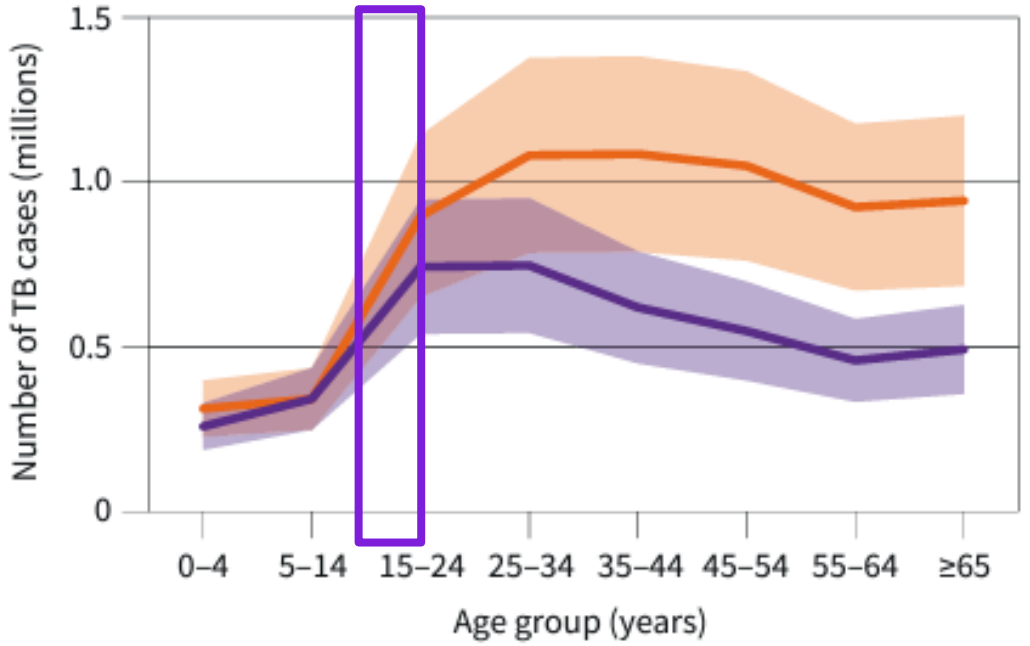



***Vaccinating adolescents alone would leave a large reservoir of future cases and sources of transmission (adults) unaddressed for multiple decades***

# TB Vaccine Pipeline

## *Vaccine candidates under clinical development*

There are 15 vaccine candidates in the pipeline as of September 2024, of which 12 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

**Platform**

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- RNA

**Trial staus**

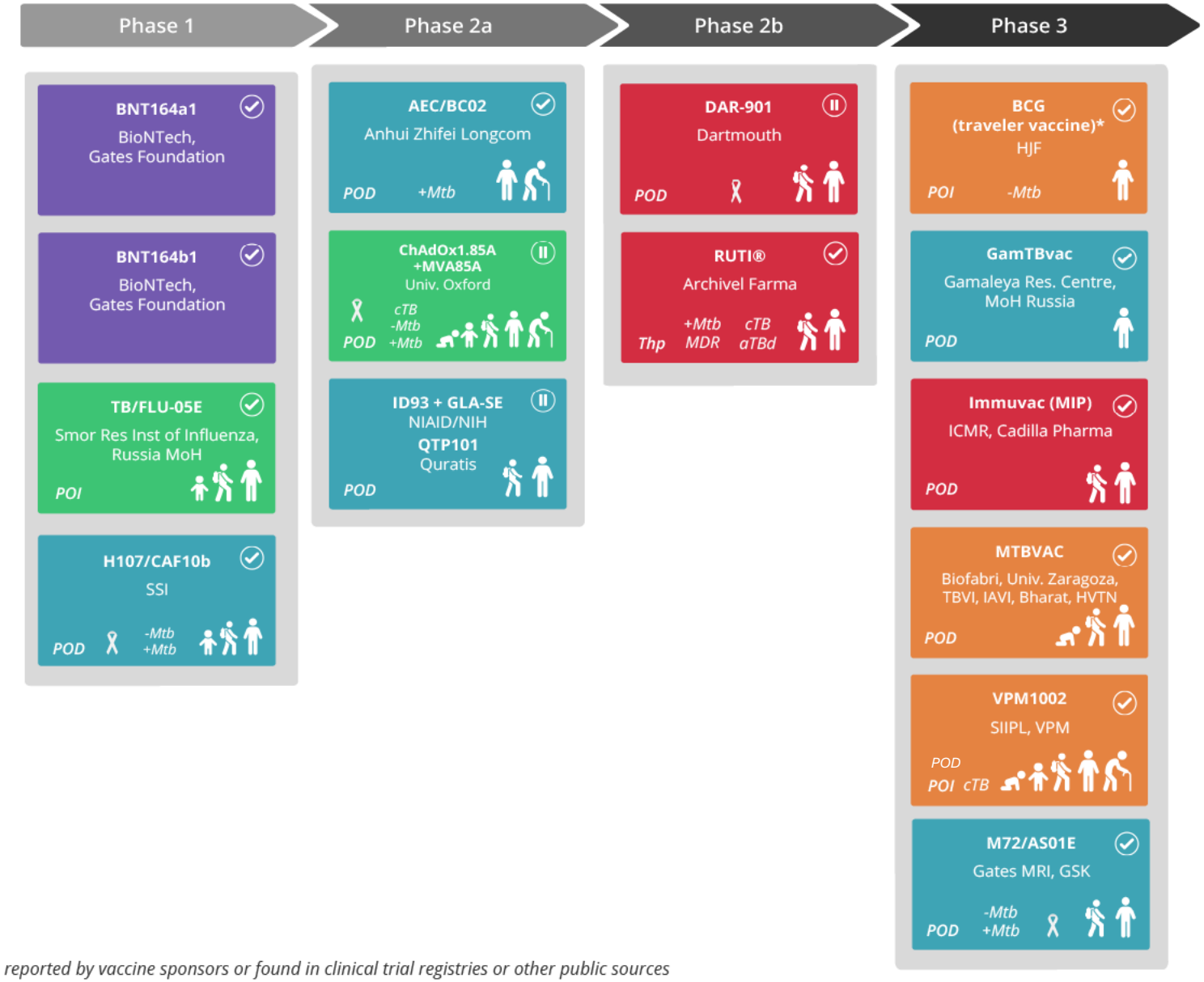
- Active trials
- No active trials

**Candidate target population**

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -Mtb — People without Mtb infection
- +Mtb — People with Mtb infection
- aTBd — People with active TB disease
- MDR — People with MDR-TB
- cTB — People cured of active TB

**Primary candidate indication**

- *POI* — Prevention of Infection
- *POD* — Prevention of Disease
- *POR* — Prevention of Recurrence
- *Thp* — Therapeutic




Stop TB Partnership
WORKING GROUP ON NEW TB VACCINES

*Information reported by vaccine sponsors or found in clinical trial registries or other public sources*

*Institutions listed are vaccine sponsors and development partners*

*Additional information, including the full list of clinical trials for each candidate, can be accessed via the QR code or at newtbvaccines.org/tb-vaccine-pipeline/*

*Last update: 2 September 2024*

**What has changed since 2023?**

# TB Vaccine Pipeline

## *Active clinical trials of TB vaccine candidates*

There are 15 active clinical trials across 13 candidates as of November 2023.

**Platform**

- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- DNA/RNA

**Trial target population**

- Elderly
- Adults
- Adolescents
- Children
- Infants
- People living with HIV
- -mTB People without mTB infection
- +mTB People with mTB infection
- aTBd People with active TB disease
- MDR People with MDR-TB
- cTB People cured of active TB

**Primary endpoint**

- *Sf* Safety
- *POI* Prevention of Infection
- *POD* Prevention of Disease
- *POR* Prevention of Recurrence
- *Thp* Therapeutic

- Development stopped
- Trial completed


Stop TB Partnership
Working Group on New TB Vaccines

*Information reported by vaccine sponsors or found in clinical trial registries or other public sources.*
*For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/*

*Last update: 30 November 2023*

# BCG Revaccination Ph2b Prevention of Infection Trial (Gates Medical Research Institute)

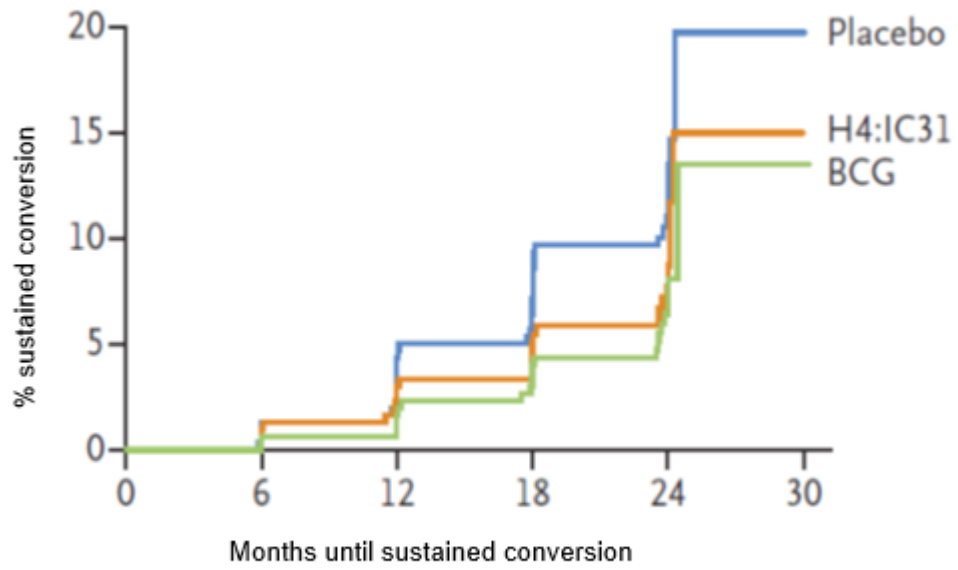
Background: BCG has had variable efficacy in multiple revaccination trials, for POD and for POI

## Aeras Phase 2 trial (C-040-404)

Secondary endpoint: sustained IGRA conversion:

N = 330 12-17 year olds/arm

VE=45% (95%CI 6.4-68%, p=0.03)




Clinicaltrials.gov NCT02075203

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

## Gates MRI Phase 2b trial

Primary endpoint: sustained IGRA conversion

N = 900 10-18 year olds (total)

Conclusion: BCG did not prevent initial or sustained IGRA conversion

Clinicaltrials.gov NCT04152161

BILL & MELINDA GATES *foundation*

# TB Vaccines - *progress report*

Ann Ginsberg

PDVAC

10 December 2024

# Late-stage candidates in Prevention of Disease trials

# M72/AS01$_{E-4}$

*adjuvanted recombinant protein*
*(antigens: Mtb32a and Mtb39a fusion protein)*

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

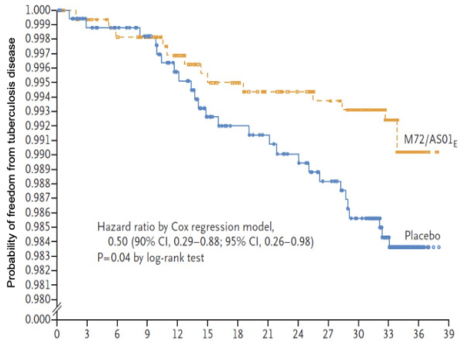
gsk

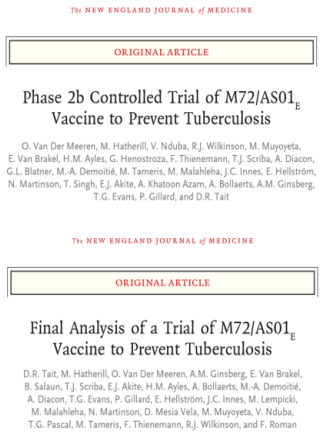
2-dose regimen; intramuscular administration

## 36 months of efficacy data

Phase 2b trial M72/AS01$_{E-4}$

- VE: reduced active pulmonary TB by 50%
- Acceptable safety profile





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

The NEW ENGLAND JOURNAL of MEDICINE

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

## Phase 3 Vaccine Efficacy Trial Design

*Enrollment started March 2024*

*Protocol Version 2, 05 Jan 2024*

- Placebo-controlled, double-blind, 1:1 randomized trial
- Assumptions:
  - Vaccine Efficacy (VE) against Disease (D) in IGRA+ individuals in per-protocol (PP) cohort is ≥55%
  - TB incidence: 0.4% per year in IGRA+
  - *Mtb* infection rate: 3% per year
- Null hypothesis: H0: VE(D) ≤ 10% (α <2.5%, lower bound of 95% confidence interval >10%)
- Event-triggered VE analysis
- N=20,000, 15 to 44 years of age
- 2 years to full enrolment (estimate)
- Follow-up up to 4 years after last participant is enrolled
- No Interim analysis
- Final analysis of primary endpoint once 110 cases are observed
- >90% power to demonstrate VE of 55% with LB>10%
- >80% power to demonstrate a VE of 50% with LB>10%

| Cohort | N |
|---|---|
| HIV-, IGRA+ cohort | 18,000 |
| HIV-, IGRA- cohort | 1,000 |
| HIV+ cohort | 1,000 |
| Total | 20,000 |

*Only TB vaccine candidate to date that has demonstrated efficacy POC and meets most WHO PPCs*

*Slide modified from Gates Medical Research Institute*

# VPM1002

*recombinant BCG*

1 dose; intradermal administration

★ *Trial complete; results pending*

## 3 TB efficacy trials:

ACTIVE TRIALS

| | |
|---|---|
| **Registry Number** | CTRI/2019/01/017026 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Indian Council of Medical Research |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults |
| | Adolescents |

★ Prevention of Disease (POD)

| | |
|---|---|
| **Registry Number** | NCT04351685 |
| **Clinical Trial Phase** | 3 |
| **Clinical Trial Sponsor** | Serum Institute of India Pvt. Ltd. |
| **Primary endpoint(s) for this clinical trial** | Prevention of Mtb infection or sustained infection |
| **Target population(s) for clinical trial** | Infants |

Prevention of Infection (POI) *(infants)*

| | |
|---|---|
| **Registry Number** | NCT03152903 / CTRI/2017/03/008266/ |
| **Clinical Trial Phase** | Phase 2/3 |
| **Clinical Trial Sponsor** | Serum Institute of India Pvt. Ltd. |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB recurrence |
| **Target population(s) for clinical trial** | Adults |
| | People cured of active TB |

★ Prevention of Recurrence

https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# IMMUVAC

*heat-inactivated M. indicus pranii (M.w)*

2-dose regimen; intradermal administration

"A Phase III, Randomized, Double-blind, three arm Placebo controlled Trial to Evaluate the Efficacy and Safety of two vaccines VPM1002 and Immuvac in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients"
[CTRI/2019/01/017026]

★ *Trial complete; results pending*

| | |
|---|---|
| **Registry Number** | CTRI/2019/01/017026 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Indian Council of Medical Research |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults |
| | Adolescents |

POD

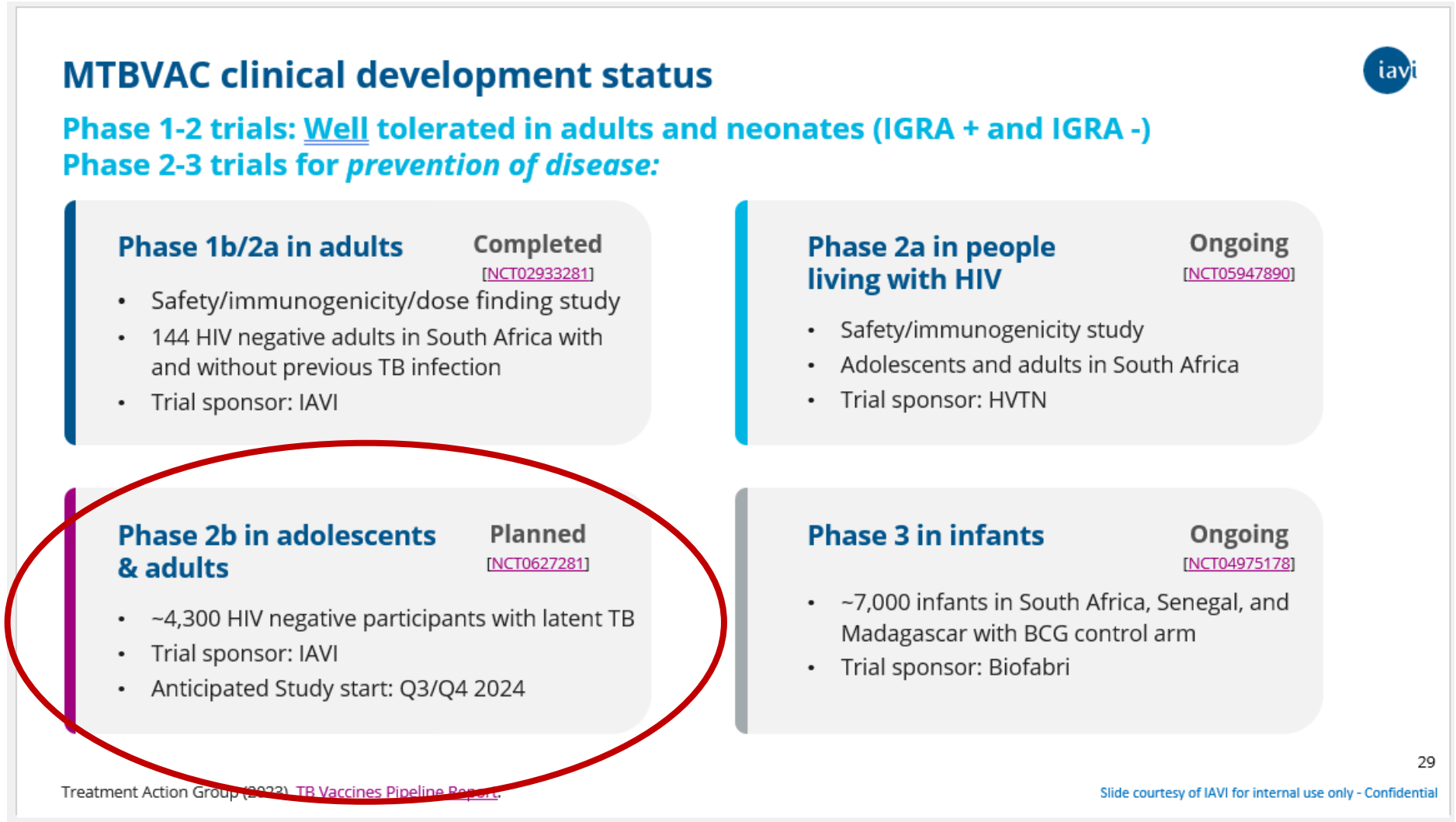
https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# MTBVAC

*live, attenuated M. tuberculosis*

1 dose; intradermal administration

Enrollment start anticipated 1Q 2025




*Modified from Dr. Elana van Brakel, IAVI*

N.F. Gamaleya Federal Research Centre for Epidemiology and Microbiology, Ministry of Health of the Russian Federation

# GamTBVAC

*adjuvanted recombinant protein (3 antigens: Ag85A, ESAT6-CFP10 fusion protein; adjuvant: Dextran 500 kDa and DEAE-Dextran 500 kDa covered with CpG oligonucleotides)*

2-dose regimen; subcutaneous administration

| | |
|---|---|
| **Registry Number** | NCT04975737 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults<br>People without Mtb infection |

3590 participants;
randomized 1:1

https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# Next 5 years – *an unprecedented bolus of efficacy trial results*

| Vaccine candidate | Results anticipated (my current best guess based on public information) |
|---|---|
| VPM1002 | |
| POD; also, IMMUVAC (MIP) | 4Q 2024 ★ |
| POR | 2024 |
| POI | 2026 |
| MTBVAC | |
| POD (infants) | 4Q 2028 |
| POD (adolescents/adults) | 2028-2029 ★ |
| BCG revac - POI | *2024 – No VE demonstrated* |
| M72/AS01$_E$ - POD | 2028 ★ |
| H56:IC31 - POR | *2024 – No POR VE demonstrated* |
| RUTI (adjunct to treatment; improved outcomes) | 4Q 2025 |
| GAMTBVAC - POD | 4Q 2025 ★ |

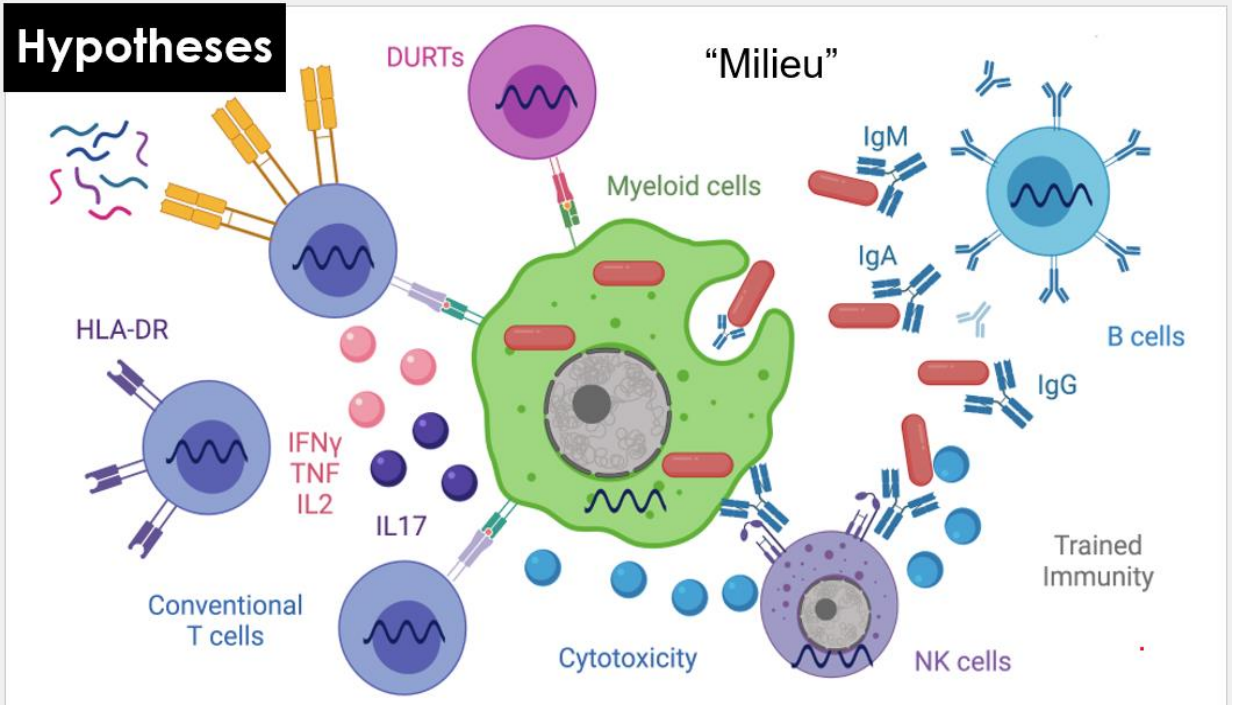
★ Adolescent/adult POD efficacy trial

# Correlates Discovery Program

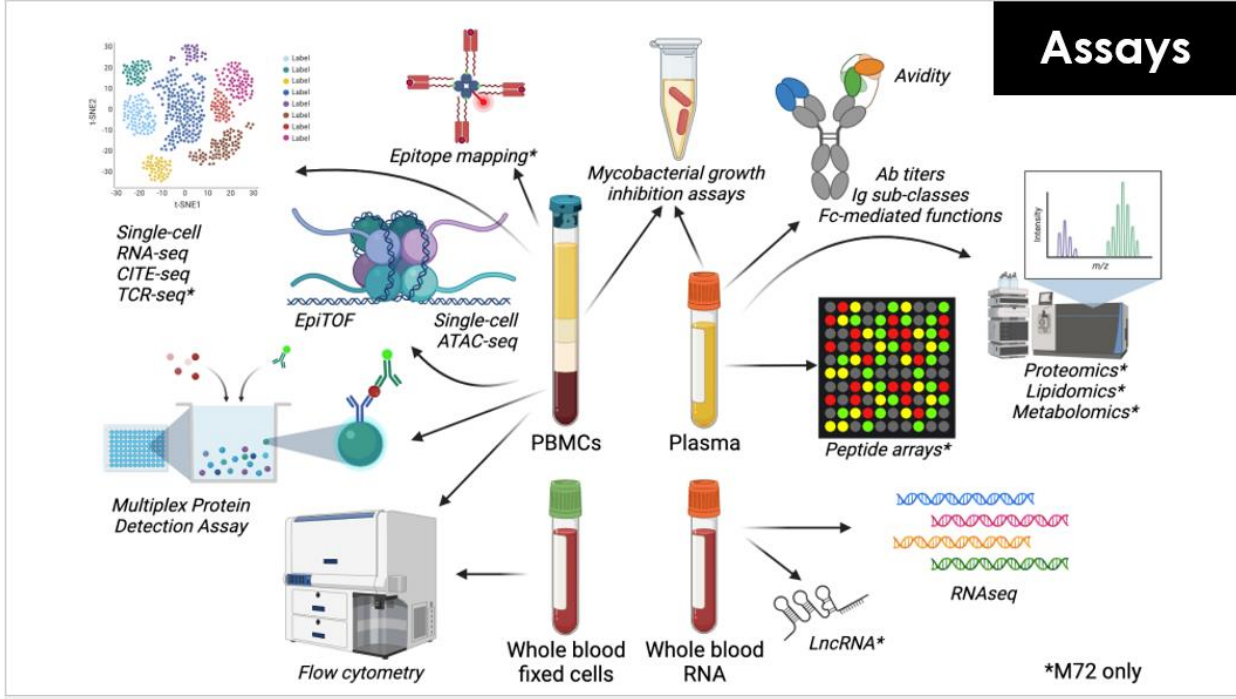
*Led by Gates MRI (Nicole Frahm) in collaboration with SATVI/UCT (Elisa Nemes, Tom Scriba)*

[Funded by Gates, Wellcome and US NIAID]

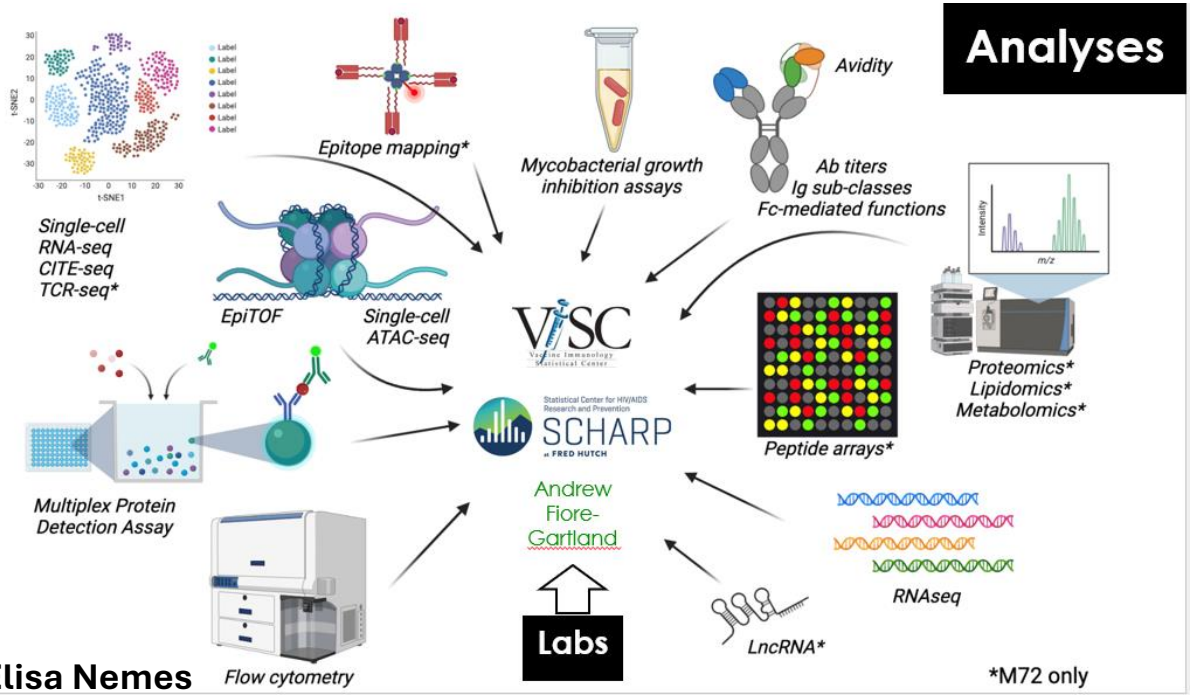
## Hypotheses




## Assays




## Analyses

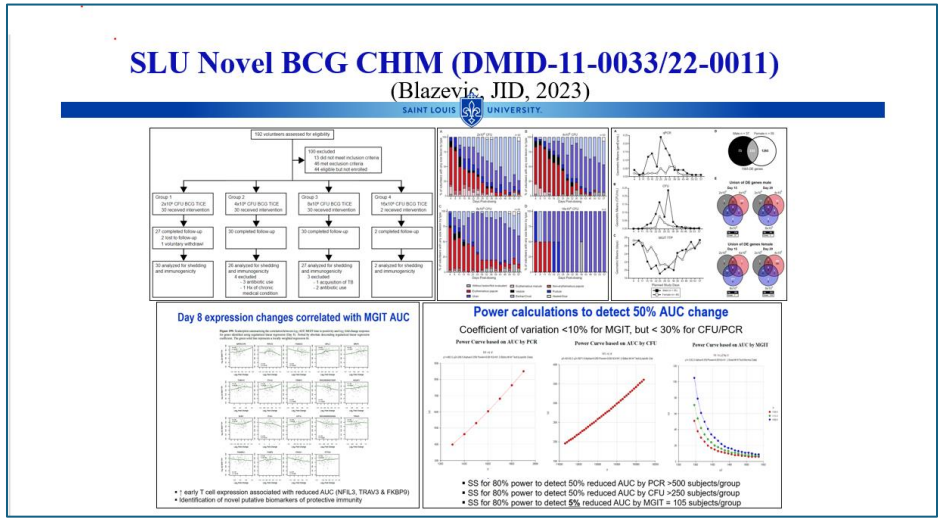



**M72** pilot studies ongoing; case/control analyses planned for 2026 – final results expected 2027

Nemes, Fiore-Gartland et al, Vaccine Insights 2022

**Slide modified from Elisa Nemes**

# Controlled Human Infection Models in Development




**BCG challenge; intradermal (Dan Hoft, St. Louis U.)**

## Aerosol BCG CHIM studies

BCG naïve volunteers

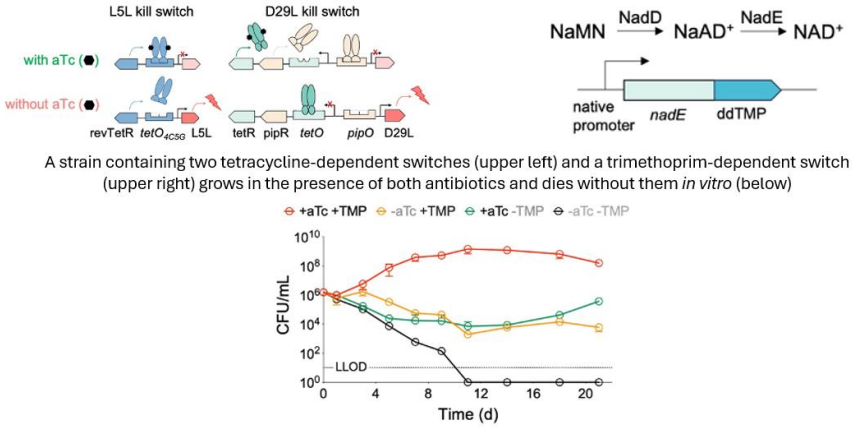
- TB041
  - Dose escalation $10^4$ – $10^7$cfu aerosol BCG
  - Bronchoscopy @ D14
  - Blood taken at multiple time points
  - ID BCG control group
  - Satti et al, Lancet Infectious Diseases 2024
- TB043
  - $10^7$cfu inhaled BCG, inhaled saline control group
  - Bronchoscopy @ D2,7,14,28,56
  - Blood taken at multiple time points
  - Marshall, Satti et al, submitted

BCG vaccinated volunteers

- TB044
  - Dose escalation $10^4$ – $10^7$cfu aerosol BCG
  - Bronchoscopy @ D14
  - Blood taken at multiple time points
  - Fredsgaard-Jones, Harris et al, submitted
- TB045
  - Evaluation of prior BCG and ID93/GLA-SE vaccination
  - Aerosol BCG challenge and bronchoscopy @ 2 weeks
  - Immune correlate evaluation

**BCG challenge; intradermal or aerosol (Helen McShane, Oxford)**

## A growth- regulated Mtb strain for CHIM




A strain containing two tetracycline-dependent switches (upper left) and a trimethoprim-dependent switch (upper right) grows in the presence of both antibiotics and dies without them *in vitro* (below)

**Attenuated *M. tb* challenge; aerosol (Eric Rubin/Sarah Fortune, Harvard)**

Thank you!

# Today's agenda

1. Status of vaccine candidates in the pipeline. Ann Ginsberg (BMGF).
2. Results from the recent H56 prevention of recurrence trial, with implications for trial design, endpoints and licensure. Mark Hatherill (SATVI, UCT).
3. Considerations for including asymptomatic TB in vaccine efficacy trials. Overview by Gavin Churchyard (Aurum), and sample size implications and next steps by Richard White (LSHTM).
4. TB vaccine accelerator update. Gitte Giersing (WHO).
5. Discussion.

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# Questions for PDVAC

1. Should novel TB vaccine be able to prevent **asymptomatic TB**? What is the pathway toward including asymptomatic TB as an endpoint in future efficacy trials?
2. Is there still value in developing a *'policy position statement'* on the preference for a **prevention of disease endpoint**? If yes, should asymptomatic TB be included?
3. What role should the TB Vaccine Accelerator and its working groups play in facilitating/informing the **vaccine manufacturing/commercialization strategy** for new TB vaccines?

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# BCG Revaccination Ph2b Prevention of Infection Trial (Gates Medical Research Institute)

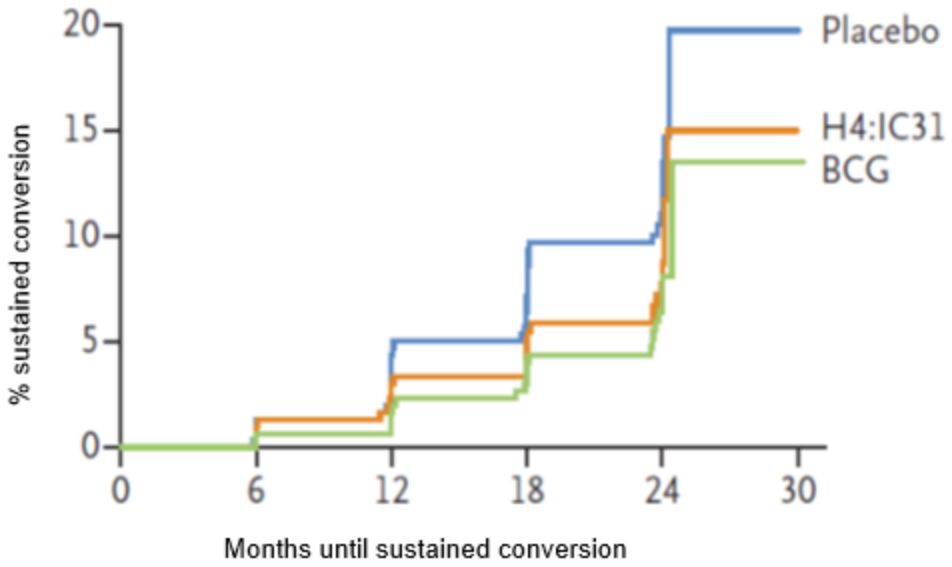
Background: BCG has had variable efficacy in multiple revaccination trials, for POD and for POI

## Aeras Phase 2 POI trial (C-040-404)

Secondary endpoint: sustained IGRA conversion:

N = 330 12-17 year olds/arm

VE=45% (95%CI 6.4-68%, p=0.03)




Clinicaltrials.gov NCT02075203

Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

## Gates MRI Phase 2b POI trial

Primary endpoint: sustained IGRA conversion

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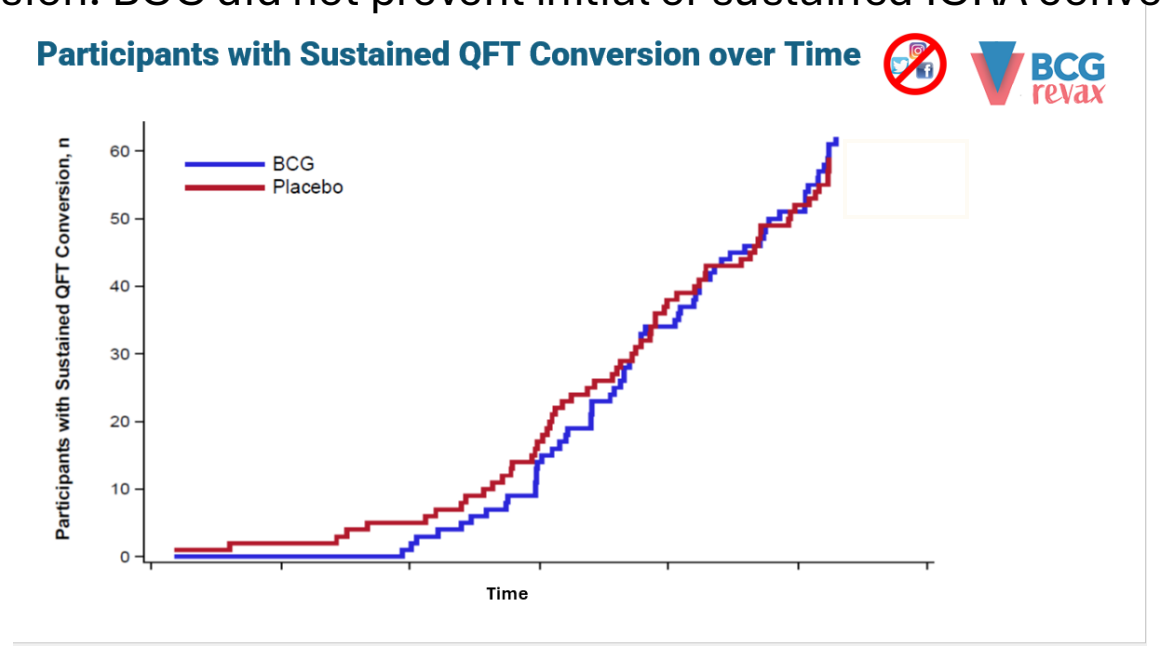
Conclusion: BCG did not prevent initial or sustained IGRA conversion




Clinicaltrials.gov NCT04152161

*Figure courtesy of Gates MRI*

NOTE: cannot draw any conclusions about POD

# Late-stage candidates in Prevention of Disease trials

# M72/AS01$_{E-4}$

*adjuvanted recombinant protein (antigens: Mtb32a and Mtb39a fusion protein)*

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

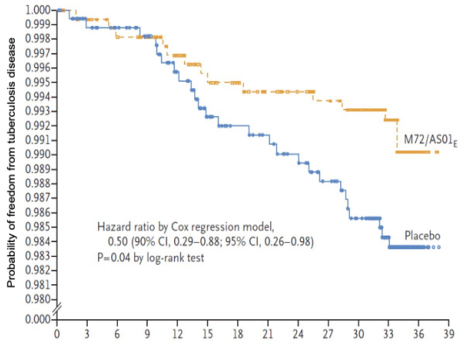
gsk

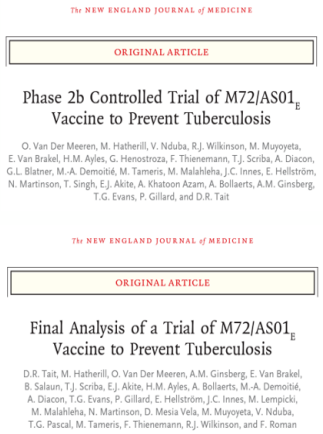
2-dose regimen; intramuscular administration

## 36 months of efficacy data

Phase 2b trial M72/AS01$_{E-4}$

- VE: reduced active pulmonary TB by 50%
- Acceptable safety profile





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

The NEW ENGLAND JOURNAL of MEDICINE

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

## Phase 3 Vaccine Efficacy Trial Design

*Enrollment started March 2024*

*Protocol Version 2, 05 Jan 2024*

- Placebo-controlled, double-blind, 1:1 randomized trial
- Assumptions:
  - Vaccine Efficacy (VE) against Disease (D) in IGRA+ individuals in per-protocol (PP) cohort is ≥55%
  - TB incidence: 0.4% per year in IGRA+
  - *Mtb* infection rate: 3% per year
- Null hypothesis: H0: VE(D) ≤ 10% (α <2.5%, lower bound of 95% confidence interval >10%)
- Event-triggered VE analysis
- N=20,000, 15 to 44 years of age
- 2 years to full enrolment (estimate)
- Follow-up up to 4 years after last participant is enrolled
- No Interim analysis
- Final analysis of primary endpoint once 110 cases are observed
- >90% power to demonstrate VE of 55% with LB>10%
- >80% power to demonstrate a VE of 50% with LB>10%

| Cohort | N |
|---|---|
| HIV-, IGRA+ cohort | 18,000 |
| HIV-, IGRA- cohort | 1,000 |
| HIV+ cohort | 1,000 |
| Total | 20,000 |

*Only TB vaccine candidate to date that has demonstrated efficacy POC and meets WHO PPCs*

*Slide modified from Gates Medical Research Institute*

# VPM1002

*recombinant BCG*

1 dose; intradermal administration

★ *Trial complete; results pending*

## 3 TB efficacy trials:

ACTIVE TRIALS

| | |
|---|---|
| **Registry Number** | CTRI/2019/01/017026 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Indian Council of Medical Research |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults |
| | Adolescents |

★ Prevention of Disease (POD)

| | |
|---|---|
| **Registry Number** | NCT04351685 |
| **Clinical Trial Phase** | 3 |
| **Clinical Trial Sponsor** | Serum Institute of India Pvt. Ltd. |
| **Primary endpoint(s) for this clinical trial** | Prevention of Mtb infection or sustained infection |
| **Target population(s) for clinical trial** | Infants |

Prevention of Infection (POI) *(infants)*

| | |
|---|---|
| **Registry Number** | NCT03152903 / CTRI/2017/03/008266/ |
| **Clinical Trial Phase** | Phase 2/3 |
| **Clinical Trial Sponsor** | Serum Institute of India Pvt. Ltd. |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB recurrence |
| **Target population(s) for clinical trial** | Adults |
| | People cured of active TB |

★ Prevention of Recurrence

https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# IMMUVAC

*heat-inactivated M. indicus pranii (M.w)*

2-dose regimen; intradermal administration

"A Phase III, Randomized, Double-blind, three arm Placebo controlled Trial to Evaluate the Efficacy and Safety of two vaccines VPM1002 and Immuvac in Preventing Tuberculosis (TB) in Healthy Household Contacts of Newly Diagnosed Sputum Positive Pulmonary TB Patients"
[CTRI/2019/01/017026]

★ *Trial complete; results pending*

| | |
|---|---|
| **Registry Number** | CTRI/2019/01/017026 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Indian Council of Medical Research |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults |
| | Adolescents |

POD

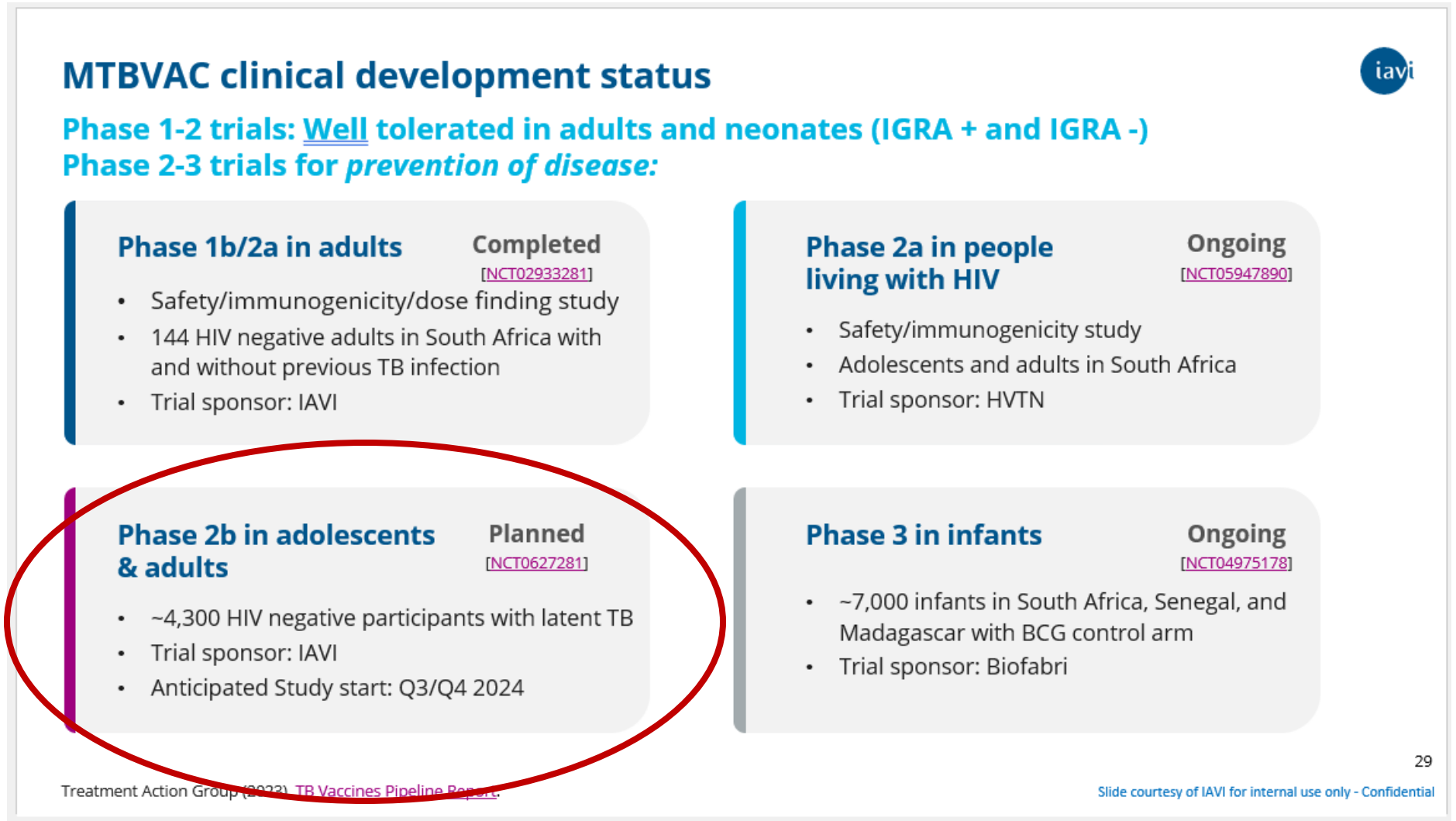
https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# MTBVAC

*live, attenuated M. tuberculosis*

1 dose; intradermal administration

Enrollment start anticipated 1Q 2025




*Modified from Dr. Elana van Brakel, IAVI*

N.F. Gamaleya Federal Research Centre for Epidemiology and Microbiology, Ministry of Health of the Russian Federation

# GamTBVAC

*adjuvanted recombinant protein (3 antigens: Ag85A, ESAT6-CFP10 fusion protein; adjuvant: Dextran 500 kDa and DEAE-Dextran 500 kDa covered with CpG oligonucleotides)*

2-dose regimen; subcutaneous administration

| | |
|---|---|
| **Registry Number** | NCT04975737 |
| **Clinical Trial Phase** | Phase 3 |
| **Clinical Trial Sponsor** | Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation |
| **Primary endpoint(s) for this clinical trial** | Prevention of TB disease |
| **Target population(s) for clinical trial** | Adults |
| | People without Mtb infection |

3590 participants; randomized 1:1

https://newtbvaccines.org/vaccine/vpm1002/ *(Stop TB Working Group on New Vaccines)*

# Next 5 years – *an unprecedented bolus of efficacy trial results*

| Vaccine candidate | Results anticipated (current best guess) |
|---|---|
| VPM1002 | |
| POD; also, IMMUVAC (MIP) | 4Q 2024 ★ |
| POR | 2024 |
| POI | 2026 |
| MTBVAC | |
| POD (infants) | 4Q 2028 |
| POD (adolescents/adults) | 2028-2029 ★ |
| BCG revac - POI | *2024 – No VE demonstrated* |
| M72/AS01$_E$ - POD | 2028 ★ |
| H56:IC31 - POR | *2024 – No POR VE demonstrated* |
| RUTI (adjunct to treatment; improved outcomes) | 4Q 2025 |
| GAMTBVAC - POD | 4Q 2025 ★ |

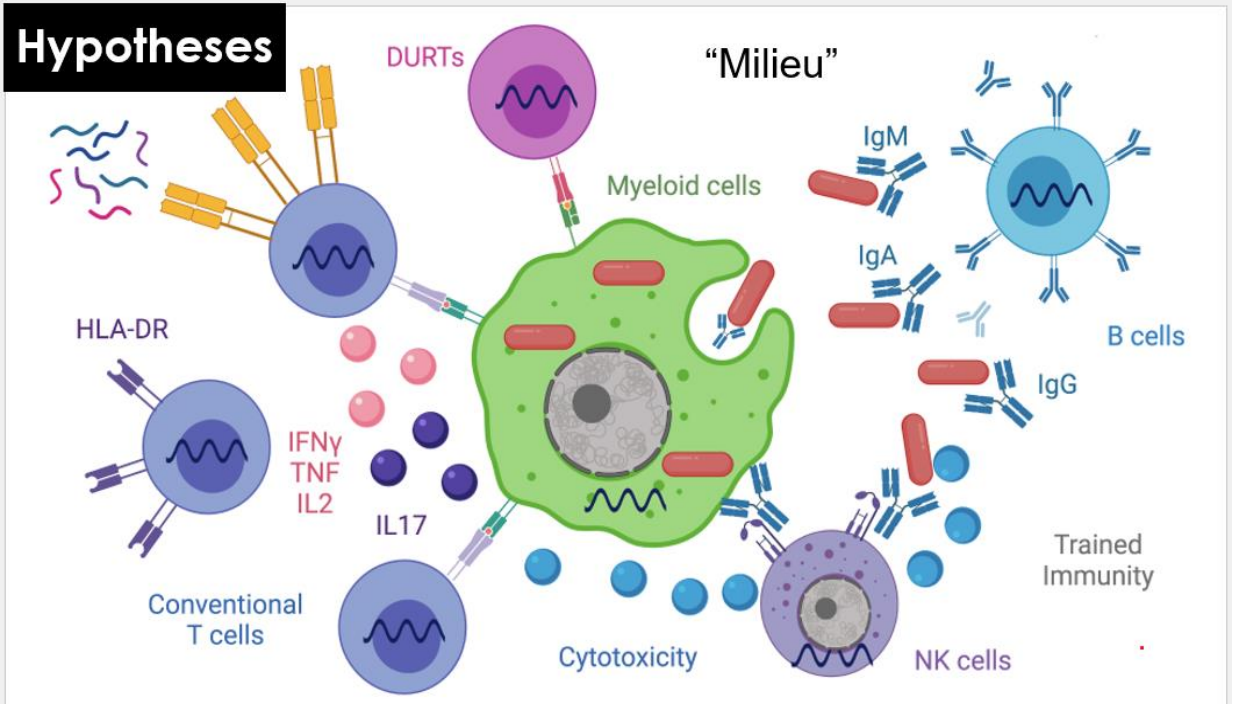
★ Adolescent/adult POD efficacy trial

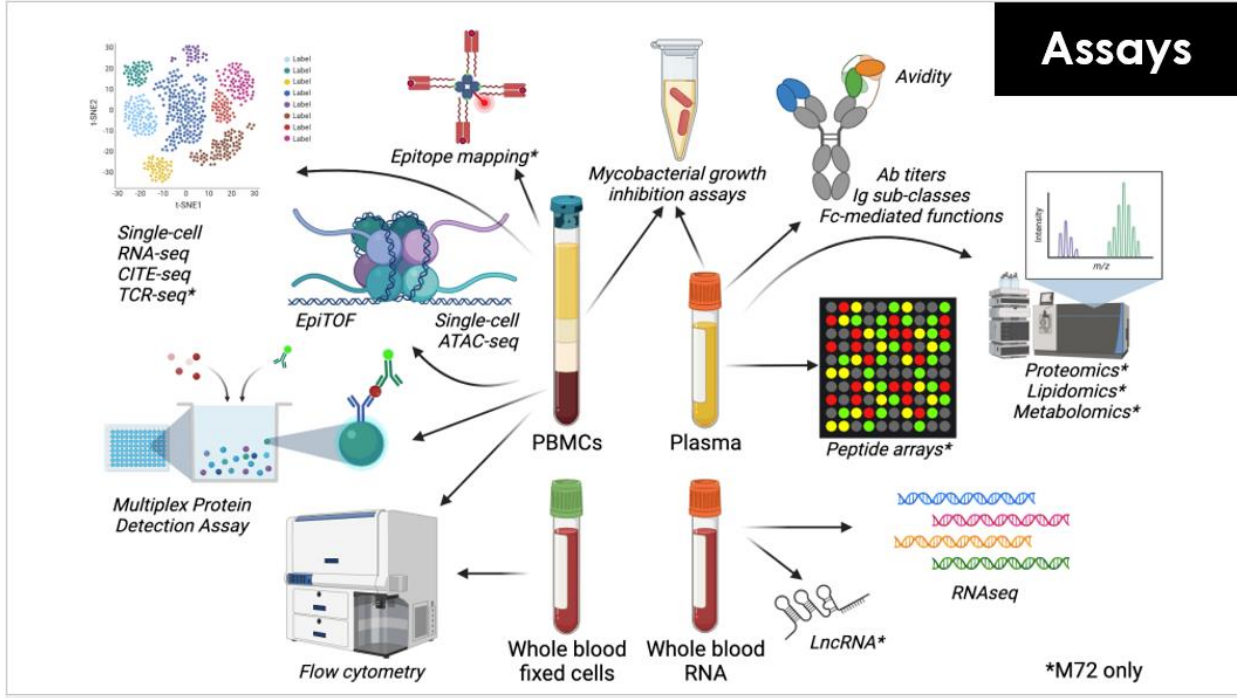
KEY ENABLER #1:

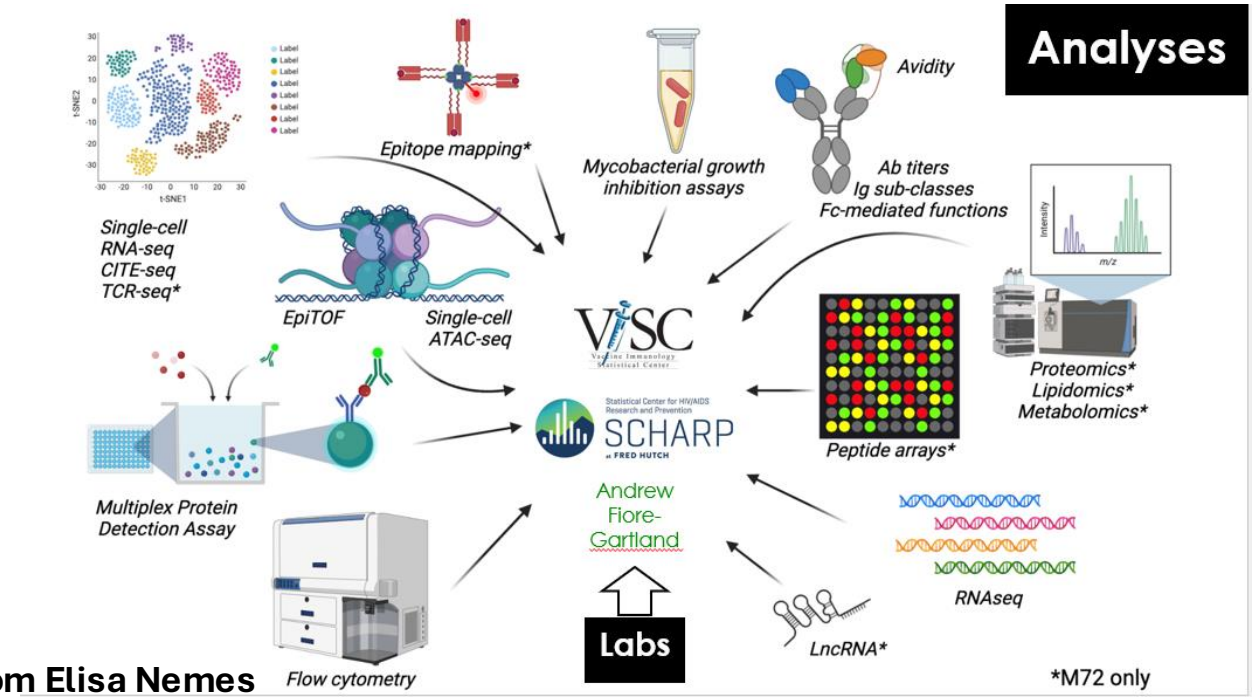
# Correlates Discovery Program

*Led by Gates MRI (Nicole Frahm) in collaboration with SATVI/UCT (Elisa Nemes, Tom Scriba)*

[Funded by Gates, Wellcome and US NIAID]



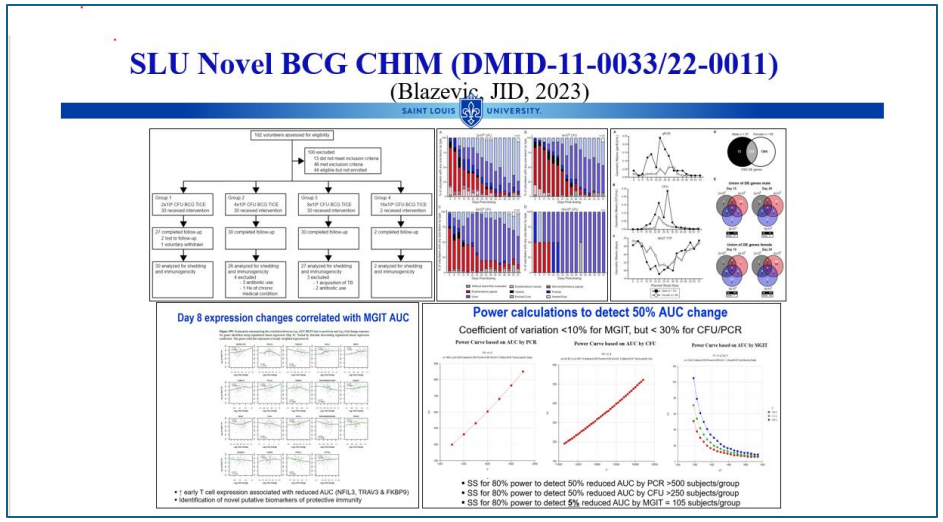

**M72** pilot studies ongoing; case/control analyses planned for 2026 – final results expected 2027

Nemes, Fiore-Gartland et al, Vaccine Insights 2022

**Slide modified from Elisa Nemes**

KEY ENABLER #2:

# Controlled Human Infection Models in Development




**BCG challenge; intradermal (Dan Hoft, St. Louis U.)**

## Aerosol BCG CHIM studies

BCG naïve volunteers

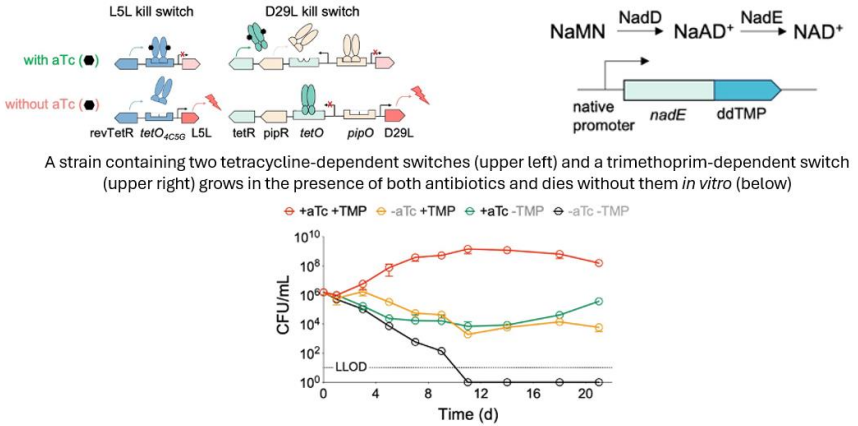
- TB041
  - Dose escalation $10^4$ – $10^7$cfu aerosol BCG
  - Bronchoscopy @ D14
  - Blood taken at multiple time points
  - ID BCG control group
  - Satti et al, Lancet Infectious Diseases 2024
- TB043
  - $10^7$cfu inhaled BCG, inhaled saline control group
  - Bronchoscopy @ D2,7,14,28,56
  - Blood taken at multiple time points
  - Marshall, Satti et al, submitted

BCG vaccinated volunteers

- TB044
  - Dose escalation $10^4$ – $10^7$cfu aerosol BCG
  - Bronchoscopy @ D14
  - Blood taken at multiple time points
  - Fredsgaard-Jones, Harris et al, submitted
- TB045
  - Evaluation of prior BCG and ID93/GLA-SE vaccination
  - Aerosol BCG challenge and bronchoscopy @ 2 weeks
  - Immune correlate evaluation

**BCG challenge; intradermal or aerosol (Helen McShane, Oxford)**

## A growth- regulated Mtb strain for CHIM




**Attenuated *M. tb* challenge; aerosol (Eric Rubin/Sarah Fortune, Harvard)**

Thank you!

# Asymptomatic TB: implications for TB vaccine trial designs and development

PDVAC

10th December 2024

Prof. Gavin Churchyard

MBBCh, FCP (SA), FRCP (Edin), MMED (WITS), PhD (WITS)

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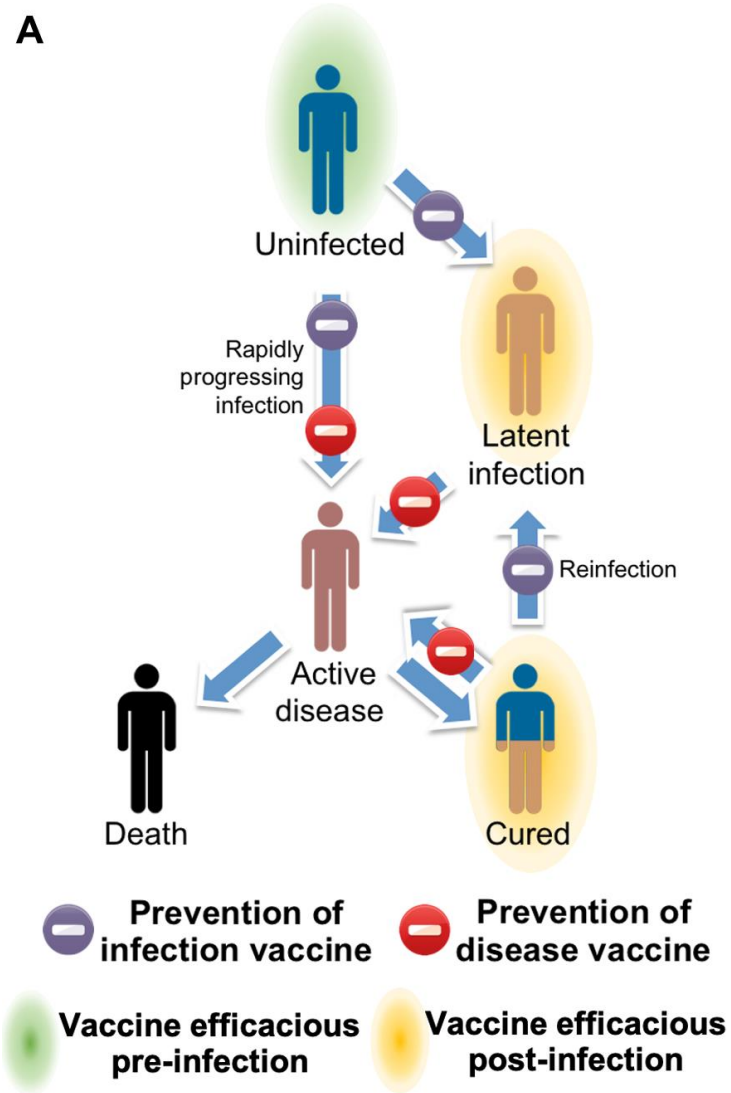
# Overview

- Background
- Subclinical TB
  - Clinical characteristics
  - Implications of infectious scTB for POD TB vaccine trials
  - Trial design options
- Conclusion

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# Background

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# Background

- WHO Definition (2024): A person with TB disease who did not report symptoms suggestive of TB during screening, which may be bacteriologically confirmed or unconfirmed
- Asymptomatic TB (aTB) accounts for half of prevalent TB globally
- Empirical data on transmissibility of aTB and its post-TB sequelae are very limited
- The WHO Preferred Product Characteristics for POD TB vaccines do not consider the implications of aTB
- The TB vaccine Roadmap identifies aTB as a research gap
- Regulators typically require efficacy endpoints to be specific, it is therefore likely that only microbiologically confirmed aTB would be counted as an efficacy endpoint

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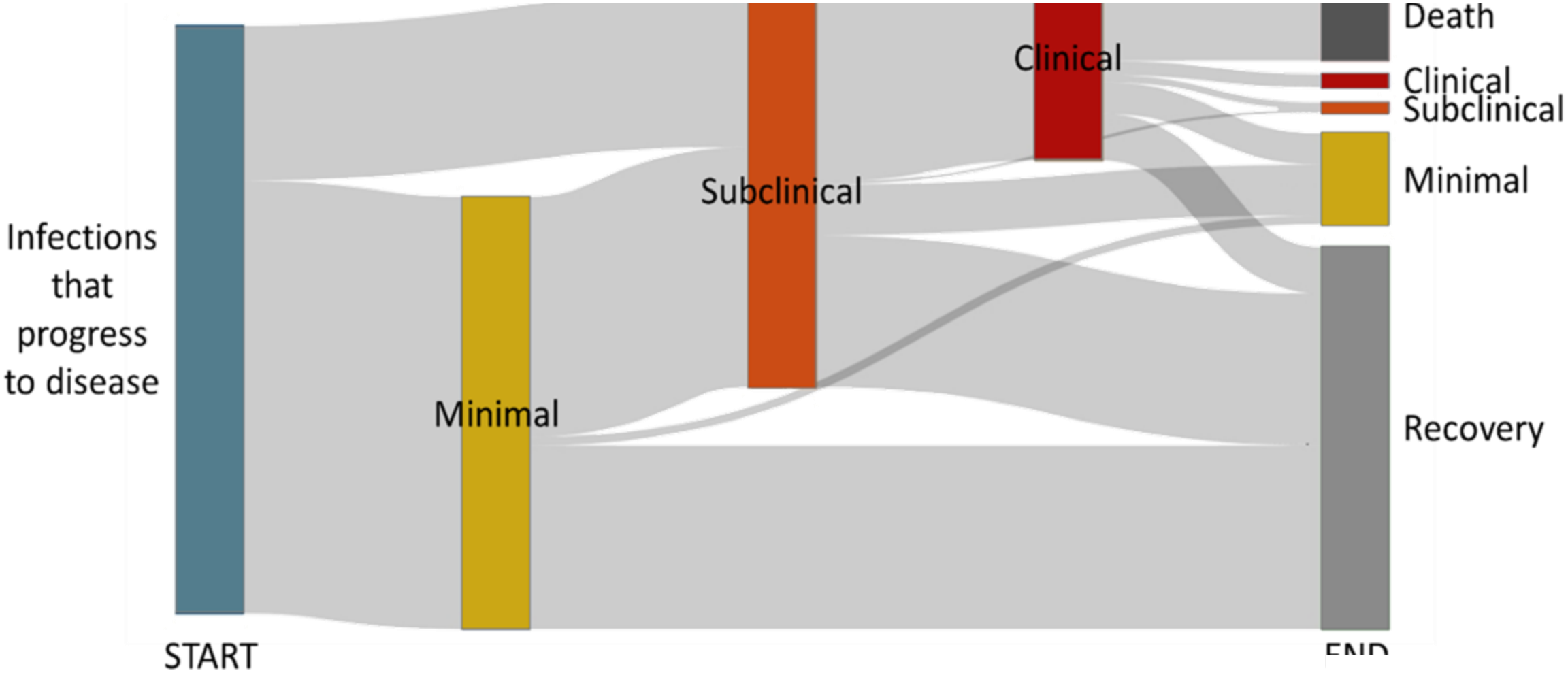
# Model estimated pathways over 10 years following *Mtb* infection




Horton KC. Proc Natl Acad Sci USA. 2023

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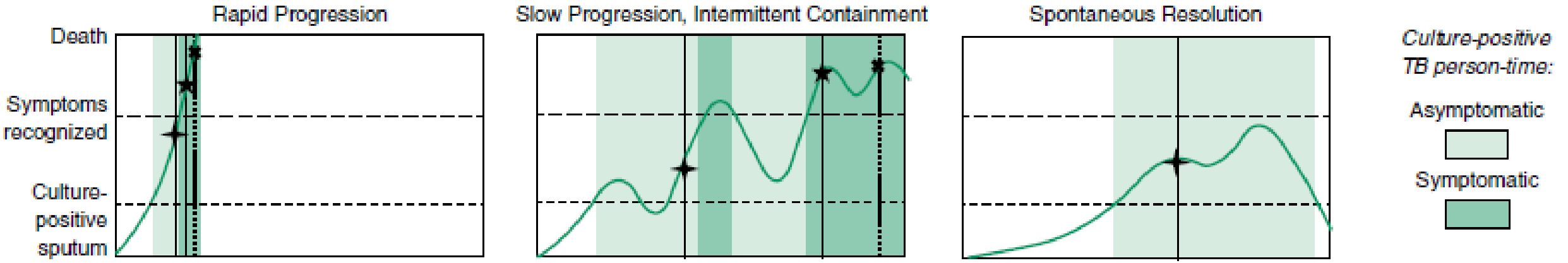
# Natural history




Kendall. Am J Respir Crit Care Med, 2021

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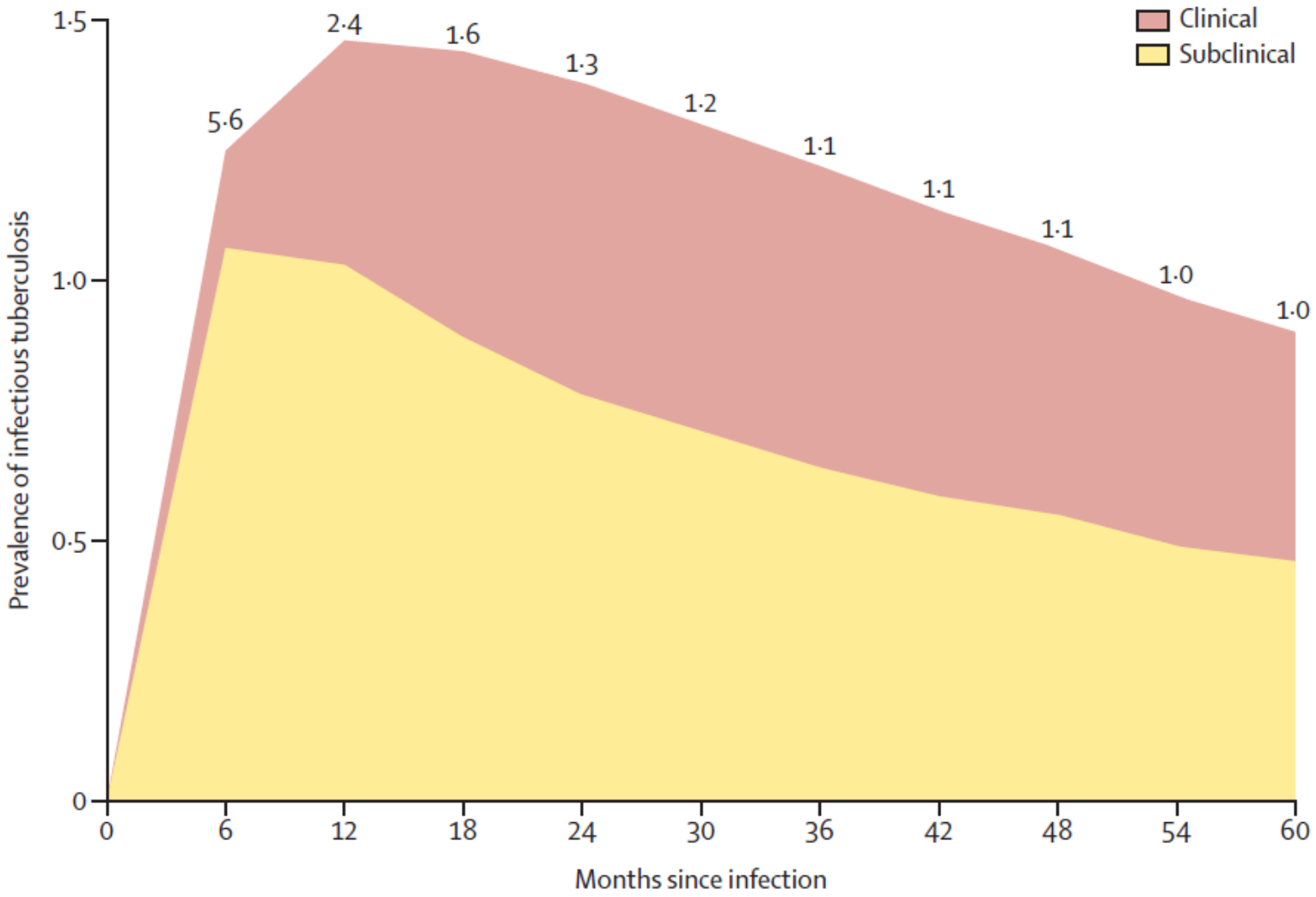
# Model estimated ratio of scTB vs cTB after infection




Horton KC. Proc Natl Acad Sci USA. 2023

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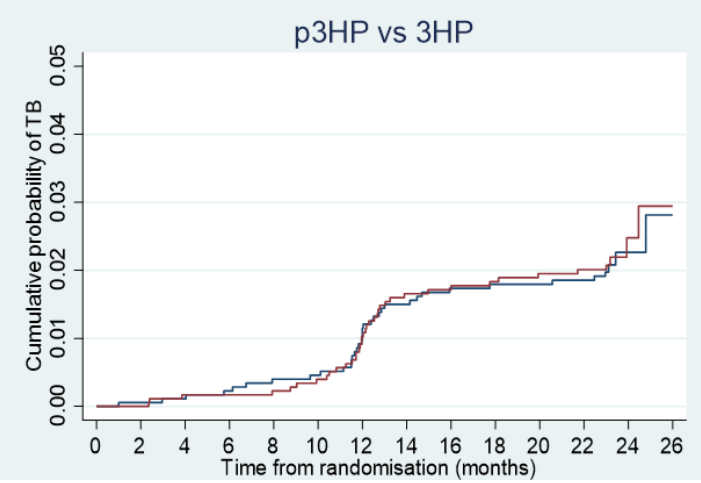
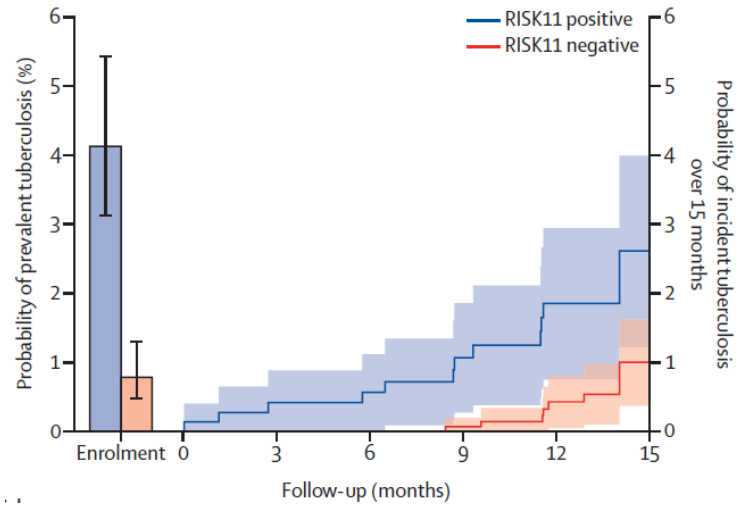
# scTB & POD TB vaccines

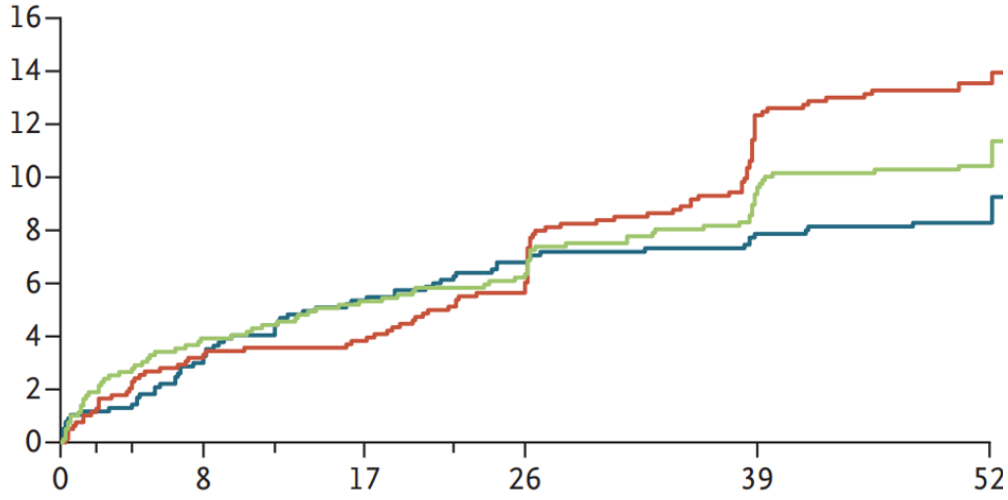
- Screening for TB in TB preventive treatment trials and treatment of disease trials detected a sizable burden of scTB




**WHIP3TB**
**Annual screen**




**CORTIS**
**Screen end of trial**




**S31/A5349**
**Screened 6 monthly post end of Rx**

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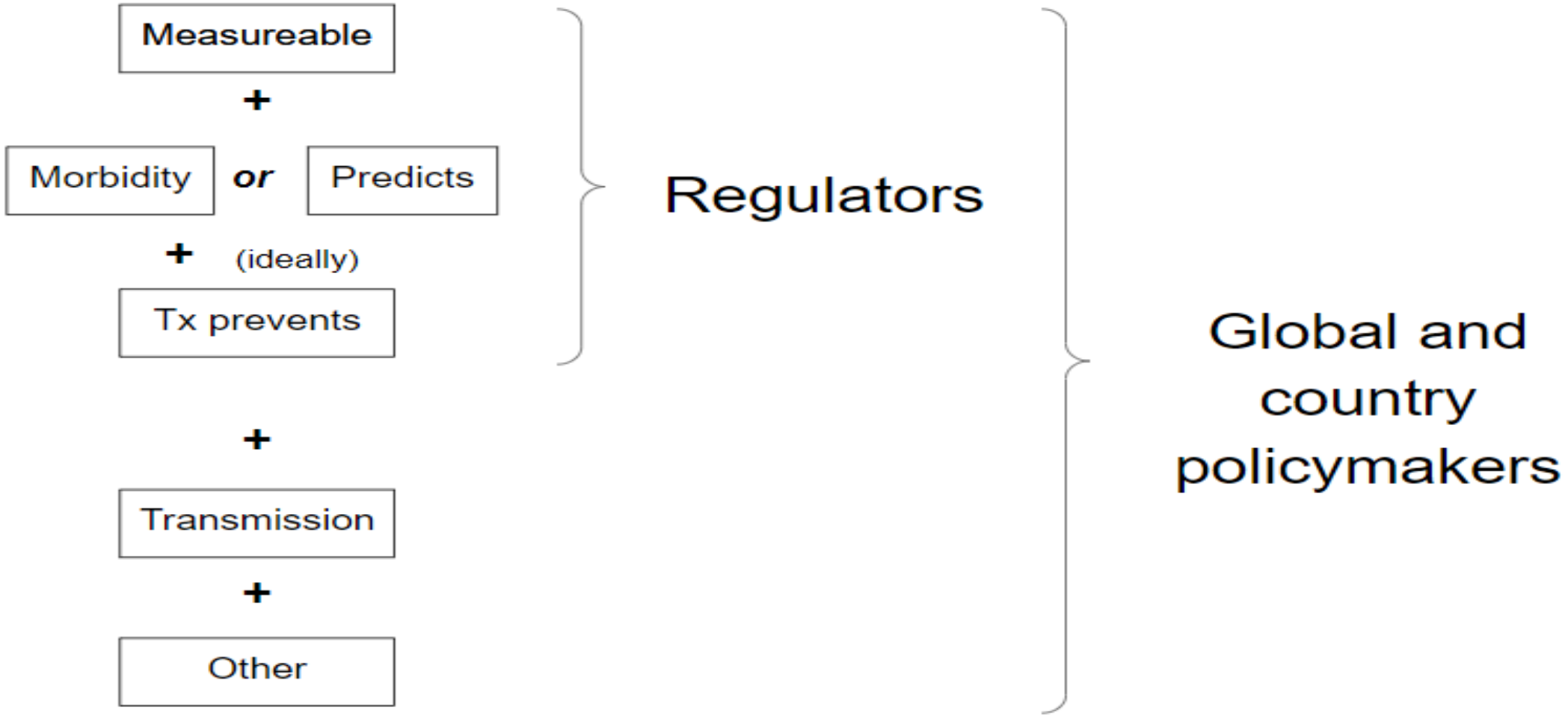
# What evidence is required to include infectious aTB as a co-primary endpoint?

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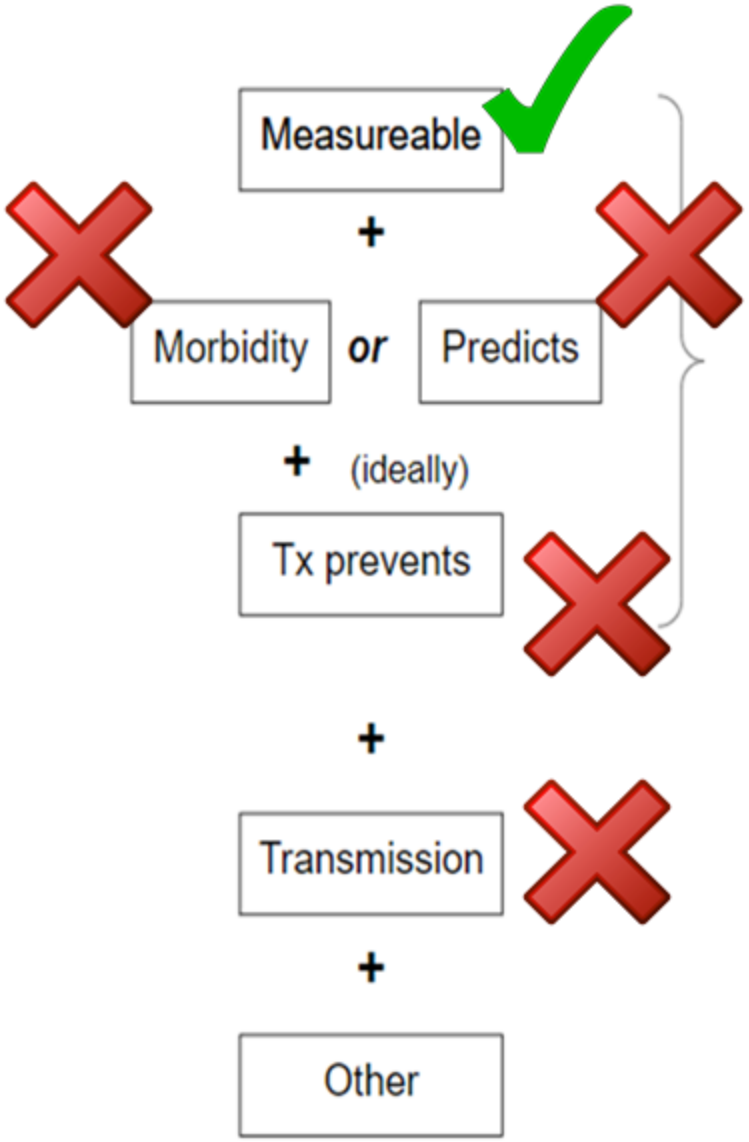
# We don’t know enough….




Regulators

Global and country policymakers

# Clinical characteristics

The available data is limited and either not on the endpoint of interest (i.e. infectious asymptomatic TB), or is not of high enough quality for regulators

# Clinical characteristics

Scoping review of scTB (1)

- Not well described
- Less extensive disease
- Higher treatment success
- Lower mortality

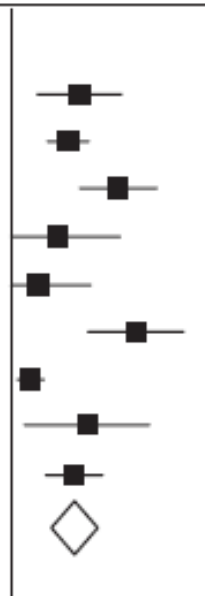
**Comparison of chest computed tomography findings of active and subclinical tuberculosis diseases (2)**

| Radiographic findings | All patients (n = 412) | Active TB disease (n = 331) | Subclinical TB disease (n = 81) |
|---|---|---|---|
| Multiple lobe involvement | 168 (36.1–45.6%) | 144 (38.3–48.9%) | 24 (20.8–40.3%) |
| Tree-in-bud sign | 247 (55.1–64.6%) | 191 (52.3–62.9%) | 56 (58.4–78.1%) |
| Cavitation | 165 (35.4–44.9%) | 129 (33.9–44.3%) | 36 (34.1–55.3%) |
| Consolidation | 242 (53.9–63.4%) | 204 (56.3–66.7%) | 38 (36.4–57.7%) |
| Fibrotic scar | 73 (14.3–21.7%) | 65 (15.7–24.3%) | 8 (5.1–18.3%) |
| Atelectasis | 71 (13.9–21.2%) | 62 (14.9–23.3%) | 9 (6.0–19.8%) |
| Emphysema | 58 (11.1–17.8%) | 45 (10.3–17.7%) | 13 (9.6–25.5%) |
| Bronchiectasis | 82 (16.3–24.0%) | 67 (16.3–24.9%) | 15 (11.6–28.3%) |

1. Teo. Eur Respir Rev. 2024; 2. Min et al. BMC Pulm Med (2020) 20:316

# Progression from bacteriology negative to positive TB disease

| | Patients who progressed (n) | Cohort size (n) | Follow-up (months) | Annualised rate (95% CI) |
|---|---|---|---|---|
| **Active** | | | | |
| Frimodt-Moller et al (1965)[33] | 25 | 86 | 36 | 0·10 (0·04–0·17) |
| Okada et al (2012)[52] | 51 | 309 | 24 | 0·09 (0·06–0·12) |
| Cowie et al (1985)[31] | 88 | 152 | 58 | 0·16 (0·11–0·22) |
| Nørregaard et al (1990)[51] | 8 | 28 | 48 | 0·07 (0·00–0·17) |
| Borgen et al (1950, 1951)[28,29] | 2 | 24 | 30 | 0·04 (0·00–0·12) |
| Aneja et al (1979)[24] | 21 | 110 | 12 | 0·19 (0·12–0·26) |
| National Tuberculosis Institute (1974, 1976, 1978, 1982)[42–50] | 36 | 271 | 60 | 0·03 (0·01–0·05) |
| Beeuwkes et al (1942)[25] | 13 | 43 | 33 | 0·12 (0·02–0·21) |
| Hong Kong Chest Service (1979, 1981, 1984)[34–37] | 71 | 176 | 60 | 0·10 (0·05–0·14) |
| **Random-effects model** | | | | **0·10 (0·06–0·13)** |
| Heterogeneity: Q=40·8, df=8 (p<0·0001); $I^2$=77·4%, $\tau^2$=0·0020 | | | | |



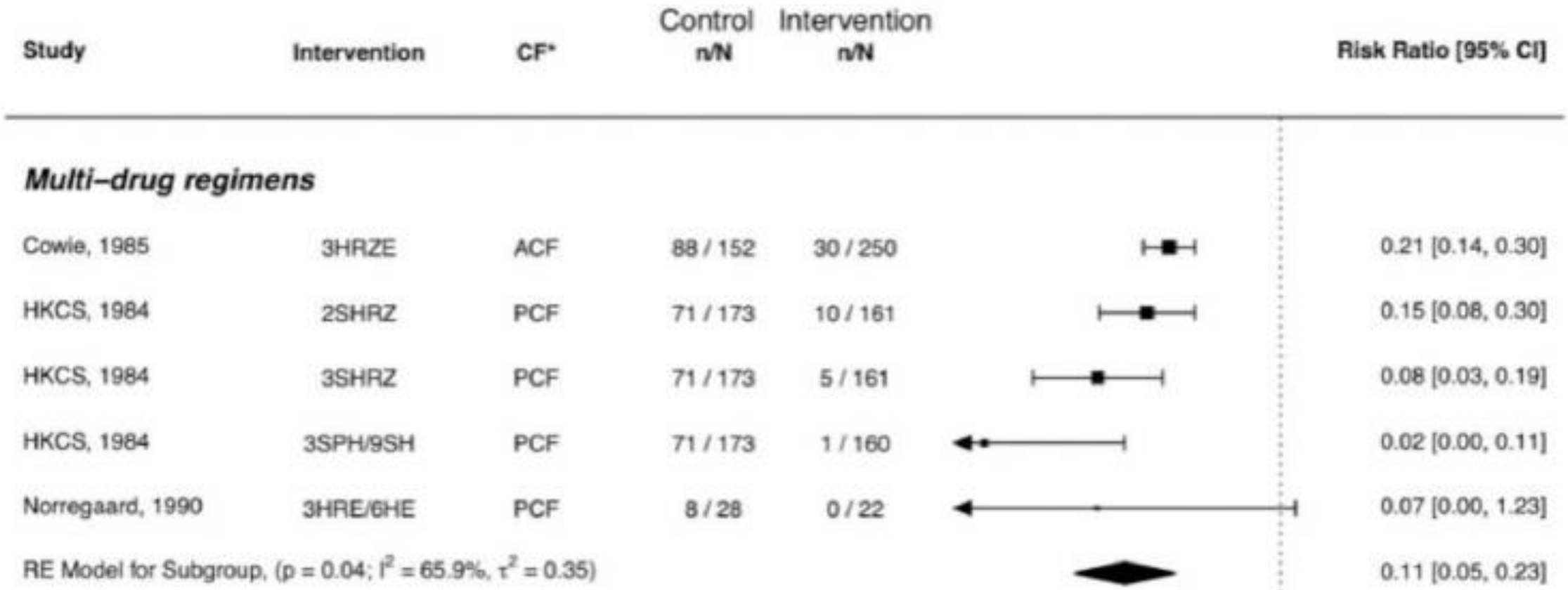
Among persons with CXR evidence of TB, negative microbiology, untreated, and with, without or unknown symptoms suggestive of TB, 10%/year progressed to bact+ve TB

In 3 studies that included people with non-infectious subclinical TB, the rates of progression to bacteriologically positive TB were similar (range 4-12% per year).

(Sossen. Lancet RM. 2023)

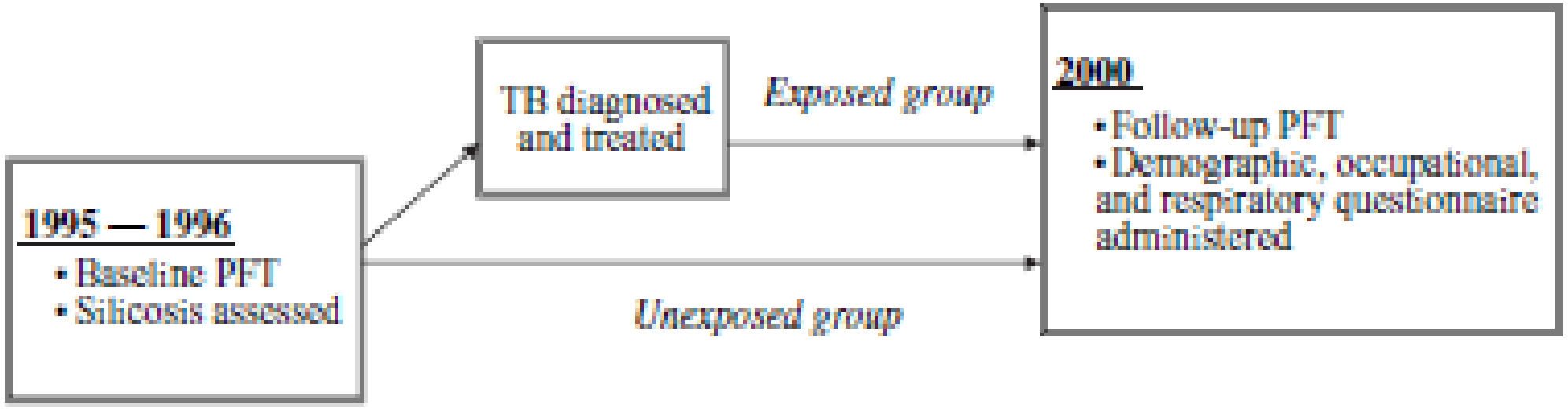
# Treatment prevents progression

Multidrug treatment of patients with radiological TB and negative sputum cultures prevents progression to culture positive TB




(Gray. PLOS One, 2023)

# Post TB lung function impairment




Lung function impairment was less in miners with TB: detected by CXR screening, less extensive disease, and smear negative

(Ross J. Thorax. 2010)

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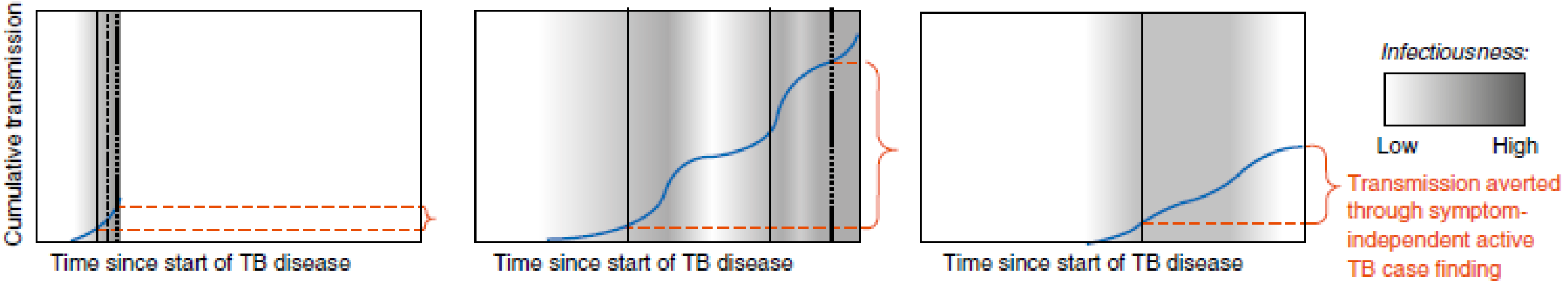
# scTB and transmission




**scTB may contribute substantially to transmission on a population level because of its high prevalence and long duration**

Kendall. Am J Respir Crit Care Med, 2021

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# TB vaccine POD trial design options for evaluating efficacy in preventing infectious aTB & sTB

**Churchyard. Lancet Microbe. 2024**

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# Trial design options

**Design 1**
Symptom TB screen

**Endpoint**
1°: sTB

**Design 2**
Symptom-independent TB screen at end of study follow up

**Endpoint**
1°: sTB

2°: aTB-end of follow-up

**Design 3**
Symptom-independent TB screen during & end of follow up. Testing differed to end of study

**Endpoint**
1°: sTB

2° : aTB during & end of follow-up

**Design 4**
Realtime symptom-independent TB investigations during and at end of follow up

**Endpoint**
1°: Composite aTB & sTB

**In all designs, TB is excluded prior to enrolment using a symptom screen and sputum for Xpert**

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# Trial design options

**Design 1**
Symptom TB screen

**Endpoint**
1°: sTB

**Design 2**
**Symptom-independent TB screen** at end of study follow up

**Endpoint**
1°: sTB

2°: aTB-end of follow-up

**Design 3**
**Symptom-independent TB screen** during & end of follow up. Testing differed to end of study

**Endpoint**
1°: sTB

2° : aTB during & end of follow-up

**Design 4**
Realtime **symptom-independent TB investigations** during and at end of follow up

**Endpoint**
1°: Composite aTB & sTB

**In all designs, TB is excluded prior to enrolment using a symptom screen and sputum for Xpert**

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# Trial design options

**Design 1**
Symptom TB screen

**Endpoint**
1°: sTB

**Design 2**
Symptom-independent TB screen at end of study follow up

**Endpoint**
1°: sTB

2°: aTB-end of follow-up

**Design 3**
Symptom-independent TB screen during & end of follow up. Testing differed to end of study

**Endpoint**
1°: sTB

2° : aTB during & end of follow-up

**Design 4**
Realtime symptom-independent TB investigations during and at end of follow up

**Endpoint**
1°: Composite aTB & sTB

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# Special considerations: CXR screening

- Including a chest radiograph at study entry and or follow up for Designs 2–4 might yield important information to understand the effects of the vaccine on non-infectious aTB
- However, implications for inclusion criteria and treatment would need to be addressed
- Possible options for including chest radiography at study entry and follow up include
  - Do not look, therefore can't treat
  - Look and do not treat
  - Look and treat

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# Trial design options

**Design 4a**

Baseline: symptoms + sputum for Xpert

Follow up: realtime symptom-independent TB investigations (sputum for Xpert/culture)

**Endpoint**

Composite

aTB & sTB

**Design 4b**

Baseline: symptoms, ***CXR***, & sputum for Xpert

Follow up: Realtime symptom-independent TB investigations (***CXR***),

If new CXR abnormality, Ix for TB

**Endpoint**

Composite

***CXR***+/bact+

Symptom+/bac+

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# Design 4: benefit & risks of using a composite endpoint

Benefits

- In a trial that actively screens for and detects aTB in real time, infectious aTB will substantially contribute to the number of endpoints in a trial using a composite endpoint of aTB and sTB
- The benefit of using a composite endpoint is that it would
  - Require a  smaller sample size
  - Be faster to implement
  - Cost less

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# Design 4: benefit & risks of using a composite endpoint

Risks

- RA's do not currently recognise aTB as a co-primary endpoint
- If we actively screen for, detect and treat aTB, then we prevent possible progression to sTB
- This approach would compromise our ability to show efficacy in preventing sTB
- Experience from BCG, M72/ASO1e, COVID19, influenza, rotavirus, pertussis, and pneumococcal vaccines, suggests that vaccines may have differential efficacy in preventing severe and milder forms of disease

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# Design 4: benefit & risks of using a composite endpoint

Risks

- If the vaccine is more efficacious in preventing symptomatic TB than aTB, there is a risk of rejecting a potentially efficacious vaccine for preventing sTB
- If the vaccine is more effective in preventing aTB than sTB, potentially we could have a false positive result
- Use of a composite endpoint may be acceptable if there is evidence that a vaccine has similar efficacy in preventing aTB and sTB
- A signal of differential efficacy could be obtained in a phase 2b trial using the Design 3 option and collecting and storing sputum during and end of follow

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# Regulatory & ethical considerations

- Regulators recognise sTB as the primary endpoint as it is well characterised, is associated with morbidity, mortality & transmission
- Symptom screening only during follow up accepted by regulators & ethics committees
  - aTB not detected & treated
- Screening for aTB at end of follow up acceptable to regulators and ethics committees
- Collection & storage of sputum for culture and Xpert during follow up may be acceptable to regulators & ethics committees
- Collection & real-time processing of sputum for culture and Xpert during follow up will be acceptable to ethics committees, but regulators may not accept aTB being included in a composite endpoint without further evidence
  - Treating aTB would prevent possible progression to sTB

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# Conclusion

- aTB accounts for half of prevalent TB and likely to be an important driver of transmission and result in morbidity
- If aTB is associated with morbidity and transmission, it is important to know whether TB vaccines are effective in preventing symptomatic and asymptomatic TB
- Various clinical trial design options would allow the efficacy of TB vaccines in preventing symptomatic and asymptomatic TB to be determined
- Evidence needed to support including aTB as part of a composite primary endpoint
- Policy and practice with respect to screening for and treating aTB is rapidly evolving

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# Acknowledgements


- **Richard White**
- **Rein Houben**
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- Vidya Mave
- Alemnew Dagnew
- Alexander Schmidt
- Ann Ginsburg
- Puneet Dewan
- Kristin Croucher
- Frank Cobelens
- Willem Hanekom
- Philip Hill
- Lewis Schrager
- Rebecca Clark
- Margaret Stanley
- Helen Rees
- Puck Pelzer
- Joel Ernst
- Johan Vekemans
- Mike Frick
- Tom Evans
- Sujatha Nambiar


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# Duration/sample size implications & next steps to evaluate the feasibility of infectious asymptomatic endpoints as a pivotal endpoint

Problem

- Won't get another $500m to fund POD ph3
- Need alternatives…

Takeaways

1. Modelling suggests may get ~2x endpoints if include infectious asymptomatic TB
2. Modelling suggests trials could be ~50% shorter / smaller
3. But currently don't know enough about infectious asymptomatic TB to convince regulators, WHO, countries, …
4. Need to have structured discussions to ensure we are getting all the data we need
5. Will cost, but all cheaper than one ph3!

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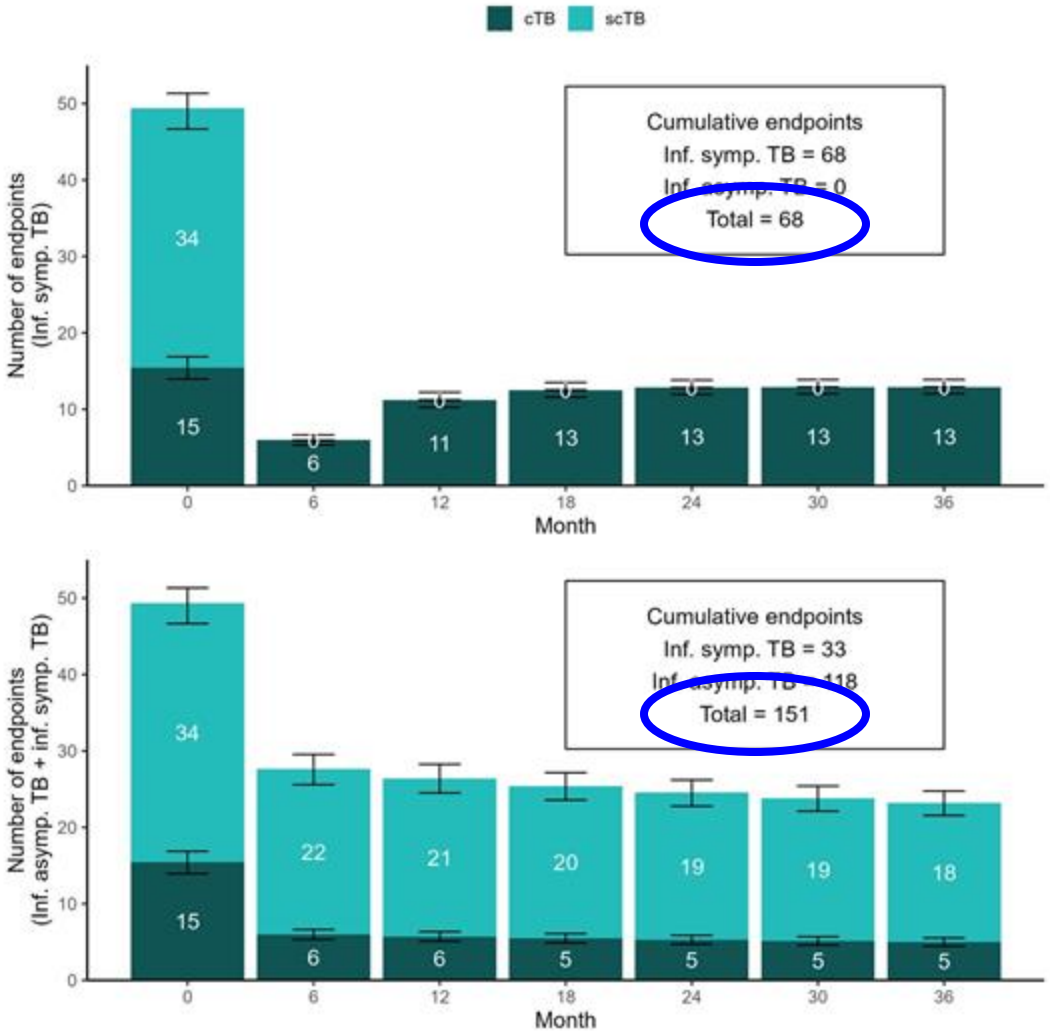
# Modelling suggests may get ~2x as many endpoints if include infectious asymptomatic TB




Assume

- N=10,000 in each arm, 3 years f/up. 300/100k infectious sympt. TB incidence before trial screening
- No direct data on incidence of inf. asympt. vs sympt. TB or progression from inf. asympt. to inf. sympt. TB
- Fit *Model* to to best available current data on other things

Results suggest

- **~2x as many endpoints if include inf. asympt. TB**

**Big data gaps** - results most sensitive to

- Probability of prog. from inf. asympt. to inf. sympt. TB
- Sensitivity/specificity of screening/diagnostic tools for aTB vs sTB



*Katherine Horton, LSHTM, unpublished,.Please do not cite* *

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# Modelling suggests trials could be ~50% shorter or enrol ~50% participants

Assume

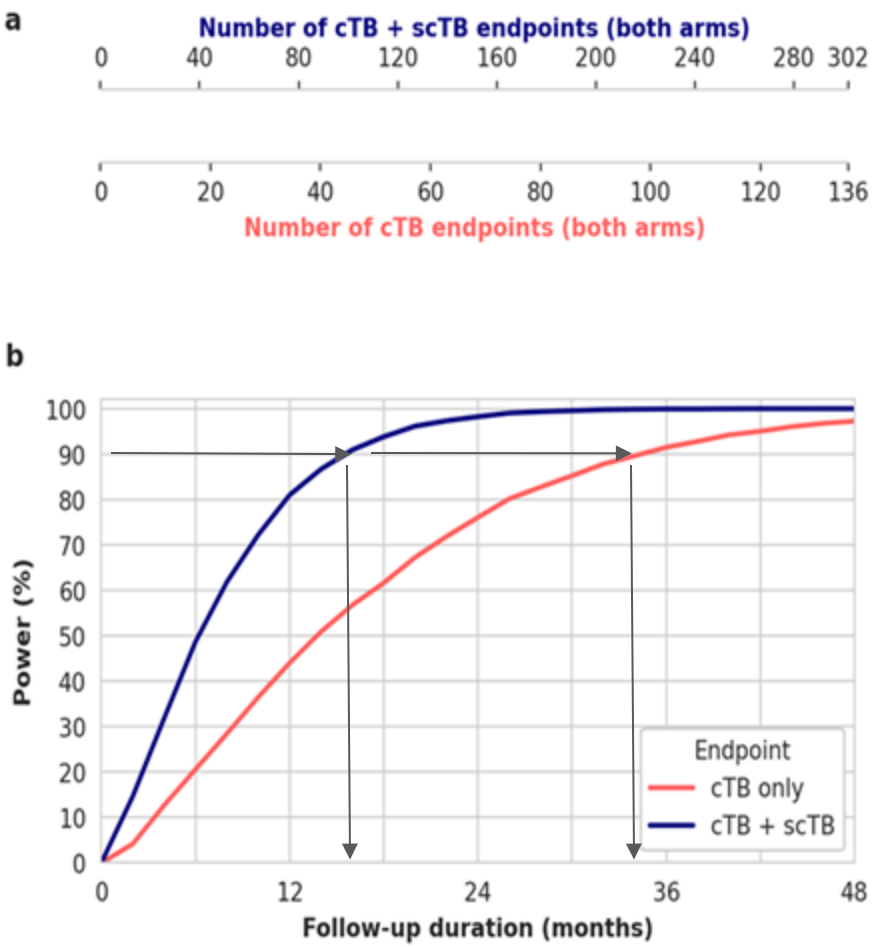
- N=10,000 in each arm, 3 years f/up. 300/100k inf. sympt. TB incidence before trial screening
- Vaccine 50% efficacy on inf. asympt & inf. sympt. TB

Results suggest

- 90% power to detect a vaccine with an efficacy 95% CI lower bound greater than 0%
  - 34 months for inf. sympt. TB only endpoint
  - 16 months for inf. asympt. + inf. sympt. TB endpoint
- **Trials could be ~50% shorter or enrol ~50% participants (~5,000 per arm)**

**Big data gaps** - results most sensitive to

- Probability of progression from inf. asympt. to inf. sympt. TB
- Relative efficacy of vaccine on asympt and sympt TB

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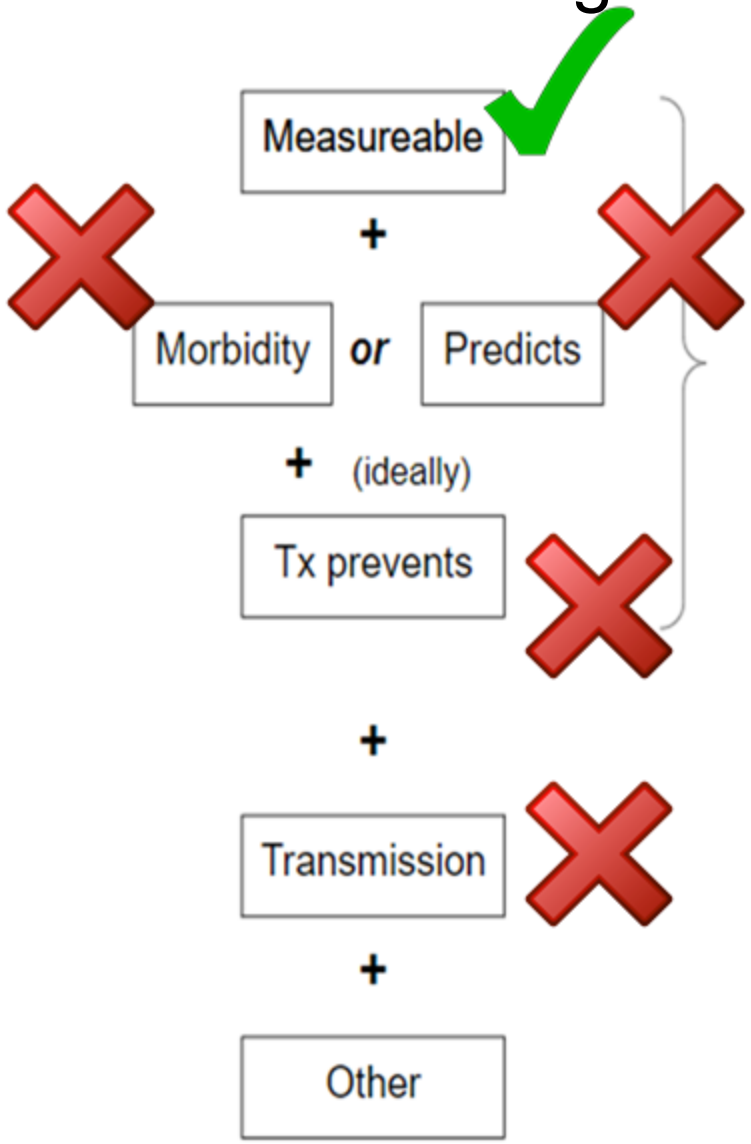
# We don’t know enough….




Regulators

Global and country policymakers

# Key data gaps are fillable….

| Design | Morbidity | Predicts progression | Tx Prevents | Transmission |
|---|---|---|---|---|
| **Systematic reviews & meta analyses** | X | X | X | X |
| **Secondary analysis of existing data** | X | X | X | |
| **Cross sectional studies of symptom-agnostic community-based screening or prevalence surveys** | X | | | |
| **Prospective observational cohort studies** | X | X | X | |
| **Prospective follow-up of HHCs without symptoms suggestive of TB randomised to continued follow-up or TB investigations** | X | X | X | |
| **Randomised trial of treatment or no-treatment of inf. asympt. TB** | X | X | X | |
| **cRCT of symptom-based vs. symptom-agnostic ACF** | X | | | X |

# Key data gaps are <u>being filled…</u>

| Study | Morbidity | Predicts progression | Tx Prevents | Transmission |
|---|---|---|---|---|
| Transmission study in prisons; IGRA on people sharing cell of asymp or symp TB; phylogenetic inferred transmission comparisons of asymp or symp TB **Completed** | | | | X |
| TBfacemask: Face mask sampling of sympt vs asympt people with C+ TB identified in community screening in Uganda including Tx outcomes; **2025** | X | | | X |
| Prospective biomarkers of inf. asymp. TB; South Africa; 42 sites; CoVPN 3008 TB sub-study; **2025** | X | | X | |
| Molecular epi & GWAS in PLHIV in Mozambique **2028** | X | X | | X |
| RADIO TB. Trial to id appropriate treatment duration for bac-neg TB in ZAF, ZIM, PAK **2029** | X | | X | |

+ at least 6 studies proposed

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# Next steps

- Need to ensure data being collected will characterise aTB ‘well enough’ for regulators etc
- Need discussion with broader range of
  - Regulators
  - WHO PQ
  - Country decision makers
- Ongoing trials need to measure impact on inf. asympt. TB


- **Inf. asympt. TB research and policy evaluation needs $s, but would probably all be cheaper than just one ph3 POD Vx trial**

# Duration/sample size implications & next steps to evaluate the feasibility of infectious asymptomatic endpoints as a pivotal endpoint

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The subclinical TB evidence gap: Evidence required to evaluate the use of infectious subclinical TB as a primary endpoint in prevention of disease TB vaccine licensure trials

v2024_11_06

White, G, Richard [1], Gavin Churchyard* [2], Katherine Horton* [1], Andrew Fiore-Gartland* [3], Marcel A Behr**[4], Rebecca A Clark** [1], Frank Cobelens**[5,6], Joel D. Ernst** [7], Hanif Esmail**[8], Alberto L. Garcia-Basteiro**[9], Sri Rezeki Hadinegoro**[10], Willem A Hanekom**[11], Katherine Jeffery**[12], Philip C Hill**[13], Rudzani Muloiwa**[14], Puck T. Pelzer**[15], Lele

Epidemiology, London School of Hygiene & Tropical Medicine, Hygiene & Tropical Medicine, London, UK
Africa. Department of Medicine, Vanderbilt
Faculty of Health Sciences, University of
Center, Seattle, WA, USA
University of





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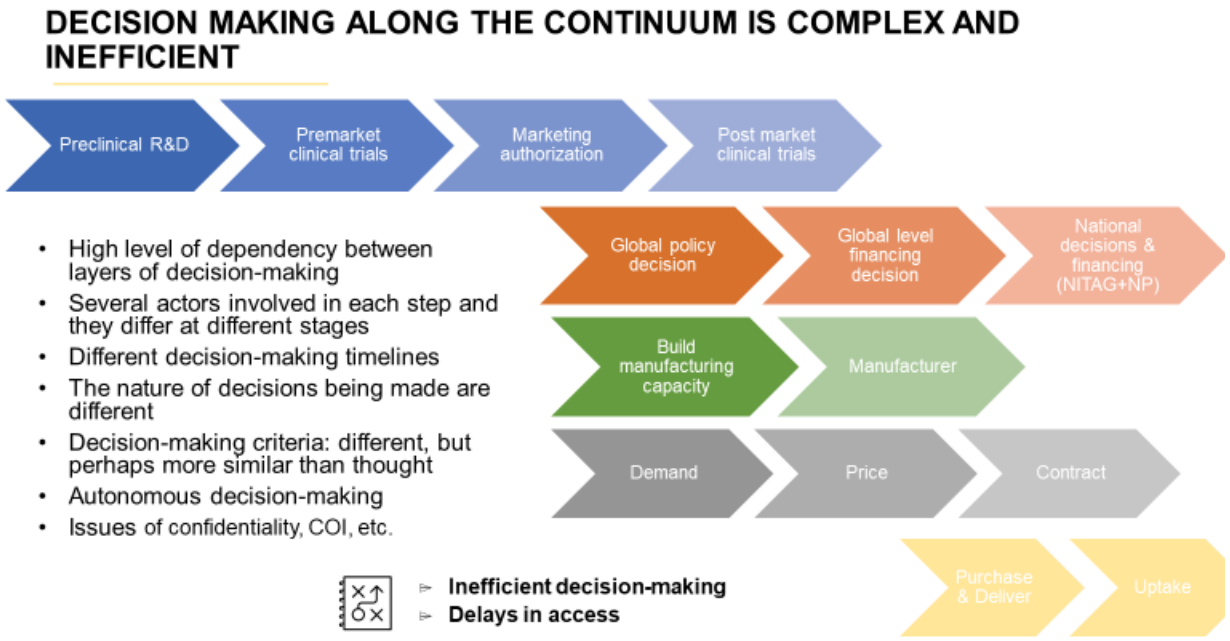
World Health Organization

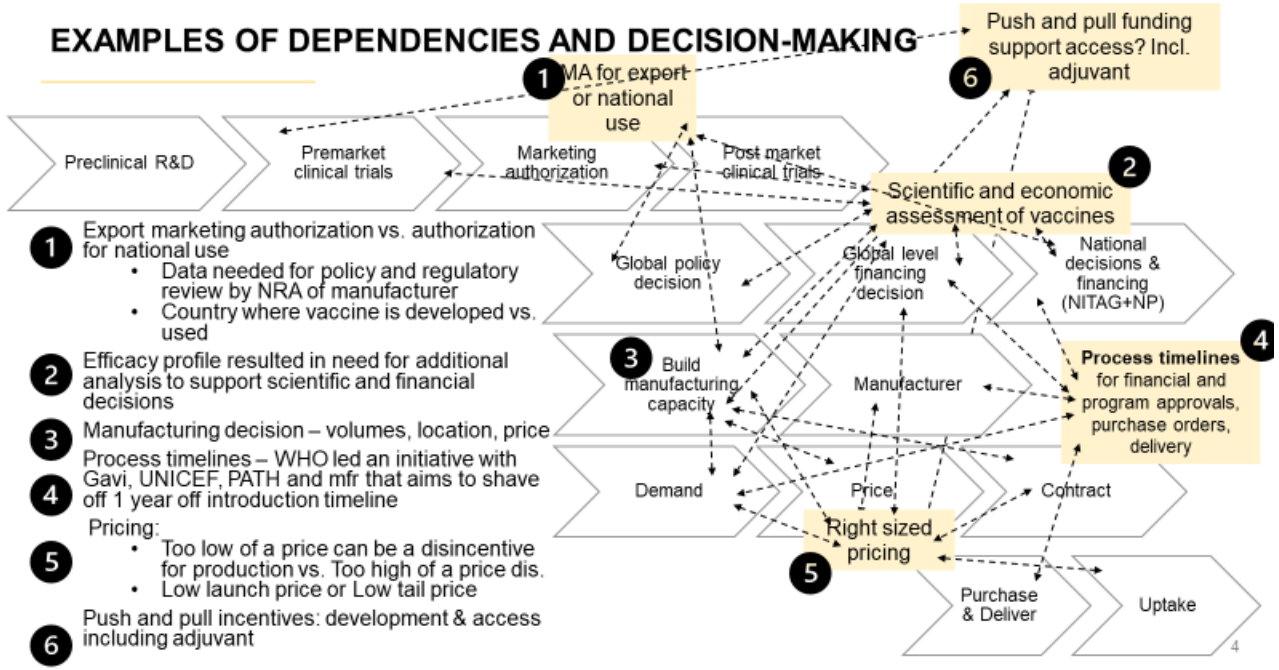
# Update on the TB Vaccine Accelerator

Birgitte Giersing, PhD
Lead, TB vaccines and TB Vaccine Accelerator
Team lead, Vaccine prioritization and platforms,
Product & delivery research unit
**Department of Immunization, Vaccines & Biologicals (IVB)**

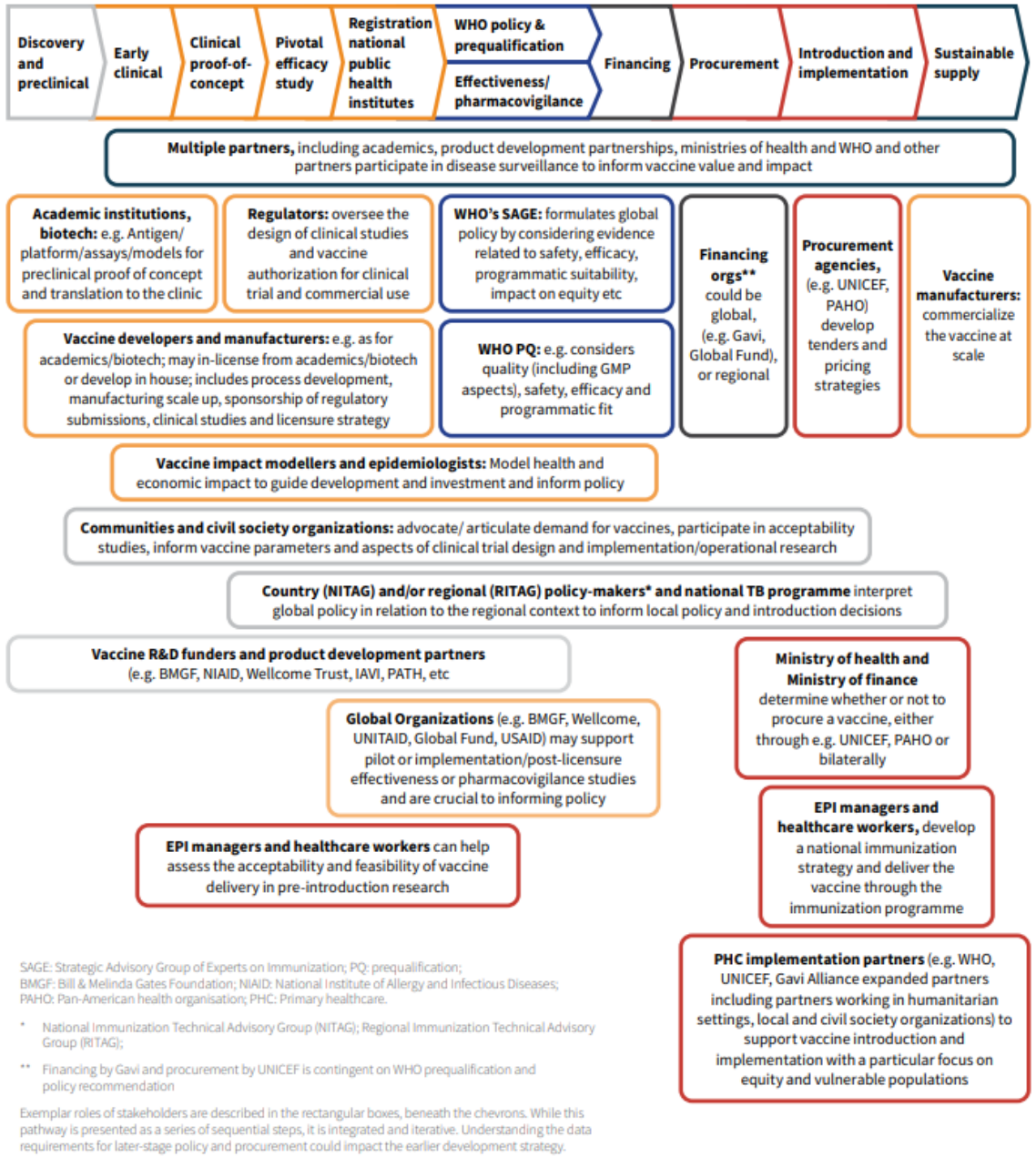
PDVAC
10 December 2024

# The problem the Accelerator is seeking to solve for:




*Slides courtesy of Shanelle Hall, from the WHO convened TB vaccine roadmap series in 2022 Precursor stakeholder meetings to the ECVP and Country Framework for Country Introduction of New Vaccines for adults and adolescents*




Source: Evidence considerations for vaccine policy: https://iris.who.int/bitstream/handle/10665/376907/9789240093980-eng.pdf?sequence=1

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**Multiple stakeholders at the country, regional and global level engaged in TB vaccine product development, ensuring supply and equitable access and preparing for uptake**

**Stakeholder co-ordination is key to accelerating vaccine development and implementation**

# In 2023, WHO DG launched the TB Vaccine Accelerator Council

**Dr Nísia Trindade Lima (Co-chair)**
*Minister of Health, Brazil*

**Dr Budi Gunadi Sadikin (Co-chair)**
*Minister of Health, Indonesia*

**Mr Aurélien Rousseau**
*Minister of Social Affairs and Health, France*

**Dr Susan Nakhumicha Wafula**
*Cabinet Secretary for Health, Kenya*

**Ms Dao Hong Lan**
*Minister of Health, Viet Nam*

**Dr Malik Mukhtar Ahmed Bharath**
*Coordinator to Prime Minister on Health, Pakistan*

**Dr Mathume Joseph Phaahla**
*Minister of Health, South Africa*

**Dr Teodoro J. Herbosa**
*Secretary of Health, Philippines*

**National Institutes of Health**
*National Institutes of Health, United States of America*

**Dr Akinwumi Adesina**
*President, African Development Bank Group*

**Dr Trevor Mundel**
*President of Global Health, Bill and Melinda Gates Foundation*

**Ms Nadia Calvino**
*President, European Investment Bank*

**Dr Juan Pablo Uribe**
*Global Director for Health, Nutrition & Population and the Global Financing Facility, World Bank*

**Dr Sania Nishtar**
*Chief Executive Officer, Gavi, the Vaccine Alliance*

**Mr Peter Sands**
*Executive Director, Global Fund*

**Dr Philippe Duneton**
*Executive Director, Unitaid*

**Dr John-Arne Røttingen**
*Chief Executive Officer, Wellcome Trust*

**Dr Lucica Ditiu**
*Executive Director, Stop TB Partnership*

**Mike Frick**
*Co-Director of Tuberculosis Project, Treatment Action Group*

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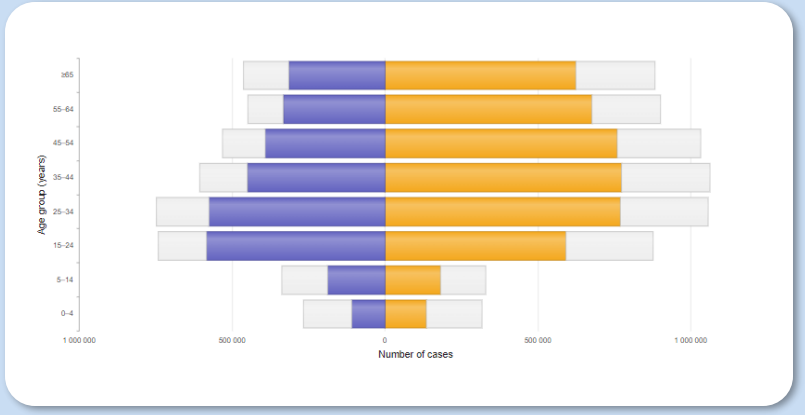
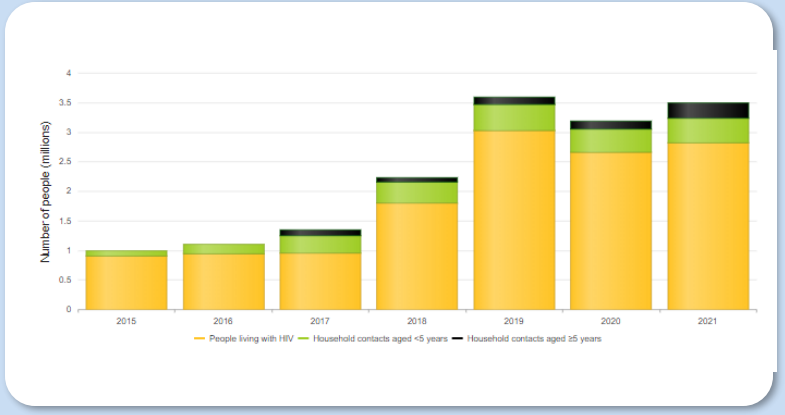
- identify needs for, and **types of innovative sustainable market and financial solutions**, to ensure access
- incentivize TB vaccine development, and to **ensure that the R&D ecosystem is positioned to rapidly manufacture and distribute vaccines equitably** and at scale, once they are available
- Advocate with decision makers to strengthen commitment and concerted action to **develop and expand access to novel effective TB vaccines, including through political platforms** such as the African Union, ASEAN, BRICS, G20, G7 and others.

# Why do we need to prepare for TB vaccine implementation now?


TB impacts low- and middle-income countries. Many are not Gavi-eligible.

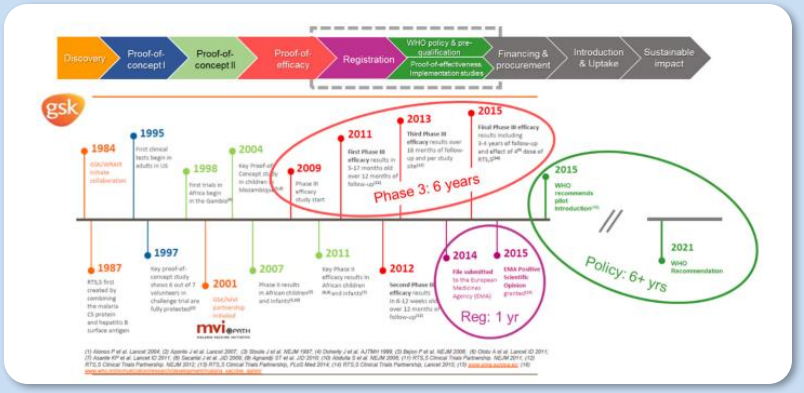



TB incidence and transmission is highest in adolescents and adults. Delivery platform?

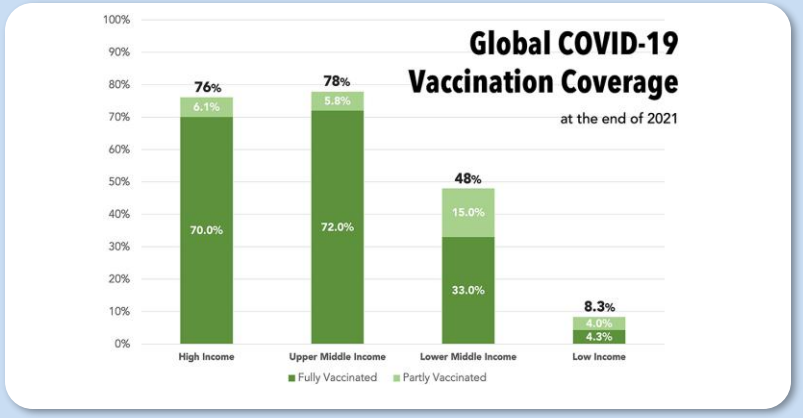



TB preventative treatment (TPT) coverage is increasing. How will vaccines fit?

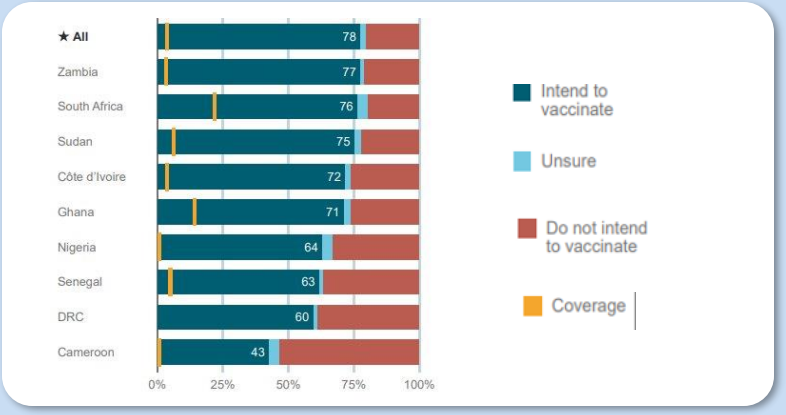
## Lessons learned:




Need to understand the evidence needs for policy to avoid a delay in recommendation.

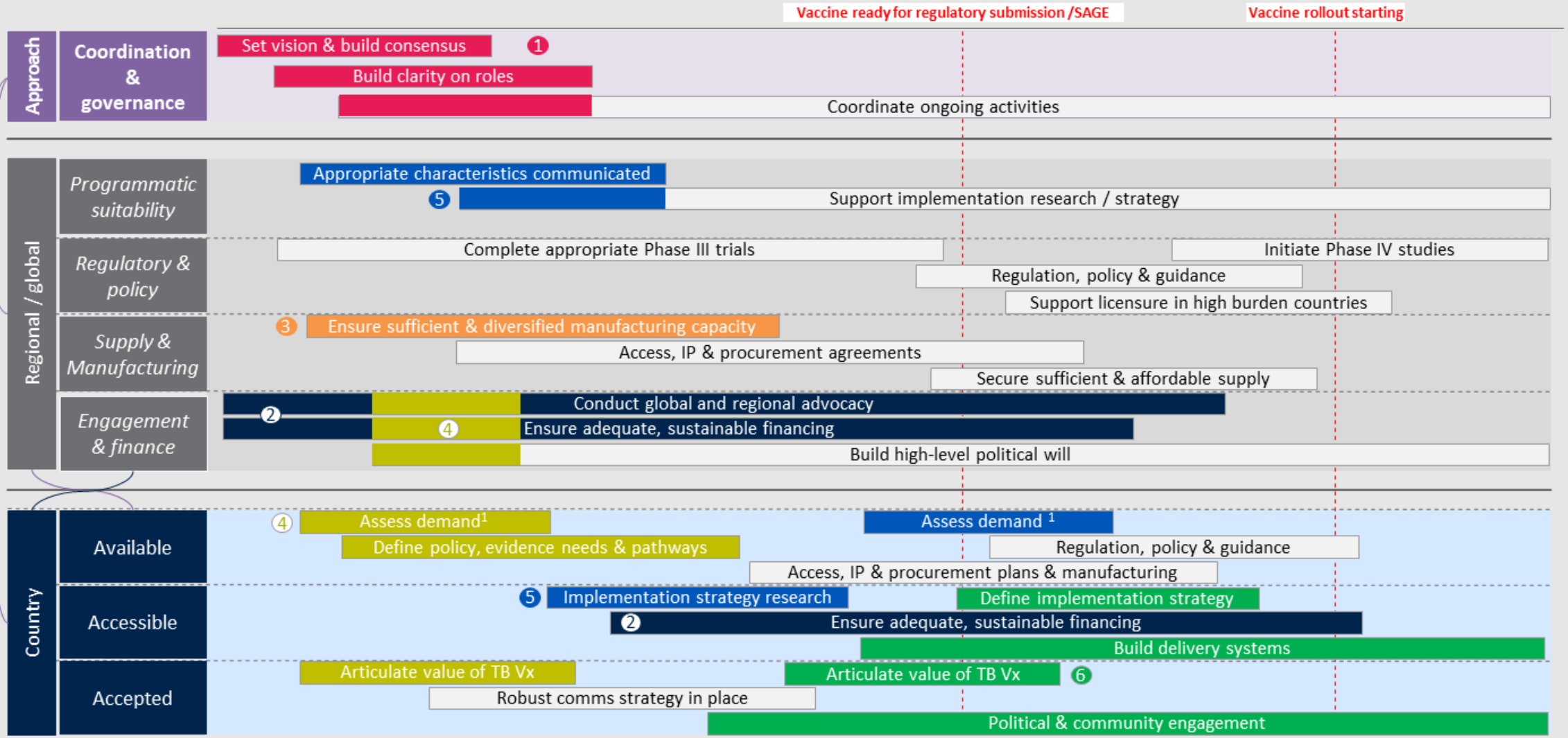



Need strategies to ensure vaccine is available and provisions in place for equitable access.




Need to build vaccine acceptance through partnership with communities

# The requisite activities on the pathway to approval, policy, commercialization and use are *highly integrated*

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Bill & Melinda Gates foundation

BCG

World Health Organization

# WHO has developed a Framework that maps out the activities that are needed to prepare for vaccine implementation


https://www.who.int/publications/i/item/9789240086593

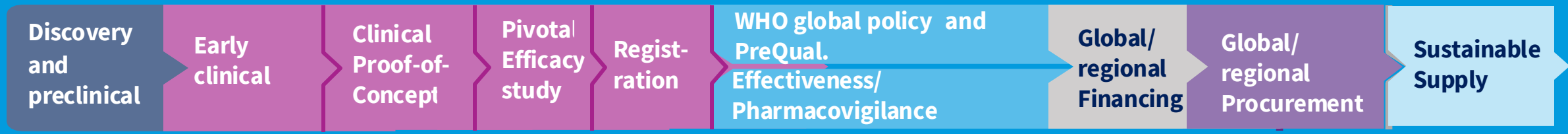
| | | | | |
|---|---|---|---|---|
| **Vision & Purpose** | **A world free of TB, with zero deaths, disease, and suffering due to TB** | | | |
| | **Facilitate rapid introduction and coverage scale-up of new adult and adolescent TB vaccines** | | | |
| **Goals** | **Available**<br>Sufficient, sustainable, and timely supply | **Accessible**<br>Equitable delivery aimed at all who could benefit | **Accepted**<br>Policymakers, end-users and health systems requirements met | |
| **Milestones** | • **Demand assessed** (e.g., no. of doses in short, medium and long term for priority populations; in context of other interventions; with country stakeholders engaged)<br>• **Policy, evidence needs, and pathways defined** (e.g., safety and vaccine efficacy; regulatory approvals; specific populations; in-country trials; recommendations for use; import licensing)<br>• **Procurement plans in place** (e.g., agreements with local, regional and global manufacturers, including on price, quantity and timing) | • **Implementation strategy defined** (for priority populations; vis-á-vis interaction between primary health care, TB, HIV, school health, EPI programs; with private providers and communities)<br>• **Delivery systems in place** (capacity; infrastructure; supply chains; adequate numbers of trained health and community workers; data monitoring; pharmacovigilance; phase IV studies)<br>• **Sustainable financing strategy in place** (e.g., national health sector strategy, external donors, private payers) | • **Value defined** (i.e., at individual and population levels and from perspective of health workers, policymakers, vaccinees)<br>• **Communities engaged as partners in decision-making** (i.e., priority populations, TB survivors, health workers, community health workers, advocates, policymakers)<br>• **Robust communications strategy in place** (e.g., localized; responsive to community concerns and priorities) | |
| **Approach** | **Accelerated, Coordinated, Integrated, People-centred, Equity-driven, Evidence-based** | | | |
| **Enablers** | **Programmatic suitability** | **Regulatory and Policy** | **Supply and manufacturing** | **Financing and political engagement** |
| | • Appropriate presentations<br>• Funded implementation research | • Appropriately designed phase III efficacy trials<br>• Rapid, harmonized regulatory pathways to approval<br>• WHO guidance/ recommendation on vaccine use, aligned with broader TB control efforts<br>• WHO prequalification | • Affordable vaccines<br>• Sufficient supply<br>• Sufficient and diversified manufacturing capacity<br>• Access, IP and procurement agreements | • High level political will (G20/G7)<br>• Adequate financing<br>• Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF) |

To inform the council we propose to:

# Establish 4 key technical and strategic working groups across the TB vaccine value chain







## Vaccine Research

**For example:**

- Systems biology
- Immunology
- Cohort studies
- Correlates
- New antigens and platforms (incl adjuvants)
- Preclinical and clinical model development
- Assay development and harmonization
- Novel vaccine delivery mechanisms

## Product development, manufacturing and policy

**For example:**

- (Innovative) clinical trial design
- Case detection and clinical endpoints
- Regulatory strategy and PQ
- Evidence generation for national and global policy (Vx and TB)
- Manufacturing scale-up incl., tech transfer
- Capacity building (regulatory, mfg, clinical)
- Vaccine impact modelling (global level)

## Financing & Access

**For example:**

- Global demand forecasting
- Global introduction scale up strategy
- Refine investment case for new TB vaccines
- Market shaping, including potential new mechanisms to incentivize investment and ensure access
- Develop innovative financing and procurement options
- Pricing?
- Facilitate high level policy, financing and procurement related dialogue with heads of states, financing agencies.

## Country readiness, advocacy & Community partnership

**For example:**

- Epidemiology and surveillance, vaccine impact
- Potential allocation framework for priority populations
- Vaccine impact modelling at the country level
- Strategic, political and programmatic integration of Vx and TB
- Nat'l immunization programme, Nat'l TB programme, Nat'l advisory groups
- Assessment of health system and country readiness
- Ethics

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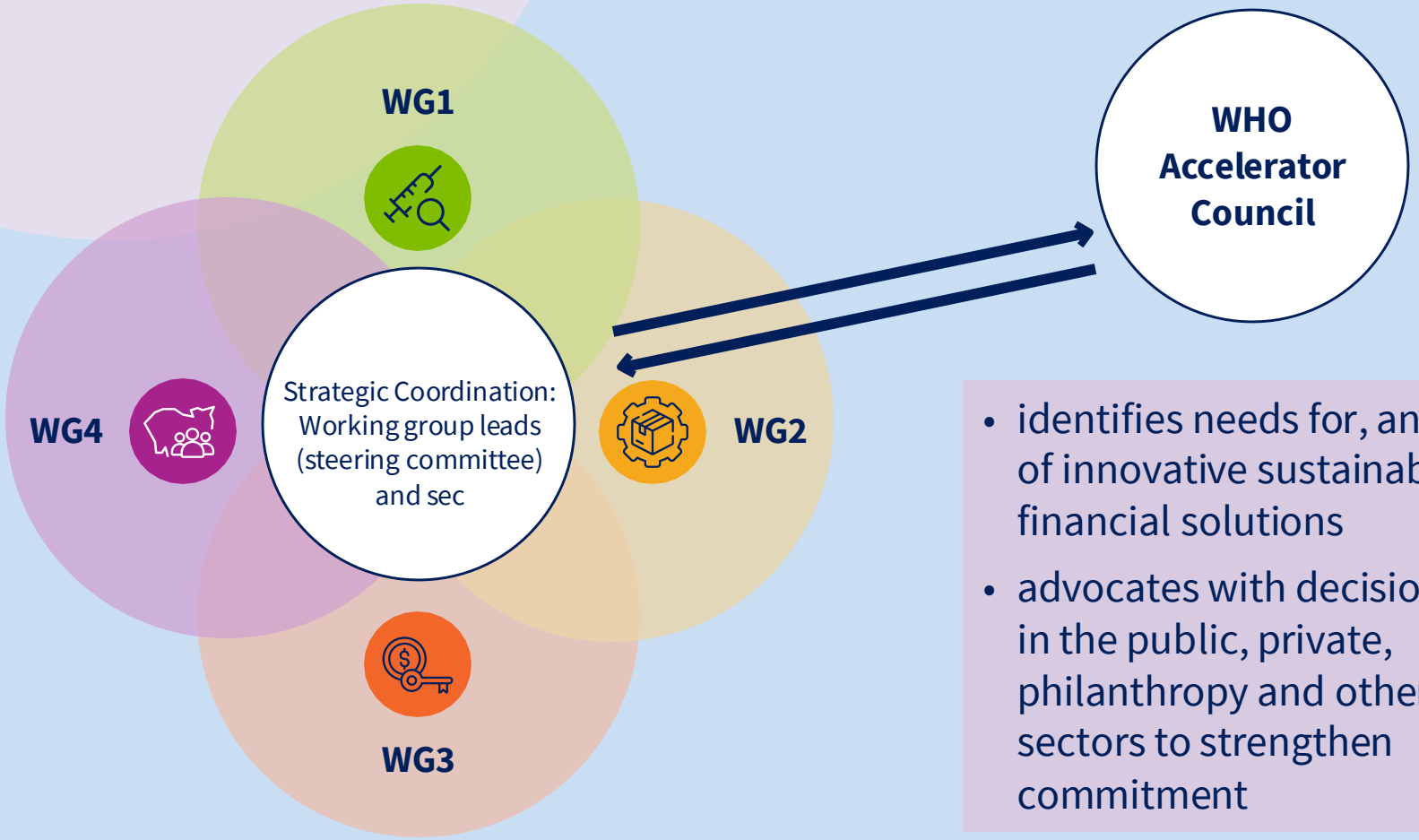
# Scope of the working groups is highly integrated

## Activities and assumptions of one depend on inputs from another

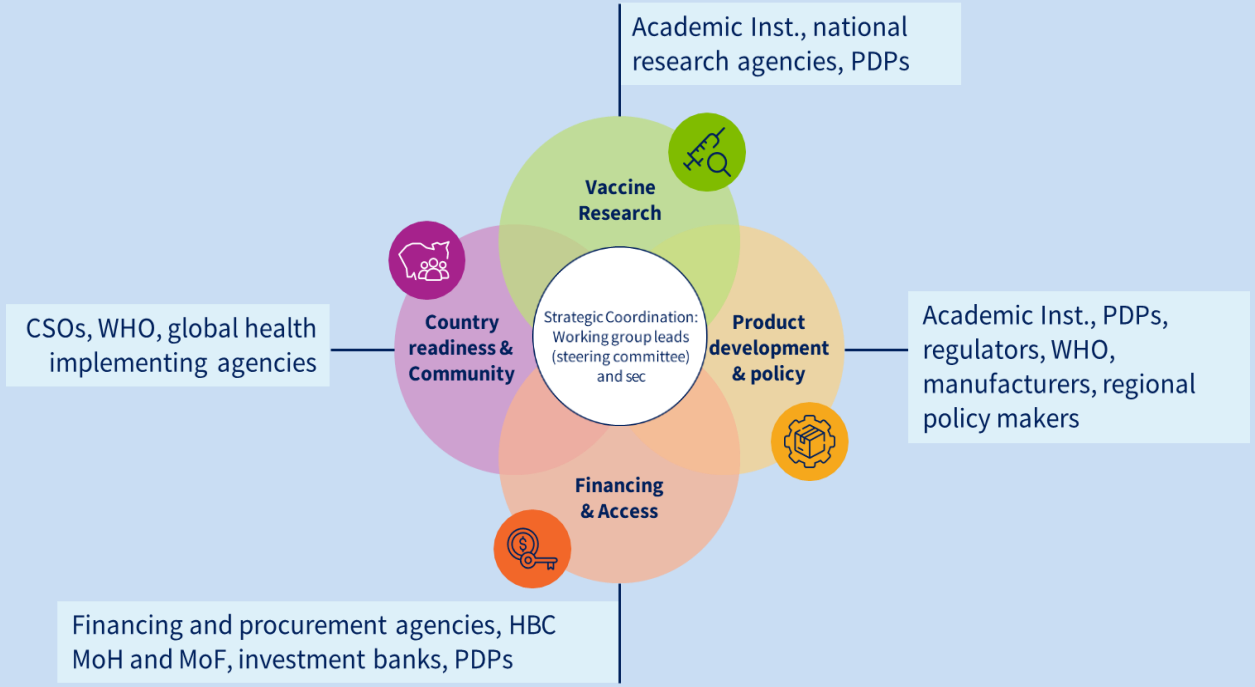



- identifies needs for, and types of innovative sustainable financial solutions
- advocates with decision makers in the public, private, philanthropy and other relevant sectors to strengthen commitment


Committment to convene stakeholders in 2025 to discuss **options for procurement and financing of late-stage vaccines**

# In mid 2024, WHO put out a request for proposals for a strategic co-ordination office to establish Accelerator working groups and their scope

- Confirmed support from the community for the need for strategic co-ordination mechanism, and interest to participate and co-lead Accelerator working groups
- Significant interest received from vendors in response to the RFP
- The funding environment is currently challenging. WHO has needed to pivot to setting up the Accelerator WGs in a staggered, but closely co-ordinated fashion



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# VACCINE DEMAND: What kind of support are countries likely to need for access?
# ILLUSTRATIVE ONLY

**Decreasing level of self-reliance**

**Access streams**

| | | | |
|---|---|---|---|
| Local R&D & production | TT for local bulk production | TT for local fill & finish | Import |
| Self financing vaccine | Loan for vax purchase | Price guarantees | Demand guarantee | Donor funding for vaccines |
| Self financing for programme | Loan for programme support | | Donor programme support |
| Self procurement | Regional procurement | | Global procurement |
| National policy making | Regional policy making | | Global policy making reliance |
| National regulation | Regional regulation or SRA reliance | | Global regulatory reliance |

**Support agencies[1]**

Regional Development Banks · MedAccess · World Bank Group · European Investment Bank · The Global Fund · PEPFAR · USAID

Africa Pool Procurement · Pan American Health Organization

European Medicines Agency · AMA · SRAs

Gavi · unicef · World Health Organization SAGE

**Countries**

**Middle-income, self procuring**

**Lower-income, Gavi-eligible**

Slide courtesy of Tania Cernuschi and Nebiat Gebreselassie, WHO (adapted)

## Vaccine Research

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- Immunology
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World Health Organization

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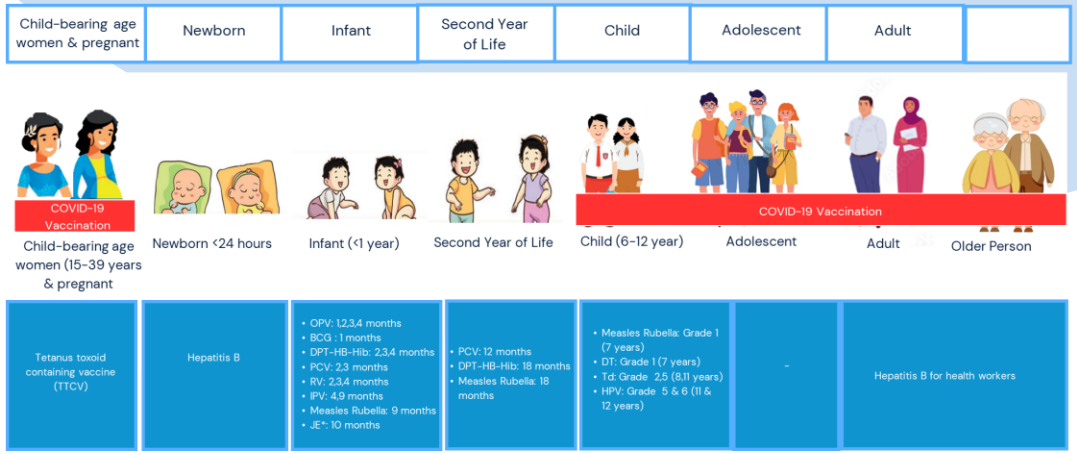
# Meeting in Indonesia was framed by criteria that have recently been identified by ITAGI* for vaccine introduction

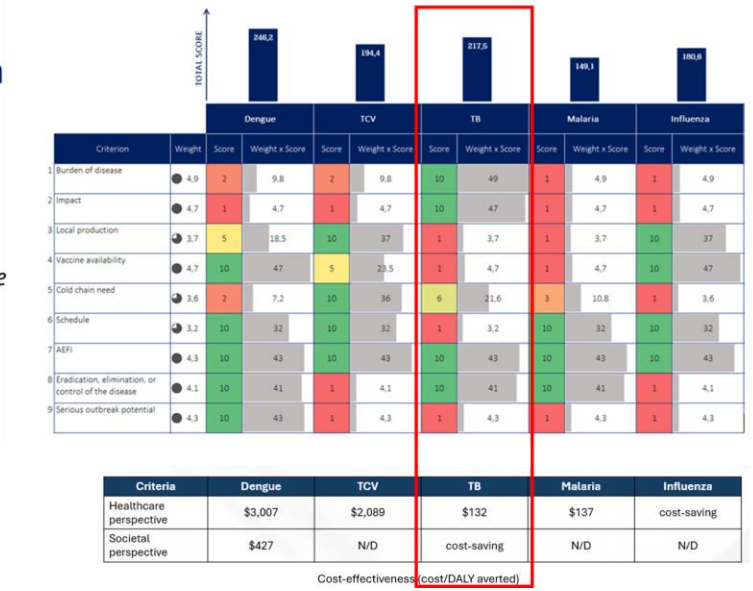




| Criteria | Indicator | Weight (1-5) | Scoring scale |
|---|---|---|---|
| Disease burden | DALY | 4.9 | 1: the lowest; 10: the highest |
| Impact | DALY averted | 4.7 | 1: the lowest; 10: the highest |
| Local production | Availability of locally manufactured vaccines | 3.7 | 1: locally produced;<br>5: locally produced and able to cover national needs, but gradually over the next five years;<br>10: locally produced and able to cover national needs |
| Cold chain need | Sufficient cold chain | 3.6 | 1: largest dimension per vaccinee<br>10: smallest dimension per vaccinee |
| Vaccine availability | Vaccine availability according to national needs | 4.7 | 1 : available but insufficient to cover national needs;<br>5: able to cover national needs, but gradually over the next five years;<br>10: able to cover national needs |
| Schedule | Compliance with existing immunization schedules | 3.2 | 1: unable to be integrated with existing vaccine administration schedules;<br>10: able to be integrated with existing vaccine administration schedules |

## Decision Question

*"Which new vaccines will have the highest priority to introduce into the national immunization program, and what is the order to prioritize new vaccine introductions in Indonesia?"*




| Criteria | Dengue | TCV | TB | Malaria | Influenza |
|---|---|---|---|---|---|
| Healthcare perspective | $3,007 | $2,089 | $132 | $137 | cost-saving |
| Societal perspective | $427 | N/D | cost-saving | N/D | N/D |

Cost-effectiveness (cost/DALY averted)

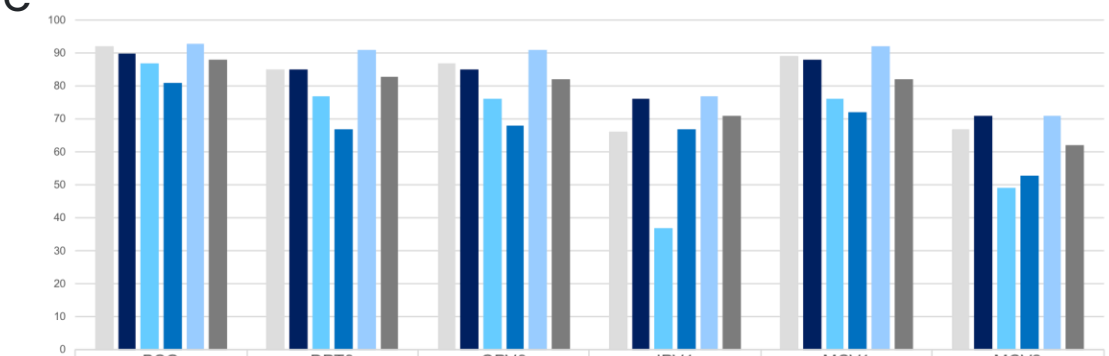
*NITAG in Indonesia

Slides courtesy of Rodri Tanoto, WHO

# TB in Indonesia

- 2nd highest TB burden globally
- 18,100 islands
- Decentralised to the district level (514)
- High political committment
- Non Gavi-eligible

- Strong EPI programme for vaccine delivery
- Active case finding for TB through screening
- Approx. 50% coverage for TB Preventive Treatment




| | BCG | DPT3 | OPV3 | IPV1 | MCV1 | MCV2 |
|---|---|---|---|---|---|---|
| 2018 | 92 | 85 | 87 | 66 | 89 | 67 |
| 2019 | 90 | 85 | 85 | 76 | 88 | 71 |
| 2020 | 87 | 77 | 76 | 37 | 76 | 49 |
| 2021 | 81 | 67 | 68 | 67 | 72 | 53 |
| 2022 | 93 | 91 | 91 | 77 | 92 | 71 |
| 2023 | 88 | 83 | 82 | 71 | 82 | 62 |

Source : WHO – UNICEF JRF Estimate

2018 2019 2020 2021 2022 2023

- Who are the relevent depts and decision makers?
- How are high risk populations identified and prioritized?
- What is the strategy for delivery to adults and adolescents?
- How do the immunization and TB programmes work together?

# WHO and the Indonesian Ministry of Health convened the first national consultation on new TB vaccines for adults and adolescents

**Meeting objectives:**

- Discuss the TB vaccine R&D pipeline and potential considerations for integration into TB and immunization programs.
- Chart evidence requirements and key decision-makers that will be involved in regulatory approval, policy recommendations, financing, and procurement for new TB vaccines for adults and adolescents.
- Build a foundation for ongoing dialogue and multi-sectoral collaboration amongst national and global stakeholders to accelerate new TB vaccine implementation

**Indonesian policymakers and stakeholders:**

- Ministry of Health
- Indonesian TB Expert Committee
- Bappenas Ministry of Planning
- National Agency for Research and Innovation (BRIN)
- National Food and Drug Agency (BPOM)
- Indonesian Immunization Technical Advisory Group (ITAGI)

**Global observers:** Gates MRI, Wellcome Trust, UNICEF, World Bank, USAID, US CDC, IAVI, CHAI, TAG

**Preliminary findings:**

Availability – Indonesia will develop a national strategic plan, with a phased introduction and scale up of new TB vaccines by target geographies, initiating in provinces with the highest disease burdens; willing to import vaccines, with the future goal of local manufacturing.

Accessibility – Develop sub-national health impact models to inform the most cost-effective implementation strategies for new TB vaccines; conduct cost-effectiveness modelling and budget impact studies based on sub-national disease and health systems data

Acceptability –Continued proactive stakeholder engagement will create an enabling environment for future TB vaccines, especially with community leaders and patient advocates.

- ***Priority recommendations to be published Q1 2025.***
- ***Additional consultations in high burden, non-Gavi supported countries in 2025 and 2026***

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World Health Organization

# WHO will launch a Technical advisory Group on clinical and policy considerations for new TB vaccines in January 2025

Terms of reference:

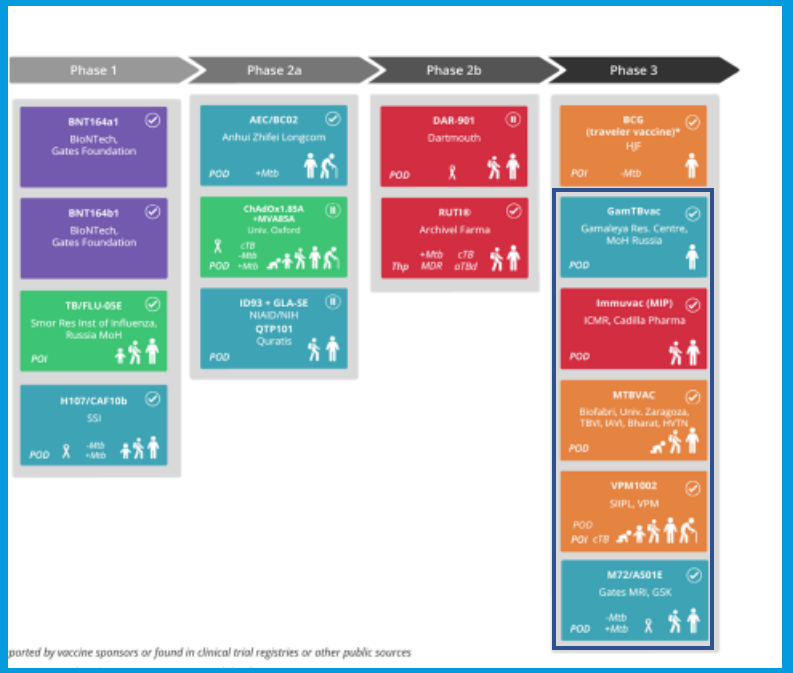
- To provide independent evaluation of the scientific and strategic clinical, regulatory and policy aspects related to new TB vaccine candidates, including but not limited to safety, immunogenicity, efficacy, anticipated impact and effectiveness, resulting in recommendations on data requirements, study designs, clinical trial protocols and regulatory strategies.

- To advise WHO on evidence to support policy formulation, optimal programmatic delivery strategies and where appropriate implementation science to accelerate the pathway to recommendation, introduction and use of new TB vaccines at the country and global levels.

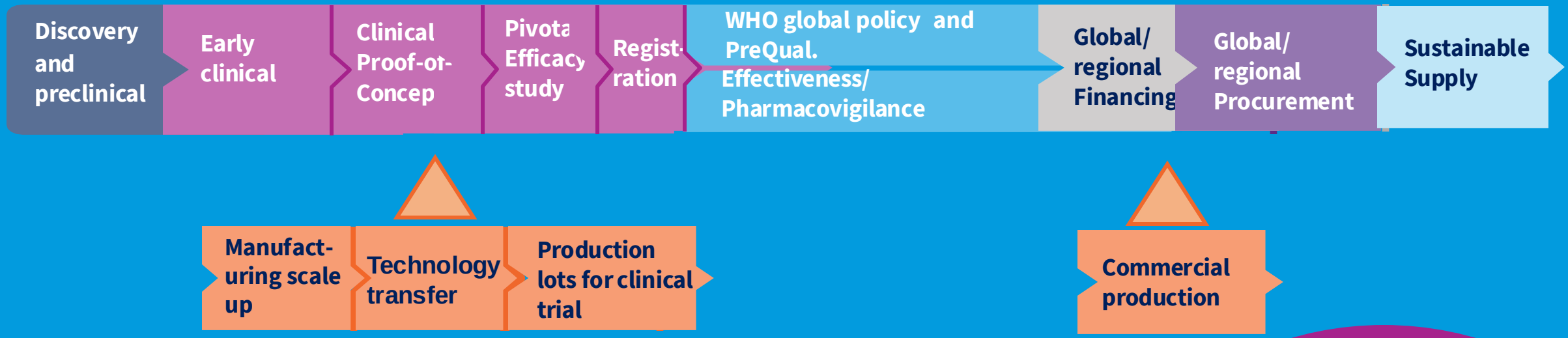
- To assist the secretariat in developing novel guidance / communication on WHO positions with respect to aspects such as clinical endpoints, case definitions, expected data and evidence needs, trade-offs, to inform investment and introduction decision-making.

World Health Organization

**Requested a TB session at SAGE in 2025**



# It’s not just about the clinical studies… Manufacturing scale up strategy is critical to approval and implementation




The need for vaccine manufacturers is often not visible on vaccine development timelines – they’re critical!

- Serve as the market authorization holder
- Drive regulatory approval strategy and timeline
- Supply of vaccine

**Understanding demand size and scale-up is crucial to investment, scale up and developing a healthy vaccine market**

# TB vaccine Accelerator priorities for 2025


Establish the PD, Mfg and policy WG, to review integrated product development plans (incl. manufacturing and commercialization plans)

- Incudes the WHO TAG and more
- SAGE session to socialize opportunities and risk of late-stage candidates

Establish the Finance and Access WG, to co-develop financing options for different country archetypes

- Global demand forecast to inform vaccine scale, and scale up
- Convening in late 2025 on financing options

Work collectively with countries and stakeholders under-taking demand workshops, to:

- refine supply estimates
- prepare for early adoption (decision making, evidence)
- Facilitate manufacturing options
- Inform global priorities (demand and evidence needs)

Huge thanks to BMGF for their funding support!!!!

BILL & MELINDA GATES foundation

And the many, many experts who have co-developed, co-designed and co-convened on guidance documents and stakeholder consultations


**The "TB IS OVER" art installation by Paulina Siniatkina outside the main hall during the 7th Global Forum, November 2024. Photo courtesy of the Global Forum on TB Vaccines.**

# Questions for PDVAC

1. Should novel TB vaccine be able to prevent **asymptomatic TB**? What is the pathway toward including asymptomatic TB as an endpoint in future efficacy trials?
2. Is there still value in developing a *'policy position statement'* on the preference for a **prevention of disease endpoint**? If yes, should asymptomatic TB be included?
3. What role should the TB Vaccine Accelerator and its working groups play in facilitating/informing the **vaccine manufacturing/commercialization strategy** for new TB vaccines?

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