Global Vaccine and Immunization Research Forum Webinar

New Tuberculosis Vaccines for Adults and Adolescents: Progress, Prospects, and Perspectives

22nd February 2024

15.00 – 18.30 CET

Overview of the webinar

PART 1: BCG is not enough

PART 2: TB vaccines for adults and adolescents on the horizon

PART 3: Innovation and new tools in TB vaccine development

PART 4: Preparing for success

Panel discussions will consider:

- What are the major bottlenecks to TB vaccine development for this new population, and what is needed to de-risk investment?
- Do we have the tools needed to identify and down-select new TB vaccine targets?
- What are the priorities to prepare the pathway for new TB vaccine implementation, particularly for adults and adolescents?

Latest information and materials from past meetings are available at:
https://www.technet-21.org/en/hot-topics-items/15105-gvirf

Questions? Please email gvirf@who.int

NIH National Institute of Allergy and Infectious Diseases

BILL & MELINDA GATES foundation

World Health Organization

With support from TechNet-21 The Technical Network for Strengthening Immunization Services

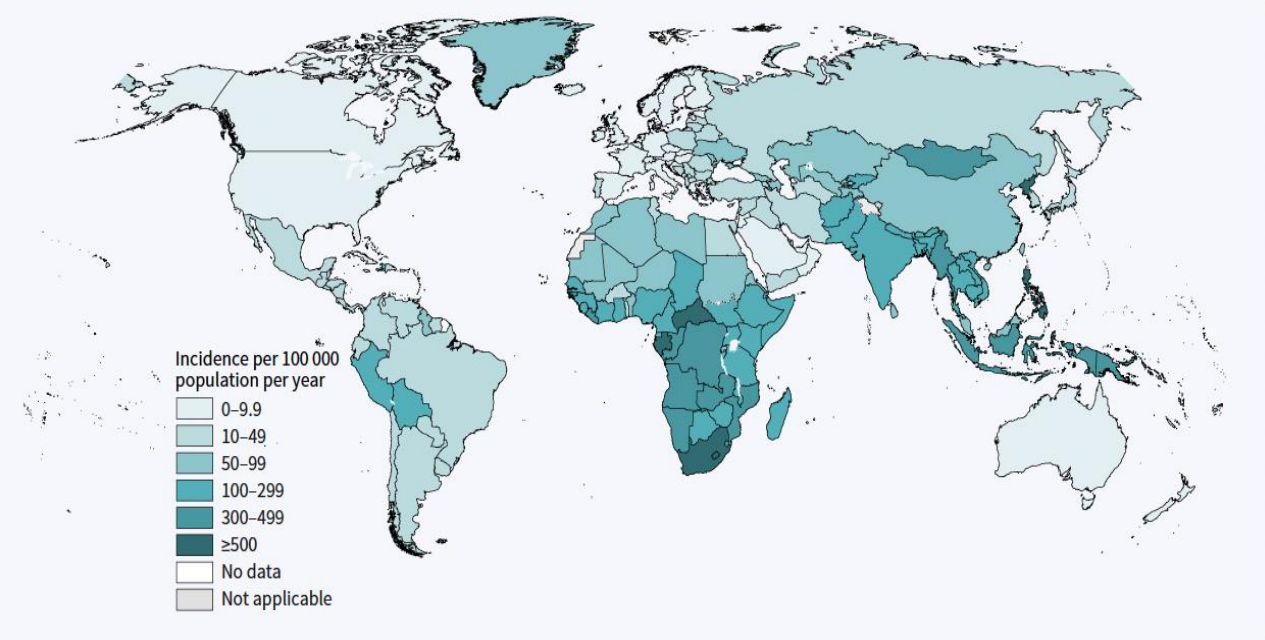
Part 1

Current status of the global TB epidemic

Nebiat Gebreselassie
Global TB Programme

World Health Organization

TB affects every country of the world, but its magnitude & impact are greatest in low-and-middle income countries.



- ✓ Approximately 87% of global TB cases are in 30 high TB burden countries
- ✓ Eight countries accounted for 68% of global cases in 2022

World Health Organization

TB REMAINS ONE OF THE TOP

INFECTIOUS KILLERS IN THE WORLD

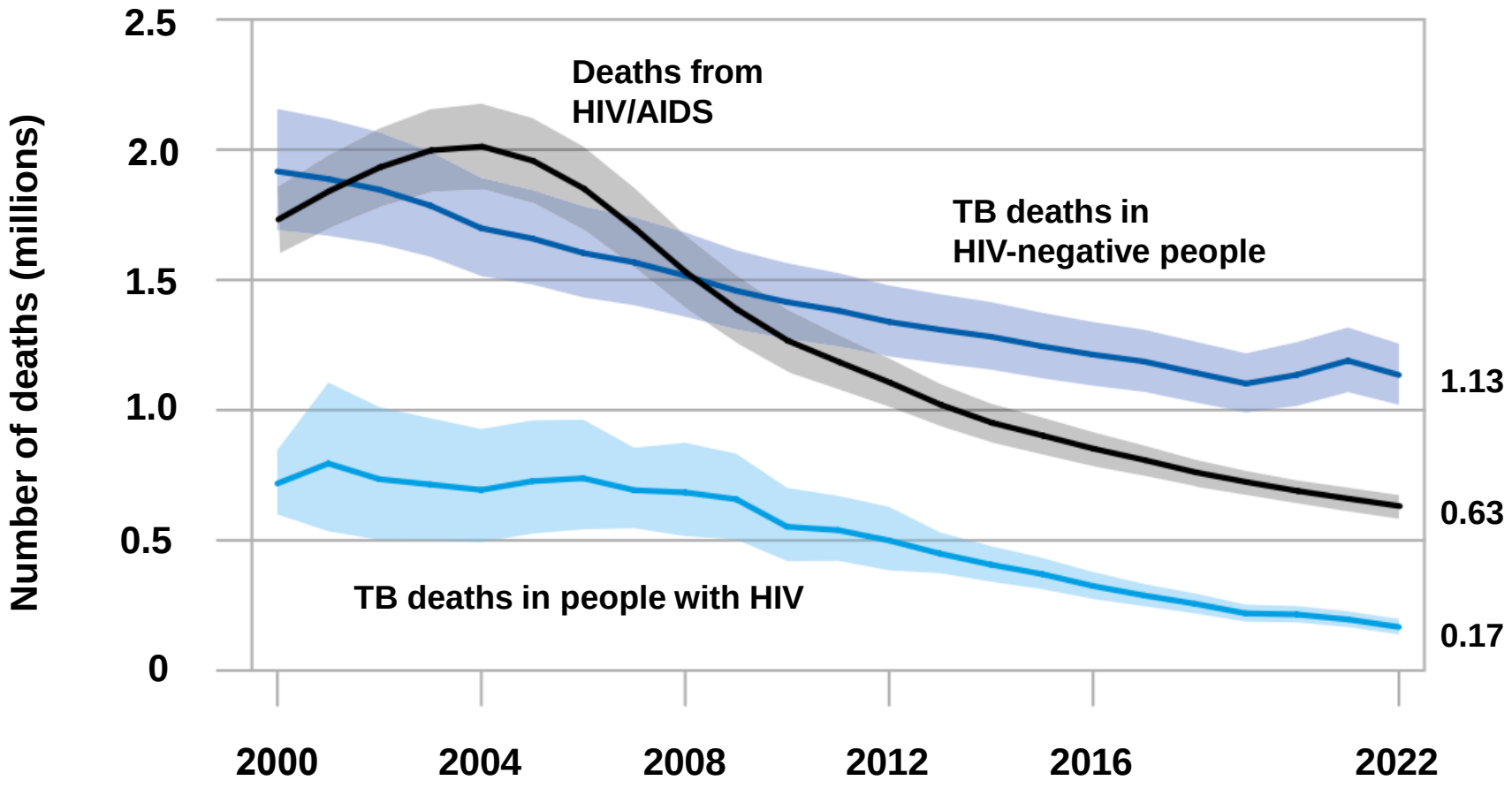
It is the leading cause of death of people with HIV and a major contributor of antimicrobial resistance related deaths

In 2022,

- **1.3 million** people died from TB
- **10.6 million** people fell ill with TB

About a quarter of the global population is estimated to have been infected with TB bacteria

TB more badly impacted than HIV



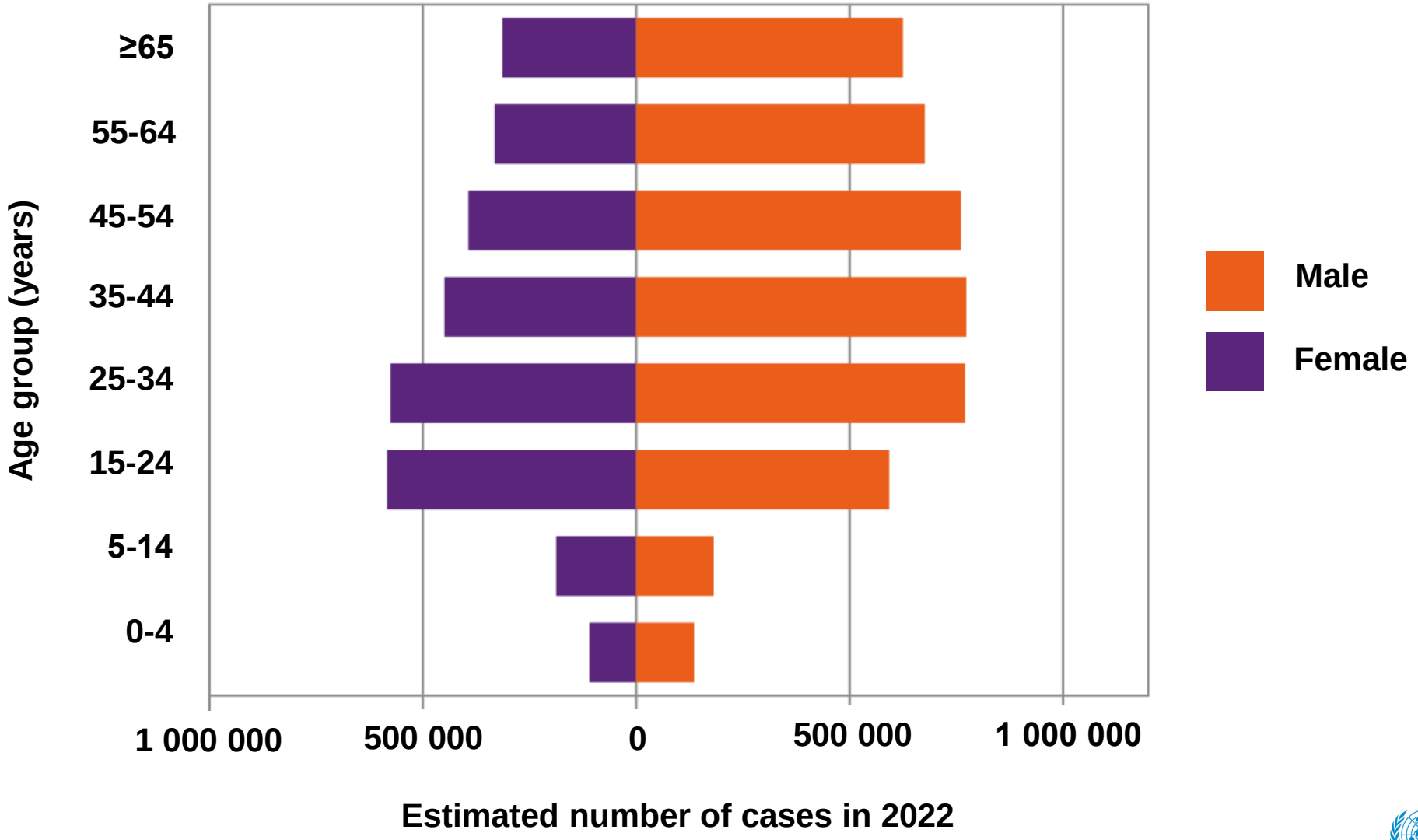
Deaths from TB in 2022 almost double those from HIV/AIDS, which continued to fall

Shaded areas show 95% uncertainty intervals

World Health Organization

Distribution by age and sex

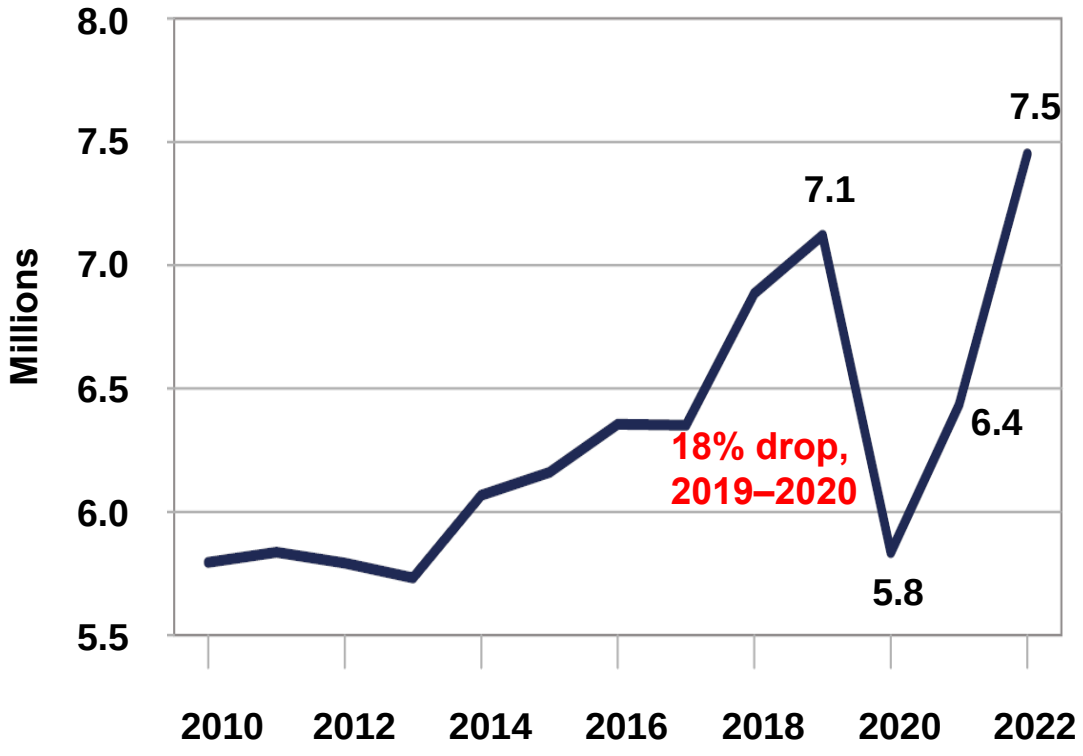
5.8 million men (55%), 3.5 million women (33%), 1.3 million children (12%)



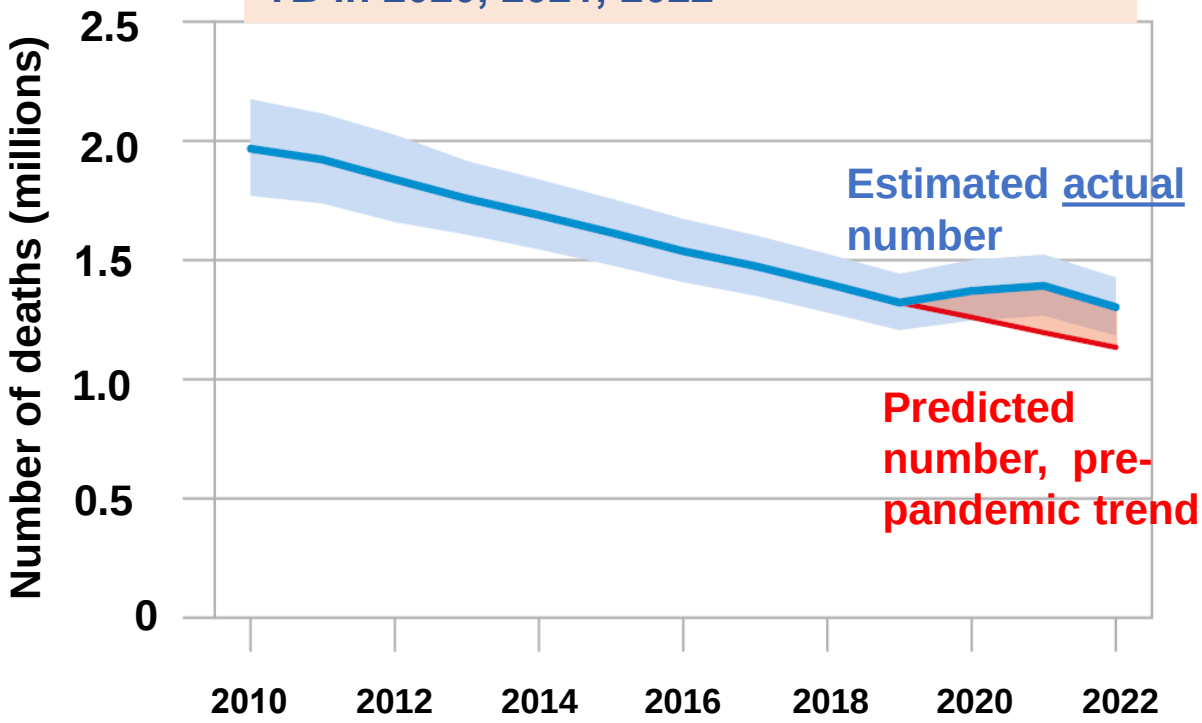
World Health Organization

Global recovery in reported number of people newly diagnosed with TB

7.5 million in 2022: highest number since WHO started global TB monitoring in mid-1990s

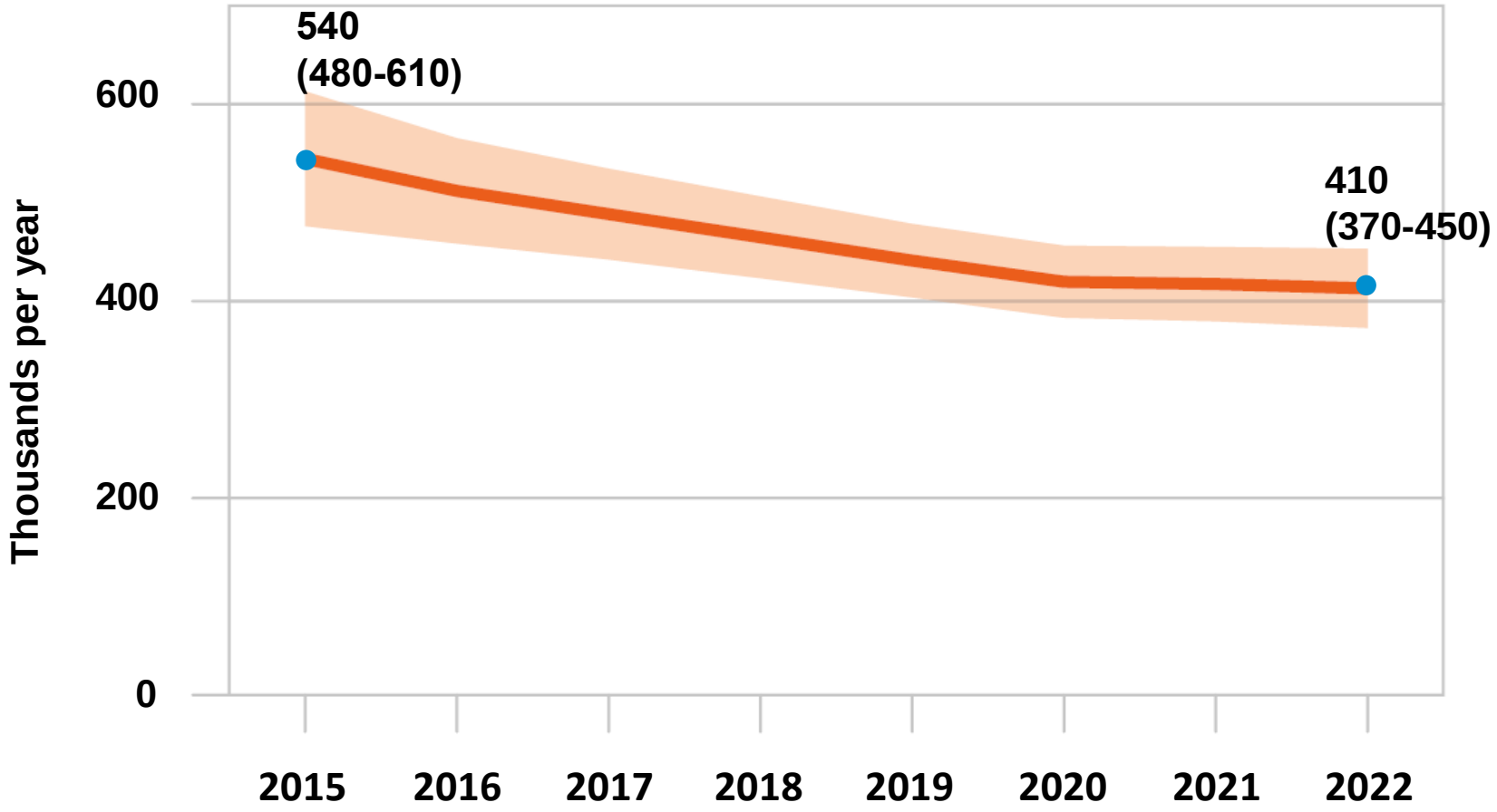


COVID-related disruptions resulted in about half a million excess deaths from TB in 2020, 2021, 2022



World Health Organization

Estimated number of people developing MDR/RR-TB relatively stable from 2020–2022

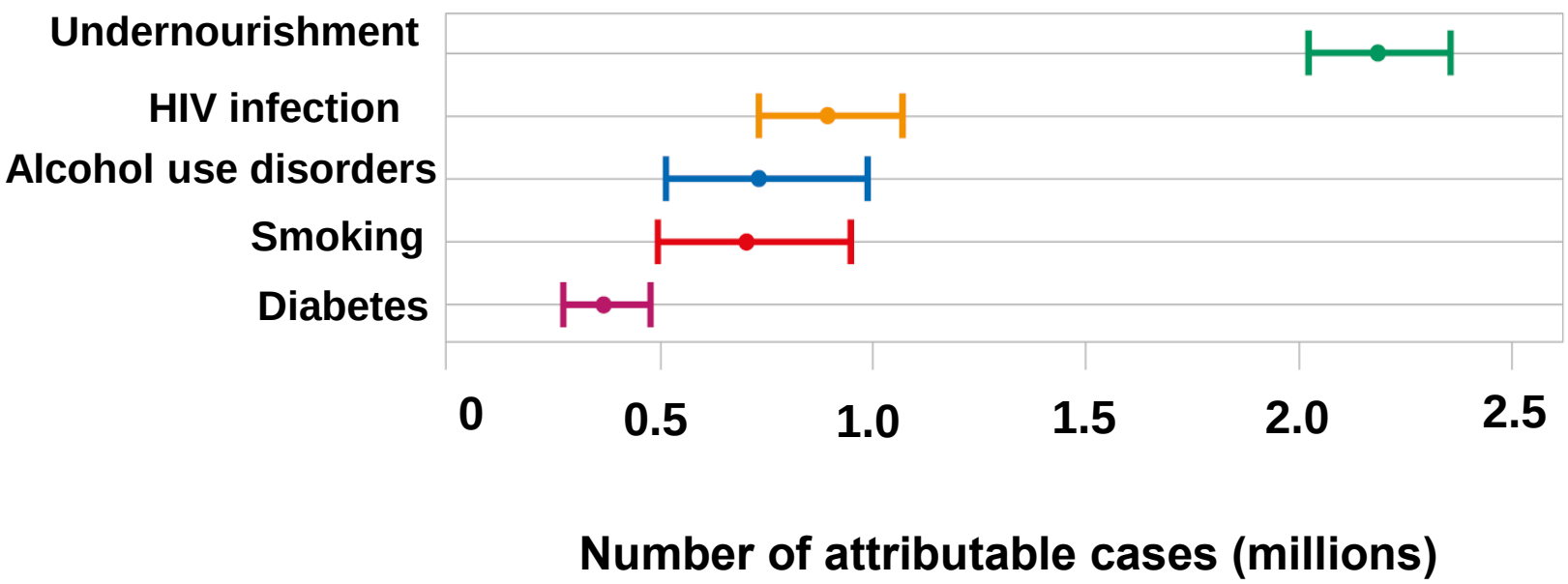


- **Two in five people with MDR/RR-TB** did not access treatment
- **63%** treatment success rate (latest cohort data)

Shaded area shows 95% uncertainty interval

World Health Organization

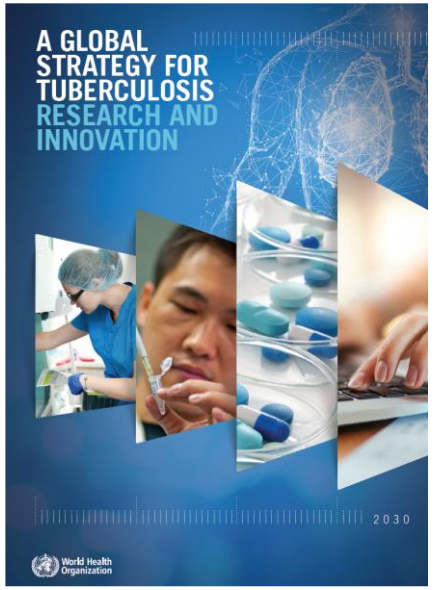
GLOBAL ESTIMATES OF TB CASES ATTRIBUTABLE TO 5 RISK FACTORS IN 2022



- TB is driven by complex health and social determinants such as undernutrition and poverty.
- Approximately half of people who develop TB disease face significant financial hardship because of their illness.

World Health Organization

Progress with respect to TB research and innovation



Status of clinical development pipeline for diagnostics, drugs and vaccines (August 2023)

3 new diagnostic products to detect drug-resistant TB recommended by WHO in 2023

28 drugs for treatment of TB disease in clinical trials

16 vaccine candidates in clinical trials

29+ clinical drug trials and other research studies for treatment of TB infection

World Health Organization

Global tuberculosis targets -2023 UNGA political declaration on TB

TB treatment coverage	**90% by 2027**

Coverage of TB preventive treatment for priority groups (household contacts of people with TB; people living with HIV)	**90% by 2027**

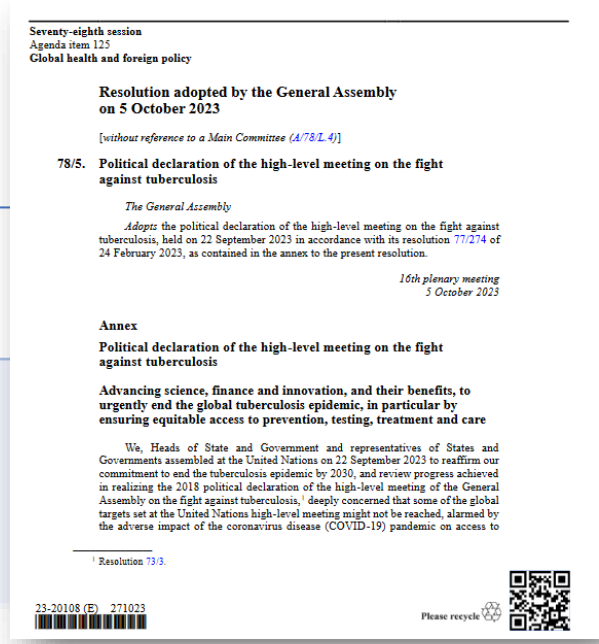
Coverage of rapid diagnostic testing for TB	**100% by 2027**

Coverage of health and social benefits package for people with TB	**100% by 2027**

Development and availability of new TB vaccines that are safe and effective	**Rollout initiated, preferably within 5 years**

Annual funding for universal access to quality prevention, diagnosis, treatment and care for TB	**US$ 22 billion by 2027, US$ 35 billion by 2030**

Annual funding for TB research	**US$ 5 billion by 2027**



Seventy-eighth session
Agenda item 125
Global health and foreign policy

Resolution adopted by the General Assembly on 5 October 2023

[*without reference to a Main Committee (A/78/L.4)*]

78/5. Political declaration of the high-level meeting on the fight against tuberculosis

The General Assembly

Adopts the political declaration of the high-level meeting on the fight against tuberculosis, held on 22 September 2023 in accordance with its resolution 77/274 of 24 February 2023, as contained in the annex to the present resolution.

16th plenary meeting
5 October 2023

Annex

Political declaration of the high-level meeting on the fight against tuberculosis

Advancing science, finance and innovation, and their benefits, to urgently end the global tuberculosis epidemic, in particular by ensuring equitable access to prevention, testing, treatment and care

We, Heads of State and Government and representatives of States and Governments assembled at the United Nations on 22 September 2023 to reaffirm our commitment to end the tuberculosis epidemic by 2030, and review progress achieved in realizing the 2018 political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis,[1] deeply concerned that some of the global targets set at the United Nations high-level meeting might not be reached, alarmed by the adverse impact of the coronavirus disease (COVID-19) pandemic on access to

[1] Resolution 73/3.

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FOR MORE INFORMATION

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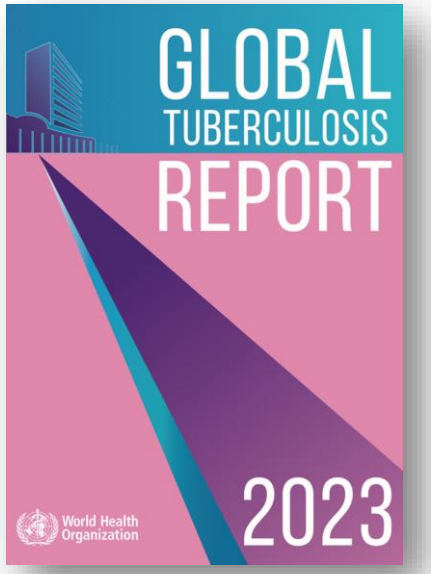

THANK YOU!

END TB

World Health Organization

Part 1

The Investment Case for New TB vaccines

Richard White, Nick Menzies, Rebecca Clark, Allison Portnoy, Christinah Mukandavire, Chathika Weerasuriya, Danny Scarponi, Arminder Deol, Andrew Iskauskas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond Hutubessy, Birgitte Giersing, Mark Jit, Rebecca Harris, So Yoon Sim, Inés Garcia Baena, Nobuyuki Nishikiori, Jean-Louis Arcand, Edith Patouillard,

and many, many others

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

iavi

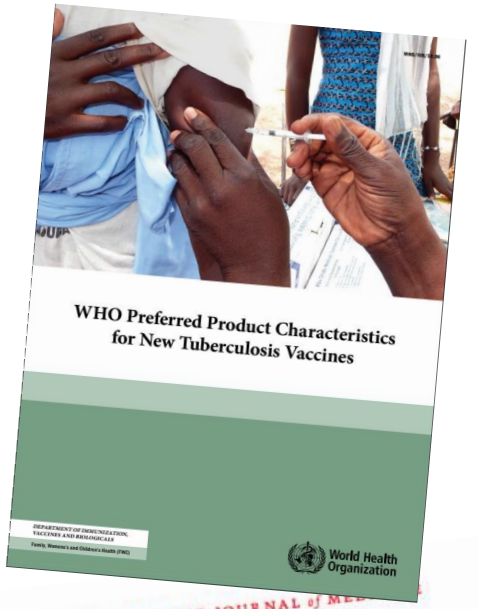
HARVARD UNIVERSITY

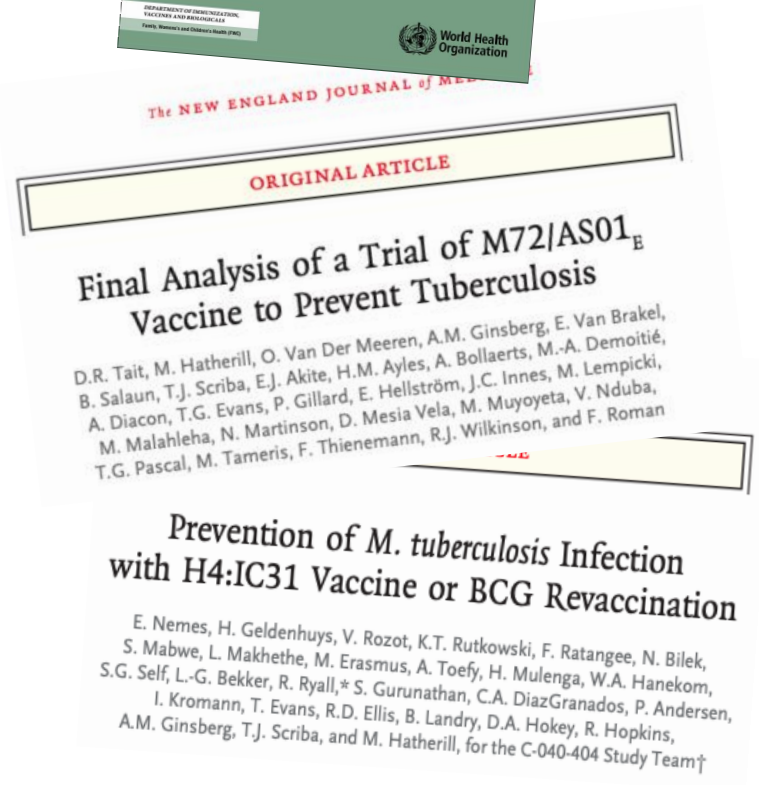
Background

TB Vaccines

- Key to reaching WHO End TB goals
- WHO created preferred product characteristics (PPCs) for new infant and adolescent/adult vaccines
- Development expensive and long and licensure needs phase III field efficacy study (later today)
- Poorly known market size (later today) and ROI
- Lack of market incentives to invest

Objectives: Estimate the potential health, economic and wider impact in LMICs of vaccines meeting the technical specifications of the WHO PPCs





Apply Full Value of Vaccines Assessment (FVVA) Framework

- Lack of market incentives to invest
- Essential to address value beyond direct health impact
- Apply FVVA to capture broader economic and wider impacts

	Health		Non-health (Societal/Economic)	
	Direct	Indirect	Direct	Indirect
Individual	Traditional Direct Risk/Benefit	Full Public Value		
Population				

Health estimation methods

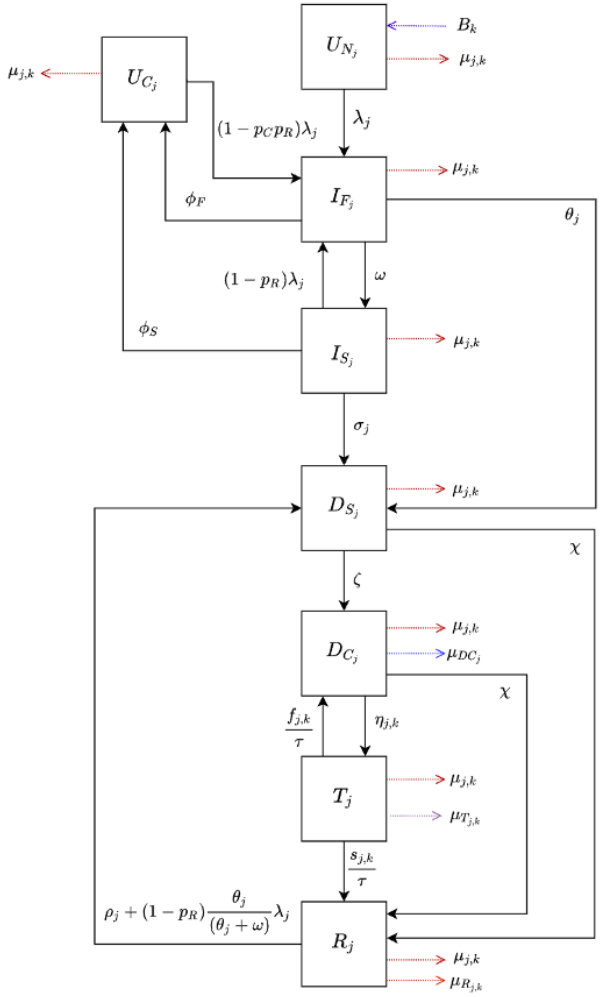
- TB infection transmission and economic model (*TBVax*)

- Model separately 105 low and middle income countries
- Captured 93% of TB incidence in LMICs

- Model forward to 2050 without no new vaccine introduction (*"No-New-Vaccine"* baseline)
- Compare to scenarios with a new vaccine modelled

Outcomes

- Cumulative cases, treatments & deaths averted
- Between year of vaccine introduction (varies) and 2050
- Countries grouped into
  - WHO region,
  - World Bank income group,
  - WHO high TB burden countries



D_C = Clinical Disease, D_S = Subclinical Disease; I_F = Infection-Fast, I_S = Infection-Slo
R = Resolved, T = On-Treatment, U_C = Uninfected-Cleared, U_N = Uninfected-Naive

Vaccine profile methods

Informed by WHO Preferred Product Characteristics for New Tuberculosis Vaccines

Vaccine Age Group	Infection status at time of vaccination required for vaccine efficacy	Prevents	Vaccine Efficacy	Duration of Protection
Adolescent / Adult	Pre and Post Infection with *Mtb*	Disease	50% (75%)	10 years

Clark RA, Mukandavire C, Portnoy A, et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low-income and middle-income countries: a modelling study. *Lancet Glob Health*, 2023: doi: https://doi.org/10.1016/S2214-109X(23)00045-1

Vaccine delivery methods

Basecase vaccine coverage after 5 years
Neonatal: 85%
9-year-olds: 80%
10+: 70%

Accelerated Scale-up

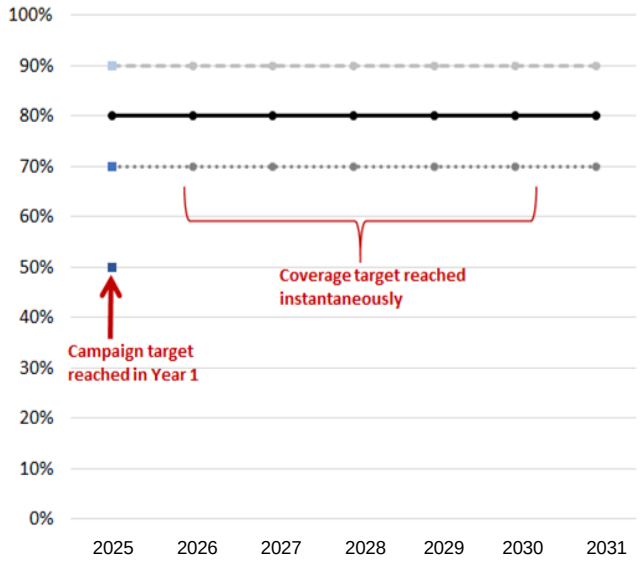
- All countries introduce in 2025
- Instant scale-up to coverage
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+

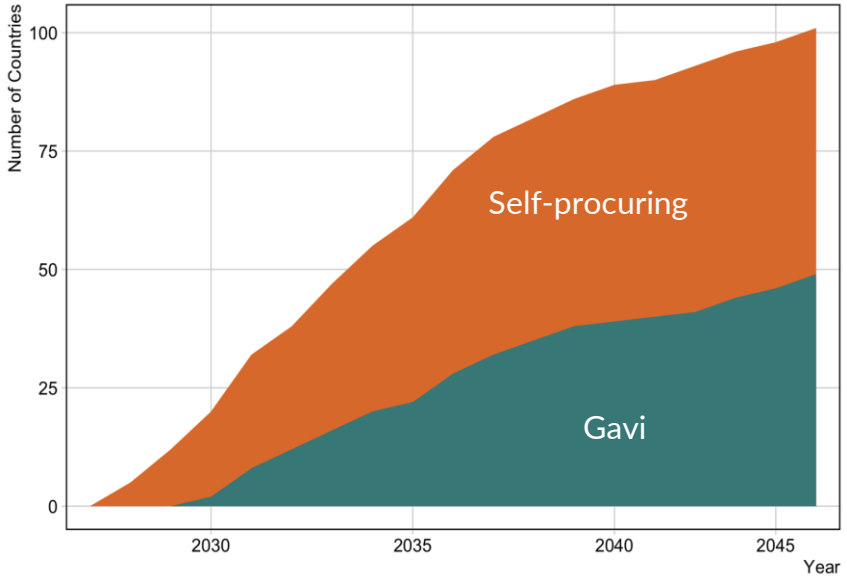
Basecase

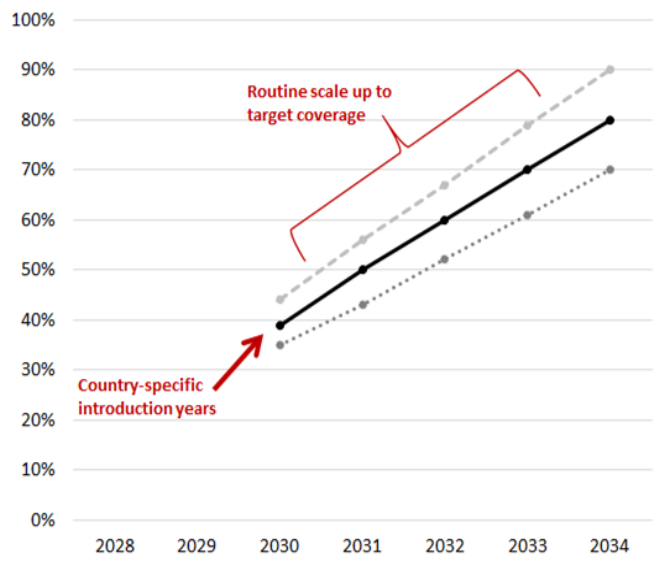
- Country-specific intro years
- Scale-up to coverage over 5 years
- Infant vaccine: Routine neonatal
- Adolescent/adult vaccine: routine 9-year-olds; 1 campaign ages 10+

Routine Only

- Country-specific intro years
- Scale-up to coverage over 5 years
- Adolescent/adult vaccine: routine 9-year-olds

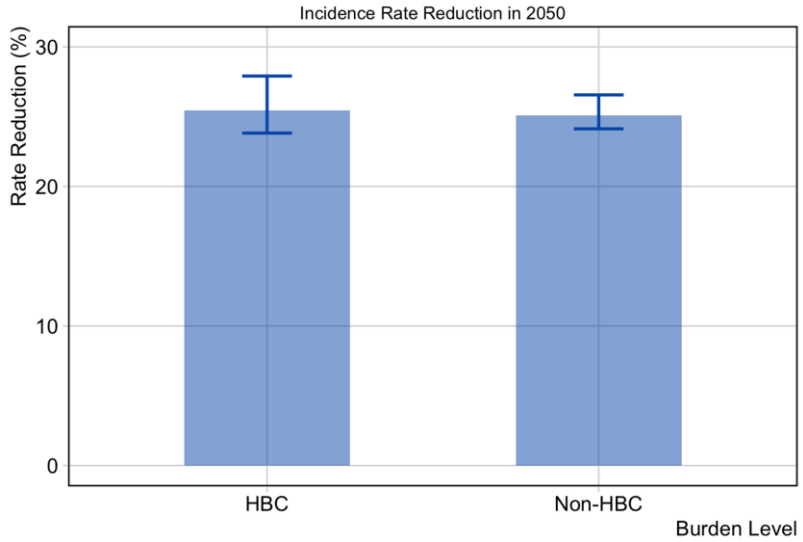






An adolescent/adult TB vaccine may reduce incidence rates in 2050 by 25%

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage



In line with previous LMIC modelling (Knight 2014)

- Important health impact

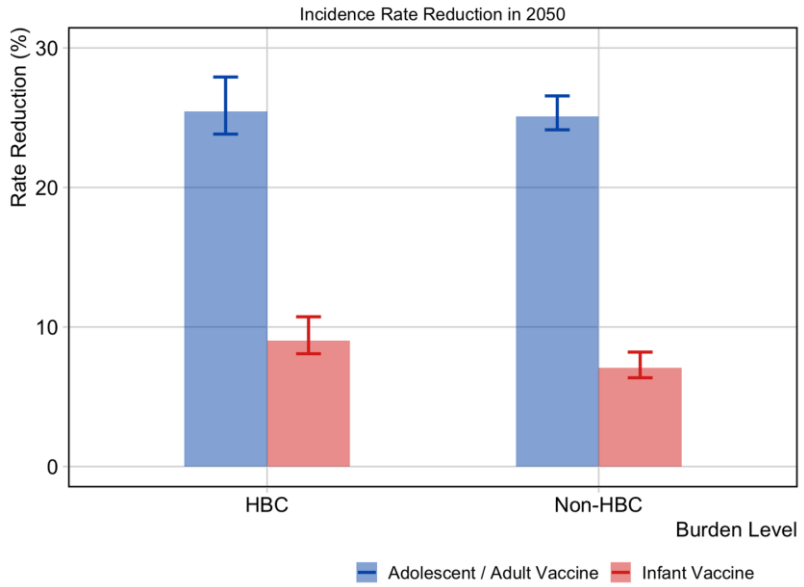
  → **~25%** reduction in cases in 2050

Vaccination adolescent/adults may lead to greater & more rapid incidence rate reductions in 2050, than vaccinating infants

vs Infant, 80% efficacy, Basecase delivery, 10y protect, med coverage

Greater impact from an adolescent / adult vaccine vs. infant vaccine before 2050

→ Targeting the age group with the largest burden



An adolescent/adult vaccine may avert ~44m cases, ~25m treatments, and ~5m deaths by 2050

Adol/Adult, 50% efficacy, Basecase delivery, 10y protect, med coverage

Cumulative cases averted between vaccine introduction and 2050

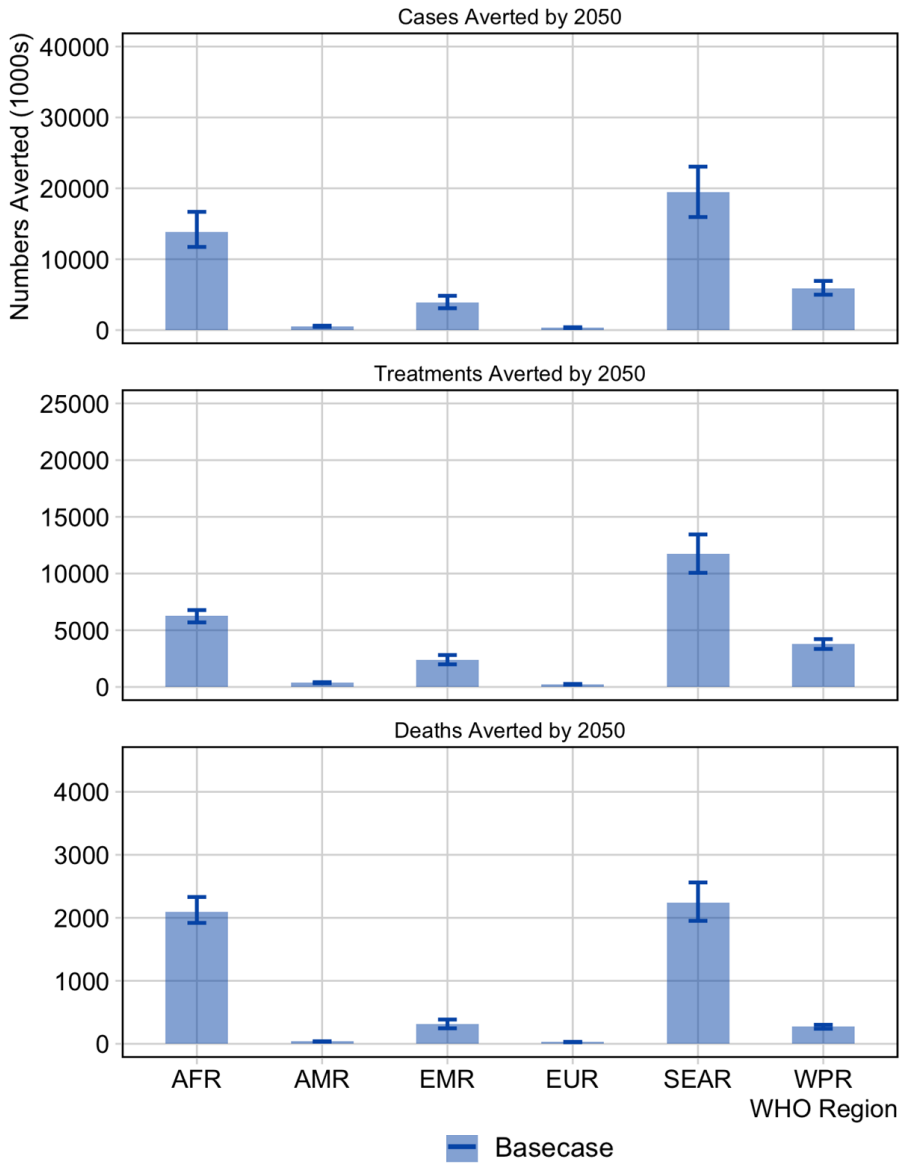
- Potential to avert **~44 million** cases
  - Particularly in AFR and SEAR

Cumulative treatments averted between vaccine introduction and 2050

- Potential to avert **~25 million** treatments by 2050
  - Valuable contribution to averting antimicrobial resistance

Cumulative deaths averted between vaccine introduction and 2050

- Potential to avert **~5 million** deaths by 2050



Introducing at rate of COVID-19 vaccination may avert ~50-60% more cases/deaths, than introducing at rate of other earlier vaccines

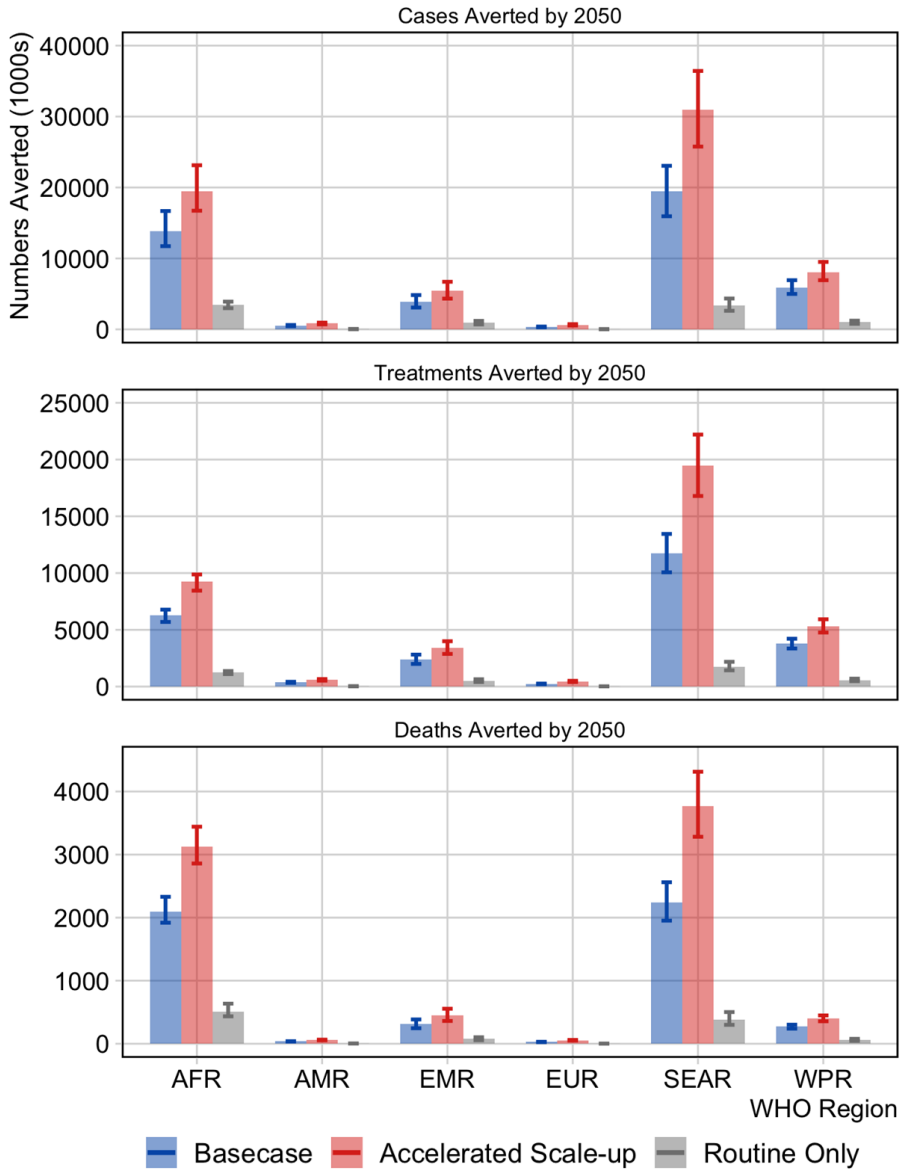
Adol/Adult, 50% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:

We assumed more 'realistic' introduction & scale up scenarios than previous modelling

In the *Basecase* scenario, **~44 million** cases, **~25 million** treatments, and **~5 million** deaths were averted.

An increased scale-up speed (*Accelerated Scale-up*) could prevent **~21 million additional** cases, **~14 million additional** treatments, and **~3 million additional** deaths **(~50–60% more)**



Routine only delivery may avert ~80-90% fewer cases/deaths, than the routine & campaign

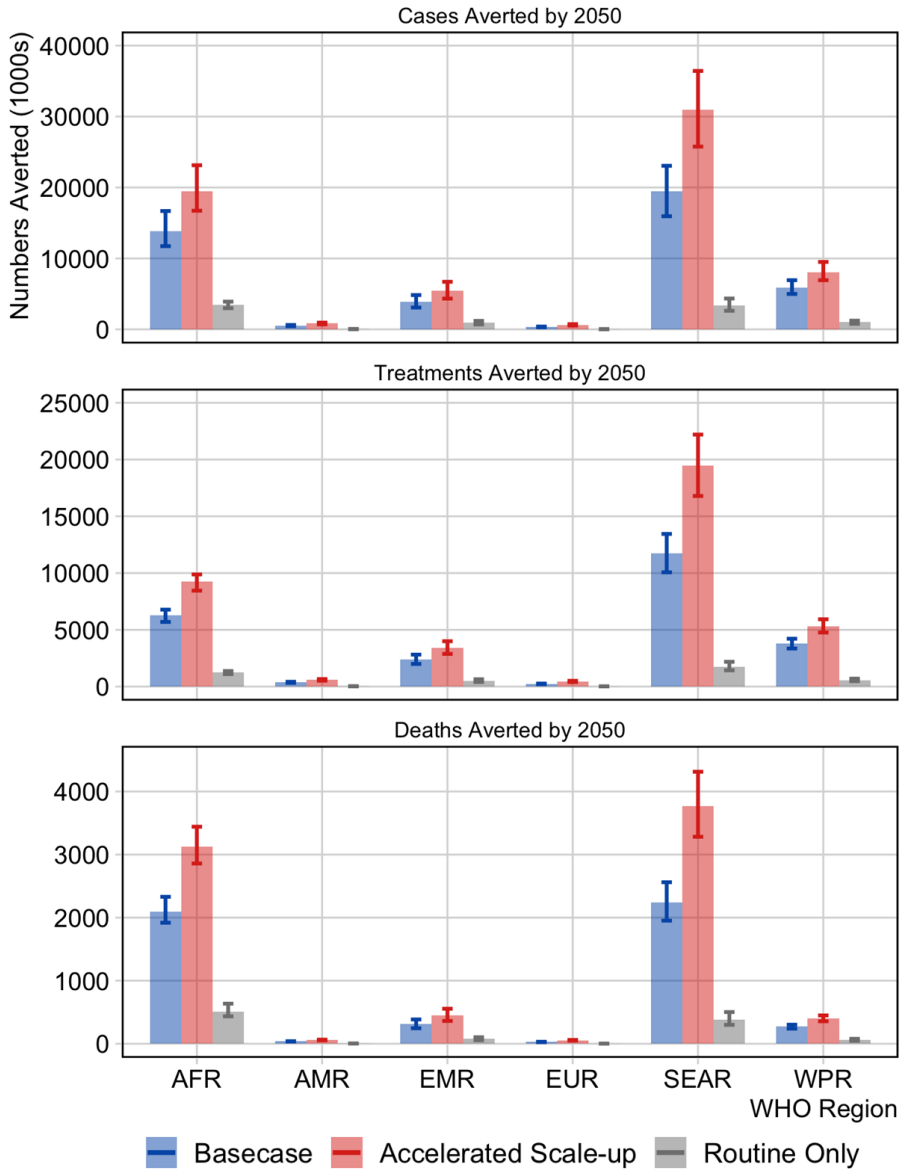
Adol/Adult, 50% efficacy, varying delivery, 10y protect, med coverage

Cases, treatments, and deaths averted by delivery:

We assumed more 'realistic' introduction & scale up scenarios than previous modelling

In the *Basecase* scenario, **~44 million** cases, **~25 million** treatments, and **~5 million** deaths were averted.

- An increased scale-up speed (*Accelerated Scale-up*) could prevent **~21 million additional** cases, **~14 million additional** treatments, and **~3 million additional** deaths **(~50–60% more)**
- By only offering this new TB vaccine routinely to adolescents (*Routine Only*), ~**35 million fewer** cases, **~22 million fewer** treatments, and **~4 million** fewer deaths would be averted **(~80-90% fewer)**



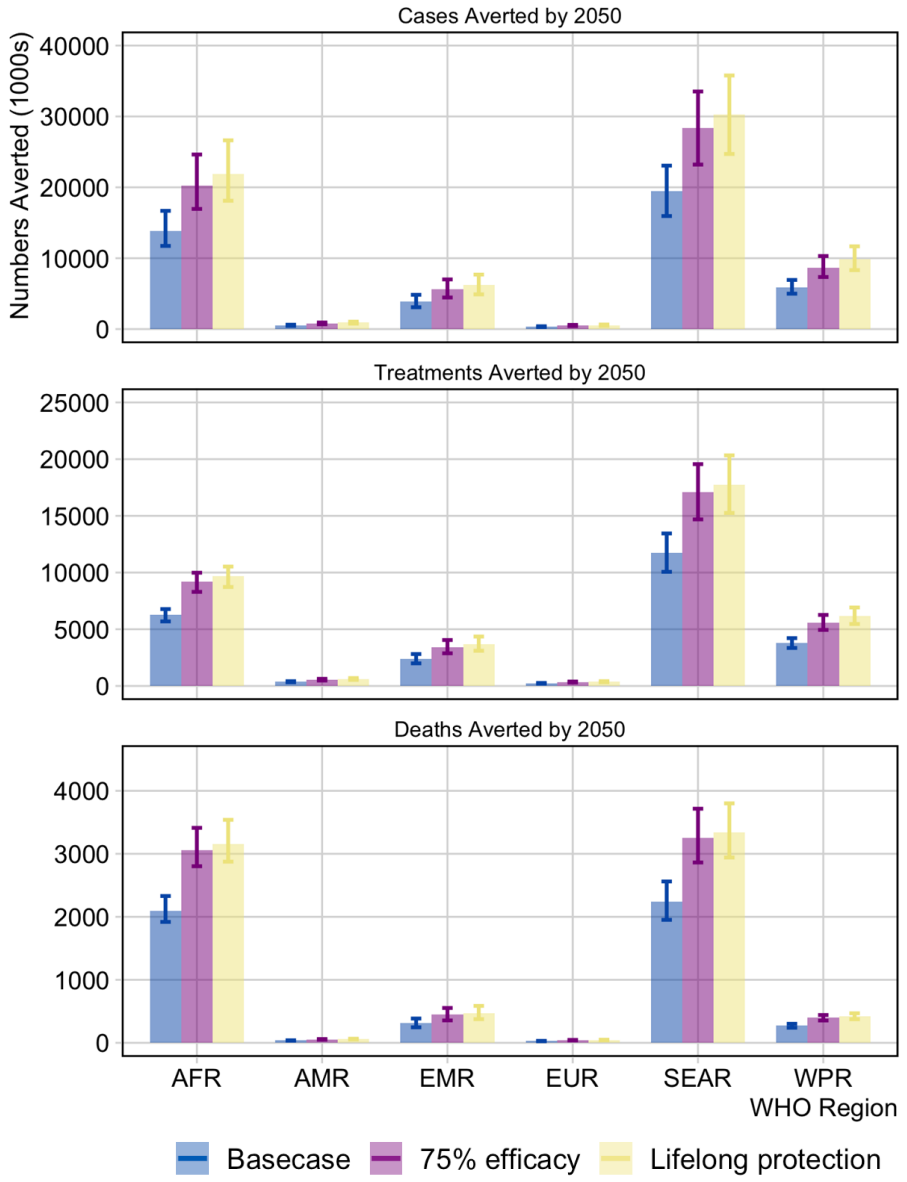
A 75% efficacy vaccine may avert ~50% more cases/deaths, than a 50% efficacy vaccine

Adol/Adult, 50% / 75% efficacy, Basecase, 10y protect , med coverage

Cases, treatments, and deaths averted by Basecase delivery with 50% vs 75% efficacy and 10 years vs lifelong protection

In the *Basecase* scenario, **~44 million** cases, **~25 million** treatments, and **~5 million** deaths were averted.

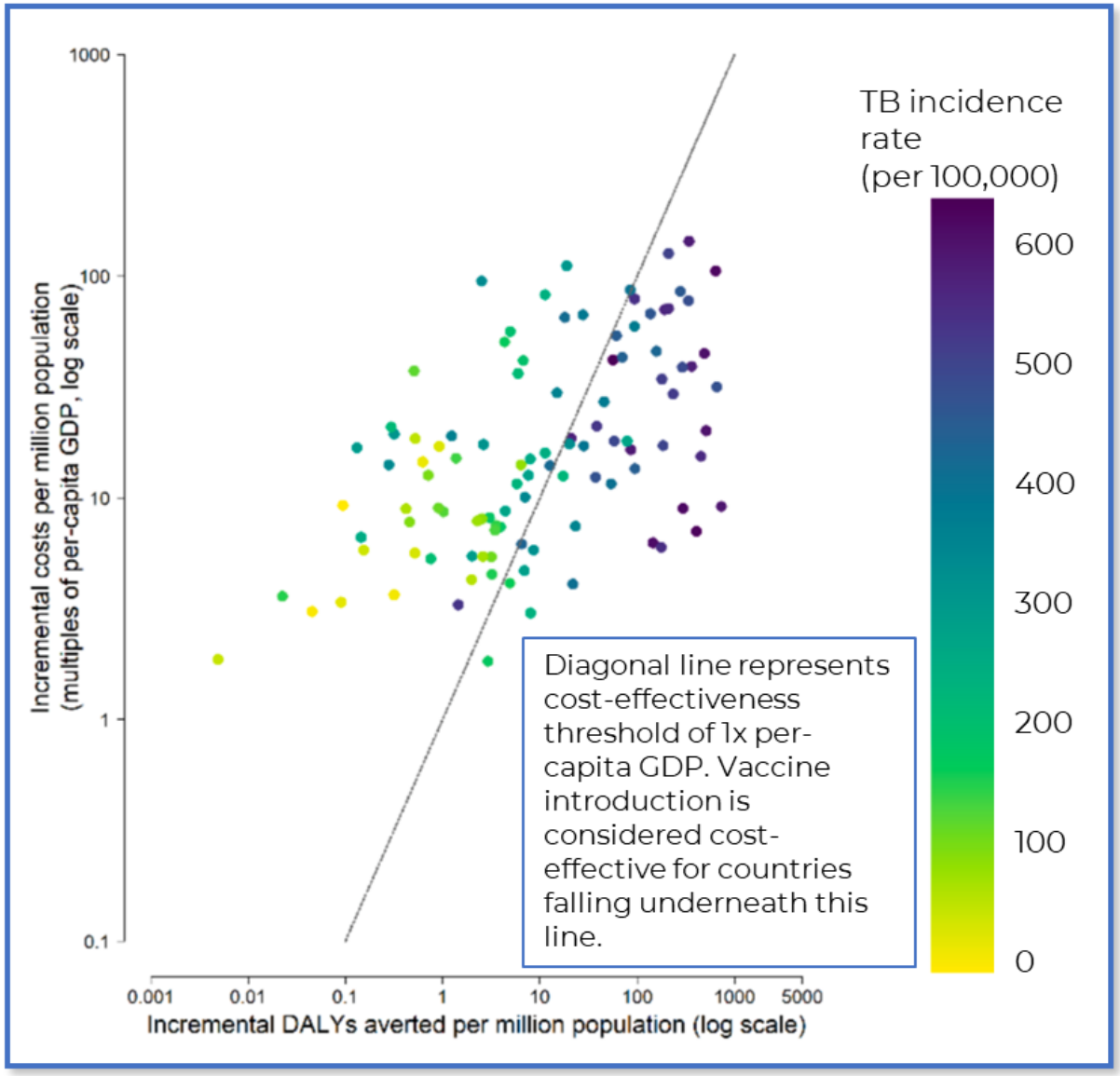
- A vaccine with 75% efficacy could prevent **~20 million additional** cases, **~14 million additional** treatments, and **~2 million additional** deaths **(~50% more)**



Infant TB vaccines cost-effective in 45% of countries (89% high-burden countries)

- Higher country incidence rate associated with higher impact per capita, more favorable CE

Health system perspective

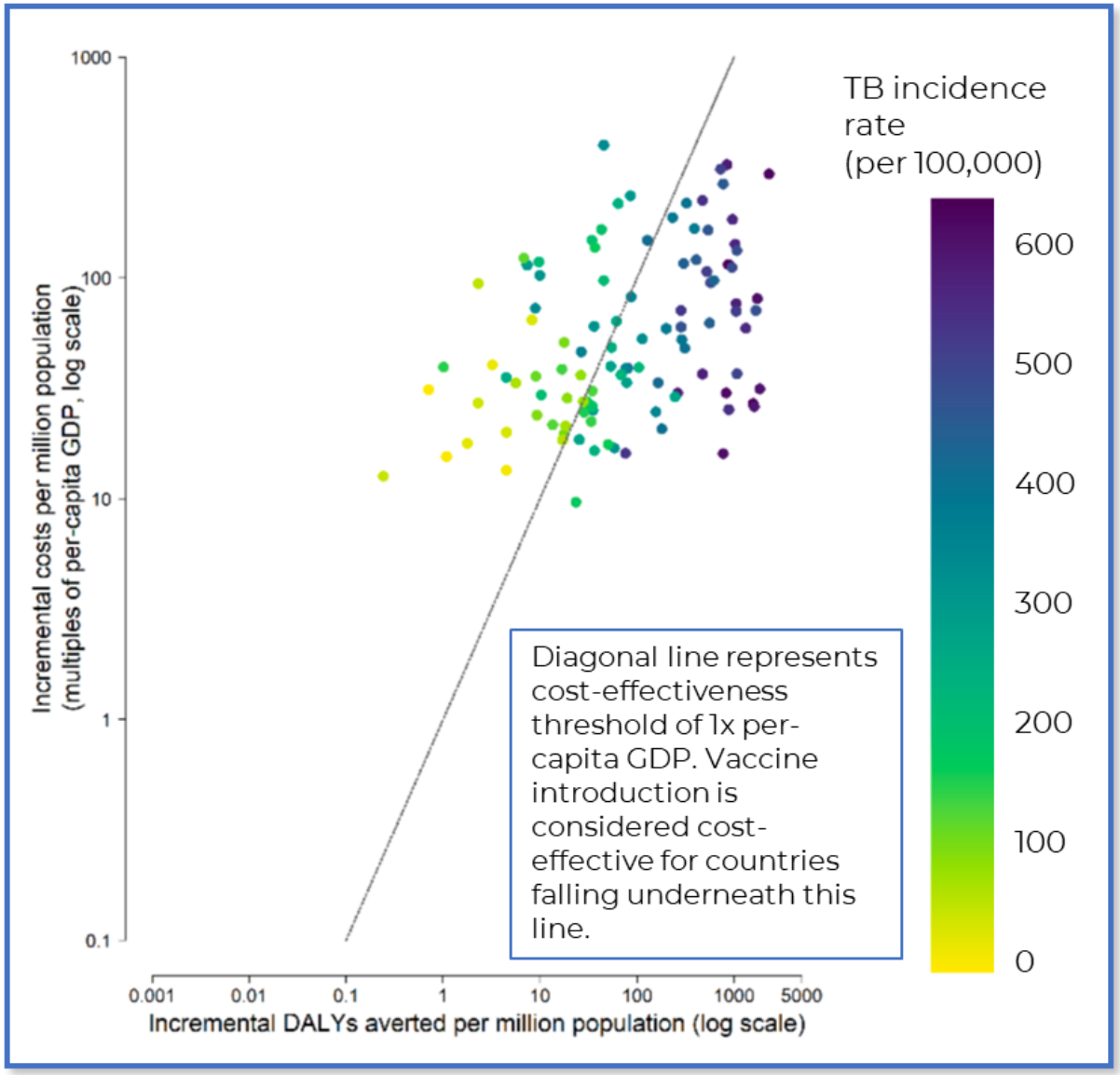


Portnoy A, Clark RA, Quaife M et al. The cost and cost-effectiveness of novel tuberculosis vaccines in low- and middle-income countries: A modeling study. *PLOS Med,* 2023; doi: https://doi.org/10.1371/journal.pmed.1004155.

Adol/Adult TB vaccines cost-effective in 61% of countries (100% high-burden countries)

- Higher country incidence rate associated with higher impact per capita, more favorable CE
- Same story for adult vaccine, but higher average costs and impact

Health system perspective



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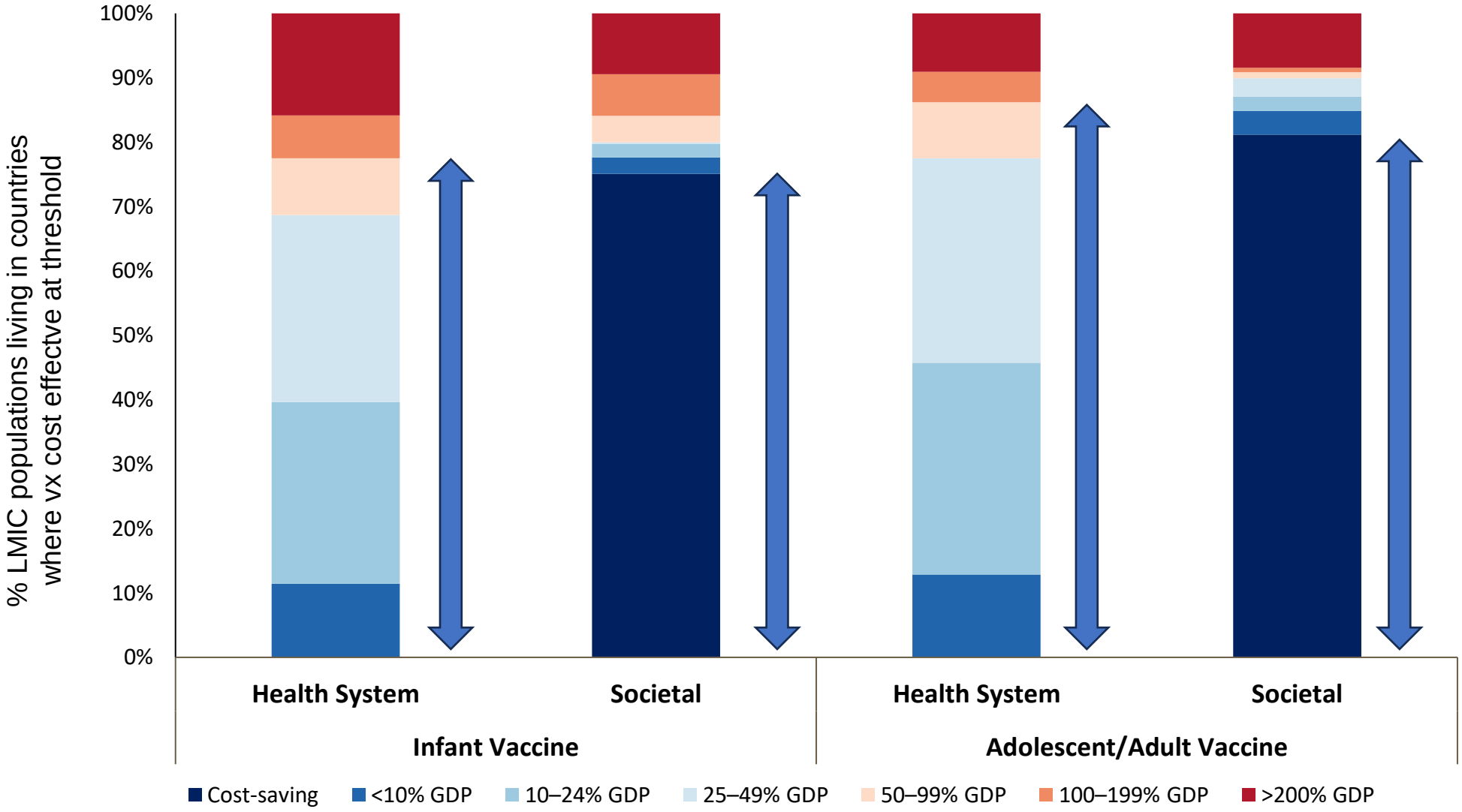
TB vaccines may be cost-saving from societal perspective



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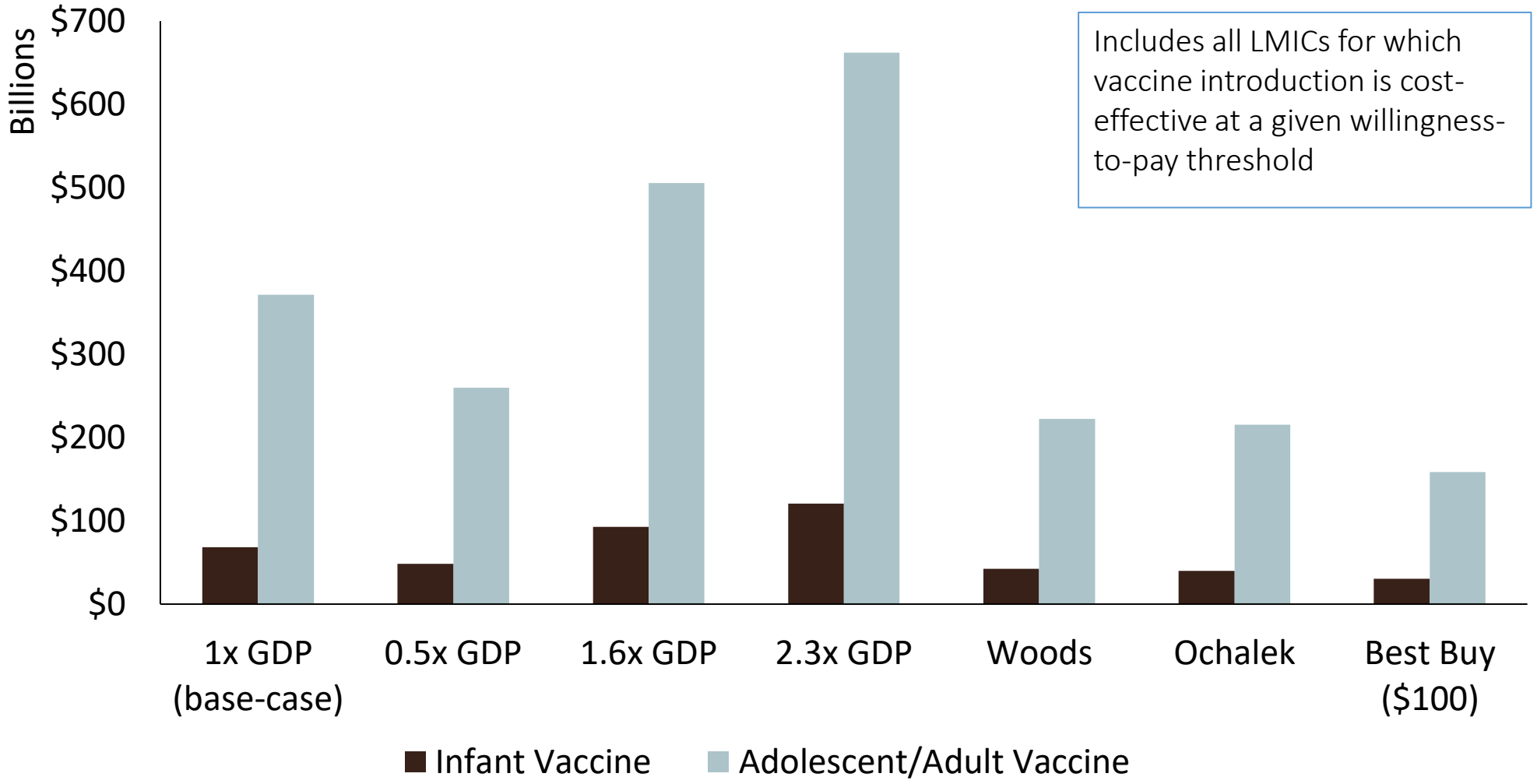
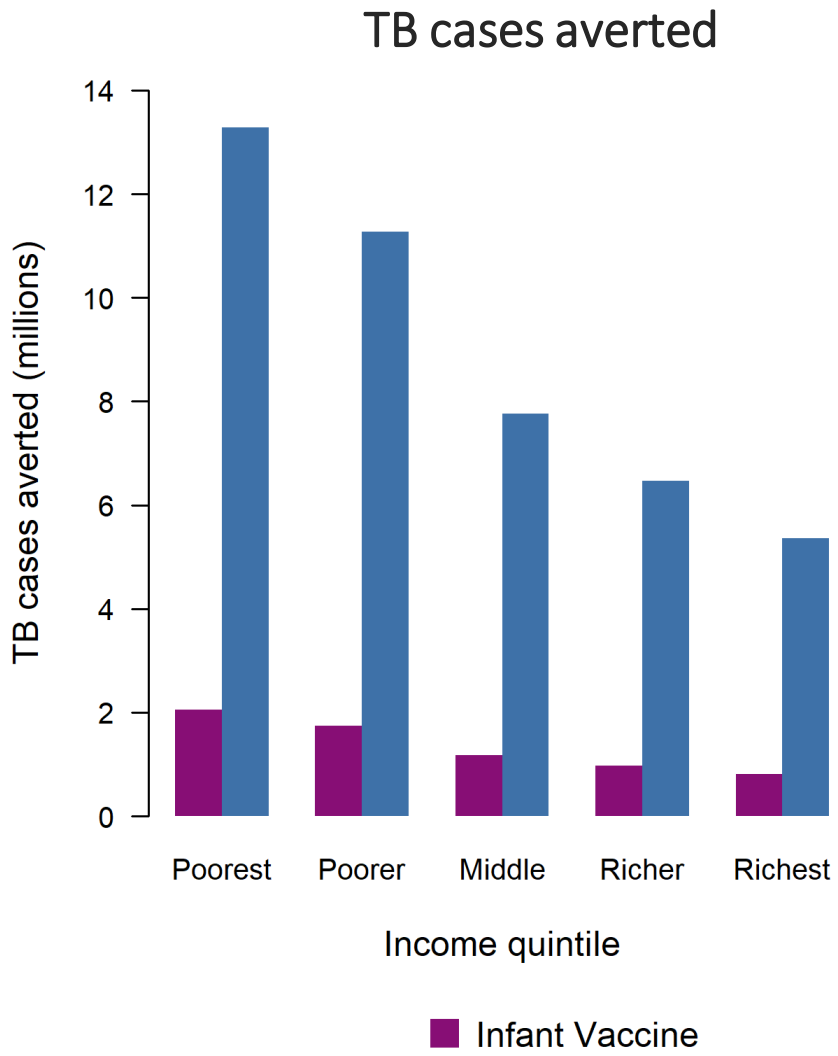
$7 in health and economic benefits, for every $1 invested in adolescent/adult TB vaccines

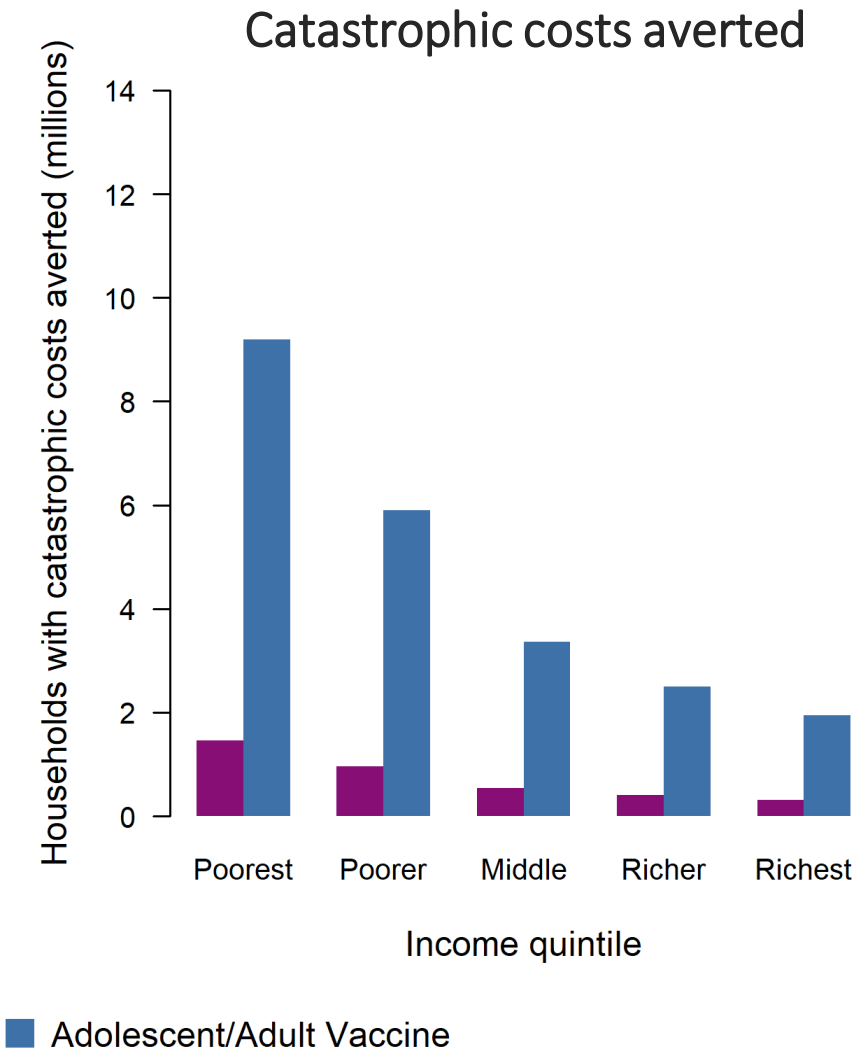


TB vaccines may advance health equity, with ~56% of benefits in poorest 40% of the population

Lower income quintiles:

- Higher TB incidence
- Greater proportion with catastrophic costs



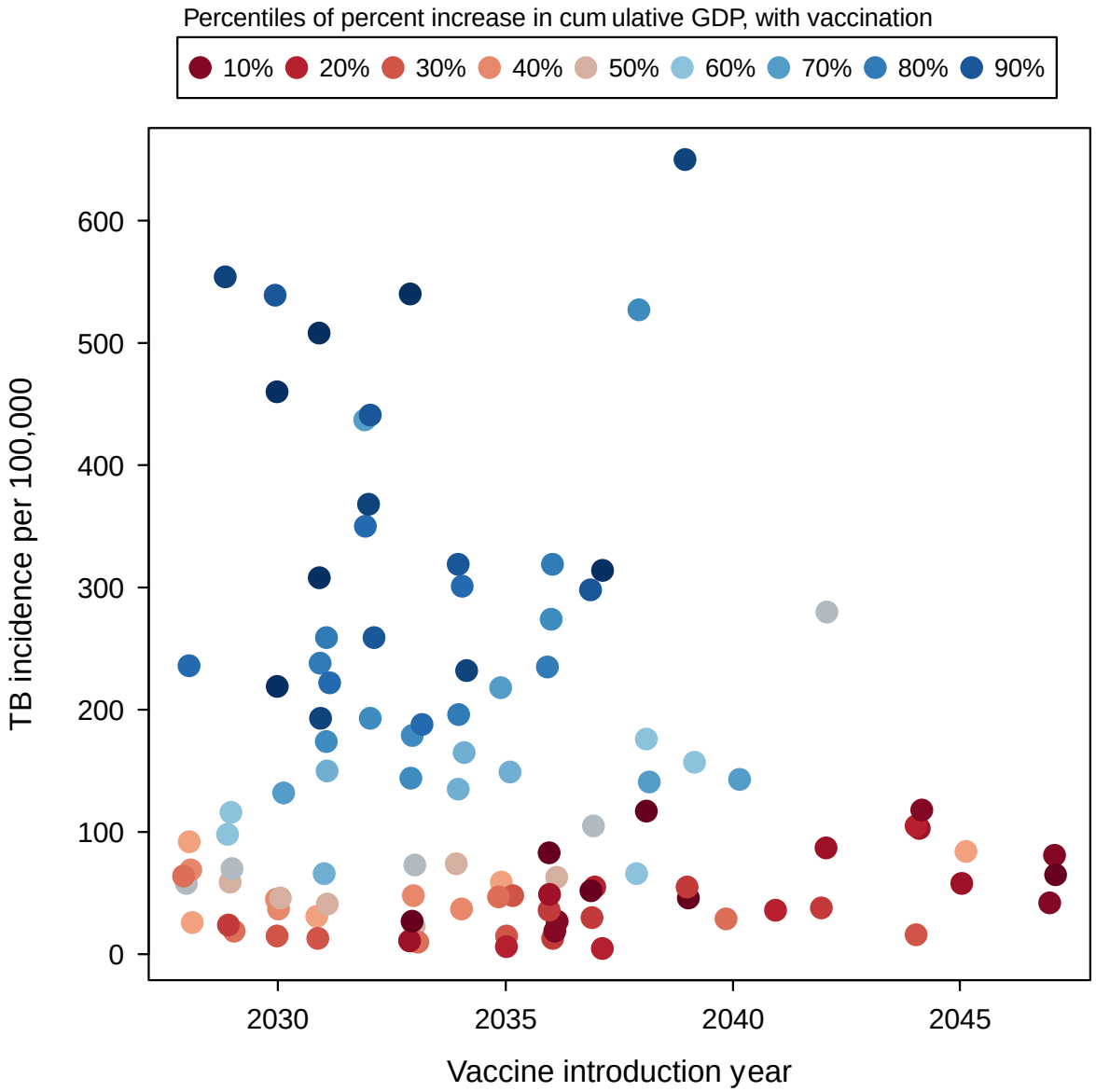


Infant Vaccine

Adolescent/Adult Vaccine

Adol/Adult TB vaccines may increase LMIC GDP by $1.6 trillion by 2080

- Macroeconomic impact strongly related to current TB incidence level
- Earlier vaccine introduction, lower current GDP per capita also related to greater % impact



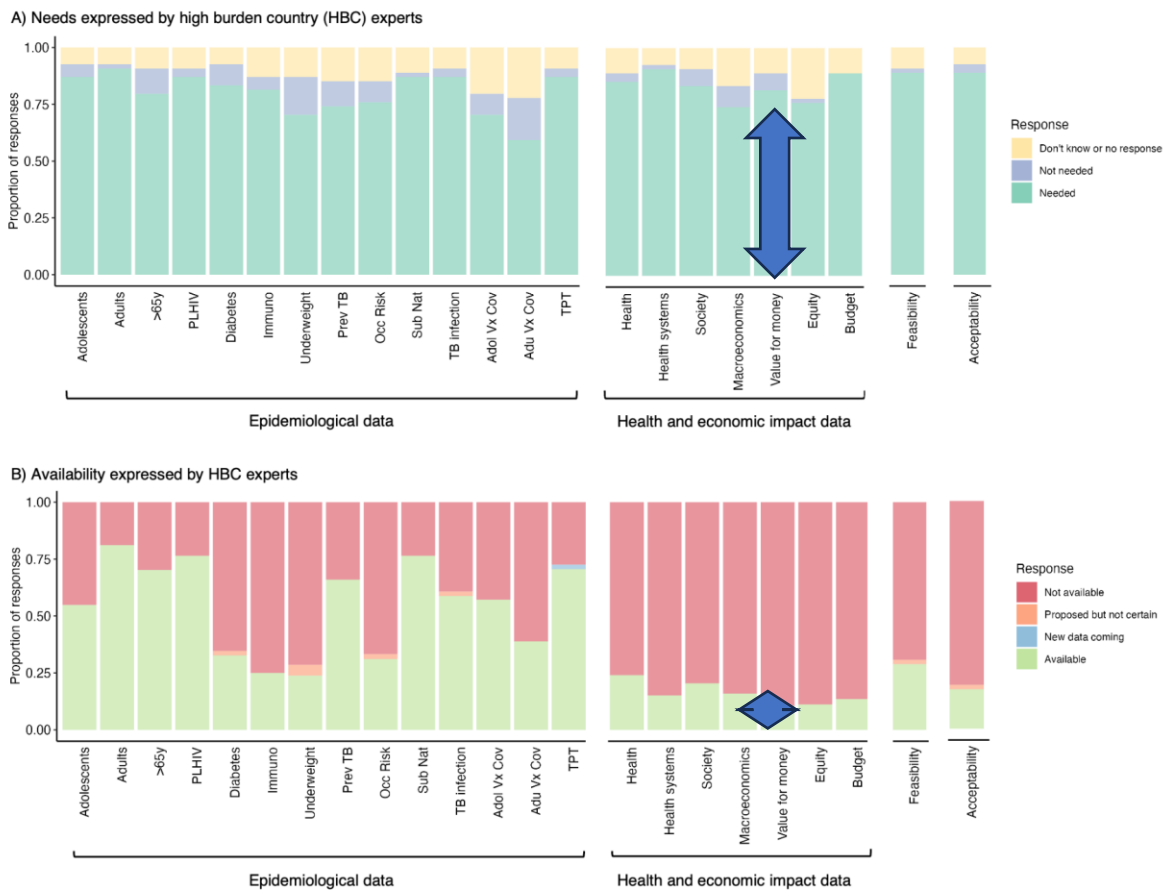
Portnoy A, Arcand J-L, Clark RA, et al. The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries. *medRxiv,* 2022; doi: https://doi.org/10.1101/2022.11.23.22282690

Summary

- Case for new adolescent/adult TB vaccines is strong
- Potentially impactful, reduce AMR, cost effective (even cost-saving), advance health equity, increase GDP
- Adol/adult vaccine likely quicker & larger impact than infant vaccine
- But really need for campaigns to get this impact, not just routine
- Need to include poor and other higher burden groups to maximize impact and advance equity

Needs

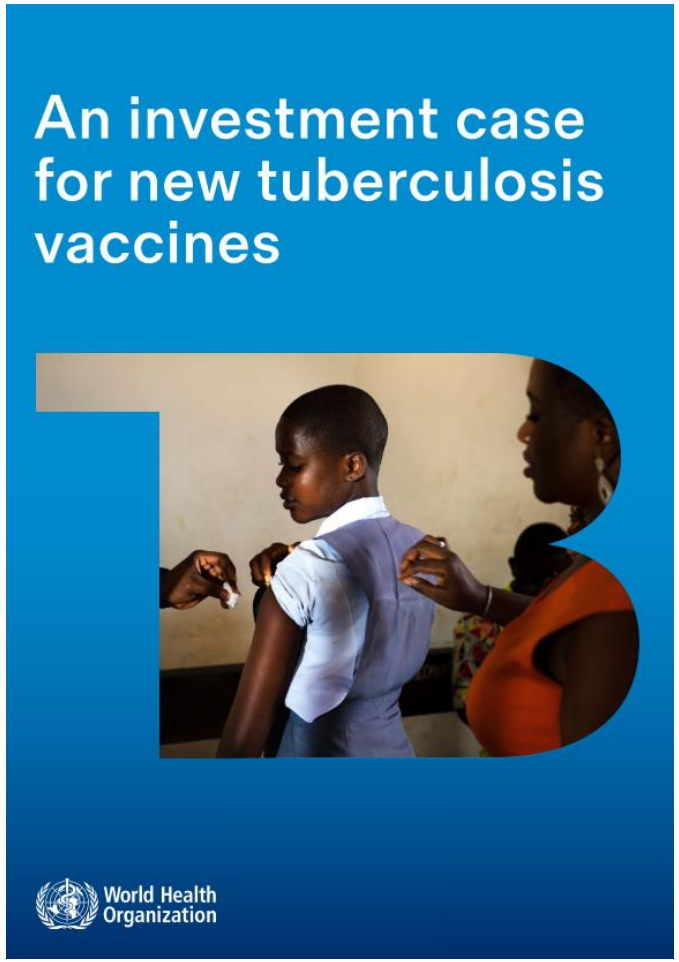
- Adol/adult vaccine(s) will (hopefully) be licensed, but will be for ~15–44 year olds
- Many key risk groups, and/or more operationally feasible groups, lie outside
- Will need rapid
  - Age de-escalation for younger adolescent
  - Age escalation for older groups
- Big gap between country level decision makers data needs and data availability
  - Eg 20 HBCs experts said >74% need potential vx impact data but only <24% have data
  - Need coordinated data collation, collection & generation needed



Clark et al, in review

Summary of…

Policy Brief



Health Impact

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

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

Summary

Background Tuberculosis is a leading infectious cause of death worldwide. Novel vaccines will be required to reacl global targets and reverse setbacks resulting from the COVID-19 pandemic. We estimated the impact of nove tuberculosis vaccines in low-income and middle-income countries (LMICs) in several delivery scenarios.

Cost and cost effectiveness

PLOS MEDICINE

RESEARCH ARTICLE

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

Allison Portnoy[1*], Rebecca A. Clark[2,3,4], Matthew Quaife[2,3,4], Chathika K. Weerasuriya[2,3,4], Christinah Mukandavire[2,3,4], Roel Bakker[2,3,4,5], Arminder K. Deol[2,3,4,6], Shelly Malhotra[7,8], Nebiat Gebreselassie[9], Matteo Zignol[9], So Yoon Sim[10], Raymond C. W. Hutubessy[10], Inés Garcia Baena[9], Nobuyuki Nishikiori[9], Mark Jit[3,4,11], Richard G. White[2,3,4‡], Nicolas A. Menzies[1,12‡]

Equity and financial protection

Original research

BMJ Global Health

The potential impact of novel tuberculosis vaccines on health equity and financial protection in low-income and middle-income countries

Allison Portnoy ,[1,2] Rebecca A Clark,[3,4,5] Chathika K Weerasuriya,[3,4,5] Christinah Mukandavire,[6] Matthew Quaife,[3,4,5] Roel Bakker,[3,4,5,7] Inés Garcia Baena,[8] Nebiat Gebreselassie,[8] Matteo Zignol,[8] Mark Jit,[3,5,9] Richard G White ,[3,4,5] Nicolas A Menzies [2,10]

Macroeconomic growth

PLOS MEDICINE

RESEARCH ARTICLE

The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries: A modeling study

Allison Portnoy[1,2*], Jean-Louis Arcand[3,4,5,6], Rebecca A. Clark[7,8,9], Chathika K. Weerasuriya[7,8,9], Christinah Mukandavire[10], Roel Bakker[7,8,9,11], Edith Patouillard[12], Nebiat Gebreselassie[13], Matteo Zignol[13], Mark Jit[8,9,14], Richard G. White[7,8,9], Nicolas A. Menzies[2,15]

The Investment Case for New TB vaccines

Richard White, Nick Menzies, Rebecca Clark, Allison Portnoy, Christinah Mukandavire, Chathika Weerasuriya, Danny Scarponi, Arminder Deol, Andrew Iskauskas, Roel Bakker, Matthew Quaife, Shelly Malhotra, Nebiat Gebreselassie, Matteo Zignol, Raymond Hutubessy, Birgitte Giersing, Mark Jit, Rebecca Harris, So Yoon Sim, Inés Garcia Baena, Nobuyuki Nishikiori, Jean-Louis Arcand, Edith Patouillard,

and many, many others

richard.white@lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

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HARVARD UNIVERSITY

Part 2

The TB Vaccine Pipeline

Strengths, Weaknesses, Opportunities & Threats

GVIRF Webinar
New Tuberculosis Vaccines for Adults & Adolescents
22 February 2024

Mark Hatherill
South African Tuberculosis Vaccine Initiative (SATVI)
University of Cape Town

WHO COVID-19 vaccine tracker

1. - Number of vaccines in clinical development	183
2. - Number of vaccines in pre-clinical development	199

3. - Candidates in clinical phase

Filter: Phase 3 — Select phase of development (default is all)

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	23	46%
VVnr	Viral Vector (non-replicating)	3	6%
DNA	DNA	2	4%
IV	Inactivated Virus	10	20%
RNA	RNA	7	14%
VVr	Viral Vector (replicating)	1	2%
VLP	Virus Like Particle	3	6%
VVr + APC	VVr + Antigen Presenting Cell	0	0%
LAV	Live Attenuated Virus	1	2%
VVnr + APC	VVnr + Antigen Presenting Cell	0	0%
BacAg-SpV	Bacterial antigen-spore expression vector	0	0%
		50	

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

30th March 2023

COVID-19 Vaccine Development

>40 efficacy trials
>400,000 volunteers
12 WHO approved vaccines in <3 years

Grana et al, Efficacy and safety of COVID-19 vaccines, Cochrane Database of Systematic Reviews 2022

Reid et al, The Lancet Commission on Tuberculosis, Lancet 2023

183 COVID-19 vaccines in clinical pipeline

50 COVID-19 vaccines in Phase 3 alone

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 16 vaccine candidates in the pipeline as of September 2023, of which 11 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
- DNA/RNA

Trial staus

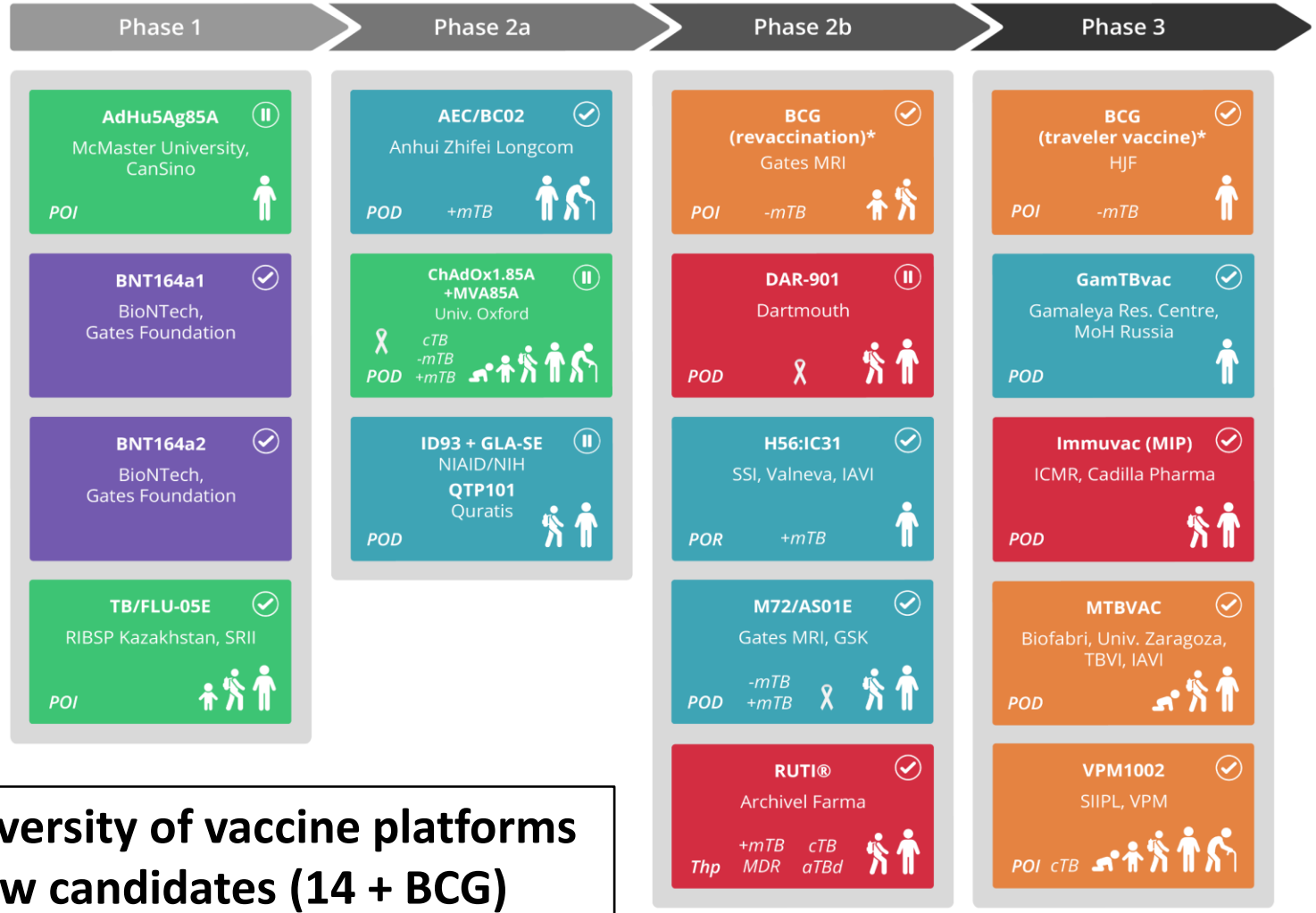
- Active trials
- No active trials

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



Strength: Diversity of vaccine platforms

Weakness: Few candidates (14 + BCG)

Few novel antigens

**BCG appears twice in the pipeline to distinguish between the investigation of its use in BCG-naïve individuals (traveler vaccination) and in individuals who have previously been vaccinated with BCG (revaccination).*

Stop TB Partnership
Working Group on New TB Vaccines

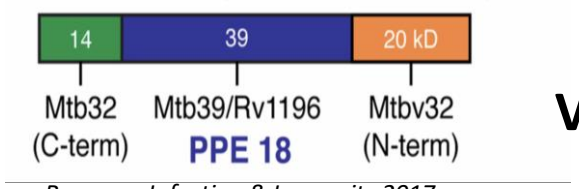
Information reported by vaccine sponsors or found in clinical trial registries or other public sources.

For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/

Last update: 28 September 2023

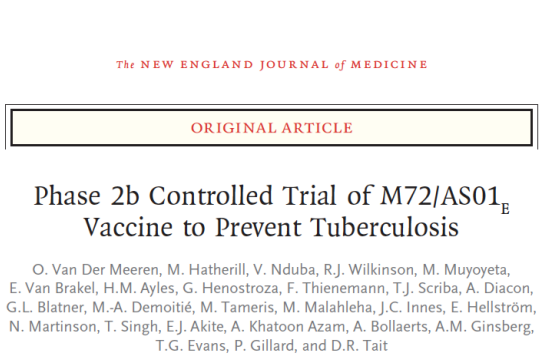
Strengths:	**Lead candidate with efficacy signal**
	Partially meets WHO PPC (50% VE IGRA+)
Weakness:	**Partially meets WHO PPC (No VE data IGRA-)**
Opportunity:	**→ Phase 3 trial**

M72/AS01$_E$



Brennan, Infection & Immunity 2017

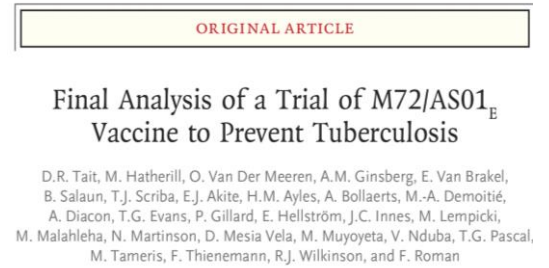
Phase 2b IGRA+ adults 18+
Vaccine Efficacy 49.7% over 3 years


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


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

Entering large Phase 3 licensure trial (Q1 2024): Results expected 2028

20,000 adolescents and adults aged 15-44 years (20,000 IGRA+; 1,000 IGRA- and HIV-)

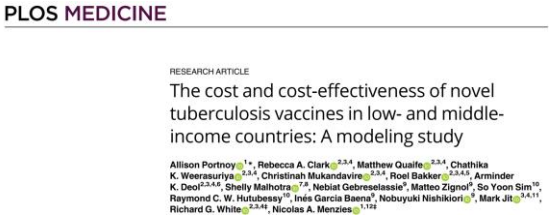
Efficacy, safety, and immunogenicity

- Safety & immunogenicity adolescents, adults, PLWHIV, IGRA+/-
- VE prevention of TB disease (IGRA+)

Modelling projections M72/AS01$_E$ 50% VE

- Could prevent up to 76 Million TB cases and 8.5 Million TB deaths (25 years)
  - If VE in IGRA+ and IGRA-


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


PLOS MEDICINE

RESEARCH ARTICLE

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

TB Vaccine Pipeline

Active clinical trials of TB vaccine candidates

There are 14 active clinical trials across 12 candidates as of September 2023.

Platform

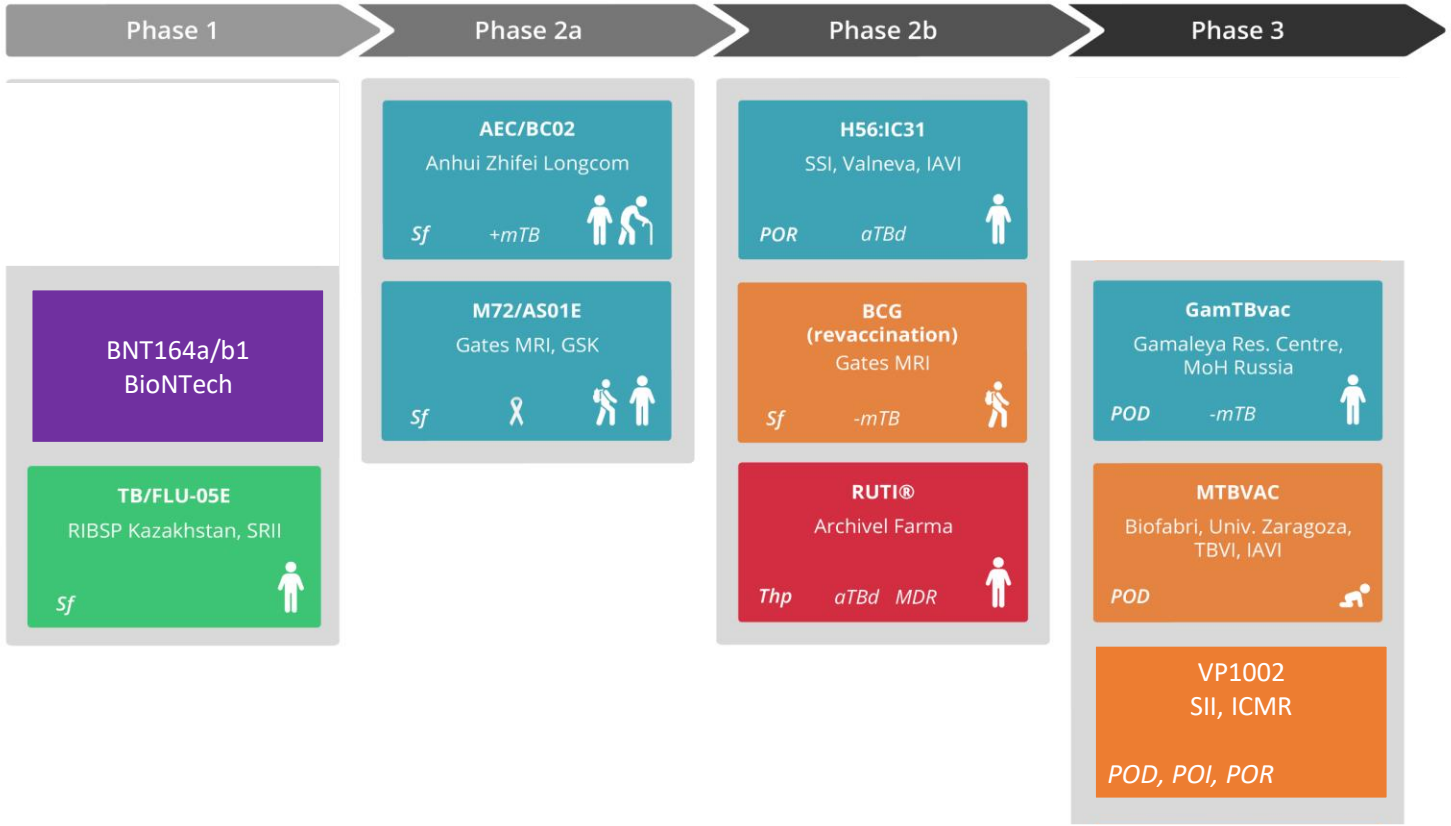
- Mycobacterial - Live attenuated
- Mycobacterial - Inactivated
- Viral vector
- Protein/Adjuvant
- DNA/RNA

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



Strength:	**Several candidates in Phase 2b-3**	**(5 + BCG)**
Weaknesses:	**Few candidates in active trials**	**(9 + BCG)**
	Few new candidates in Phase 1-2	**(BNT164a/b1)**
	“Non-traditional” efficacy trials	**(POI; POR; Tx; POD HHC)**

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: 28 September 2023

TB Vaccine Pipeline

Active clinical trials of TB vaccine candidates

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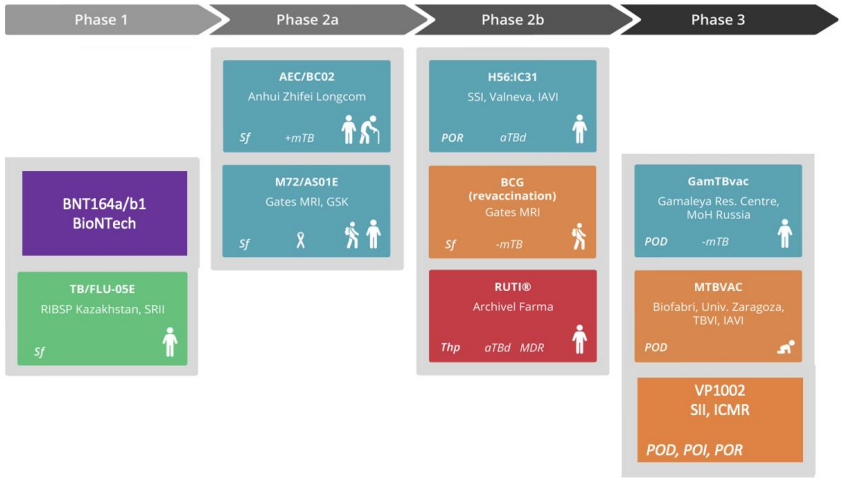

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For the full list of completed trials for each candidate, visit www.newtbvaccines.org/tb-vaccine-pipeline/

Last update: 28 September 2023

Weakness: "Non-traditional" efficacy trials

May not lead to global licensure

POD HHC	**VPM1002**
POR/Tx	**H56:IC31; VPM1002; RUTI**
POI	**BCG REVAX; VPM1002**

Opportunity: **Efficacy results positive (2024 - 2028) → ☺ funder/stakeholder sentiment, risk tolerance**

Threat: **Efficacy results negative (2024 - 2028) → ☹ funder/stakeholder sentiment, risk aversion**

Impact investment in new trials?

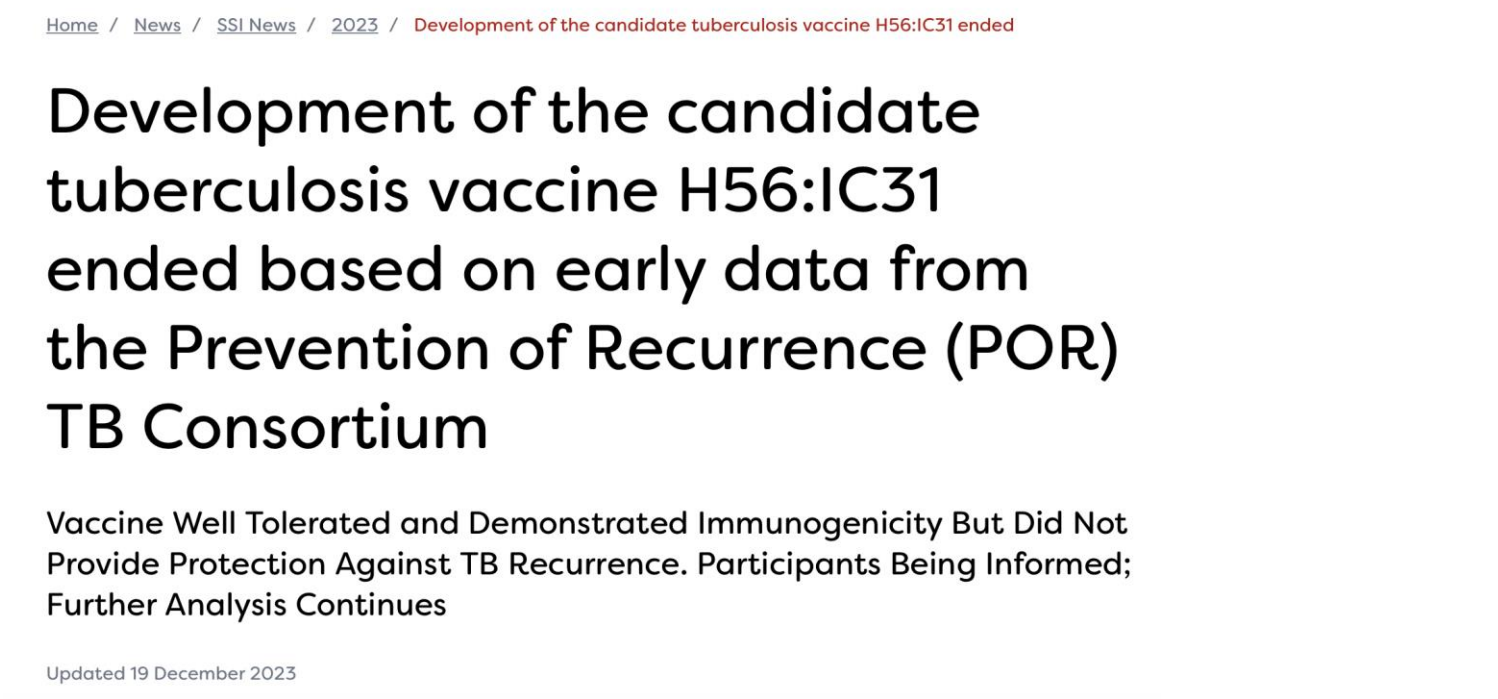
→ study design (POI/POR/POD); study population; vaccine platform (live/inactivated/subunit)

Threat: Efficacy results if negative (2024 - 2028): H56:IC31 POR

NCT03512249

Study Population: Adult TB patients aged 18-60 years, HIV-, pulmonary DS-TB, sputum smear-negative at EOT

Primary objective: Efficacy of H56:IC31 compared to placebo in reducing the rate of recurrent TB disease @ 12 months



Home / News / SSI News / 2023 / Development of the candidate tuberculosis vaccine H56:IC31 ended

Development of the candidate tuberculosis vaccine H56:IC31 ended based on early data from the Prevention of Recurrence (POR) TB Consortium

Vaccine Well Tolerated and Demonstrated Immunogenicity But Did Not Provide Protection Against TB Recurrence. Participants Being Informed; Further Analysis Continues

Updated 19 December 2023

Impact on stakeholder sentiment?

POR/Therapeutic trials in TB patients? TB vaccine field in general?

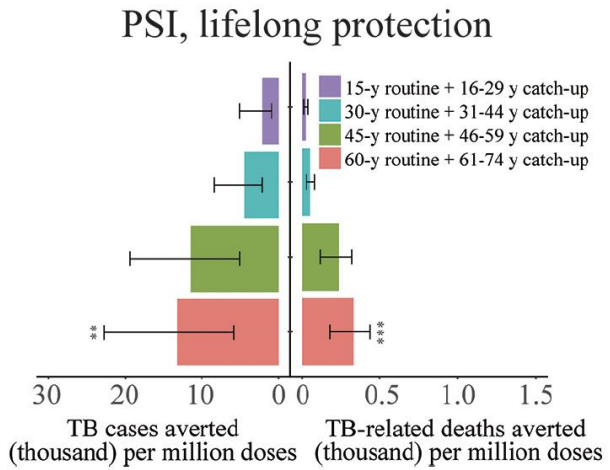
Opportunity: Efficacy results if positive (2024 - 2028): *M. vaccae* POD

Original research

BMJ Global Health

Population-level health and economic impacts of introducing Vaccae vaccination in China: a modelling study

Jun-Jie Mao [1], Xiao Zang [2], Wan-Lu Yue [3], Pei-Yao Zhai [3], Qiong Zhang [4], Chun-Hu Li [1], Xun Zhuang [5], Min Liu [6], Gang Qin [1,7]



NCT01979900
Anhui Zhifei Longcom
N=10,000
Aged 15 – 65 years
TST 15mm+
6 doses *M. vaccae* vs placebo
Follow up 2 years
Study completion Nov 2017

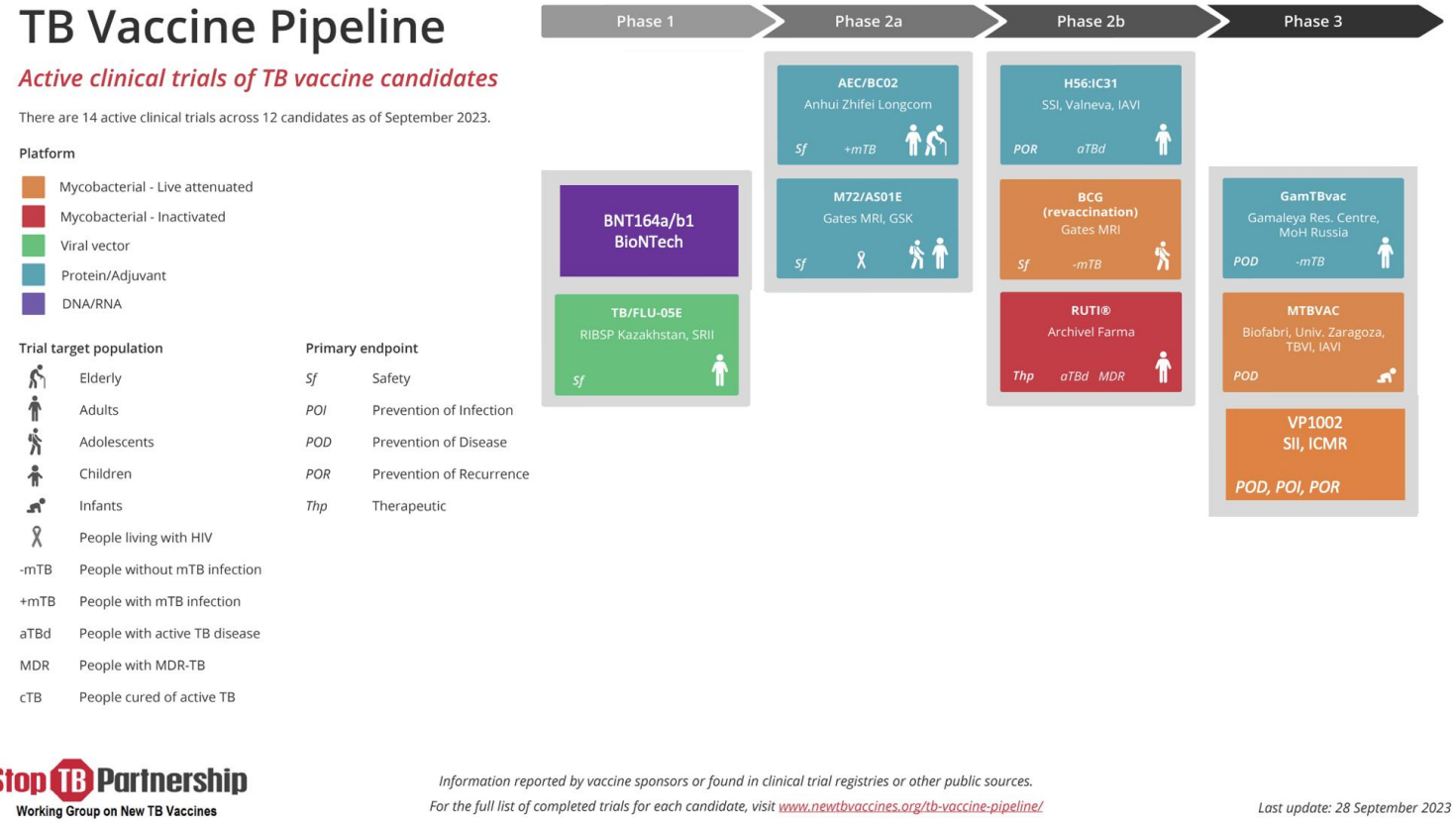
Case definition	Vaccae			Placebo			Vaccine efficacy (% [95% CI])
	No. of incident cases	Person-yr of follow-up	Rate per 100 person-yr (95% CI)	No. of incident cases	Person-yr of follow-up	Rate per 100 person-yr (95% CI)	
Definite pulmonary TB disease	29	8846.3	0.328 (0.228, 0.472)	64	8838.2	0.724 (0.567, 0.925)	54.7 (29.8, 70.8)
Microbiological pulmonary TB disease	8	8858.3	0.090 (0.045, 0.181)	16	8872.2	0.180 (0.110, 0.294)	49.9 (-17.0, 78.6)
Smear or culture-positive pulmonary TB disease	7	8858.3	0.079 (0.038, 0.166)	8	8878.5	0.090 (0.045, 0.180)	12.3 (-141.8, 68.2)
Definite Xpert MTB/Rif positive pulmonary TB disease	1	8863.2	0.011 (0.002, 0.080)	8	8879.8	0.090 (0.045, 0.180)	87.5 (-0.1, 98.4)
Clinical TB disease	21	8851.7	0.237 (0.155, 0.364)	48	8852.1	0.542 (0.409, 0.720)	56.2 (26.9, 73.8)

Opportunities:

- Pending efficacy trials
  - M72/AS01$_E$ (Phase 3)
  - MTBVAC (Phase 2b/3)
  - QTP101 (Phase 2b/3)
  - ID93+GLA/SE (Tx/POR)

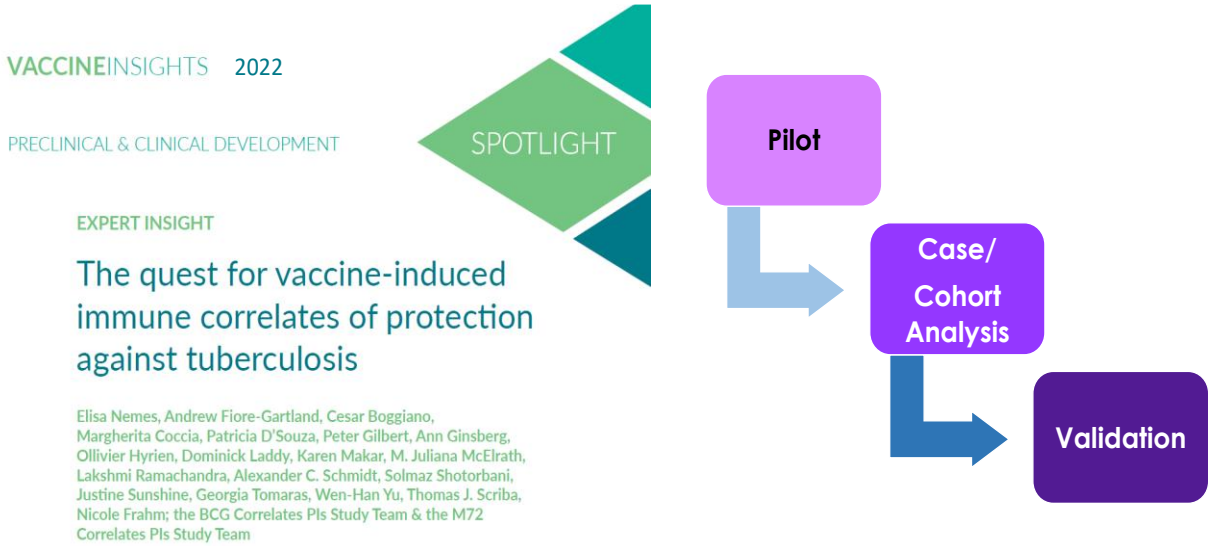
- Pending trials PLWH + ART
  - VPM1002 and BCG
  - MTBVAC and BCG

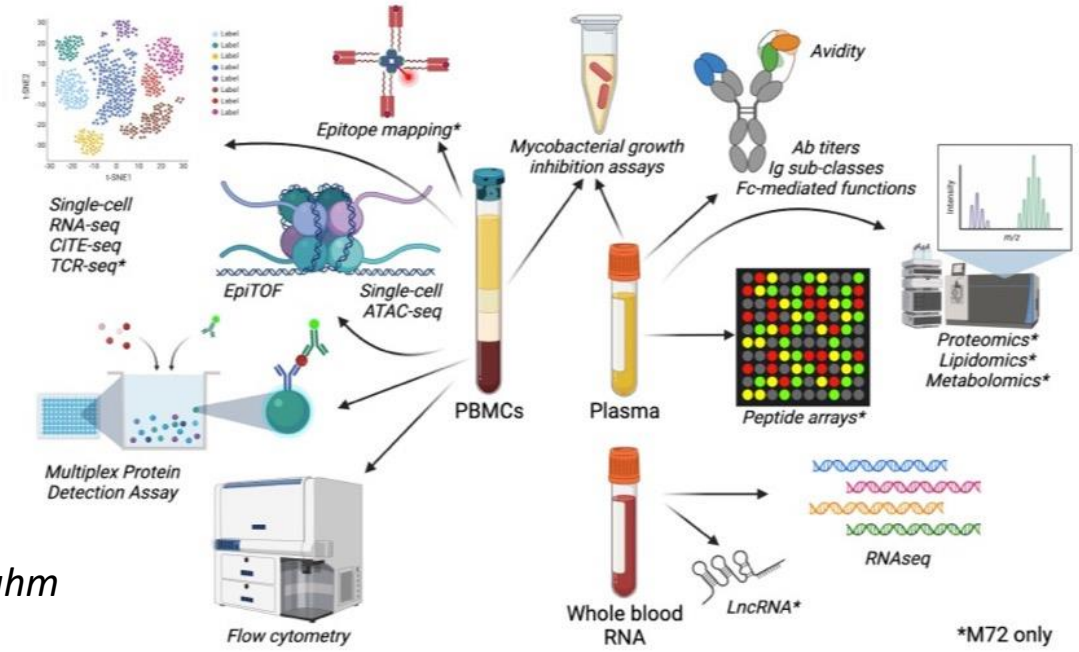
- Pending Phase 1 FIH trials
  - H107
  - CMV vector (VIR-2020)



"Recharging" of the TB vaccine pipeline?

Opportunity: Discover & validate immune correlates of vaccine-mediated protection





Courtesy Elisa Nemes, Tom Scriba, Nicole Frahm

Key questions:

Will Phase 2b correlates be validated? (POI BCG REVAX; POD M72/AS01$_E$)

Single correlate, or signature of multiple correlates?

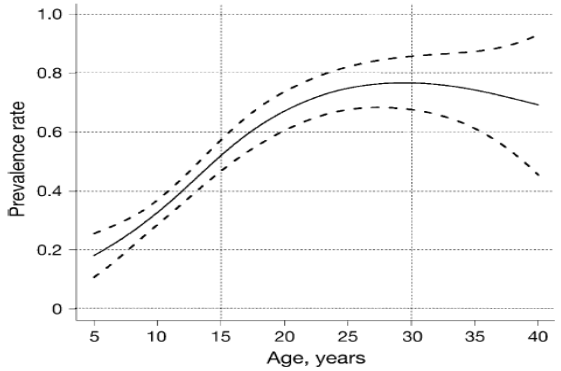
Specific to a vaccine/antigen, or generalizable to other candidates?

Generalizable to other populations?

<u>Discriminatory performance sufficient to avoid efficacy trial?</u>

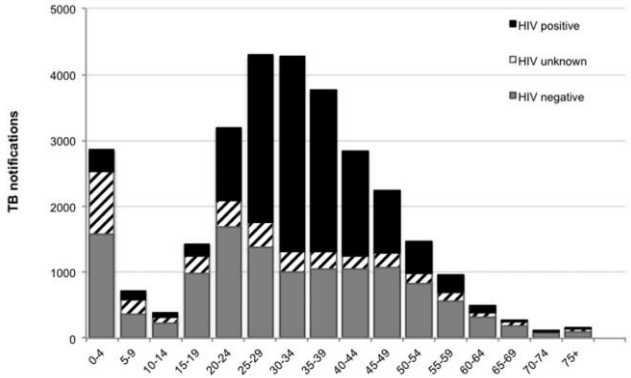
Threat: Lack POD efficacy data IGRA- and pre-adolescents
Disconnect between value proposition vs deliverable data (IGRA-; pre-adolescents)

Mtb infection



Wood (TST) IJTLD 2010

TB Disease



Wood, PLoS ONE 2011

TB disease incidence (18-25 years)	**IGRA+**	**800 per 100,000**	*Van Der Meeren NEJM 2018*
TB disease incidence (SA adolescents)	**IGRA-**	**220 per 100,000**	*Mahomed, PLoS ONE 2011*

→ Sample size Phase 2b POD in IGRA- ~ n=14,000
→ Sample size Phase 3 POD in IGRA- ~ n=80,000

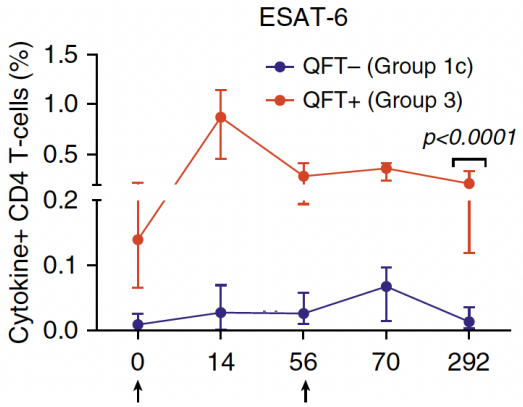
May never validate IGRA+ POD findings in IGRA-, pre-adolescent population

Threat: Lack POD efficacy data IGRA- and pre-adolescents

Immuno-bridging? CD4 T cell response is different in IGRA- and IGRA+
H56:IC31; MTBVAC; M72/AS01E; ID93+GLA-SE; MVA85A; BCG; H1:IC31

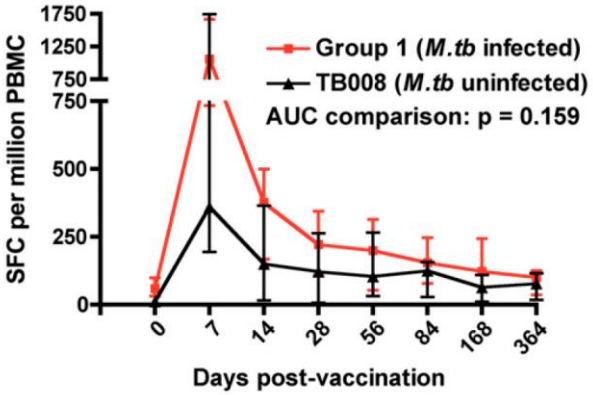
Dose Optimization of H56:IC31 Vaccine for Tuberculosis-Endemic Populations
A Double-Blind, Placebo-controlled, Dose-Selection Trial

Sara Suliman[1,2*], Angelique Kany Kany Luabeya[1,2*], Hennie Geldenhuys[1,2], Michele Tameris[1,2], Soren T. Hoff[3], Zhongkai Shi[4], Dereck Tait[5], Ingrid Kromann[3], Morten Ruhwald[3], Kathryn Tucker Rutkowski[4], Barbara Shepherd[4], David Hokey[4], Ann M. Ginsberg[5], Willem A. Hanekom[1,2], Peter Andersen[3], Thomas J. Scriba[1,2†], Mark Hatherill[1,2†], and the H56-035 Trial Group

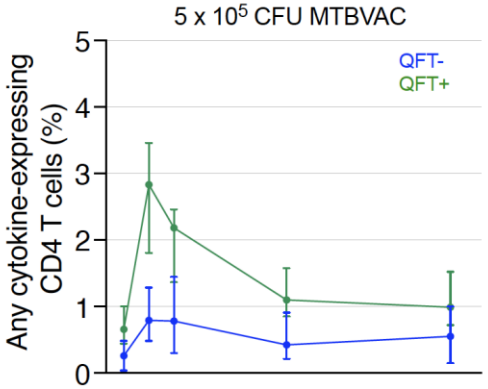


A Phase IIa Trial of the New Tuberculosis Vaccine, MVA85A, in HIV- and/or *Mycobacterium tuberculosis*–infected Adults

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†]



Unpublished data
ClinicalTrials.gov NCT02933281



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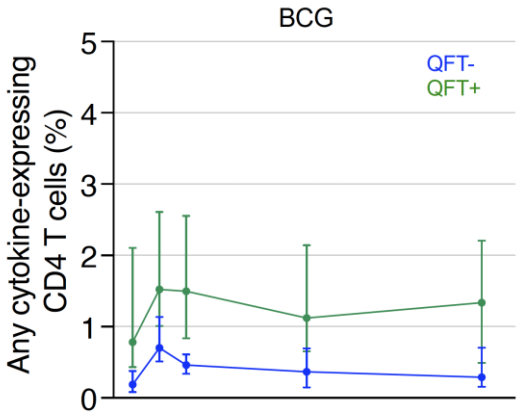
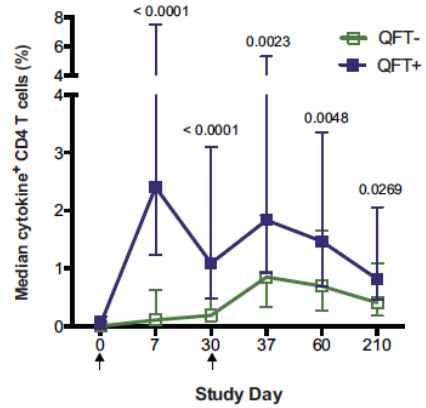
ClinicalTrials.gov NCT02933281



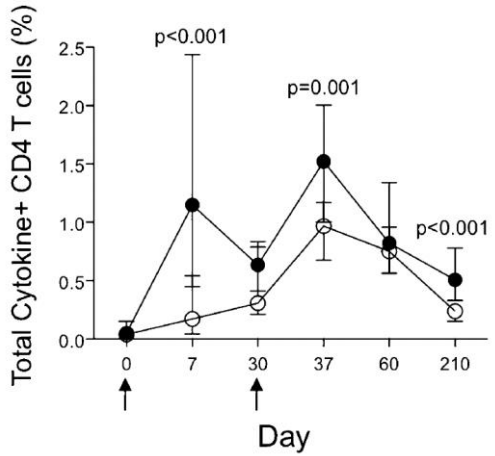
Safety and immunogenicity of candidate vaccine M72/AS01$_E$ in adolescents in a TB endemic setting

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



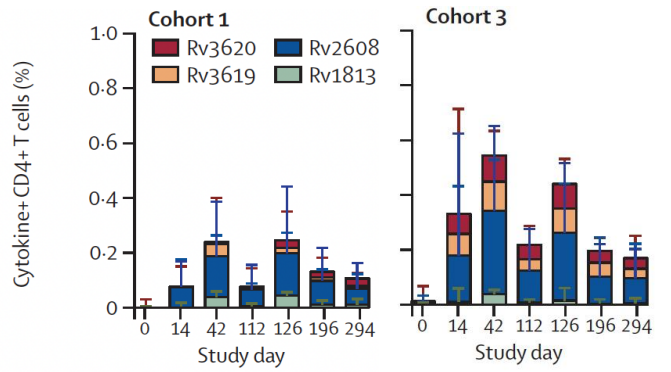
Induction and Regulation of T-Cell Immunity by the Novel Tuberculosis Vaccine M72/AS01 in South African Adults

Cheryl L. Day[1,2,3,*], Michele Tameris[1,*], Nazma Mansoor[1], Michele van Rooyen[1], Marwou de Kock[1], Hennie Geldenhuys[1], Mzwandile Erasmus[1], Lebohang Makhethe[1], E. Jane Hughes[1], Sebastian Gelderbloem[1,†], Anne Bollaerts[4], Patricia Bourguignon[4], Joe Cohen[4], Marie-Ange Demoitié[4], Pascal Mettens[4], Philippe Moris[4], Jerald C. Sadoff[5,§], Anthony Hawkridge[1], Gregory D. Hussey[1], Hassan Mahomed[1], Opokua Ofori-Anyinam[4,‡], and Willem A. Hanekom[1,‡]



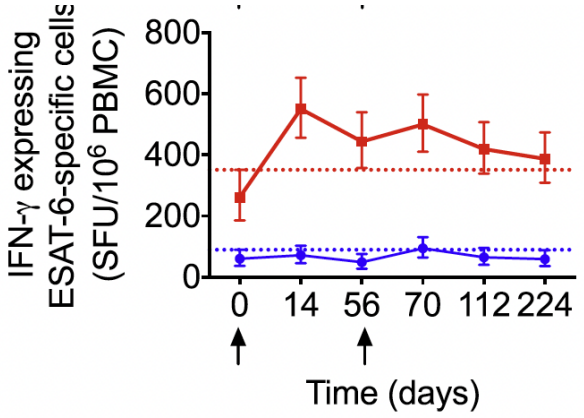
Safety and immunogenicity of the novel tuberculosis vaccine ID93 + GLA-SE in BCG-vaccinated healthy adults in South Africa: a randomised, double-blind, placebo-controlled phase 1 trial

Adam Penn-Nicholson*, Michele Tameris*, Erica Smit, Tracey A Day, Munyaradzi Musvosvi, Lakshmi Jayashankar, Julie Vergara, Simbarashe Mabwe, Nicole Bilek, Hendrik Geldenhuys, Angelique Kany-Kany Luabeya, Ruth Ellis, Ann M Ginsberg, Willem A Hanekom, Steven G Reed, Rhea N Coler, Thomas J Scriba†, Mark Hatherill†, and the TBVPX-114 study team†



H1:IC31 vaccination is safe and induces long-lived TNF-α$^+$IL-2$^+$CD4 T cell responses in *M. tuberculosis* infected and uninfected adolescents: A randomized trial

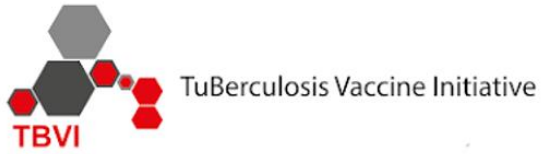
Helen Mearns[a,1], Hennie D. Geldenhuys[a,1], Benjamin M. Kagina[a,2], Munyaradzi Musvosvi[a], Francesca Little[b], Frances Ratangee[a], Hassan Mahomed[a,3], Willem A. Hanekom[a], Søren T. Hoff[c], Morten Ruhwald[c], Ingrid Kromann[c], Peter Bang[c], Mark Hatherill[a], Peter Andersen[c], Thomas J. Scriba[a,*], the THYB04 study group[4]



STRENGTHS	WEAKNESSES
- Diversity of vaccine platforms	Few novel antigens - Few candidates (14 plus BCG) - Few candidates in active trials (9 plus BCG) -
- Several candidates in Phase 2b-3 (5 plus BCG)	Few new candidates in Phase 1-2 (BNT164a/b1) -
- Lead candidate with efficacy sign (M72/AS01$_E$)	raditional" efficacy trials → global licensure?
- Partially meets WHO PPC (IGRA+)	Lead candidate with efficacy signal (M72/AS01$_E$) - Partially meets WHO PPC (IGRA-) -
OPPORTUNITIES	**THREATS**
- Pending efficacy results if positive (2024-	- Pending efficacy results if negative (2024-

CHANGE

Acknowledgments



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

Part 2

BILL & MELINDA GATES foundation

Challenges in TB Vaccine Product Development

GVIRF Webinar

Ann M. Ginsberg, MD, PhD

22 February 2024

Urgent need vs. substantial challenges

TB Vaccine Development's Three 'Valleys of Death'

Complex multi-stage disease
Pathogen expressing ~4000 antigens
Protective antigens not fully known
Lack of validated animal model
Only partial understanding of protective immunity
Lack of validated correlate of protection

Dose and regimen selection based on imperfect knowledge
No established human challenge model

No validated correlate of protection/surrogate endpoint

High cost of late-stage clinical trials

Efficacy trials large, long and expensive
Limited subnational epi data to support trial designs
Limited experienced global site capacity to conduct multiple, simultaneous late-stage efficacy trials
Variable regulatory requirements across NRAs and multinational regulatory bodies; long regulatory timelines; variable experience with TB vaccine clinical trials across NRAs

Inadequate mechanisms in place to sustainably deliver adolescent/adult vaccines

Label extensions require additional large trials
Uncertain market and procurement mechanism
Unclear sources and funding mechanisms

Inadequate funding and political will; market failure

Adapted from World Economic Forum sept. 18, 2018 Ditiu and Huh: https://www.weforum.org/agenda/2018/09/tb-is-the-worlds-deadliest-infectious-disease-we-have-one-shot-to-stop-it/ (accessed Feb. 11, 2024)

Discovery and Early Development Challenges

Complex multi-stage infection and disease

Complex pathogen expressing ~4000 antigens

Full complement of protective M.tb target antigens not yet known

Lack of validated nonclinical model predictive of human protection

Only partial understanding of protective immune mechanisms

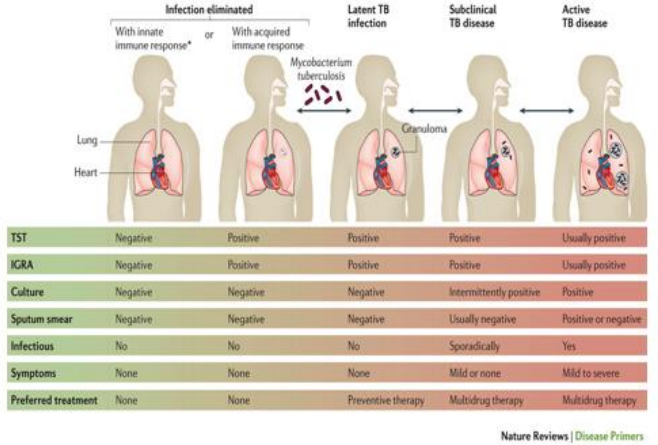
Lack of validated correlate of protection in animal models or humans

- These challenges mean **TB vaccine discovery is still largely empiric**

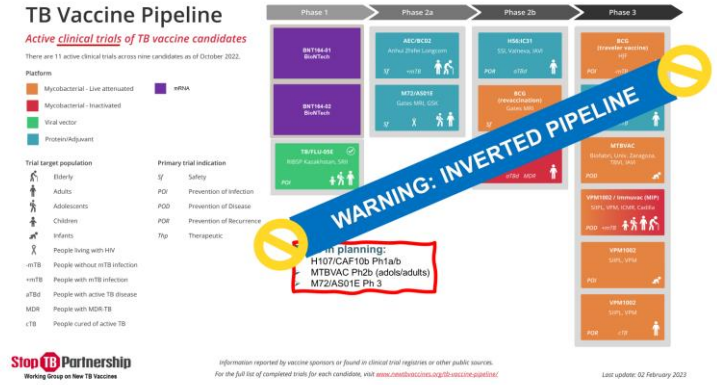
Inadequate funding for R&D (~1/8th of HIV and 1/1000 of COVID-19 vaccine R&D investments)

- **Above challenges plus lack of strong market driver limit pharma interest and investment**

Current status: relatively small, inadequately diverse, “inverted” pipeline of clinical candidates



Pai, M. *et al.* (2016) Tuberculosis. The*Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76



Clinical Development and Licensure Challenges

First 'valley of death' – moving from preclinical into human testing – challenging to build a convincing preclinical dataset to ensure funding

Dose and regimen selection based on imperfect knowledge (no vaccine-induced CoP)

No established human challenge model (some in development; *see McShane presentation*)

Second 'valley of death' – advancing into efficacy trials and late-stage development

Due to chronic nature of disease (slow course; only 5-10 % of infected individuals progress to active disease: ¼ of world tests positive by skin test or IGRA; ~10 million cases of active disease per year=0.125% of world population), **clinical trials to evaluate vaccine efficacy are large and long and therefore expensive** – leads to "2nd valley of death" (moving from early phase clinical testing of safety and immunogenicity – to efficacy trials)

Limited subnational epi data to support trial designs

Limited experienced global site capacity to conduct multiple, simultaneous late-stage efficacy trials

Variable regulatory requirements across NRAs and multinational regulatory bodies; long regulatory timelines; variable experience with TB vaccine clinical trials across NRAs

Extension of label post-initial licensure to additional age groups, geographies, etc. will require additional large trials until a CoP is identified and validated for regulatory endpoint use

CoP = Correlate of Protection; IGRA = Interferon-Gamma Release Assay (blood test for prior exposure to M.tb)

Challenges from Licensure to Implementation

- *Priority for development is vaccine(s) to prevent TB disease in **adolescents and adults***

Third 'valley of death' - ensuring sustainable implementation and access

Little to no experience and infrastructure to efficiently deliver vaccines to adolescents and adults in most countries

Relatively few high-burden countries are GAVI-eligible but all are LMICs

Uncertain demand (no new TB vaccine in 100 years; few adolescent/adult vaccines for any disease in LMICs)

Unclear procurement and delivery/implementation strategy(ies)

Recent landscape analysis conducted by WHO with Boston Consulting Group identified six key gaps in preparation for successful implementation:

Key gaps identified from interviews:

1. **Global coordination & consensus** on goals, expectations & how to deal with uncertainties
2. **Finance** across the value chain (both global & country-specific), particularly for **procurement** & delivery
3. **Manufacturing:** how to act given the complexity of decision-making and uncertainty
4. **Awareness & alignment** on Vx candidates for adults & adolescents, need / impact, & timelines outside immediate community
5. **Country-specific data** (e.g., on demand, priorities, hesitancy, implementation considerations etc.) for adults & adolescents
6. **Delivery, health systems readiness & engagement** (including e.g., supply chain, workforce & targeted / tailored comms for adults & adolescents)

1. Demand defined as the number of doses needed in short, medium & long term

Much to do - but amazing progress

For the first time in history:

Multiple candidates in late-stage clinical development - representing a variety of vaccine platforms and express varying antigens and adjuvants to drive protection, including whole mycobacterial genomes – so **multiple "shots on goal"**

Extensive correlates of protection discovery ongoing which could enable future immuno-bridging / surrogate trial endpoints

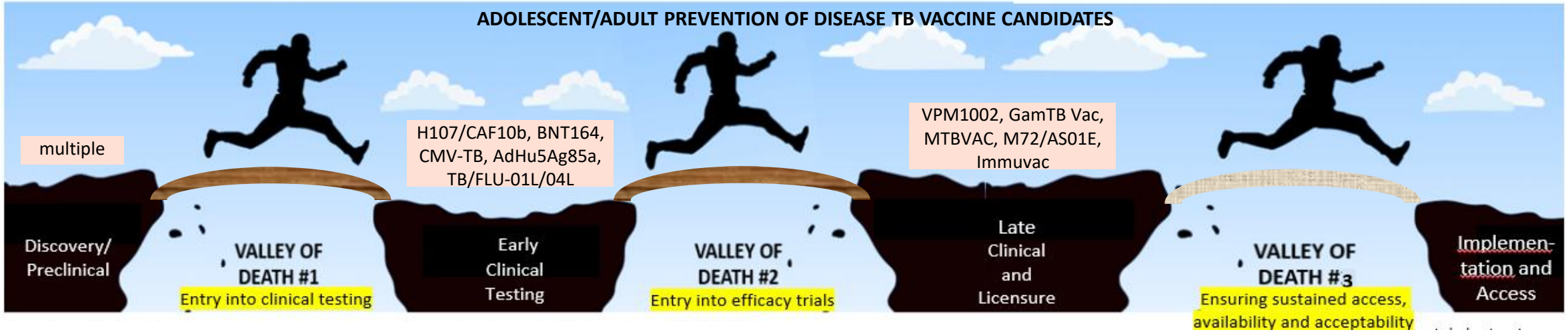
Multiple R&D **funders** at the table

Increasing **advocacy, community engagement and partnership** in developing vaccines and preparing for success

WHO strongly engaged, including establishment of a ministerial level **TB Vaccine Accelerator Council**

GAVI, Global Fund, other multilaterals paying attention and along with other **implementers beginning to come together** to plan and prepare

Policymakers at global, regional and national levels beginning to prepare, including exploring best ways to integrate adolescent/adult TB vaccines into existing healthcare systems



Thank you!

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

Part 3

Status of correlates development for TB vaccines

Nicole Frahm, PhD
Head of Biomarker Development

GVIRF Webinar:
New Tuberculosis Vaccines for Adults and Adolescents:
Progress, Prospects, and Perspectives
February 22nd, 2024

Why do we need correlates of protection (CoP)?

- New TB vaccines that can protect adolescents and adults are urgently needed
- TB vaccine development is challenging for many reasons:
  - There is no animal model that predicts prevention of TB disease
  - Incidence rates are highly heterogeneous and relatively low, thus large clinical endpoint trials are needed to demonstrate vaccine efficacy
- There is limited interest in industry to invest in TB vaccine R&D because programs cannot be de-risked prior to spending hundreds of millions on a Phase 3 program
- If a CoP for prevention of TB disease were identified, confirmed, and accepted by health authorities for licensure of novel TB vaccines, Phase 3 trials could be much smaller and less costly

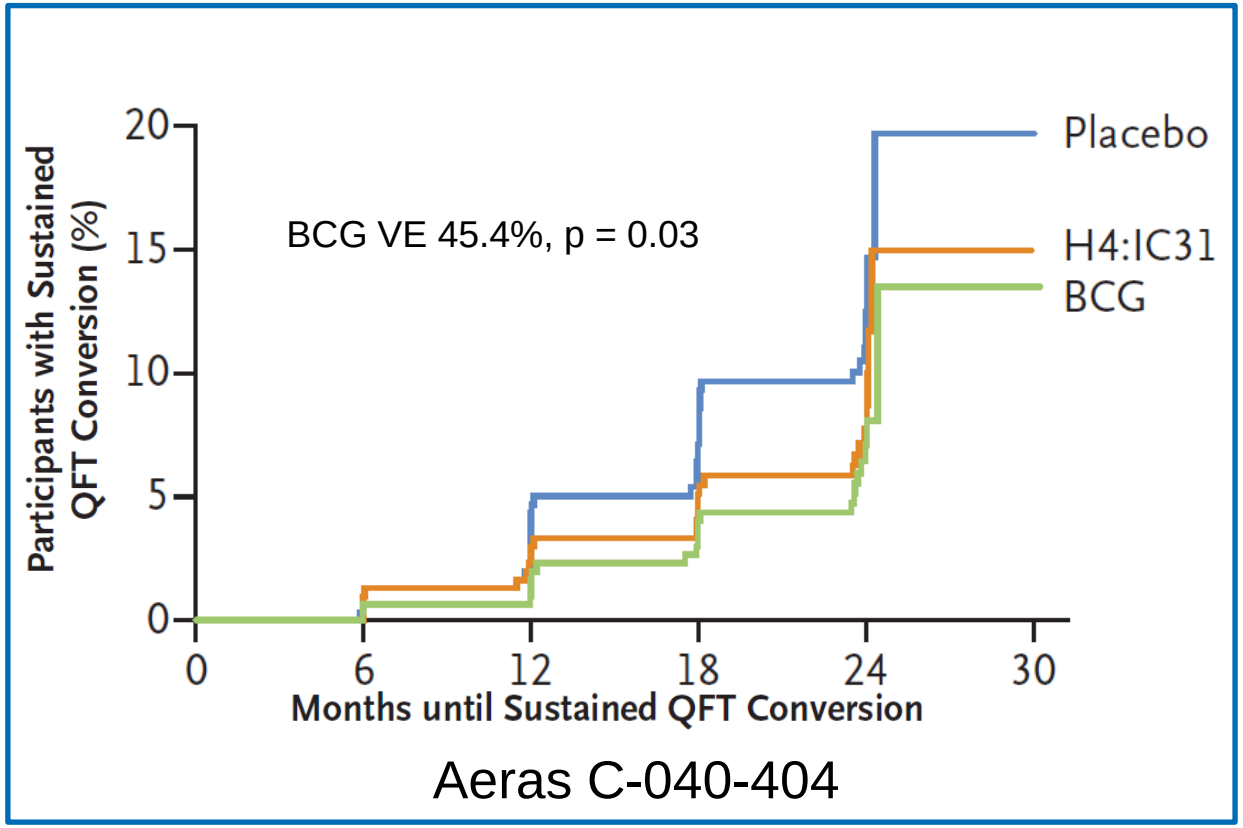
Assumptions regarding mechanisms of protection

- There is consensus that TB-specific T cells likely play a major role in protection from TB disease
  - Mouse and human data point to IFN-γ as a major mediator of protective immunity; but…
  - Data from the investigational MVA85A vaccine trial suggest IFN-γ may be necessary but not sufficient for protection
- Immune responses beyond IFN-γ-expressing T cells likely contribute to protection
  - Antibody responses may contribute to protection based on new data in humans and NHP
  - IV BCG vaccination points to IL-17 as critical
  - BCG is known to induce epigenetic modifications that afford some level of protection beyond TB
  - Non-classical T cells may also play a role

A comprehensive assessment of immune responses induced by vaccination and their association with protection in human clinical trials would be valuable to provide guidance for vaccine development

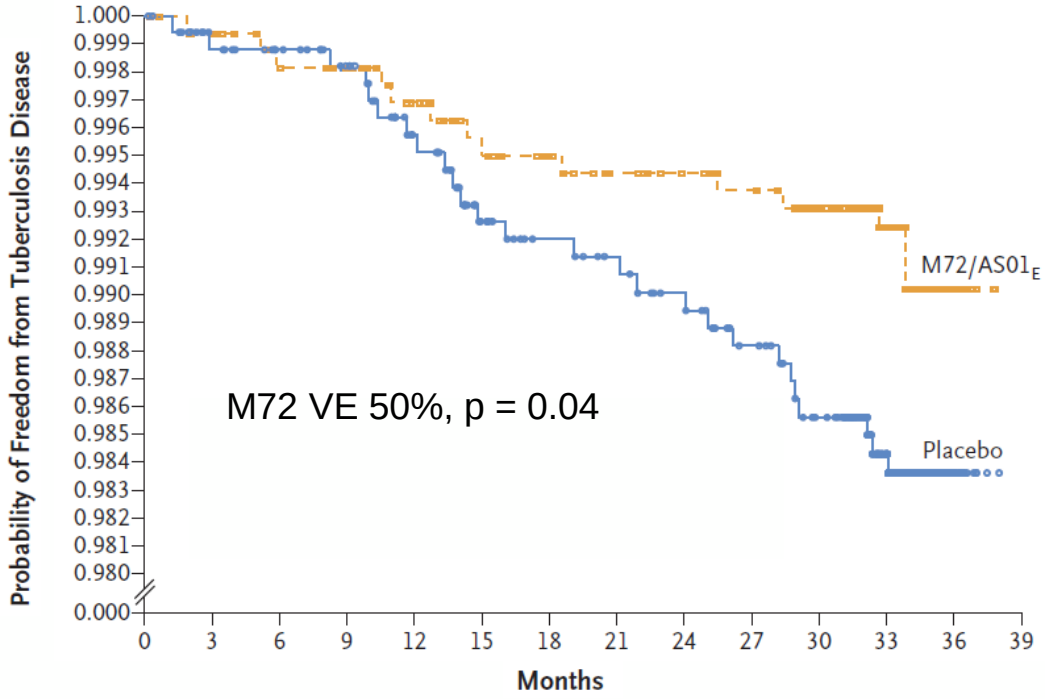
Opportunity: 2018 was the year of TB vaccines

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



Aeras C-040-404

Tait *et al*, NEJM 2019, DOI: 10.1056/NEJMc2001364



GSK TB-018

Two vaccine trials with ~50% efficacy and established sample repositories allowed for the creation of the TB Immune Correlates Program

Caveat: CoP are defined for a specific "P" and are often vaccine platform-dependent

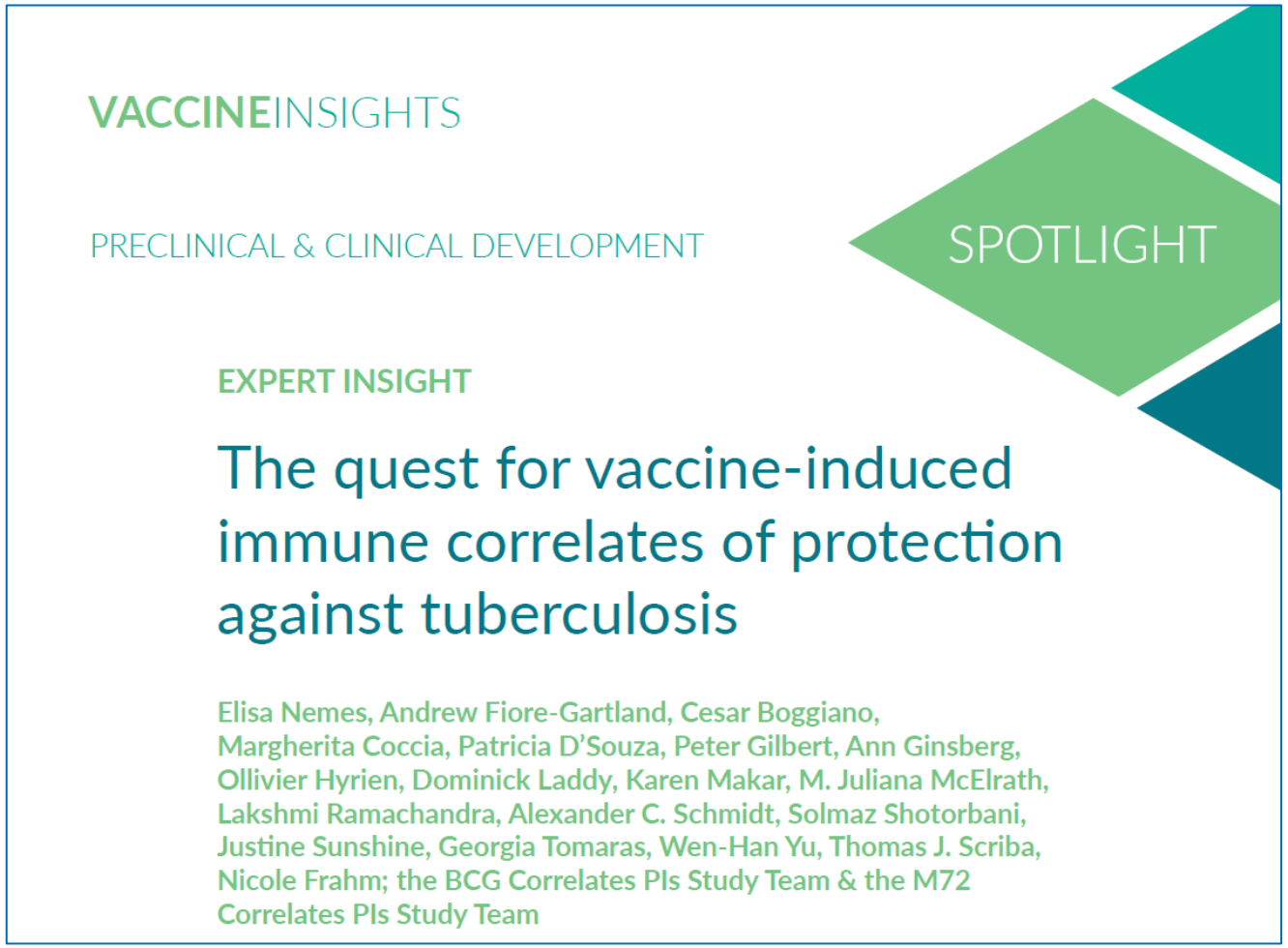
- BCG revaccination
  - IGRA-negative adolescents
  - Protection from sustained infection
    - Measured as sustained QFT conversion
  - Complex vaccine with ~4000 ORFs
    - Intrinsically adjuvanted

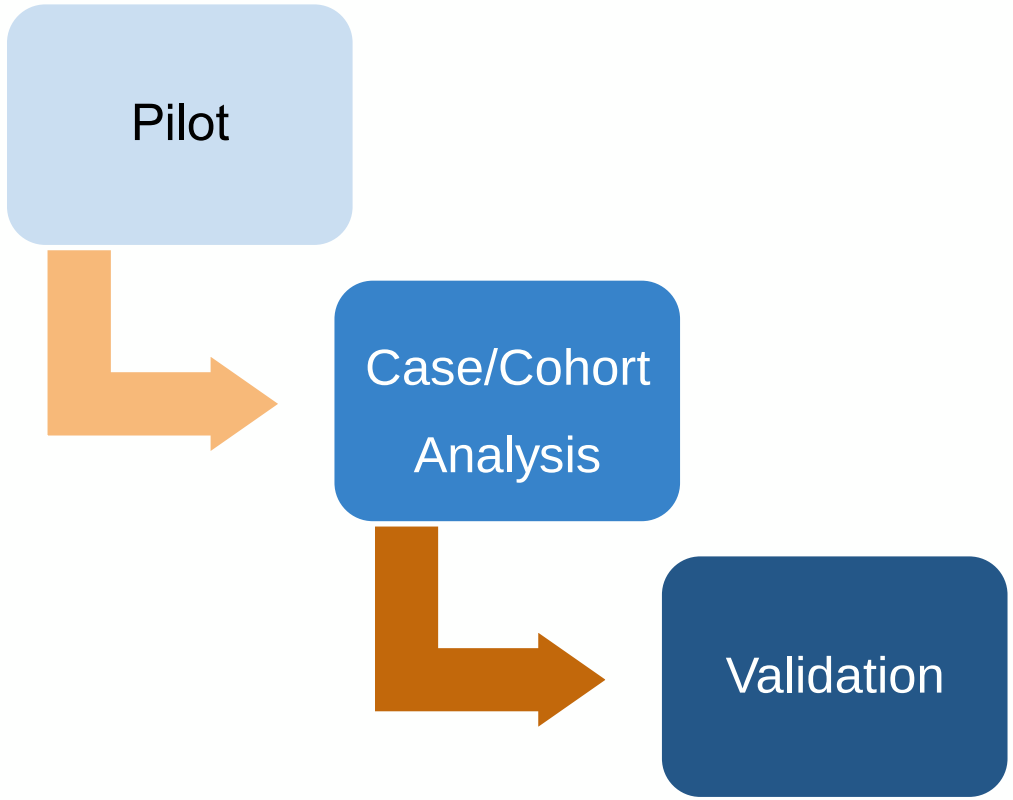
Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

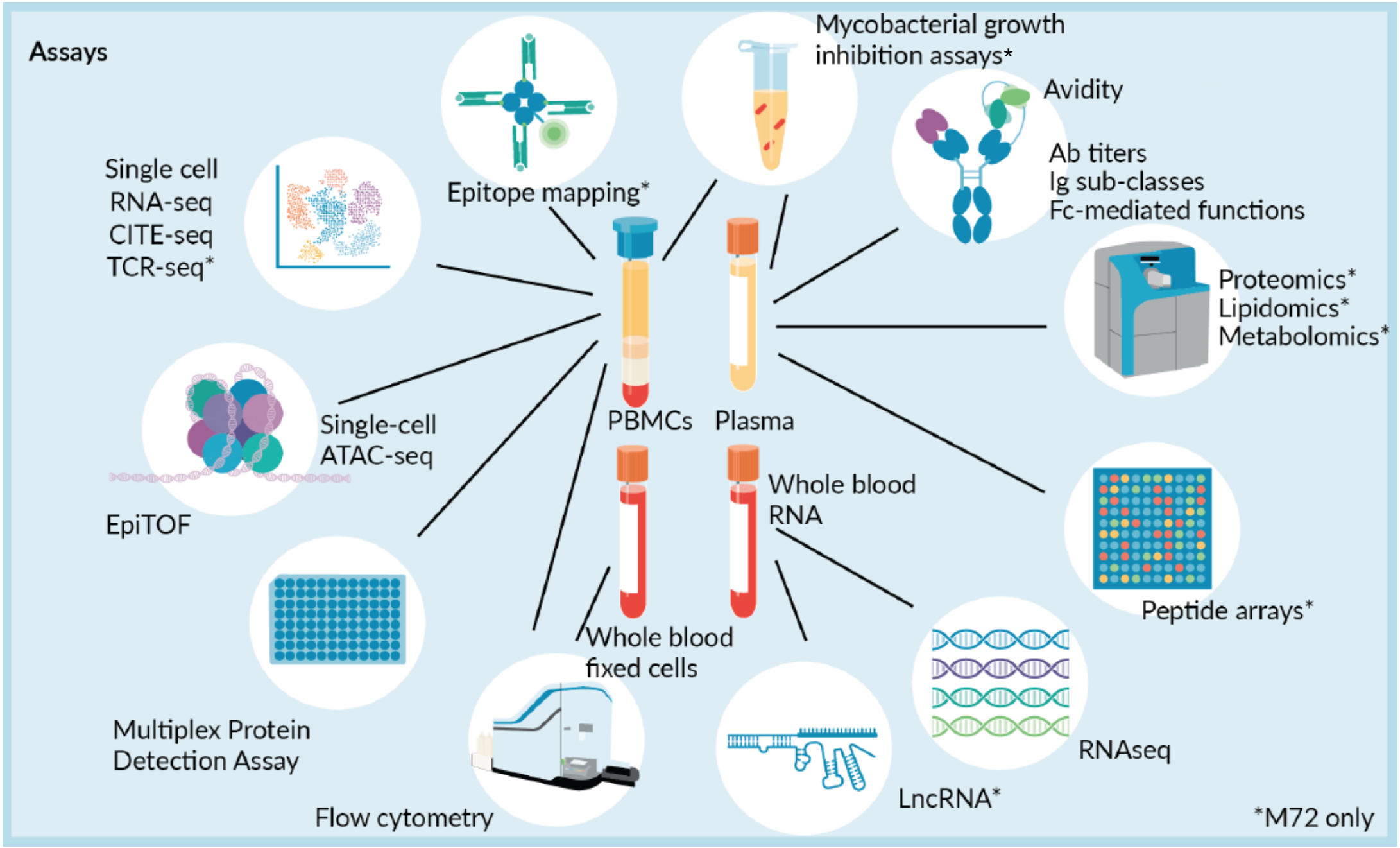
- M72/AS01$_E$ vaccination
  - IGRA-positive adults
  - Protection from pulmonary TB disease
    - Measured as microbiologically confirmed pulmonary TB in participants with clinical symptoms
  - Defined vaccine consisting of 2 *Mtb* ORFs
    - Adjuvanted with AS01$_E$

Tait *et al*, NEJM 2019, DOI: 10.1056/NEJMc2001364

TB Immune Correlates Program



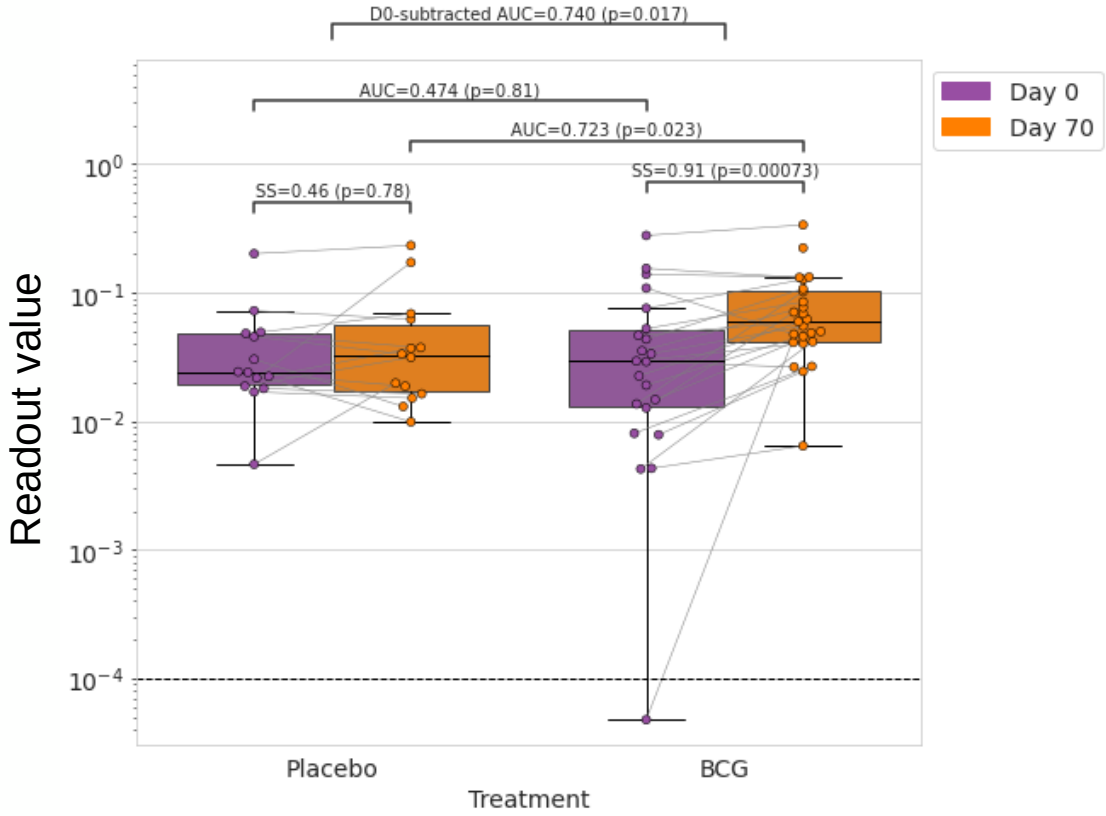




Nemes and Fiore-Gartland, "*The quest for vaccine-induced immune correlates of protection against tuberculosis*". Vaccine Insights. 2022

Criteria for prioritization of assays and primary markers

- Every readout is measured from the same samples
- Samples: pre- and post-vaccination
  - 24 BCG and 12 placebo recipients, Day 0 vs. Day 70
  - 40 M72 and 10 placebo recipients, Day 0 vs. Day 37
- We devised statistical criteria for identifying biomarkers that have high *potential* to be detected as a CoP
  1. Robust vaccine-induced effect
  2. Broad, biologically-relevant dynamic range among vaccine recipients after vaccination
  3. Low temporal variability (among placebo recipients)
  4. Some pre-vaccine variability expected
  5. Readouts should occupy their own niche of immunologic space (low correlation)
  6. Low technical measurement error



Cytokine producing CD4 T cells by ICS
Andersen-Nissen/McElrath, CHIL

Potential confirmation of candidate CoP

Gates MRI clinical trials

- BCG Revaccination (TBV01-201)
  - 1800 IGRA-negative adolescents randomized 1:1 to receive BCG or placebo in South Africa
  - Primary endpoint: prevention of sustained IGRA conversion
  - Biospecimen collection consistent with C-040-404
  - Clinicaltrials.gov NCT 04152161
- M72/AS01$_E$ (TBV02-301)
  - Planned: 20,000 adolescents and adults randomized 1:1 to receive 2 doses of M72/AS01$_E$ or placebo
  - Primary endpoint: prevention of bacteriologically confirmed pulmonary TB
  - Biospecimen collection consistent with C-041-972
  - Clinicaltrials.gov NCT06062238

Acknowledgments

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Part 3

Identification of potential new TB target antigens using T-cell repertoires.

New Tuberculosis Vaccines for Adults and Adolescents, Progress, Prospects, and Perspectives

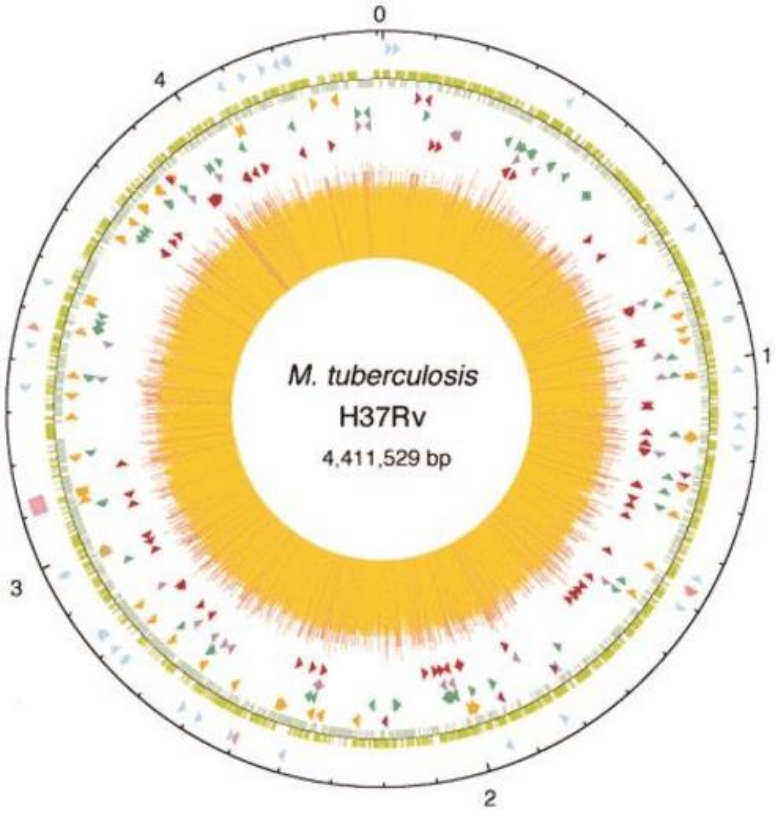
Part 3: Innovation and new tools in TB vaccine development

Munyaradzi Musvosvi

22 Feb 2024

Challenge: Which antigens to include?

- **TB has over 4000 possible vaccine targets**



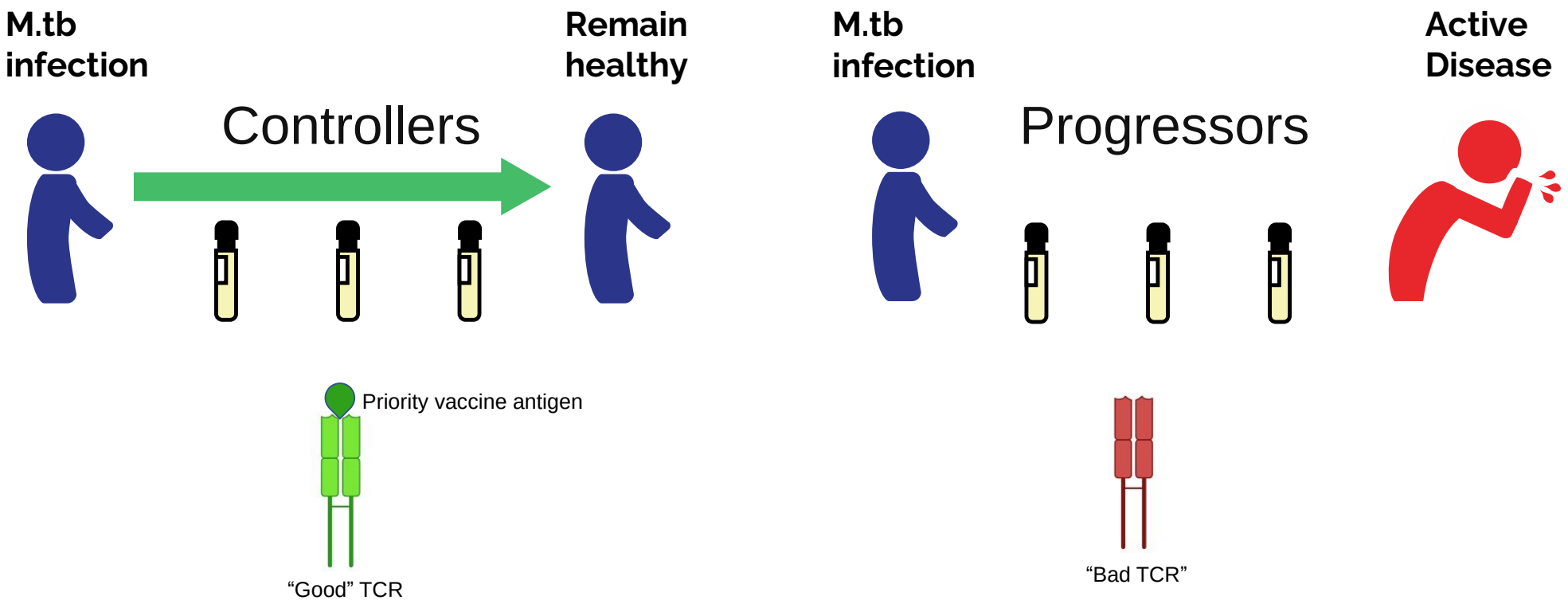
Cole et al., 1998

Table II. *Vaccine-induced protection against Mtb*

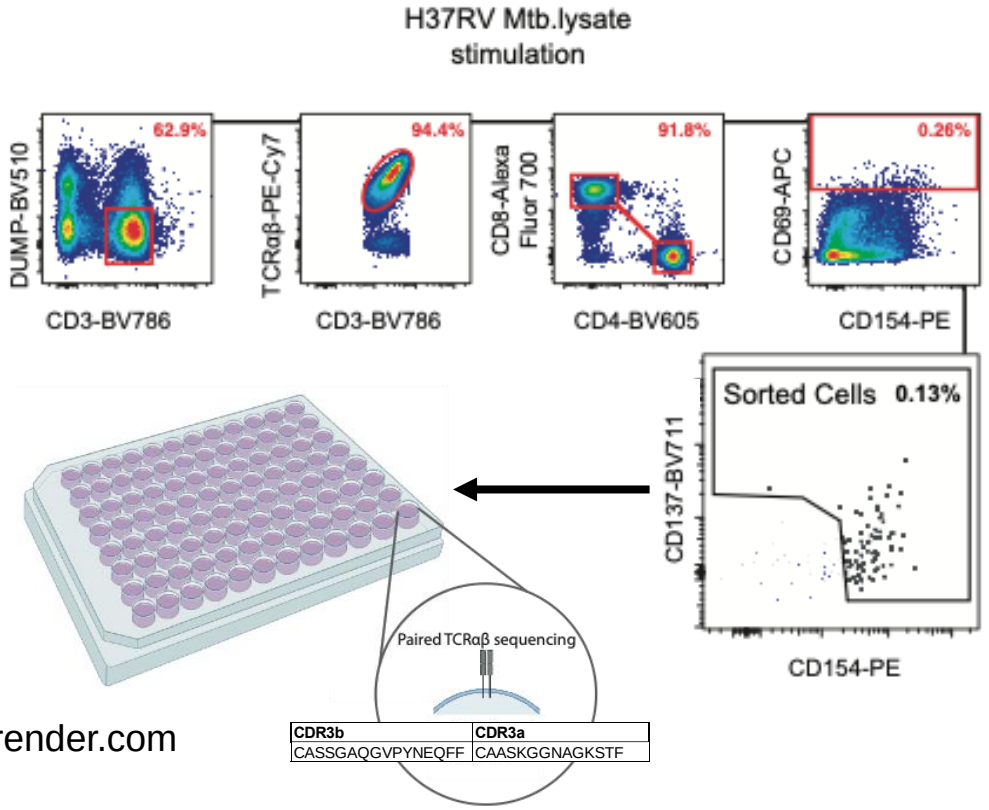
CFU Reduction (Log_{10}) ± SEM[a]							
<0.1		0.1–0.3			>0.3		
Rv0164[b]	Rv2450	Rv0496	0.11 ± 0.08	S[c]	Rv0577	0.36 ± 0.07	S[c]
Rv0410	Rv2623	Rv0733	0.23 ± 0.10	S	Rv1626	0.32 ± 0.07	S
Rv0455	Rv2626	Rv0831	0.13 ± 0.06	S	Rv2608	0.58 ± 0.16	P
Rv0655	Rv2801	Rv1411	0.11 ± 0.11	S	Rv2875	0.44 ± 0.18	S
Rv0952	Rv2866	Rv1569	0.12 ± 0.05	M	Rv3044	0.43 ± 0.06	H
Rv1211	Rv2945	Rv1789	0.15 ± 0.16	P	Rv3478	0.66 ± 0.15	P
Rv1270	Rv3029	Rv1813	0.14 ± 0.14	H	BCG	0.78 ± 0.07	
Rv1410	Rv3133	Rv1860	0.19 ± 0.07	S			
Rv1590	Rv3204	Rv1886	0.20 ± 0.04	S			
Rv1738	Rv3407	Rv2220	0.25 ± 0.11	S			
Rv1818	Rv3541	Rv3020	0.17 ± 0.07	E			
Rv1884	Rv3620	Rv3619	0.24 ± 0.05	E			
Rv1926	Rv3628						
Rv1984	Rv3810						
Rv2032	CpG						
Rv2389	(−0.09 ± 0.05)						

Bertholet et al., 2008

Is control of M.tb infection associated with certain mycobacteria-specific T cell clonotypes?

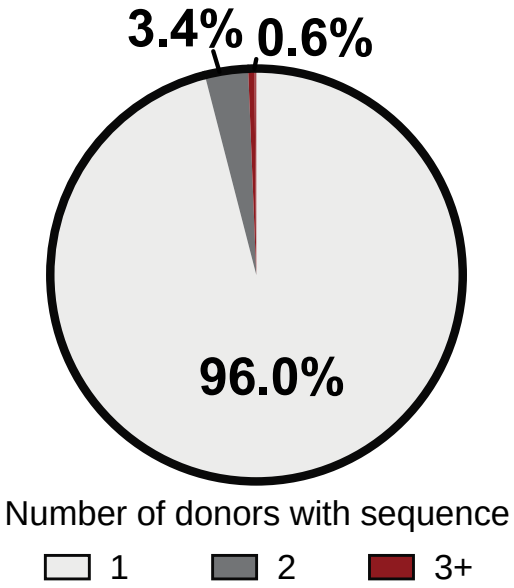


Identifying M.tb-specific T cell receptor (TCR) sequences.



Biorender.com

Identifying differentially abundant M.tb TCR clusters in controllers and progressors.

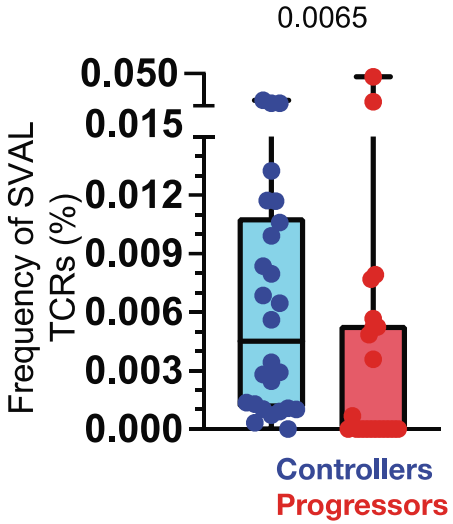


GLIPH2 clusters TCRs with likely shared specificity

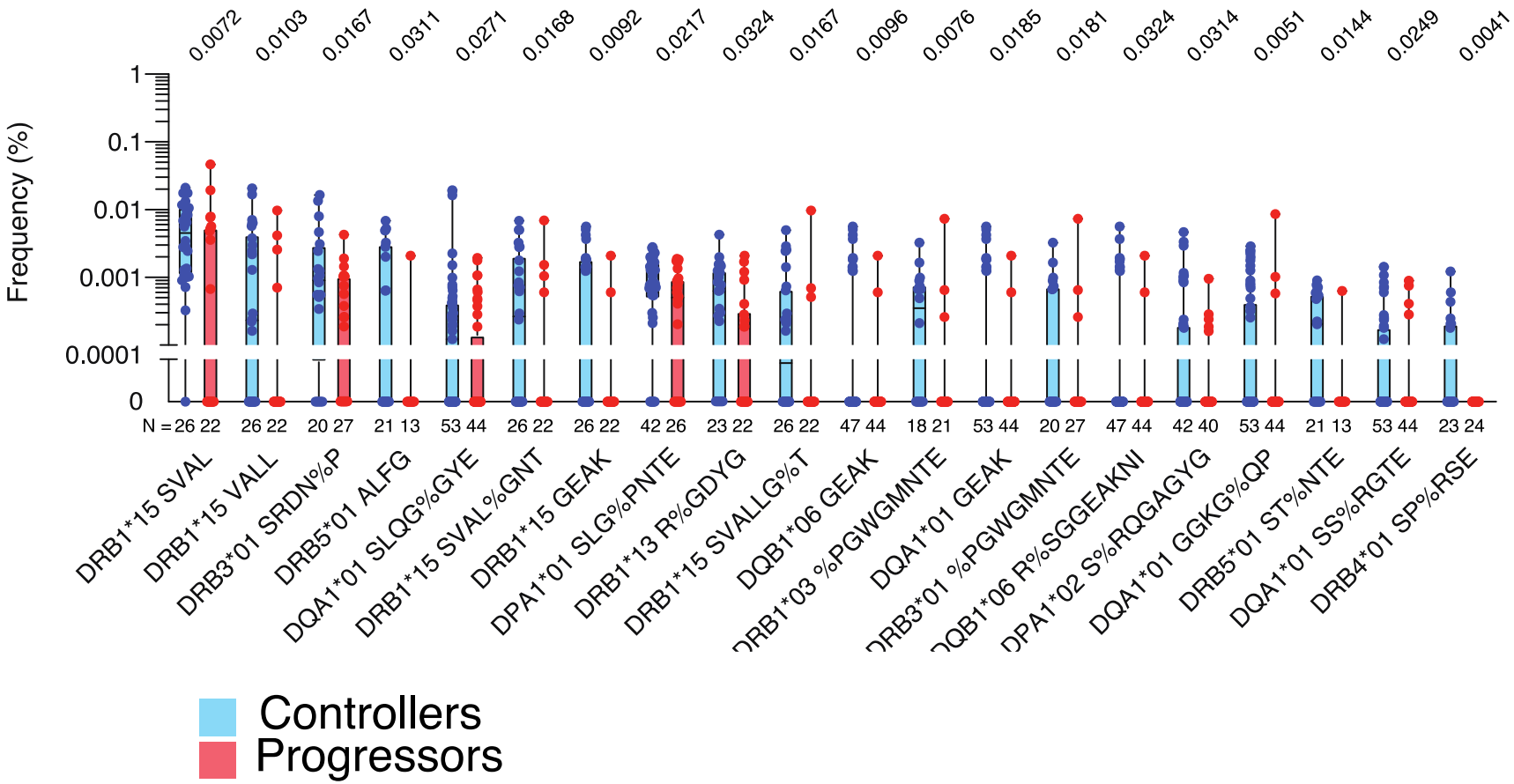
CDR3β

CASSVALSNYGYTF
CASSVALFSNTQYF
CASSVALLAGTQYF
CASSVALSGSGYTF
CASSVALFGETQYF
CASSVALGAGEQYF
CASSVALAGANGYTF

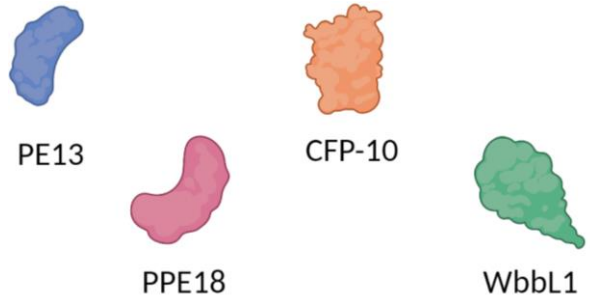
Compare cluster frequencies in controllers and progressors



Identifying differentially abundant M.tb TCR clusters in controllers and progressors.



Priority M.tb antigens



Biorender.com

Controllers had **higher frequencies of CD4** against epitopes to PE13, CFP-10, WbbL1, and PPE18

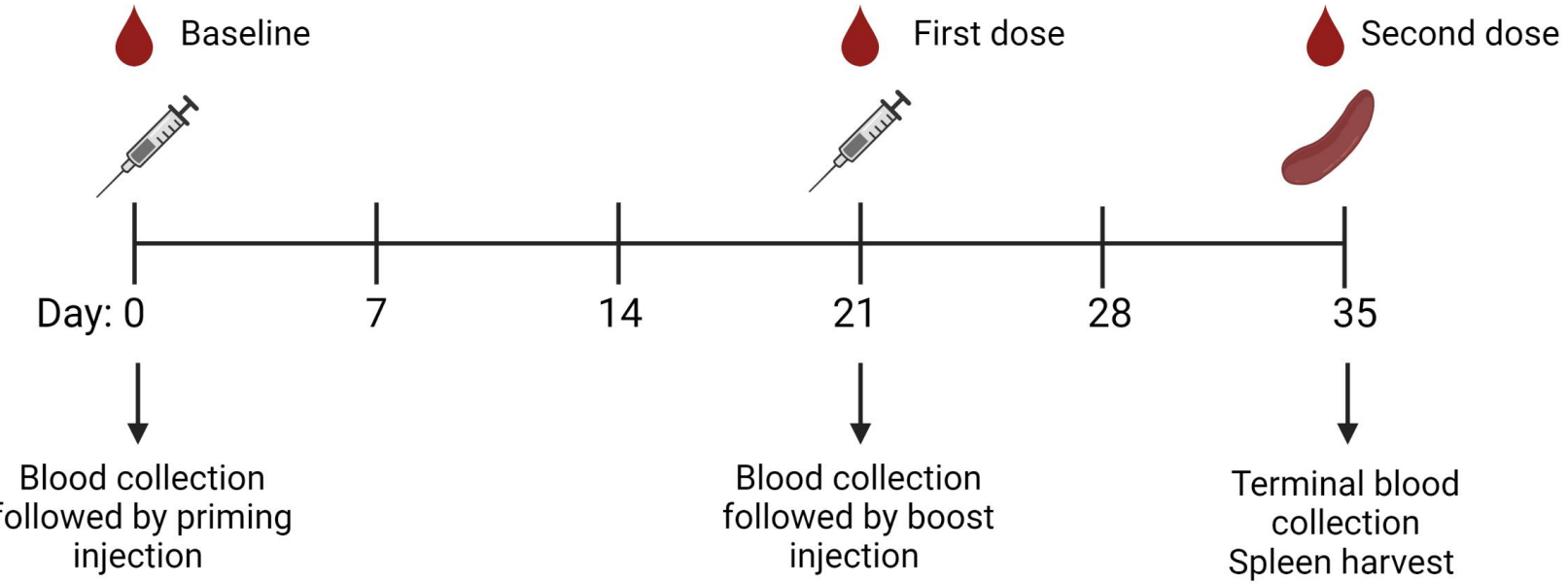
Take home message 1

- We identified dozens of M.tb TCR specificity groups that associated with controllers or progressors.
    - This approach has applications for clinical studies of specific T cell responses to vaccination, infection, and other immunological indications.
    - May represents a platform for rational antigen selection for candidate subunit vaccines

Proof of concept study: Immunogenicity

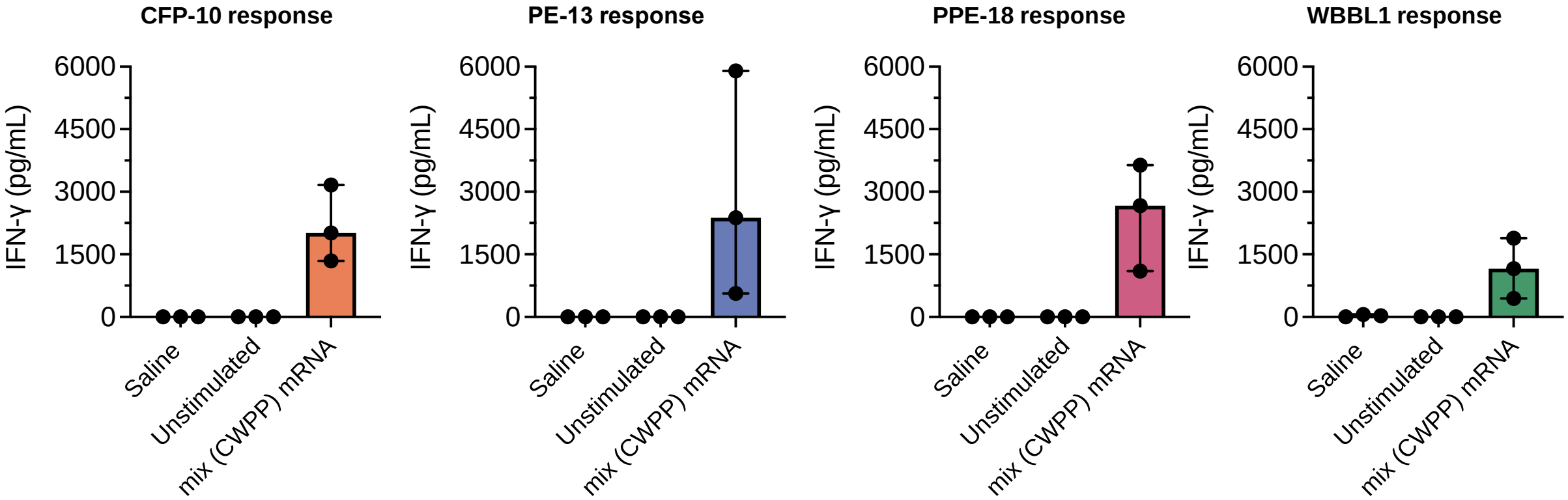
C3HeB/FeJ
(Kramnik)

Biorender.com



Groups	Dose
Saline	-
Mix of PE13/PPE18/CFP-10/WbbL1	**2.5µg/2.5µg/2.5µg/2.5µg**

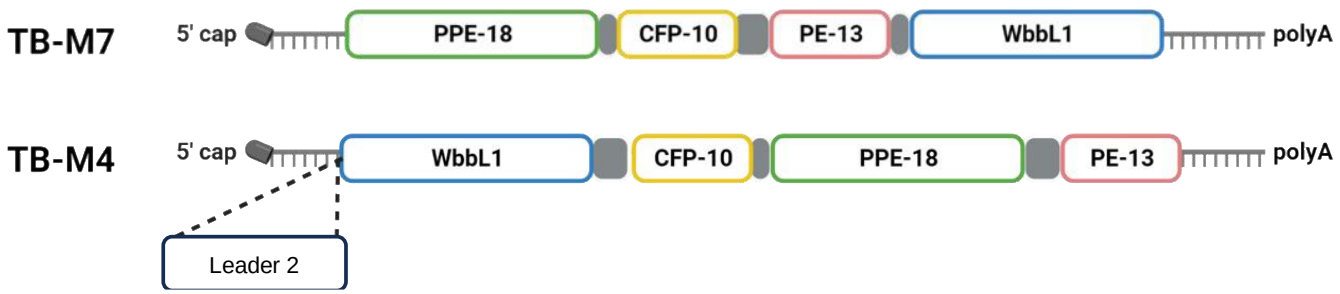
Proof of concept study: Immunogenicity

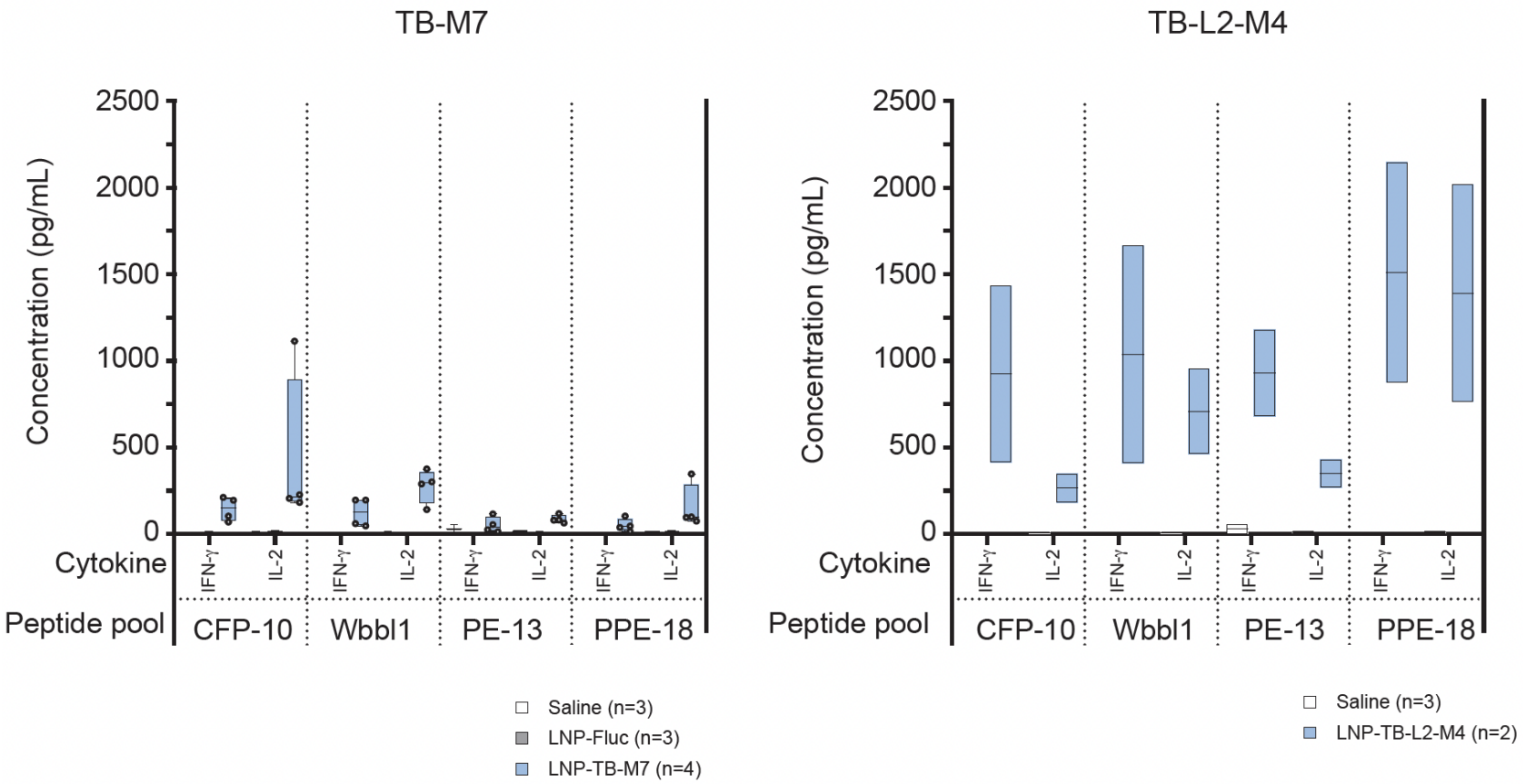


mix (CWPP) mRNA = mix of PE13/PPE18/CFP-10/WbbL1
Day 35 *ex vivo* stimulation of splenocytes from mice

Preliminary data

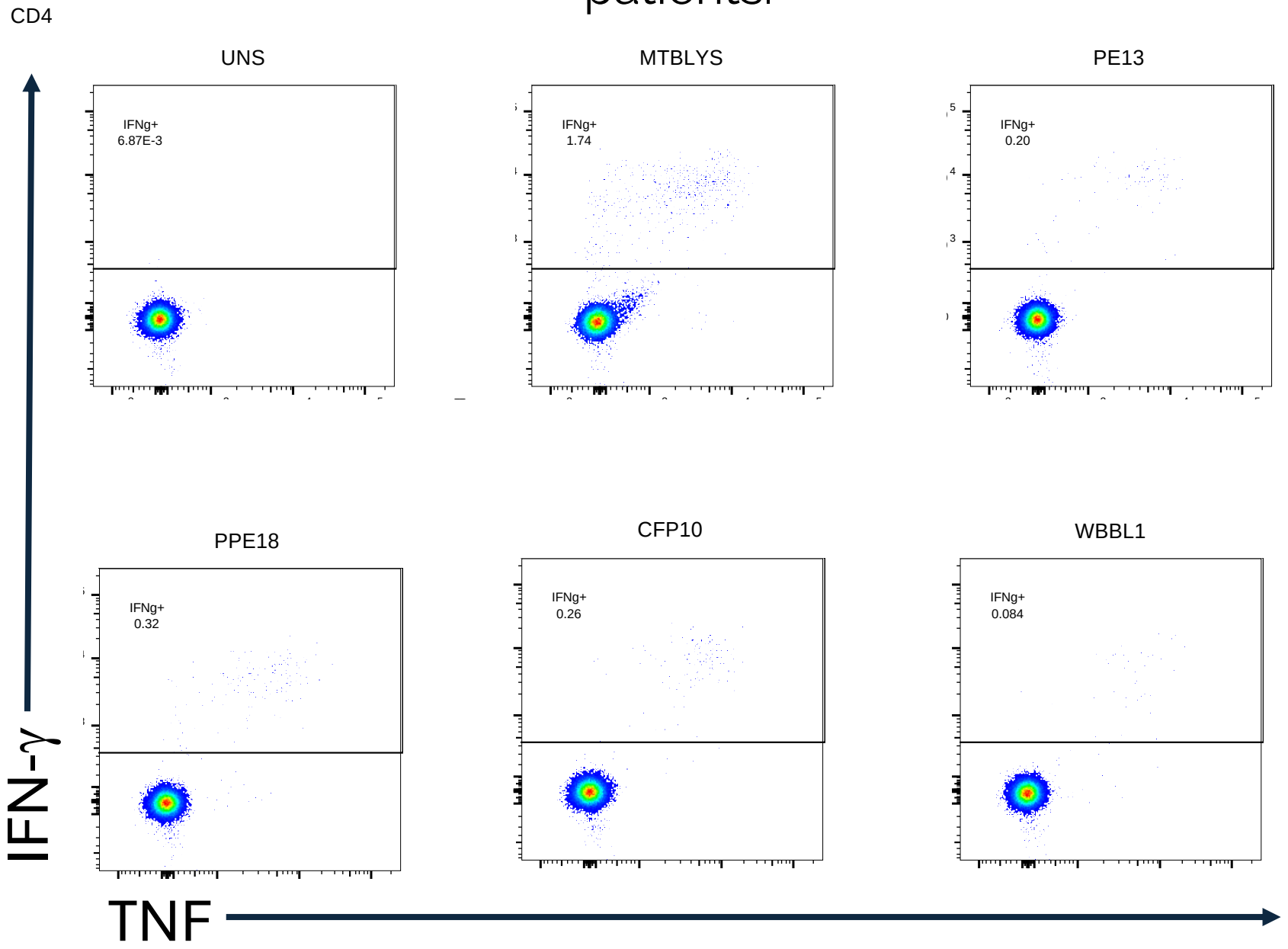
Proof of concept study: Immunogenicity (polyprotein constructs)





Preliminary data

TITAN-specific T cell response in uninfected adults, M.tb infected adults, and TB patients.



Preliminary data

Take home message 2

- Preliminary preclinical data shows promising immunogenicity.
- Selected 2 priority polyprotein mRNA constructs.
- Murine challenge experiments are ongoing.
- Assessment of baseline antigen-specific response in IGRA-, IGRA+, and persons with active TB is ongoing.

satvi
TOWARDS A WORLD WITHOUT TB

Thomas Scriba
Monika Looney
Virginie Rozot
Constance Schreuder
Tim Reid
Onke Nombida
Michelle Fisher
Elisa Nemes
Ashley Veldsman
Pia Steigler
Melissa Murphy
Anele Gela
Mark Hatherill
…and many more

Stanford MEDICINE

Huang Huang
Chunlin Wang
Qiong Xia
Gerlinde Obermoser
Akshaya Krishnan
Gilly Padalon Brauch
Weiqi Wang
Peter Acs

The Human Immune Monitoring Center at Stanford
Immunology for the People!

Xuhuai Ji
Jing Guo
Holden Maecker
Yueh-hsiu Chien
Purvesh Khatri
Mark Davis

Afrigen
Biologics & Vaccines
An Avacare Health & IDC Company

Pia Steigler
Caryn Fenner
Gerhardt Boukes

UCT IP Management, Development and Commercialisation

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Tom Ottenhoff
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…and many more

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bei RESOURCES
SUPPORTING INFECTIOUS DISEASE RESEARCH

saMRC
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Part 3

BILL & MELINDA GATES foundation

NIH National Institute of Allergy and Infectious Diseases

Department of Veterans Affairs

ADVANCES IN MODELS TO EVALUATE NEW TB CANDIDATES

New TB Vaccines for Adults and Adolescents, Progress, Prospects, and Perspective

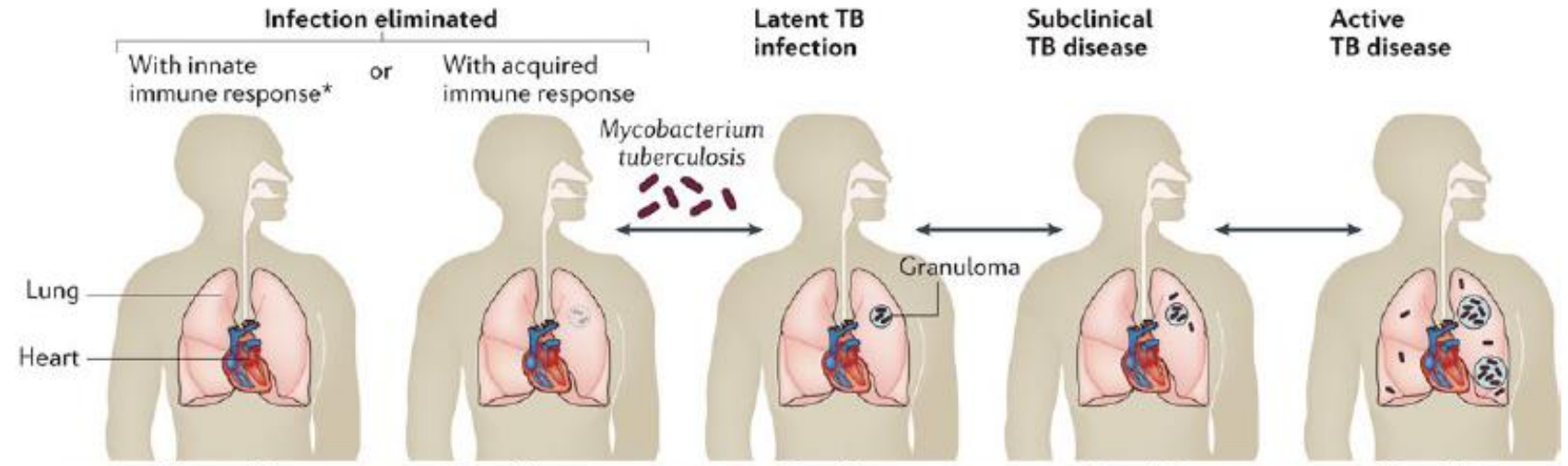
David Lewinsohn, MD, PhD
Professor, Pulmonary & Critical Care Medicine

February 22, 2024

OREGON HEALTH & SCIENCE UNIVERSITY

OHSU

DOERNBECHER CHILDREN'S HOSPITAL FOUNDATION



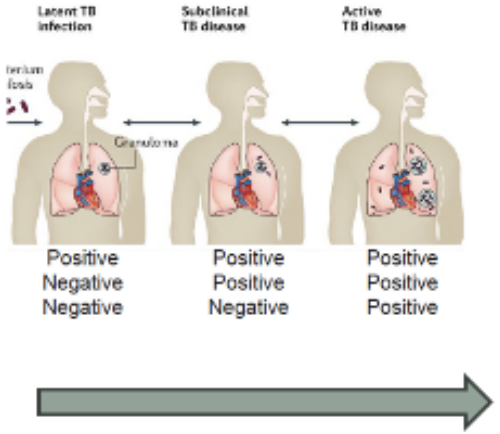
IGRA	Negative	Positive	Positive	Positive	Positive
PET-CT	Negative	Negative	Negative	Positive	Positive
GeneXpert	Negative	Negative	Negative	Negative	Positive

Prevention of Infection

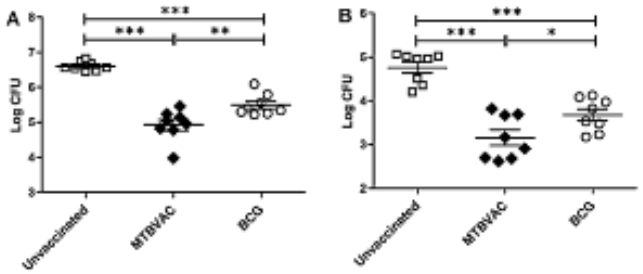
Prevention of Disease

Pai, M. *et al.* (2016) Tuberculosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.76

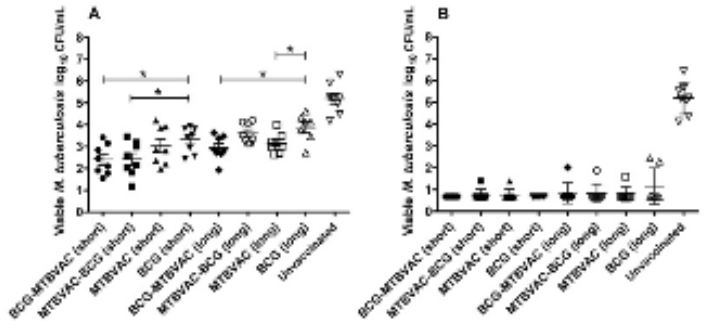
Prevention of Progression – Standard Models



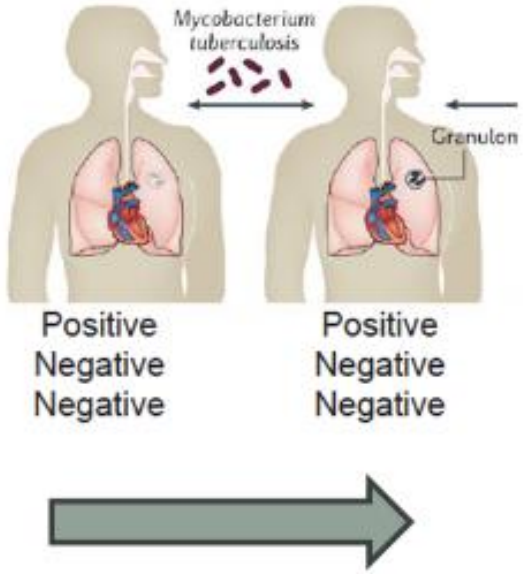
Arbues et al, Vaccine 2013



Clark et al., JID 2017



Prevention of Infection – Natural Transmission

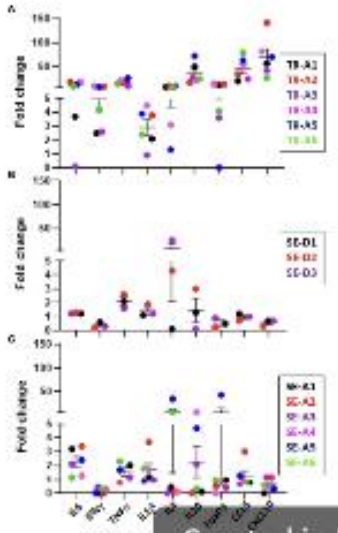


Wu et al., PNAS 2015

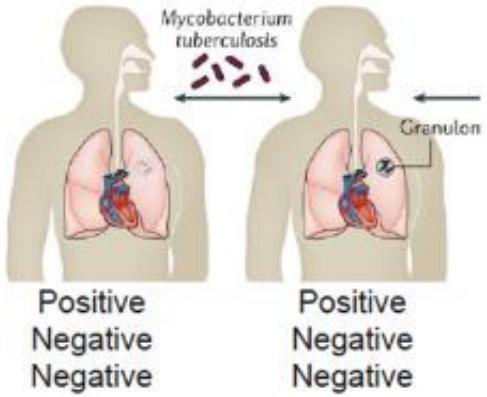
Table 3 Gross pathology of transgenic cattle challenged by transmission experiment

Animal	No. of lobes infected*	Lung score	No. of lymph nodes infected†	Lymph node score	Total score	Mean ± SD‡
Transgenic group 1	1	2	1	1	4	4.7 ± 2.1
	0	0	0	0	0	
	0	0	0	0	0	
Transgenic group 2	3	3	2	4	7	
	2	2	1	2	4	
	0	0	0	0	0	
Transgenic group 3	0	0	0	0	0	
	0	0	0	0	0	
	0	0	0	0	0	
Control group 1	7	10	6	15	25	17.8 ± 5.8
	4	13	5	10	23	
	3	10	3	8	18	
Control group 2	4	12	4	10	22	
	3	9	3	9	18	
	2	8	3	6	12	
Control group 3	3	8	3	9	17	
	3	7	2	5	12	
	2	2	1	5	7	

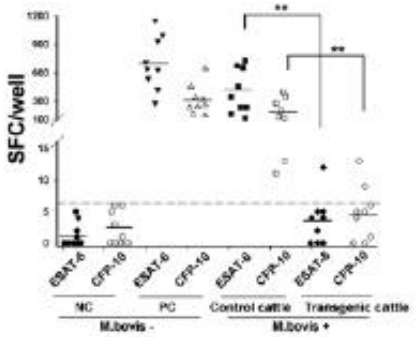
Gupta et al., Frontiers in Cellular Infection Microbiology 2022



Prevention of Infection - Following Challenge

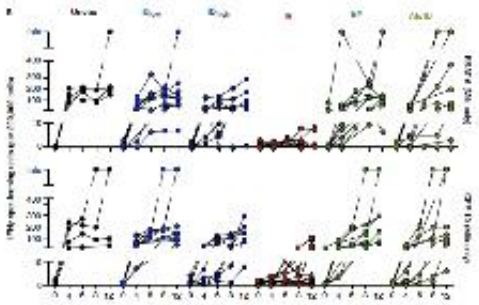


Wu et al., PNAS 2015



Darrah et al., Nature 2020

Plumlee et al., Cell Host and Microbe 2020
Plumlee et al., PLoS Pathogens 2023



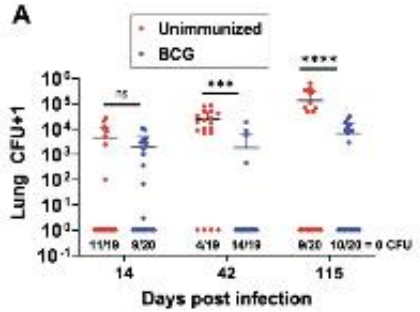


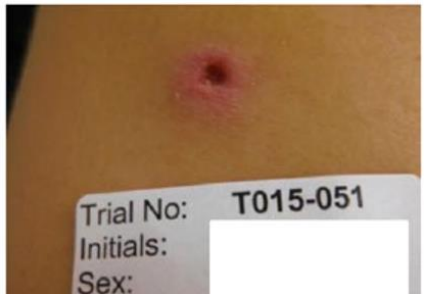
Table 1. Group sizes needed to assess vaccine-mediated prevention of detectable infection.

		Minimum sample size per group	
Prevalence	Vaccine efficacy	80% Power	90% Power
61.6%	20%	259	342
61.6%	30%	112	155
61.6%	40%	66	84
61.6%	50%	40	55
61.6%	60%	28	37
61.6%	70%	21	25
61.6%	80%	16	18
61.6%	90%	12	16

Minimum sample size required per group for specified power to detect a given vaccine efficacy (prevalence in unimmunized mice assumed to be 61.6%).

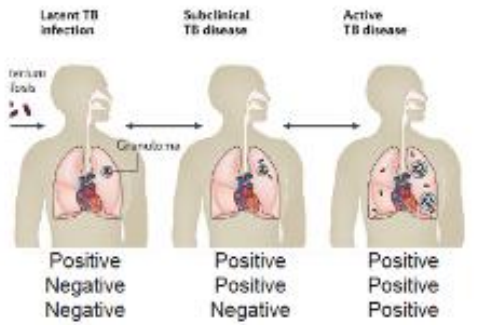
Why do we need a human mycobacterial challenge model?

- To provide a biological signal of efficacy with new vaccines
- To identify potential immune correlates of protection
- As a model of the immunobiology of disease

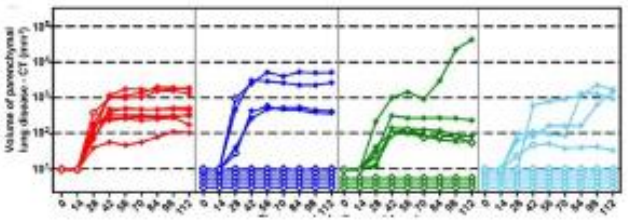


Helen McShane, Oxford University

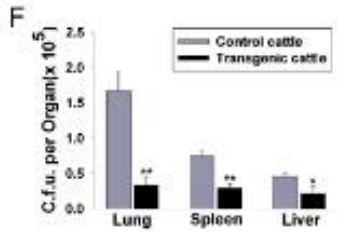
Prevention of Disease Following Infection



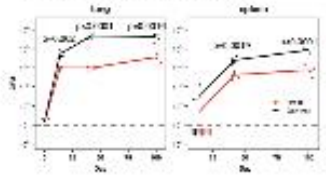
Hansen et al., Nature Medicine 2018



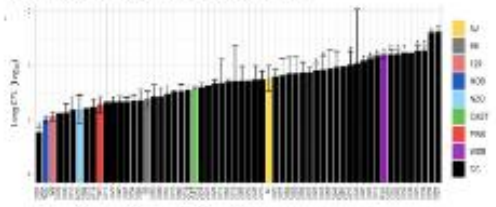
Wu et al., PNAS 2015



Kupz et al., *PLoS ONE* 2016
Nemeth et al., *PLoS Pathogens*. 2020



Smith et al., eLife 2022



Concluding Remarks

- “Fit for Purpose” Animal Models
  - Prevention of Infection
  - Sterilizing Immunity
- Standardization
- Correlates of Protection

Part 4

Preparing the pathway for new TB vaccines for adults and adolescents

Demand considerations

Shelly Malhotra
Executive Director, Global Access, IAVI

IAVI gratefully acknowledges the generous support provided by the following major funders

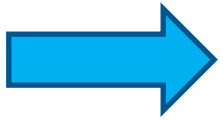
Biomedical Advanced Research and Development Authority (BARDA) | Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | Broadway Cares/Equity Fights AIDS | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of January 2024

In the lead up to launch, several key enablers critical to ensure timely supply of vaccines that meet country needs

Informed supply planning and manufacturing scale up a priority, with linkages to others key enablers



WHO GLOBAL FRAMEWORK FOR COUNTRY INTRODUCTION OF NEW ADOLESCENT AND ADULT TB VACCINES

Vision & Purpose

- A world free of TB, with zero deaths, disease, and suffering due to TB
- Facilitate rapid introduction and scale up of new adult and adolescent TB vaccines

Goals

Available	Accessible	Accepted
Sufficient, sustainable, and timely supply	Equitable delivery aimed at all who could benefit	Policymakers, end-users and health system requirements met

Milestones

Available	Accessible	Accepted
• **Demand assessed** (for short, medium and long term for priority populations; with regard to other interventions) • **Policy, evidence needs, and pathways defined** (e.g., approvals, recommendations, efficacy, and safety data required, specific populations; country testing) • **Procurement plans in place** (e.g., agreements with local and global manufactures, 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; private providers) • **Delivery systems in place** (capacity; infrastructure; supply chains; pharmacovigilance; vaccine efficacy; phase IV studies) • **Sustainable financing strategy in place** (e.g., national health sector strategy, the Global Fund, Gavi, private pay)	• **Value defined** (i.e., at individual and population levels and from perspective of health workers, policy makers, vaccinees; vis-á-vis safety and efficacy) • **Community engaged** (i.e., priority populations, TB survivors, health workers, advocates, policymakers) • **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 • Funded implementation research	• Appropriate phase III efficacy trials • Rapid, harmonized regulatory pathways • Licensure in high-burden countries • WHO guidance/recommendation • WHO prequalification	• Affordable vaccines • Sufficient supply • Sufficient and diversified manufacturing capacity • Access, IP and procurement agreements	• High level political will (G20/G7) • Adequate financing • Clarity on roles of funding partners (e.g., Gavi, the Global Fund) and procurement partners (e.g., PAHO, UNICEF)

Manufacturing scale-up requires considerable lead time and expense

Scaling up clinical trial manufacturing for commercial manufacturing continues to pose a significant **challenge**.

Design facility	Build	Engineering	Equipment	Validation/ Maintenance	Regulatory Req.	RA Audit	GMP Compliance	Market Supply

TIME
✓ To build, start-up and validate a facility could take several years (5 to 10 years)

INVESTMENT COSTS
✓ Manufacturing site with capacity 200 M – 300 M doses/year – **50 M USD – 500 M USD**[1]

DIRECT AND INDIRECT OPERATING COSTS (OPEX)
✓ Highly specialized work force.
✓ Administrative & manufacturing overhead, maintenance, revalidation, QMS.
✓ Alignment of the process among multiple facilities (Tech-Transfer).

MARKET FACTORS
✓ Assessment of market opportunity key to determine optimal capacity and utilization.
✓ Clear understanding of coverage, delivery strategies, realistic market share needed.
✓ Delivery strategies such as mass vaccination will require extra production effort for a limited period. (Overcapacity = increased costs/ Undercapacity = not sustainable).

VACCINE PRICE
✓ Manufacturing facility represents a significant fixed and ongoing maintenance cost – scale of investment has implications on vaccine cost & potential price.

Decision-making to scale-up:

Optimal utilization of manufacturing facilities

MANUFACTURER

MARKET ?

PROCESS

[1] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. Vaccine. 2017 Jul 24;35(33):4064-4071. doi: 10.1016/j.vaccine.2017.06.003. Epub 2017 Jun 21. PMID: 28647170; PMCID: PMC5518734.

To support planning, independently-built forecasting models developed to refine understanding of TB vaccine market and demand

CLINTON HEALTH ACCESS INITIATIVE

- Insights on major factors influencing demand materialization in 5 TB high burden countries
- MAA for M72AS01e assumed to be in 2029
- Indication: POD
- Target age: 16-34 Years*
- Introductions between 2027-2033 and scale up between 2031-2035 in all countries included
- 2 doses needed

CHAI 1

iavi

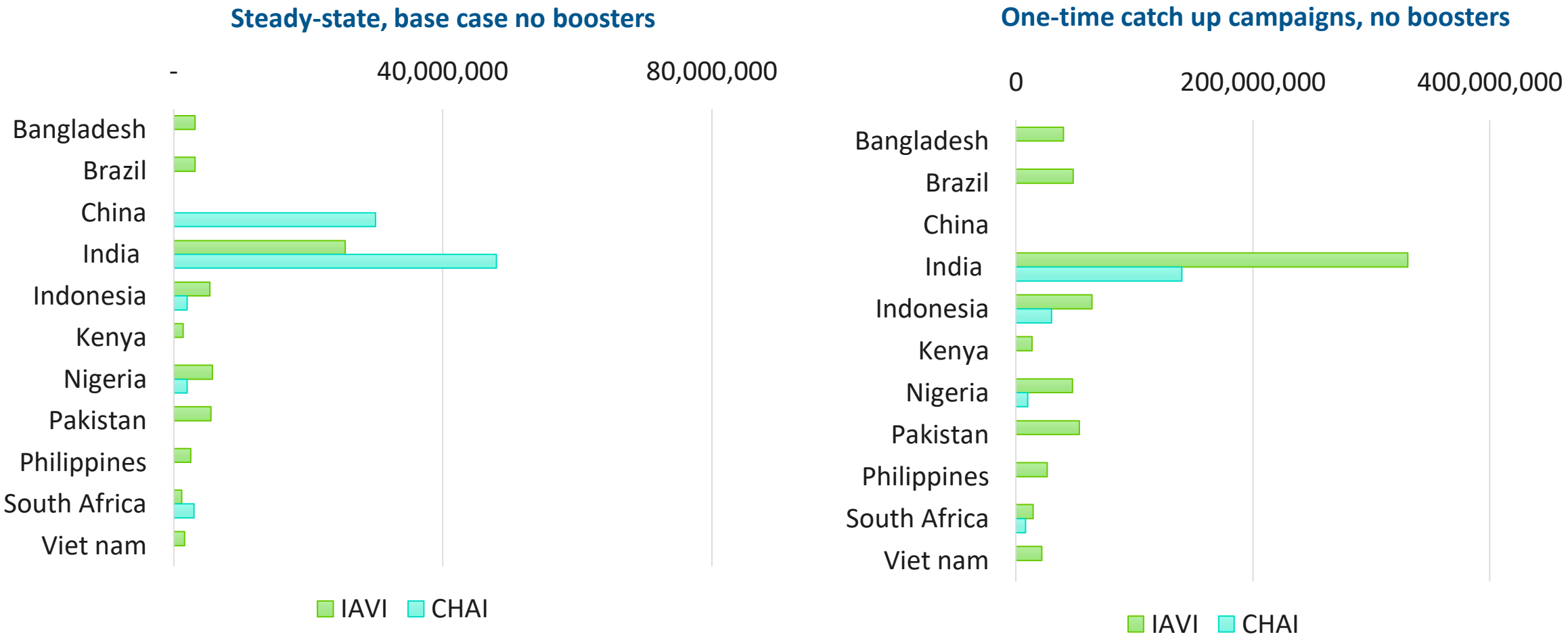
- Demand analysis for 55 countries, 26 TB high burden countries for global manufacturing planning under different scenarios
- MAA assumed to be in 2029
- Indication: POD
- Target ages 16-60 years initially, then 16-44 years, with varying rates of coverage
- Gradual introduction of countries from 2030 and within country scale up over 5 years
- 1 dose needed (as per MTBVAC target product profile)

IAVI 2

*PIII POD trial for M72/As01$_E$ as initially planned for 20,000 individuals aged 16-34 years- reference TAG Pipeline report 2021

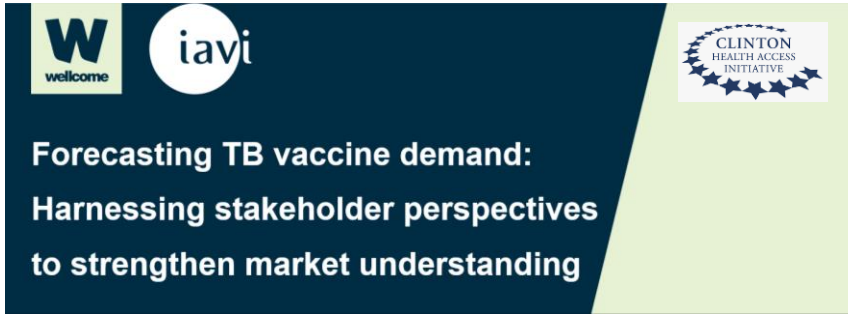
Different demand assumptions across the models (V1) impact projected supply requirements

Illustrative number of doses required to meet annual demand for a sample of highest burden countries



Forecasting TB Vaccine Demand meeting to refine understanding of TB vaccine market

Union conference, Paris
Side meeting November 17, 2023



Meeting Objectives

1. Present multi-country/global TB vaccine market demand assessment efforts to understand methodology and assumptions, limitations and gaps.

2. Gather feedback on assumptions to inform forecast refinement

3. Discuss evidence needs and coordination opportunities for demand estimation with key stakeholders

Participants

Funders and financing partners	BMGF UNITAID Wellcome Global Fund GAVI Open Philanthropy USAID
Technical partners	CHAI MMGH IAVI Gates MRI Boston Consulting Group
Academic partners	LSHTM
	Imperial College London
	Johns Hopkins Bloomberg School of Public Health
Implementation and Country stakeholders	Baylor College of Medicine – Uganda
	Ministry of Health – Brazil
	PATH Ukraine
	National TB program – Uganda
	National TB program – South Africa
	KNCV Indonesia
	KNCV Netherlands
	Yayasan KNCV Indonesia
	Aurum Institute
Industry	GSK
Global advocacy partners	Treatment Action Campaign
Global guidance	WHO SAGE, WHO GTB

Feedback from *Forecasting TB Vaccine Demand* consultation

- **Implementation and delivery assumptions will vary by country** depending on the epidemiology& program delivery channels:
  - Need to engage a broader set of countries and country-based stakeholders.

- **TB vaccination likely to be implemented through the national vaccination programs:**
  - NTPs have limited resources/access to broader populations to support roll out)

- **Initially likely to target the highest risk populations** based on risk/vulnerability, including potentially:
  - PLHIV (on antiretroviral treatment)
  - Populations linked to TB programs - latent TB, household contacts of TB patients, those exposed and tested for TB,
  - Health care workers
  - People living/spending a large proportion of their time in congregate settings e.g. miners, prisoners, correctional services,
  - Those with diabetes mellitus, smokers, and pregnant women (post partum)

- **After initial phase, plan to move to broader (age-based)/routine role** out through delivery linkage points (e.g. schools/universities) to ensure impact.
  - Risk-based approaches not preferred as they may be onerous to implement and stigmatizing.

- **Further data on vaccine hesitancy, acceptability, feasibility, willingness to pay, and programmatic implications** needed.

- **Future iterations should include**:
  - Key product-related aspects based on TPP and pricing considerations
  - Supply constrained scenario-planning
  - Context of other interventions (eg long acting TPT) and of a vaccine landscape with multiple options.

Current forecasts assume constraints posed by the lack of existing delivery pathways– this provides an opportunity and imperative in lead up to launch to strengthen

Key takeaways and next steps

- **Clear understanding of demand for new TB vaccines is critical:**
  - To ensure accurate planning for manufacturing scale up
  - To inform volume-based pricing strategies to sustain fragile market while ensuring affordability
  - To inform financing decisions, including potential for de-risking mechanisms for manufacturing scale up
  - To help attract additional commercial manufacturers, as needed

- **Additional stakeholder validation of demand forecasts needed:**
  - From a broader range of country-specific settings
  - Across key constituencies (TB stakeholders, Immunization stakeholder, providers, implementers, policy-makers, procurers, financing bodies, communities)
  - Future iterations could consider product related factors in more depth, potential pricing scenarios, supply models, and alternative interventions.
  - In parallel, investment in strengthening delivery pathways and more robust evidence generation needed in the lead up to launch.

- **Joint consultations planned to further validate demand assumptions** *(stay tuned!)*

World Health Organization Gavi The Vaccine Alliance iavi & Others!

SMART4TB:
Efforts to assess TB vaccine readiness

February 2024

Rupali Limaye, PHD and Andrew Kerkhoff, MD

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SMART4TB Consortium

Several TB vaccine candidates are in phase IIb/III trials

TB Vaccine Pipeline

Vaccine candidates under clinical development

There are 16 vaccine candidates in the pipeline as of January 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

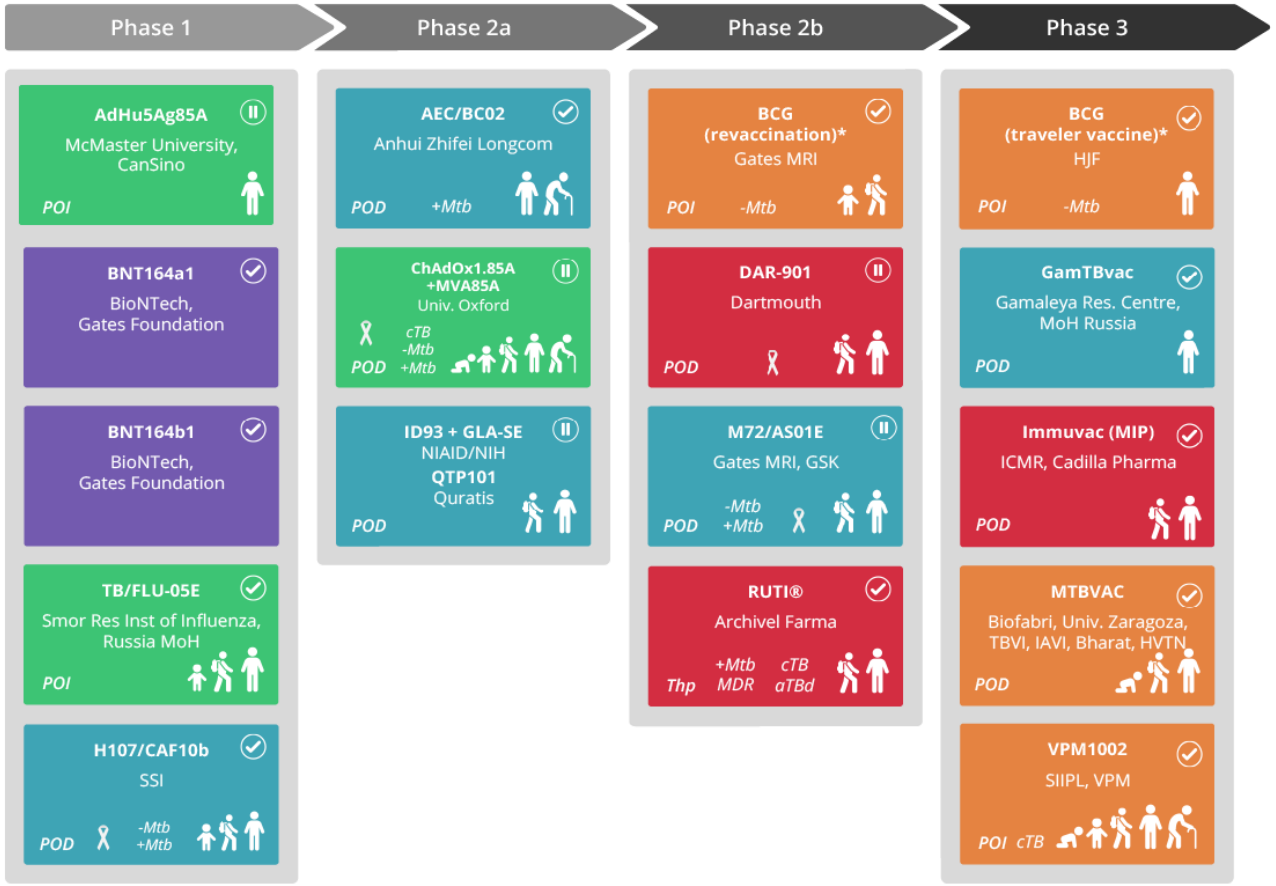
- Active trials
- No active trials

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



**BCG appears twice in the pipeline to distinguish between the investigation of its use in BCG-naïve individuals (traveler vaccination) and in individuals who have previously been vaccinated with BCG (revaccination).*

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 TBVI Pipeline at https://newtbvaccines.org/tb-vaccine-pipeline/ — *Last update: 8 January 2024*

Stop TB Partnership
Working Group on New TB Vaccines

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Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

We have a great opportunity to build demand and strengthen health systems for new TB vaccines

- Vaccines do not save lives; ***vaccination*** saves lives
- Opportune moment: restore trust and confidence in vaccines and health systems ***before*** vaccine roll-out
- ***Inter-disciplinary research*** is critical to guide the design and evaluation of targeted strategies to generate and sustain demand as well as improve health system delivery
- ***Community engagement*** should be at the center for all vaccine preparatory and introduction activities

Y2 Proposed Activities

1) Conduct mixed-methods research in two TB priority countries *to assess health facility and systems readiness for TB vaccine delivery* (Research Questions 1, 3)

2) Conduct mixed-methods research in two TB priority countries *to explore decision-making factors for TB vaccine acceptance* (Research Questions 1, 2)

3) Create a repository to hold TB vaccine readiness tools, documents, and resources (Research Questions 1, 2, 3, 4)

4) Undertake advocacy activities around TB vaccine access policy and vaccine R&D (Research Questions 1, 2, 3, 4)

Countries for Y2: South Africa and Kenya

Priority Research Questions

1) What populations and settings will most benefit from the introduction of a new TB vaccine?

2) What are the barriers to access and uptake for those likely to benefit from a TB vaccine, and what may overcome such barriers?

3) What is the state of readiness of local and national health systems to adopt a novel TB vaccine and scale-up TB vaccination?

4) What is the anticipated acceptability, feasibility, cost-effectiveness and epidemiological impact of different TB vaccine implementation strategies in real-world settings?

Activity 1: Assess health facility and systems readiness for TB vaccine delivery

Health System Readiness

This activity will **assess capacity for vaccine delivery**, including vaccine cold chain, vaccine management, disease surveillance and reporting, injection safety, and waste management, among others

Review health facility and systems readiness tools related to adult and adolescent to delivery

Develop a checklist to assess health facility and systems readiness for new TB Vaccines

Administer tool to a diverse set of health facilities in two states in two countries

Activity 2: Explore decision-making factors for TB vaccine acceptance

Demand

This activity will **explore the demand** for a new TB vaccine through the 5 Cs and BeSD frameworks:

- **Review and develop demand tools** related to adult and adolescent vaccine acceptance
- **Conduct in-depth interviews** with a range of stakeholders, including potential beneficiaries, healthcare providers, and policymakers
- **Perform surveys and choice experiments** among community members and healthcare workers

Y3 Proposed Activities: Co-Creation

- **Co-creation process with key stakeholders to operationalize findings from Y2 mixed-methods research into outputs for countries to prepare for TB vaccines.**
  - Through multiple stakeholder workshops, we will use data collected from the first year of engagement to identify key outputs needed for country readiness to deliver a TB vaccine to adults and adolescents
  - Stakeholder types for co-creation engagement: potential vaccine beneficiaries, NITAG members, health care providers, community leaders, EPI, NT
- **Many potential outputs – meant to be most useful to local and national stakeholders**
  - Supporting the development of implementation plans
    - Including tailored implementation and delivery strategies
  - Supporting the development of communication and demand strategies
  - Supporting the development of health systems strengthening plans
  - Policy briefs for NITAG

SMART4TB is made possible by the generous support of the American people through the United States Agency for International Development (USAID) and is implemented under cooperative agreement number 7200AA20CA00005. The consortium is managed by prime recipient, Johns Hopkins University.

Thank you!

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Supporting, Mobilizing, and Accelerating Research for Tuberculosis Elimination

SMART4TB Consortium

WHO activities to accelerate new TB vaccine development and use

Birgitte Giersing, PhD
Vaccine Product & Deivery Research
Dept of Immunization, Vaccines & Biologicals,
WHO

GVIRF webinar on New TB Vaccines
22nd February, 2024

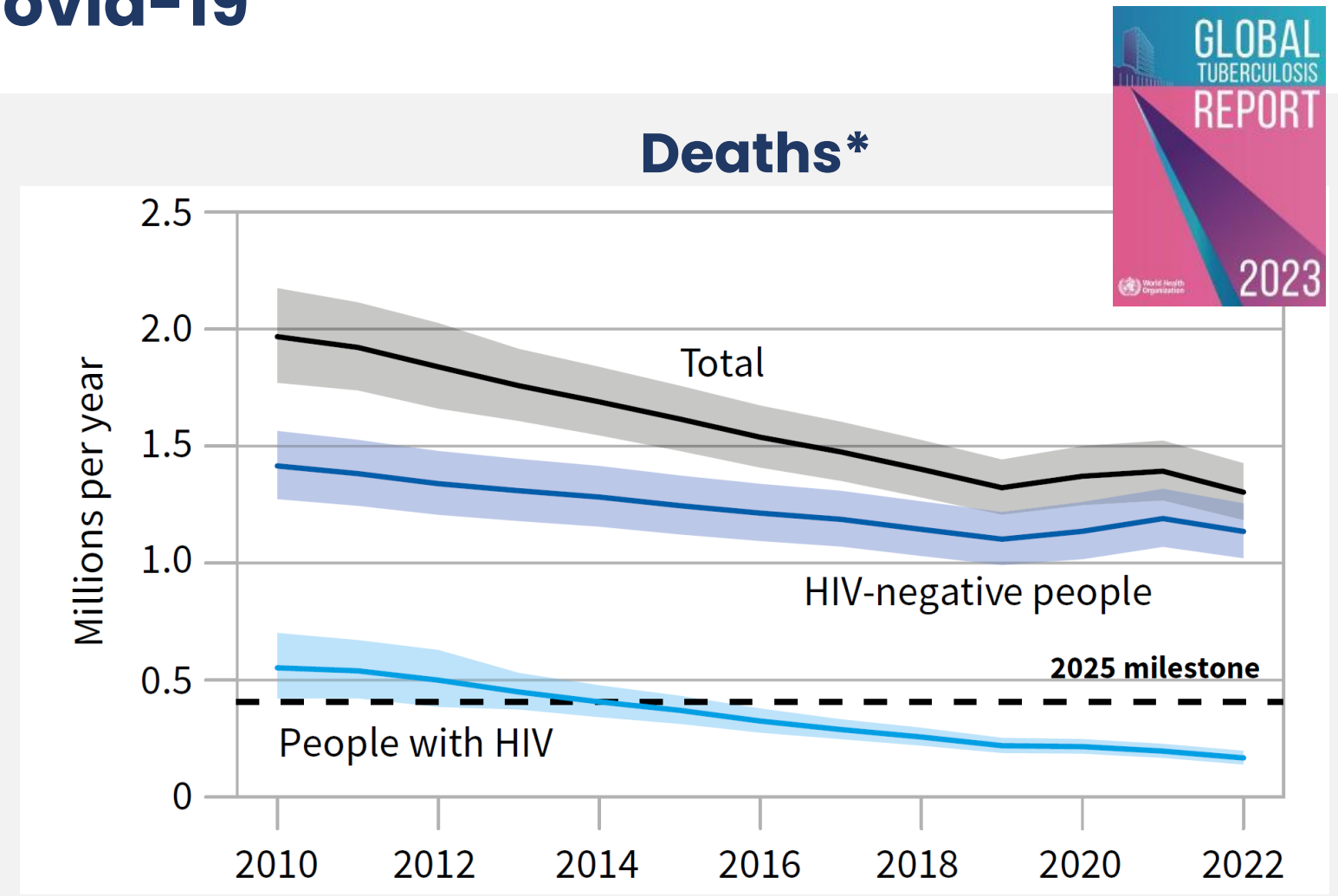
TB remains the second leading cause of death from a single infectious agent, after Covid-19

In 2022, an estimated 10.6 million people fell ill with TB.

1.3 million people died.

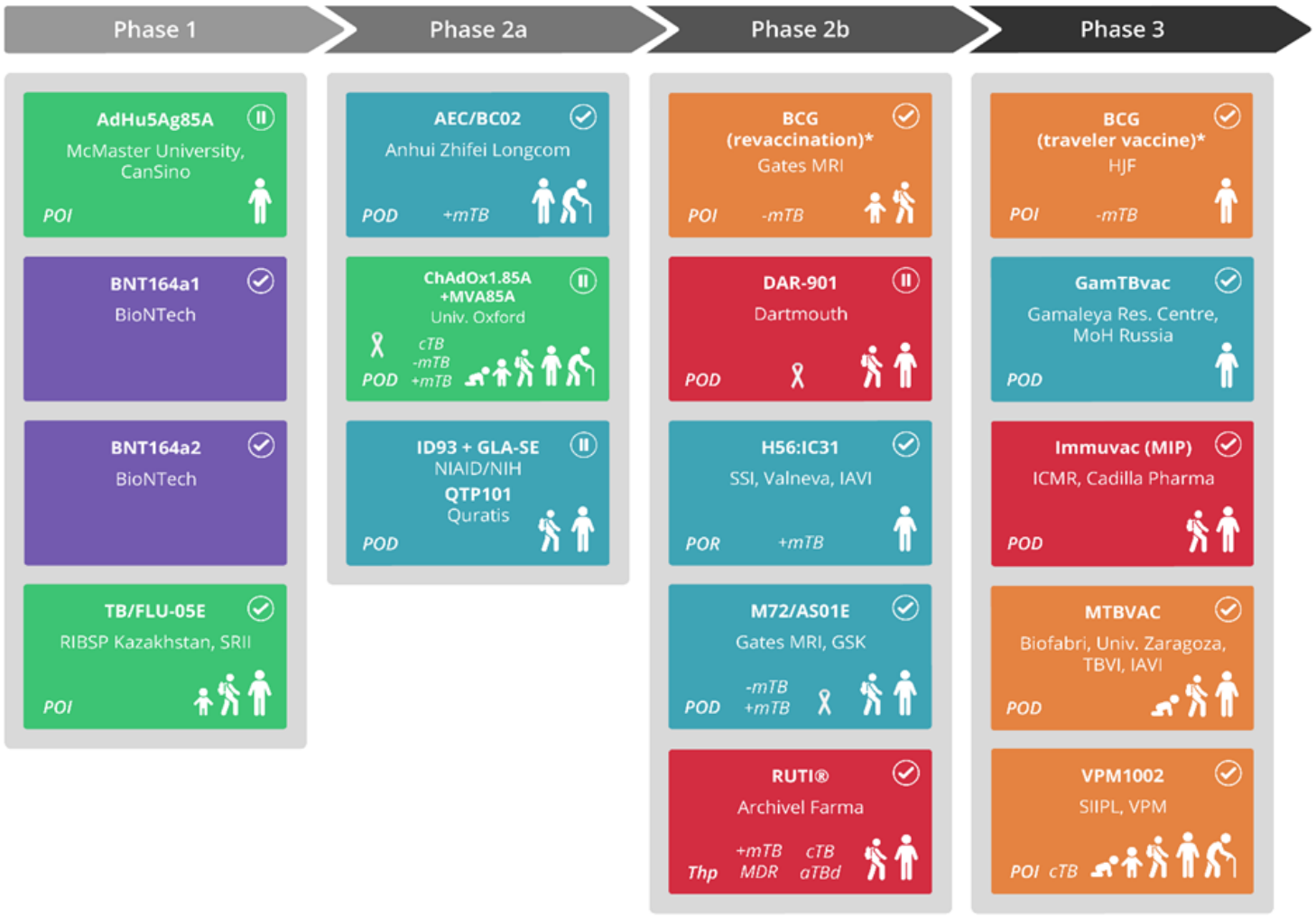
COVID severly impacted the ability to detect cases and treat, causing an excess 0.5 million deaths between 2020 –2022.

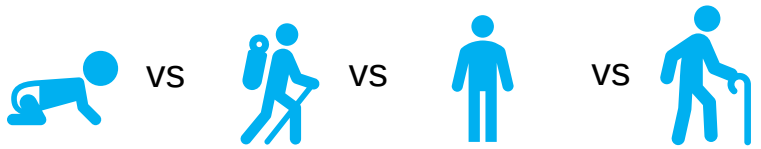
We urgently need a vaccine that prevents against TB disease.



*167 000 deaths among people living with HIV

A catalytic time for new TB vaccine development





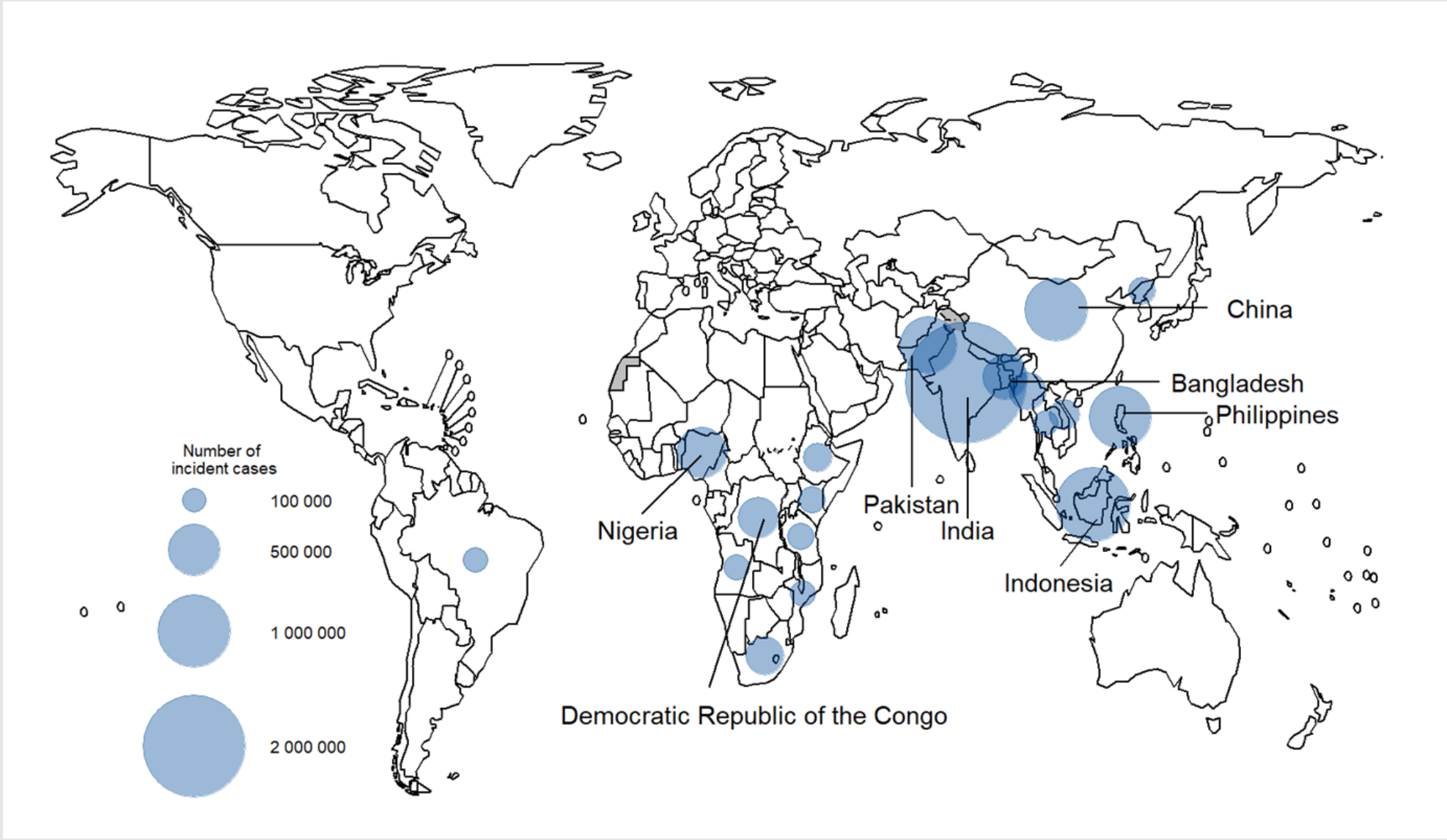
Target population

Vaccine target product attributes

Regulatory and implementation strategy

Source : Stop TB Partnership, https://newtbvaccines.org/pipeline-sortable/

Where TB is most common – many are middle-income economies



WHO. Global TB Report. 2023

There are two pathways to recommendation and use

National regulatory approval and implementation pathway:

Middle income self-procuring countries

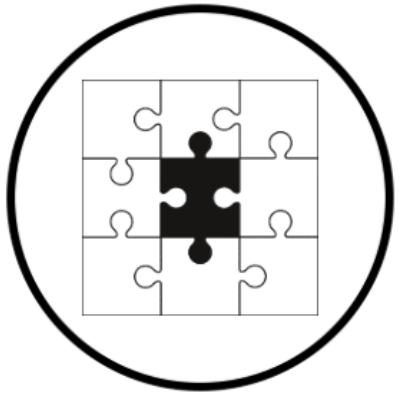
Global regulatory approval and implementation pathway:

Countries seeking financial support / pooled procure-ment

Why do we need to build the path to TB vaccine introduction?

Prioritise critical questions

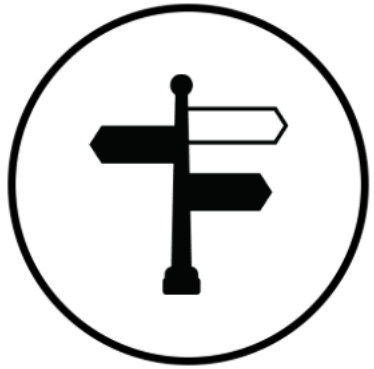
Highlight evidence gaps



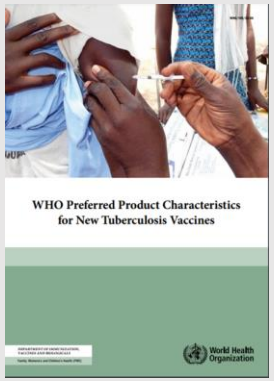
Identify risks and trade offs

Develop possible use cases

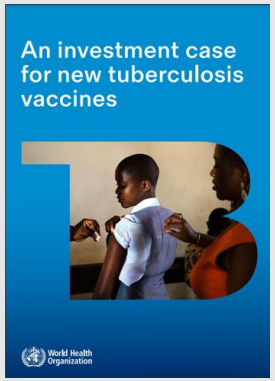
Proactively provide guidance



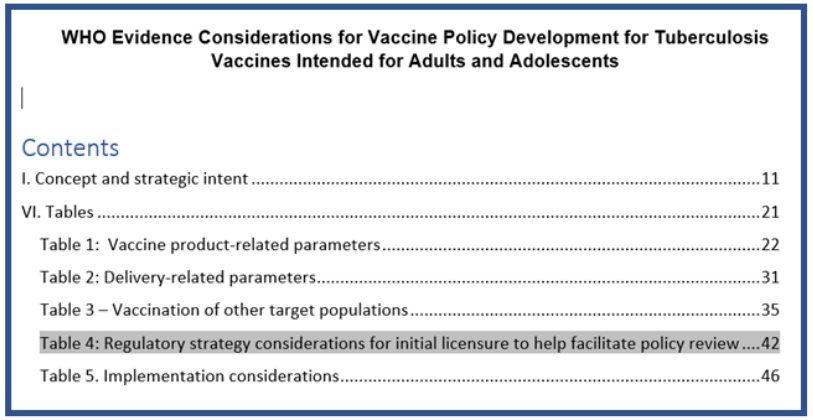
What is WHO doing to address these challenges?



Efficacy targets against prevention of disease

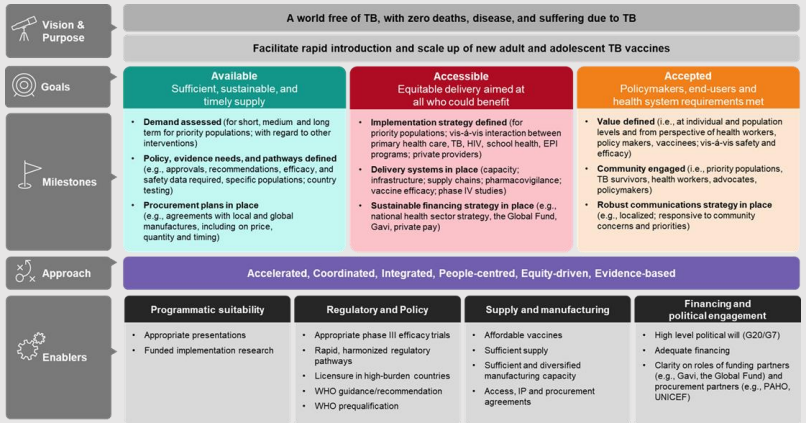


Modelled **vaccine impact** aligned with WHO PPCs


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

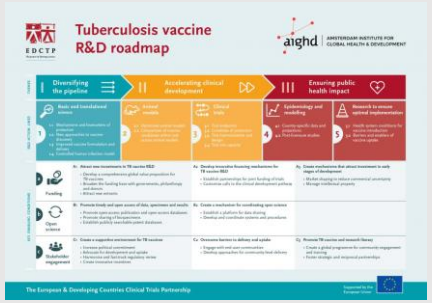
Contents

Anticipates data and evidence for global policy and WHO prequalification to **reduce the gap between regulatory approval and global policy**



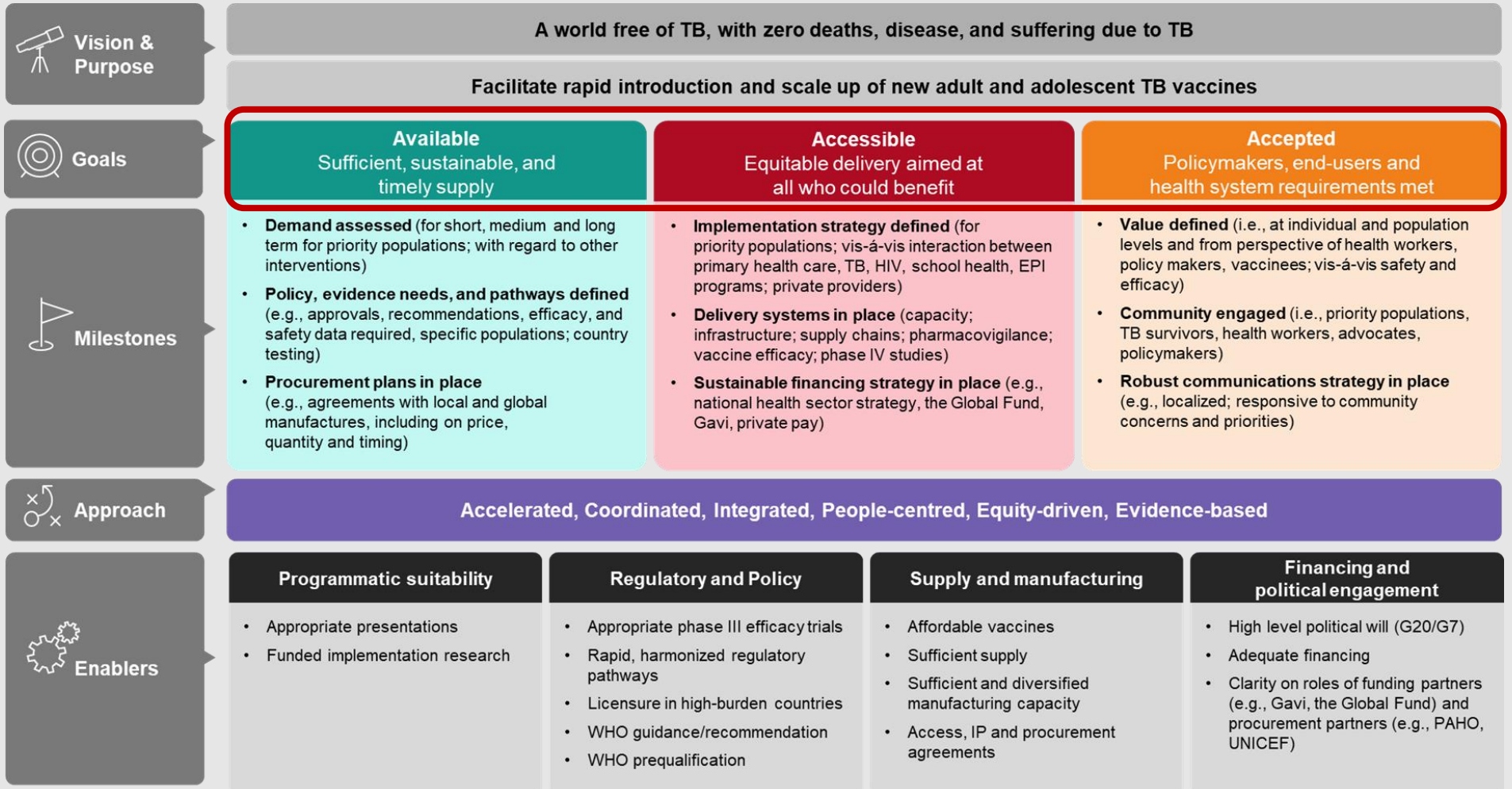
Looks at what **data, evidence and activities are needed at the country level,** to prepare for introduction decision making

Identifies the **key barriers to TB vaccine R&D**, and potential ways in which they might be overcome



These documents can be navigated to from the **WHO Vacccine Product and Delivery Research** webpage

WHO global framework to prepare for country introd'n of new adolescent and adult TB vaccines



What are (some of) the challenges ahead?

Health systems for targeting adults and adolescents with vaccines are poorly developed; the vaccine may be delivered outside usual vaccination sites

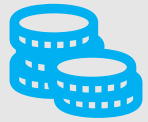
Identifying the optimal delivery strategy; it is not feasible to assess PoD in young adolescents, and vaccinating young adolescents requires a long duration of protection to cover peak age of risk

Range of epidemiological & health system contexts (burden, awareness, vaccine acceptability/interest, health system strength, political will…)

Currently operating in the hypothetical – lack of alignment on vaccine attribute 'absolutes' and use cases - creates challenges for demand generation and demand assessment

Mechanisms and clarity exist to establish what data needed for regulatory approval, but not for global or national policy recommendations

No established financing mechanism for procurement of TB vaccines, particularly in high burden, middle income countries.



Uncertainty for investment from manufact-urers.

Global alignment and co-ordination of stakeholders will be key

Aims to facilitate the development, testing, authorization, and use of new TB vaccines

Work-planning underway:

- To leverage, rather than duplicate, existing initiatives
- To help address gaps that require this kind of unique, high-level forum
- Address a clear ask for a focus on financing mechanisms and market solutions.

Members of the Ministerial Board

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