Investigational Tuberculosis Vaccines in Africa

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genda

- TB epidemiology
- WHO Guidance
- Opportunities & Challenges
- Two investigational vaccines in development for POD in adolescents & adults
  - Biofabri MTBVAC (live-attenuated vaccine) in Phase 2b
  - Gates MRI M72/AS01$_E$ (adjuvanted subunit vaccine) in Phase 3
- Evidence available at the time of dossier submission
- Evidence gaps and considerations for vaccine introduction

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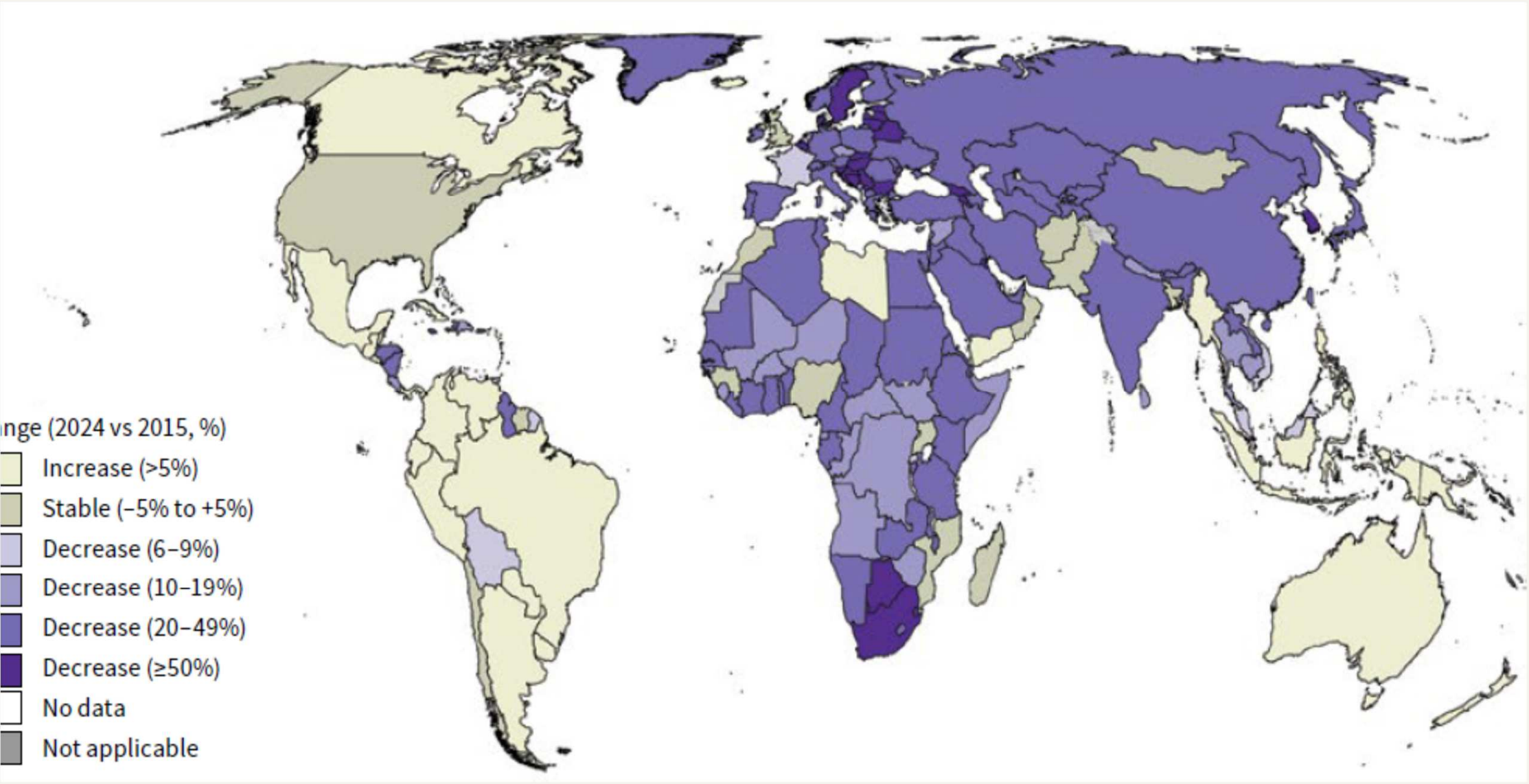
ange (%) in the estimated TB incidence rate (new cases per 100 000 population per year) at untry level, 2024 compared with 2015



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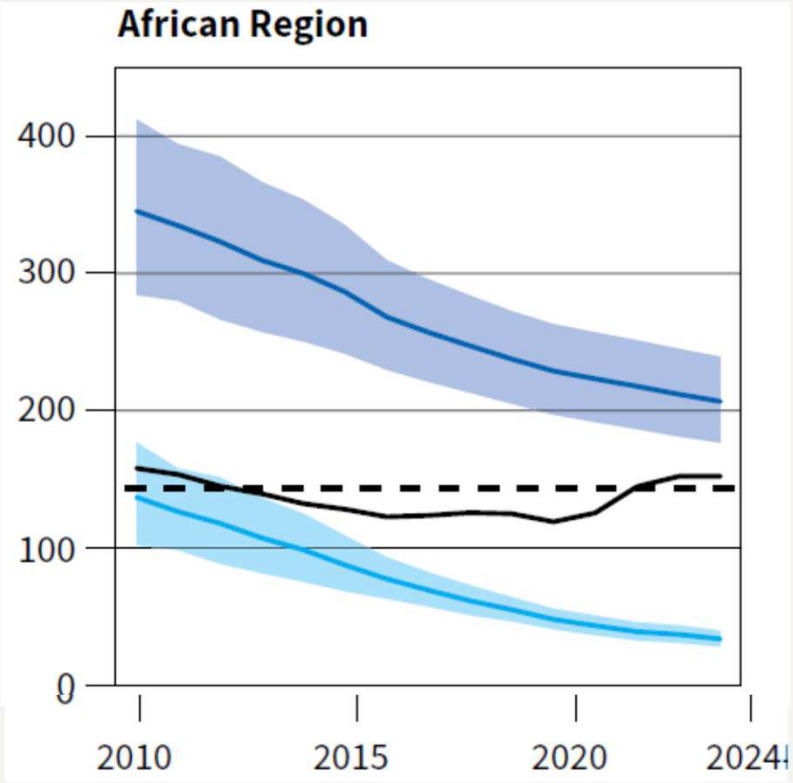
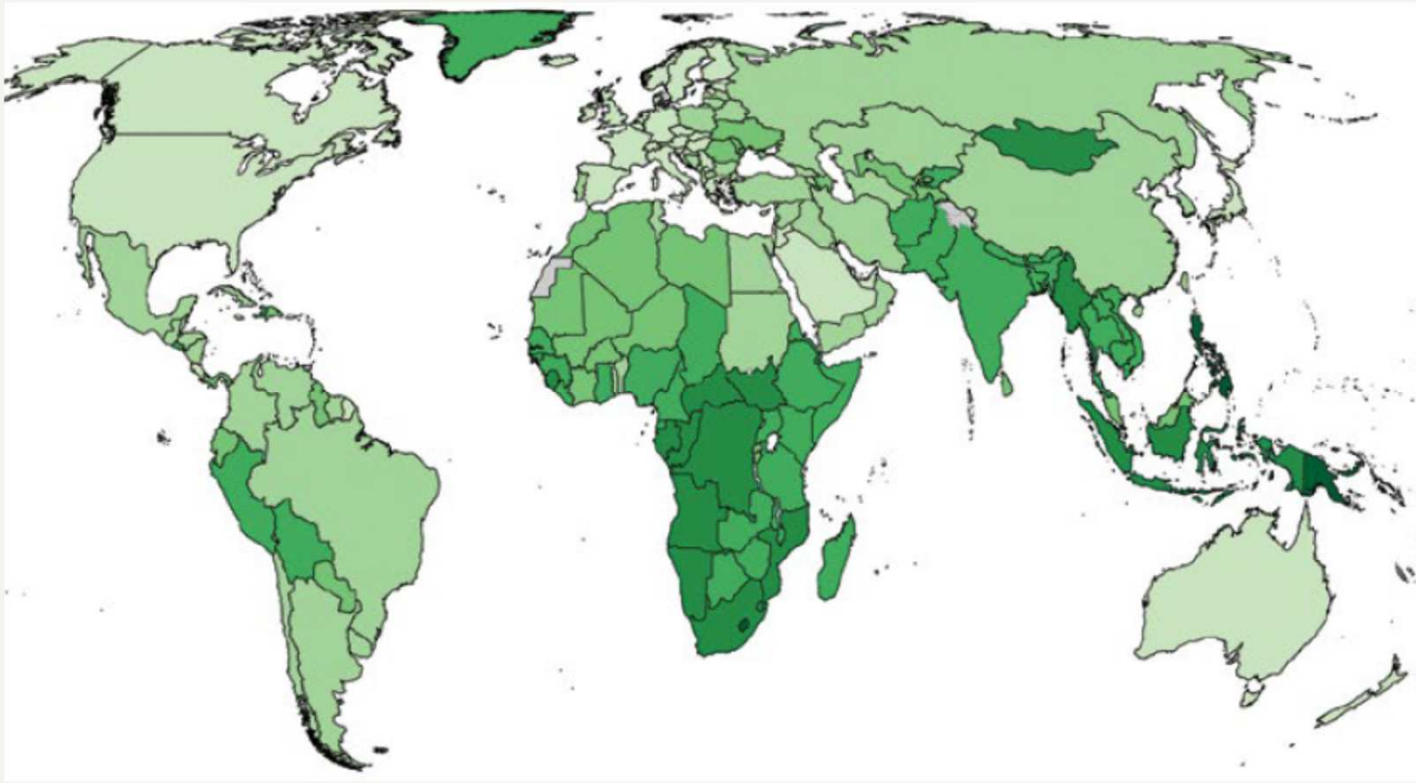
B Incidence Rates are highest in Africa and South & SE Asia





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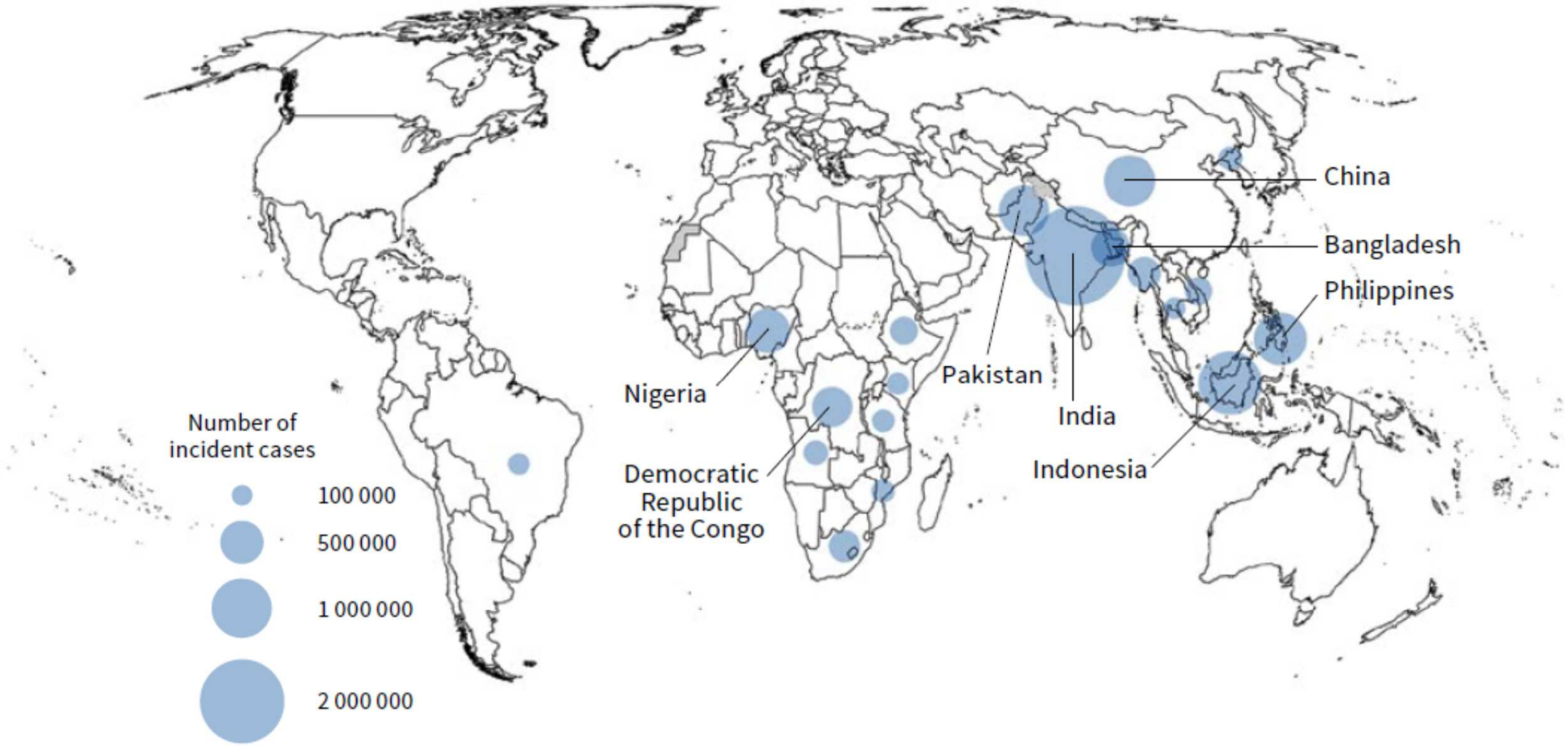
stimated number of incident TB cases for countries with at least 100 000 incident cases, 2024[a]



The labels show the eight countries that accounted for two thirds of the global number of people estimated to have developed TB in 2024.

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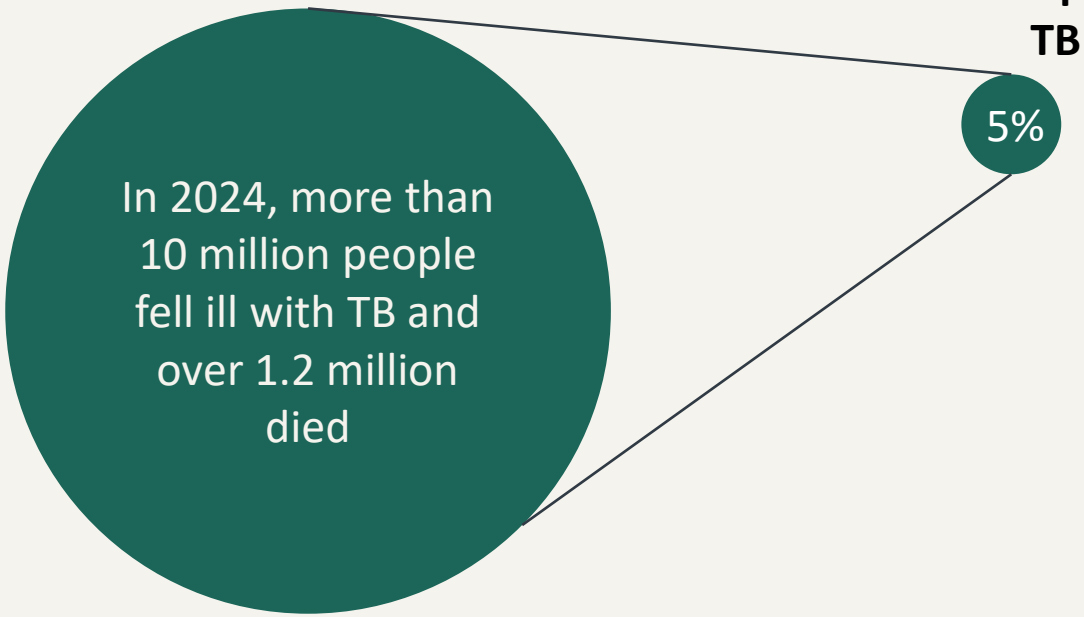
B epidemiology – Implications for TB Vaccine Development



Approx. 5% of infected people develop TB disease within 3 years of infection

- Undernutrition (inverse correlation btw BMI & ris of TB), RR=2.0, 1 million attributable cases
- Diabetes mellitus, RR=1.6, 0.9 million attributable TB cases
- HIV infection, RR=12, 0.6 million attributable TB cases
- Smoking, RR=1.6, 0.7 million attributable TB cases
- Alcohol use disorder, RR=3.3, 0.7 million attributable TB cases
- Poverty, poor housing, mining, immunosuppressio
- In very high burden settings, >50% of incident cases of TB disease are due to Mtb reinfection & relapse

Mtb infection and reinfection are frequent in high burden settings (3% to 5% per person-year)
Mtb is not very infectious
95% of Mtb-infected people are doing alright

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HO Preferred Product Characteristics
for New Tuberculosis Vaccines

OF IMMUNIZATION,
D BIOLOGICALS
and Children's Health (FWC)

World Health Organization

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

- Development of a POD vaccine for adolescents & adults is a key WHO priority

- Modellings indicates that a POD vaccine has faster & bigger impact than a POI vaccine

World Health Organization

otential TB Vaccine Indications

OD: **P**revention **o**f Pulmonary TB **D**isease, microbiologically confirmed by positive sputu
ulture and/or NAAT/GeneXpert

OI: **P**revention **o**f *M. tb* **I**nfection, as indicated by (sustained) IGRA conversion from
egative to positive (e.g., BCG Revaccination)

OR: **P**revention **o**f TB Disease **R**ecurrence, in recently cured patients (due to either
einfection or reactivation with original *M. tb* strain (e.g., VPM1002)

x Vx: Therapeutic vaccine, given as adjunct to drug treatment during treatment course
e.g., RUTI)

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VHO Evidence Considerations for TB Vaccine Policy (POD)

L. Vaccine product-related parameters

rameters gh priority, edium priority)	Preferred vaccine product attributes	Data expected
sease indication *ndition that the ccine is intended to event, e.g., (severe) ease, infection, nsmission)*	Prevention of active pulmonary TB disease (POD). See T1.4 for preferred efficacy.	**IP:** Data demonstrating POD.
iority population(s) *e populations who l be the primary ipients of the vaccine er licensure)*	Adults and adolescents (12–18 years of age) with or without evidence of prior Mtb infection. People living with HIV (PLHIV). Additional target populations are described in Table 3.	**IP: Safety and efficacy data** in adults with evidence of prior Mtb exposure. **Safety and immunogenicity** data in adults without evidence of prior Mtb infection. **Safety and immunogenicity** data in PLHIV . Phase III efficacy studies should not exclude people with diabetes or people with malnutrition.

Efficacy *(percentage reduction of outcomes of interest in the vaccinated compared to the unvaccinated group under optimal conditions)*	50% or greater efficacy in preventing confirmed pulmonary TB in the priority populations described in T1.2 *(10)*.	**IP:** Data from sufficiently powered randomized, placebo-controlled studies conducted in high-burden countries, with broad inclusion criteria, in the priority populations (see T1.2). Although demonstration of efficacy in all subpopulations will not be possible, licensure studies should be broadly representative of target populations and conducted so as to provide supportive evidence for use in Mtb uninfected individuals.

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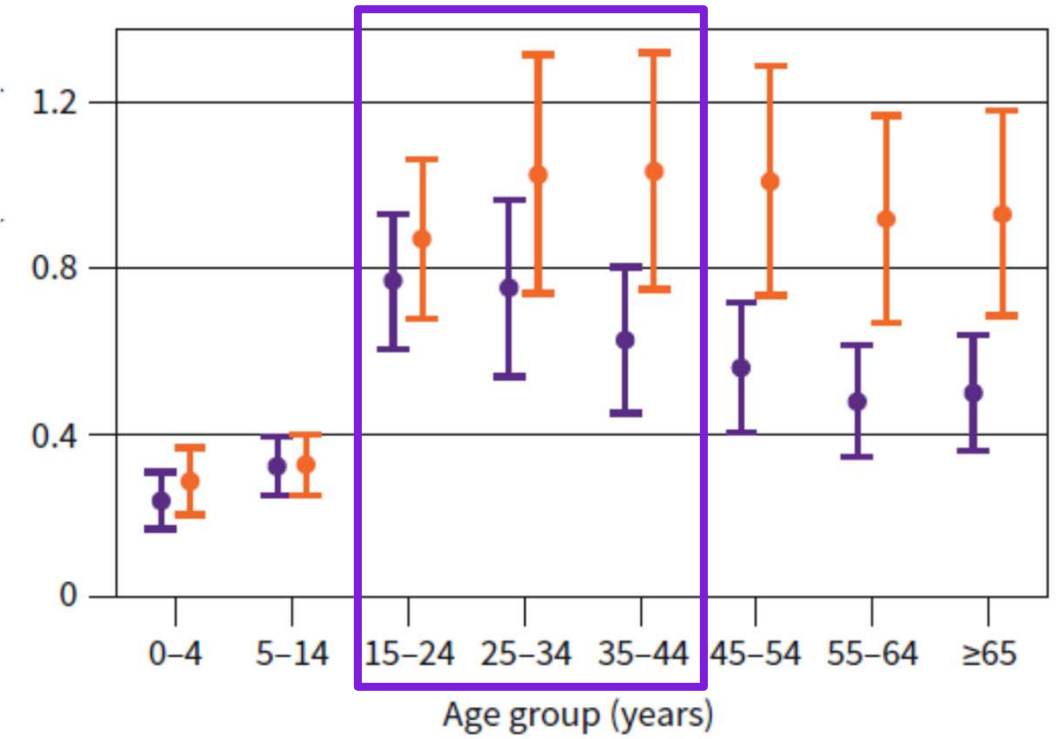
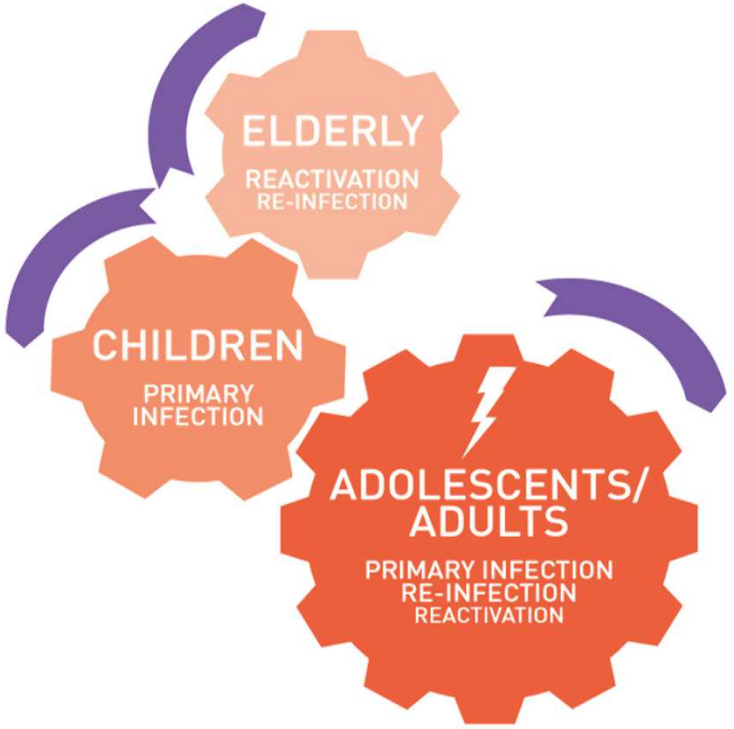
revention of pulmonary TB in adolescents and young adults is key ecause this age group is the main source of TB transmission

lobal estimates of TB incidence (absolute umbers) disaggregated by age group and sex emale in purple; male in orange), 2024

ots and error bars show best estimates and 95% ncertainty intervals, respectively.





Need safe, effective, accessible TB vaccines targeted at adolescents and adults to decr transmission and protect all age groups

adza et al, South African J Science 2013;109(9/10);
Preferred Product Characteristics for New Tuberculosis Vaccine; https://www.who.int/publications/i/item/WHO-IVB-18.06

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B Vaccine Development Opportunities

Burden of Disease is enormous: 10 million fall ill, 1.2 million die every year

A TB vaccine for adolescents & adults with 50% vaccine efficacy for the prevention of TB disease (P

- Would increase health equity
- Would lead to increased productivity and economic growth
- Is projected – assuming a price of $4.60 - to be cost-effective in 73 of 105 LMICs and cost-saving 58 of 105 LMICs (societal perspective), including 96% of countries with higher TB burden.
- When considering the monetized value of health gains, it is estimated that introduction of an adolescent/adult vaccine could produce $283 to 474 billion in economic benefits by 2050.
- Return on Investment is estimated to be >$7 per dollar invested

Portnoy et al., 2023, https://doi.org/10.1371/journal. pmed.1004155

Portnoy et al, PLoS Med 2023, doi: 10.1371/journal.pmed.1004155

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B Vaccine Development Challenges

- Limited understanding of mechanism of protection & protective antigens
- No correlate of protection for vaccine-induced Prevention of Disease (POD)
- No animal model that predicts TB disease in people
- Low rate of progression from infection to disease (≤3% within 2 years of infection)
- Even in high burden settings, the incidence rate of laboratory-confirmed TB disease is low (0.2% to 0.5% per person year)
- Large clinical endpoint trials are needed for licensure
- Likely no dual market unless efficacy is very high, with limited or no return on investment for R&D

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wo Investigational Vaccines in Late-Stage Development

MTBVAC: live-attenuated *Mycobacterium tuberculosis* strain

M72/AS01E: adjuvanted subunit vaccine

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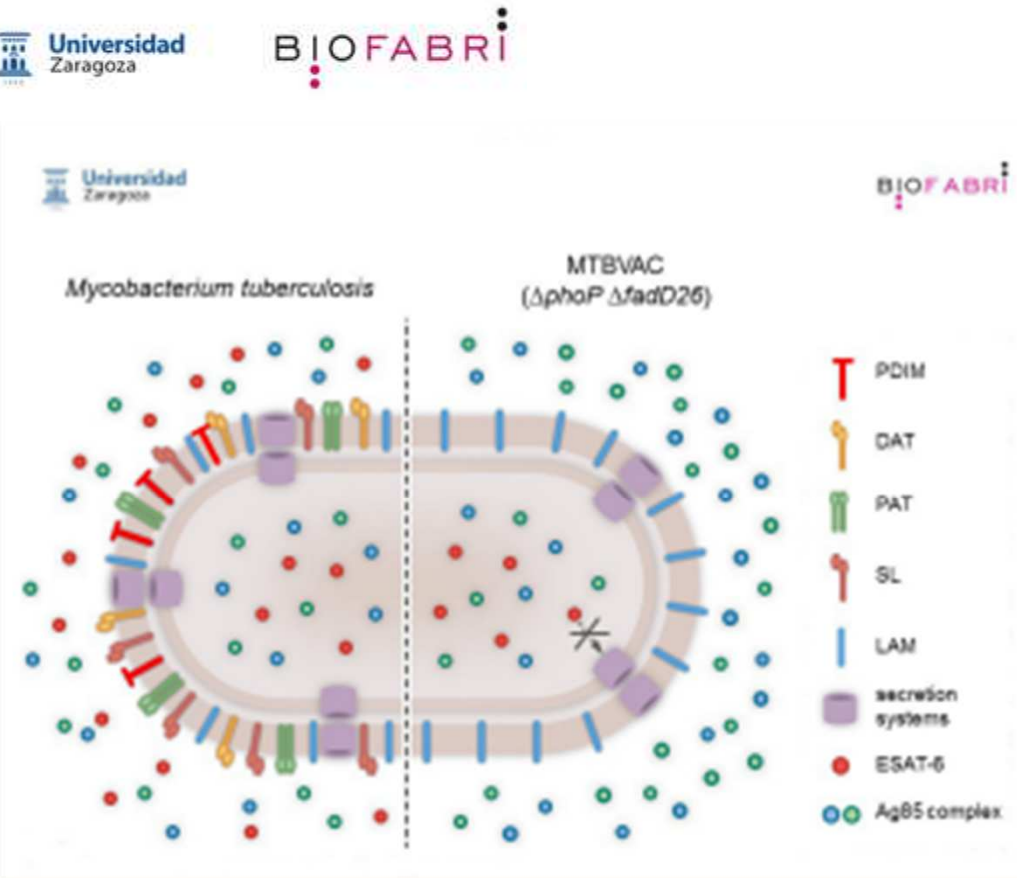
ITBVAC

ive, attenuated M. tuberculosis



ttps://www.iavi.org/wp-ontent/uploads/2025/01/iavi_fact_sheet_MTBVAC.pdf

Registry Number	NCT06272812
Clinical Trial Phase	Phase 2b
Clinical Trial Sponsor	International AIDS Vaccine Initiative
Primary endpoint(s) for this clinical trial	Prevention of TB disease
Target population(s) for clinical trial	Adolescents
	Adults
	People with Mtb infection
	People without HIV infection

Actively Recr

https://newtbvaccines.org/vaccine/mtbvac/

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TBVAC (live-att. *Mtb*), Biofabri, IAVI & Bharat

AGINE trial: A Phase 2b, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety an
munogenicity of MTBVAC against TB disease in IGRA-positive adolescents and adults aged 14-45 years.
T06272812. Sponsor: IAVI

- Approx. 4,300 IGRA-pos. participants to be randomized 1:1. Protocol amendment adds 1200 IGRA-neg participants, to be randomized 2:1
- Primary efficacy endpoint in IGRA-pos.: bacteriologically confirmed pulmonary TB disease in IGRA-pos. mITT
- Primary endpoint analysis once 35 cases have accrued (assumed VE 65%, LB of 95% CI = 0)
- Futility analysis with 12 cases, second IA w/ 26 cases
- Primary efficacy analysis likely in 2028

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TBVAC

ase 2a trial in PLWHIV (HVTN605, NCT05947890)

- Protocol was amended; sponsorship changed from DAIDS to Fred Hutch, now funded by GF & OP/EG
- Enrollment in SA to resume once protocol amendment is approved and IP Shipment received (likely Q1 2026), year f/u
- Target enrolment: 276 participants, 12 to 55 years of age

oduct development in India with Bharat Biotech (NCT06997367)

- Bharat Biotech is conducting a Phase 2a trial in India in HIV-neg. adolescents & adults (N=164)
- Biofabri, Bharat Biotech & ICMR are discussing potential Phase 3 trial in India

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72/AS01$_{E-4}$ Investigational Vaccine

Recombinant fusion protein plus GSK proprietary adjuvant system

2-vial presentation

2 doses administered IM one month apart

is a 72kDa recombinant fusion protein derived from the two *M. rculosis* antigens

- Mtb39a : membrane-associated protein, putative evasion factor
- Mtb32a : secreted protein, putative serine protease

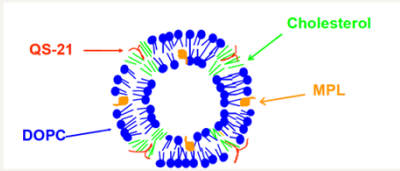
Composition of M72 lyophilized formulation per dose

Ingredient	Quantity per dose*	Function	Reference
M72	10 µg	Active ingredient	GSK Bio 300723
Sucrose	25 mg	Cake stability	Ph. Eur. 0204
Polysorbate 80	0.1 mg	Protein recovery	Ph. Eur. 0428
Tris	0.97 mg	Buffering agent	Ph. Eur. 1053

* Does not include overage
Ph. Eur.: European Pharmacopoeia
Pharmaceutical form: freeze-dried, white pellet

es Medical Research Institute. All rights reserved. Confidential information.

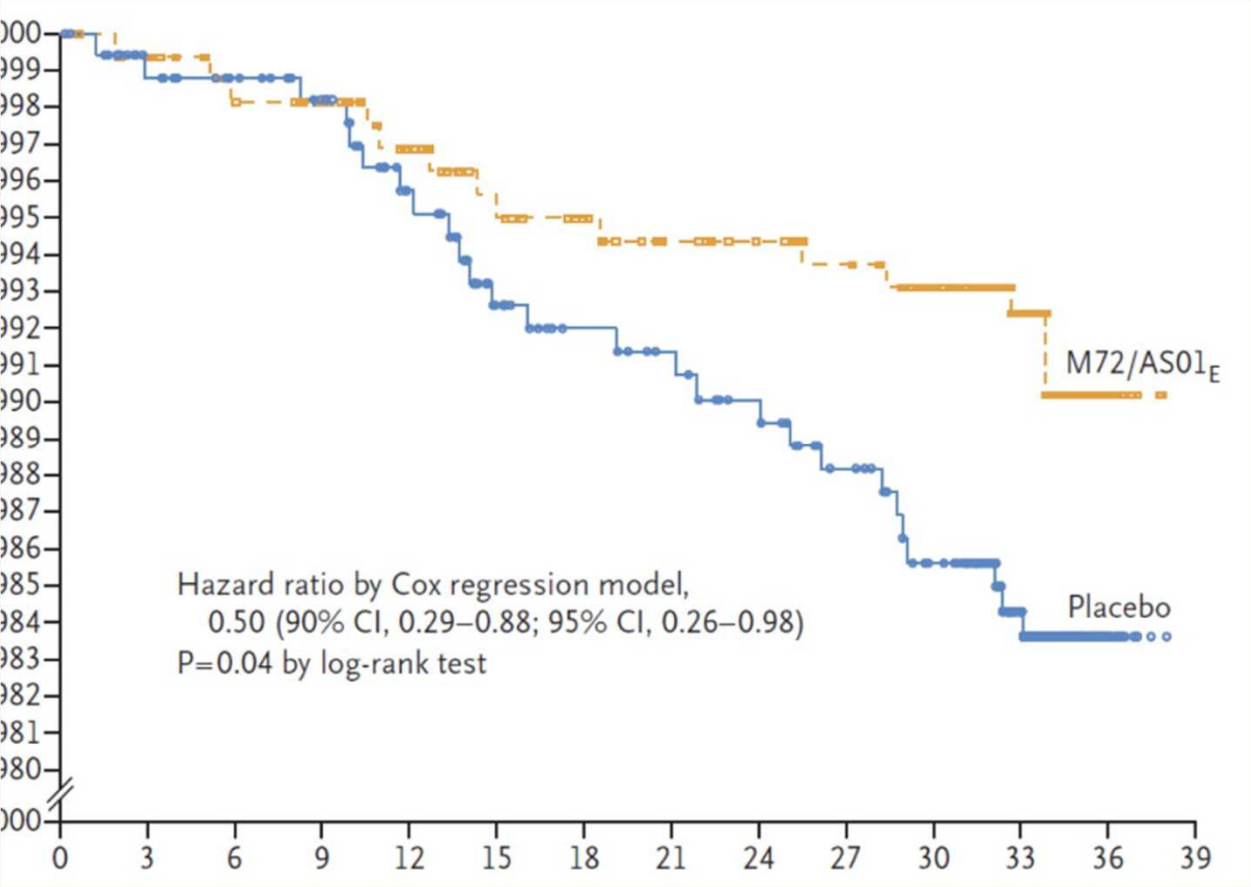
AS01E-4 adjuvant system (GSK proprietary) is composed of immunoenhancers, liposome and other excipients



- QS-21 (a triterpene glycoside purified from the bark of Quillaja Saponaria Molina)
- MPL (3-D Monophosphoryl lipid A)
- DOPC
- Cholesterol
- Buffer

72/AS01$_E$ Phase 2b trial (NCT06062238)

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



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

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72/AS01$_{E-4}$ Phase 2b Results

e 1. Vaccine Efficacy of M72/AS01$_E$ as Compared with Placebo against Pulmonary Tuberculosis in Adults with Evidence of Tuberculosis Infection.*

ort and Case Definition	M72/AS01$_E$			Placebo			Vaccine Efficacy	
	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	% (90% CI)	% (95% CI)
ording-to-protocol efficacy cohort								
definition	13	4427.62	0.3 (0.2 to 0.5)	26	4463.06	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
First definition: sensitivity analysis‡	7	4429.29	0.2 (0.1 to 0.3)	22	4467.51	0.5 (0.3 to 0.7)	68.0 (34.7 to 84.3)	68.0 (25.1 to 86.3)
ond definition	8	4429.69	0.2 (0.1 to 0.3)	21	4467.51	0.5 (0.3 to 0.7)	61.7 (24.1 to 80.6)	61.7 (13.5 to 83.0)
d definition	19	4427.62	0.4 (0.3 to 0.6)	30	4463.06	0.7 (0.5 to 1.0)	36.3 (–3.2 to 60.7)	36.3 (–13.2 to 64.1)
rth definition§	19	4427.62	0.4 (0.3 to 0.6)	32	44			
definition§	26	4434.21	0.6 (0.4 to 0.8)	38				
lified fifth definition	25	4434.21	0.6 (0.4 to 0.8)	36				
l efficacy cohort								
definition	13	5055.30	0.3 (0.2 to 0.4)	28				
ond definition	8	5057.38	0.2 (0.1 to 0.3)	22				
d definition	20	5055.30	0.4 (0.3 to 0.6)	32				
rth definition	20	5055.30	0.4 (0.3 to 0.6)	34				
definition	28	5061.90	0.6 (0.4 to 0.8)	38				
lified fifth definition	27	5061.90	0.5 (0.4 to 0.7)	36	5(			

The first case definition (blue box) for the primary endpoint (definite pulmonary TB) required **≥ 1** positive sputum test. The sensitivity analysis of the primary endpoint (red box) required **≥ 2** positive sputum tests.

The more stringent case definition (≥ 2 positive sputum tests) will be used as primary case definition for the Phase 3 VE trial.

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72/AS01$_E$ Phase 3 Efficacy Trial (NCT06062238)

ssumptions

- Vaccine Efficacy (VE) against Disease (D) in IGRA+ cohort is ≥ 55%
- Null hypothesis: H0: VE(D) ≤ 10% (α < 2.5%, lower bound of 95% CI > 10%)
- TB incidence: 0.4% per year in IGRA+
- *Mtb* infection rate: 3% per year

Cohort	N
HIV-, IGRA+ Cohort	18,000
HIV-, IGRA- Cohort	1000
HIV+ Cohort	1000
Total	20,000

esign

- Placebo-controlled, double-blind, 1:1 randomized trial
- N = 20,000, 15 to 44 years of age
- 2 doses of Investigational Product 1 month apart
- Correlates of Protection cohort: approx. 10,000 participants

nd of Trial

- Primary endpoint analysis once 110 cases of lab-confirmed TB are observed in the HIV-, IGRA+ Cohort
- > 90% power to demonstrate VE of 55% with LB > 10%

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72/AS01$_E$ Phase 3 Efficacy Trial: Number of Trial Sites per Country

South Africa: 34 sites
Kenya: 9 sites
Indonesia: 5 sites
Zambia: 4 sites
Malawi: 2 sites

20,000 participants enrolled from March 2024 through April 2025, in 13 months

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I72/AS01$_E$: Evidence expected to be available at initial licensure

From Phase 3 Trial:

- Safety in the overall exposed population, compared to placebo
  - Exposed: 9,000 HIV-, IGRA+ participants; 500 HIV-, IGRA- participants; 500 PLHIV of either IGRA status
- Efficacy in the HIV-, IGRA+ cohort. Success criterion: Lower bound of the 95% confidence interval >10%.
- Immunogenicity in all three trial cohorts

From MESA-TB Trial:

- Safety & Immunogenicity in PLHIV (201 participants exposed)

From Phase 2b Trial:

- Safety, immunogenicity & efficacy in HIV-, IGRA+ population 18 – 55 years of age (1786 participants exposed)

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What is the utility of the Interferon-Gamma Release Assay (IGRA)?

- IGRA-positive individuals are more likely to progress to TB disease than IGRA negative individuals.
- Estimates from South Africa indicate a three-fold higher rate of progression among IGRA-positive (nine-fold higher rate among those who had recently converted) compared to IGRA-negative adolescents.
- Enrichment of trial populations with IGRA-positive individuals therefore reduces the required sample size and trial duration by maximizing case accrual – a pragmatic choice to ensure that trials of TB vaccines are feasible.

The biological significance of a positive IGRA test result is uncertain:

- A positive result on an IGRA test reflects immune sensitization to *M. tuberculosis*, which may suggest prior exposure to, or ongoing infection with, *Mtb*.
- A positive IGRA test is neither necessary nor sufficient to conclude that a person is infected with *Mtb*: persons with active TB or with latent TB may test negative on IGRA.
- People who test positive may revert to negative within a few months. Particularly in settings with a high burden of TB, exposed persons may test negative, despite mounting an immune response.
- People who test negative may be *Mtb* naïve or Mtb infected, and may convert to IGRA-positive within a few months
- Immunogenicity will likely differ between IGRA-positive and IGRA-negative populations

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ackground Information on M72/AS01$_{E-4}$

Clinical Trial Considerations

Efficacy trials are large, long, and costly
Due to low rate of progression from infection to disease

Enroll adolescents and adults (15–44), where TB incidence is highest
(Strategy 1 to enrich end points)

Run the trial in high-burden countries
(Strategy 2 to enrich end points)

Target TB hotspot areas for enrollment
(Strategy 3 to enrich end points)

Enroll individuals with positive IGRA, aligned with WHO guidance
(Strategy 4 to enrich end points)

Programme Realities

Efficacy can only be demonstrated in IGRA+ individuals
Demonstrating efficacy in IGRA– is not feasible:

~50,000 IGRA– participants; **3.7 yrs to enrol, ~6.2 yrs to reach primary analysis** required

Safety and immunogenicity data will be available in both IGRA+ and IGRA– populations

Effectiveness can only be **established post-licensure** via real-world evidence (in the mixed / overall population)

Limiting licensure to IGRA+ individuals would prevent real-world evidence generation (in the overall population)

Regulatory precedent (e.g., Shingrix) supports a broad indication (without efficacy demonstrated across subgroups)

Evidence aligns w/ WHO guidance & supports policy recom-mendations (efficacy in IGRA+, safety/ immuno in IGRA–.

ontrasting Scenarios for TB Vaccine Licensure

1 Broad Licensure: IGRA Status Not Restrictive

- Limiting licensure to IGRA+ would **prevent real-world effectiveness** data generation in mixed population
- **Regulatory precedent** (e.g., Shingrix) supports broad licensure when efficacy is demonstrated in high-risk groups and safety/immunogenicity data support other subpopulations
- **IGRA status is not fixed**, up to 11.9% revert within 1 year (observed in high TB-burden settings), supporting vaccine rollout irrespective of IGRA status in high TB-burden settings

Regulatory: License for broad adult population regardless of IGRA status.

Programmatic: No IGRA testing; straightforward rollout.

Evidence Needs: Post-licensure real-world data in mixed population (IGRA+ and IGRA–) will fill the evidence gaps over time, generated by national TB Programs, WHO surveillance, research networks, etc.

Demand: Aligns with high global projections.

Policy: WHO/SAGE accepts uncertainty in IGRA– but relies on safety, immunogenicity, and later effectiveness data.

2 Narrow Licensure Limited to IGRA+

- **Prevents collection of effectiveness data** in the mixed population (IGRA+ and IGRA–) because IGRA– individuals would not be eligible t receive the licensed vaccine.
- **Severely limits public health value**, equity, and introduction in high-burden countries.
- **Ignores regulatory precedent** allowing broad indications without efficacy in every subgroup.
- **Drastically reduced demand** and is not economically sustainable.

Regulatory: Narrowest label.

Programmatic: Would require IGRA testing - operationally impossible a scale, adds substantial cost and complexity.

Evidence Needs: Cannot generate needed data → hinders policy expansion.

Demand: Demand collapses, dramatically reducing forecast volumes.

- **Lower volumes increase** COGS for the antigen manufacturer due to l of scale efficiencies.
- **Procurement costs rise** for Gavi and public health programs, reducing affordability.
- **Risk to long-term supply sustainability**, as unfavorable economics m threaten ongoing vaccine production.

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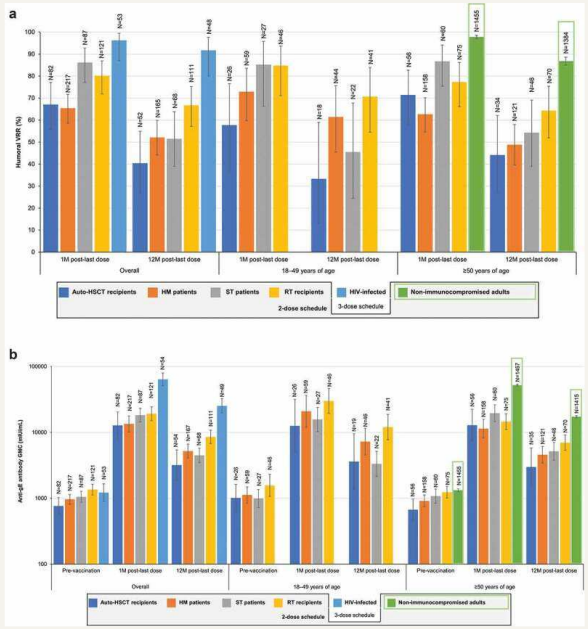
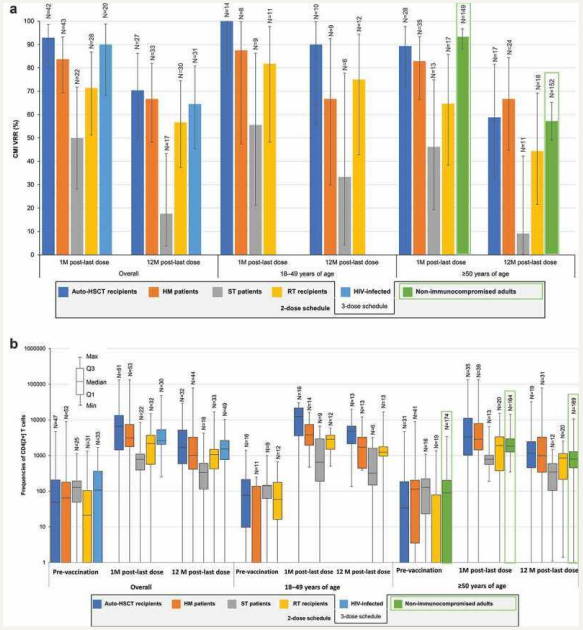
Shingrix: Broad Indication Despite Lack of Efficacy Data in All Immunocompromised Populations





Dagnew AF et al. Hum Vaccin Immunother. 2021;17(11):4132–4143.

Shingrix indication: Prevention of shingles in adults aged 18 years and older who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy

Broad Indication Supported by Efficacy in Hematopoietic Stem Cell Transplant Recipients, Post-Hoc Efficacy in Hematologic Malignancies, and Immunogenicity in Four Immunocompromised Populations—All in the Absence of a CoP

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few Considerations for Vaccine Introduction

Programmatic feasibility (adolescents & adults)

Logistical feasibility (national level, province level, district level)

Impact on burden of disease (high-risk groups, population size of high-risk groups)

Equity considerations

Financing, cost, & cost effectiveness

Vaccine supply

Pharmacovigilance capabilities

Focus on highest risk groups vs generating population-level effectiveness data?

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hank
ou!

e: Courtesy of Prof. Norbert Ndjeka ,TB Vaccine Introduction Preparedness Workshop, July 2025

ased Implementation & Equity Considerations for SA

opulation	No. of people in the country in 2023	TB burden in 2023 (incidence)
dolescents (12-17 years)	5.3 million (UN Population)	427 in 100k population[1]
dults (18-64 years)	37.4 million (UN Population)	427 in 100k population[1]
eople living with HIV	10.2 million (IHME)	4200 per 100,000 population[6]
ousehold contacts	0.26 million (WHO TB Report)	1300 per 100,000 population[6]
ealthcare workers	0.2 million (WHO)	1470 per 100,000 population[6]
eople living with diabetes	4.5 million (Diabetes Atlas)	1240 per 100,000 population[6]
formal settlements	5.5-6 million (Statistics South Africa)	4500 per 100,000 population[6]
mates	157,000 (RSA Dept of Correctional Services)	3900 per 100,000 population[6]
iners	471,882 (Statistics South Africa)	3000 per 100,000 population[6]

vaccine cost necessitates targeted roll-out:
e 1: Prioritize high-risk groups (e.g., PLHIV, healthcare workers, adolescents in high TB burden areas).
e 2: Broader population groups as affordability and supply improve.
y risks if vaccine only available in high burden provinces or urban areas.
for targeting strategies using subnational TB burden data.