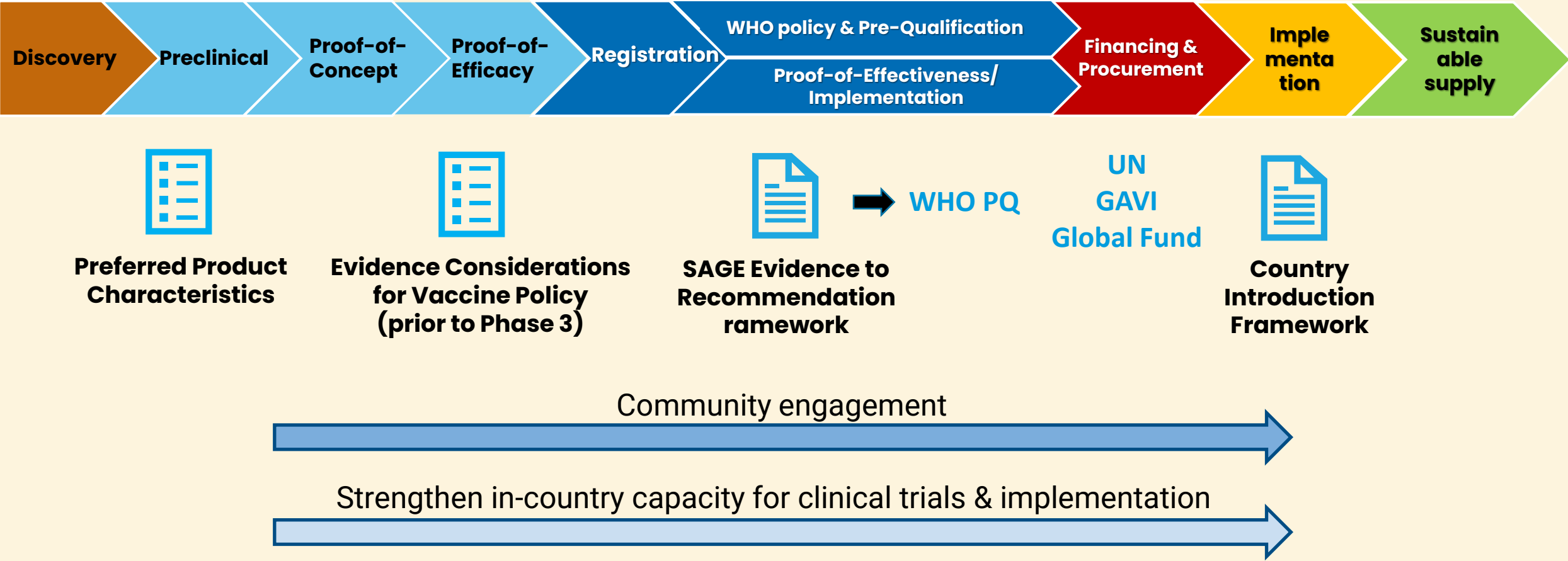


# **BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE**

## Clinical development considerations for mRNA-based TB vaccines

Alexander Schmidt, MD PhD  
Head of Vaccine Development  
Gates MRI

# Path to licensure, recommendation, and use



# Vaccine Development 101

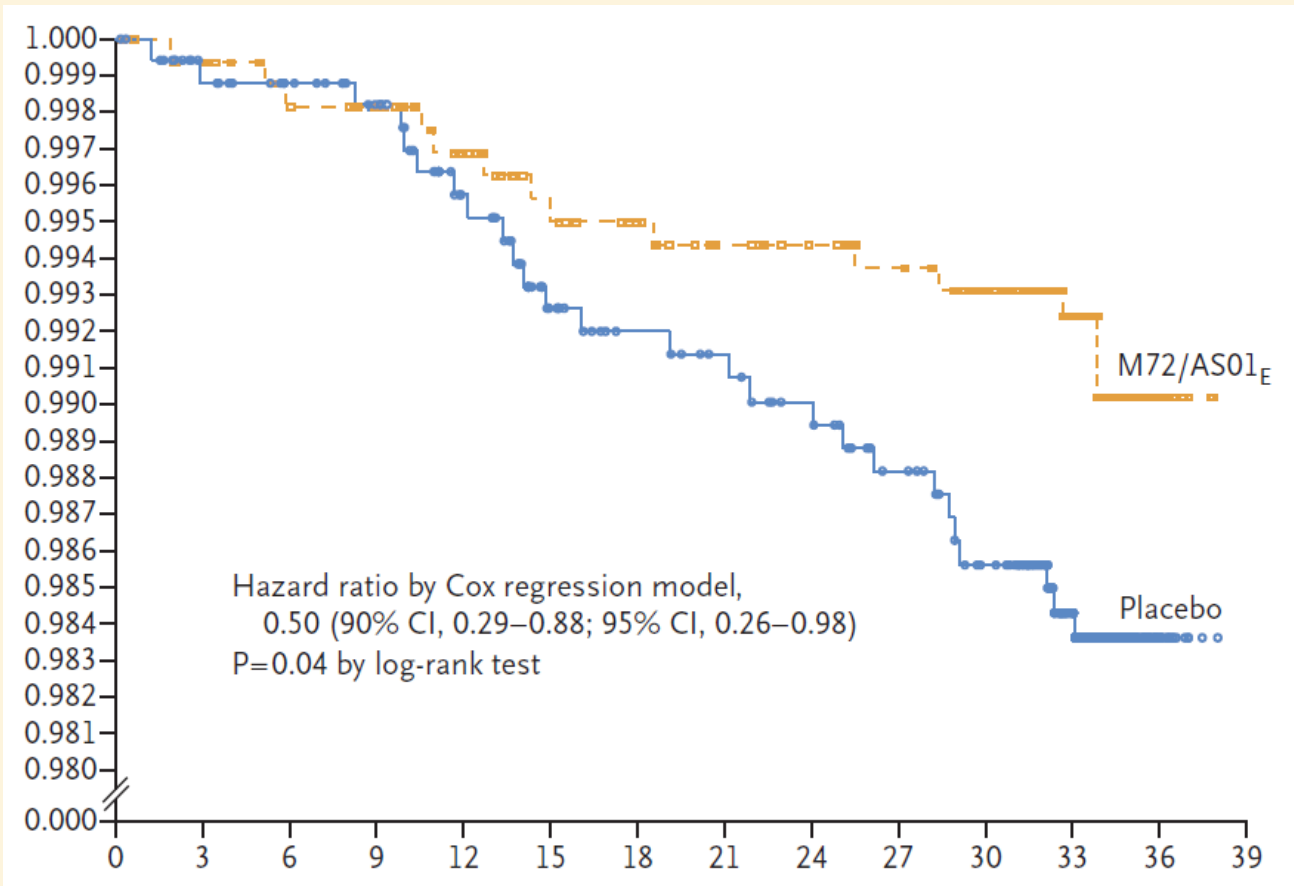
1. Agree on target pathogen and on target product profile (medical need, WHO PPC, country priorities)
2. Agree on assumed protective mechanism of action to induce
3. Agree on assumed protective antigen(s) and platform for antigen expression
4. Develop antigen manufacturing process and define critical quality attributes for the antigen(s)
5. Develop assays to assess immunogenicity
6. Evaluate immunogenicity in preclinical models
7. Evaluate efficacy in preclinical model
8. Evaluate safety & immunogenicity in humans (dose-range, schedule, age, priming, pre-existing conditions)
9. Assess efficacy, prevention of disease or prevention of infection (Phase 2b)
10. Agree with health authorities on data needed for registration (safety, efficacy, quality)
11. Agree with technical advisory groups & policy groups on data needed for recommendation & implementation
12. Design & execute Phase 3 registration trial(s)
13. File for registration ...

## **Proposed Indication for M72/AS01<sub>E-4</sub>**

**“Active immunization to prevent active pulmonary TB in children and adults, 15 years of age & older”**

# Phase 2b Results: Prevention of Disease (POD) in IGRA-positive adults

- Vaccine Efficacy Point Estimate: 50%
- Acceptable safety profile



DOI: [10.1056/NEJMoa1803484](https://doi.org/10.1056/NEJMoa1803484) & DOI: [10.1056/NEJMoa1909953](https://doi.org/10.1056/NEJMoa1909953)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Phase 2b Controlled Trial of M72/AS01<sub>E</sub> 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<sub>E</sub> Vaccine to Prevent Tuberculosis

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

# Phase 3 Vaccine Efficacy Trial Assumptions & Trial Design

- Vaccine Efficacy (VE) against Disease (D) in IGRA+ in per-protocol (PP) cohort is  $\geq 50\%$
- Null hypothesis:  $H_0: VE(D) \leq 10\%$  ( $\alpha < 2.5\%$ , lower bound of 95% confidence interval  $> 10\%$ )
- Event-triggered VE analysis
- TB incidence: 0.3% per year in IGRA+
- *Mtb* infection rate: 3% per year
- Placebo-controlled, double-blind, 1:1 randomized trial
- N=26,000, 15 to 44 years of age
- 2.5 years to full enrolment
- Follow-up up to 5 years after last participant is enrolled
- Interim analysis (IA) of primary endpoint once 100 cases are observed
- Opportunity to file for registration following IA if  $VE > 50\%$ ,  $LB > 10\%$
- Final analysis of primary endpoint once 150 cases are observed

Cohort	N
HIV-, IGRA+ cohort	20,000
HIV-, IGRA- cohort	4,000
HIV+ cohort	2,000
Total	26,000

## Data Anticipated at the End of Phase 3 to Support the Proposed Indication

- Phase 3 VE point estimate based on 150 cases of lab-confirmed pulmonary TB
- Supportive: Phase 2b VE data based on 39 cases
- Safety database on approx. 15,000 M72/AS01<sub>E-4</sub>-exposed trial participants from Phase 2b trial, Phase 2 MESA-TB trial, and Phase 3 trial
  - / ~ 11,700 baseline HIV-negative, IGRA-positive participants
  - / ~ 2,000 baseline HIV-negative, IGRA-negative participants
  - / ~ 1,300 PLHIV of either IGRA-status
- Phase 3 immunogenicity data on up to 400 participants per cohort (1,200)

To support the proposed indication for “Active immunization to prevent active pulmonary TB in children and adults, 15 years of age & older”

# TB Vaccine Development – challenges & mRNA enablers

1. Agree on target pathogen and on target product profile (medical need, WHO PPC, country priorities)
2. Agree on assumed protective mechanism of action to induce No Correlate of Protection yet
3. Agree on assumed protective antigen(s) and platform for antigen expression No Correlate of Protection yet
4. Develop antigen manufacturing process, define critical quality attributes, and manufacture & release vaccine lots
5. Develop assays to assess immunogenicity
6. Evaluate immunogenicity in preclinical models
7. Evaluate efficacy in preclinical model No predictive preclinical model yet
8. Evaluate safety & immunogenicity in humans (dose-range, schedule, age, priming, pre-existing conditions)
9. Assess efficacy for prevention of disease (Phase 2b) Large clinical endpoint trial
10. Agree with health authorities on data needed for registration (safety, efficacy, quality)
11. Agree with technical advisory groups & policy groups on data needed for recommendation & implementation
12. Design & execute Phase 3 registration trial(s) Even larger clinical endpoint trial
13. File for registration



# Thank you & Questions