7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

Driving innovation from discovery to access

Clinical development of new TB vaccines: State of the field

Elana van Brakel, IAVI

8 October 2024

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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

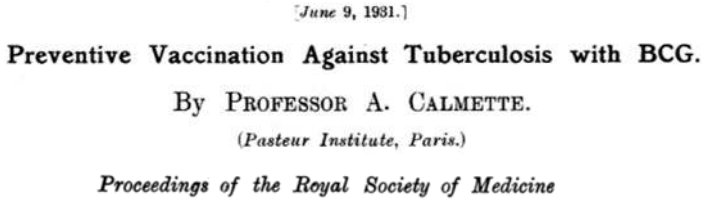
As of July 2024

Contents

The world urgently needs new TB vaccines

An estimated 10.6M people fell sick with TB and 1.3M died (2022)

1921 – First use of BCG in an infant
Proc R Soc Med 1931:241(11);1481-90.



[June 9, 1931.]

Preventive Vaccination Against Tuberculosis with BCG.

By PROFESSOR A. CALMETTE.

(Pasteur Institute, Paris.)

Proceedings of the Royal Society of Medicine

Box 2. The End TB Strategy at a glance

VISION	A WORLD FREE OF TB — zero deaths, disease and suffering due to TB			
GOAL	END THE GLOBAL TB EPIDEMIC			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	2030	2035
Percentage reduction in the absolute number of TB deaths[a] (compared with 2015 baseline)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of TB-affected households facing catastrophic total costs due to TB[b] (level in 2015 unknown)	0%	0%	0%	0%

WHO Global TB Report 2023

TB disease spectrum

No disease*

M.tb infection

No macroscopic pathology

Not infectious

No signs or symptoms

Disease*

Subclinical TB

Non-infectious

- Macroscopic pathology
- Not infectious
- No symptoms and signs

Infectious

- Macroscopic pathology
- Infectious
- No symptoms and signs

Clinical TB

Non-infectious

- Macroscopic pathology
- Not infectious
- Symptoms and signs

Infectious

- Macroscopic pathology
- Infectious
- Symptoms and signs

Coussens et al. Lancet Resp Med 2024

*All states have viable Mycobacterium tuberculosis and a host response

Strategies for TB vaccine development

Endpoint definition

Garcia-Basteiro et.al., Eur Resp rev 2022

Pre-*M.tb* infection: **Prevention of Infection (POI)**

- Steppingstone to larger efficacy trials?
- Indirect tests of *M.tb* infection: cellular immune response to *M.tb* antigen exposure
- More stringent endpoint of sustained IGRA conversion (persistent *M.tb* infection)

Post-*M.tb* infection: **Prevention of Disease (POD) *NB strategy to meet End TB 2035 goals**

- Optimize endpoint selection: “What is the definition of TB disease?”
  - Reduce rate of incident TB OR development of any TB, incl. subclinical TB
    - Symptoms + microbiological confirmation / serial sputum tests for all new potentially contagious cases impacting transmission

Immunotherapeutic: Therapeutic/**Prevention of Recurrence (POR)**

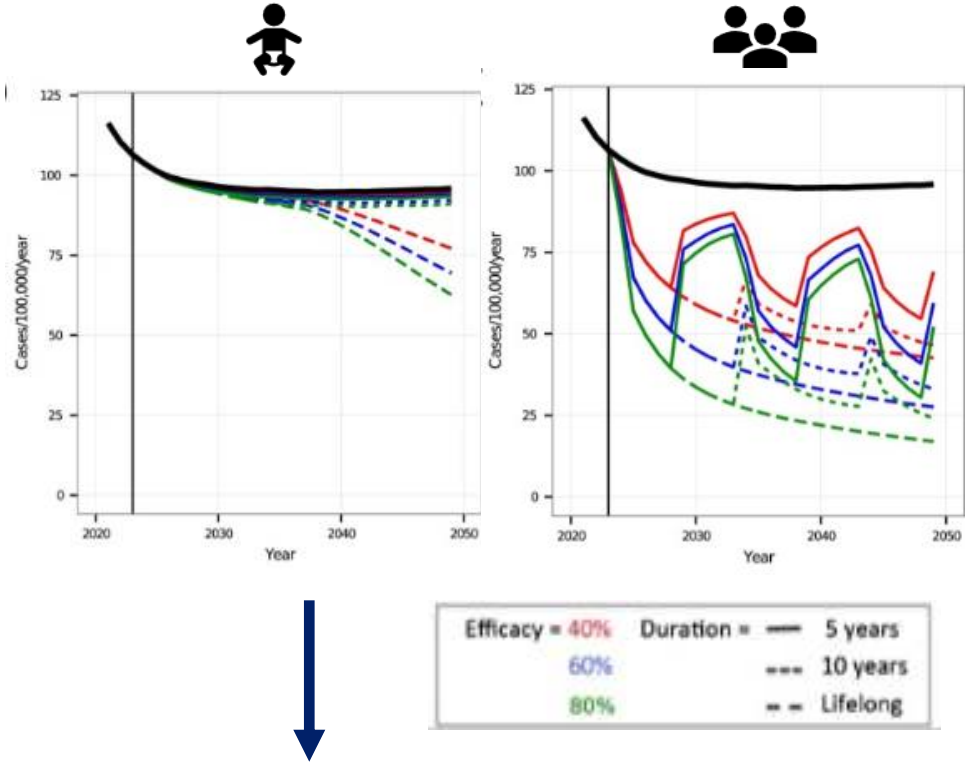
- Shorten course of chemotherapy for active TB/Prevent recurrence
- Timing of vaccination important
- Potential to fast-track vaccine development?

Prevention of subclinical TB disease as an endpoint?

Join us in Plenary 3! Chuchyard et. al., Lancet Microbe 2024

Strategies for TB vaccine development

New TB vaccines for infants or for adolescents and adults



TB DISEASE AVERTED

VACCINE FOR ADOLESCENTS AND ADULTS
37.2–76 million

VACCINE FOR INFANTS
5.8–18.8 million

DEATHS AVERTED

VACCINE FOR ADOLESCENTS AND ADULTS
4.6–8.5 million

VACCINE FOR INFANTS
0.8–2.6 million

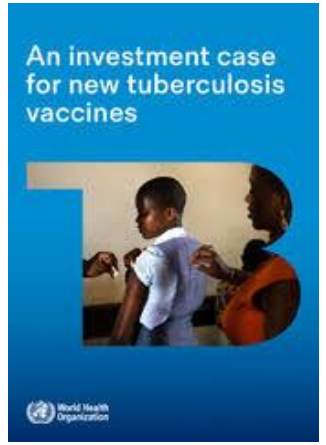
Almost 90% of people with TB disease are adolescents and adults

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‡]



VACCINE FOR ADOLESCENTS AND ADULTS
US$ 372 (283–474) billion averted

VACCINE FOR INFANTS
US$ 68.6 (44.5–100) billion averted

Adult vaccine with only 40% VE and 5-year protection will have more impact on TB incidence by 2050 due to reduction in *M.tb* transmission than an infant vaccine with 80% VE and lifelong protection

Knight et. al., Proc Natl Acad Sci USA 2014

14 Candidates + BCG
(12 in active trials)

<u>3 mycobacterial live-attenuated</u>
- *M. tuberculosis* (MTBVAC)
- rBCG (VPM1002)
- BCG (traveler)

<u>3 mycobacterial inactivated</u>
- *M. obuense* (DAR-901)
- *M. tuberculosis* (RUTI)
- *M. indicus pranii* (Immuvac (MIP))

<u>5 Protein/Adjuvant</u>
- M72/AS01$_E$
- GamTBvac
- ID93+GLA-SE (QTP101)
- AEC/BC02
- H107/CAF10b

<u>2 Viral vector</u>
- ChadOx185A
- TB/FLU-05E

<u>2 mRNA</u>
- BNT164a1
- BNT164b1

TB Vaccine Pipeline

Vaccine candidates under clinical development

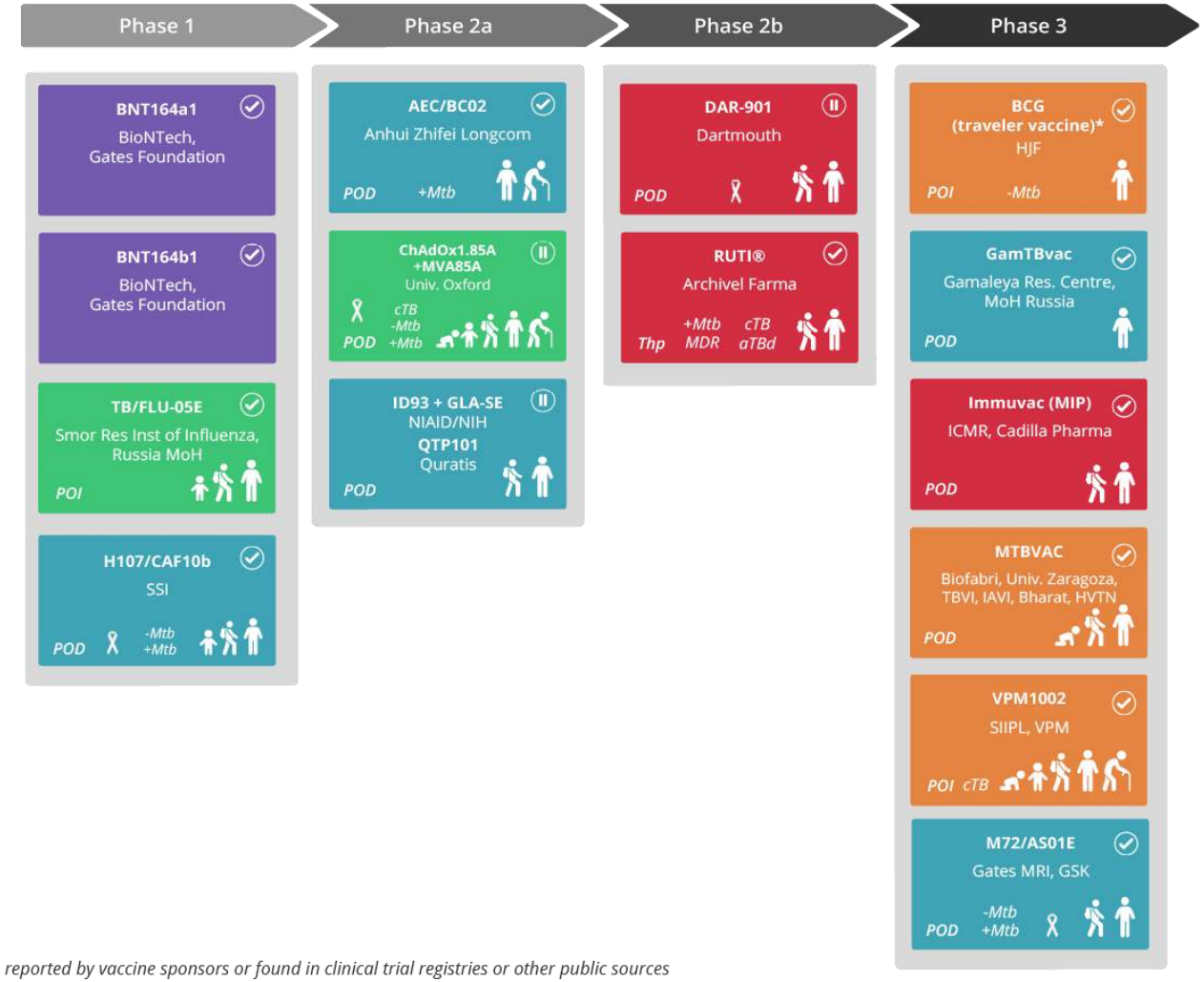
There are 15 vaccine candidates in the pipeline as of September 2024, of which 12 are in active trials. The candidates are placed under the phase which corresponds to the most advanced ongoing or completed trial.

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

Trial staus
- Active trials
- No active trials

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

Primary candidate indication
- *POI* Prevention of Infection
- *POD* Prevention of Disease
- *POR* Prevention of Recurrence
- *Thp* Therapeutic



Stop TB Partnership
WORKING GROUP ON NEW TB VACCINES

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

Institutions listed are vaccine sponsors and development partners

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

Last update: 2 September 2024

Current pipeline

Strengths

Late-stage trials

Exciting candidates in POD late-stage development

Trials contributing to correlates of immune protection biorepositories

Vaccine platform diversity

Mycobacterial live-attenuated and inactivated

Protein/adjuvant subunit vaccines

Viral vectors

First-ever TB vaccine constructs based on mRNA entered Ph 1 testing

Trial populations

Adolescent and adults in late-stage POD trials

HIV exposed, uninfected infants in VPM1002 and MTBVAC Ph 3

Better representation of PLHIV

- HIV/AIDS Clinical Trials Networks (NIH) increasing TB vaccine activity

Household contacts enrolled in Ph3 POD trial

Current pipeline

Weaknesses: "Inverted" nature

Number of candidates

Relatively few in preclinical and early clinical development

Few novel candidates in Ph 1-2

BCG revaccination and subunit vaccine H56:IC31 not in current pipeline

"Vaccine development approach too narrow"

Lack of antigenic diversity

Limited set of candidate *M.tb* antigens currently considered

Suboptimal in eliciting protection?

- Stimulating classical CD4+ T helper (Th1) cells
- Antigens that are known *M.tb* virulence factors

Routes of administration

Lack of varying routes of administration:

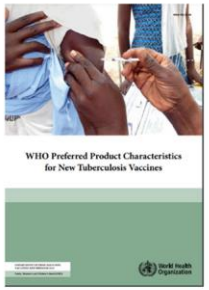
- Intramuscular and intradermal administration predominantly
- One candidate for aerosol/intranasal administration

Ethical consensus on how to incorporate TB preventive therapy (TPT) into TB vaccine trials
Rangaka et.el., Lancet Resp Med 2023

WHO Preferred Product Characteristics (PPC)

Efficacy targets against prevention of disease in adolescents and adults

In 2014, WHO developed guidance on the preferred product characteristics for new vaccines to inform developers



The WHO PPC document captures most key clinical and regulatory considerations for TB vaccines:

- ✓ Indication
- ✓ Target population
- ✓ Outcome measure; efficacy
- ✓ Duration of protection (at licensure; eventually)
- ✓ Safety
- ✓ Schedule
- ✓ Co-administration

Please see WHO vaccine PPC & Roadmap guidance documents under: Product Development for Vaccines Advisory Committee and PPCs

VI. PPC FOR NEW TUBERCULOSIS VACCINES: USE IN ADOLESCENTS AND ADULTS

Parameter	Preferred Characteristic	Comments
Indication	Immunization for prevention of active pulmonary TB disease.	
Target population	Adolescents and adults.	Adolescents and adults with TB disease represent the most common sources of *Mtb* spread and are therefore the WHO priority target for TB vaccine development. Demographic changes in some high endemicity countries justify inclusion of older adults in the target population. The optimal timing for paediatric evaluation should be discussed with regulators and policy makers but a paediatric clinical development program should certainly be considered when proof of concept is established in adolescents and adults.
Outcome measure and efficacy	50% or greater efficacy in preventing confirmed pulmonary TB.	A vaccine with lesser vaccine efficacy against confirmed TB in adolescents and adults, if widely used in areas of high TB endemicity, may still prove valuable and contribute to reducing the spread of *Mtb* in a cost-effective way *(4)*, but this would fall short of the requirements necessary to meet the End TB goals by the 2035 target date.
Schedule	A minimal number of doses and boosters required.	A requirement for more than three doses to achieve primary immunization would not be desirable due to logistical and cost concerns.

http://apps.who.int/iris/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf5

World Health Organization

Adolescents and adults

- 50% or greater efficacy
- Protect with/post- and pre-*M.tb* infection
- Protect in diverse geographies
- Safe in PLHIV, elderly, pregnancy
- 10+ years protection

Infants

- Superior efficacy and safety vs BCG
- Safe in HIV-infected infants
- 10+ years protection

M72/AS01E Ph2b results:

- TB cases meeting first case definition, sensitivity analysis and confirmed by at least 2 bacteriologic tests
- **VE:68%, LB 95% CI = 25%**
- **A POTENTIALLY LICENSABLE TARGET**

Late-stage trials

Setbacks and advances

PO(S)I: BCG REVAX

NCT04152161

BCG vaccine SSI vs placebo

Adolescents

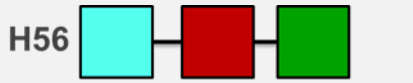
Phase 2b: BCG revaccination of healthy adolescents to prevent sustained *M.tb* infection

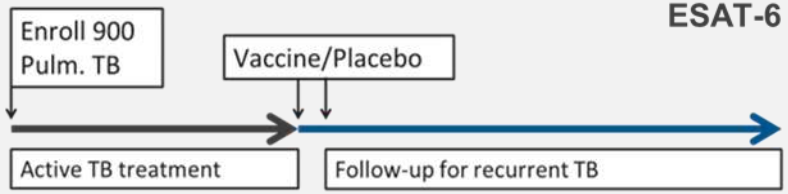
POR: H56:IC31 - Subunit

NCT03512249

Adults

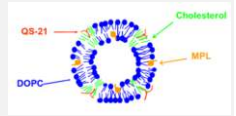
Phase 2:





POD: M72/AS01$_E$ – Subunit

NCT06062238



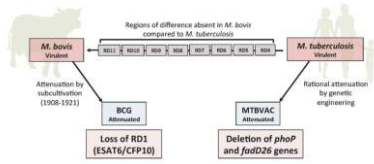
Phase 3:

Efficacy and pivotal registration trial

Adults and adolescents 15-44 years of age

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

POD: MTBVAC – *M.tb* live attenuated



Phase 3 Infants NCT04975178

Phase 2a safety and immunogenicity in PLHIV NCT05947890

Phase 2b (IMAGINE trial) Adolescents & Adults NCT06272812

More details will be provided in Plenary 3!

Strategies to accelerate TB vaccine development

Correlates of immune protection

Collect biospecimens to identify CoP in all ongoing and planned late-stage trials

Identify CoP for TB disease from ph2 and ph3 trials that have shown protection

Validate CoP for TB disease

- Immunogenicity studies
- New trials with clinical POD endpoint
- Controlled human infection model (CHIM)

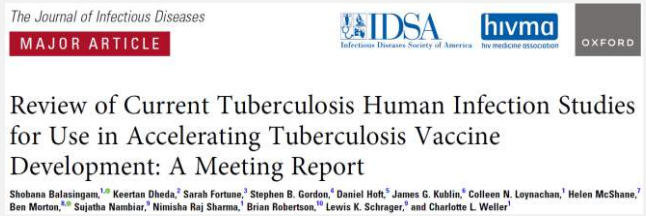
Controlled human infection models

Facilitate breakthroughs in understanding disease pathogenesis

Identify CoP

Develop diagnostic tools

De-risk vaccine development


The Journal of Infectious Diseases
MAJOR ARTICLE

Review of Current Tuberculosis Human Infection Studies for Use in Accelerating Tuberculosis Vaccine Development: A Meeting Report

Shobana Balasingam,[1,a] Keertan Dheda,[2] Sarah Fortune,[3] Stephen B. Gordon,[4] Daniel Hoft,[5] James G. Kublin,[6] Colleen N. Loynachan,[1] Helen McShane,[7] Ben Morton,[8,9] Sujatha Nambiar,[1] Nimisha Raj Sharma,[1] Brian Robertson,[10] Lewis K. Schrager,[1] and Charlotte L. Weller[1]

Clinical trials

Standardized POD endpoints that better capture TB disease states in diverse target populations

Better POI endpoints

Quantify clinical translation of POI into POD

Harmonize clinical trial protocols

More efficient trial designs

Trial site capacity

Promote community engagement

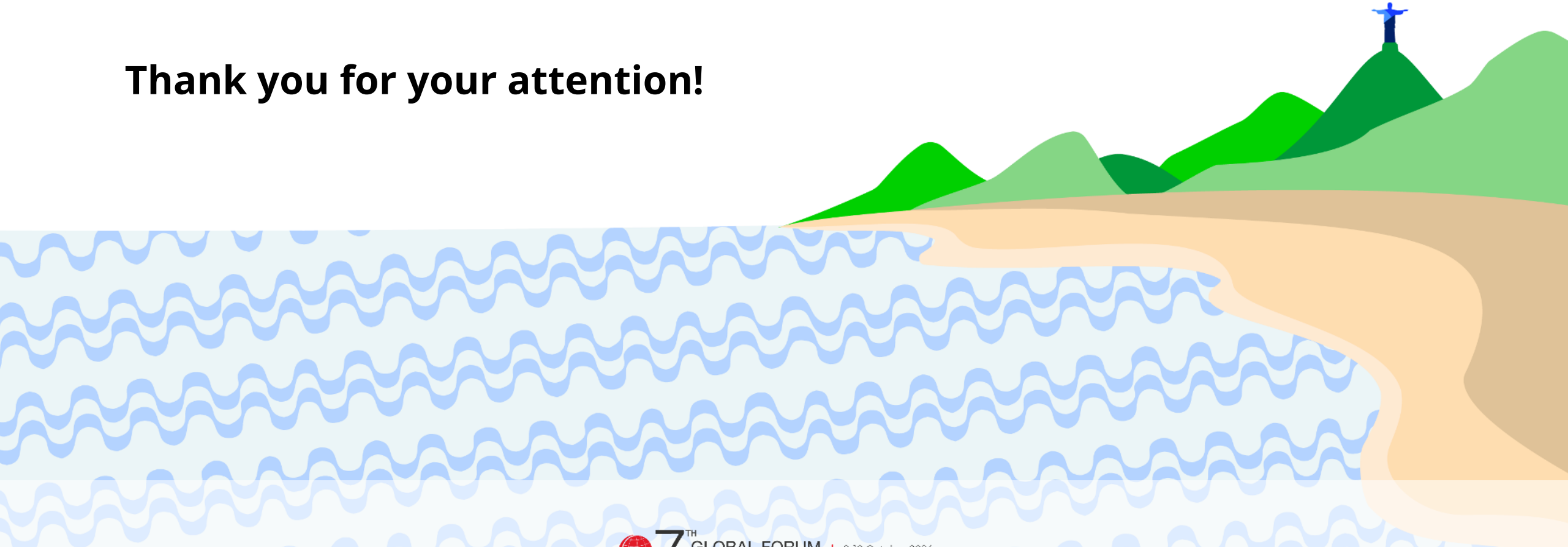
http://www.edctp.org/web/app/uploads/2021/04/TB-Vaccine-Roadmap-Background-document.pdf

Conclusion

1. Vaccines are the only way to meet the End TB goals
2. Vaccination of adults and adolescents for a POD indication is the most effective means of meeting these goals
3. Increasing focus on subclinical TB and inclusion in POD endpoints
4. **Late-stage trails that have the potential to deliver long-awaited new TB vaccines**
   - **Efficacy trials with promising constructs: M72/AS01$_E$ and MTBVAC**
5. Collaborations to identify immune correlates of protection using samples from two successful phase 2 studies (M72 and BCG Correlates) with current and planned late-stage trials also contributing (M72 phase 3, MTBVAC)
6. mRNA vaccine candidates in phase 1 trials
7. Roadmap with various strategies to diversify the pipeline and to accelerate clinical development

This is a historic time for TB vaccine development!

Thank you for your attention!



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Driving innovation from discovery to access

An international convening of the

Stop TB Partnership

WORKING GROUP ON NEW TB VACCINES

iavi

Translating science into global health impact

TBVI

TuBerculosis Vaccine Initiative

Organized in collaboration with

SUS

MINISTÉRIO DA SAÚDE

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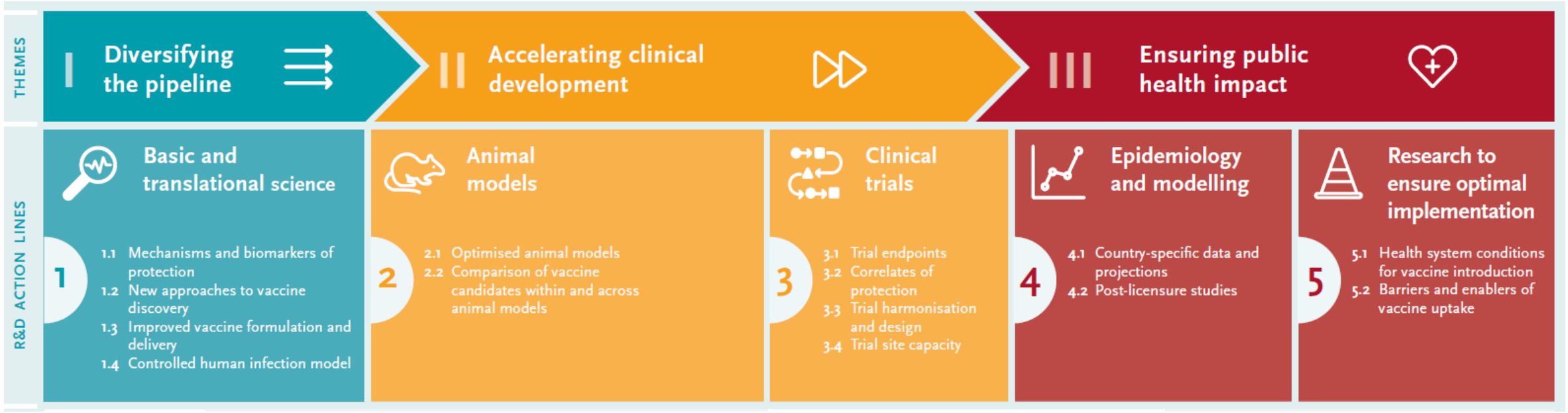
REDE-TB

Back-up slides

Strategies to accelerate clinical development



http://www.edctp.org/web/app/uploads/2021/04/TB-Vaccine-Roadmap-Background-document.pdf

- Predictive animal model(s) and a more robust and diverse preclinical pipeline
- Correlate(s) of immune protection
- Induce mucosal immune response: New vaccine concepts, adjuvants, platforms, administration routes
- Controlled human infection models to close basic knowledge gaps and down-select candidates, platforms
- Standardized POD endpoints (HIV status, *M.tb* infection status, age and geography effects on vaccine efficacy
- Better POI endpoints
- Prepare for access, adoption and delivery to end users

Strategies to diversify the pipeline

Beyond CD4+ Th1 cells

Role of non-conventional cellular immunity, antibody responses and trained immunity

Correlates of immune protection to identify biomarkers and biosignatures that correlate with vaccine-induced protection

New approaches to discovery

New vaccine concepts that can induce alternative immune responses

Mucosal immune responses

Genome-wide strategies for antigen discovery

Improved formulation & delivery

Different adjuvants, vaccine platforms and *M.tb* challenge strains

New routes of vaccine administration

- Aerosol
- IV

Delivery platforms to induce mucosal immune responses

Controlled human infection models

Immunobiology studies:

- Close gaps in basic knowledge
- Inform down-selection of candidate vaccines, platforms and routes of administration