TB Vaccines and Therapeutics: The Opportunities

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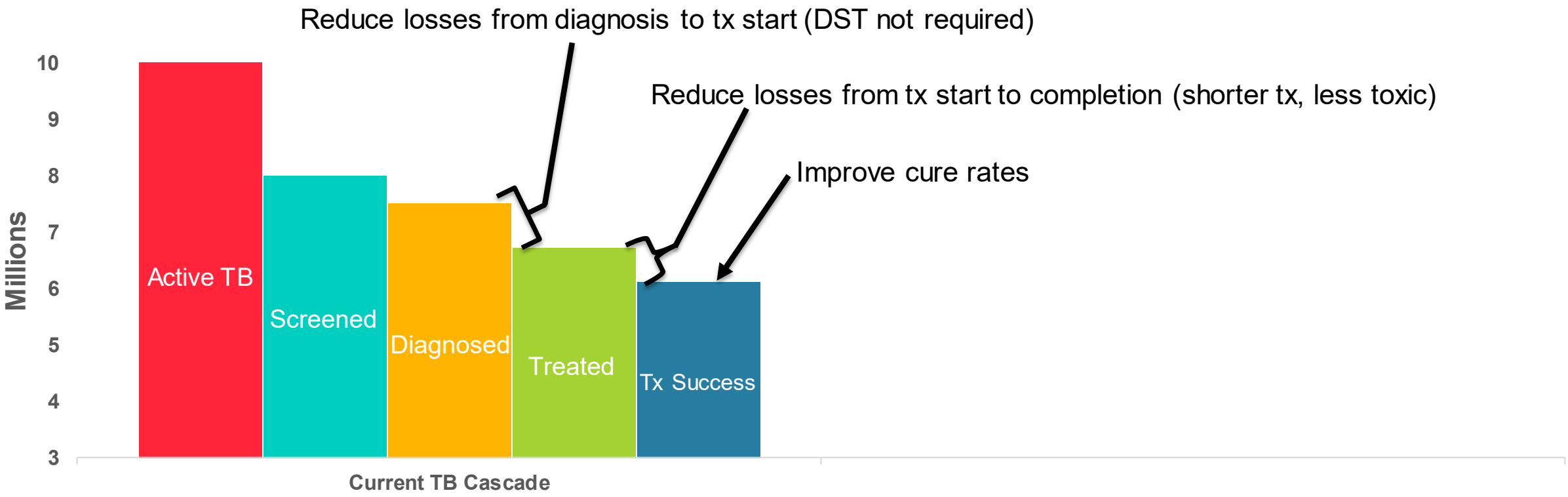
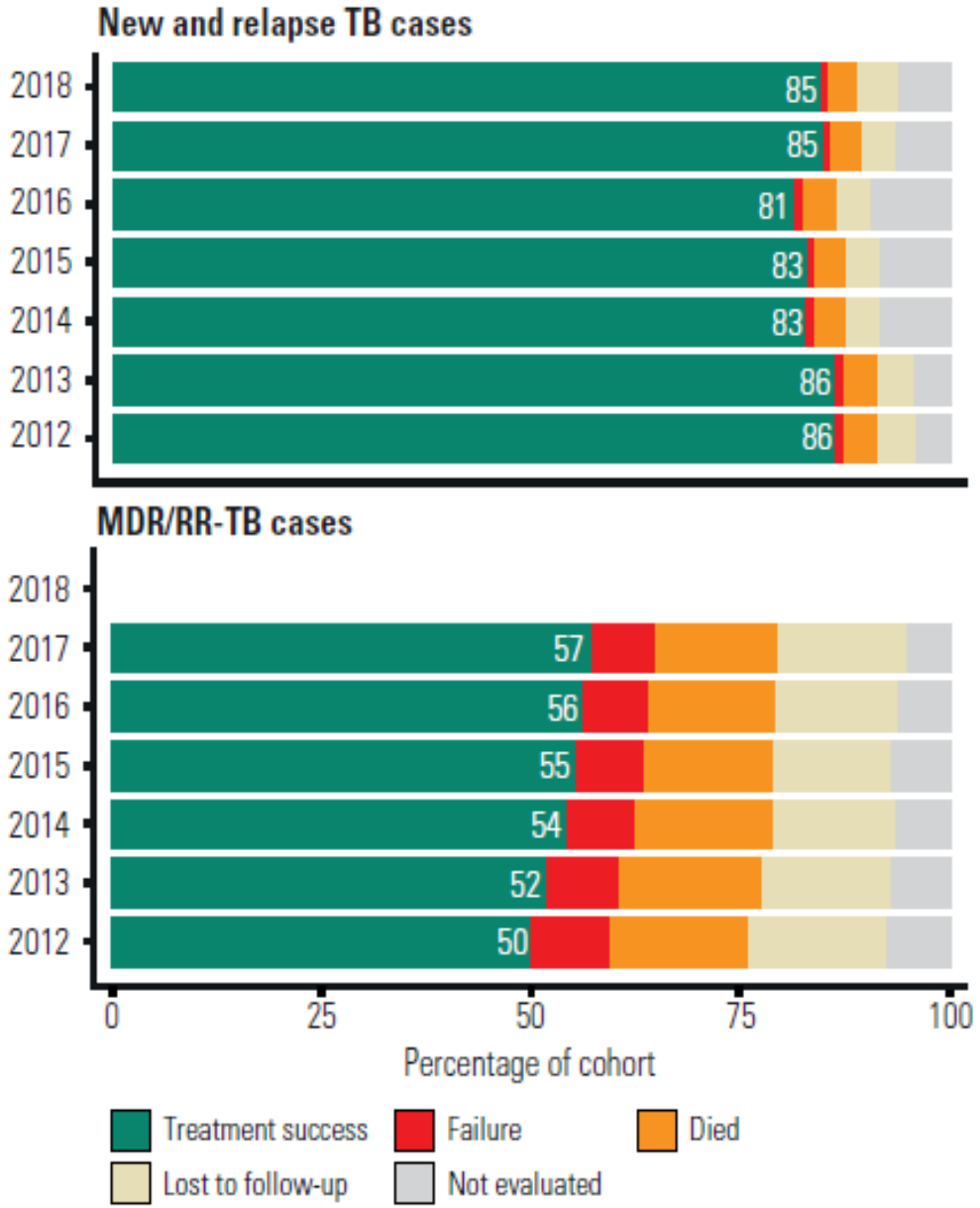
RATIONALE FOR IMPROVED TREATMENT PARADIGM



RATIONALE FOR NOVEL REGIMENS

- Issues with current standard of care
  - Too long
    - 6 months duration → ↑ loss to follow-up
  - Too toxic
    - Hepatitis, neuropathy, eye toxicity, skin reaction, joint pains
  - Too many drug interactions
    - Most important: Hormonal contraceptives and HIV antiretrovirals
- Current DS TB treatment success rates stagnant for years
- Standards of MDR TB treatment changing rapidly but still long & toxic

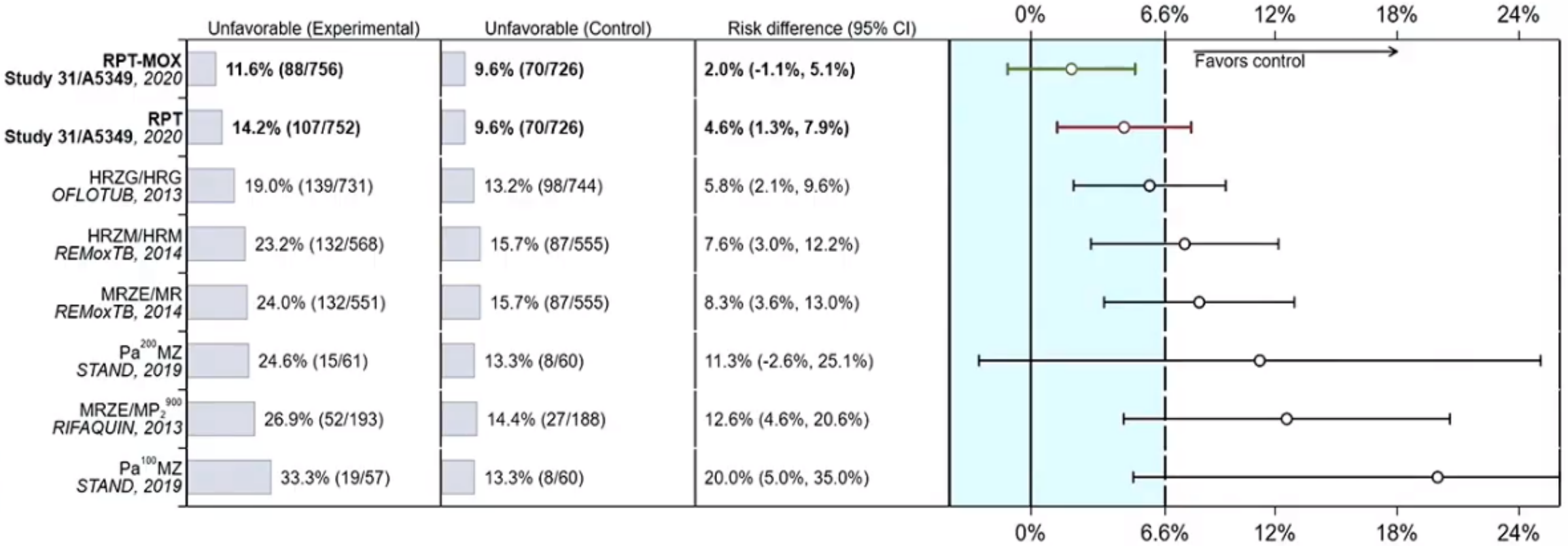


OPTIMAL TARGET REGIMEN PROFILE
ENABLE "TEST AND TREAT" PARADIGM

TPP Criteria	Hypothesis
Pan TB	No DST required; fewer patients lost to system after diagnosis
Shorter	≤ 3 months → improves adherence → improves outcomes → less transmission
Safe	No baseline/ongoing safety monitoring; well tolerated → improves adherence
Simpler	All Oral (no injectables), QD administration, no DDIs to manage
Efficacy	Short, forgiving regimen non-inferior to SoC to minimize efficacy – effectiveness gap
Affordable	Low barrier to uptake

A history of 4-month DS-TB regimens in RCTs

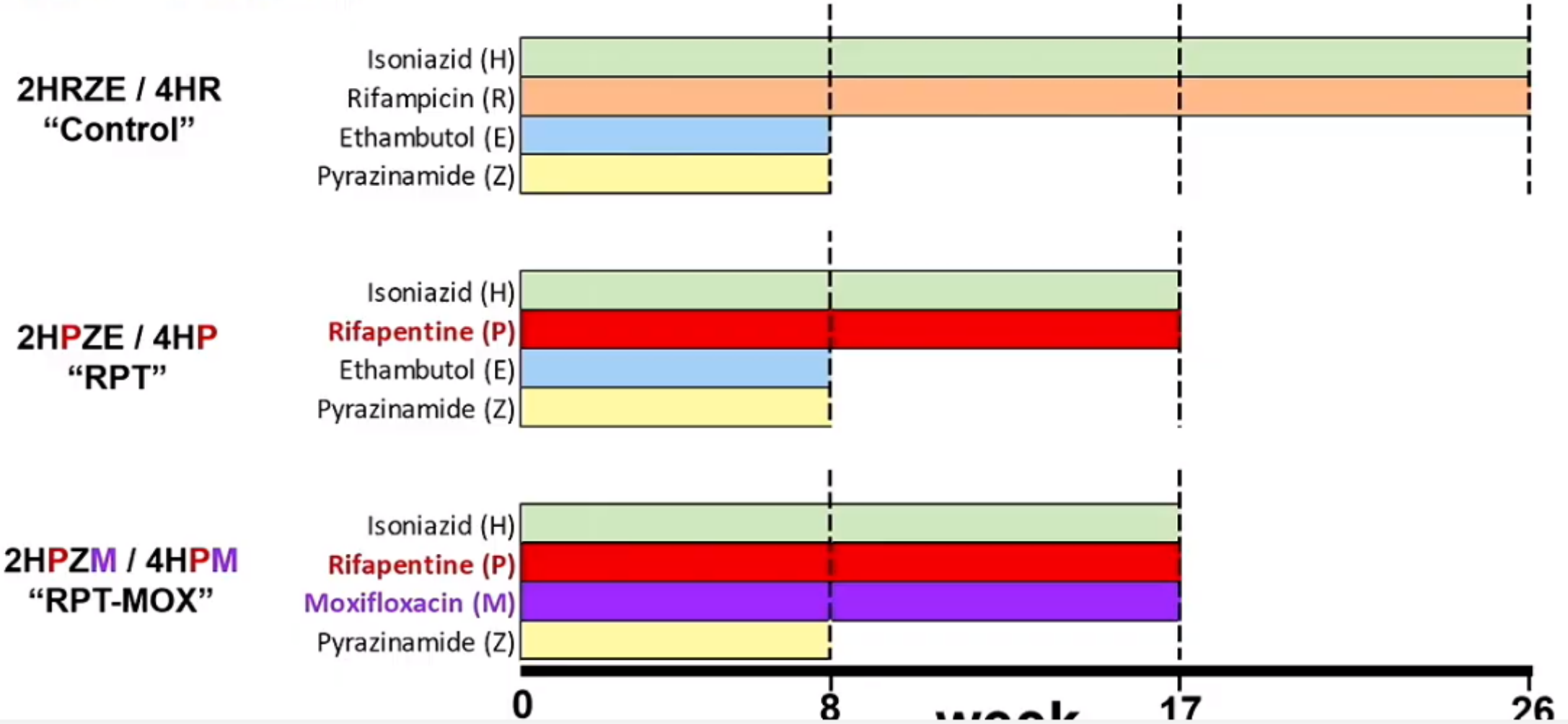
Assessable analysis population (often labelled as 'MITT' in other trials)



E – Ethambutol, G – Gatifloxacin, H – Isoniazid, R – Rifampicin, M – Moxifloxacin, P – Rifapentine, Pa - Pretomanid

S31/A5349 Interventions

All treatment 7 days/week *rifapentine 1200 mg qd* *moxifloxacin 400 mg qd*



2021 Global New TB Drug Pipeline [1]

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

PanD inhibitors
- Indazole sulfonamides

Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors

Mtb energy metabolism
- Macrolides
- Mycobacterial Gyrase Inhibitors

Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase

Oxazolidinones

Early Stage Development
- JSF-3285*
- MPL-446, 447*
- CPZEN-45*
- NTB-3119*
- TB-47*
- TZY-5-84
- FNDR-20081*
- Spectinamide – 1810*

GMP / GLP Tox.
- GSK-839*
- OTB-658
- Sanfetrinem

Phase 1
- BVL-GSK098*
- GSK-286*
- TBAJ-587
- TBAJ-876
- TBI-223
- Macozinone* (PBTZ-169)
- TBI-166

Phase 2
- SPR720*
- BTZ-043*
- TBA-7371*
- GSK-656* (070)
- OPC-167832*
- Delpazolid
- Sutezolid
- Telacebec* (Q203)
- SQ-109*
- Macozinone*

Regulatory Market Approvals
- Bedaquiline*
- Delamanid*
- Pretomanid*
- Rifapentine / Moxifloxacin (4-month regimen)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical. Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2020

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2021

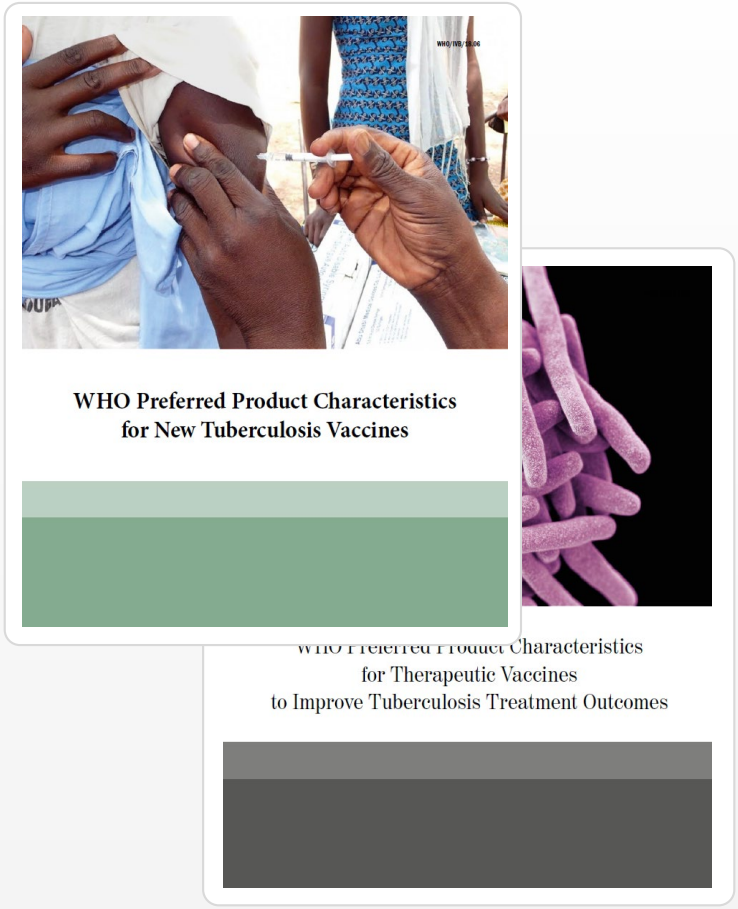
The TB Drug Accelerator

Tuberculosis Drug Accelerator

PAN-TB Collaboration

Focused on achieving Pan-TB Target Regimen Profile

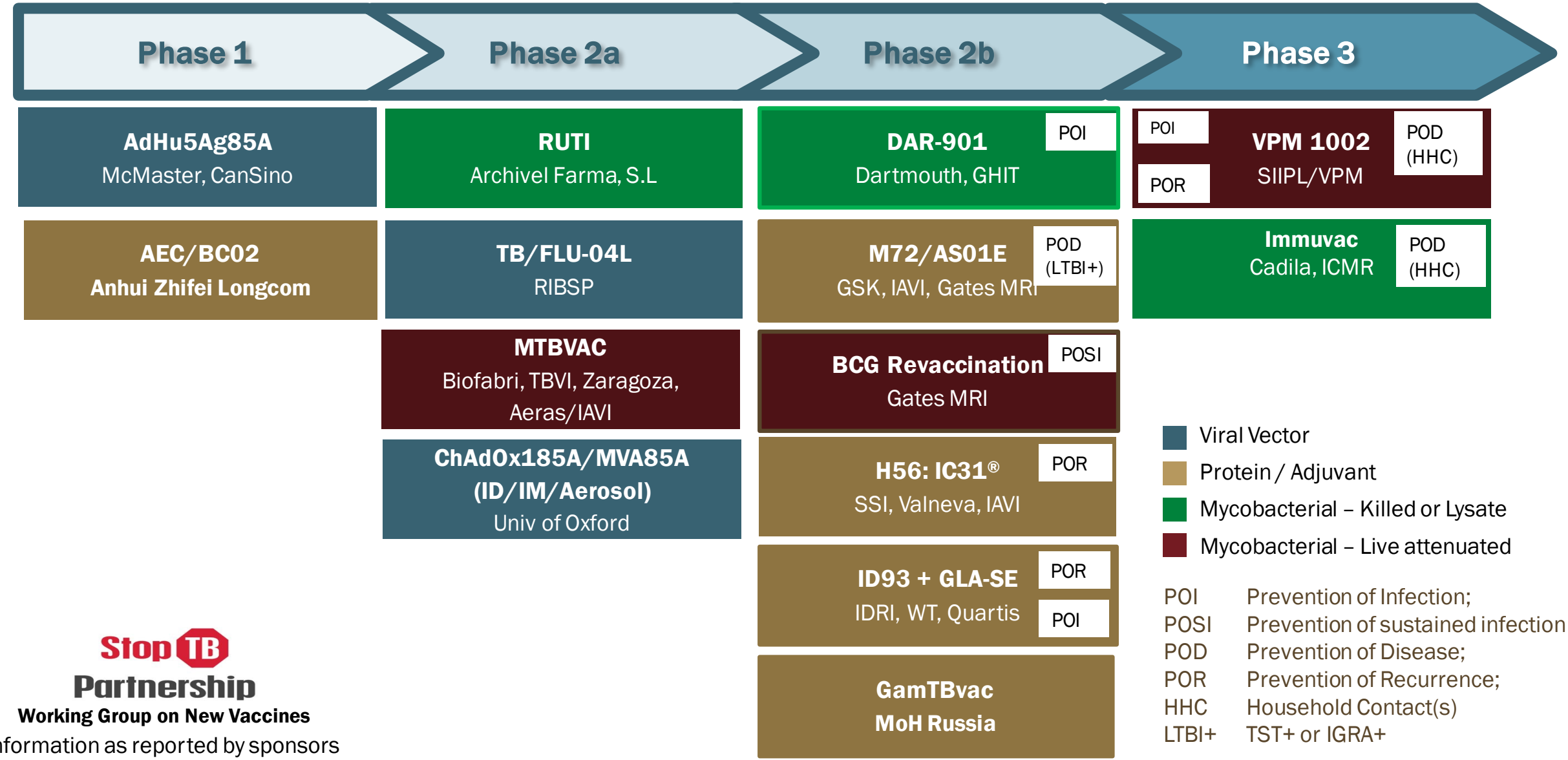
NEW TB VACCINES ARE NEEDED TO ACCELERATE THE END OF THE TB EPIDEMIC



WHO priority targets:

1. Developing a safe, effective and affordable TB vaccine for adolescents and adults
   - Immunization for **P**revention **O**f active pulmonary TB **D**isease (POD)
   - **P**revention **O**f *Mtb* **I**nfection (POI) if relationship btw. POI and POD can be established
2. Developing an affordable TB vaccine for neonates and infants with improved safety and efficacy as compared to BCG
   - Prevention of TB disease, including severe, disseminated TB, TB meningitis and pulmonary TB, in infants and young children
3. Therapeutic Vaccines
   - Protection against TB recurrence, following initial cure
   - Increase the proportion of cure at end of drug treatment

GLOBAL CLINICAL PIPELINE OF CANDIDATE TB VACCINES



Stop TB Partnership
Working Group on New Vaccines
Information as reported by sponsors

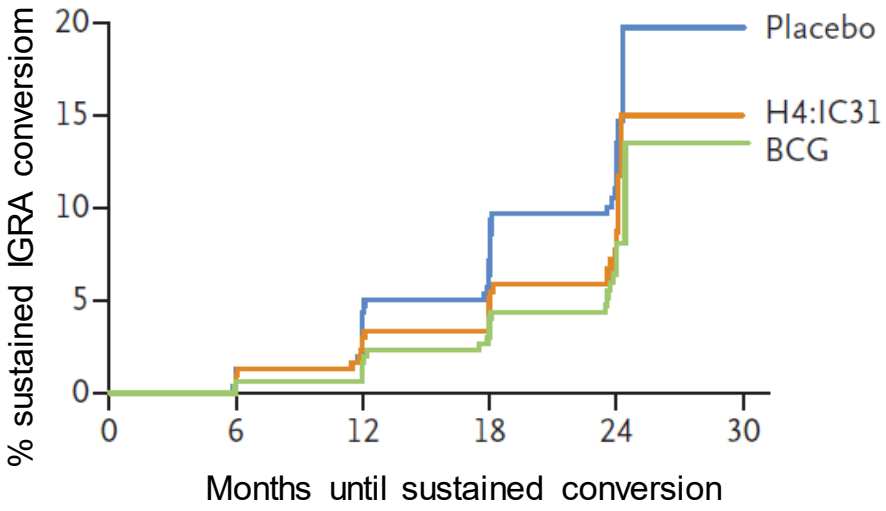
BCG REVACCINATION OF ADOLESCENTS FOR POSI

Aeras C-040-404 trial: 330 participants per group

- BCG Revaccination is associated with 45%: reduction in sustained IGRA conversion

ORIGINAL ARTICLE

Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination



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

Gates MRI BCG ReVax trial

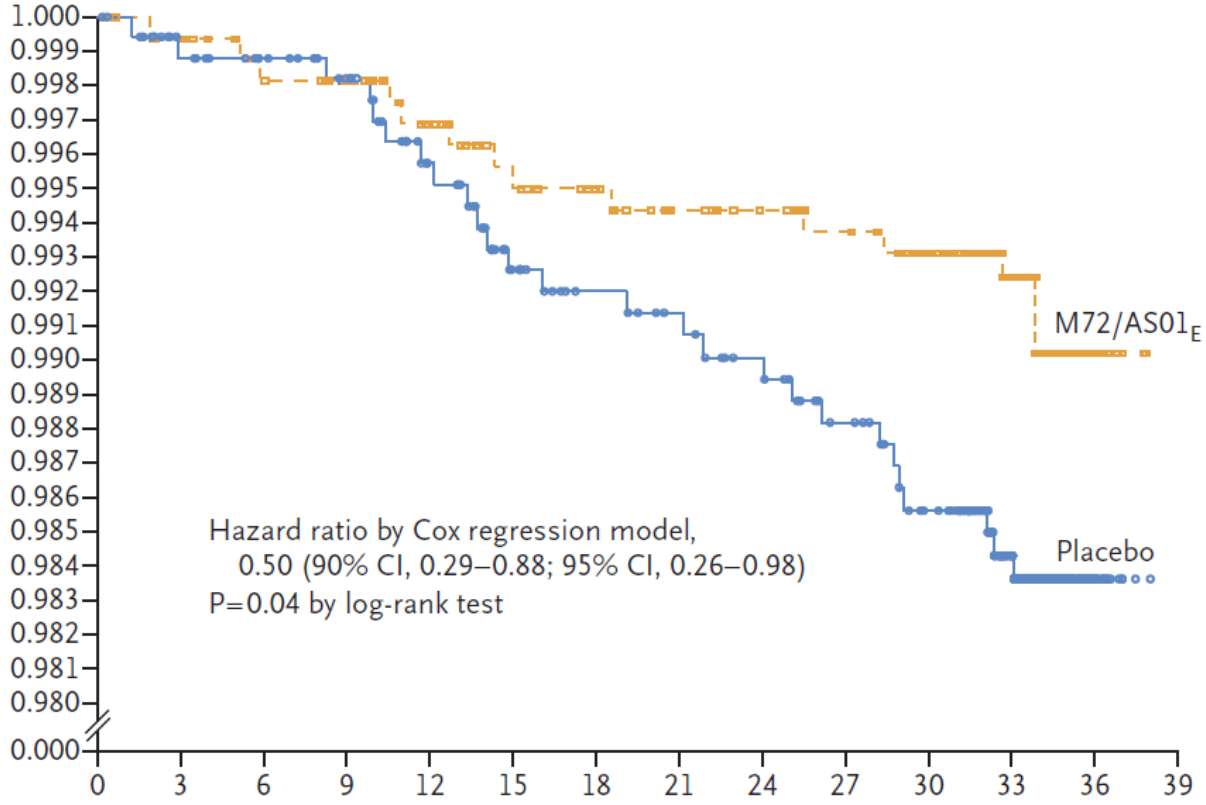
- Randomized, controlled, observer-blind Phase 2b trial
- 1,800 IGRA-negative participants 10-18 years of age are randomized 1:1 to receive BCG or placebo
- Follow-up for 48 months with biannual IGRA test & post- conversion evaluation
- Primary objective: To demonstrate the efficacy of BCG revaccination against sustained *Mtb* infection
- Event-triggered analysis once 118 cases are observed
- Other objectives (selected):
  - Evaluate safety & reactogenicity
  - Evaluate durability of efficacy
  - Explore and/or develop candidate correlates of risk (CoRs) and correlates of protection (CoPs)

ClinicalTrials.gov NCT04152161

M72/AS01$_E$ & PREVENTION OF TB DISEASE

PHASE 2B TRIAL IN A IGRA-POSITIVE POPULATION

- Vaccine Efficacy (VE) 49.7% (95% CI 2.1 to 74.2%)
- 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

DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

M72/AS01$_E$ PRODUCT DEVELOPMENT

Gates MRI obtained a commercial license from GSK to enable continued development and potential use in LMICs

CMC

- Process development
- Scale up manufacturing for Phase 3 & commercial supply
- Develop release assays
- Develop look-alike placebo
- Status: Work ongoing, Phase 3 material release expected in late 2022

Phase 2 trial in PLHIV

- Goal: enable inclusion of PLHIV in pivotal Phase 3 trial
- Randomized, controlled, observer-blind Phase 2 trial in 400 PLHIV 16-35 yoa in South Africa
- Status: Enrolment completed in July 2021

Epi study & capacity

- Goal: Identify clinical trial sites with very high incidence of TB and build Phase 3 capacity where needed
- Enrol 8,000 participants 15-34 years of age at 50 sites in 12 to 15 countries
- Determine IGRA positivity by site by age at baseline and conduct active & enhanced passive TB surveillance, switch to Phase 3 asap
- Status: Enrolment start in Q1 2022

Phase 3 VE trial

- Goal: Demonstrate VE for POD & support licensure irrespective of IGRA status, incl. PLHIV
- Global study in Africa, Asia and LatAm
- Up to 20,000 participants, incl. PLHIV and IGRA-negative participants
- Intended first dossier submission in South Africa
- Status: Enrolment start in 2023

Perspectives

- After COVID-19 is (hopefully) brought under control, TB will return to being the largest infectious disease cause of global mortality.

- The ongoing response against COVID has demonstrated the importance of focused political commitment/coordination, and enhanced funding to address the challenges.

- The technical/scientific “substrates” for improved and impactful TB therapies and vaccines exist. Their continued development requires (minimally) the same level of global engagement and funding as that for the COVID response.

