THE TB DRUG LANDSCAPE AND CHALLENGES

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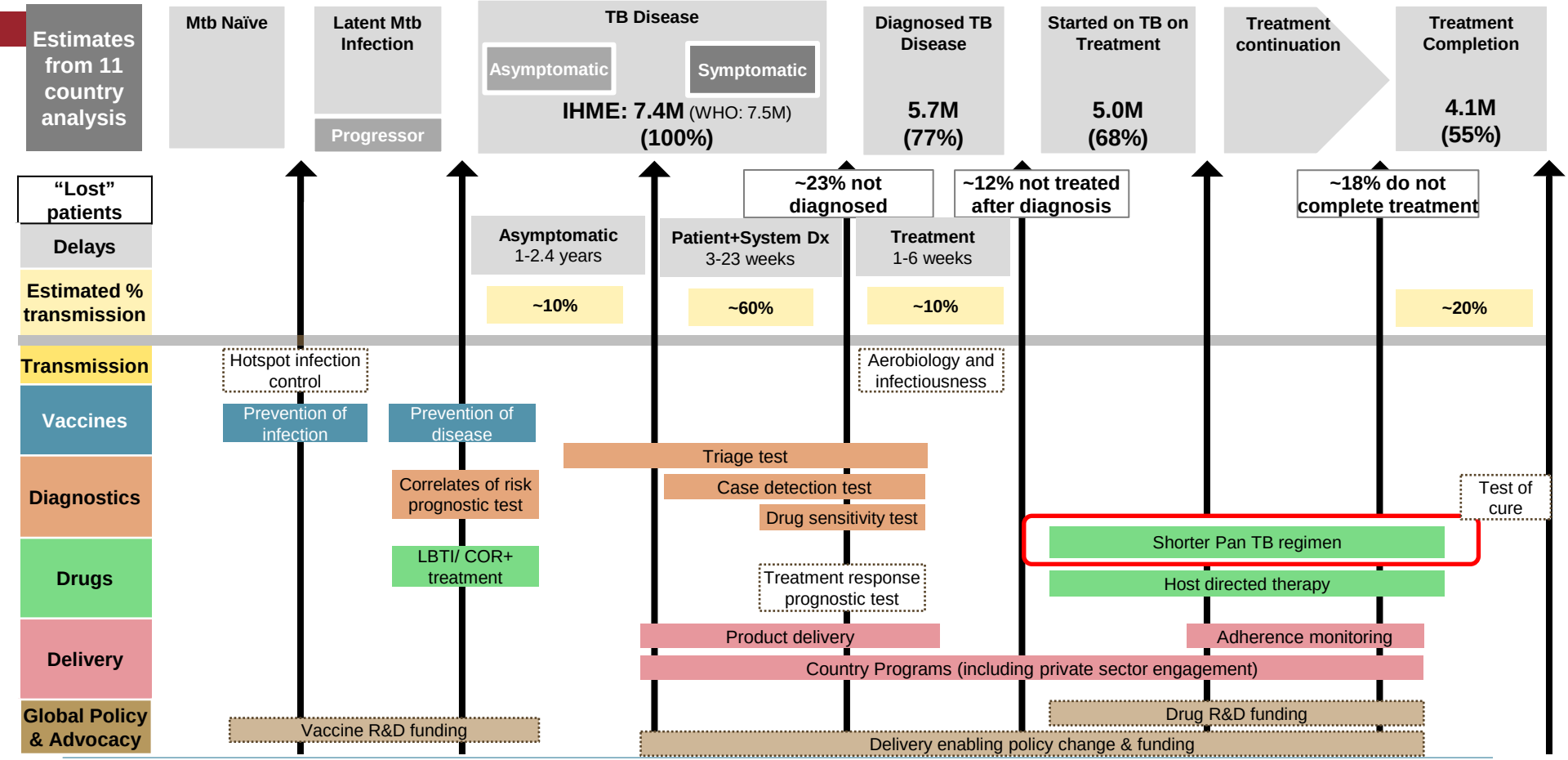
PATIENT PATHWAY ANALYSIS INDICATES MULTIPLE OPPORTUNITIES FOR IMPROVEMENT



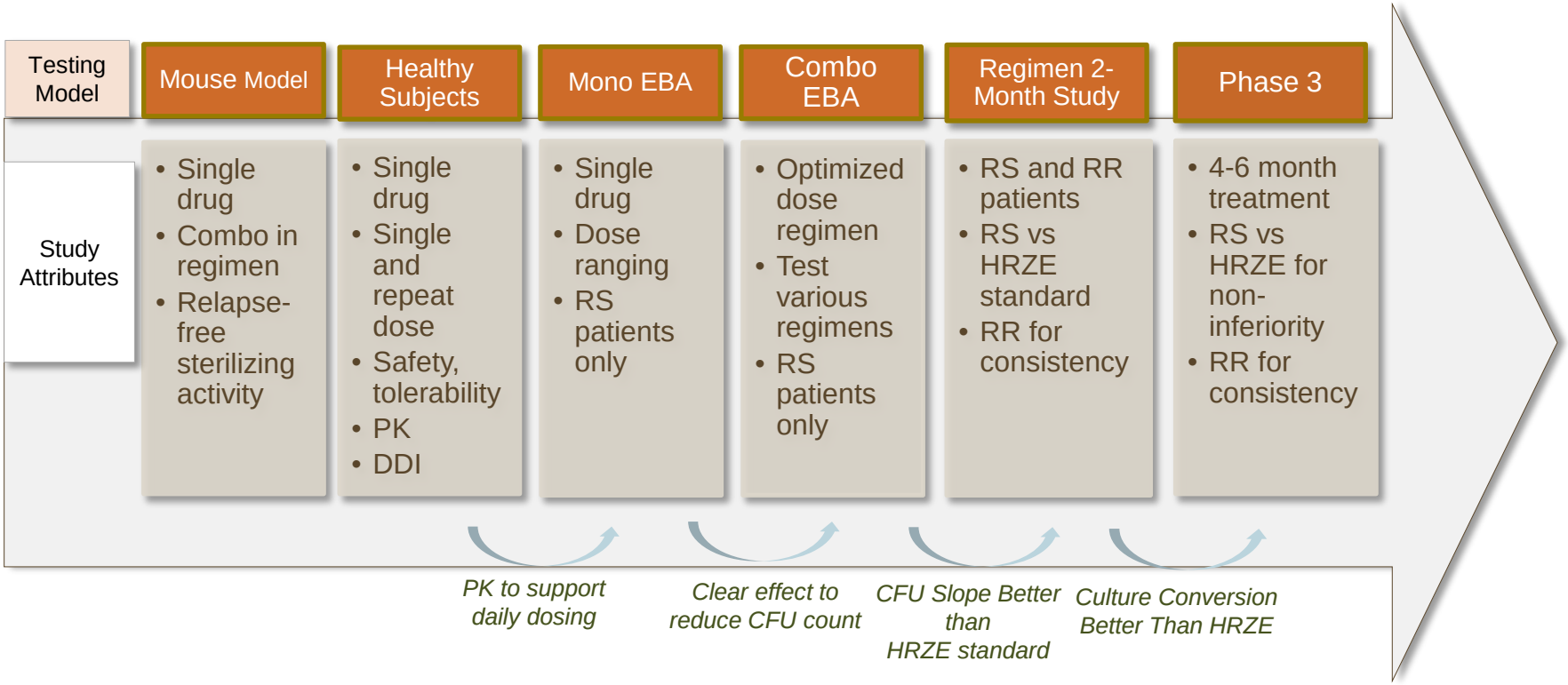
BMGF PORTFOLIO OF INTERVENTIONS FOCUSES ON KEY GAPS IN CARE CASCADE

DEVELOPMENT OPTIONS IN TB

Strategy	Efficacy	Safety	Convenience/ Duration	Lower Cost	Development Time	Risk of Resistance	Example
Add-on to OBR (MDR)	√	X	X	X	√	X	BDQ, DLM
Substitution (MDR)	√	?	?	?	√	X	STREAM 1
Last Resort (XDR/ MDR)	√	√	√	?	√	√	BDQ-Pa-L
Single Substitution (RS)	√	?	√	?	X	√	ReMox
Unified (MDR/RS)	√/-	√	√	?	X	√	tbd

=BMGF Focus

UNIFIED DEVELOPMENT PATH: RS AND RR TOGETHER

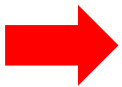


OPTIONS FOR ACCELERATING TB DRUG DEVELOPMENT

- Option 1: Combine MAD and EBA
  - Patients are used in Phase 1 in other therapeutic areas (oncology, virology)
  - Obtain safety data in population of interest
- Option 2: Link monotherapy and combination 14-day EBA
  - Evaluate additional contribution of combination to antibacterial activity
  - Obtain safety, DDI information on potential regimens
  - Prerequisites for evaluation of novel combinations
    - Diligence on potential for overlapping toxicities with recommendations for clinical monitoring
    - Consider need for preclinical toxicology studies on combinations
- Option 3: Combine Options 1 and 2
- Option 4: Adaptive Phase 2/3 designs
  - Assess antibiotic activity after 4-8 weeks of treatment to select most promising regimens
  - Requires treatment response biomarkers with faster turnaround time than current CFU assay

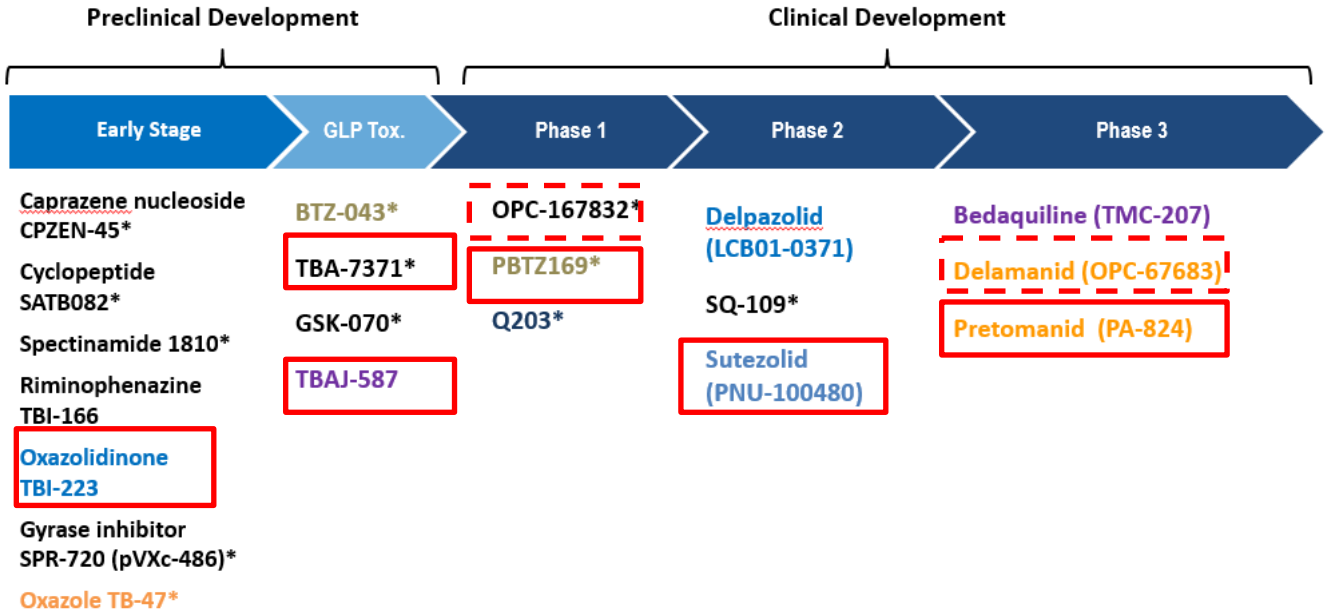
THE HUNT FOR A PAN-TB REGIMEN

- Shorter (<6 months)
- Simpler
  - Initiate treatment upon diagnosis (no requirement for DST)
  - All oral, once daily (long acting injectables may be considered)
  - Fixed dose combinations where feasible
- Safer
  - No or very limited clinical or laboratory monitoring
  - No need for dose adjustments (enables development of FDCs)
  - Low DDI liability (esp with ARV and anti-diabetics)



At an affordable cost

Global New TB Drug Pipeline [1]



New chemical class* Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[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 can be viewed at http://www.newtbdrugs.org/pipeline/discovery

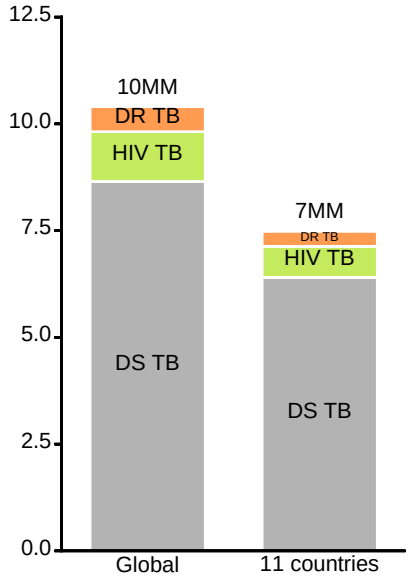
WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org
Updated: June 2017

= BMGF-supported

CHALLENGES OF THE NEW TB DRUG LANDSCAPE

- The TB drug pipeline is increasing in number and diversity
  - Nitroimidazoles, diarylquinolones, oxazolidinones, Dpre1 inhibitors, MmpL3 inhibitors, Leucyl-tRNA synthesis inhibitor, cytochrome C oxireductase inhibitor
  - Need holistic approach to data from in vitro, in vivo and clinical studies to identify most promising regimens for late-stage evaluation
- Short duration studies (≤2 months) may not reduce risk of failure for treatment-shortening regimens
- Treatment response biomarker would revolutionize drug development and, potentially, indicate which patients have achieved cure with shorter regimens
  - Sputum and non-sputum assays
  - Imaging
  - Immune Response Marker
- Risk of drug resistance requires regimen development
  - Are preclinical combination safety toxicology studies helpful?
  - How best to identify the most promising combinations?

OVER 10MM PATIENTS ARE WAITING FOR BETTER TREATMENT



Note: 11 countries include India, China, Indonesia, Nigeria, Pakistan, S Africa, Bangladesh, Myanmar, DRC, Mozambique, and Ethiopia.

Source: Global Tuberculosis Report 2016;
WHO (2015); End TB Strategy (2016)