CPTR-NIAID 2017 Workshop

TB Drug Discovery and Development: Challenges and Goals

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TARGET PRODUCT PROFILE

TARGET indication

3 or 4 drug regimen Indicated as First Line treatment of active pulmonary TB infection, regardless of rifampin resistance – **Universal or Pan TB Regimen**

SIMPLER

- No Drug Sensitivity Testing to establish Treatment
- All Oral (no injectables), Fixed Dose Combination
- No DDIs (particularly with ARVs), no dose modification of ARVs or TB drugs

SAFER

- No Routine Safety Lab or ECG Monitoring

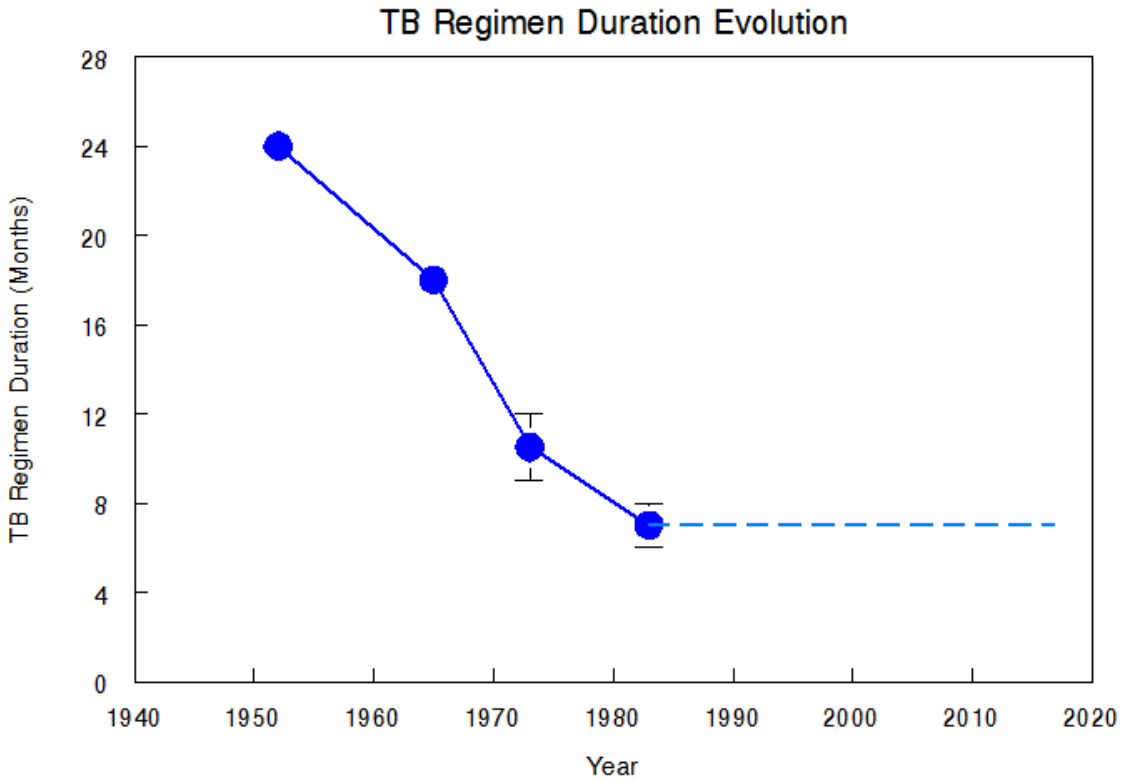
SHORTER

- $\leq$ 4 months

AFFORDABLE

TARGET DURATION

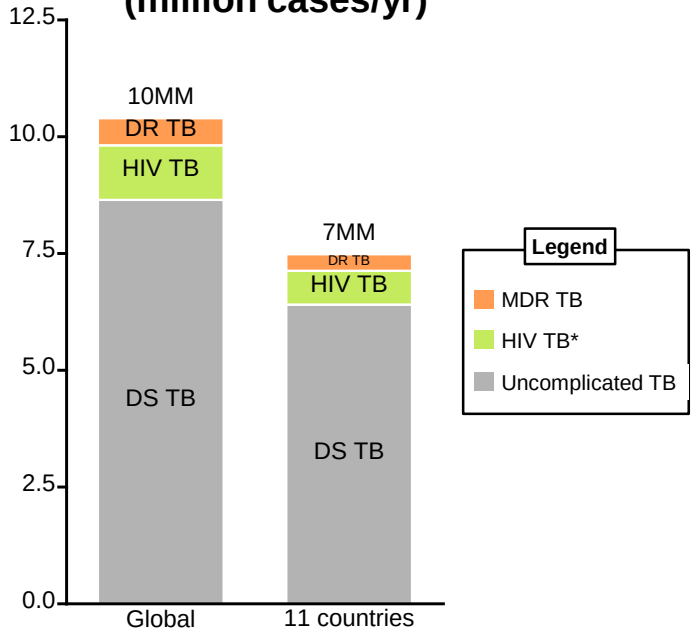
- Standard DS TB regimen duration stands at 6 months
- WHO Universal Regimen TPP
  - Minimum 6 months
  - Optimum ≤ 4 months
- BMGF Drug Initiative
  - Aspirational Target 1-2mos
  - Current Clinical Trials
    - Evaluating 4 months in DS
    - Contingency, 6 months in DS
    - MDR 6 months



TARGET POPULATION – PAN TB

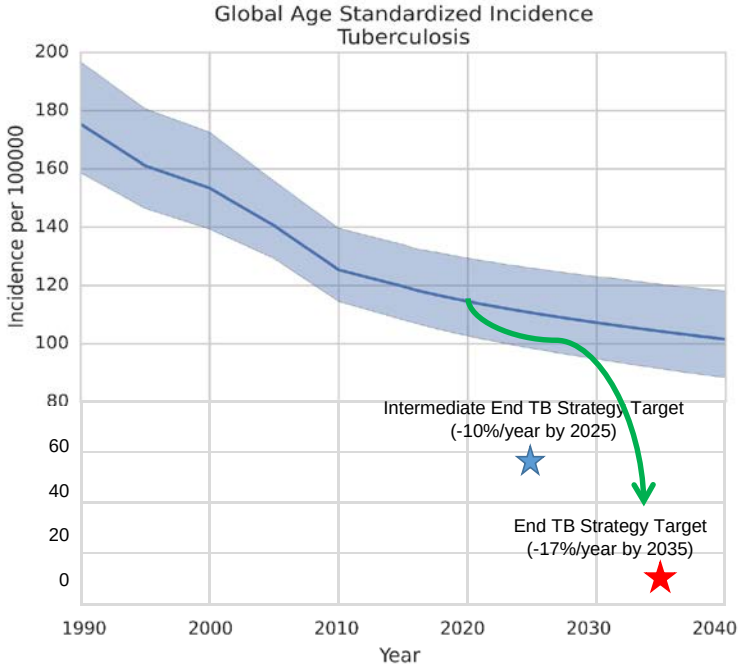
ACCELERATE DECLINE IN EPIDEMIC – TARGET DS TB TO IMPACT EPIDEMIC, IMPACT BUDGETARY BURDEN – TARGET MDR

2015 TB burden (million cases/yr)



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

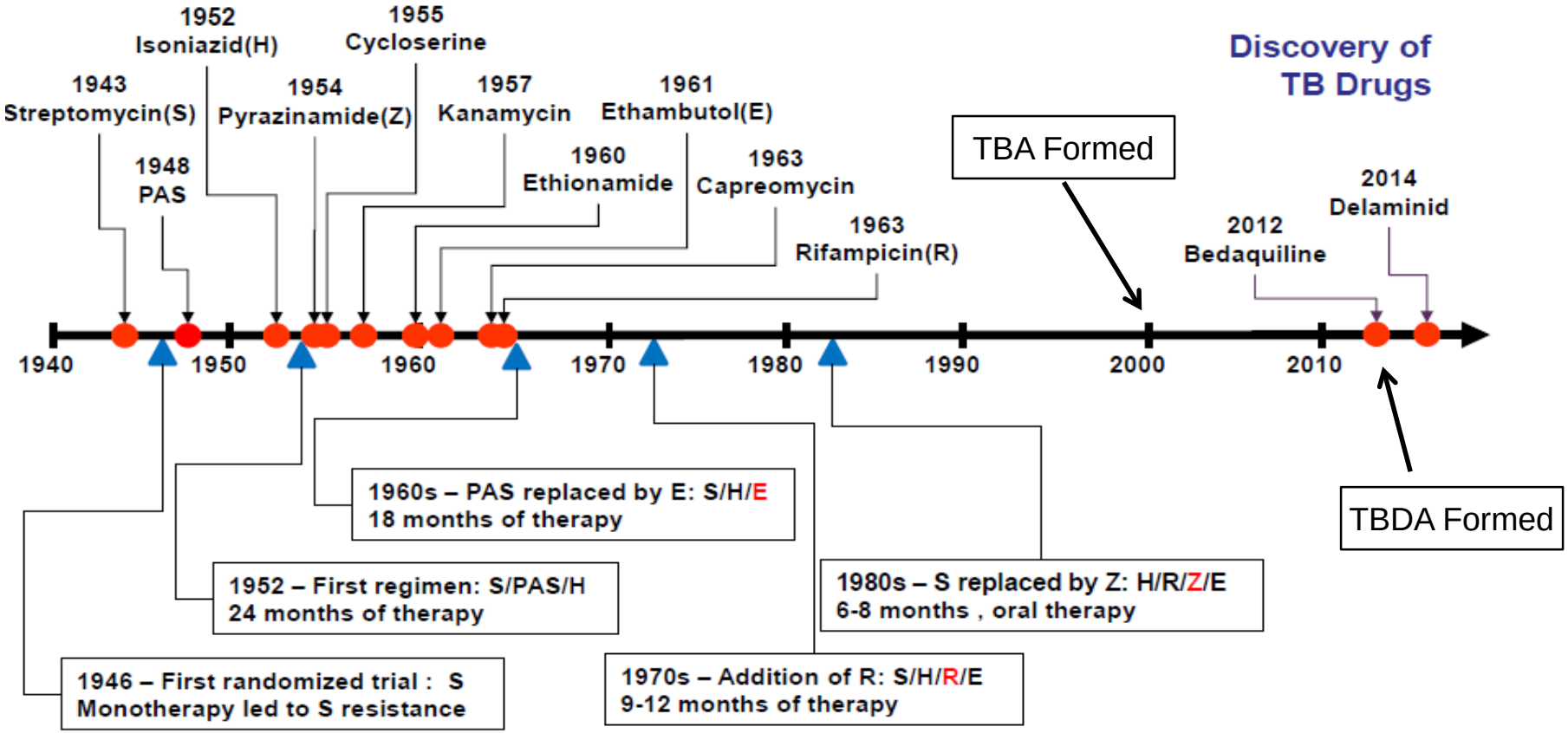
Projected reduction in TB incidence



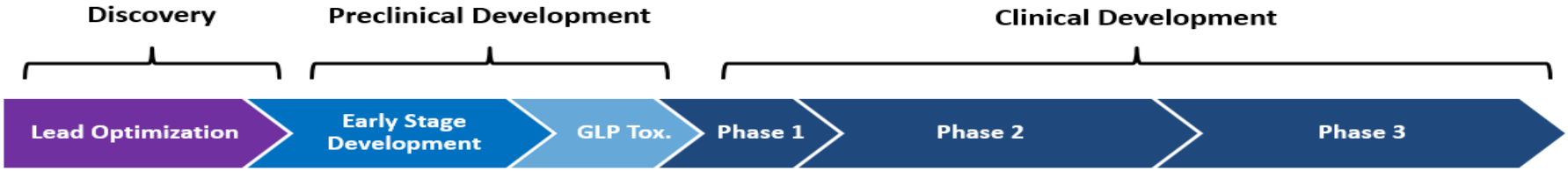
Source: IHME (does not include HIV co-infected incidence)

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

HISTORY OF TB DRUG APPROVALS



Global TB Drug Pipeline [1]



Lead Optimization

- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Ruthenium(II)Complexes
- Translocase-1 Inhibitors, Clp, MmpL3, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Early Stage Development

- CPZEN-45*
- SATB082*

GLP Tox.

- BTZ-043*
- PBTZ169*
- TBA-7371*
- GSK-070*
- TBAJ587
- Lee 1810*

Phase 1

- Q203*
- PBTZ169*
- TBI-166
- OPC-167832

Phase 2

- Sutezolid (PNU-100480)
- Linezolid EBA
- SQ-109*
- High Dose Rifampicin for DS-TB
- Bedaquiline (TMC207)-Pretomanid (PA-824) - Pyrazinamide Regimen
- Levofloxacin with OBR for MDR-TB

Phase 3

- Rifapentine - Moxifloxacin for Drug Sensitive TB
- Delamanid (OPC-67683) with OBR for MDR-TB
- Pretomanid-Moxifloxacin-Pyrazinamide Regimen (STAND)
- Bedaquiline-Pretomanid-Linezolid NiX-TB Regimen
- Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)
- Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)
- High Dose Rifampicin for DS-TB (RIFASHORT)

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, , imidazopyridine amide. New chemical class*

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: April 2017

HOW WE CURRENTLY DEVELOP TB DRUGS / REGIMENS

Translational Development

Pre-clinical

- BALB/c mice 4wk & 8w, mono and combos evaluated empirically, best regimen(s) graduate
- Mouse relapse model to explore regimen duration and best candidate(s) for shortening graduate

Ph I / IIa

- SAD / MAD HVTs
  - No *ex vivo PK/PD*
- *14-Day EBA Mono*
- *14-Day EBA Combo, best regimens graduate to SSCC[1]*

Late Phase Development

Ph IIb/ III

- Phase IIB 2-month SSCC, regimen(s) with culture conversion result "better" than HRZE graduate to Phase III. How much "better" to support 2, 3, or 4mos regimen in Phase III?
- Phase III regimen shortening, Non-Inferiority, n=300/arm, ~$75M USD
  - DS[2] HRZE (6m)
  - DS Test Regimen (6m)
  - DS Test Regimen (4m)
  - MDR[3] Test Regimen (6m)

Hi uncertainty and risk carried into Ph III

1 Serial Sputum Culture Conversion 2 Drug Sensitive TB 3 Drug Resistant TB

EMERGING CHALLENGES IN TB

- How do we find the best compound within a class, across organizations?
- How do we systematically and efficiently find the optimal drug/exposure combination from a large pool of possibilities?
- How do we improve translation from Ph 2 to Ph 3 for regimen shortening and De-Risk late stage development? Take attrition early.
- How do we efficiently evaluate new combinations in late stage development?
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