

Cascades: Improving TB Drug Treatment

New Drugs, New Regimens, New Opportunities for MDRTB



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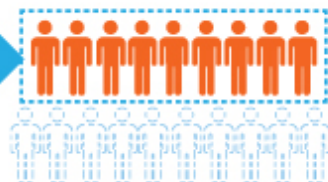
81% of people with DR-TB
don't get effective
treatment



of the
19%

that do,
ONLY

HALF
are cured.



WE NEED BETTER TREATMENT NOW



IT CAN TAKE

DAY 1

20 pills swallowed + 1 painful injection

DAY 240

4,800 pills swallowed
240 painful injections received

DAY 365

7,300 pills swallowed

DAY 730

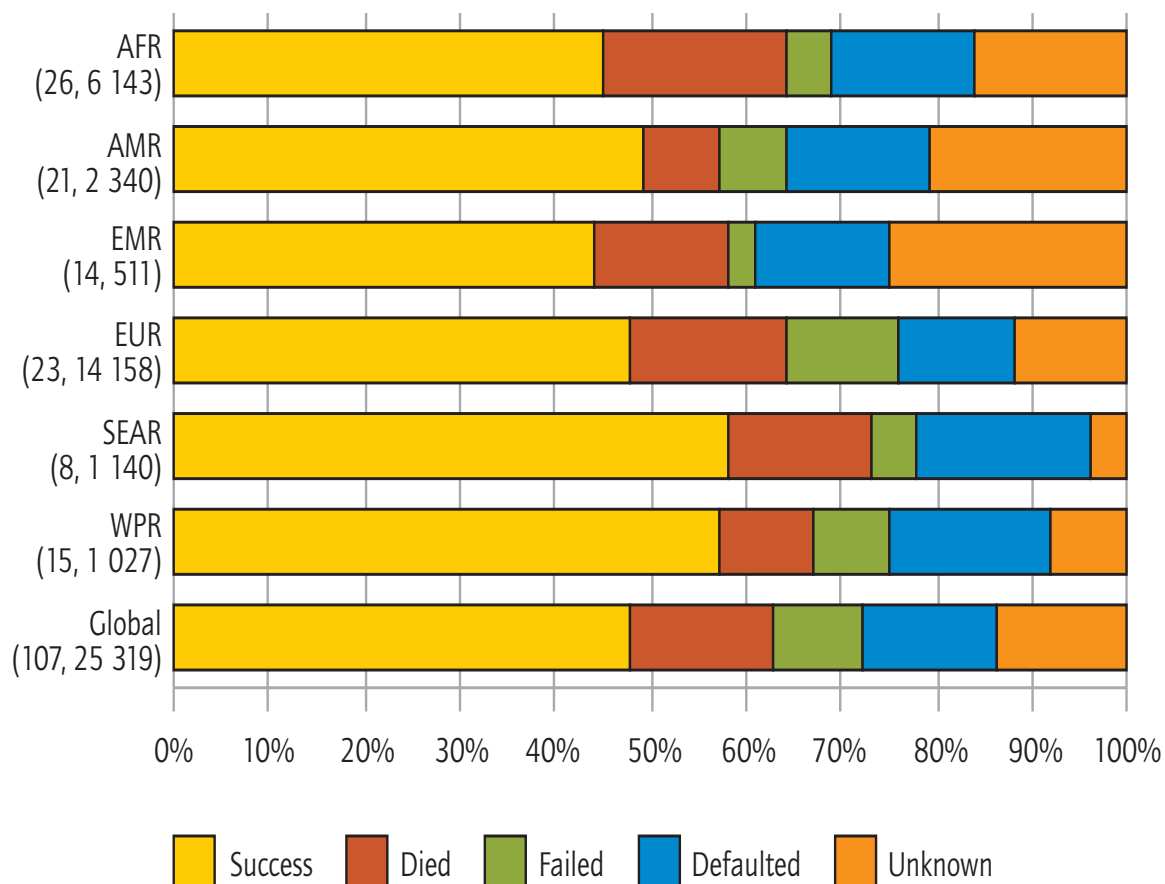
14,600 pills swallowed

FINISH

2 YEARS
TO TREAT DRUG-
RESISTANT TB

FIGURE 4.8 Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts.

The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.



The issues - DRTB treatment

Old – last approved new drug was 50 years ago

Long – Treatment takes two years

Complex – multiple tablets, 8 months of injectable agents, needs tailored to individual resistance patterns. Hard to scale-up.

Expensive – Can cost up to \$3000 in drug costs alone

Toxic – Side effects range from hearing loss to intractable nausea to psychosis

Inadequate – high default rates, low cure rates, generates further resistance, no paediatric FDC

Unproven – No RCT or prospective trials exist for the current regimen.

Game Changer: An Ideal Regimen

1. Contain at least two new classes of drug and does not combine drugs of same class
 2. Effective against MDR and XDR
 3. Contain 3 to 5 effective drugs
 4. All-oral, simple dosing schedule
 5. Good side effect profile with limited monitoring
 6. Duration 6 months or less
 7. Have minimal interactions with anti-retrovirals
 8. Efficacy 80% or higher
- Patient effects
 - Increase adherence
 - Increase cure
 - Patients will not have to “shut down” their lives for 2 years
 - Health system effects
 - Decentralizable
 - Enables task shifting
 - Market effects
 - Consolidates demand
 - Allows increased pooling (more country regimens harmonized)
 - No injectable=potential lower costs
 - Larger volume market can support generic competition

Global TB Drug Pipeline ¹

Discovery

Lead Optimization

Cyclopeptides
Diarylquinoline
DprE Inhibitors
InhA Inhibitor
LeuRS Inhibitor
Macrolides
Mycobacterial Gyrase
Inhibitors
Pyrazinamide Analogs
Ruthenium(II)
Complexes
Spectinamides
Translocase-1 Inhibitor

Chemical classes: fluoroquinolones
benzothiazinone

IT WAS THE BEST
OF TIMES ☺

IT WAS THE WORST
OF TIMES ☹

Phase III

delamanid
(OPC-67683)
nitroimidazole
oxifloxacin
pazinotam

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 Combination regimens: NC-001 -(J-M-Pa-Z), phase 2a, [NCT01215851](#); NC-002-(M-Pa-Z), phase 2b, [NCT01498419](#); NC-003-(C-J-Pa-Z), phase 2a, [NCT01691534](#); PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, [NCT01785186](#).

Trials

- **STREAM (4KCMEHZP/5MEZC)**
 - 9 months (key populations), higher efficacy (?), WHO endorsed for operational research and countries taking up OR
 - 7 drugs up front, injectable, ? Efficacy with SLD resistance, cost still \$2000
- **STREAM additional arms**
 - Potential for addition of BDQ and elimination of injectable
 - Shorter duration?
- **MARVEL (JPaULZ various combos)**
 - All-oral, use of >2 new classes, 6 months?
 - Timeline?
- **Nix (JPaU+/-Z)**
 - All-oral, use of >2 new classes, 6-8 months
 - XDR-only

How Long Will We Wait?

2014 2015 2016 2017 2018 2019 2020 2021 2022

Delamanid Ph 3

STREAM

Bedaquiline Phase 3

Nix-TB

MARVEL Phase 2/3

Time to implementation of a novel regimen?

Just because
TB is slow
growing,
doesn't mean
we have to be



Accelerating Access to Current and Future Tools

- Use diagnostics to uncover the epidemic
- Price – breaking the paradigm of expensive regimens, especially MICs
- Availability
 - Compassionate use
 - Wide registration applications and speedy approval
 - Ensure antibiotic stewardship (COE? Private sector select sites?)
- Rapid adoption of new drugs and regimens
 - WHO advice and guidelines – how much data is sufficient?
 - Scale up STREAM as OR for key populations
 - Potential for market consolidation – especially if broadly effective regimen
- Speed new trials
 - Use of 6 month or EOT conversion
 - Internal controls slowing results? What is our SOC?
 - Regulatory pathways for accelerated approval of novel regimens
 - Improve access to medicines and data on study drugs....



Yeah, Heard It All Before....



Innovative Medicines Initiative

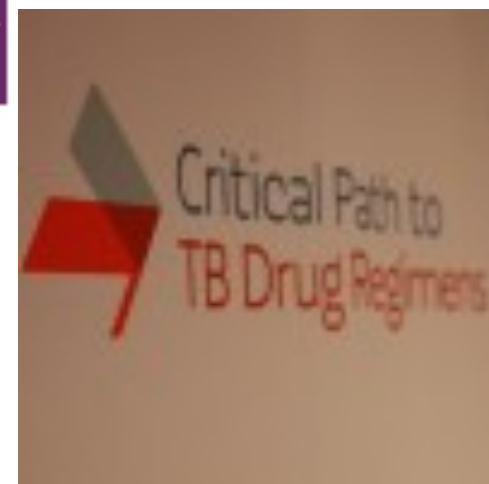
RESIST-TB

Research Excellence to Stop TB Resistance



WIPO | Re:Search

Sharing Innovation
in the Fight Against
Neglected Tropical Diseases



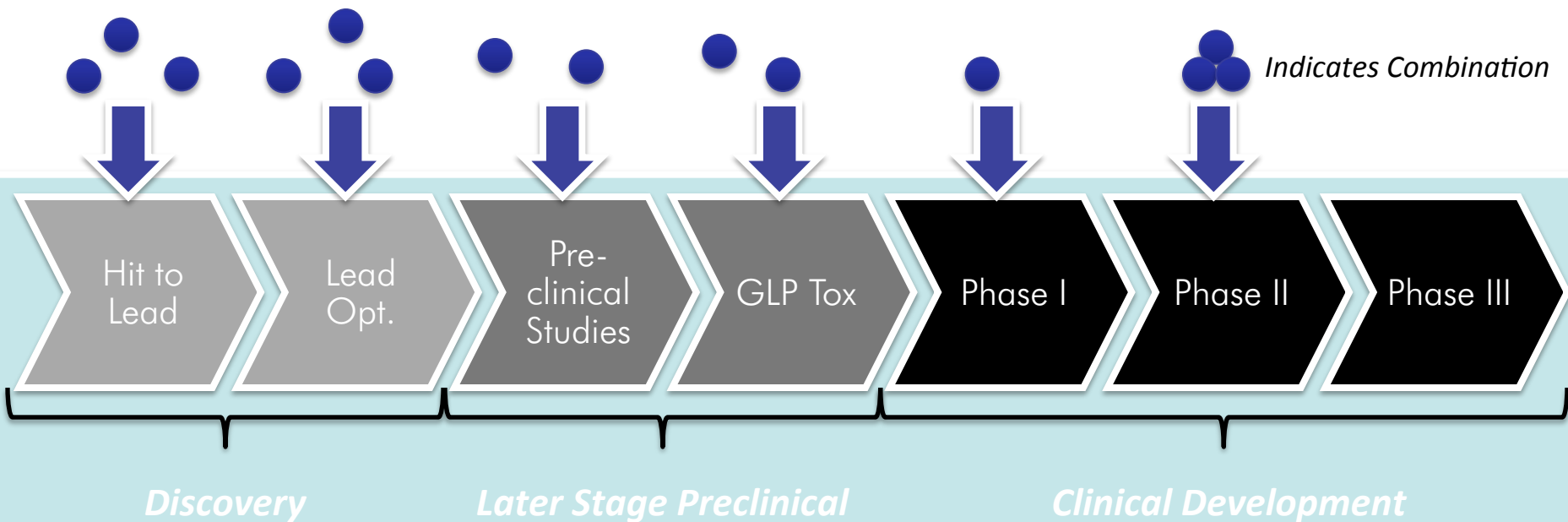
Incentivizing R&D for Public Health

- De-link R&D goals from eventual profit motivation
 - Increases public health needs driving R&D
 - Facilitates collaboration
- Opportunity for change?
 - Push mechanisms – grants linked to TPPs
 - Pull mechanisms – variable rewards that incentivize sharing IP and based on meeting TPP (including regimen development)
 - IP pools – enable more rapid regimen development



Ideal
Regimen

A Different Path



★ Small, early-stage Milestone Prize (Size 1; mix of small financial and recognition prizes) for licensing the compound to the Open Collaborative Framework

Legend

● Various TB Compounds

★ Milestone Prizes

→ Grant funding

★ Milestone Prize (Size 2) for entering clinical development (Phase I)

Grant funding for studies from the fund

★ Milestone Prize (Size 3) for combination regimen successfully completing Phase II

Grant funding for Phase III from existing and new sources

Thank you!

