Pediatric TB Therapeutic Advances and Strategies

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UNIVERSITY OF WISCONSIN
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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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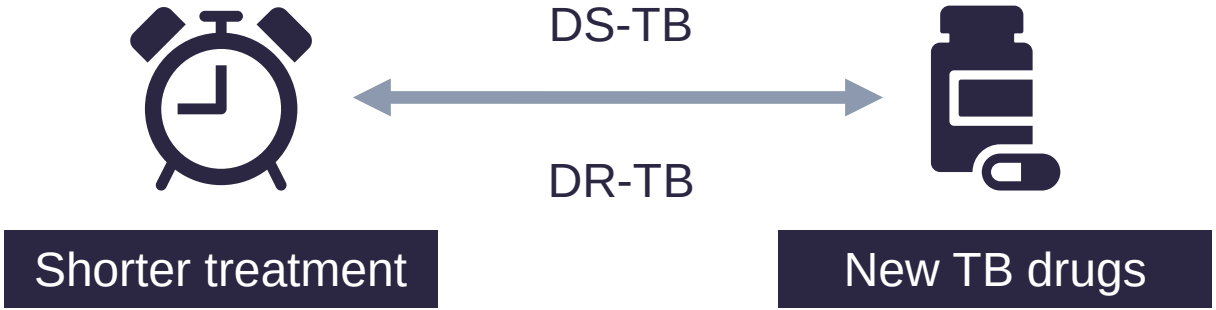
Every breath counts

Pediatric TB therapeutics research: Framework



1. Immediate needs	2. Short-to-medium term, DR-TB	3. Short-to-medium term, DS-TB
Addressing urgent gaps between adult, peds treatment options	More rapid pediatric development of new TB drugs	Further shortening treatment for DS-TB

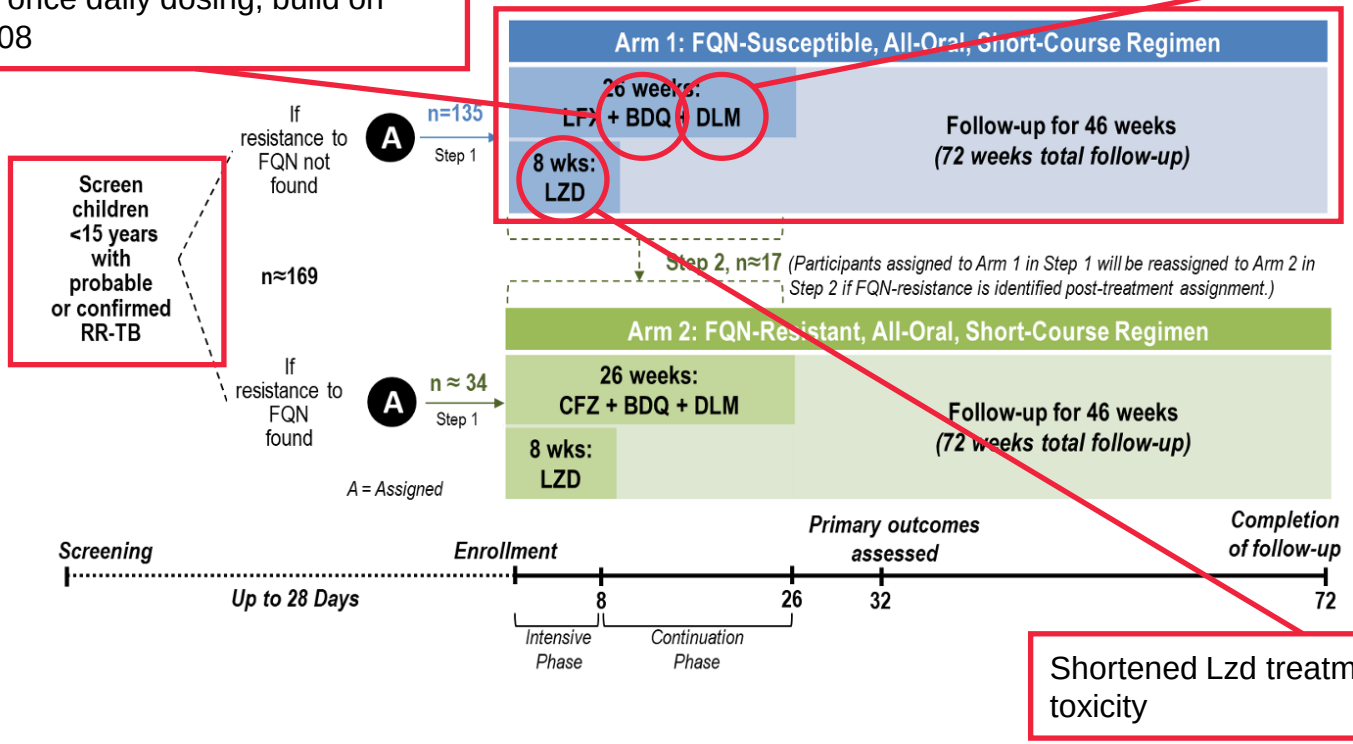
Immediate priorities

	DS-TB	RR/MDR-TB
Evidence	Study 31/A5349	TB-PRACTECAL, Ze-Nix, Nix
New WHO Recs for adults	2HPMZ/2HPM	6BPaLM/BPaL
Pediatrics gaps	RPT PK, safety (RADIANT Kids)	Pa PK, safety (I2034, f/u study)
Alternatives	2HRZ(E)/2-4HR	*4-6B·Lf·Cf·Z·Em·H^{h}·Et/ 5Lf·C·Z·Em OR 12-18 months indiv reg*

IMPAACT 2020: 6-month all-oral regimens for children with RR/MDR-TB

Dlm substitute for Pa
Confirm once Dlm daily dosing

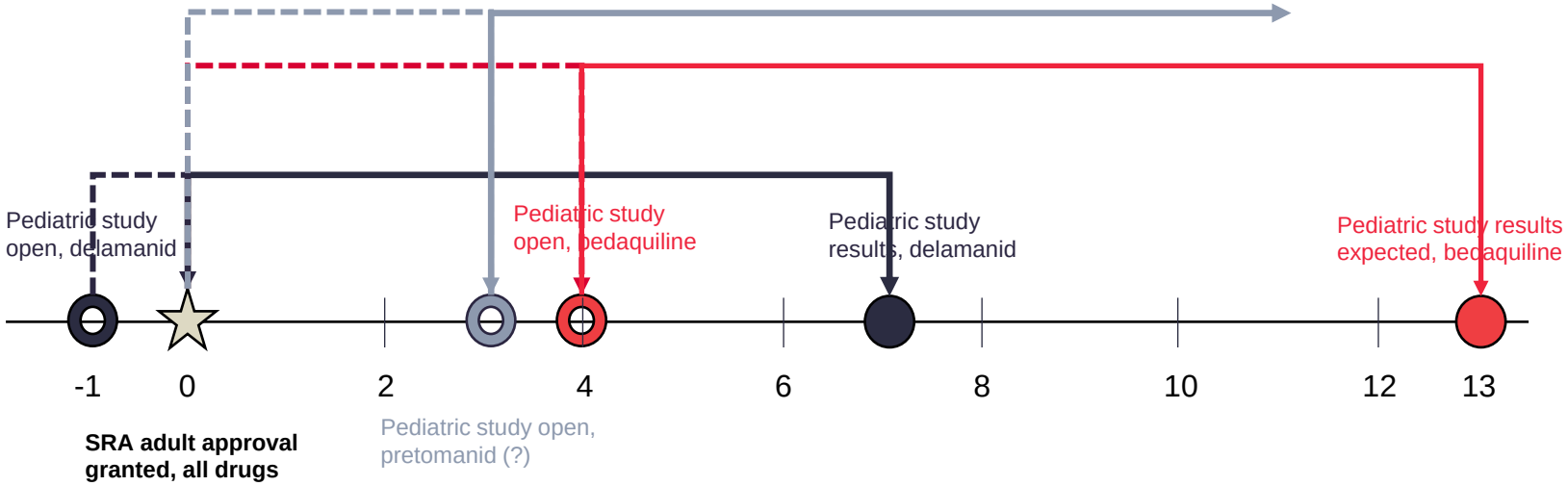
Bdq once daily dosing, build on P1108



Shortened Lzd treatment, driver of toxicity

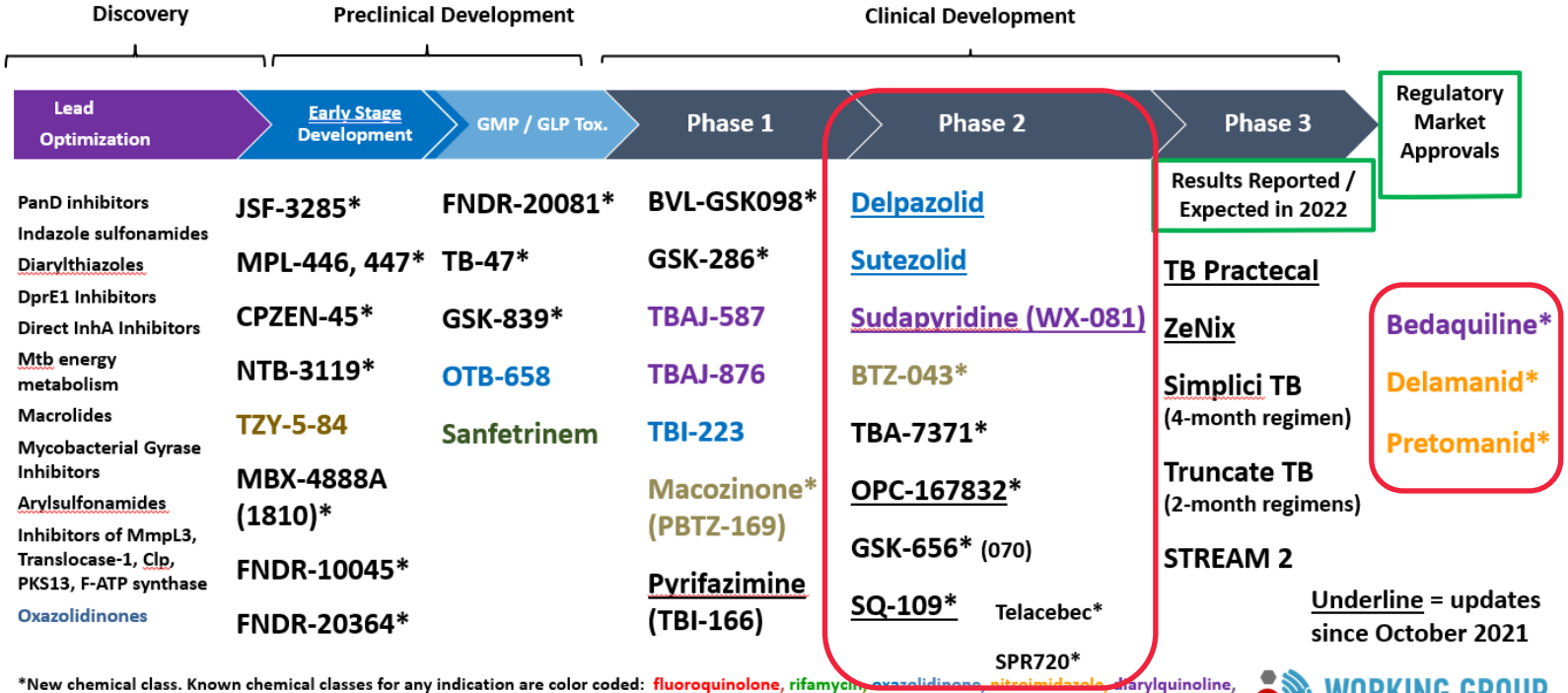
DR-TB: More rapid pediatric development of new TB drugs

Timelines for Pediatric TB Research & Development Remain Too Long



Delayed opening of pediatric trials	Slow implementation of pediatric trials
Limited pressure/incentive for timely pediatric development Lack of technical expertise in childhood TB trial design among sponsors/manufacturers	Sub-optimal trial design Insufficient trial sites/infrastructure Inefficient, fragmented processes with stand-alone studies

2022 Global New TB Drug Pipeline[1]



Underline = updates since October 2021

*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

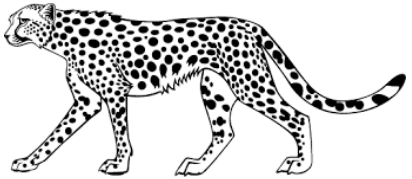
Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2022

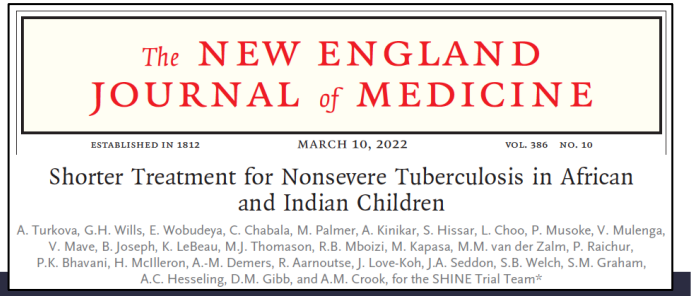
Potential strategy: CHEETA



- **CHEETA** = **C**hasing **E**xpedited and **E**quitable **T**reatment **A**ccess for Children
  - Platform trial using a master protocol to implement phase I/II pediatric trials of PK, dose, safety of TB drugs in children
  - Hyper-focused on advancing investigations of new TB compounds
  - Supra-network initiative, increase opportunities overall in this space
- **Cross-cutting solution to current challenges:** limit barriers to timely peds development, optimal design, increase site capacity, limit inefficiencies
- **CHEETA Task Force** – Seed funding, WHO's GAPf (Garcia-Prats, McKenna, TAG)
  - Map trial site capacity globally, focus high DR-TB burden settings
  - Engage with current industry partners with compounds in phase II development
  - Develop full funding proposal, protocol, and seek funding for trial, site development

DS-TB: Further shortening treatment

SHINE Trial


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

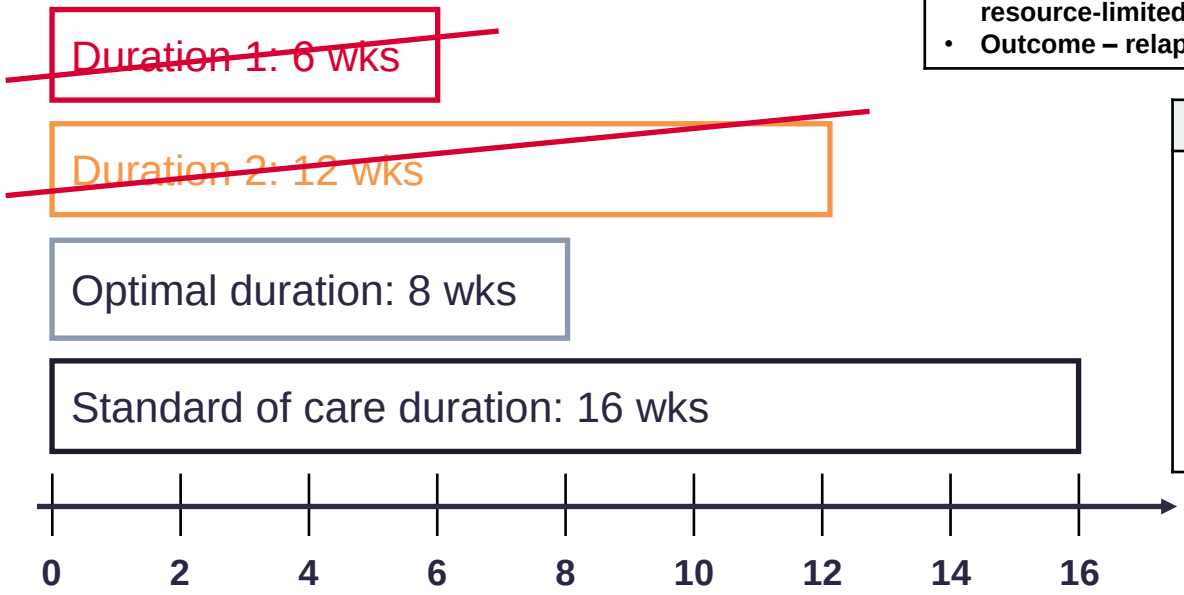
A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

Rationale	• Children have paucibacillary, less severe PTB than adults • May be successfully treated with shorter, less intense regimens than adults
SHINE TB Trial	• Open-label phase 3 randomized controlled non-inferiority trial of 4 vs 6 m of standard first-line TB treatment in children <16y with non-severe TB • N=1204, 16 vs 18 study endpoints (death, LTFU, failure, recurrence) for 4 vs 6 month • Main results – 4 months non-inferior to 6 months • WHO recommendation 2022
Future considerations	• Can treatment be shortened further? **Very likely yes.**

Challenges with further treatment shortening in children

Challenge 1: Design

- **Phase 3 non-inf trial, short arm vs SOC**
- **Large (~1200 pts), long (5+ years), costly, complex to manage across multiple sites in resource-limited settings**
- **Outcome – relapse-free cure**



Challenge 2: Selecting duration

- **High-risk given large investment if "wrong"**
- **Too long: trial "successful" but failed to reduce as much as possible**
- **Too short: trial "unsuccessful", no shortening achieved, risk to pts**
- **Little *a priori* data to inform duration selection: cannot extrapolate from adults, no good pre-clinical models**

Duration randomization trial

Clinical Trials
2018, Vol. 15(5) 477–488

DOI: 10.1177/1740774518778027
journals.sagepub.com/home/ctj
SAGE

Rethinking non-inferiority: a practical trial design for optimising treatment duration

Matteo Quartagno[1,2], A Sarah Walker[1], James R Carpenter[1,2], Patrick PJ Phillips[1] and Mahesh KB Parmar[1]

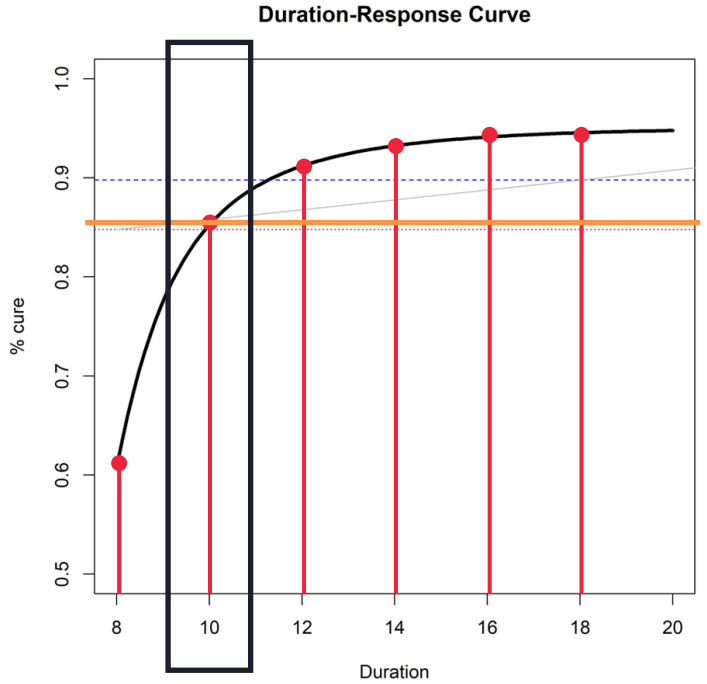
Clinical Trials
2020, Vol. 17(6) 644–653

DOI: 10.1177/1740774520944377
journals.sagepub.com/home/ctj
SAGE

The DURATIONS randomised trial design: Estimation targets, analysis methods and operating characteristics

Matteo Quartagno, James R Carpenter, A Sarah Walker, Michelle Clements and Mahesh KB Parmar

- **Challenges:** Deciding on minimal duration, acceptability frontier, handling different disease severity, regimen, minimizing risk for participants
- **Progress:** Concept for phase II study in children with DS-TB (REDUCE) developed; select duration for definitive phase 3 trial



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