IMPAACT TB SCIENTIFIC COMMITTEE UPDATE: 2018

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

TBSC core members

- Anneke Hesseling (chair) – DTTC, South Africa
- Amita Gupta (vice-chair) – JHU/India
- Kelly Dooley – JHU
- Bob Husson – Boston Children's
- Anne-Marie Demers – DTTC, South Africa
- Vanessa Rouzier – Gheskio, Haiti
- Carol Onyango – Uganda
- Lindsay McKenna – TAG, NY
- Avy Violari – PHRU, South Africa

Aims

To evaluate novel approaches for TB prevention, treatment and diagnosis in HIV-infected infants, children, adolescents, and pregnant women regardless of DS and DR-TB status

Strategy

- Collaboration with industry
- Rapid uptake of findings into policy and practice
- Phase I/II trials where efficient
- Phase III as required
- Earlier inclusion of adolescents
- Inclusion of pregnant women

Estimated total TB cases in children	**1 000 000 (10% global burden)**
Childhood cases notified	360 000
TB deaths	136 000 (81 000 HIV-) 13.6% case fatality rate
TB infections	6.6 million
MDR-TB estimates	30-50 0000
MDR-TB infection	500 000

WHO 2015 Global TB report www.who.int

Global TB Drug Pipeline [1]

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

Lead Optimization → **Early Stage Development** → **GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3**

Lead Optimization

- Diarylquinolines
- DprE Inhibitors
- InhA Inhibitor, Ureas
- Macrolides, Azaindoles
- Mycobacterial Gyrase Inhibitors
- Pyrazinamide Analogs
- Ruthenium(II)Complexes
- Spectinamides
- Translocase-1 Inhibitors, Clp, Mmp13, Oxazolidinones, Pyrimidines DprE1, Aryl Sulfonamides, PKS13, Squaramides

Early Stage Development / GLP Tox.

TBI-166	BTZ-043*	Q203*
CPZEN-45*	PBTZ-169*	PBTZ169*
1599*	TBA-7371*	OPC-167832*
SATB-082*	GSK-070*	

Phase 1

- 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 2

- 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)

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: October 2016

Treatment considerations: children

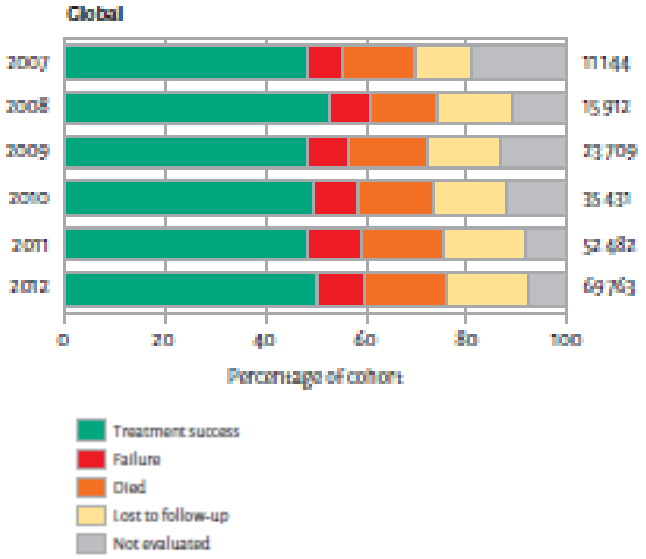
- >75% pulmonary /intrathoracic TB
- Wide spectrum of disease
- Paucibacillary disease compared to adult pulmonary TB (fewer lung cavities)
- Severe and disseminated TB (TBM and miliary TB) especially in young
- Treatment outcome in children generally good provided initiated early (paucibacillary)
- All treatment data extrapolated from adult studies

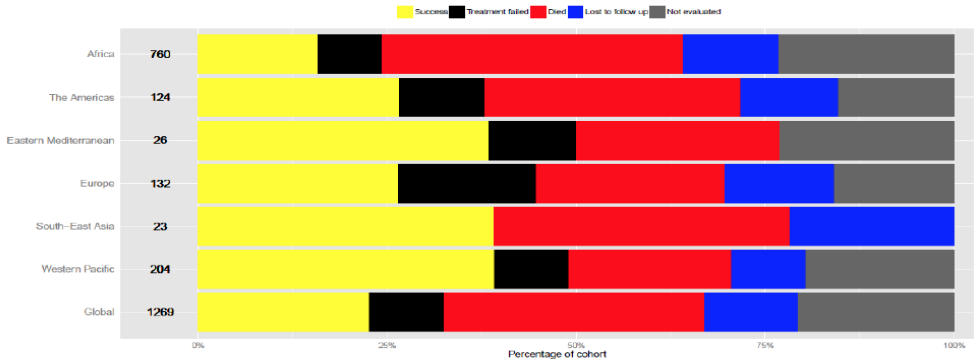
MDR-TB in children

- Estimated 50 000 cases paediatric MDR-TB annually world wide[1]
- Limited evidence base to inform MDR-TB treatment in children
  - Single systematic review; no paediatric IPD meta-analysis[2]
- Guidelines for treatment of TB extrapolated from adults
- Specific paediatric considerations
  - Paucibacillary disease
  - Broad spectrum of disease
  - Study definitions: confirmed vs clinical cases; definition of treatment outcomes in absence of much culture data
- Good response to antituberculosis treatment (81.7% treatment success in children[2] vs 54% in adults[3])

[1] Jenkins et al. Lancet. 2014 May 3; [2] Ettehad et al. Lancet Infec Dis 2012; [3]Ahuja et al. PLoS Med. 2012

Low Treatment Success and High Mortality





*number of cases observed shown over the bars

MDR TB: 50% treatment success, 16% death

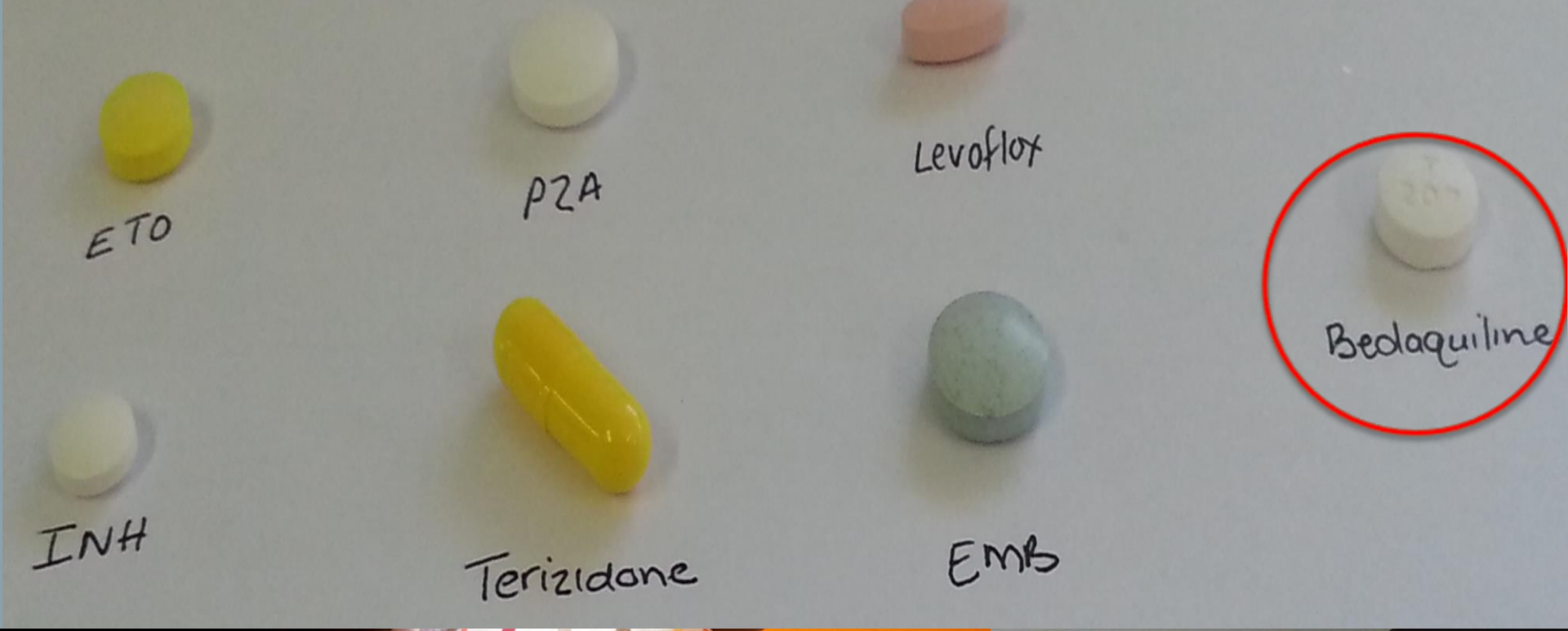
XDR TB: 24% treatment success, 30% death

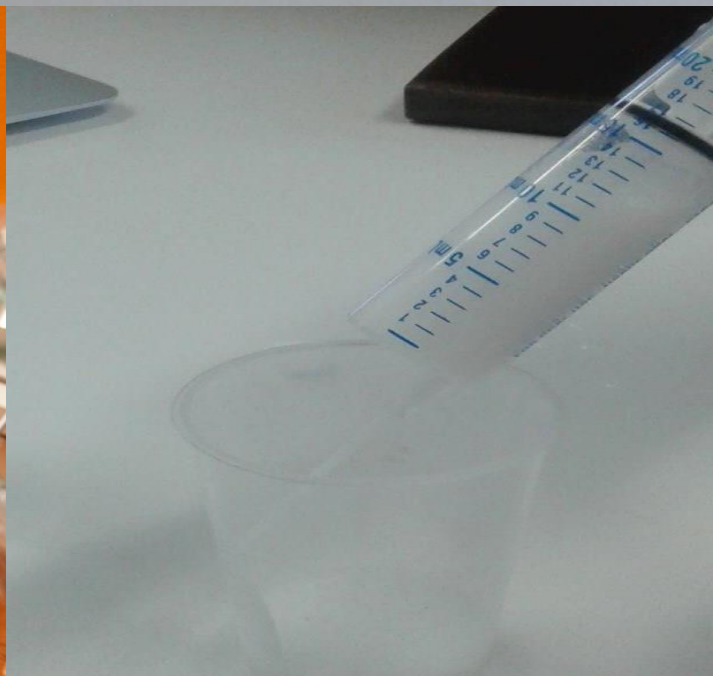
WHO Global TB Report 2015

Summary of treatment outcomes for children with multidrug-resistant tuberculosis

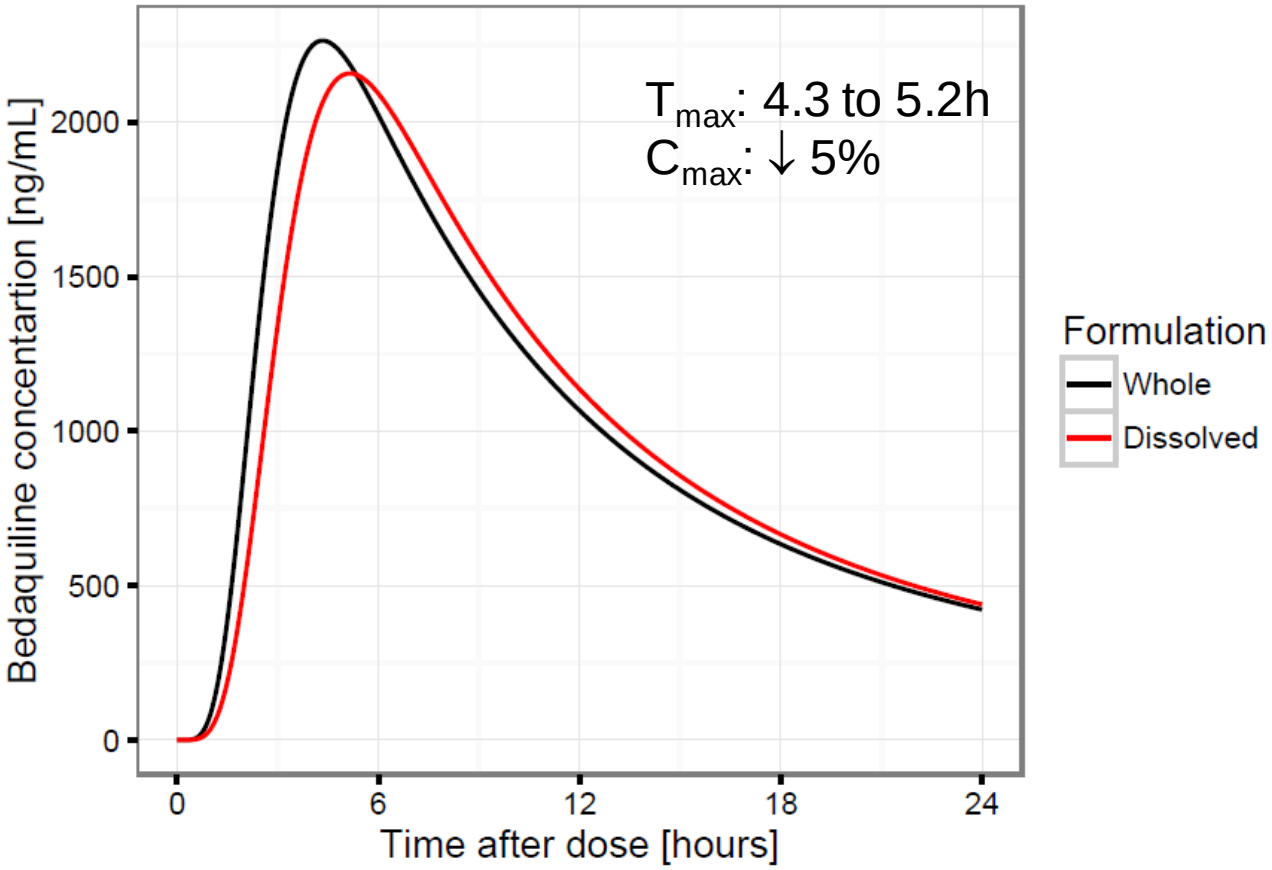
	Clinically diagnosed MDR-TB n=238	Confirmed MDR-TB without confirmed XDR-TB n=701	Confirmed XDR-TB n=36
Cured	46 (19.3%)	327 (46.6%)	23 (64%)
Completed treatment	166 (69.7%)	209 (29.8%)	7 (19%)
Fail or relapse	0	14 (1.9%)	1 (3%)
Death	7 (2.9%)	73 (10.4%)	3 (8%)
Lost-to-follow-up	19 (8%)	77 (11%)	2 (6%)

Harausz et al, in progress


ETO
PZA
Levoflox
Bedaquiline
INH
Terizidone
EMB



BDQ CRUSH: impact of dissolving on a typical bedaquiline PK profile

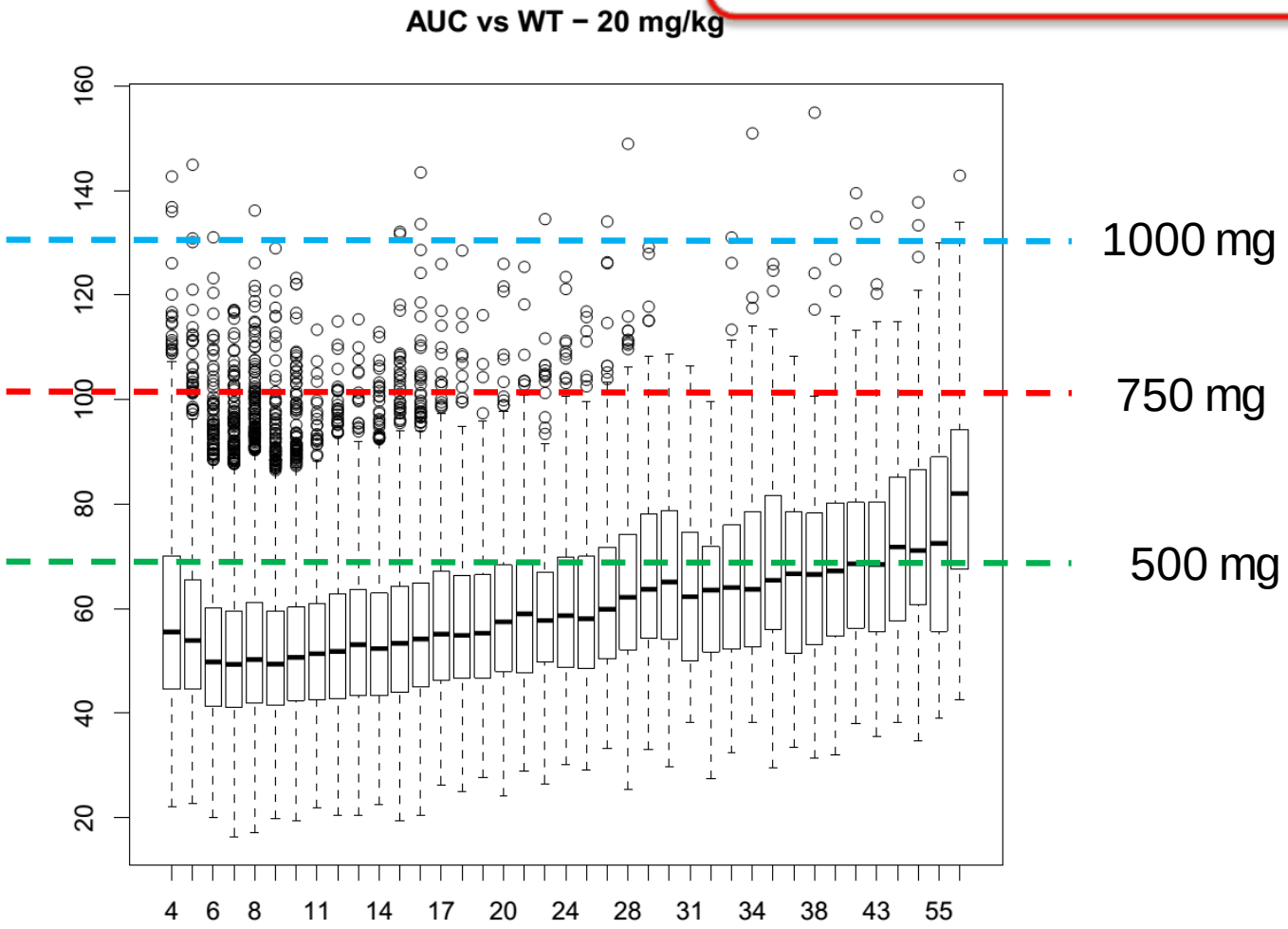


In press, Svensson

Levofloxacin: Simulated AUC

Assuming 20 mg/kg dosing

N=109, median age 2.1y (0.3-8.7), HIV+ 14.7%



Denti, Garcia-Prats, AAC, 2018

PK STUDIES	ONGOING PAEDIATRIC STUDIES
PK/safety studies *Standard first- and second-line drugs-Establishing doses that achieve adult-equivalent exposures*	• **DATiC:** PK/safety first-line TB drugs (enrolment completed 2016): NICHD R01: McCilleron • **STEP-TB:** New pediatric dispersible formulations of first-line drugs (TBA, Unitaid) • **Infant PK study:** low Rif exposures (TBA/Unitaid): Hesseling/Bekker • **MDR PK** 1: PK, safety second-line drugs in children with/without HIV: levo, moxi, oflox, amik, HD INH, ethio, PAS, cycloserine) completed (NICHD R01) - Hesseling • **MDR PK 2**: Optimizing Levofloxacin, moxifloxacin, linezolid (NICHD R01): Garcia-Prats • **Rifabutin** in children, NIRT (terminated; NICHD): Moultrie • **OptiRIF Kids**: high-dose rifampicin PK safety: opened 2017 (TB Alliance/Unitaid): Hesseling
PK/safety studies *New drugs* *Establishing doses that achieve adult-equivalent exposures*	• **Study 35**- Rifapentine/isoniazid in HIV+/-children < 12 years of age TBTC • **P1108 and** Jansen C211: Bedaquiline in children–BDQ in HIV-uninfected children (Janssen);) • **232/233-** Delamanid in children- Otsuka (Otsuka) • **P2005** -injectable-sparing DLM-based regimen in children with and without HIV infection: 2017 (Dooley) • **P2001**: safety and PK of rifapentine in HIV-infected pregnant women • **P1026S:** including new TB drug arms
HIV/TB DDI studies	• **DNDi:** Ritonavir boosting of LPV/r in TB/HIV: completed • **NICHD PK**: first-line TB drugs with ART: completed • **P1101:** RAL-based ART with standard TB drugs: ongoing

EFFICACY STUDIES	ONGOING TRIALS
TB prevention *Prevention of TB in children (high risk of TB progression)*	• **A5300 PHOENIX: delamanid vs. SD INH for MDR-TB prevention: 2018** • TB-CHAMP: Levo vs placebo for MDR-TB prevention: 2016 • VQUIN: levo vs. placebo for MDR-TB prevention: open • **ACTG5279: one month of rifapentine+isoniazid daily for DS-TB prevention** • P4v9 Trial: 4 months RIF vs 9 months INH for DS-TB prevention: ongoing • TBTC 37: RPT 6 weeks vs. local SOC (RIF 4 mo or RPT/INH q week x 3 mo): planned • **P1078: IPT in HIV-infected pregnant women**
DS-TB disease *Reduce mortality, improve neurocognitive dysfunction*	• TBM-KIDS: High-dose RIF +/- Levo for children with TBM (NICHD R01 - Dooley • SURE Kids: Gibb
Non-severe DS-TB *Reduce treatment duration for children with non-severe disease*	• SHINE: 4 vs. 6 months standard TB Rx (new FDCs, nested PK): open label (MRC CTU; Gibb) • N=1200 (accrual will be completed June 2018)
MDR-TB disease	• **SMART-KIDS: P2020**

Data needed for MDR to inform regimens: rapid and efficient designs needed

1. PK and safety of BDQ (including in HIV+)
2. PK and safety of once-daily DLM
3. PK and safety of PA-824 in
4. PK and safety of DLM/BDQ co-treatment: 2020
5. PK and safety of linezolid, clofazimine in children: MDR PK 2
6. PK and safety: sutezolid
7. MDR TB and pregnancy: PHOENIX, 2026S

MDR TB 2 year plans: children, pregnant women

- Complete P1108 (Bedaquiline phase I, II) HIV+/-
- Implement P2005 (Delamanid Phase I, II) HIV+/-
- Implement A5300 and pregnancy sub study
- Implement P2020
- Complete Linezolid, clofazimine PK, safety
- Implement P1026 S (new MDR-TB arm with DLM, BDQ)
- TB trial registry: pregnancy

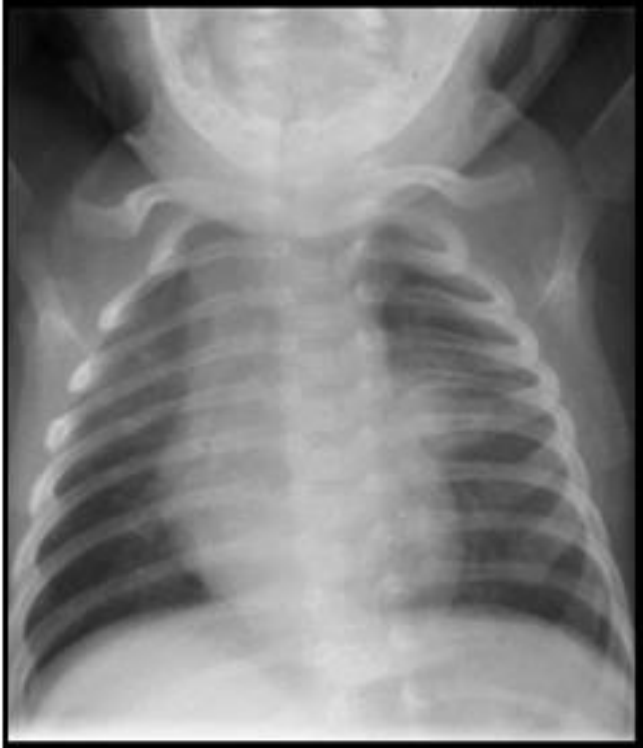
IMPAACT MDR-TB: 5 year plan

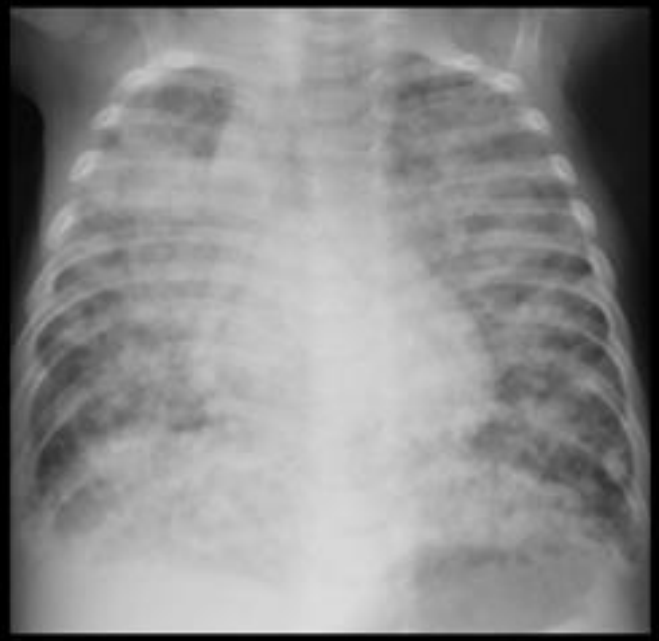
- Develop PA-824 phase I/II in children
- Develop Sutezolid phase I/II in children
- Complete PHOENIX, 2020
- Build capacity for paediatric MDR TB trials

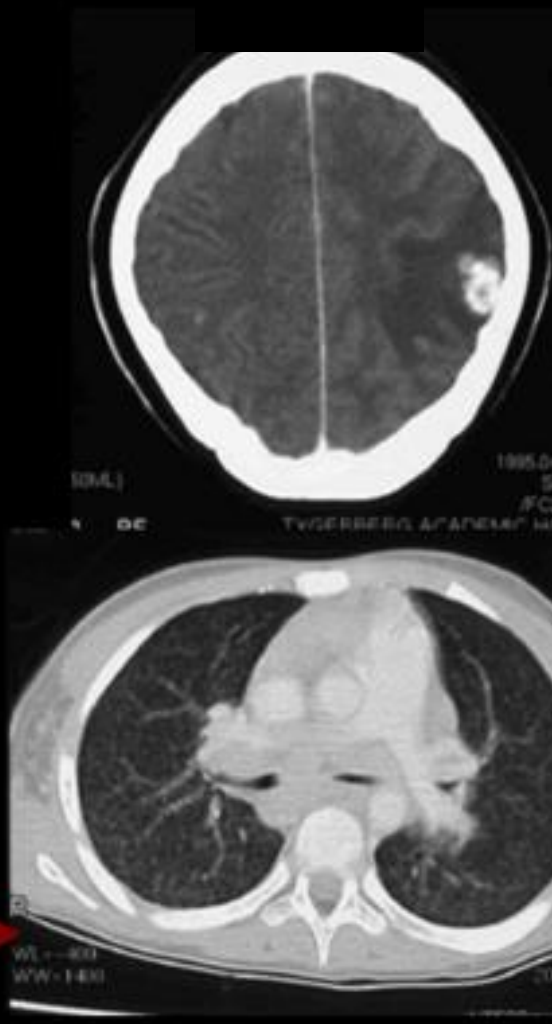
DS-TB	Gaps for children	Priority studies
	• Prevention: RFTP INH 1 month • Optimal treatment for TB meningitis (levofloxacin, high dose rifampin) • Rifampicin dose optimization (severe disease not addressed in SHINE, treatment shortening): OptiRif Kids • Treatment shortening: non-severe and severe disease • And need for treatment regardless of DST in future	• PK and safety in children, pregnant women • PK and outcome (TBM Kids; NICHD; Dooley) : opened Q2 2017 ; SURE KIDS • Priority: building on SHINE, rifampin dose optimization • Opened Q1 2017; cohort 1 completed; cohort 2: n=12 • SHINE+: Priority – complementing SHINE and TBM Kids, Optirif Kids

NON-SEVERE TB

SEVERE TB (INCLUDING DISSEMINATED)







Wiseman, Ped Infect Dis J 2014

Trial sponsor

UCL

Co-ordinating centre

MRC Clinical Trials Unit

Collaborating groups

SHINE

Shorter treatment for minimal TB in children

A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children

N=1200
1130 enrolled
New FDCs

Collaborating gro

MU-JHU Care Ltd, Kampala, Uganda

Stellenbosch University, South Africa

University Teachin Hospital, Lusaka, Zambia

National Institute Research in Tuberculosis, Chennai
BJ Medical College Pune, India

Funders

MRC Medical Research Council

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UKai from the Departmen International Develo

Summary Information Type	Summary Details
Short Name Title of Trial	**SHINE** (Shorter treatment for minimal TB in children)
Long Title of Trial	A randomized trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children
Version	1.0
Date	24-Mar-2014
ISRCTN #	ISRCTNXXXXXXXX
Study Design	Parallel group, randomised, non-inferiority, open label, 2 arm phase III clinical endpoint trial
Type of Participants to be Studied	Children < 16 years with suspected minimal (limited) TB disease, with or without HIV infection, will be screened
Setting	South Africa (Cape Town); Zambia (Lusaka); Uganda (Kampala) and India (Chennai and Pune)
Interventions to be Compared	**4-MONTH REGIMEN** The experimental arm will be standard daily first-line anti-TB treatment for 16 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks Isoniazid (H) , Rifampicin (R), Pyrazinamide (Z) with or without Ethambutol (E) according to local practice, HRZ(E), followed by continuation of 8 weeks HR. **6-MONTH REGIMEN** The control arm will be standard daily first-line anti-TB treatment for 24 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks HRZ(E), followed by continuation of 16 weeks HR.

Group	AUC_{0-24h} (h · mg/L)	C_{max} (mg/L)*
10 mg/kg (control)	26.3 (21.3–40.9)	7.4 (6.1–9.9)
20 mg/kg	113 (77.5–162)	21.6 (16.0–31.9)
25 mg/kg	135 (91.5–228)	25.1 (16.3–34.6)
30 mg/kg	190 (84.7–436)	33.1 (17.6–55.8)
35 mg/kg	235 (166–321)	35.2 (28.6 –44.2)

Definition of abbreviations: AUC_{0-24h} = area under the time versus concentration curve up to 24 h after dose; C_{max} = peak plasma concentration.
Data are shown as geometric means and range.
*Serial venous blood samples were taken just prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after the investigational products were taken under direct supervision and with a standardized meal.

Table 1. Steady state pharmacokinetics of RMP on day 14 in adults (n=68 patients) (50)

Boeree, AJRCCM, 2015

OptiRif Kids

- **Dosing cohorts**: n=20 per cohorts: A minimum of 60 (20 children per cohort) (i.e. 3 dosing cohorts) enrolled
- Demonstrate exposures in children similar to those achieved in adults receiving 35-40 mg/kg in HIGHRIF1 over 15 days
- No age de-escalation. Children e enrolled in 3 age groups, with children in all 3 age groups included in each dosing cohort:
  - Age group 1: Age ≥ 6 to < 12 years
  - Age group 2: Age ≥ 2 to < 6 years
  - Age group 3: Age ≥ 0 to < 2 years
  - Status: Dosing cohort 1 completed (15-20 mg/kg_
  - Dosing cohort 2 open: 35 mg/kg – up to 50 mg/kg

DS-TB: 5 year plan

Children

- Complete P2001
- Develop 1 month RFPRT/INH for DS-TB prevention: PK, safety: separate paediatric and pregnant studies
- Develop phase 3 treatment shortening treatment trial (full spectrum of TB disease)
- Work towards TB treatment regardless of DST

Diagnostics and biomarkers: DS-TB and DR-TB

- Support nested diagnostics, biomarker studies
- Support expansion of site and TB lab capacity: MDR-TB
- Use IMPAACT and other lab platforms
- Work with ITBSL
- Work with other investigators: serum, urine biomarkers
- Evaluate novel commercial molecular tests (Xpert Ultra), DST methods, WGS, correlates of risk
- Ideal cohorts through planned protocols: SMART-Kids, P1108, PHOENIX, diagnostic studies: prognostic markers, treatment response and diagnostic markers

TB vaccines

- Collaborate with HVTN to design and conduct studies in infants and adolescents
- P1113

Milestones

- P1078 completed
- P2001: completion 2018
- P1113 completed
- Opened to accrual: P1108, P2005
- BDQ CRUSH completed
- PHOENIX: Version 1.0; maternal sub study
- IMPAACT 2020: Version 1 .0 by July 2018
- P1026S: new TB arms

Mentored investigator graduates

- Adrie Bekker: P1106, 20126S
- Jyothi Mathad: P2001
- Vidya Mave: BJMC
- Anthony Garcia-Prats: P2005, 2020
- Elin Svensson: P1108, P2005, P2020, PHOENIX

New mentored investigators

- Ethel Weld: JHU
- Yael Hirsch-Moverman: CU
- Sylvia LaCourse: UW
- Lisa Cranmer: Emory
- Jeff Tornheim: JHU
- Mandar Paradkar: BJMC
- Pauline Howell: Sizwe
- Christy Beneri: Stonybrook
- Jennifer Hughes: SU
- Nicole Salazar-Austin: JHU
- Louvina van der Laan: SU

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Group