P1108: IMPACT ON POLICY AND ACCESS TO BEDAQUILINE IN CHILDREN WITH MDR-TB

Anneke C. Hesseling, MD, PhD
Desmond Tutu TB Centre
Stellenbosch University
South Africa

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

"OF TRIALS, TRIBULATIONS AND FORMULATIONS"

IMPAACT

International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

Outline

1. Global burden: MDR/RR-TB “MDR-TB”
2. Historical context: MDR TB treatment in children
3. Lack of access despite adult trials
4. P1108: challenges and opportunities
5. Impact on guidelines and access
6. Future directions

TB incidence and mortality in children and adolescents, 2022

GLOBAL TUBERCULOSIS REPORT 2023

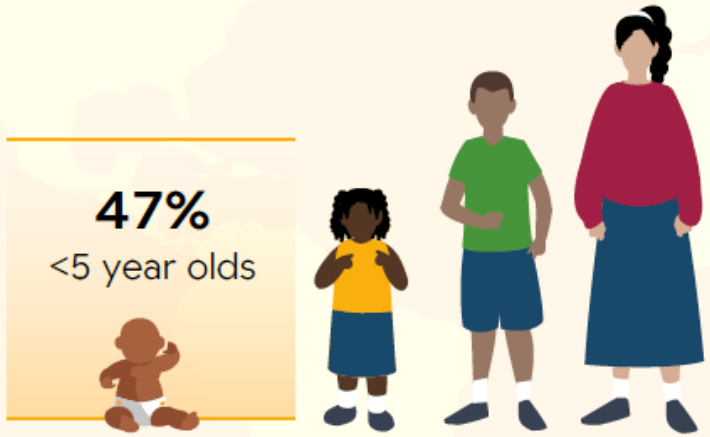
10.6 million
TB among all ages in 2022

1.3 million
TB deaths in 2022

1.25 million
children (0–14 years) developed TB in 2022 (12% of all TB)

214 000
TB deaths in 2022 (16% of all TB deaths)

47%
<5 year olds



727 000 adolescents
(10–19 year-olds) developed TB in 2012 (Snow et al, 2018)

Among deaths in HIV-negative children and young adolescents 0–14 years,
76% were in children <5 years

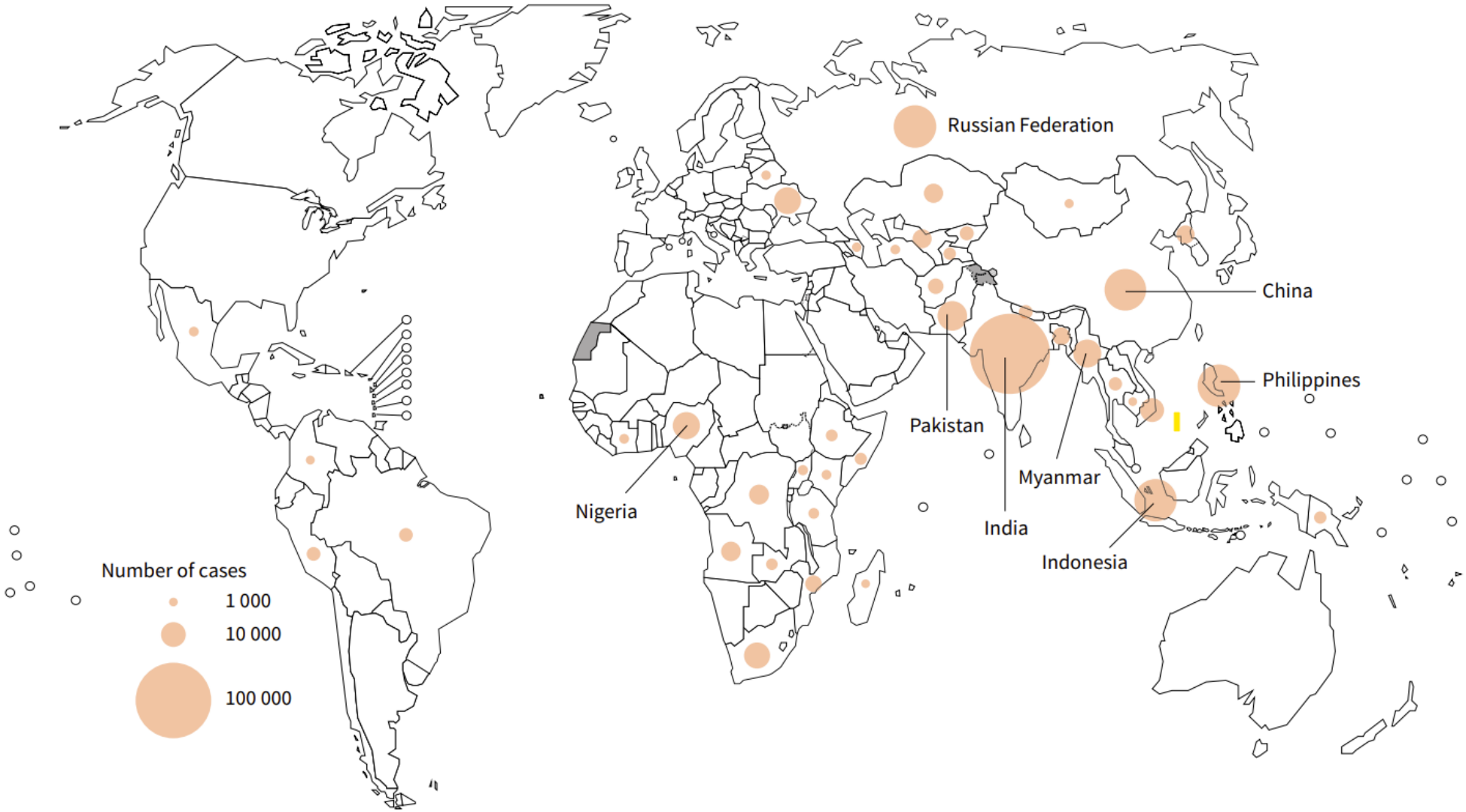
96%
of deaths occurred in children who did not access TB treatment
(Dodd et al, 2017)

31 000
(14%) TB deaths in the 0–14 year age group were among children living with HIV

World Health Organization

END TB

Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases[a]



WHO 2023 report

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

2024 Global New TB Drug Pipeline[1]

Lead Optimization

- Indazole sulfonamides
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP
- Oxazolidinones
- DnaE1 / Nargenicin analogs

Early Stage Development

- FIM-253
- TBD10 (MK-3854)
- CLB-073*
- SPR720*
- MPL-447*
- JSF-3285*
- CPZEN-45*
- NTB-3119*
- MBX-4888A (1810)*
- FNDR-20364*

GMP / GLP Tox.

- GSK-839*
- OTB-658

Phase 1

- TBD09 (MK-7762)
- GSK-286*
- TBAJ-587
- TBI-223
- Macozinone* (PBTZ-169)

Phase 2

- Telacebec* (Q203)
- Alpibectir (BVL-GSK098)*
- TBAJ-876
- Sanfetrinem
- Delpazolid, Sutezolid, Tedizolid
- BTZ-043*
- TBA-7371*
- Quabodepistat (OPC-167832*)
- Ganfeborole (GSK-656*/070)
- Pyrifazimine (TBI-166)

Phase 3

- Sudapyridine (WX-081)

Regulatory Market Approvals

- Bedaquiline*
- Delamanid*
- Pretomanid*

LAIs

*New chemical class. Known chemical classes for any indication are color coded: 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 identified: http://www.newtbdrugs.org/pipeline/discovery

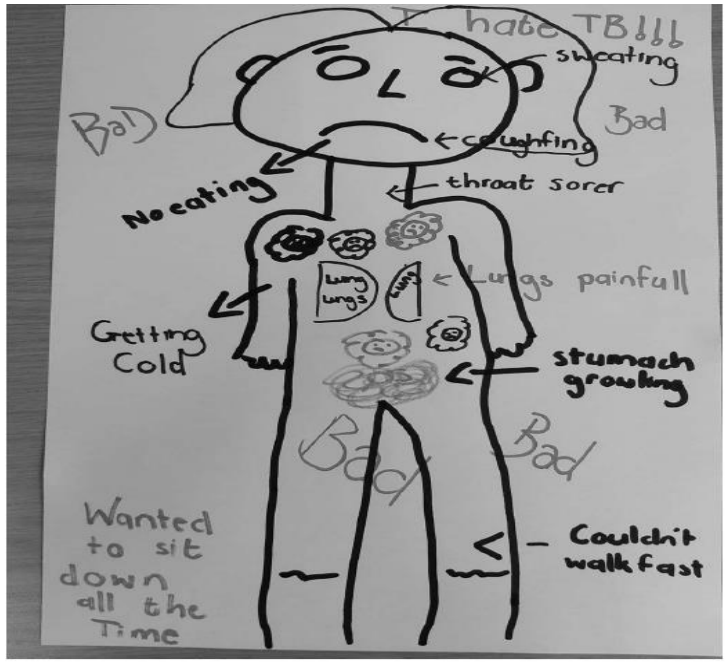
Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2024

MDR-TB



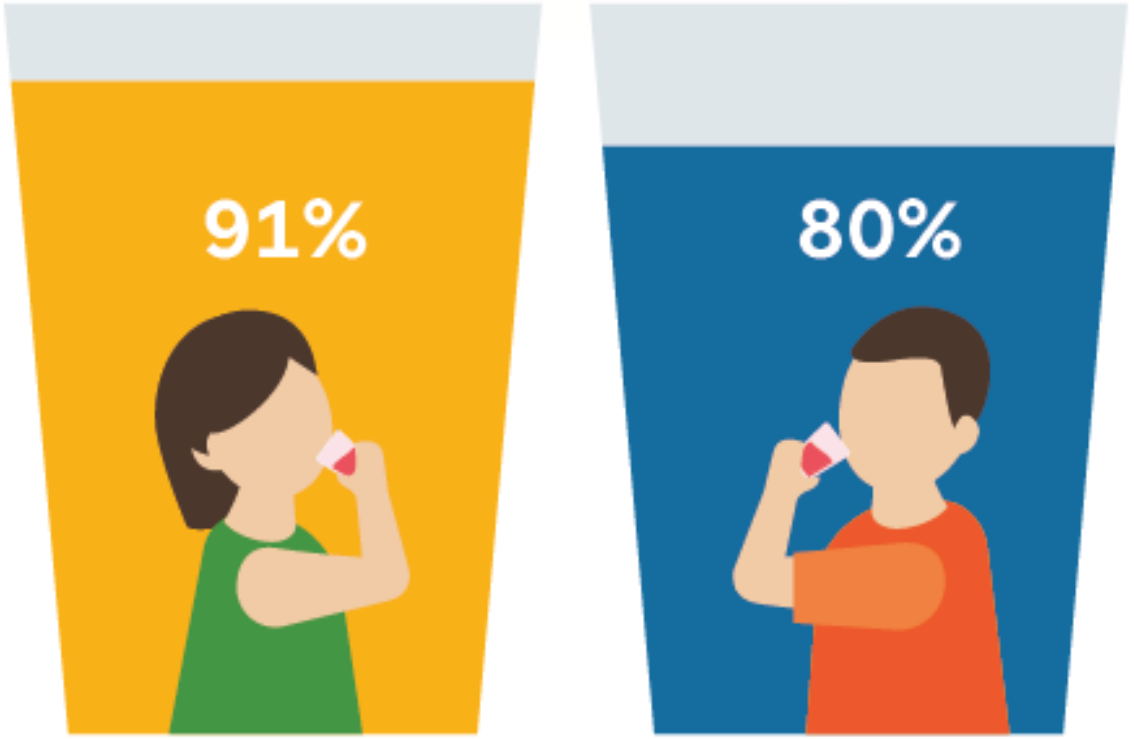
DS-TB

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Treatment outcomes

Treatment outcomes DS- and MDR/RR-TB in 0–14 years

DS-TB
Success rate
(Global Reporting for 2021 cohort)



MDR/RR-TB
Success rate
(paediatric DR-TB IPD, N=7 115)

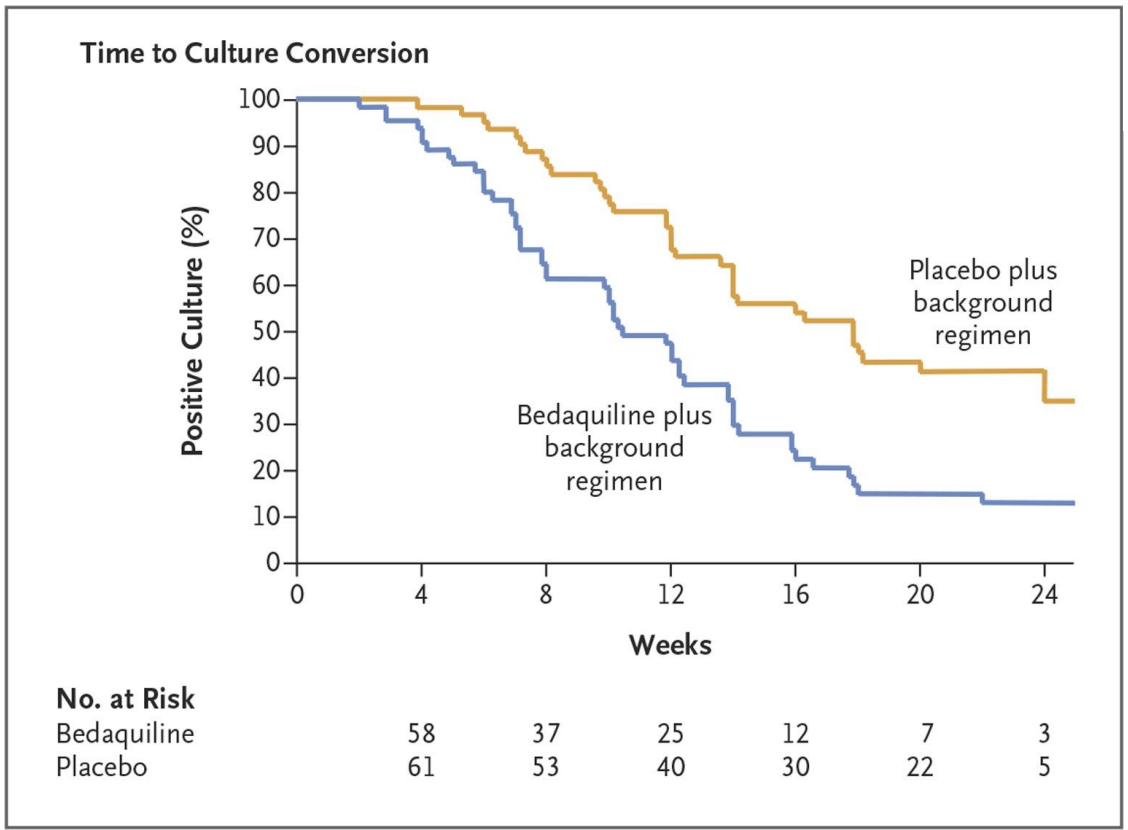
(Garcia-Prats, personal communication)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

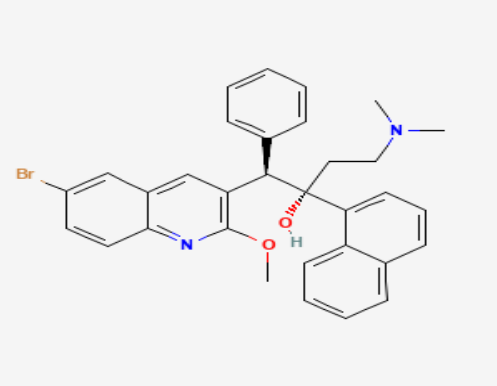
Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*



Time to Sputum-Culture Conversion in the Modified Intention-to-Treat Population.

Diacon AH et al. N Engl J Med 2014;371:723-732

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

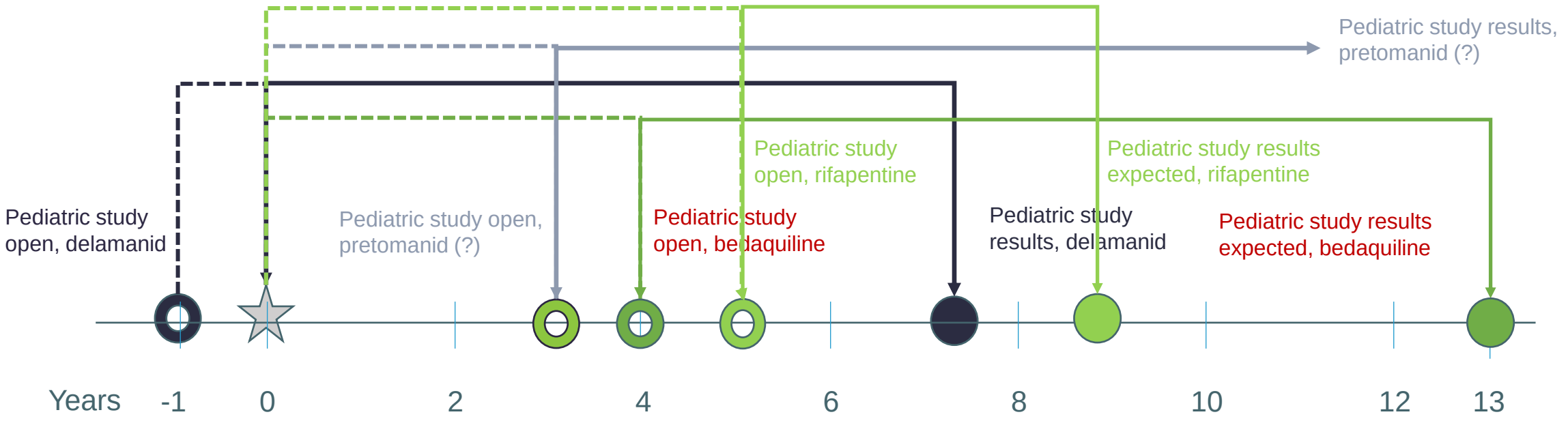


Bedaquiline

- SIRTURO, Janssen
- Diarylquinoline
- Targets ATP synthase enzyme of *M.tb* generating energy supply
- Concern: QTcF prolongation
- Initial black box warning adults
- Very long t ½
- Dramatic reduction in MDR-TB mortality

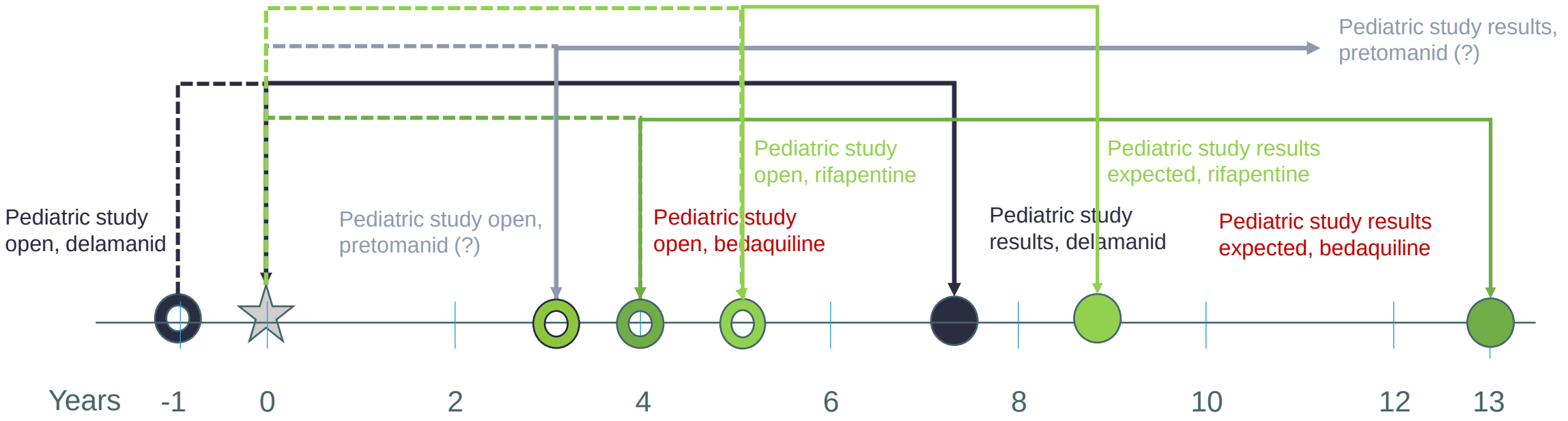
Groups & steps	Medicine	
Group A: Include all three medicines	Levofloxacin *or* Moxifloxacin	Lfx / Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs / Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	imipenem–cilastatin *OR* Meropenem	Ipm–Cln / Mpm
	amikacin (*OR* streptomycin)	Am / (S)
	ethionamide *OR* Prothionamide	Eto / Pto
	p-aminosalicylic acid	PAS

Historically delayed pediatric TB therapeutic research



Stringent Regulatory Authority (SRA) approval granted for adults, all drugs

Historically delayed pediatric TB therapeutic research



BDQ: FDA granted accelerated approval in adults: 2012 FDA paediatric (>5 y) and formulation approval: 2020

Stringent Regulatory Authority (SRA) approval granted for adults, all drugs

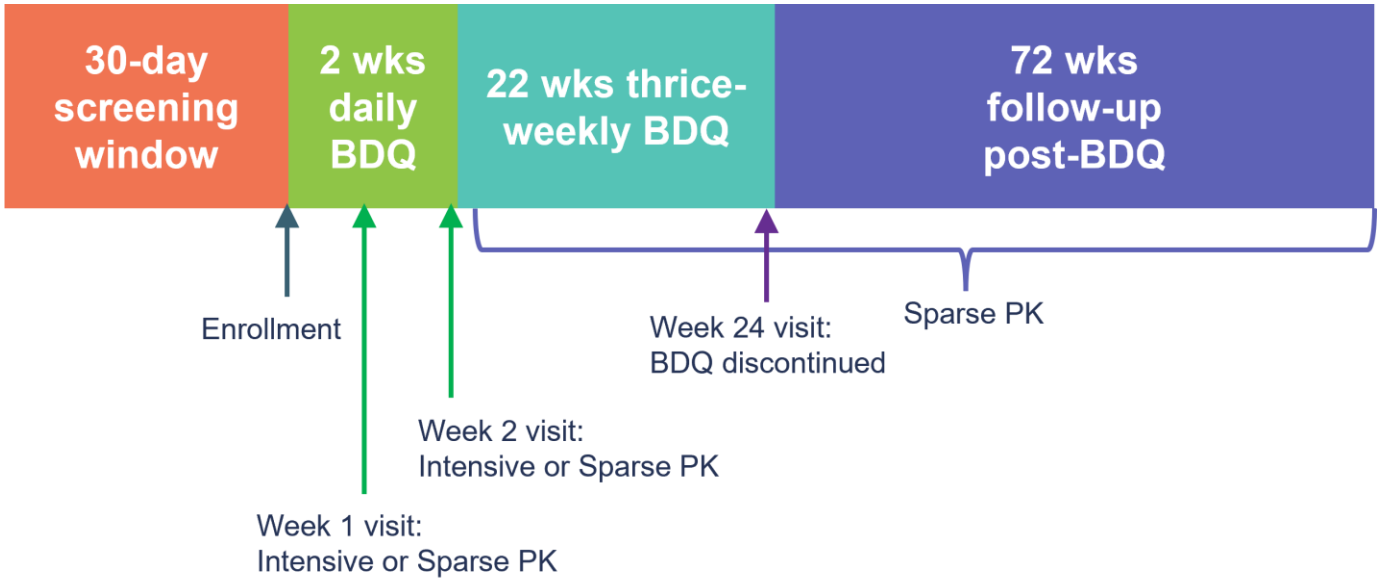
P1108: Phase I/II, Open-Label, Single Arm Study to Evaluate the PK, Safety and Tolerability of Bedaquiline Given in Combination with an Individualized RR-TB Therapy in Infants, Children, and adolescents with RR-TB Disease, Living with or without HIV

- Determine BDQ doses that achieve similar weekly exposure (AUC) of BDQ compared to adults taking BDQ at current recommended WHO dose.
- Evaluate safety and tolerability of BDQ over 24-week dosing period +2 years
- Conceived early – implemented later due to industry not implementing PIP = lack of access
- Parallel industry-funded study C211 opened later, no data yet in < 2 years, CLWH
- P1108: enrolment started 2017, completed 2023 (all under version 1.0)

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

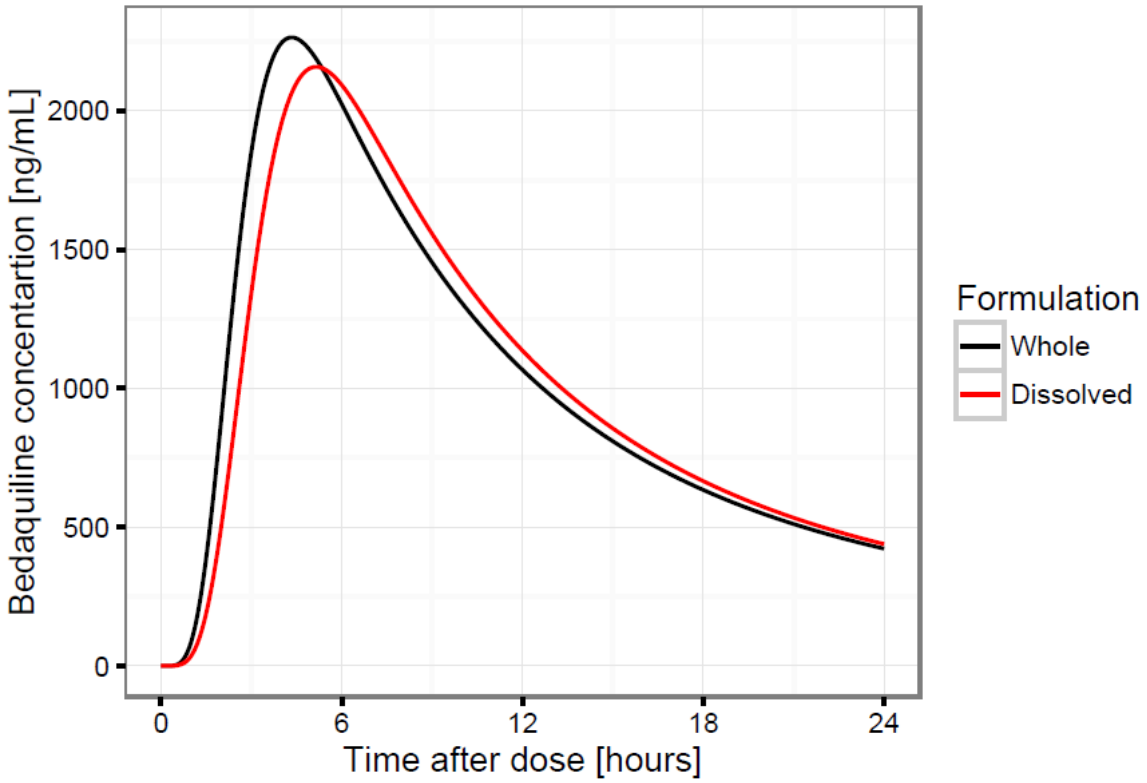
P1108 design features

- BDQ added as single drug to "optimized background regimen" – evolving
- Minimal age de-escalation
- Population PK modeling with dose adjustment
- Intensive and sparse PK sampling
- Mini-cohorts with PK and safety targets
- Real-time safety monitoring
- Pragmatic use of adult formulation
- Weight-banded dosing



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Lack of access to paediatric formulation: pragmatic solution
BDQ CRUSH Impact of dissolving on a typical BDQ PK profile



- Mean absorption time slightly longer for dissolved tablets: +23% (p=0.03, $CI_{95\%}$ 2.1-48%)
- T_{max}: 4.3 to 5.2h
- C_{max}: ↓ 5%

Difference in bioavailability dissolved vs whole tablets not statistically significant (p=0.92, $CI_{95\%}$ 94-108%) → **Bioequivalence criteria fulfilled**

Svensson, BJ Pharm 2018

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

- PK model developed from adult data with MDR-TB, study C208,C209, adapted
- Included covariate effects, adapted as data emerged. Body weight, abumin concentrations – time varying
- Age maturation function characterizing the development of *CYP3A4* with increasing age
- Apparent clearance at week 24 and weekly dose → BDQ weekly AUCss

Cohort	Age and Weight	BDQ Dosing
Cohort 1 Up to 24 participants to achieve 18 evaluable (approximately nine in each weight band)	≥ 6 to < 18 years ≥30 kg	*Participants ≥30 kg:* 400 mg once per day through the intensive PK sampling visit*, then 200 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants >7 to <30 kg* 200 mg once per day through the intensive PK sampling visit*, then 100 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants ≥ 3 to ≤ 7 kg:* 100 mg once per day through the intensive PK sampling visit*, then 50 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit
	≥ 6 to < 18 years ≥15 to <30 kg	
Cohort 2 Up to 30 participants to achieve 18 evaluable	≥ 2 to < 6 years >7 kg	
Cohort 3 Up to 30 participants to achieve 18 evaluable	≥ 0 to < 2 years ≥3 kg	

Elin Svensson

UPPSALA UNIVERSITET

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

EM Svensson et al. CPT:PSP, 2016, 5(12)

P1108 Sites

Haiti
GHESKIO (CRS 30022)

South Africa
DTTC (CRS 31790)
Sizwe (CRS 31929)
Matlosana (CRS 31976)

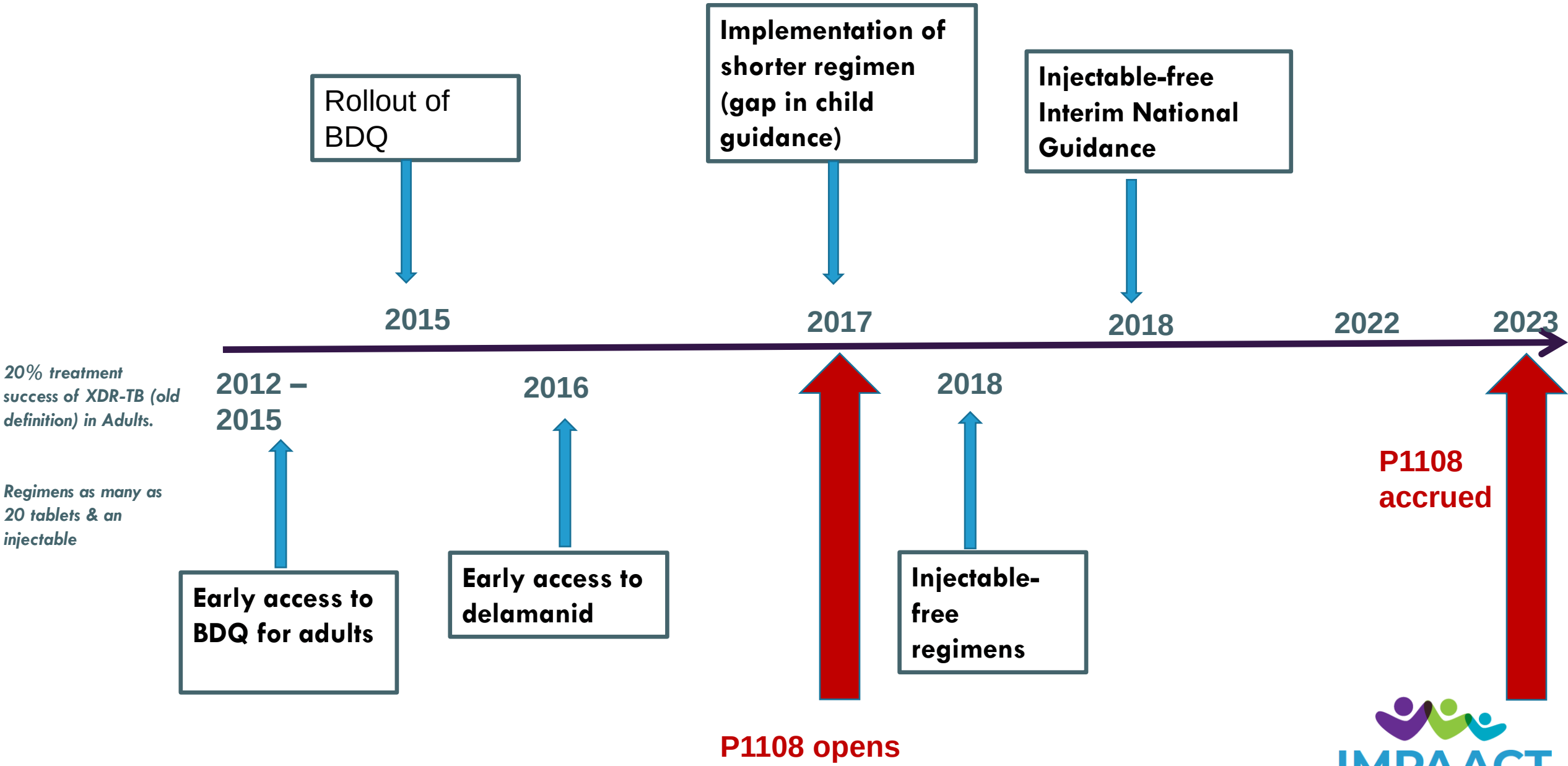
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Baseline characteristics in children enrolled in P1108 (n=54)

		Cohort 1 6-<18 y (n=18)	Cohort 2 (2-<6 y) (n=18)	Cohort 3 (0-<2 y) (n=18)	Overall N=54
Sex	Female	12 (67%)	9 (50%)	9 (50%)	30 (56%)
Race	African black	15 (83%)	10 (56%)	15 (83%)	40 (74%)
Age, years	Median	12.7 (7.0-13.9)	3.4 (2.8-4.4)	1.2 (0.7-1.8)	3.4 (1.8-7.0)
HIV status	LWH	5 (28%)	1 (6%)	2 (11%)	8 (15%)
WFA z score	Median	-1.5 (-2.3, -0.2)	-1.3 (-1.8,-0.3)	-1.9 (-2.9, 0.1)	-1.6 (-2.3-,-0.2)

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

P1108 informed WHO guidelines in real-time



South African National Guidelines

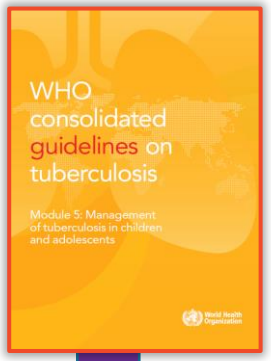
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

P1108 informed WHO guidelines in real-time

Rollout of BDQ

Implementation of shorter regimen (gap in child guidance)

Injectable-free Interim National Guidance



2015 | 2017 | 2018 | 2022 | 2023

20% treatment success of XDR-TB (old definition) in Adults.

Regimens as many as 20 tablets & an injectable

2012 – 2015

Early access to BDQ for adults

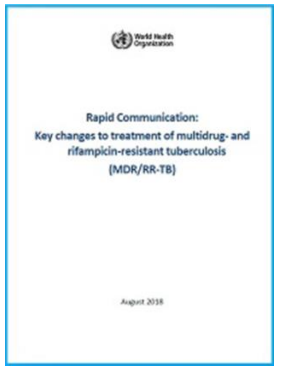
2016

Early access to delamanid

P1108 opens

2018

Injectable-free regimens



P1108 accrued

South African National Guidelines

Use of **bedaquiline** and delamanid in children

- In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used
- In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens

Remarks:

- *Applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline*
- *Complements the current WHO recommendation on longer regimens that contain delamanid*

These recommendations make it possible to build all oral regimens for children of all ages: 9-12 months

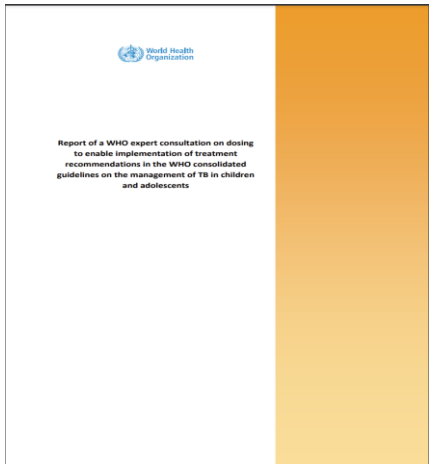
World Health Organization

END TB

Bedaquiline WHO provisional dosing recommendation

Weight range[a]	Age category	Dosing of bedaquiline[b]
3 to <5 kg	0 to <3 months	30 mg QD/10 mg TIW
	≥3 months	60 mg QD/20 mg TIW
5 to <7 kg	0 to <3 months	30 mg QD/10 mg TIW
	≥3 months	60 mg QD/20 mg TIW
7 to <10 kg	0 to <3 months	30 mg QD/10 mg TIW
	3 to <6 months	60 mg QD/20 mg TIW
	≥6 months	80 mg QD/40 mg TIW
10 to <16 kg	3 to <6 months	60 mg QD/20 mg TIW
	≥6 months	120 mg QD/60 mg TIW
16 to <24 kg	–	200 mg QD/100 mg TIW
24 to <30 kg	–	
30 to <35 kg[c]	–	400 mg QD/200 mg TIW
35 to <50 kg	–	
≥50 kg	–	

Health
ization



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

The Union
WORLD CONFERENCE ON LUNG HEALTH 2022
COMBATING PANDEMICS: TODAY & TOMORROW
Virtual Event November 8-11

Treatment outcomes in young children with RR-TB treated with regimens including bedaquiline and delamanid: a global individual patient data meta-analysis

Maria Garcia-Cremades[1,2*], Anneke C. Hesseling[3*], Vivian Cox[3], Kendra Radtke[1], Tamara Kredo[4], Alexander Floren[1], Rory Dunbar[3], Rada Savic[1], Anthony Garcia-Prats[3,5*]

[1]University of California San Francisco, Department of Bioengineering and Therapeutic Sciences, San Francisco, USA. [2]Complutense University of Madrid, Department of Pharmaceutics and Food Technology, Madrid, Spain. [3]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa. [4]Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa. [5] University of Wisconsin School of Medicine and Public Health, Department of Paediatrics ,Wisconsin, USA

E-Poster No. EP-06-651

Introduction

There is limited access to the novel drugs including bedaquiline (BDQ) and delamanid (DLM) in young children due to limited data on outcomes, dosing and safety.

We determined treatment outcomes in children< 6 years of age routinely receiving RR-TB treatment regimens including BDQ or DLM

Methods

Systematic review and IPD-MA included children and adolescents (0-19 years) treated for RR-TB.

We performed a matched analysis evaluating key outcomes using propensity-matching (age, sex) and exact matching (HIV status, previous TB treatment, bacteriologically-confirmed, AFB-positive) for:

- Children aged <6 years treated with BDQ
- Children aged <3 years treated with DLM

Results

Data from 24,231 children, from 44 studies were included, from 18 countries.

- Children <6 years who received BDQ *(n=40)* were more likely to be HIV positive, have confirmed/ smear-positive RR-TB, with no significantly difference in treatment success.
  They received shorter treatment duration and were less likely to receive an injectable (*p<0.01*).
- Children <3 years who received DLM: limited data *(n=7, all favourable outcomes)*

Discussion

Few young children globally received BDQ or DLM, given the lack of formal recommendation to use BDQ or DLM in these age groups. Overall outcomes in young children with RR-TB were excellent (Table 1, Table 5).

These data informed WHO 2022 guidelines recommending BDQ and DLM in children across the entire age spectrum.

Bedaquiline use was significantly associated with shorter RR-TB treatment duration and less injectable drug use in children <6 years

Photographs taken with written informed consent, Desmomd Tutu TB Centre

Extra Tables & Figures

Table 1. Key characteristics among children <6 years of age with RR-TB stratified by BDQ use

	No BDQ (n=1992)	BDQ (n=40)
Treatment success	1,676 (84.1%)	**30 (75.0%)**
Age in years, Mean (SD)	2.32 (1.55)	1.23 (1.66)
Male sex	977 (49.0%)	19 (47.5%)
HIV Positive	364 (20.0%)	12 (30.0%)
Bacteriologically confirmed	1237 (79.8%)	31 (96.9%)
AFB smear positive	273 (21.9%)	17 (48.6%)
Pulmonary TB	1669 (90.8%)	37 (92.5%)
Extrapulmonary TB	352 (20.1%)	2 (5.3%)
Extended resistance		
FQN or SLI resistance	83 (41.9%)	4 (66.7%)
FQN and SLI resistance	115 (58.1%)	2 (33.3%)

Table 2. Effect of BDQ on treatment success (treatment completion and cure vs. death or treatment failure)

	Bdq given (success/ total)	Bdq NOT given (success/total)	Matched multivariate model regression	
			Adjusted OR (95%CI)	*p-value*
Bdq <6 years	24/27 (89%)	485/498 (97%)	0.94 (0.09,10.3)	0.9

Intervention: All-oral regimen with BDQ
Comparator: All-oral regimen without BDQ

Table 3. Effect of BDQ on RR-TB treatment duration

	Bdq given Duration in months mean, (SD)	Bdq NOT given Duration in months mean, (SD)	Matched linear model regression	
			Estimate drug effect (months) (95%CI)	*p-value*
Bdq <6 years	13.3 (5.9)	16.4 (5.8)	-3.47 (-6.0, -0.91)	0.008

Intervention: Ay regimen with BDQ
Comparator: Any regimen without BDQ

Table 4. Effect of BDQ on the use of any injectable drug

	Bdq given (Inj given/total)	Bdq NOT given (Inj given/total)	Matched multivariate model regression	
			Adjusted OR (95%CI)	*p-value*
Bdq <6 years	6/33 (18%)	1075/1573 (68%)	0.12 (0.05,0.32)	<0.001

Intervention: Ay regimen with BDQ
Comparator: Any regimen without BDQ

Table 5. Key characteristics among children with RR-TB treated with DLM

	< 3 years of age (n=7)	3 to <6 years of age (n=14)
Treatment success	**7 (100.0%)**	**14 (100.0%)**
Age in years, Mean (SD)	1.29 (0.951)	4.071 (0.917)
Male sex	3 (47.5%)	7 (50.0%)
HIV Positive	0 (0.0%)	1 (7.1%)
Bacteriologically confirmed	5 (100%)	8 (61.5%)
AFB smear positive	2 (28.6%)	0 (0.0%)
Pulmonary TB	4 (57.1%)	6 (42.9%)
Extrapulmonary TB	3 (42.9%)	8 (57.1%)
Extended resistance		
FQN or SLI resistance	--	0 (0.0%)
FQN and SLI resistance	1 (100%)	1 (100%)

More practical dosing needed in children: proposed once-daily dosing strategy for BDQ with new WHO harmonized weight bands

Yu-Jou Lin

- Joint age- and weight- banded dosing approaches

  Harmonized weight bands across the therapeutic areas[1] were assessed

- Used published population PK model (Svensson model[2]) as a base

  Model developed using data from P1108, once daily regimen strategy

Elin Svensson

Bedaquiline

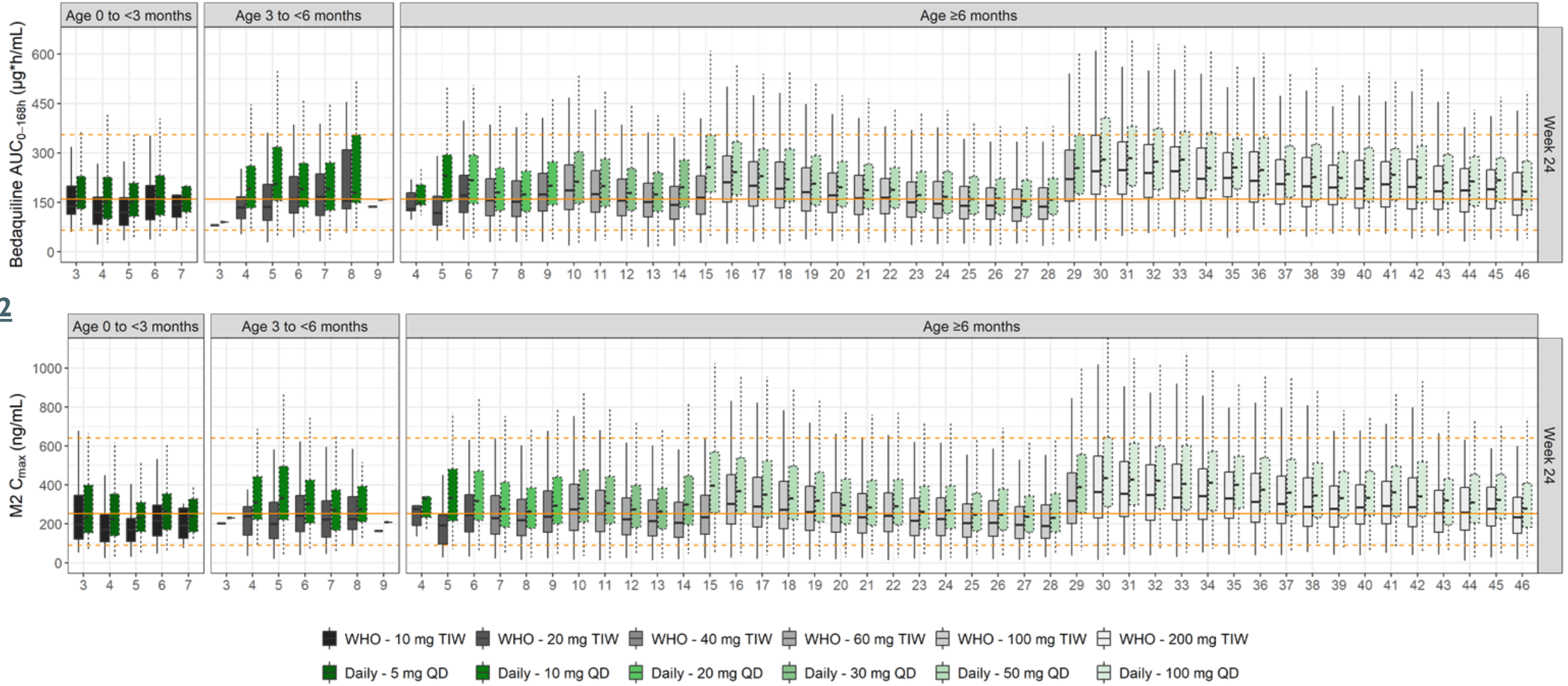
Age category	WHO weight band	WHO-recommended dosing	Harmonized weight band	Proposed once-daily dosing
0 to < 3 months	All	30 mg QD / 10 mg TIW	All	30 mg QD / 5 mg QD
3 to < 6 months	All	60 mg QD / 20 mg TIW	All	60 mg QD / 10 mg QD
≥ 6 months	3 to < 7 kg	60 mg QD / 20 mg TIW	3 to < 6 kg	60 mg QD / 10 mg QD
	7 to < 10 kg	80 mg QD / 40 mg TIW	6 to < 10 kg	80 mg QD / 20 mg QD
	10 to < 16 kg	120 mg QD / 60 mg TIW	10 to < 15 kg	120 mg QD / 30 mg QD
	16 to < 30 kg	200 mg QD / 100 mg TIW	15 to < 30 kg	200 mg QD / 50 mg QD
	≥ 30 kg	400 mg QD / 200 mg TIW	≥ 30 kg	400 mg QD / 100 mg QD

[1]Waalewijn H *et al.* Denver, Colorado; Abstract No.940. (2024)
[2]Svensson EM, Dosne A, Karlsson MO. *CPT Pharmacomet Syst Pharmacol.* (2016)

UPPSALA UNIVERSITET

Predicted exposures of bedaquiline and metabolite M2 in children

Bedaquiline



M2

Paediatric MDR-TB regimens still lag behind access in adults

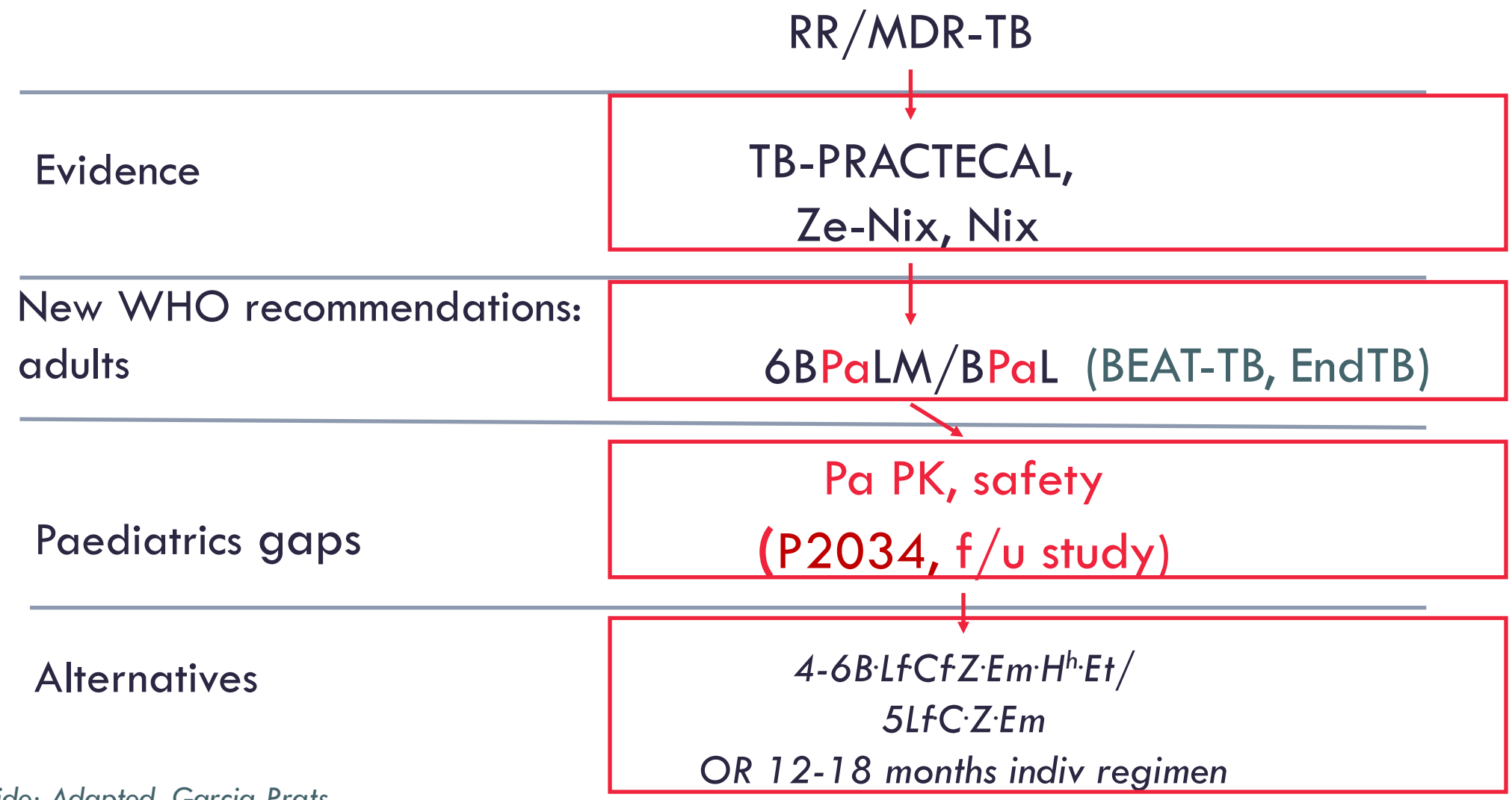
RR/MDR-TB

Evidence	TB-PRACTECAL, Ze-Nix, Nix
New WHO recommendations: adults	6BPaLM/BPaL (BEAT-TB, EndTB)
Paediatrics gaps	Pa PK, safety (**P2034**, f/u study)
Alternatives	*4-6B·Lf·Cf·Z·Em·H^{h}·Et/ 5Lf·C·Z·Em OR 12-18 months indiv regimen*

Slide: Adapted, Garcia-Prats

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Paediatric MDR-TB regimens still lag behind access in adults

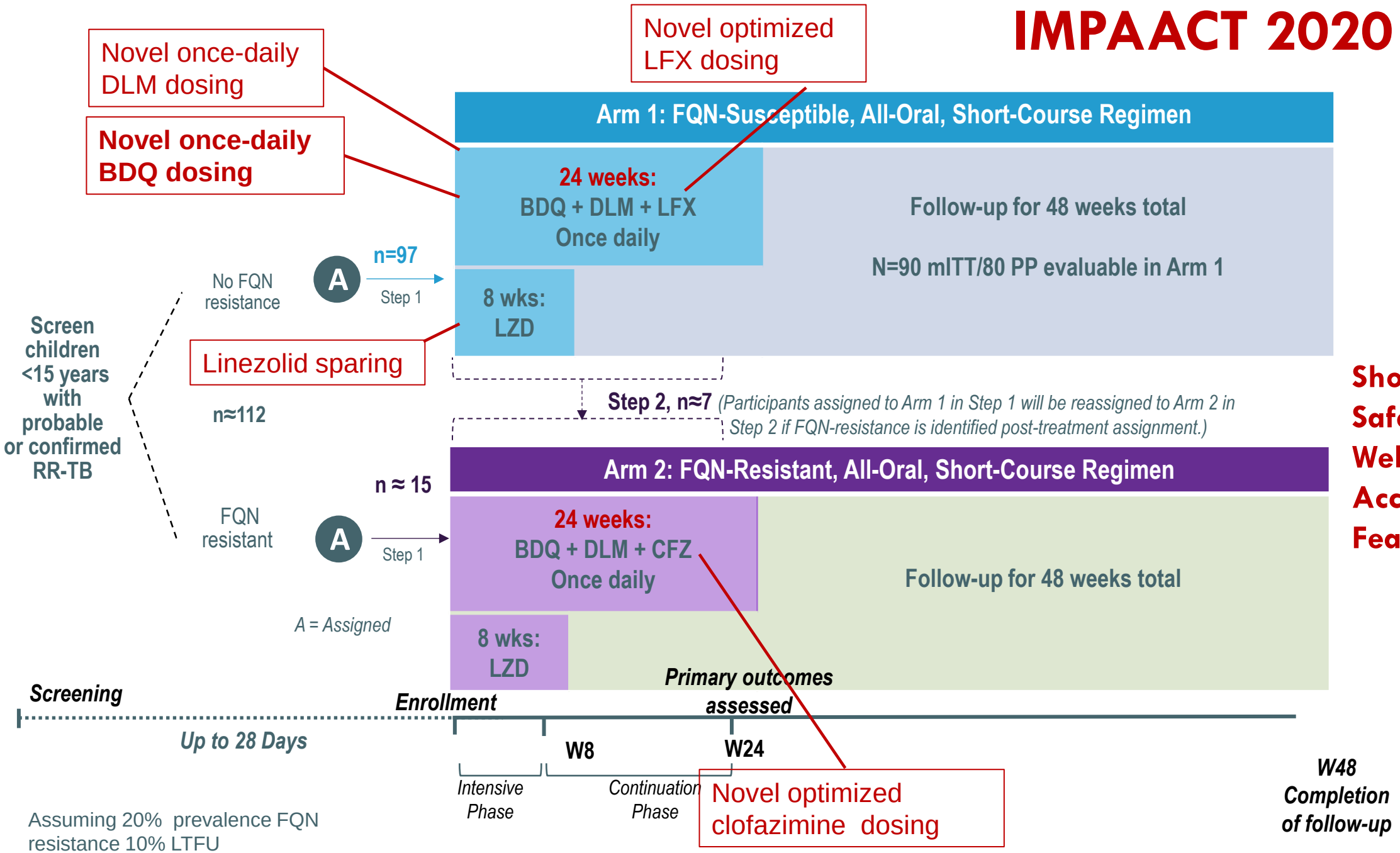


P2020

Slide: Adapted, Garcia-Prats

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2020



P1108 results: Union Late Breaker Session November 2024

Thank you to participants, families, communities, site personnel and IMPAACT P1108 team, funders

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network