Tuberculosis Scientific Committee Update

Anneke C. Hesseling and Amita Gupta
26 September 2024

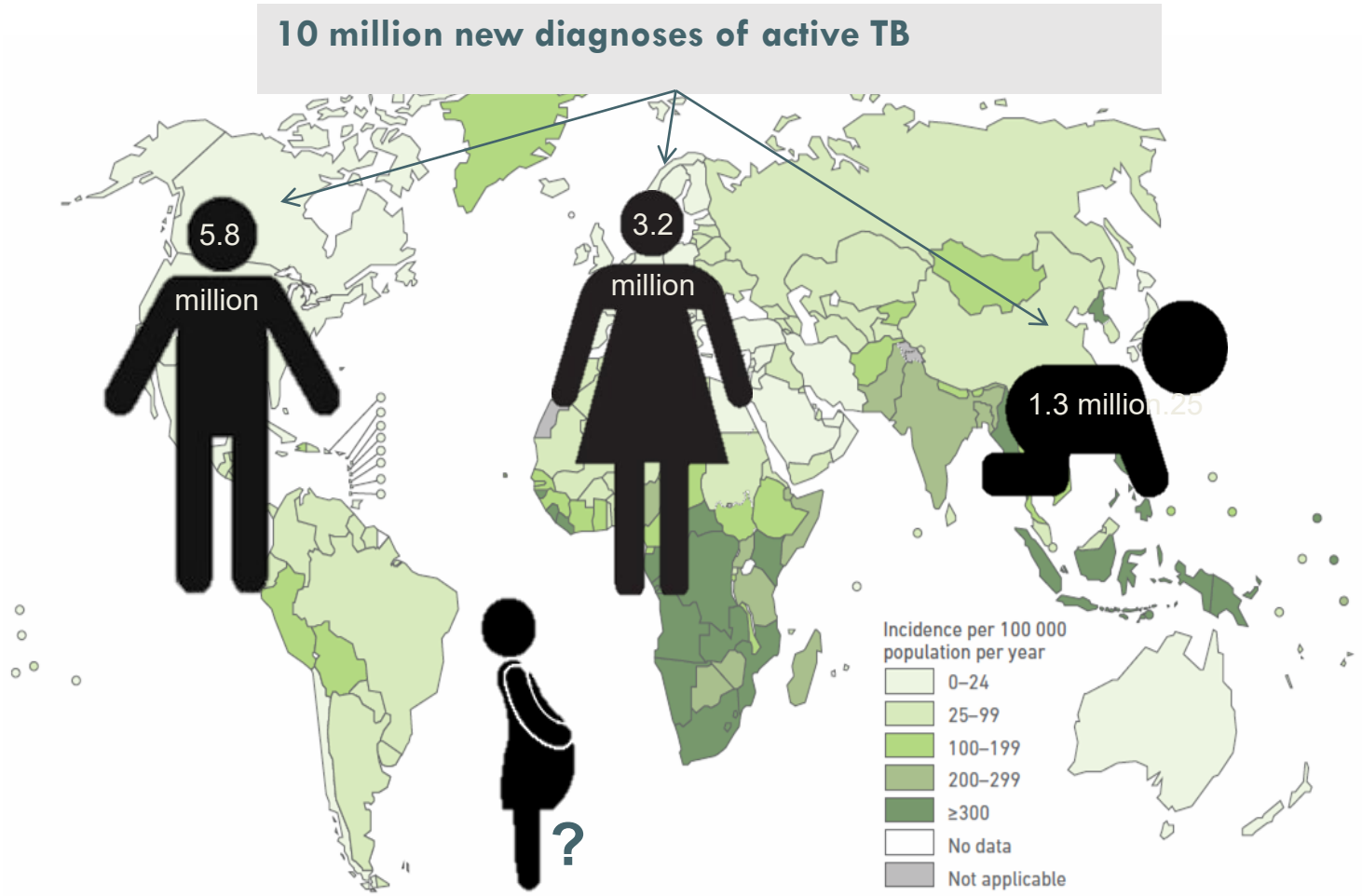
IMPAACT

International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Global tuberculosis burden: priority groups

10.6 million new diagnoses

of active TB



"Priority populations"

- Children < 15 tears
- Adolescents
- Pregnant women
- Elderly
- DM
- (PLWH)
- **Jointly – large proportion of global TB burden**

WHO 2022

IMPAACT TBSC Goals and Strategy

To evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-positive and negative infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, licensing and will result in global access and impact

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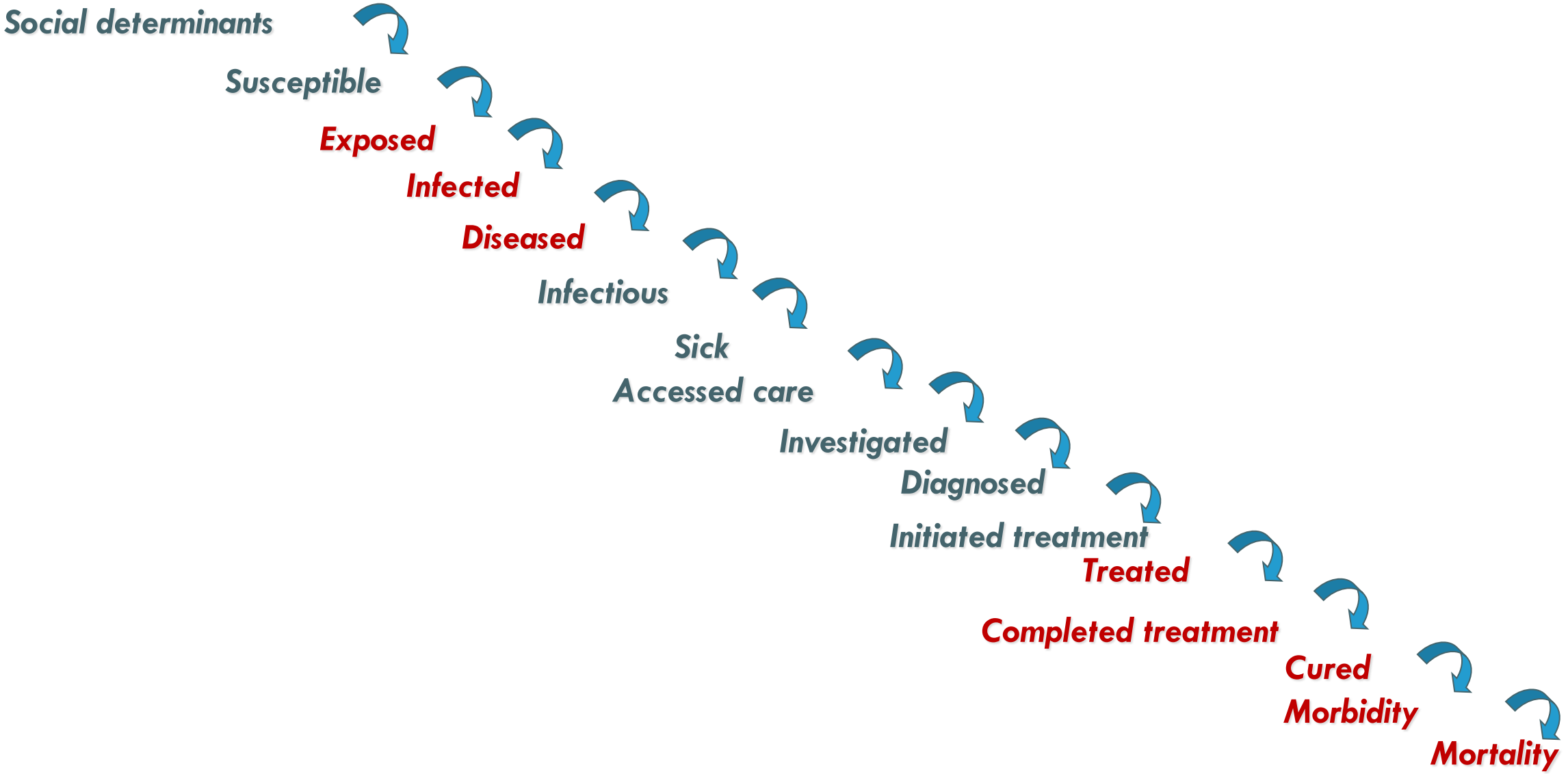
Key Transitions in Tuberculosis: role of IMPAACT



Tuberculosis Scientific Committee Members

Chair
Anneke Hesseling

Vice Chair
Amita Gupta

Committee Members
Lisa Marie Cranmer*
Anthony Garcia-Prats
Pauline Howell*
Jyoti Mathad*
Lindsay McKenna
Tisungane Mvalo*
Mandar Paradkar*
Vanessa Rouzier
Ethel Weld*

Note: Names with asterisks are new members.

Emeritus Members
Anne-Marie Demers
Kelly Dooley

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Tuberculosis Scientific Committee Members

SDMC Representatives
Mattie Bartlett
Soyeon Kim
Grace Montepiedra

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Sharon Nachman
Rachel Scheckter
Stephanie Sivalingam
Veronica Toone
Rhonda White

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Patrick Jean-Philippe
Tafadzwa Kasambira
Sai Majji
Dwight Yin

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Dichaba Siane

Laboratory Center
Afton Dorasamy

Social Behavioral Science Core Representatives
Graeme Hoddinott
Nicole Montañez

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Additional and Mentored investigators

- Christy Beneri
- Jennifer Hughes
- Louvina van der Laan
- Megan Palmer
- Susan Purchase*
- Dillon Wademan*
- Victoria Namakuta*
- Jeff Tornhem
- Sasha Horn

**integrated into main TBSC this year*

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2024 Global New TB Drug Pipeline[1]

Discovery | Preclinical Development | Clinical Development

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

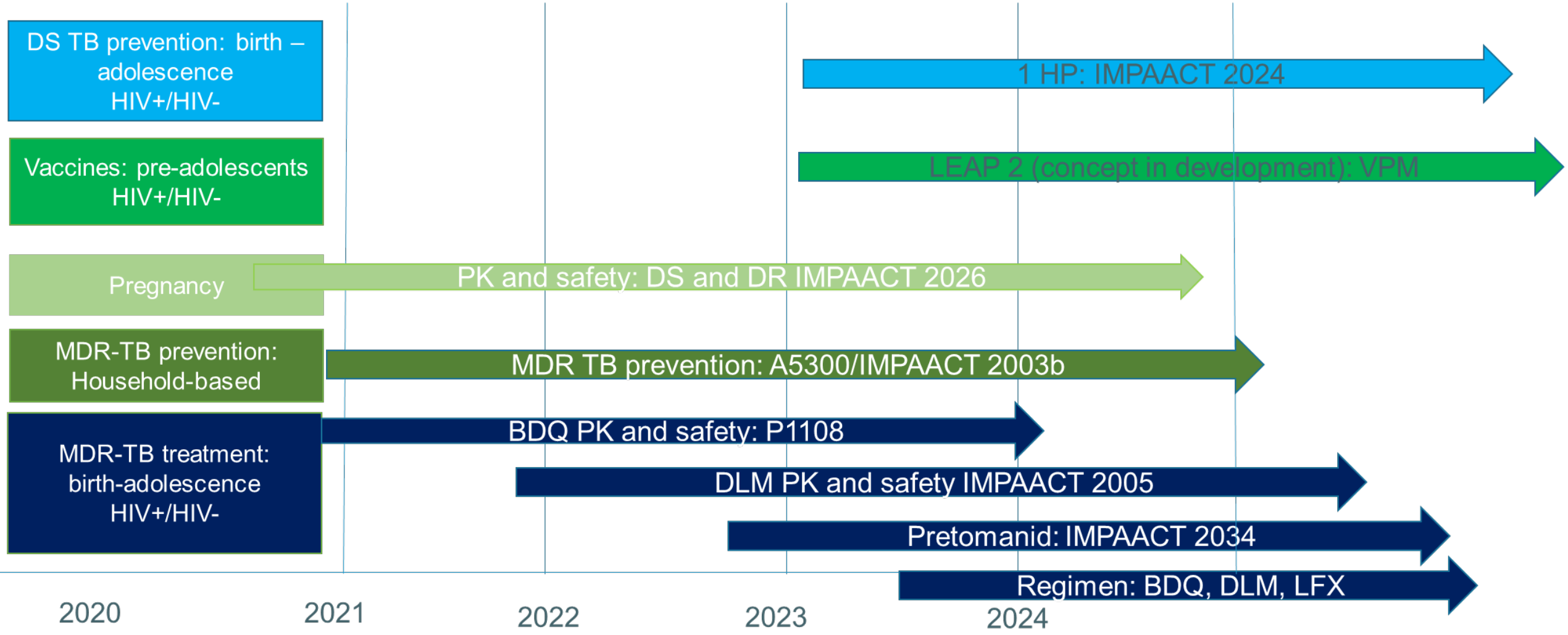
Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

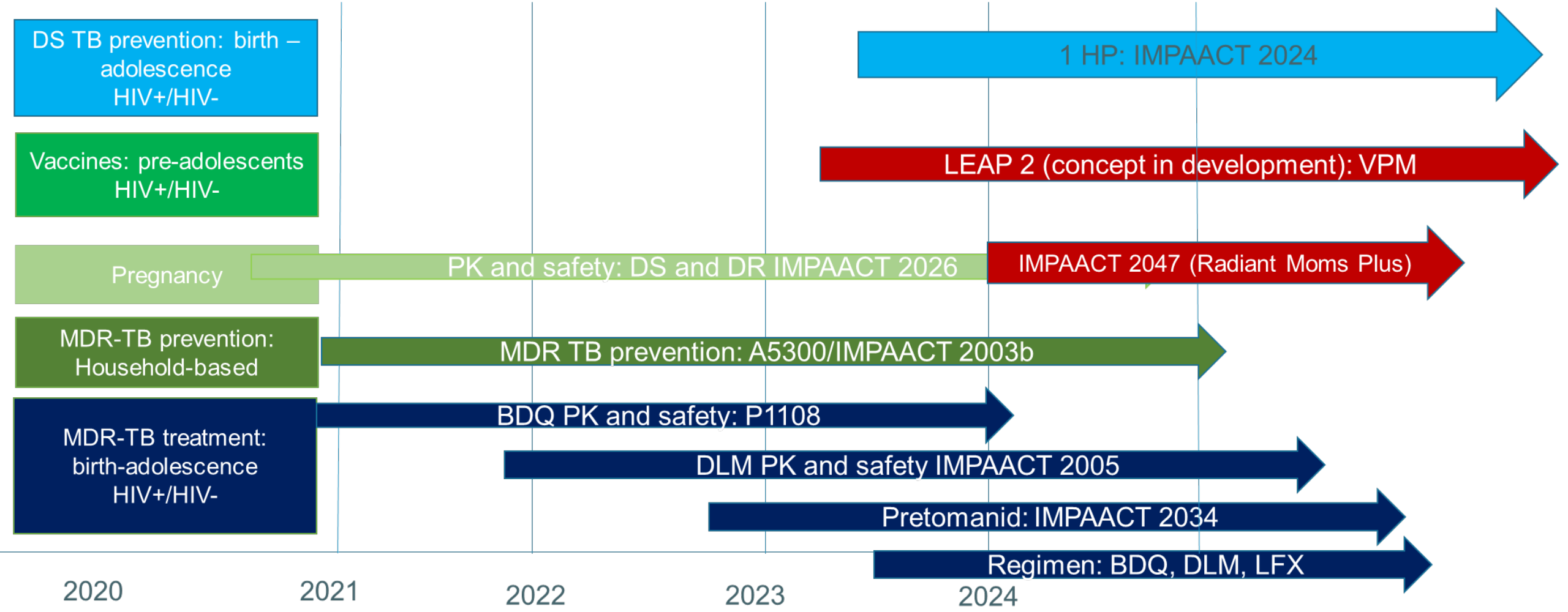
www.newtbdrugs.org

Updated: March 2024

Rich IMPAACT TBSC Roadmap 2024



Rich IMPAACT TBSC Roadmap 2024



TB prevention

IMPAACT 2024: Phase I/II Dose Finding, Safety and Tolerability Study of Daily Rifapentine Combined with Isoniazid (1HP) for Tuberculosis Prevention in Children Less than 13 Years of Age with and without HIV

Protocol Chairs: *Nicole Salazar-Austin, MD, ScM and Christy Beneri, DO*

Gap:

- Ultra-short course TPT like 1HP have the potential to substantially improve adherence, completion rates and safety of TPT and could dramatically improve TPT delivery for children globally
- 1HP dosing not known for children < 13 years

Design: Phase I/II, multi-site, open-label, non-comparative dose finding study. Sequential cohorts

Primary Objectives:

- To determine the weight-band dosing of RPT taken as part of the 1HP regimen by evaluating:
  - PK RPT exposures among children with and without HIV (match to adult exposures seen in BRIEF-TB)
  - Safety and tolerability of the 1HP regimen among children with HIV while receiving BID DTG and without HIV
- To evaluate the effect of RPT taken as part of the 1HP regimen on the PK of DTG

Current Status: resubmission to MPRG in October 2024 (with new dispersible RPT tablet)

Anticipated Timeline: Open Q2 2025; Completion in 2028

Pharmaceutical Support: None; RPT and INH purchased from Macleods

Anticipated Impact: Inclusion of 1HP for children <13 years in WHO TPT Guidelines

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14 IMPAACT Sites Approved for Participation

Cohort 1	Cohort 2
Living without HIV	Living with HIV
60 evaluable participants	30 evaluable participants

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A5300B/IMPAACT2003B

- Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients
- (A5300B/I2003B/PHOENIx)

IMPAACT TBSC

Amita Gupta MD MHS FIDSA on behalf of an incredible team
Protocol Co-chair, PHOENIX A5300B/IMPAACT 2003

ACTG Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

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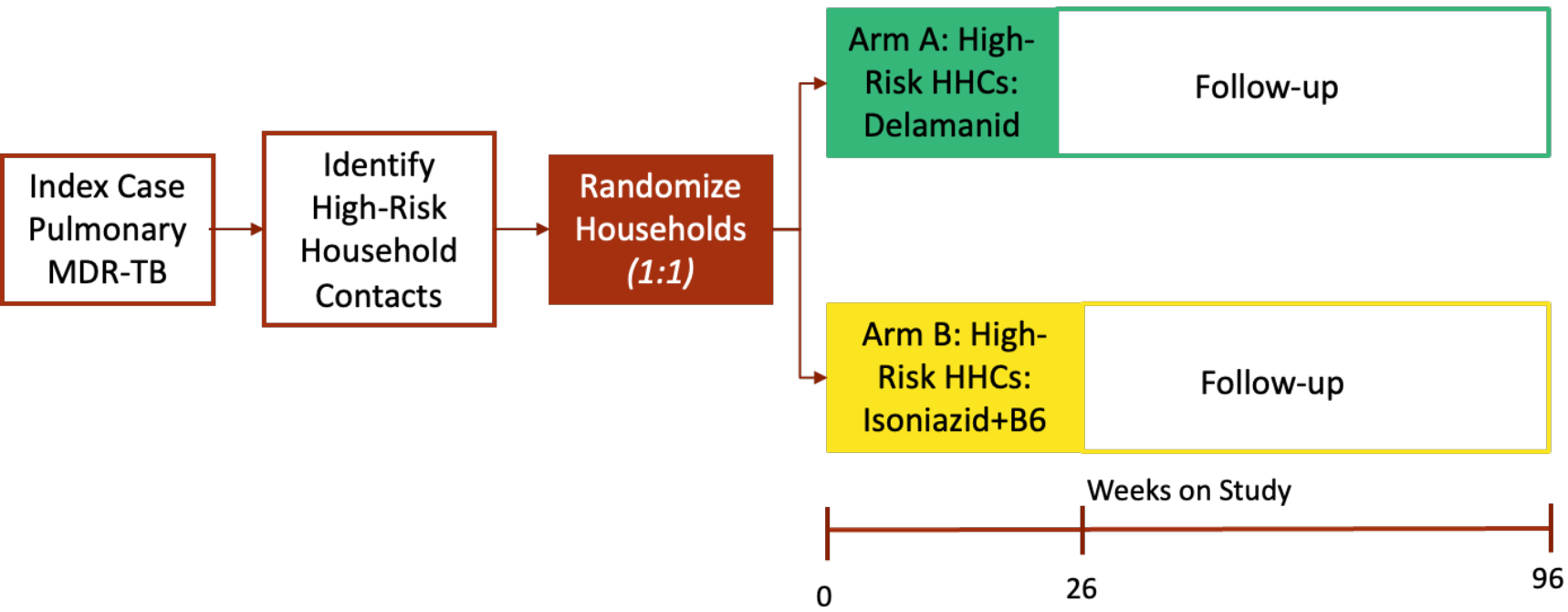
PHOENIX: Efficacy and Safety of Delamanid vs INH

3834 high-risk household contacts



Phase III open-label, multi-center, cluster-randomized, superiority trial

High-Risk Household Contacts

- Children <5 years old
- ≥5 years of age who are
  - HIV-infected or non-HIV immunosuppressed
  - TST positive (≥5mm) and/or IGRA positive

Timeline of PHOENIX trial

- **June 20, 2018:** Version 1.0
- **June 3, 2019**: Open to accrual under Version 2.0 after FDA and DAIDS changes
- **June 13, 2019:** 1st index case enrolled
- **July 10, 2019:** 1st HHC Enrolled
- **March 18, 2020:** COVID pause
- **March 31, 2020:** Version 3.0
- **15 July 2020:** COVID pause lifted
- **November 5, 2020:** pause of pediatric <15 yrs enrolment due to unanticipated neuropsychiatric side effects
- **March 13, 2021:** FDA lifted hold on pediatric enrolment
- **May 15, 2022**: RFA for additional sites
- **November 30, 2022:** Version 4.0
- **August 6, 2024:** Intensive PK study for children < 5 years fully accrued
- **September 17, 2024**: Version 5.0 open to accrual

ACTG Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections

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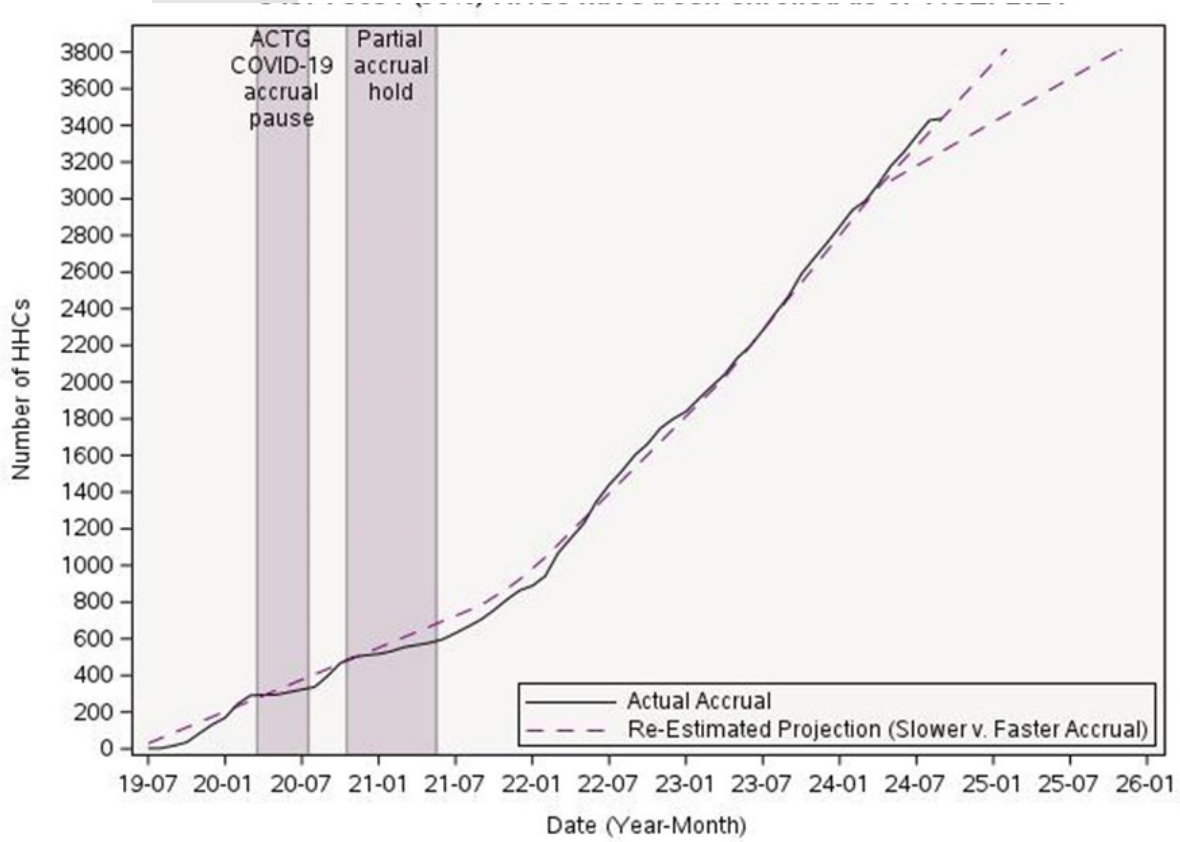
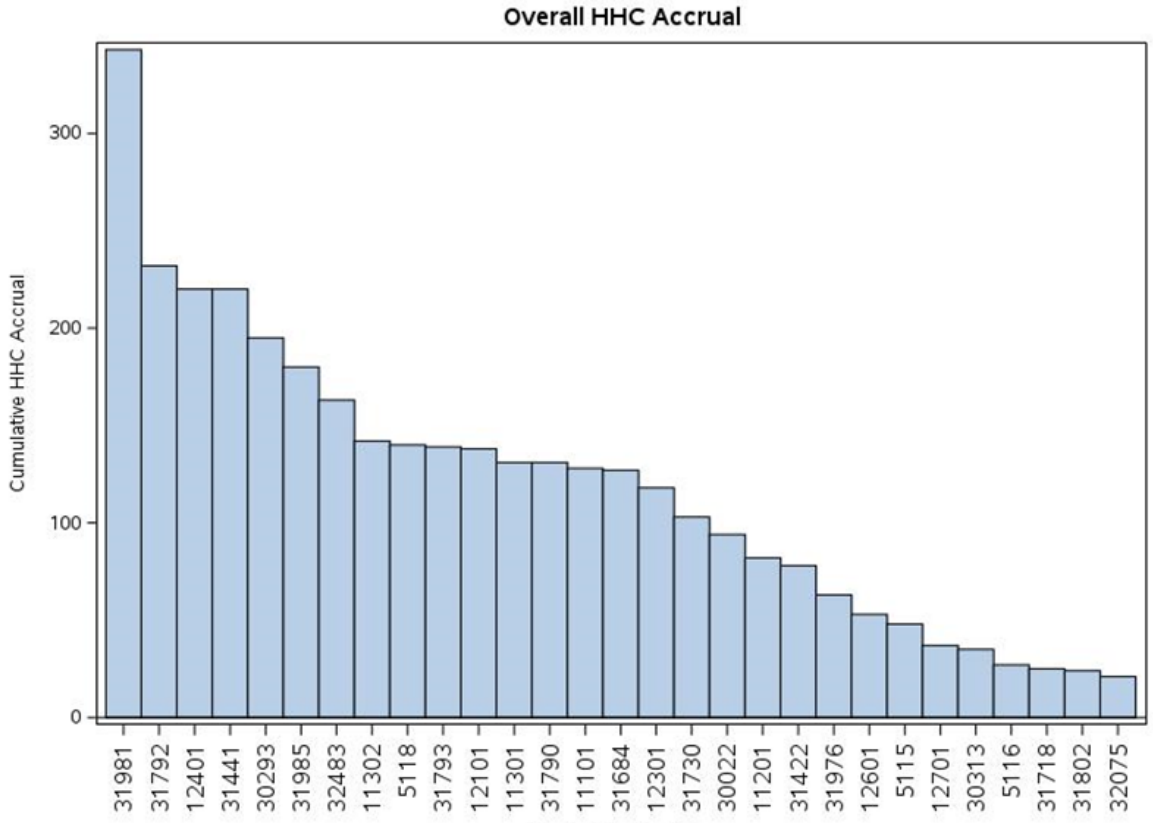
- **1789 Index cases enrolled**
- **3470/3834 (90.5%) HHCs enrolled**

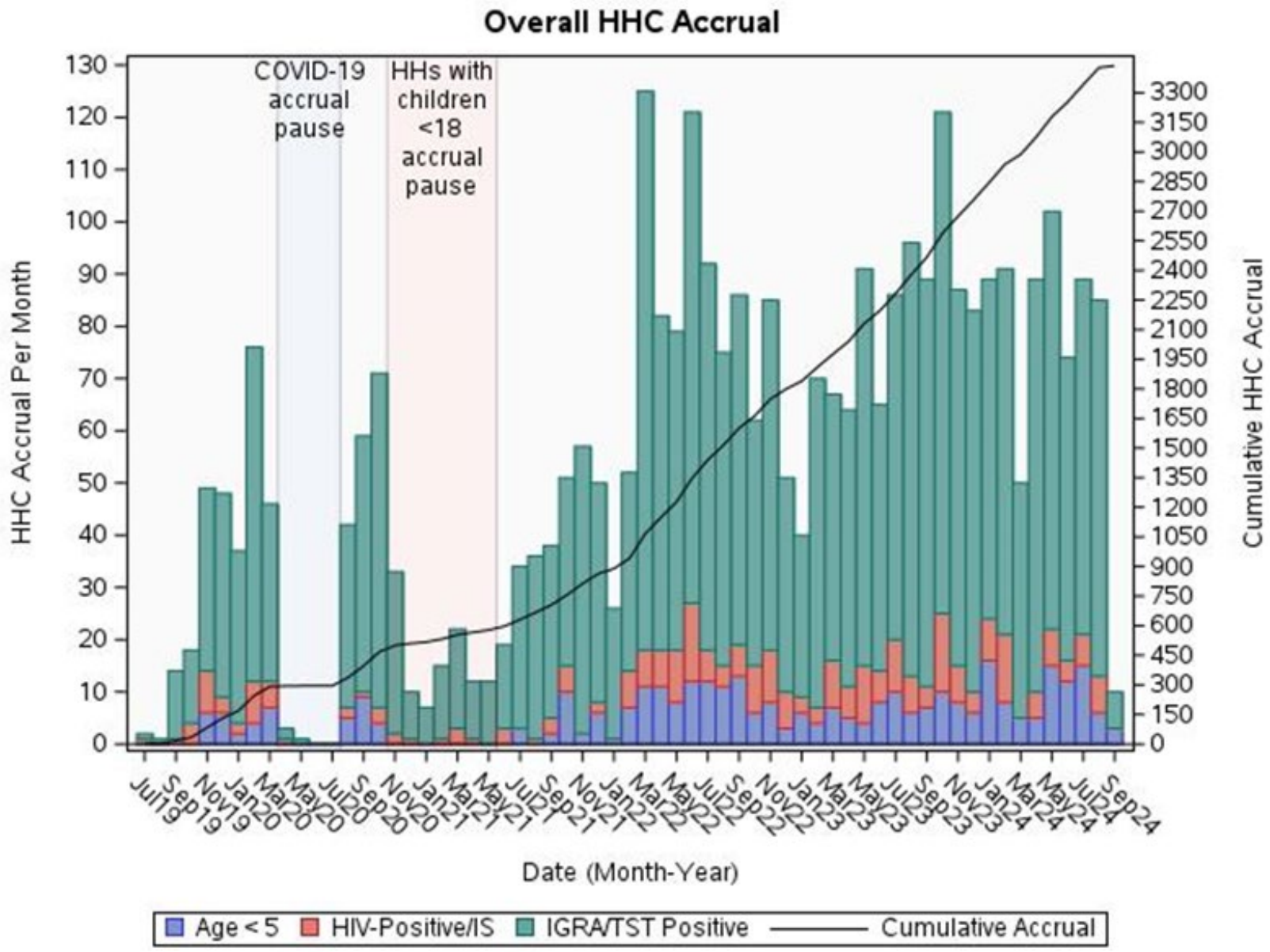
29 sites in 13 countries





Accrual of high-risk HHCs

- 26 yrs Median age
- 56% Female
- 82% LTBI+
- 35% <18 years
- 10% <5 years
- 8% HIV



Baseline Characteristics
Index Cases (N=1585)

- Median age: **37 years** (range: 18-98 years)
- **36% female**
- **27% HIV-positive**
- MDR-TB documented in 865 index cases:
  - MDR-TB: **87%**
  - Pre-XDR TB: **10%**
  - XDR-TB: **3%**
- Median time (Q1, Q3) from initiation of MDR-TB treatment to study entry was **29 (15, 54) days**

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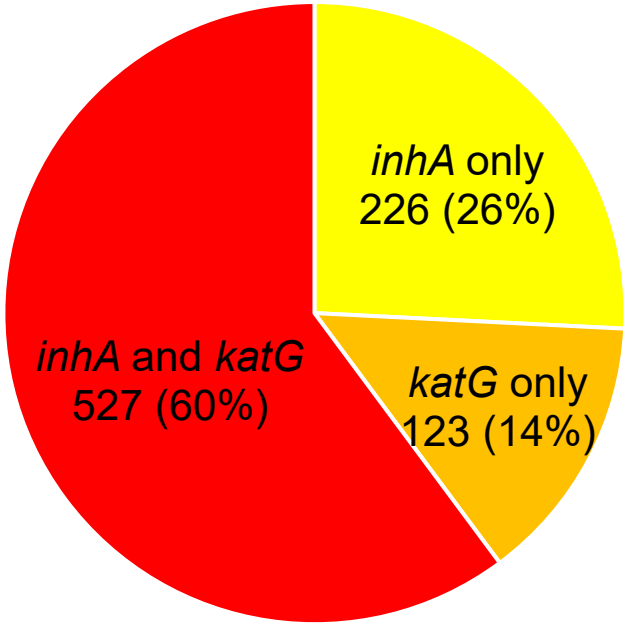
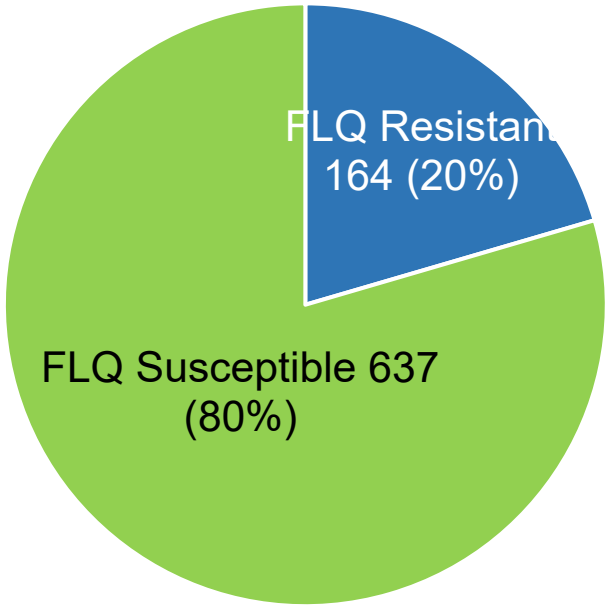
Resistance Profile of MDR TB* Index Cases (N=1355)

***inhA* promoter and *katG* mutations**
N=876



Fluoroquinolone Susceptibility
N=801

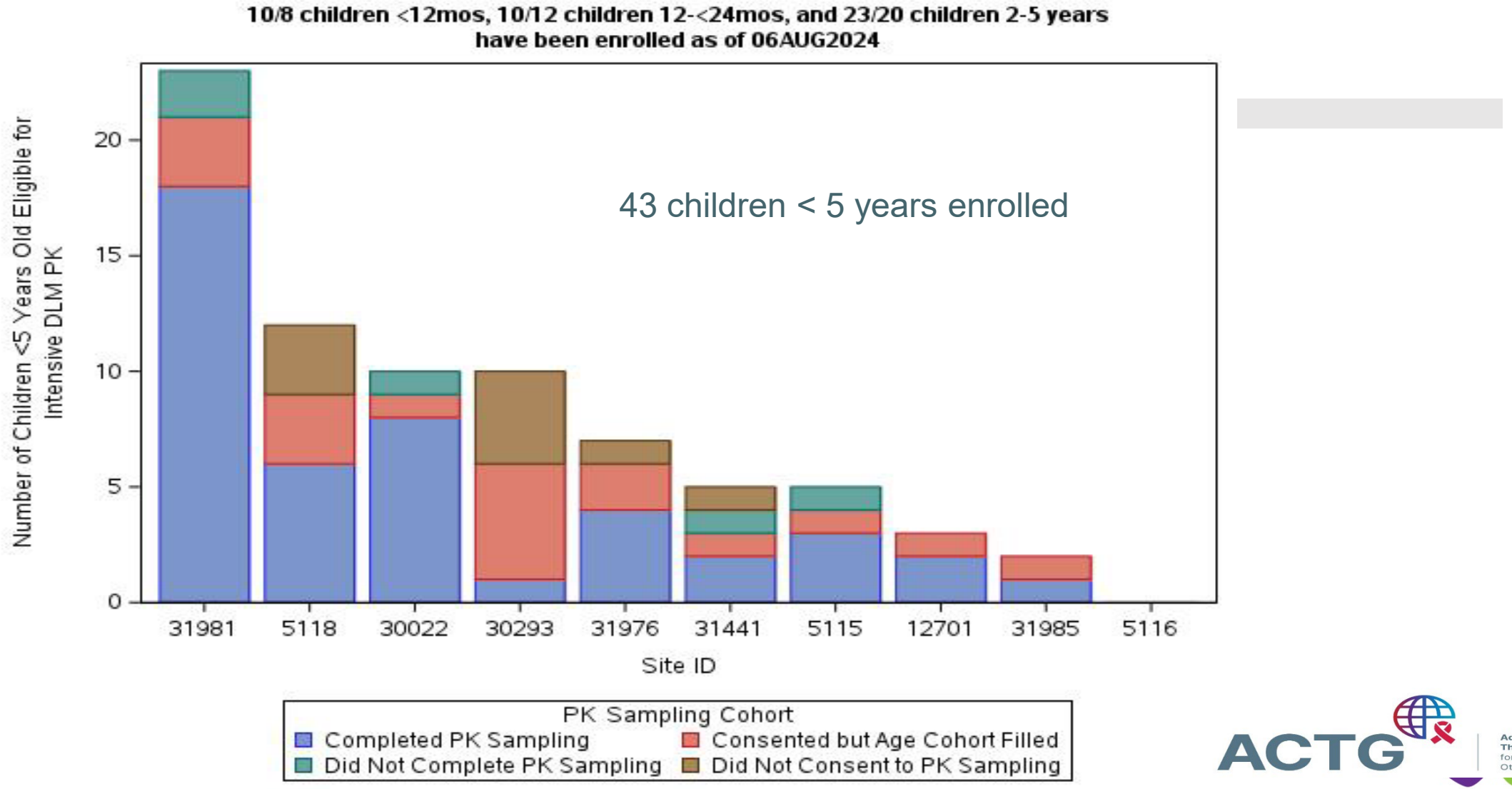


- 74% of index cases have high-level INH resistance due to katG mutations
- Documented fluoroquinolone resistance prevalence varied from 0% in Haiti (0/47) and Zimbabwe (0/6) to 86% (38/44) in Vietnam (p<0.001).

Submitted, Union 2024

* Old definitions used: Pre-XDR=MDR plus FLQ resistance or SLID resistance but not both, XDR = MDR plus both FLQ and SLID resistance

Delamanid PK study in children fully enrolled



Primary prevention: vaccines

LEAP-2: Phase 2a Study of the Safety and Immunogenicity of ID93/GLA-SE against Tuberculosis in South African Pre-Adolescents Living with and without HIV

Study Product	Living with HIV		Living Without HIV	
	IGRA+	IGRA-	IGRA+	IGRA-
ID93/GLA-SE	28	28	28	28
Placebo	14	14	14	14

- ID93/GLA-SE provided by DAIDS. Product stability of available batch under annual continuing review (Nov)
  - **Need plan to acquire product if current batch found unstable**
- MTBVAC an important candidate; consider LEAP-2 sequential design vs separate IMPAACT NWCS vs collaborative trial (IAVI/Biofabri HVTN)

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Pregnancy


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IMPAACT 2047: PK, safety and tolerability of high dose rifapentine given with moxifloxacin for tuberculosis during pregnancy (Radiant-Moms Plus: Rifapentine in High Doses in Pregnancy with TB)

Protocol Chairs: *Sylvia LaCourse, MD, MPH and Jyoti Mathad, MD, MSc*

Design: Open-label, two-arm, randomized multi-site trial to evaluate the safety and PK of 4HPMZ compared to 6HRZE in pregnant people diagnosed with DS-PTB

Primary Objectives: Among pregnant people with DS-TB and their infants

- Determine safety and tolerability of 4HPMZ compared to 6HRZE
- Compare targeted pregnancy and neonatal outcomes between 4HPMZ and 6HRZE
- Evaluate PK of RPT, MFX, INH, and PZA among pregnant people receiving 4HPMZ, and RIF, INH, PZA, and EMB among pregnant people receiving 6HRZE

Current Status: Approved for Protocol development Aug 2024

Anticipated Timeline/Pharmaceutical Support: TBD

Anticipated Impact: Better understanding of PK and safety of 6HRZE and 4HPMZ in setting of pregnancy, inclusion of 4HPMZ as an option for pregnant people in WHO DS-TB Guidelines is found to be safe, expansion of safe and shorter treatment options for DS-TB for pregnant people

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P1078

- 1 RO1 NWCS 626, **Savita Pahwa,** *Immune correlates of LTBI in HIV-exposed infants*
- 1 K23 NWCS 637 **Lisa Marie Cranmer,** Maternal-infant TB antibodies in P1078
- 1 R21 NWCS 639, **Adriana Weinberg,** Dynamics Of M. Tuberculosis-Specific Innate and Adaptive Immunity During Pregnancy and Postpartum In Women With HIV
- 1 K08 NWCS 631 **Kristina Brooks**, Biomarkers of Hepatotoxicity in Pregnant and Postpartum Women Living with HIV and Latent TB
- NWCS 640 **Clement Adu-Gyamfi,** IMPAACT ESI Award: Indoleamine 2, 3-dioxygenase as a Tuberculosis biomarker in pregnant women living with Human Immunodeficiency Virus (presentation at IMPAACT 2024)

- DR 828, **Ashenafi S Cherkos**. Effect of pregnancy versus postpartum maternal isoniazid preventive therapy (IPT) on infant growth
- DACS 721 **Grace Montipiedra**, Safety and toxicity of Isoniazid (INH) exposure by trimester: a systemic review and individual participant data meta-analysis of women who became pregnant in randomized TB prevention trials
- 9 papers published (1 NEJM, 1 Lancet Child Health, 1 eClinical Medicine, 3 CID, 1 Frontiers Immunology, 1 Clinical Pharm &Therap, 1 BMC)
- 21 Abstracts presented
- 1 under review (hepatotoxicity)
- 3 in progress (PK/PG/PD; Immune correlates, meta-analysis of safety of INH in pregnancy)

Many more in the pipeline!

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DR-TB treatment

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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)

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P1108 Sites

Haiti
GHESKIO (CRS 30022)

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

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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)

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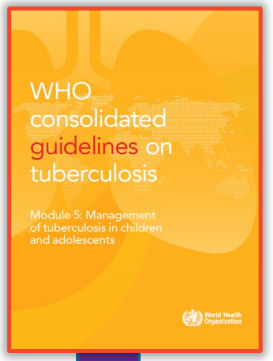
P1108 informed WHO guidelines in real-time

Rollout of BDQ

Implementation of shorter regimen (gap in child guidance)

Injectable-free Interim National Guidance



2015 2017 2018 2022 2023

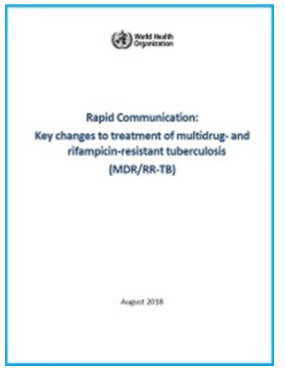
20% treatment success of XDR-TB (old definition) in Adults.

Regimens as many as 20 tablets & an injectable

2012 – 2015

2016

2018



Early access to BDQ for adults

Early access to delamanid

Injectable-free regimens

P1108 opens

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

IMPAACT 2005: A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) in Children with MDR-TB with and without HIV

Protocol Chairs: *Ethel Weld, Anthony Garcia-Prats, Kelly Dooley*

Gap:

- Optimal Dosing for delamanid (DLM) in children under 3 years of age and <15 kg (and with HIV) is unknown
- Neuropsychiatric signals in children on RR-TB treatment poorly characterized

Design: Phase I/II, multi-site, open-label, single-arm, multiple dose study

Primary Objectives:

- To evaluate the **safety** and **PK** of delamanid when added to OBR, in children with and without HIV, at model-based doses determined to be most likely to achieve exposures similar to those achieved in adults by 100 mg twice daily in the treatment trials

Current Status: Open to accrual; **34 Enrolled** (sample size: to achieve at least 36 evaluable (up to 48)

Challenges: Accrual holds; COVID lockdowns, neuropsychiatric signals; accrual closes November 2024.

Anticipated Timeline: Closed to Follow-up October 2026 *(Projected)*

Pharmaceutical Support: Otsuka -- dispersible child-friendly formulation, population PK model

Anticipated Impact: *Inform dosing in children < 3 years* and <15kg (currently only a *conditional* WHO rec); elucidate neuropsychiatric tox signals; *confirm* current WHO dosing in children 0-18 years (all *in silico* now).

IMPAACT 2005 Sites

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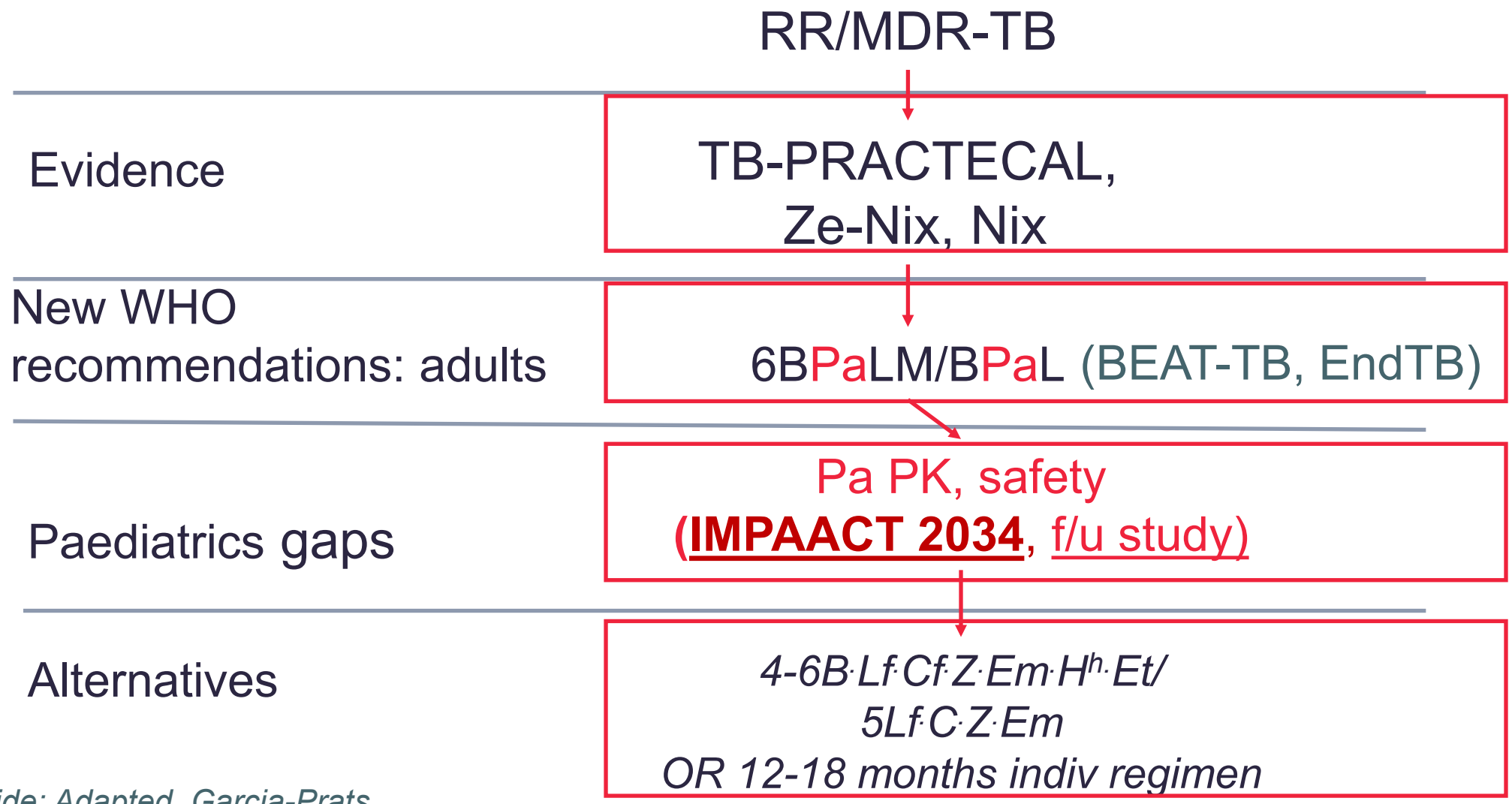
Paediatric MDR-TB regimens still lag behind access in adults



Slide: Adapted, Garcia-Prats

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IMPAACT 2034: Phase I Study of the Pharmacokinetics, Safety, and Acceptability of a Single Dose of Pretomanid Added to an Optimized Background Regimen in Children with Rifampicin-Resistant Tuberculosis

Protocol Chairs: *Ethel Weld, Anthony Garcia-Prats, Pauline Howell*

Gap:

- Pretomanid (Pa, or Pa-824) is a novel drug for TB treatment, approved by FDA in adults for treatment of drug-resistant TB in combination with bedaquiline and linezolid
- Pretomanid pharmacokinetics, safety and acceptability are unknown for children

Design: Phase I, multi-site, open-label, non-comparative, **single-dose** study (first-in-children).

Primary Objectives:

- To evaluate the PK of a single dose of pretomanid in children with RR-TB to identify the weight-banded doses of pretomanid to be evaluated in a future multiple-dose study in children

Current Status: Open to accrual. 20 Enrolled (sample size: to achieve at least 36 evaluable [up to 72]).

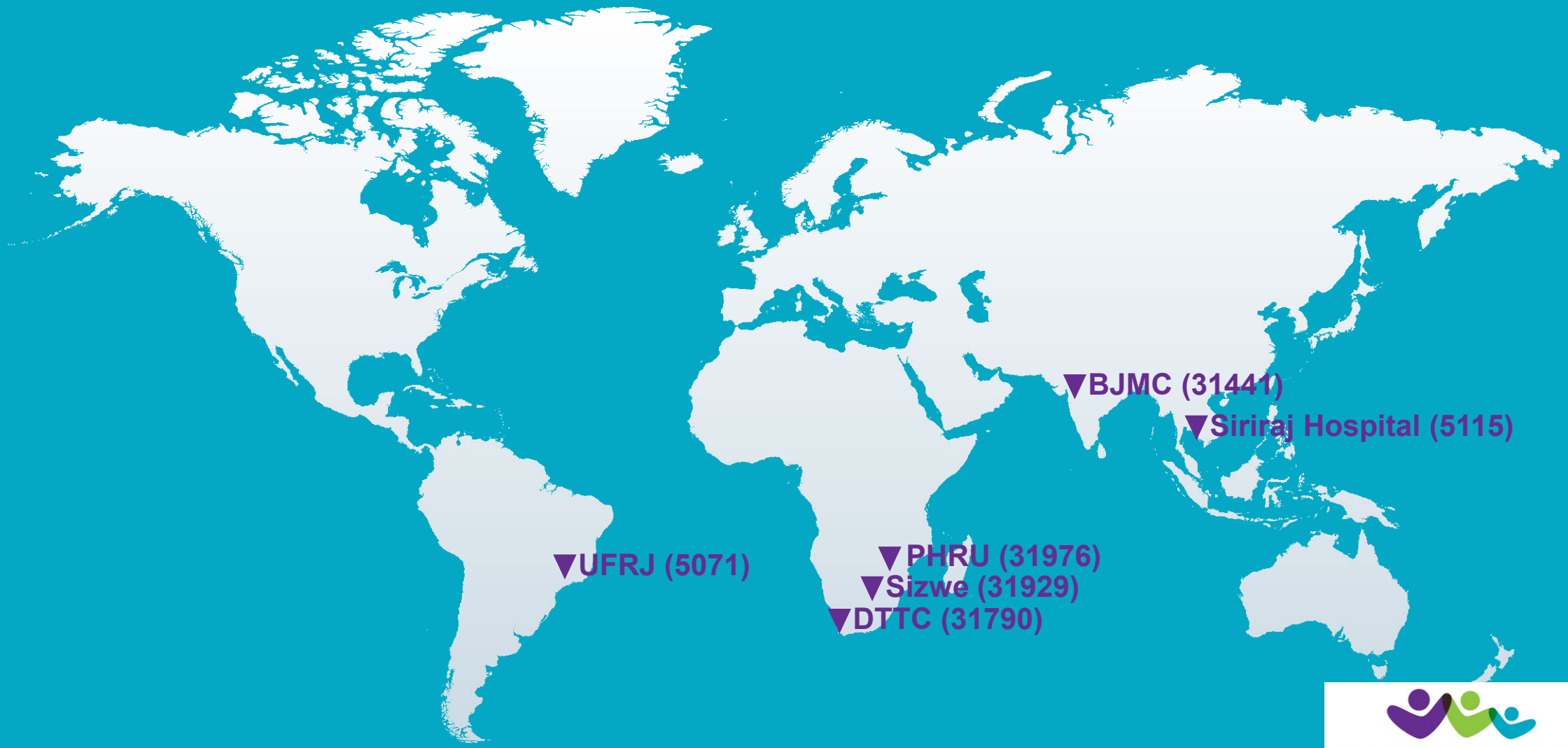
Challenges: Only female participants are eligible to participate

Anticipated Timeline: Closed to Accrual January 2026 *(Projected)*

Pharmaceutical Support: Pretomanid (TB Alliance)—dispersible child-friendly formulation

Anticipated Impact: Inform future multiple-dose study in children with rifampicin-resistant tuberculosis

IMPAACT 2034 Sites



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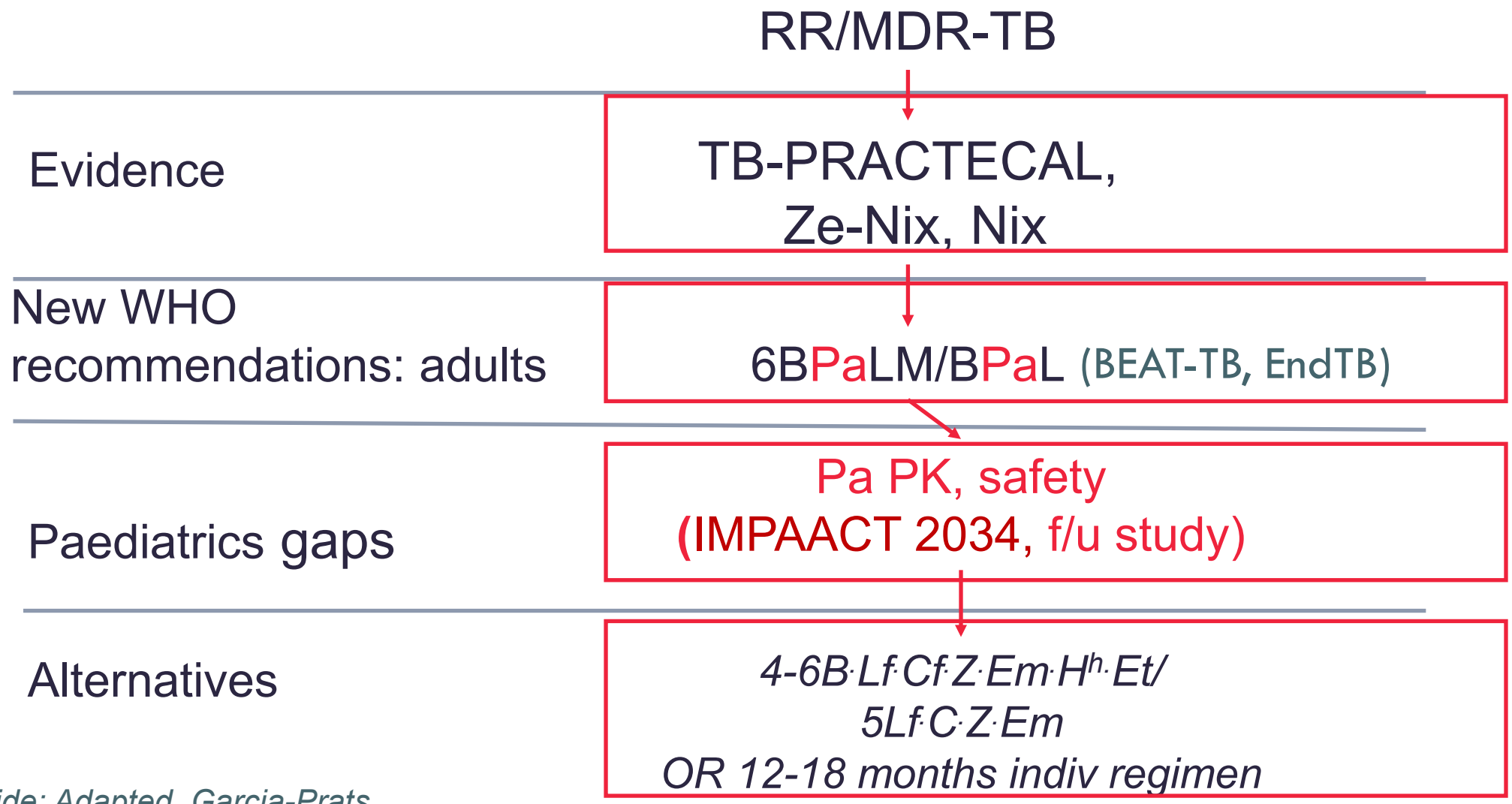
Paediatric MDR-TB regimens still lag behind access in adults



IMPAACT 2020

Slide: Adapted, Garcia-Prats

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IMPAACT 2020: Phase II Study of Shortened Oral Treatment for Rifampicin-Resistant Tuberculosis in Children

Protocol Chairs: *Anthony Garcia-Prats, Anneke Hesseling, Pauline Howell, Jennifer Hughes*

Gap: Newly recommended short, oral treatment regimens for RR-TB represent a huge advance but have important limitations for children including 1) 6 months of LZD resulting in frequent AEs and 2) complex dosing.

- 8 weeks of LZD is expected to have a more favorable risk-benefit balance for children
- A once-daily dosing approach for all medicines will improve regimen acceptability and adherence

Design: Phase II, multi-site, open-label, two-arm study

Primary Objectives: Among children with RR-TB with FQN susceptibility: to characterize the safety and tolerability of a novel all-oral, short-course, once-daily, treatment regimen through Week 24

Secondary Objective: 1) Characterize efficacy of novel, all-oral, once-daily regimen through 48 weeks; 2) characterize PK of once-daily BDQ, DLM, LFX and CFZ

Current Status: In protocol development

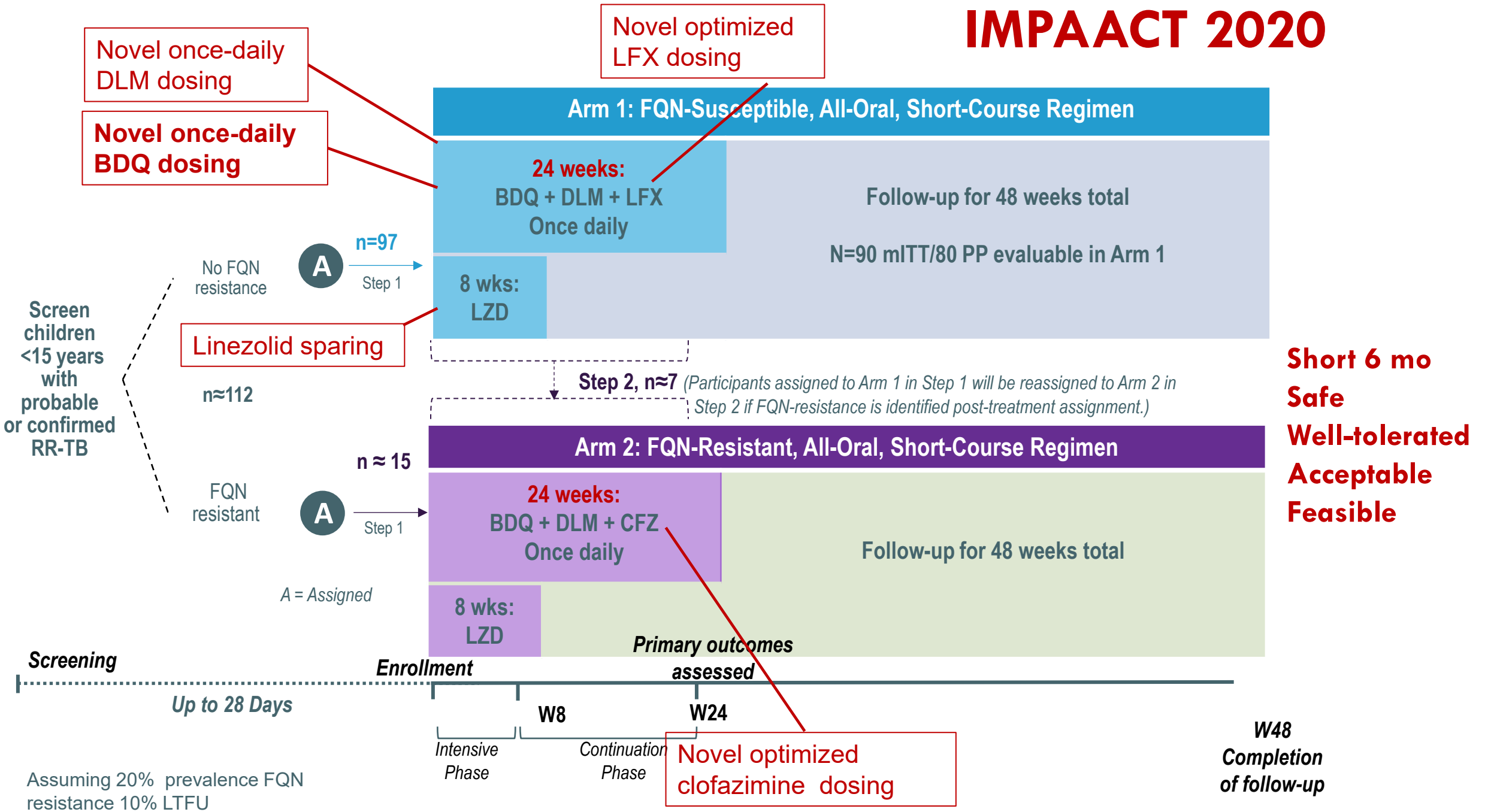
Anticipated Timeline:

Pharmaceutical Support: Janssen (BDQ), Otsuka (DLM)

Anticipated Impact: 1) Inform dosing guidelines for once-daily optimized dosing of BDQ, DLM, LFX, CFZ;

2) Provide evidence on safety and outcome of 8-week linezolid-containing regimen

IMPAACT 2020



Short 6 mo
Safe
Well-tolerated
Acceptable
Feasible

Next priority studies

1. **Pregnancy:**
   - **IMPAACT 2047: Radiant Moms Plus Trial**
   - **TB Pregnancy IPD and modelling post 2024 and modeling interventions>**
   - **Nesting pregnancy options standard across TB trials**

2. **DR TB: Open 2020, develop pretomanid multi-dose study**

3. **TB vaccine trials: LEAP2**

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