Tuberculosis Scientific Committee Update

Anneke C. Hesseling, Amita Gupta
TBSC Chair
IMPAACT Annual Network Meeting
30 June 2021

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International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Overall TB Scientific Committee Goals

"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 improved care and access.*"

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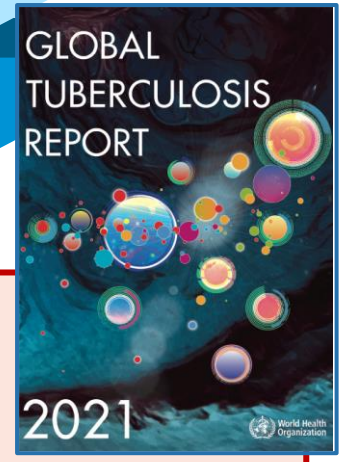
Global burden estimates (2021 Global TB report)



TB among all ages

9.9 million

TB patients in 2020

1.5 million

TB deaths in 2020

1.3m in HIV-uninfected
215k in PLHIV

7.5 million

children (0–14) infected with TB each year

(Dodd et al, 2014)

1.09 million

children (0-14 years) developed TB in 2020

47.5% <5 years olds

727 000 adolescents

(10–19 year-olds) developed TB in 2012

(Snow et al, 2018)

226 000

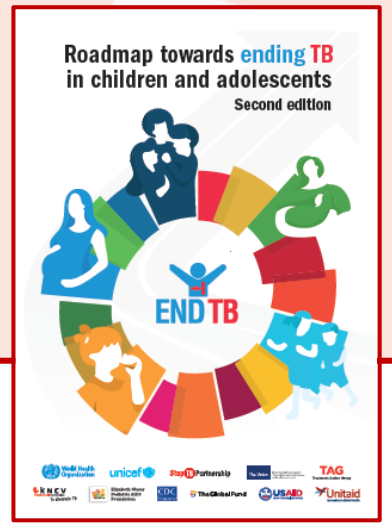
child (0-14) TB deaths in 2020

80% in children <5 years

96% of deaths in children who did not access TB treatment

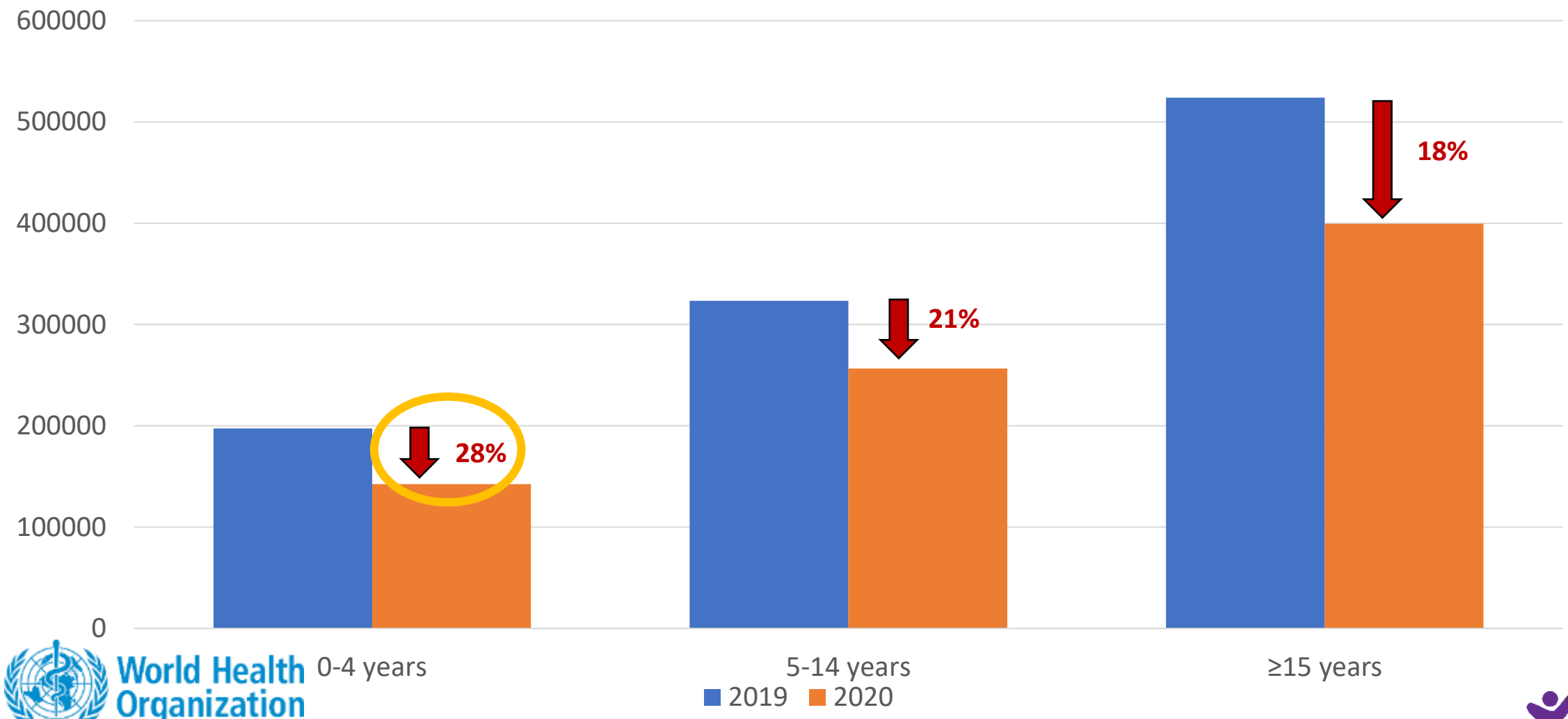
21 000 (9%) deaths among children living with HIV

(Dodd et al, 2017a)



World Health Organization

Impact of COVID-19 on TB notifications in <15years



World Health Organization

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Development of updated guidelines 2022
on the management of TB in children and adolescents

- Evidence reviewed on the following PICO questions, using GRADE* methodology:
  1. **Use of Xpert Ultra in gastric aspirate and stool specimens**
  2. **Integrated treatment decision algorithms**
  3. **Treatment shortening in children with non-severe TB**
  4. **In children with MDR/RR-TB: Use of bedaquiline in children under 6 and delamanid in children under 3 years**
  5. **Short intensive treatment regimen for TBM**
  6. **Models of care for case detection and provision of TPT (decentralized and family-centred, integrated approaches)**
- **Rapid communication** published in August 2021
- **Consolidated guidelines** with **operational handbook** released 21 March 2022

Guidelines: https://www.who.int/publications/i/item/9789240046764
Handbook: https://www.who.int/publications/i/item/9789240046832

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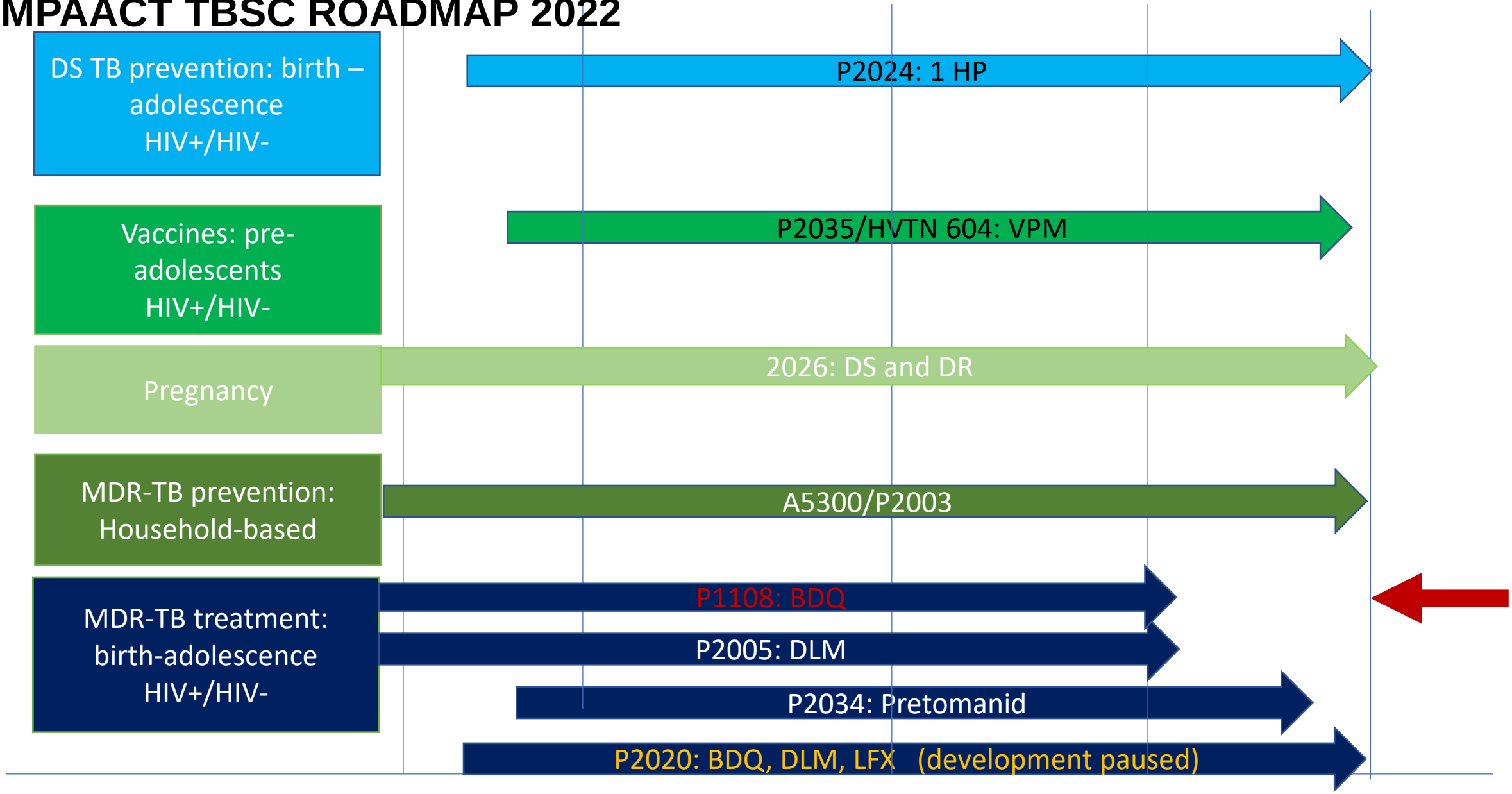

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P1108: Phase I/II trial of bedaquiline in MDR-TB
Key Milestones

- COVID pause: 2020
- N=43 of 54 evaluable enrolled (42 in 3 South African sites, 1 Haiti)
- 6 interim analyses : All PK and safety targets met across age cohorts
- Data sharing WHO : 2018: BDQ recommended in children > 6 years.
- Data sharing with WHO: 2021/22: BDQ: recommended in children > 6 years (March 2022)
- Dosing recommendations: weight banded
- Data sharing with Janssen C211
- Dissemination planned: 2023
- Version 2.0 finalized – including (20 mg)
- Formulation globally available through GDF
- Version 3.0 planned for pragmatic WHO dosing evaluation in < 16 kg

BDQ dosing by WHO weight band		
3 to < 7 kg	0 to < 3 mo	30 mg / 10 mg
	≥ 3 mo	60 mg / 20 mg
7 to < 10 kg	0 to < 3 mo	30 mg / 10 mg
	3 to <6mo	60 mg / 20 mg
	≥ 6 mo	80 mg / 20 mg
10 < 16 kg	3 to <6mo	60 mg / 20 mg
	≥ 6 mo	120 mg / 60 mg
16 < 24 kg		200 mg / 100 mg
24 < 30 kg		200 mg / 100 mg

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Chairs: Anneke Hesseling, Simon Schaaf

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: data from P1108**
- **In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens**

  (both conditional recommendations, very low certainty of the evidence)

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

World Health Organization

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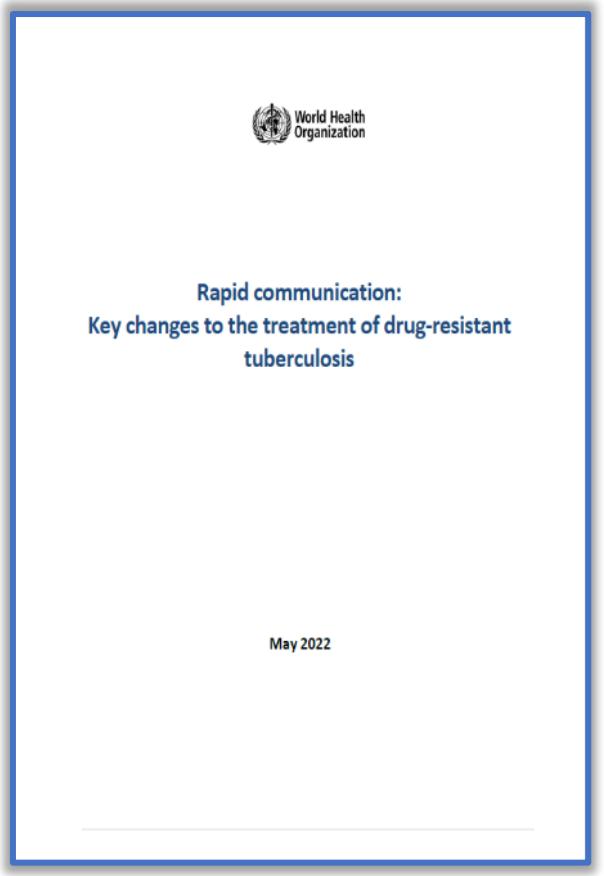
Rapid communication DR-TB (May 2022)

- **6-month BPaLM** (bedaquiline, pretomanid, linezolid (600mg), moxifloxacin) may be used programmatically (≥15y)
  - BPaL if fluoroquinolone resistant

- **9-month, all-oral, bedaquiline-containing regimens** are preferred over longer (>18 months) regimens in adults and children with MDR/RR-TB
  - 2 months of linezolid as alternative to 4 months of ethionamide
  - 4-6 Bdq [6]-Lfx [Mfx]-Lzd [2]-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E *or*
  - 4-6 Bdq [6]-Lfx [Mfx]-Eto-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E



World Health Organization

https://apps.who.int/iris/rest/bitstreams/1420701/retrieve

END TB

2022 Global New TB Drug Pipeline[1]

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

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

Lead Optimization

- PanD inhibitors
- Indazole sulfonamides
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Macrolides
- Mycobacterial Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase
- Oxazolidinones

Early Stage Development

- JSF-3285*
- MPL-446, 447*
- CPZEN-45*
- NTB-3119*
- TZY-5-84
- MBX-4888A (1810)*
- FNDR-10045*
- FNDR-20364*

GMP / GLP Tox.

- FNDR-20081*
- TB-47*
- GSK-839*
- OTB-658
- Sanfetrinem

Phase 1

- BVL-GSK098*
- GSK-286*
- TBAJ-587
- TBAJ-876
- TBI-223
- Macozinone* (PBTZ-169)
- Pyrifazimine (TBI-166)

Phase 2

- Delpazolid
- Sutezolid
- Sudapyridine (WX-081)
- BTZ-043*
- TBA-7371*
- OPC-167832*
- GSK-656* (070)
- SQ-109*
- Telacebec*
- SPR720*

Results Reported / Expected in 2022

- TB Practecal
- ZeNix
- Simplici TB (4-month regimen)
- Truncate TB (2-month regimens)
- STREAM 2

Regulatory Market Approvals

- Bedaquiline*
- Delamanid*
- Pretomanid*

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

WHO drug grouping

Group	Drug	Abbreviation
A	Levofloxacin or moxifloxacin	Lfx or Mfx (or M)
	Bedaquiline	Bdq (or B)
	Linezolid	Lzd (or L)
B	Clofazimine	Cfz
	Cycloserine or terizidone	Cs or Trd
C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin in combination with clavulanic acid (amoxiclav)	Ipm-Cln
	Meropenem in combination with clavulanic acid (amoxiclav)	Mpm
	Amikacin or streptomycin [a]	Am or S
	Ethionamide or prothionamide	Eto or Pto
	P-aminosalicylic acid	PAS

Pretomanid

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
Anthony Garcia-Prats, MD, PhD
Ethel D. Weld, MD, PhD
Kelly Dooley, MD, PhD

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Updated Rationale & Timeline for Reopening

1. **Revised model-adjusted dosing of DLM** for all ages
2. Optimal DLM dose in young, small children (< 3 years)
3. **Characterization of newly identified psychiatric AEs**
4. Public health relevance, new adult RR-TB guidelines: DLM substituted for Pretomanid?
5. N=4 enrolled (3 India, 1 SA)

Protocol Version 3.0 is finalized; only outstanding item for all sites to reopen to accrual is <u>laboratory readiness</u>.

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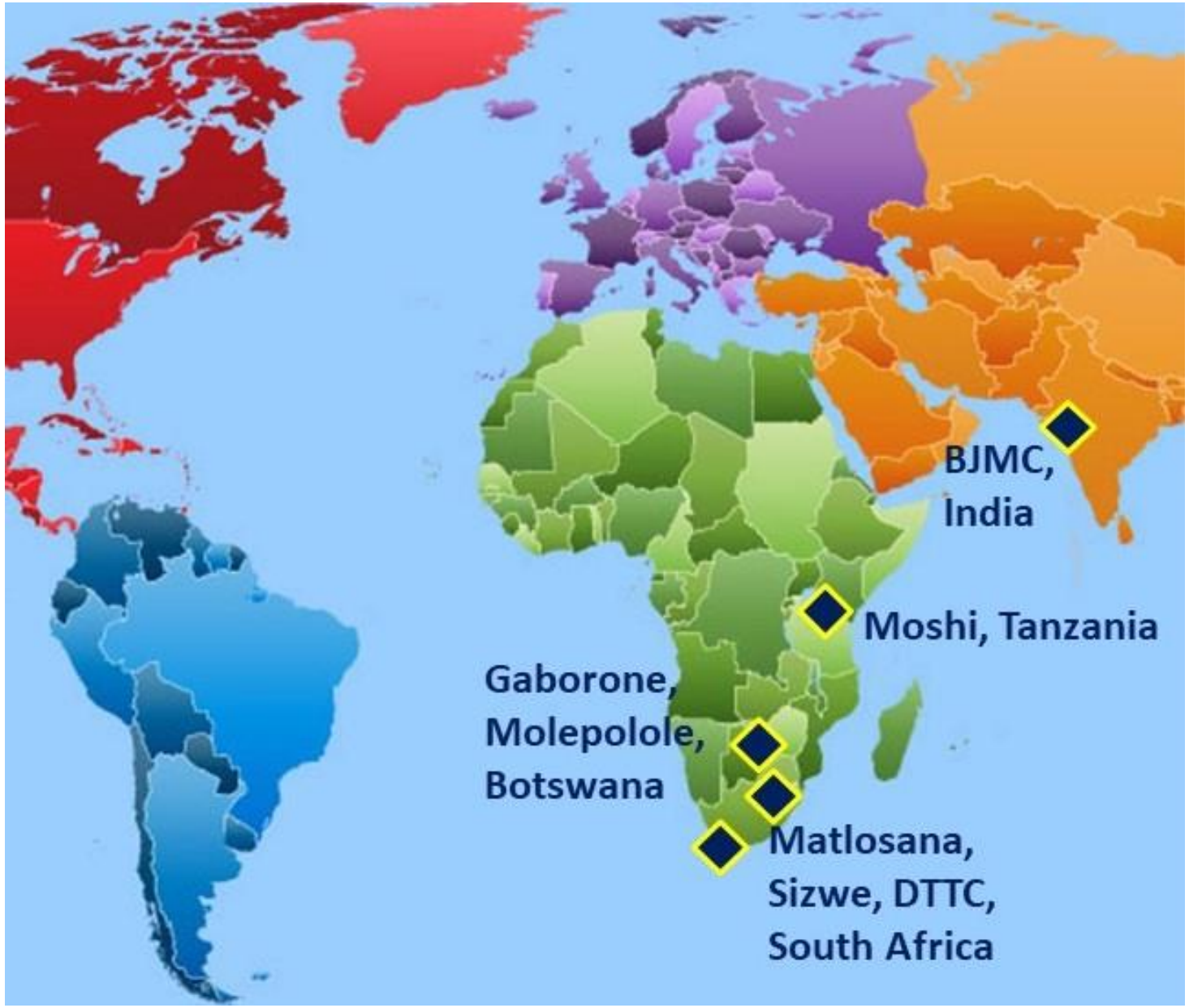
Participating Sites



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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 D. Weld, MD, PhD
Anthony Garcia-Prats, MD, PhD
Pauline Howell, MD

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IMPAACT 2034 Sites

7 sites approved for participation

BJMC (31441)

Siriraj Hospital (5115)

KCMC (5118)

Inst. Puer e Ped (5071)

PHRU (31976)

Sizwe (31929)

DTTC (31790)

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Timelines

- Obtained CSRC and MPRG approval
- Protocol Version 1.0 sent for DAIDS M.O. Review (June 2022)
- Protocol Version 1.0 finalized (projected July 2022)
- Open to accrual (projected October 2022)
- First enrollment (projected January 2023)
- Paediatric formulations ready
- Last visit (projected April 2025)
    - Updated accrual timelines, as study can now only enroll female participants per FDA stipulation

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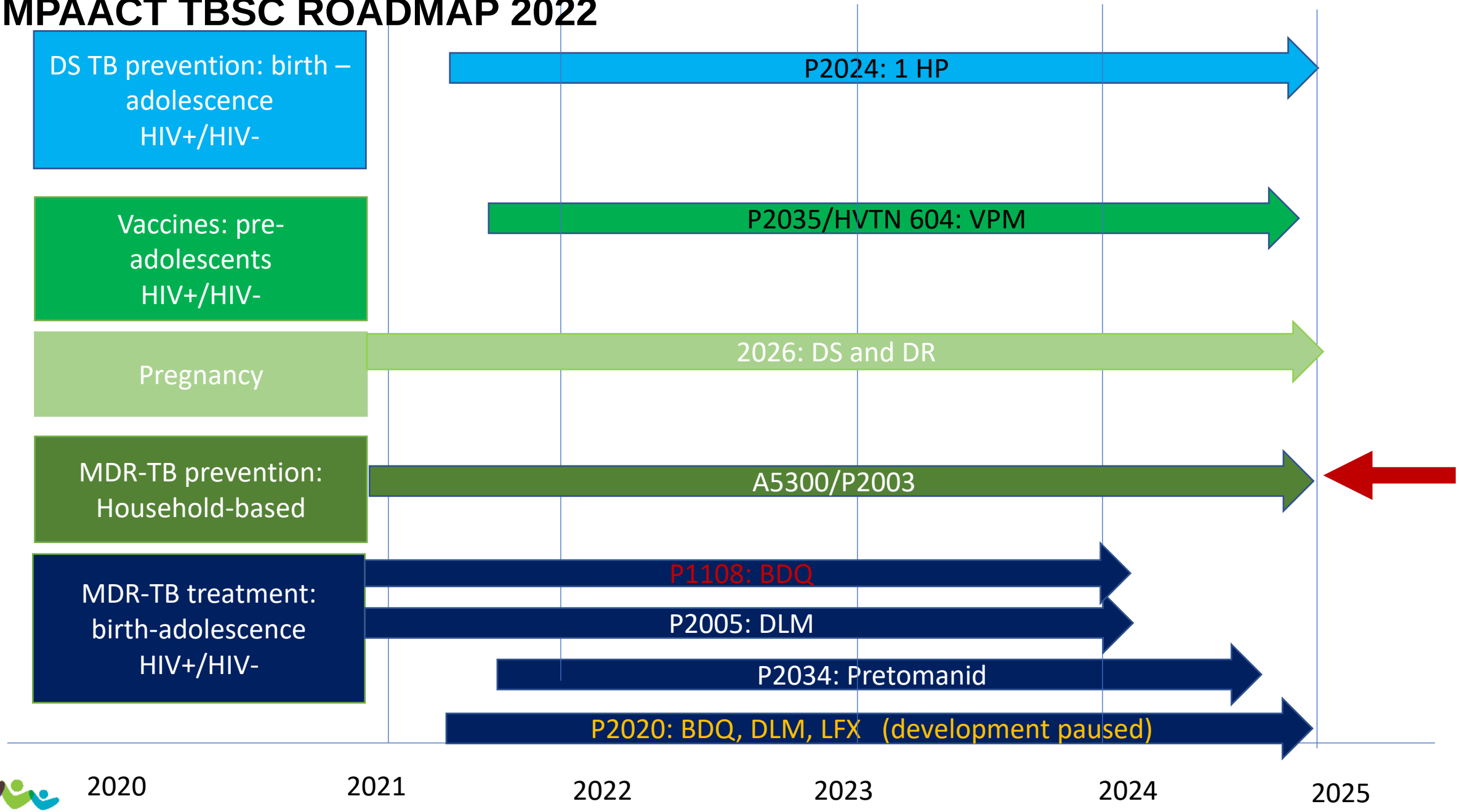

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Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/PHOENIx)

Protocol Chairs
ACTG: GJ Churchyard, S Swindells
IMPAACT: AC Hesseling, A Gupta

ACTG
AIDS CLINICAL TRIALS GROUP

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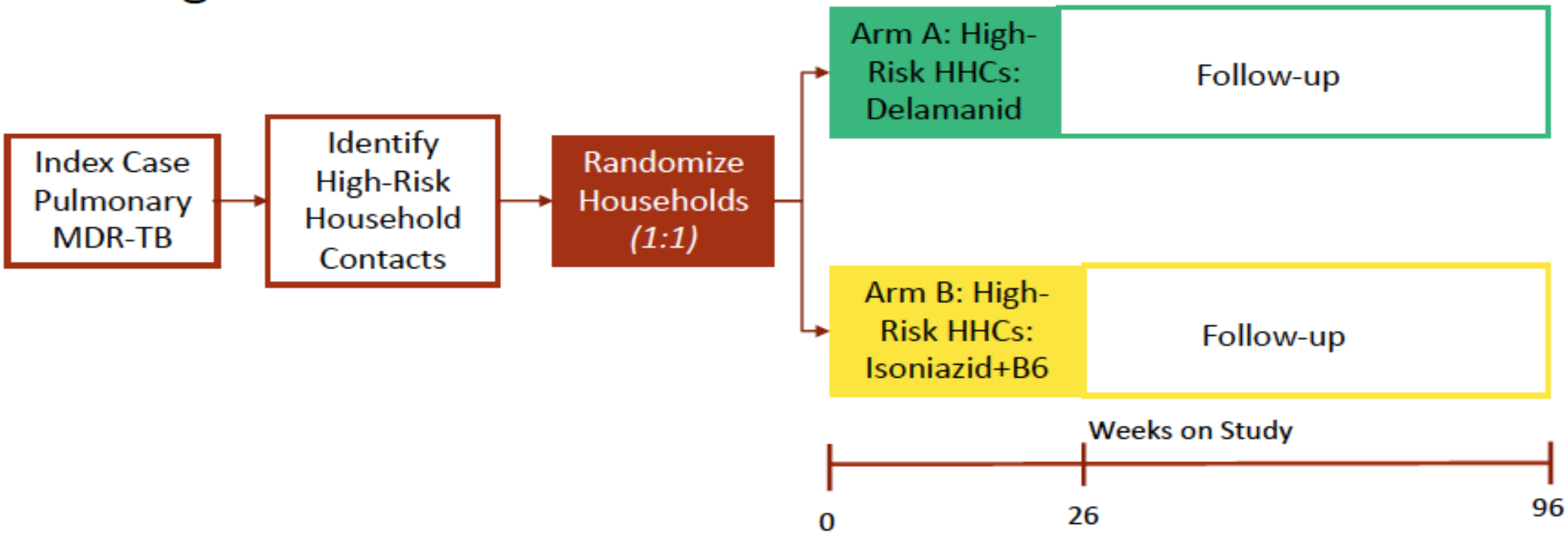
International Maternal Pediatric Adolescent
AIDS Clinical Trials Network

Overview

- **Design:** Multi-center, cluster-randomized, superiority Phase III IND trial
- **Objective**: The **efficacy and safety** of DLM vs. INH for preventing confirmed or probable active TB
- **Population**:
  - **Index cases**: An adult (18 years and older) with confirmed pulmonary MDR TB who has started appropriate treatment within the past 90 days
  - **High risk HHCs**:
    - Newborns to children <5 years old
    - HIV-infected or non-HIV immunosuppressed regardless of TST/IGRA status
    - TST positive (≥5mm) and/or IGRA positive
- **Sample size**: 3452 high risk HHCs, assuming 2 HHCs per index case

Study Design

- Multi-center, cluster-randomized, superiority Phase III IND trial
- Cluster = eligible high-risk contacts from same HH
  - Randomization balanced by site
- All eligible HHCs in same HH receive the same treatment

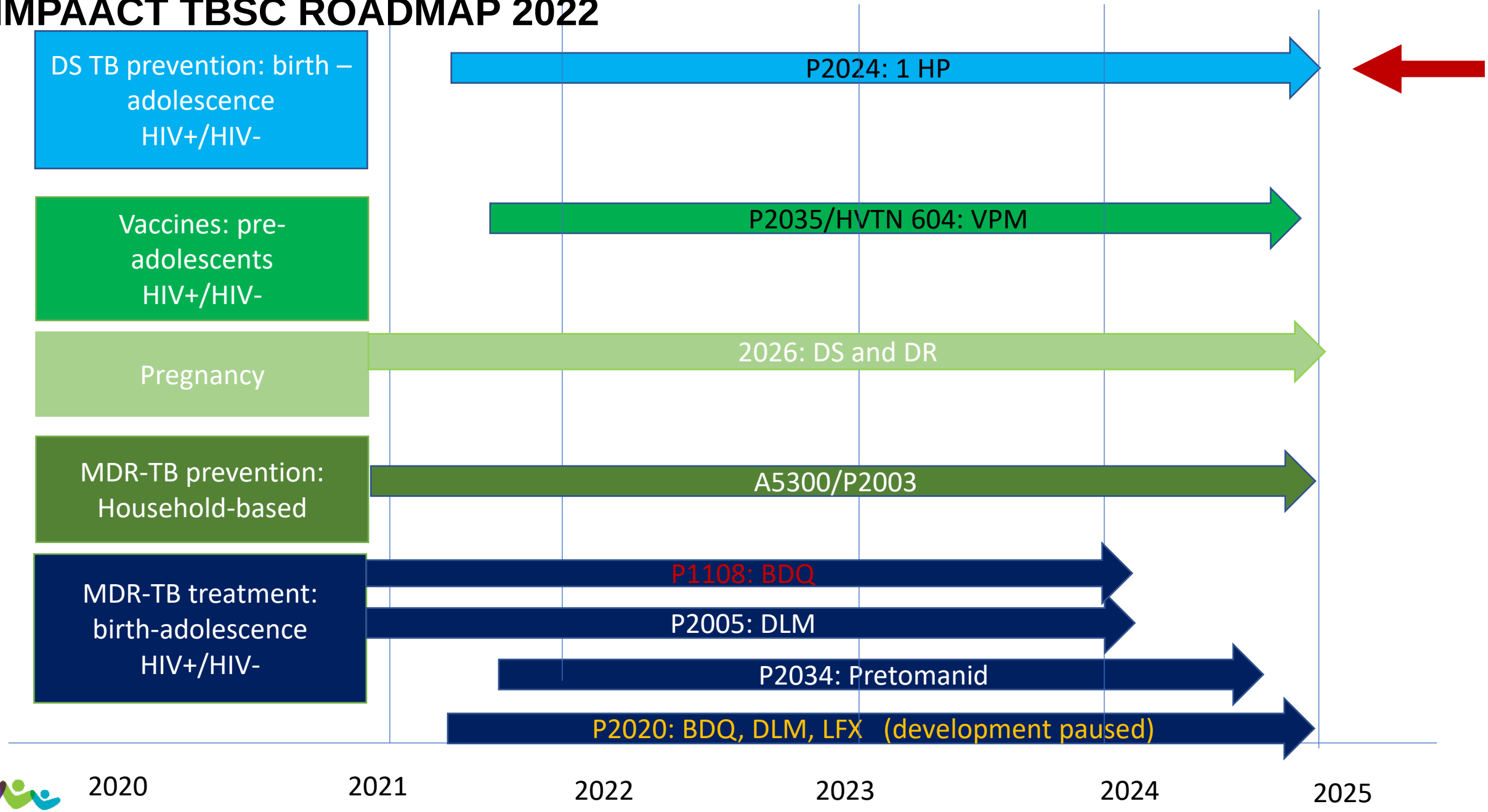


Current Status

- Version 3.0 protocol
- 26 sites activated since 2019, 2 new sites being onboarded
  - Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda, Zimbabwe
- April 2022 DSMB now will be annual meeting
- 1372 index cases and 2345 HHC screened
- **1267 HHCs enrolled** from 724 Index cases (**37% accrued**)
- Site enrollment range: 8-247 HHCs with Philippines, India, South Africa, Peru, Haiti top enrollers
- RFA for new additional sites
- Multiple papers from feasibility study completed



IMPAACT TBSC ROADMAP 2022



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

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

Primary Objectives:

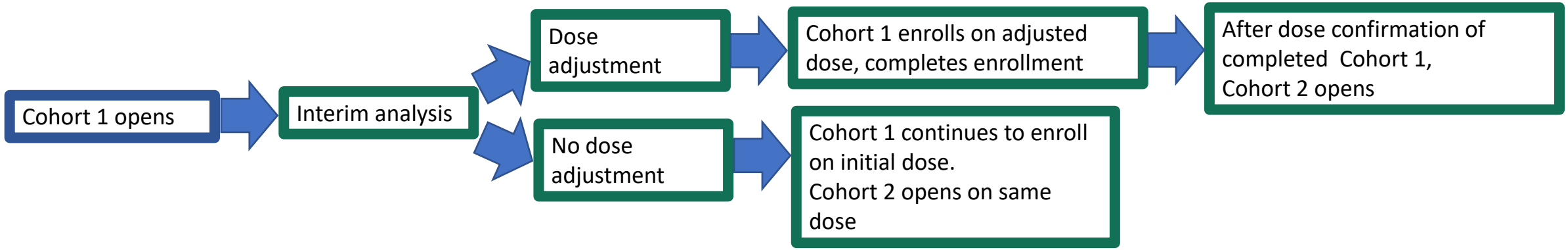
Cohort 1 and 2:

- To determine the weight-band dosing of RPT taken as part of the 1HP regimen by evaluating:
  - Plasma PK RPT exposures among children with and without HIV.
  - Safety and tolerability of the 1HP regimen, among children with HIV while receiving twice-daily DTG, and children without HIV, through 28 days of dosing.

Cohort 2:

- To evaluate the effect of RPT taken as part of the 1HP regimen on the plasma PK of DTG.

Design: Phase I/II, multi-site, open-label study with two sequential cohorts

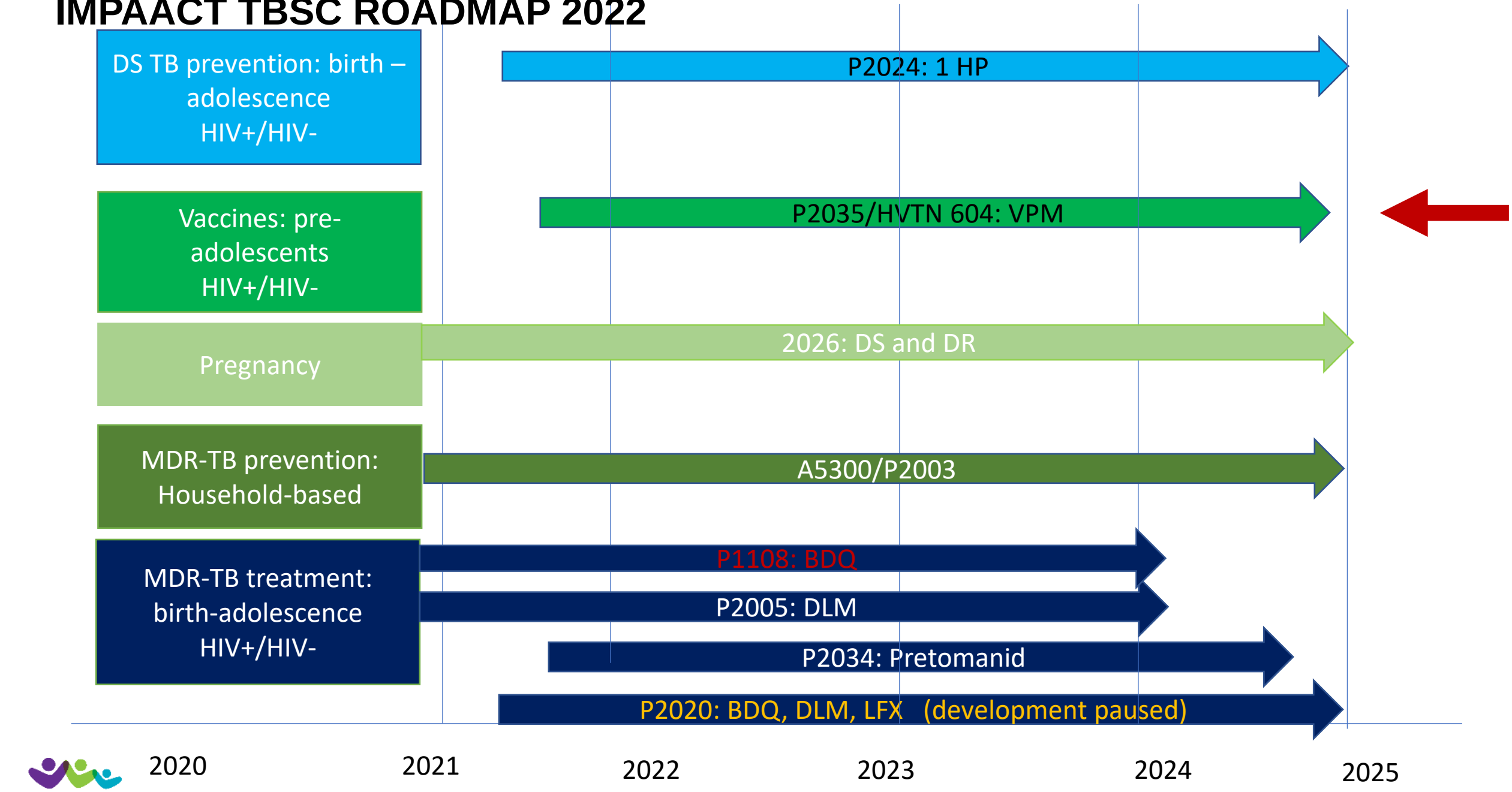


Cohort 1 and 2: 2 to <13 years of age. 4 weight bands (Group 1: 10 to 15.9 kg, Group 2: 16 to 23.9 kg, Group 3: 24 to 30.9 kg, Group 4: 31 to 44.9 kg)

Cohort 1: Without HIV **Cohort 2: With HIV on DTG containing regimen**

Sites: International sites TBD. **Timeline:** Initial MPRG review complete → Resubmit final MPRG approval pending Sanofi review → CSRC review → Open to enrollment Q2 2023

IMPAACT TBSC ROADMAP 2022



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IMPAACT 2035/ HVTN 604:

Phase I/II Randomized, Placebo-Controlled Study of the Safety and Immunogenicity of VPM1002 Vaccination or BCG Revaccination against Tuberculosis in Pre-Adolescents Living with and without HIV in South Africa

Leveraging **E**arly **A**dolescence to **P**revent TB:

LEAP Study

Protocol Chair:	Lisa M. Cranmer, MD MPH; Emory University (IMPAACT)
Protocol Vice Chair:	Cheryl L. Day, PhD; Emory University (IMPAACT)
Protocol Vice Chair:	Steve Innes, MD PhD; University of Cape Town (HVTN)

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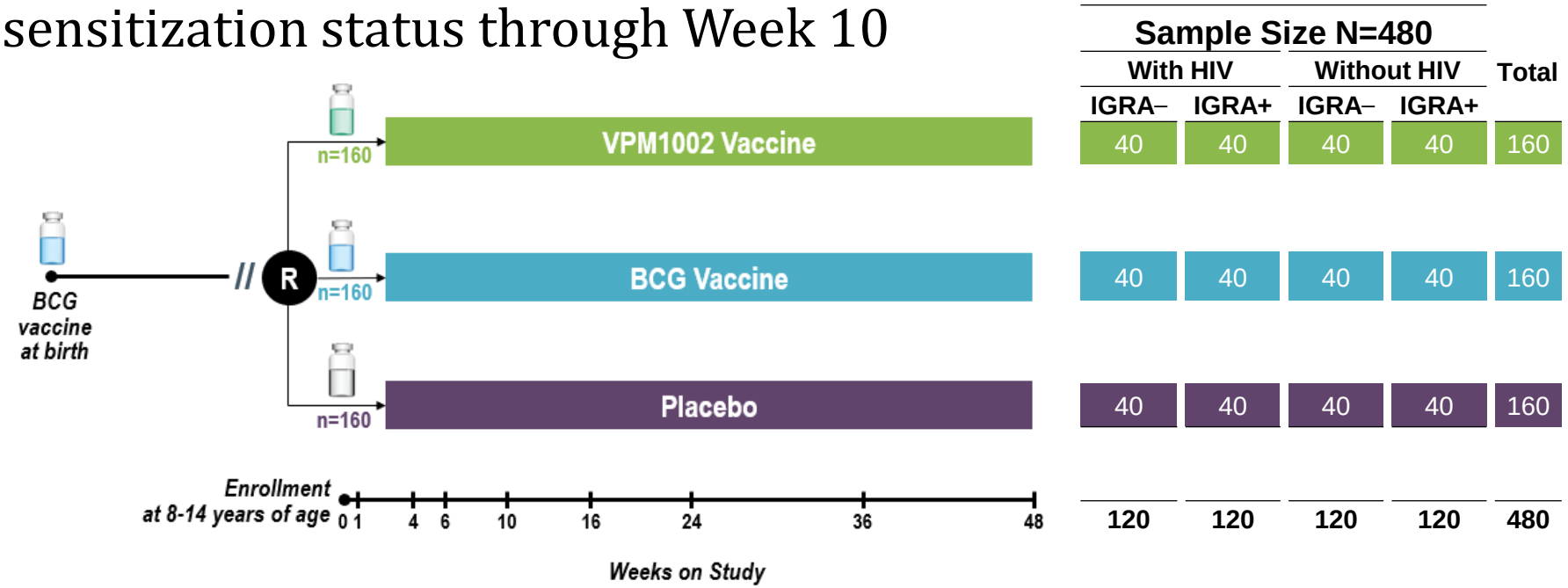
HIV VACCINE TRIALS NETWORK

IMPAACT 2035/ HVTN 604: LEAP

Primary Objectives:

1, To evaluate the safety of VPM1002 and BCG revaccination by HIV status through Week 48

2. To evaluate the cellular immunogenicity of VPM1002 and BCG revaccination by HIV and *M.tb* sensitization status through Week 10



Sample Size N=480				
With HIV		Without HIV		Total
IGRA–	IGRA+	IGRA–	IGRA+	
40	40	40	40	160
40	40	40	40	160
40	40	40	40	160
120	120	120	120	480

- Children with HIV: CD4 >200 & virologically suppressed on ART
- 9 IMPAACT & HVTN sites in South Africa
- Open to accrual ~Q4 2022/Q1 2023

HIV VACCINE TRIALS NETWORK

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Protocol chairs

Photos taken with permission, Sue Palmer, Desmond Tutu TB Centre, Cape Town, South Africa
Thanks to Sabine Verkuil , Kerri Vinery, Tiziana Masini, Annemieke Brands, WHO Global TB Program, Simon Schaaf, Sharon Nachman
FHI colleagues

THANK YOU!

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