


WHO updates

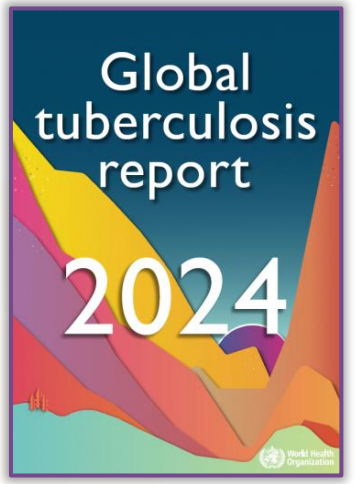
Sabine Verkuijl (on behalf of Annemieke Brands, Kerri Viney & Tiziana Masini), WHO GTB

Annual meeting of the Child and Adolescent TB Working Group
Courtyard Bali Nusa Dua Resort
11 November 2024

World Health Organization

END TB

TB incidence and mortality in children and adolescents, 2023



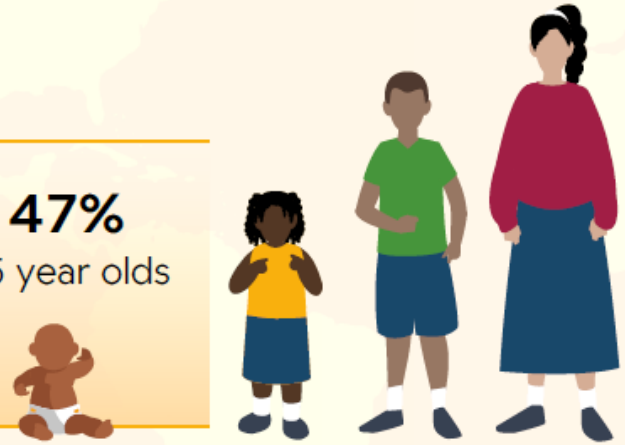
10.8 million
TB among all ages in 2023

1.25 million
TB deaths in 2023

1.25 million
children (0–14 years) developed TB in 2023 (12% of all TB)

191 000
TB deaths in 2023 (15% 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

73% were in children <5 years

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

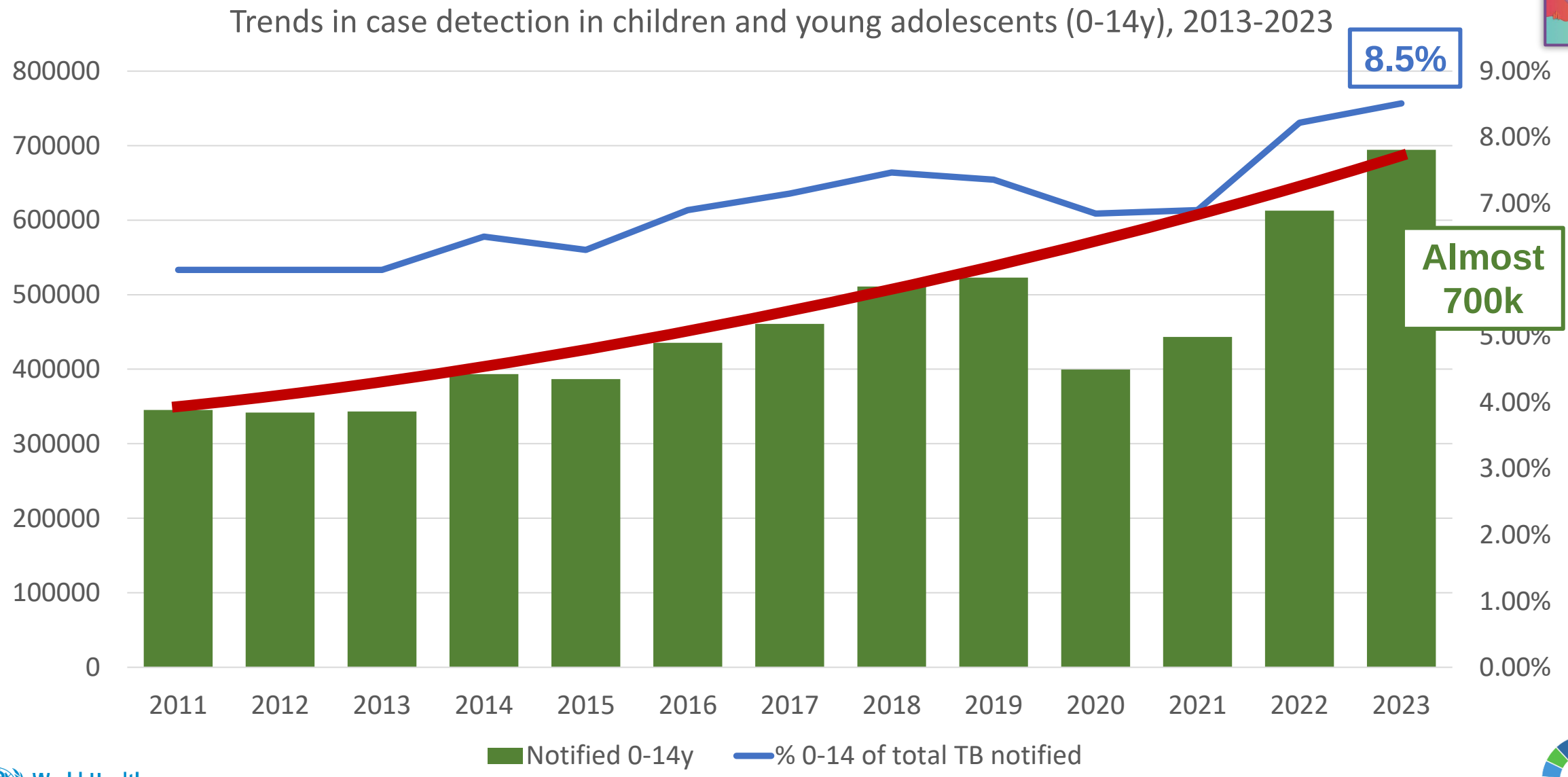
(Dodd et al, 2017)

25 000
(14%) TB deaths in the 0–14 year age group were among children living with HIV

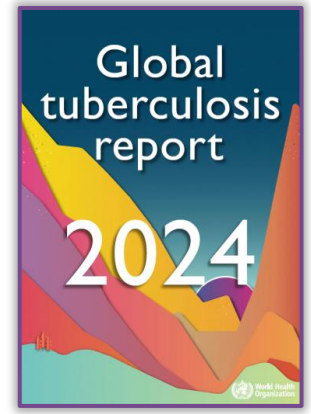
World Health Organization

END TB

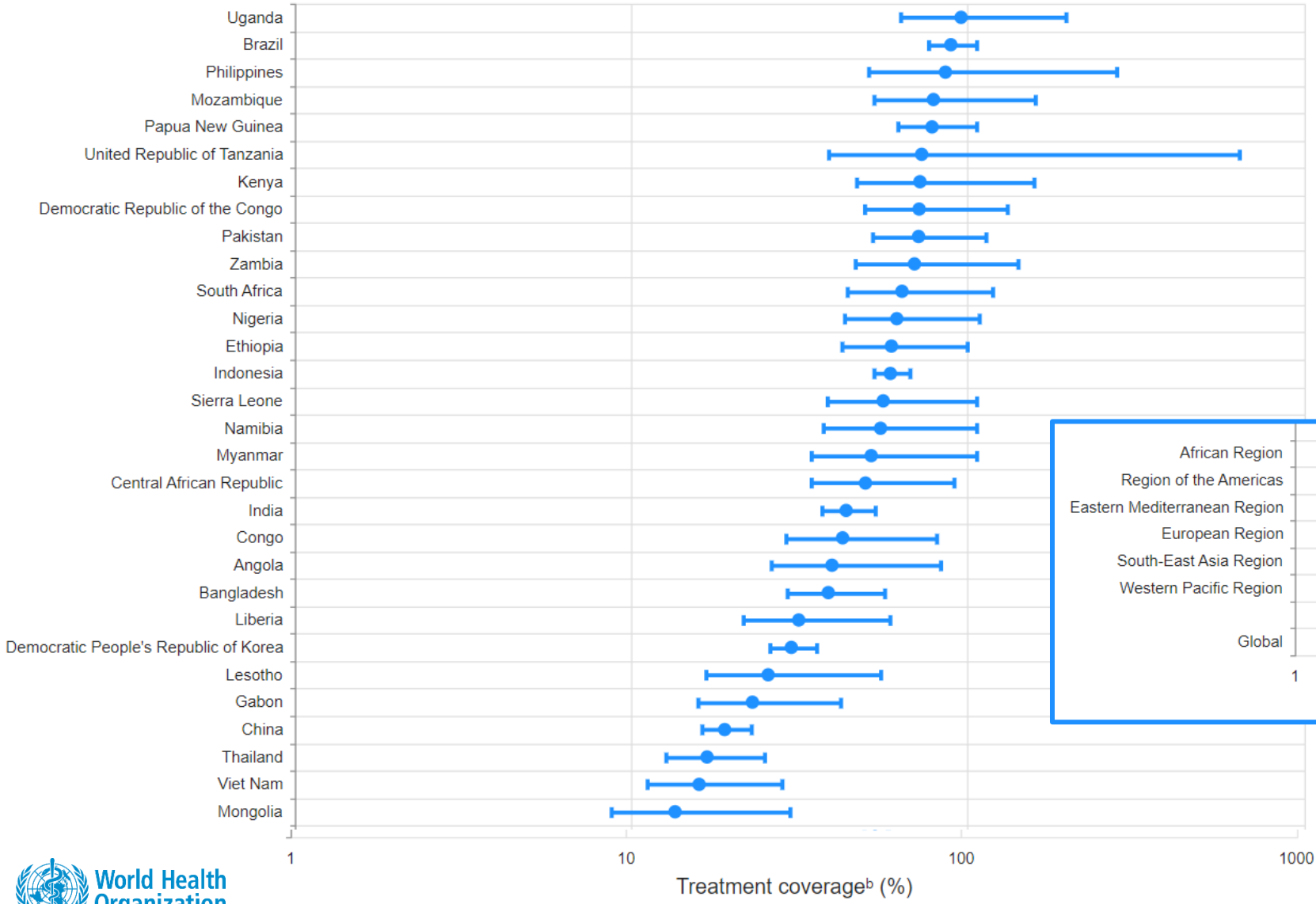
Trends in global TB notifications 0-14 years



TB treatment coverage in <15 years



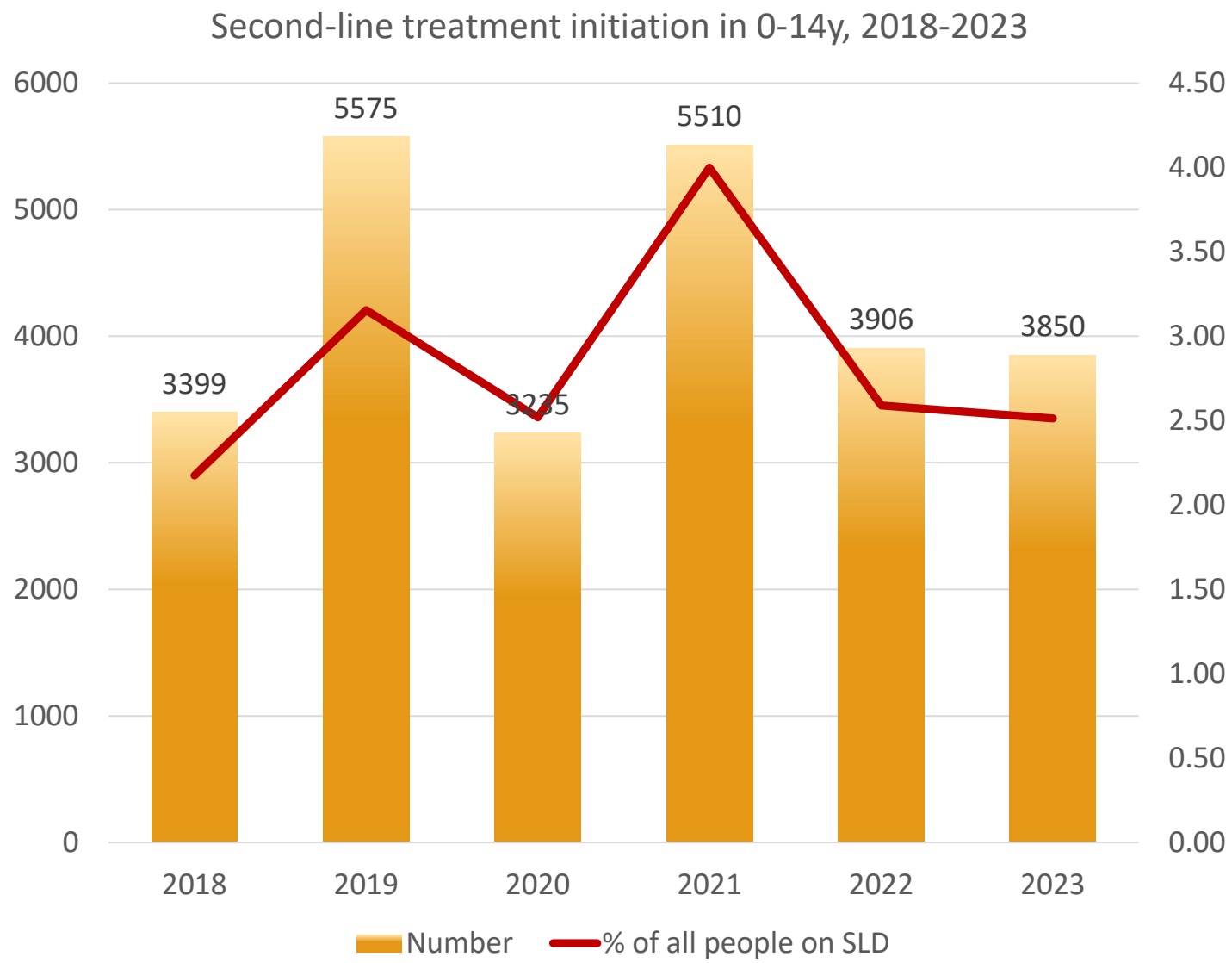
People aged 0–14 years



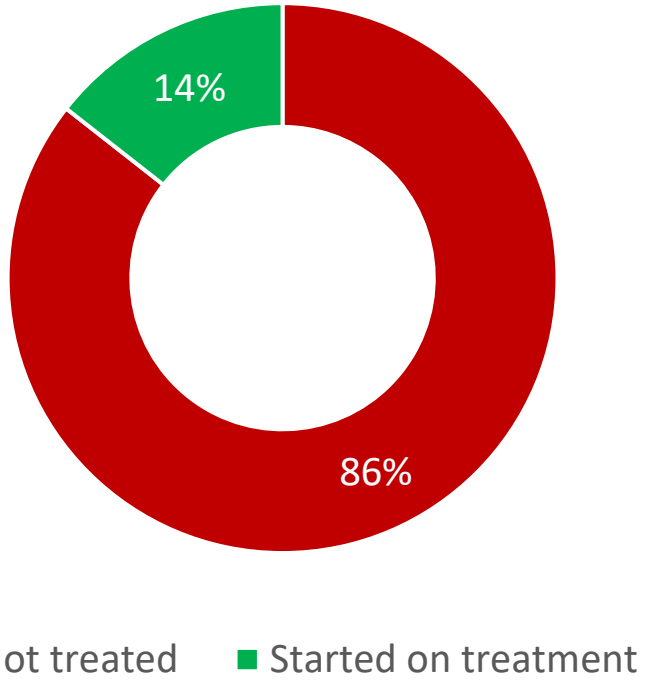
Global average: 55%

World Health Organization

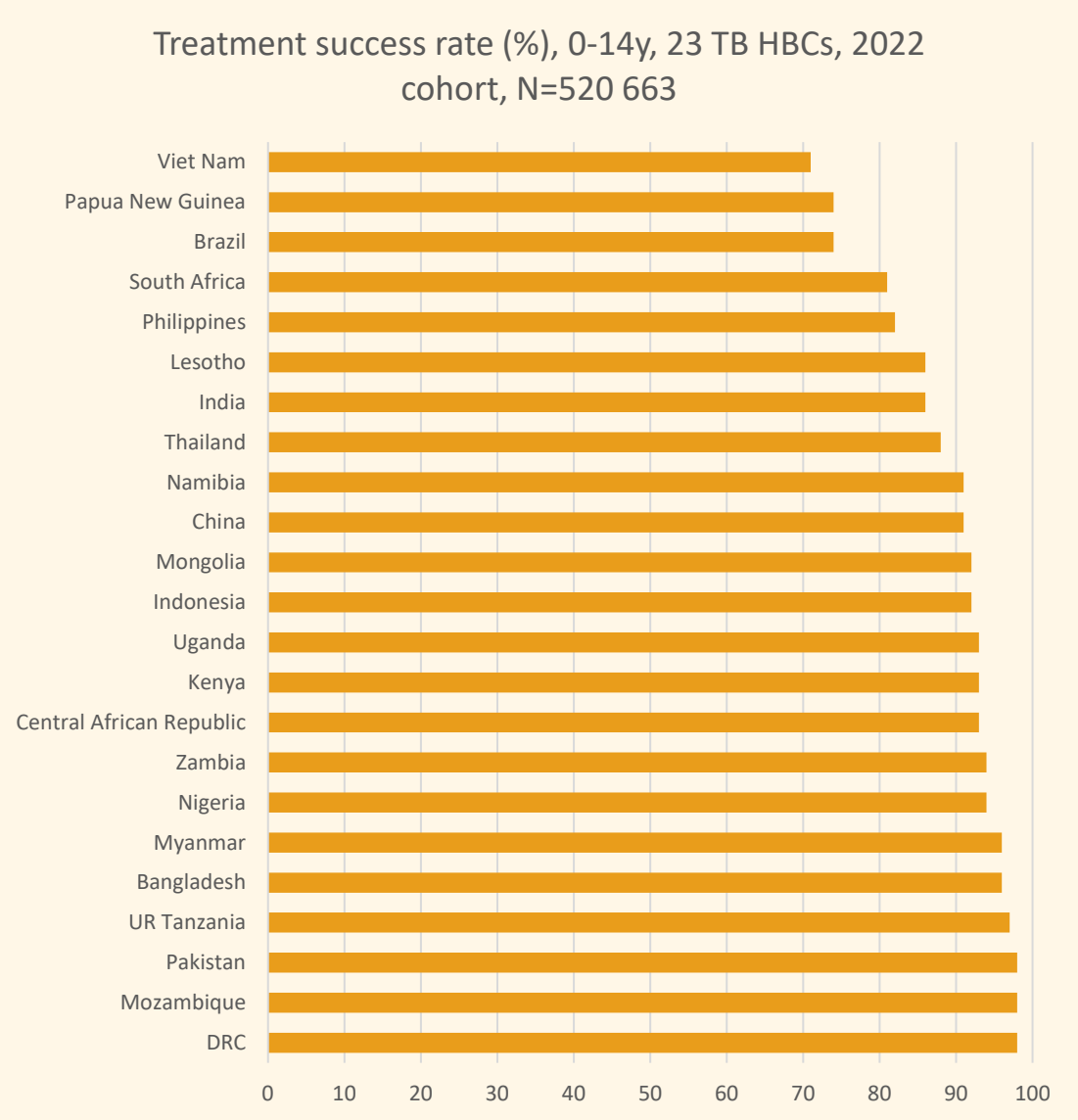
Treatment initiation in children with MDR/RR-TB

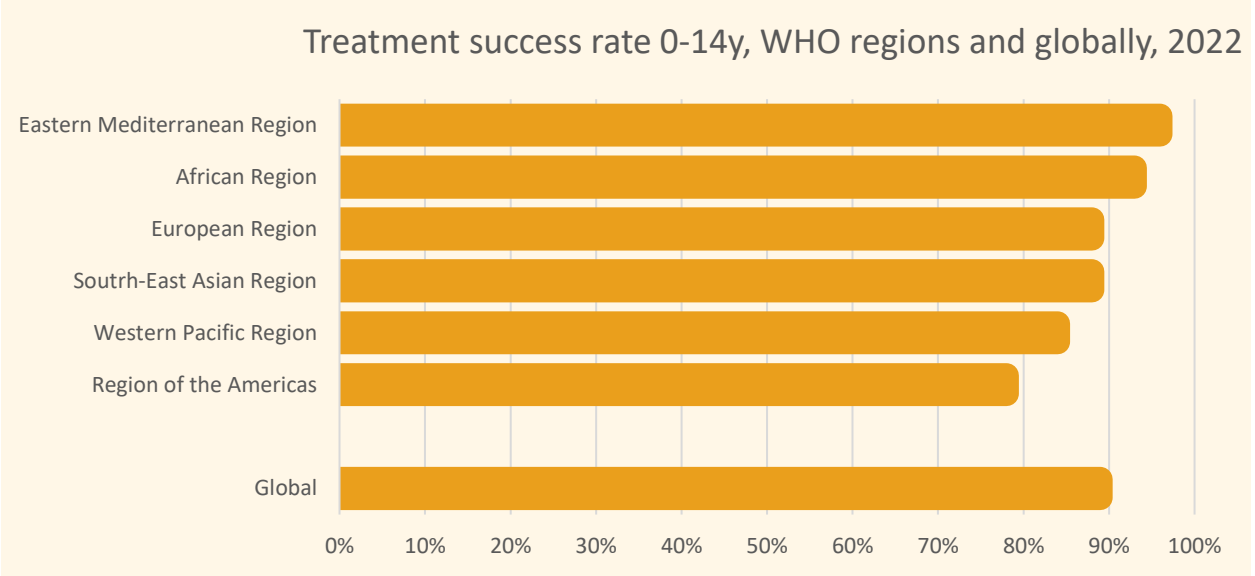


Treatment coverage: MDR/RR-TB in children and young adolescents, average for 2018-2023 (out of an estimated 30 000 per year)



Treatment success rates new/relapse <15 years



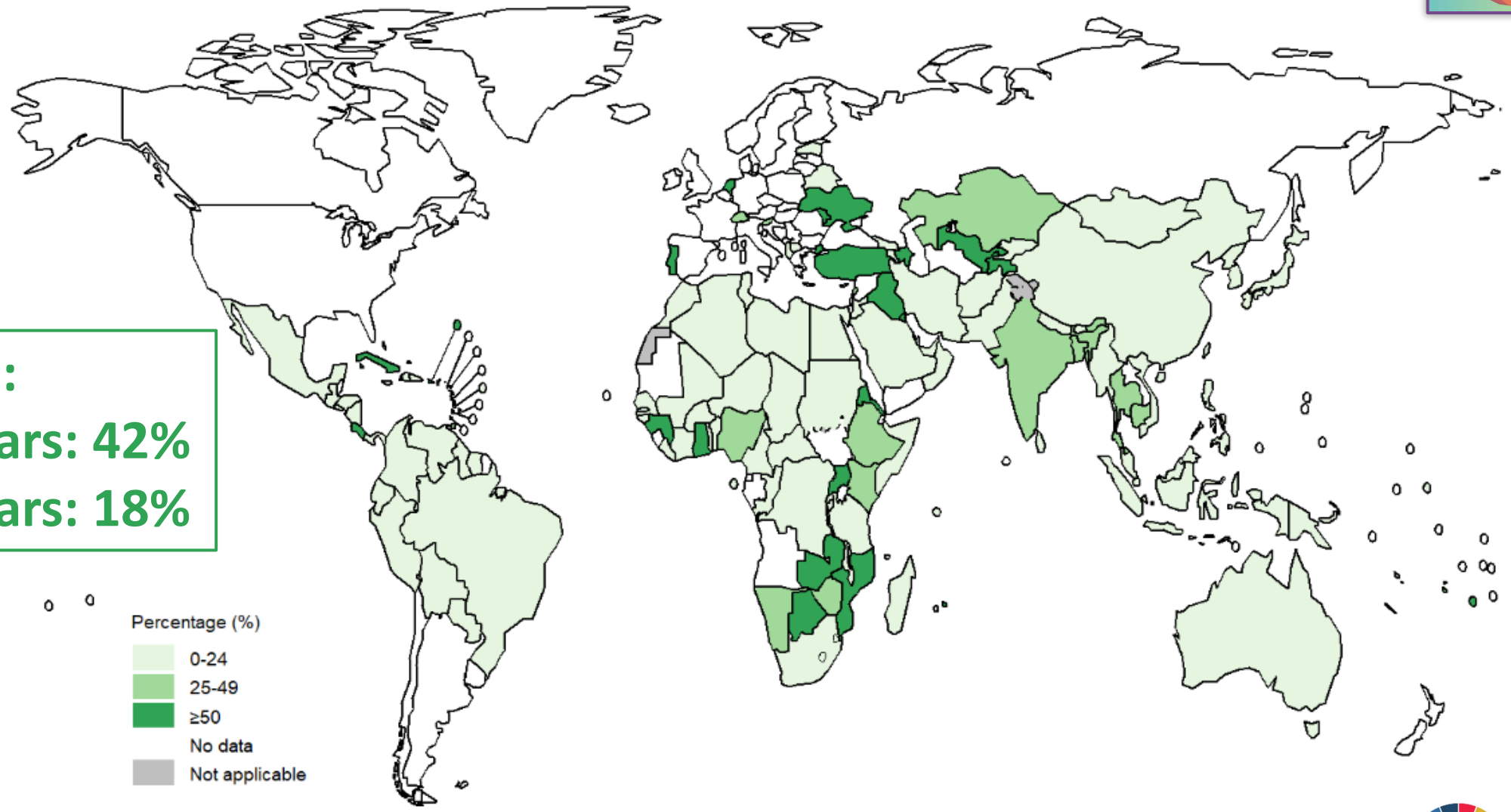


Global average 0-14y: 90%

All ages: 86%

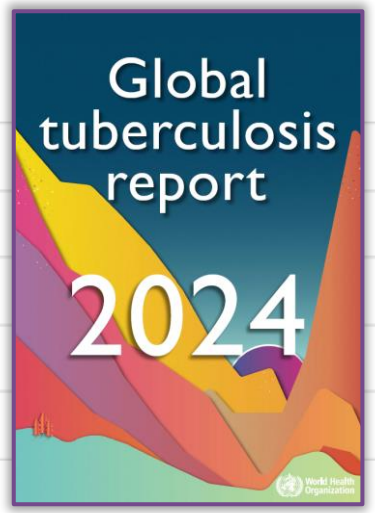
HIV-positive (all ages): 68%

% of household contacts (all ages) provided with TPT, 2023



Global average:
Contacts <5 years: 42%
Contacts ≥5 years: 18%

Number of people provided with TPT, 2015-2023



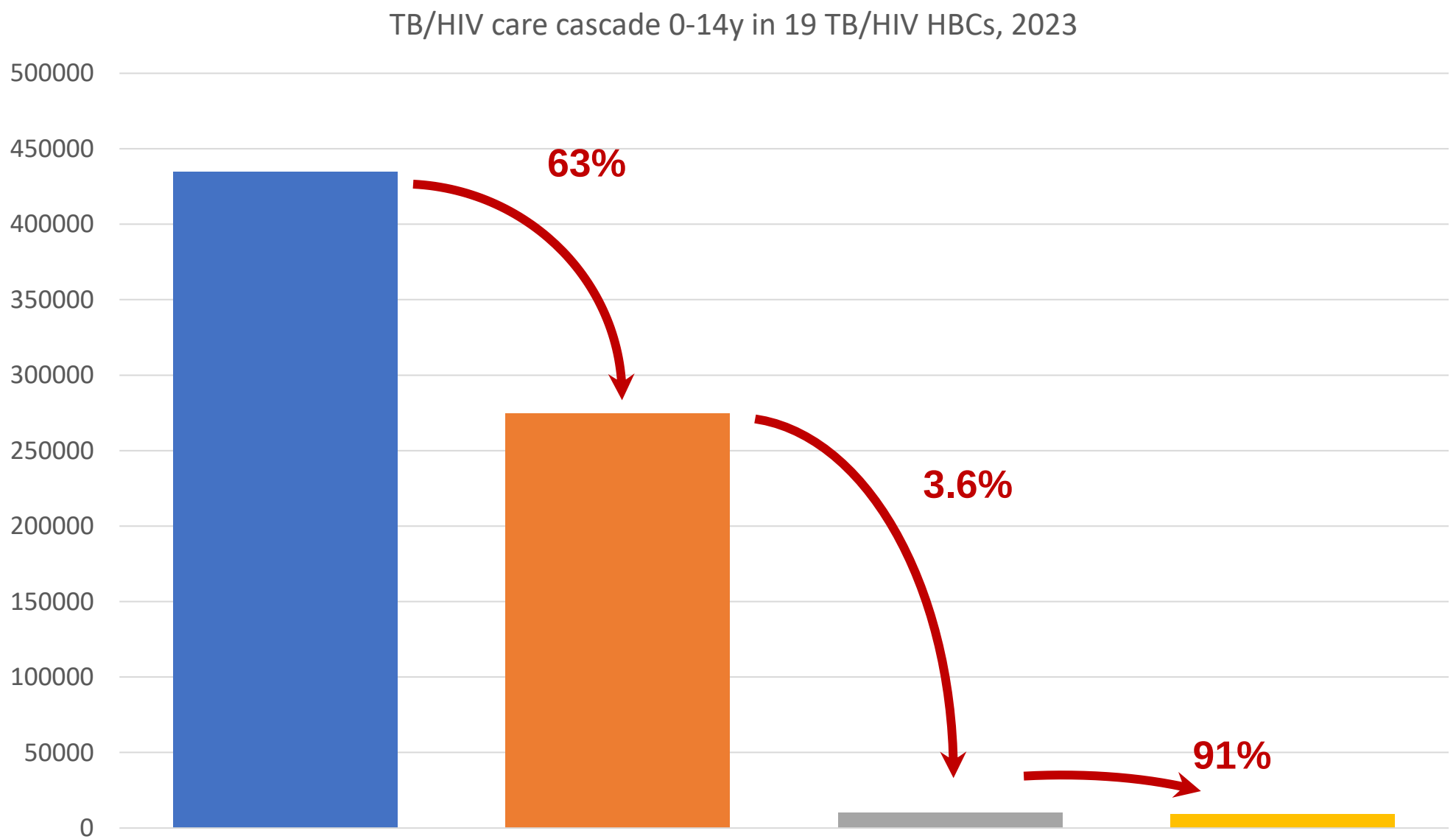
Largest increase in ages ≥5 yrs

Slowest progress in contacts <5 years

Slowdown of progress in PLHIV; no age-disaggregated data available

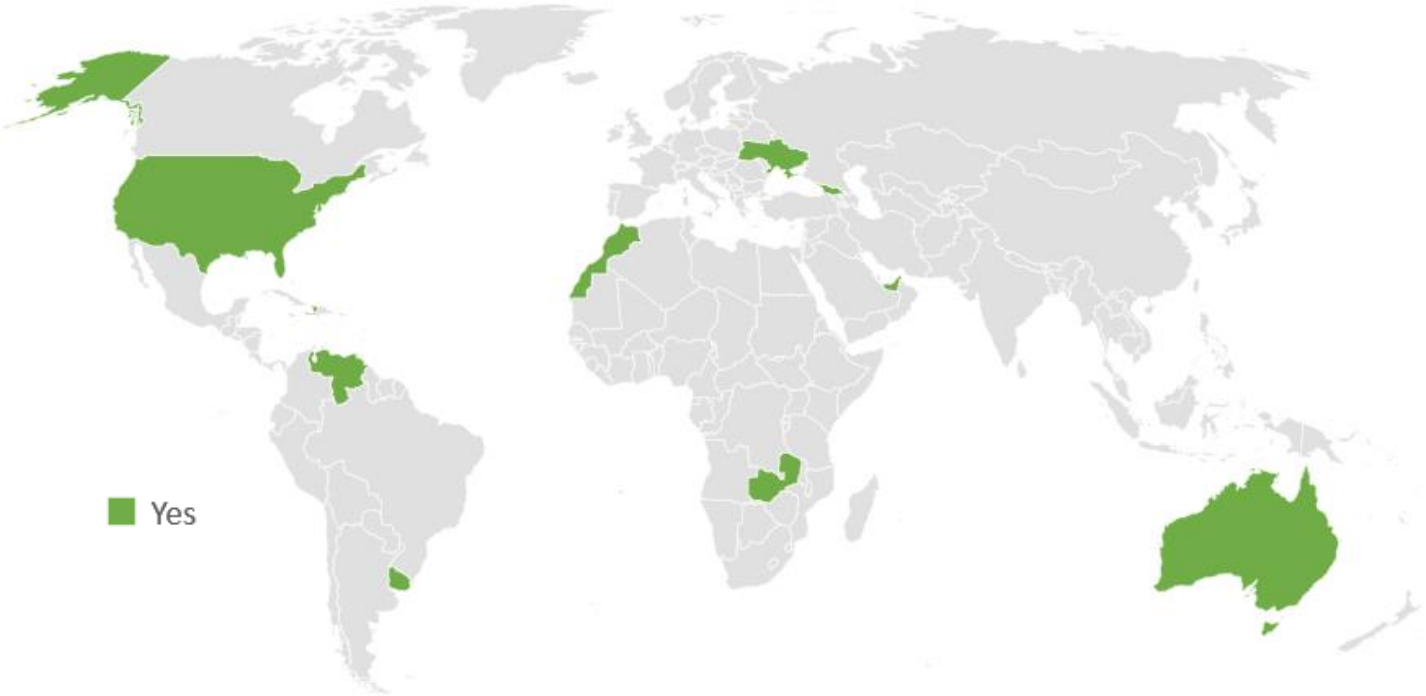
World Health Organization

TB/HIV co-infection

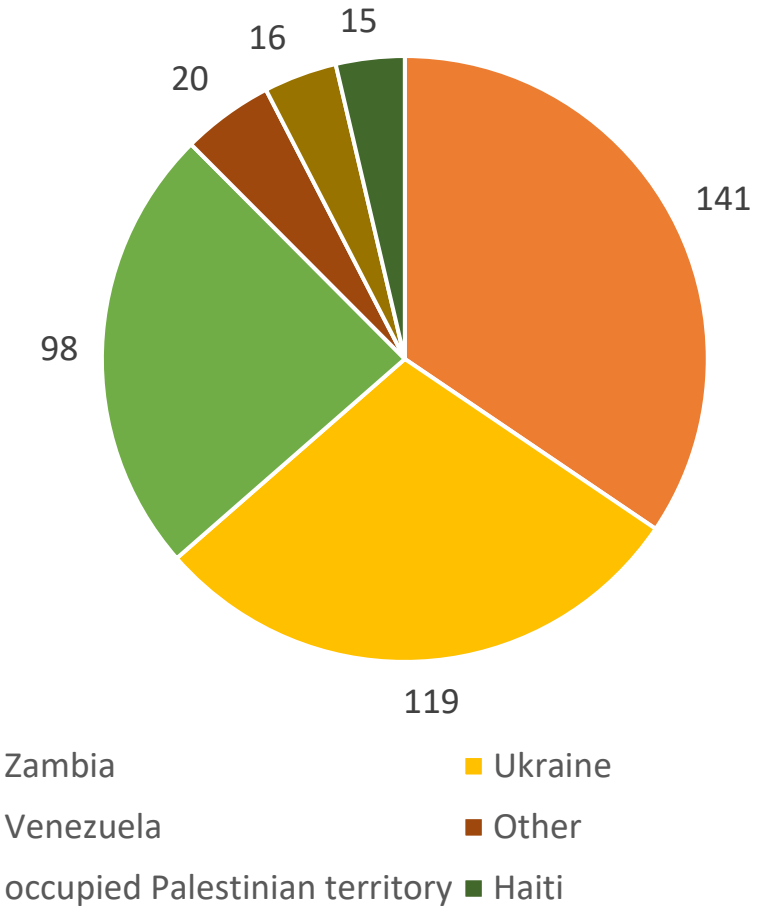


Use of the 4-month regimen for non-severe TB

Countries implementing 2HRZ(E)/2HR in 2023 (N=16)

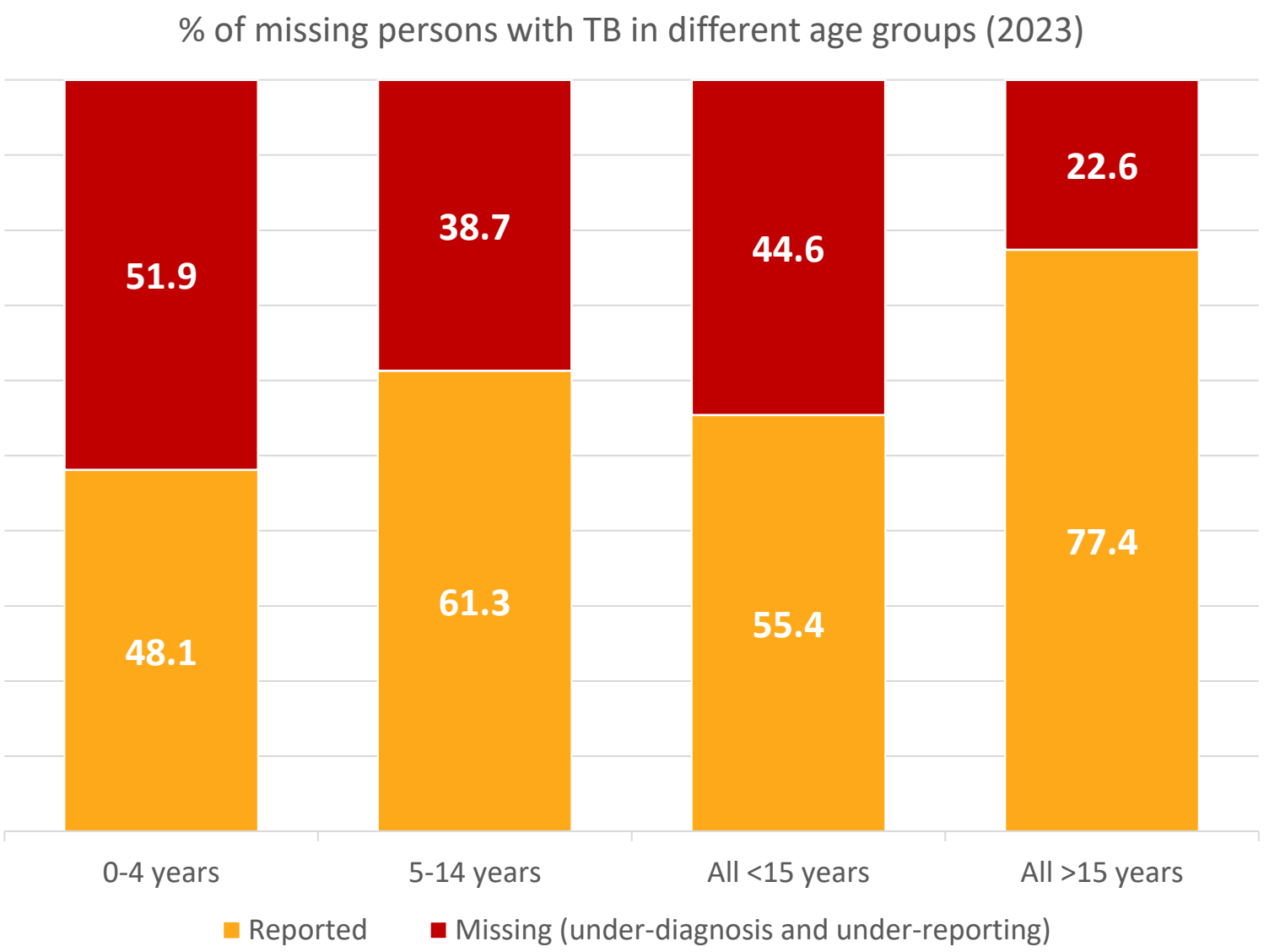


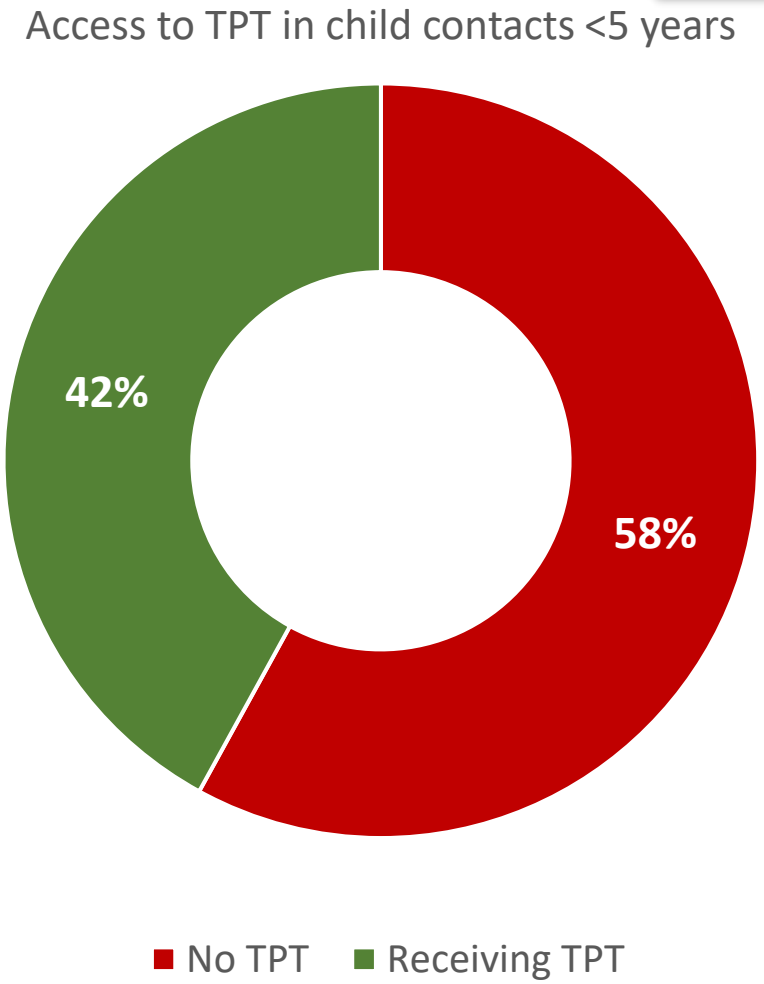
Countries starting children on 2HRZ(E)/2HR in 2023 (N=409)



Other: Australia; Dominica; Georgia; Saint Kitts and Nevis; Saint Vincent and the Grenadines; Singapore; United Arab Emirates; United States of America; Uruguay

Remaining programmatic gaps





E-courses on TB in children and adolescents

https://openwho.org/courses/TB-child-adolescent-EN

https://openwho.org/courses/TB-child-adolescent-programmatic

Register first on **openwho.org** before enrolling in the courses

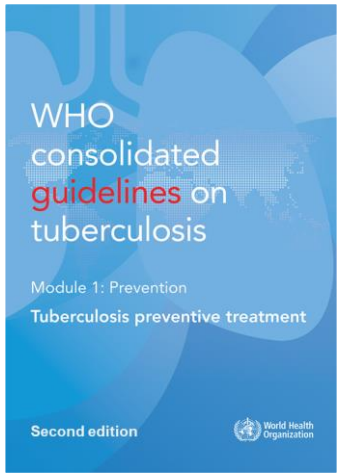
World Health Organization

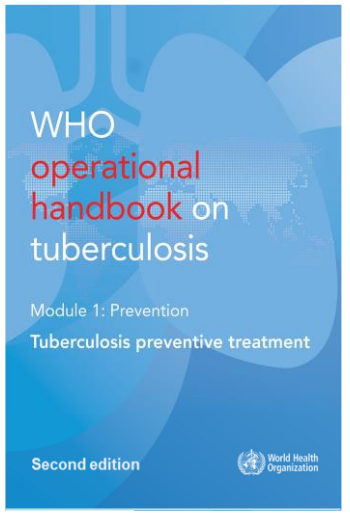
END TB

Updated WHO guidelines – TB preventive treatment

- New recommendation on **TPT for MDR-TB**:
  In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, six months of daily levofloxacin should be used as TB preventive treatment (strong recommendation, moderate certainty evidence)

- Other updates:
  - Incorporation of recommendations on screening tools (2021 screening guidelines) and antigen-based tests for TB infection (2022 diagnostics guidelines)
  - Recommendation on TPT regimens split by strongly recommended and alternative (conditionally recommended)
  - Alignment with current terminology
  - Updated research gaps
  - Updated references





Updated WHO handbook – TB preventive treatment

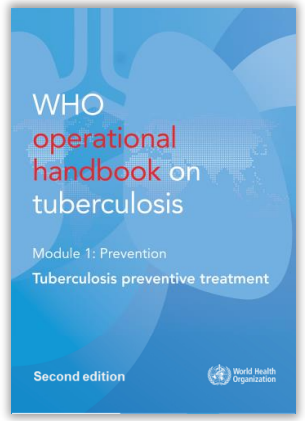
3HP dosing now available for all ages!

Age-weight-based approach for weight bands <10kg (different dosing for < and ≥ 3 months (3-<6 kg) and < and ≥ 6 months (6-<10kg)

TPT regimens and drug formulations	No. of tablets or quantity of solution by b												
	3–5.9 kg (< 3 months)	3–5.9 kg (≥ 3 months)	6–9.9 kg (< 6 months)	6–9.9 kg (≥ 6 months)	10–14								kg
Three months of weekly rifapentine plus isoniazid (3HP)													
Isoniazid 100 mg dt	0.6 (6 mL[a])	0.7 (7 mL[a])	1	1.5	2.5	3	4.5	4.5	6	6	7.5	7.5	9
Isoniazid 300 mg tab	–	–	–	–	–	1	1.5	1.5	2	2	2.5	2.5	3
Rifapentine 150 mg dt	0.5 (5 mL[d])	0.7 (7 mL[d])	1.5	1.5	2	3	4	4	5	6	6	6	6
Rifapentine 300 mg tab								2	2.5	3	3	3	3
Rifapentine 300 mg and isoniazid 300 mg FDC tab								–	–	–	–	–	3
One month of daily rifap													
Isoniazid 300 mg tab	–	–	–	–	–	–	–	1	1	1			
Rifapentine 300 mg tab	–	–	–	–	–	–	–	2	2	2			
Six months of daily levofloxacin (6Lfx)													
Lfx 100 mg dt	0.5	1	1	1.5	2	2.5	3	3.5	–	–	–	–	–
Lfx 250 mg tab	0.25 (2.5 mL[d])	0.5 (5 mL[d])	0.5 (5 mL[d])	1 (10 mL[d])	1	1.5	–	2	2	2	2	2	3
Lfx 500 mg tab	–	–	–	–	–	–	–	1	1	1	1	1	1.5

Ratio between H and P differs for lower weight bands (single dispersible formulations preferred – FDC not ideal)

Adult FDC (300/300mg) used from 50 kg



Updates:

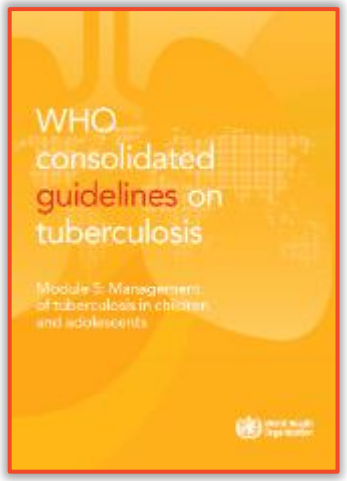
- revised weight-band drug dosing
- updated screening and TPT algorithms
- prevention and management of ADRs
- country best practices on TPT implementation
- other practical information and annexes

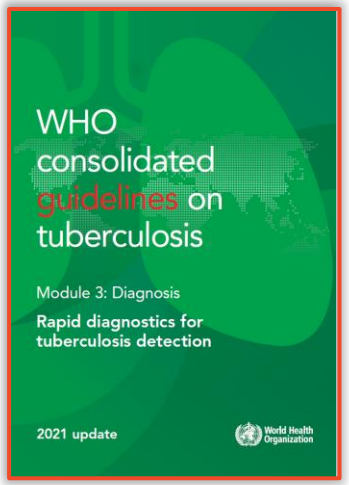
Rifapentine crush study: adult tablets achieve bioequivalent rifapentine exposures when swallowed whole or suspended in water

World Health Organization

Updates on low complexity (LC) nucleic acid amplification tests (NAATs)

- Consolidate individual product-specific recommendations into **class-based recommendations** and update the recommendations for technologies falling into the manual and automated low-complexity nucleic acid amplification test (NAAT) classes
- Concurrent use of tests for diagnosis of TB
  - **Adults and adolescents with HIV** with signs/symptoms *or* positive screening test *or* seriously ill *or* with advanced HIV disease: **LC-aNAATs (respiratory sample) and LF-LAM (urine)** *(strong recommendation, moderate certainty evidence)*
  - **Children** with signs/symptoms or positive screening test: **LC-aNAAT on respiratory samples and stool** *(**strong** recommendation, low certainty evidence)*
    - Strong recommendation as large desirable effects: rapid and accurate diagnosis in highly vulnerable population
    - Concurrent testing prioritized over use of a single molecular test
    - Evidence supports use of LC-aNAATs on sputum, gastric aspirate, stool and NPA as initial diagnostic test
  - **Children with HIV** with signs/symptoms or positive screening test: **LC-aNAAT on respiratory sample and stool and LF-LAM on urine** *(**conditional** recommendation, low certainty evidence)*





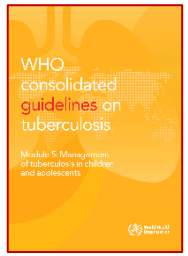
Rapid communication: https://www.who.int/publications/i/item/B09111

World Health Organization

END TB

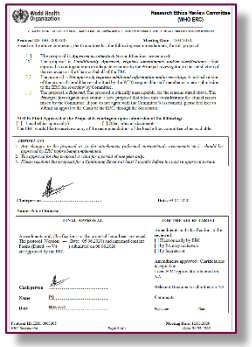
TDA4Child initiative

New WHO guidelines and handbook



March 2022

Creation of the TDA4Child initiative



June 2022

Protocol development

Aug 2022

First meeting of the writing committee Lusaka, Zambia

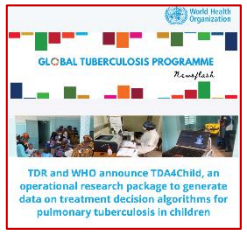
Sept 2022

Project presentation

WARN/CARN-TB

April 2023

Website launch (first generic tools)



May 2023

First generic protocol adaptations with TDR technical support

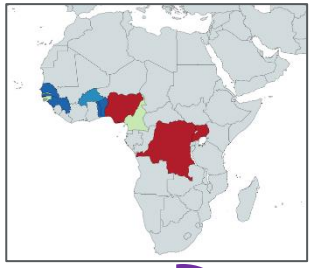
Burkina Faso, Democratic Republic of the Congo, Nigeria

June 2023

Consolidation of generic tools in English and French, first study sites opened, first meeting on progress and harmonization

Nov 2023

First results



August 2024

Second meeting on progress and harmonization

Nov 2024

50 TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO
LOCAL SOLUTIONS FOR GLOBAL IMPACT

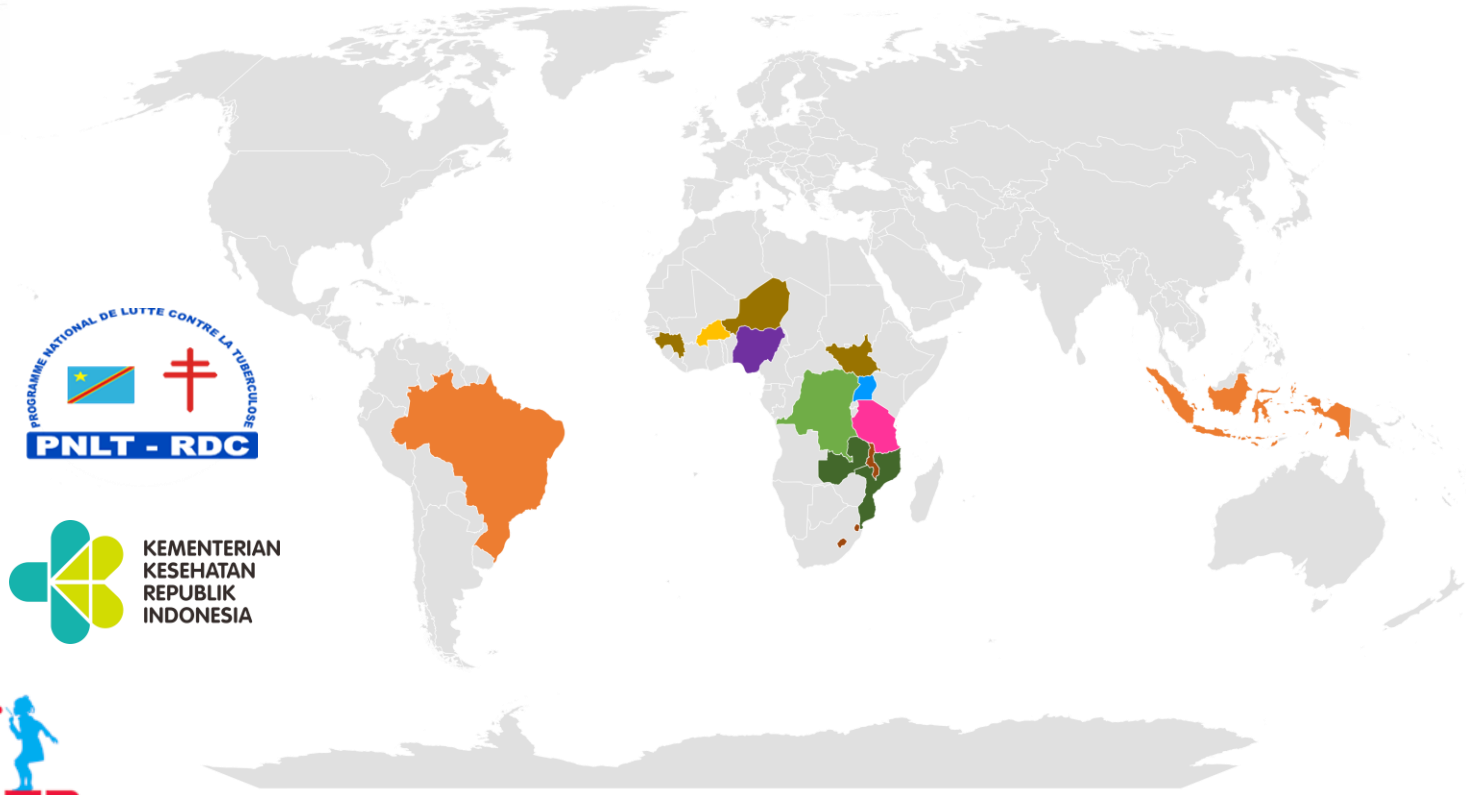
World Health Organization

https://tdr.who.int/activities/TDA4Child-initiative

END TB

TDA studies as of November 2024

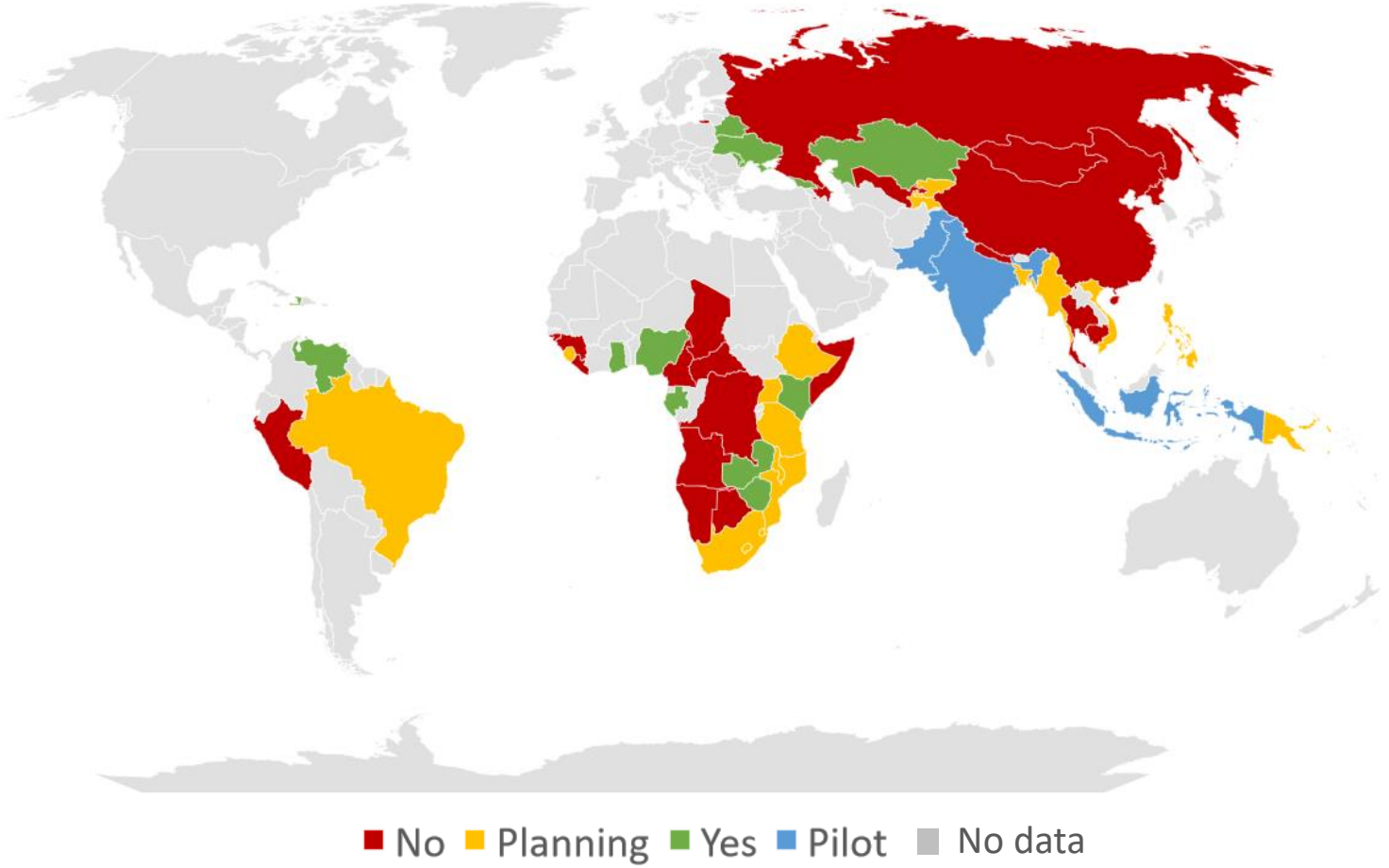
Estimated/expected cohort size: ~20,000



- Local partners
- TDA4Child
- TDA4Child, EDCPT
- TB GAPs
- MSF
- Decide TB
- TDA4Child, MSF
- EDCPT, EGPAF, TB GAPs
- EDCPT, EGPAF, TB GAPs, MSF

Implementation research on short regimen for non-severe TB

- Limited implementation up to 2024*
- Many countries struggling to determine practical guidance on how to assess eligibility/severity in programmatic settings
- TDR/GTB starting development of implementation research package
  - Evaluation of the adoption, fidelity, feasibility, acceptability, efficiency and cost impact of the four-month regimen for non-severe DS-TB in children and adolescents 3 months - 16 years



** Information may not be fully up to date!*

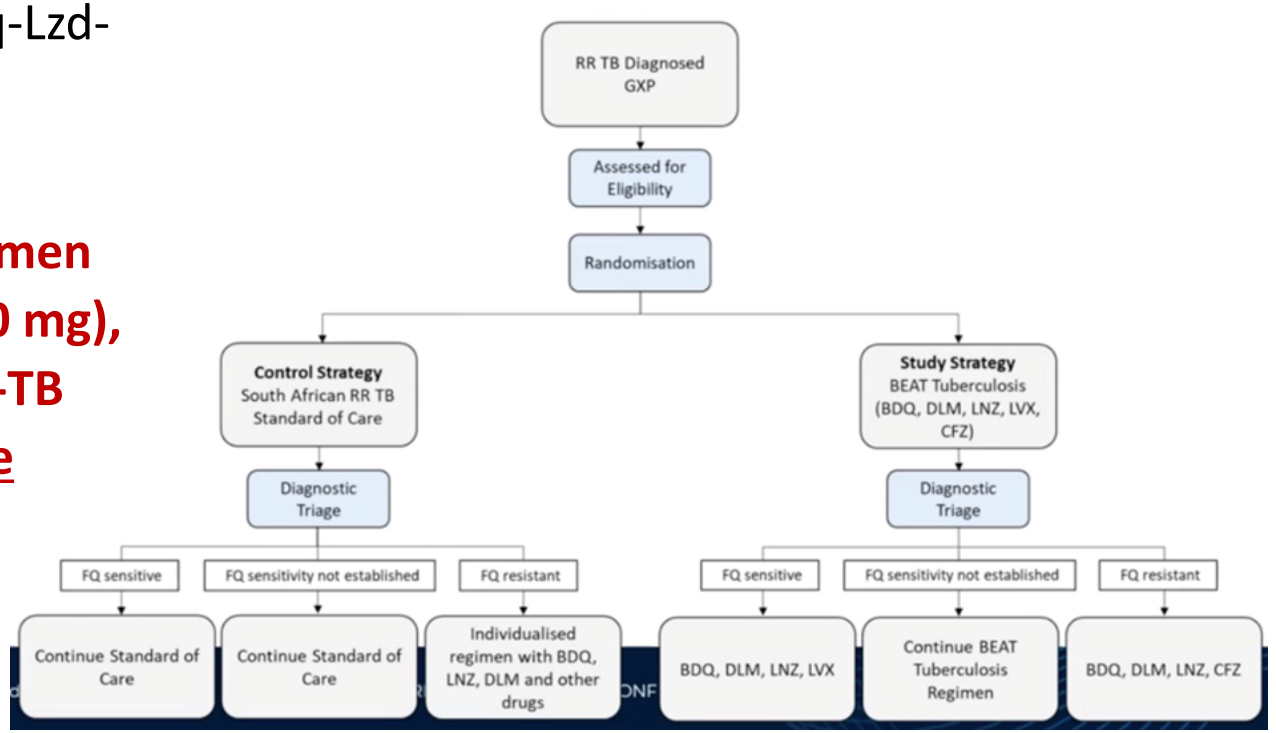
Treatment of DR-TB in children – forthcoming updates

- **BEAT-tuberculosis trial** in South Africa – 6-month Bdq-Lzd-Dlm-Lfx/Cfz (or both) vs Standard of Care

- New recommendation:

  WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance

  (Conditional recommendation, very low certainty of evidence)



- Applies to (among others):

  ☑ FQ S
  ☑ FQ R

  a. PTB TB, including **children, adolescents, PLHIV, pregnant and breastfeeding women**
  b. EPTB except CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement
  c. **Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB** (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB)

World Health Organization

Rapid communication: https://www.who.int/publications/i/item/B09123

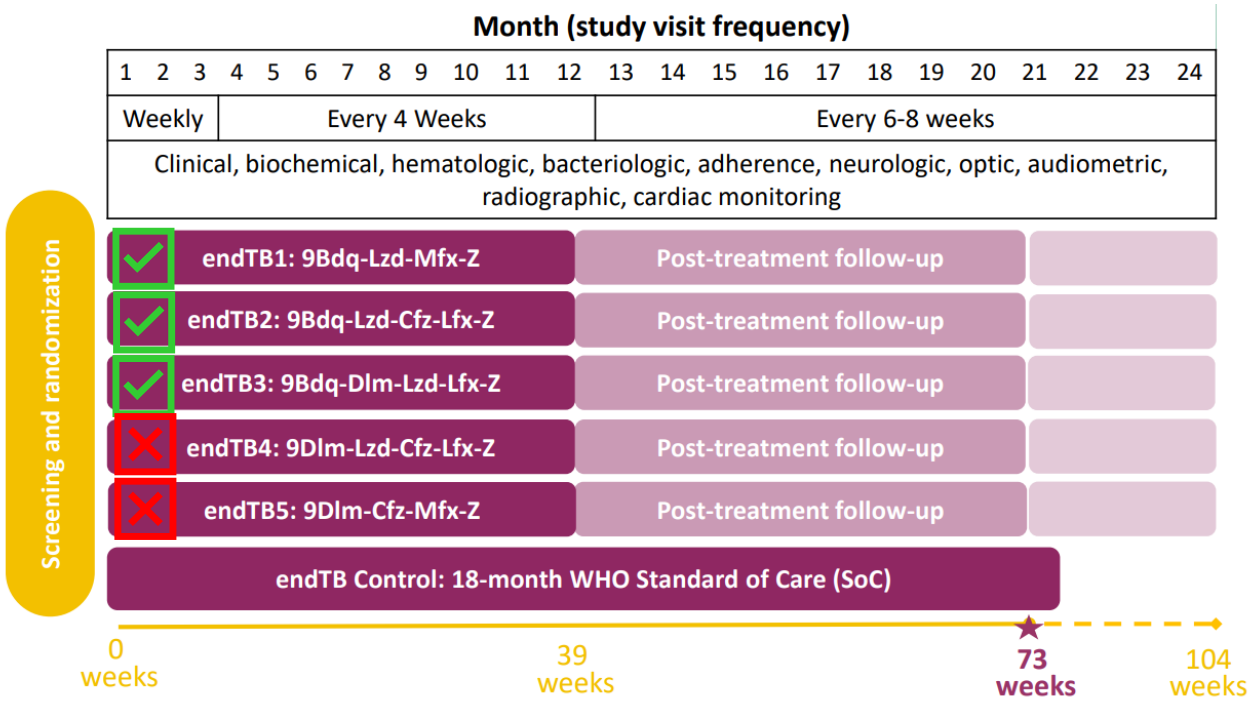
END TB

Treatment of DR-TB in children – forthcoming updates

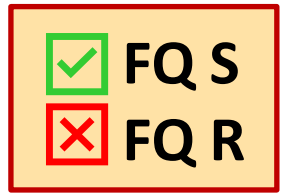
- **endTB trial** – 9-month regimens vs Standard of Care
- New recommendation:

  WHO suggests using the 9-month all-oral regimens (BLMZ, BLLfxCZ and BDLLfxZ) over currently recommended longer (>18 months) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. Amongst these regimens, using BLMZ is suggested over BLLfxCZ, and BLLfxCZ is suggested over BDLLfxZ

  (Conditional recommendation, very low certainty of evidence)



- Applies to (among others):
  a. PTB TB, including **children, adolescents, PLHIV, pregnant and breastfeeding women**
  b. EPTB except CNS, osteoarticular, or disseminated forms of TB with multi-organ involvement
  c. **Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB** (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB)

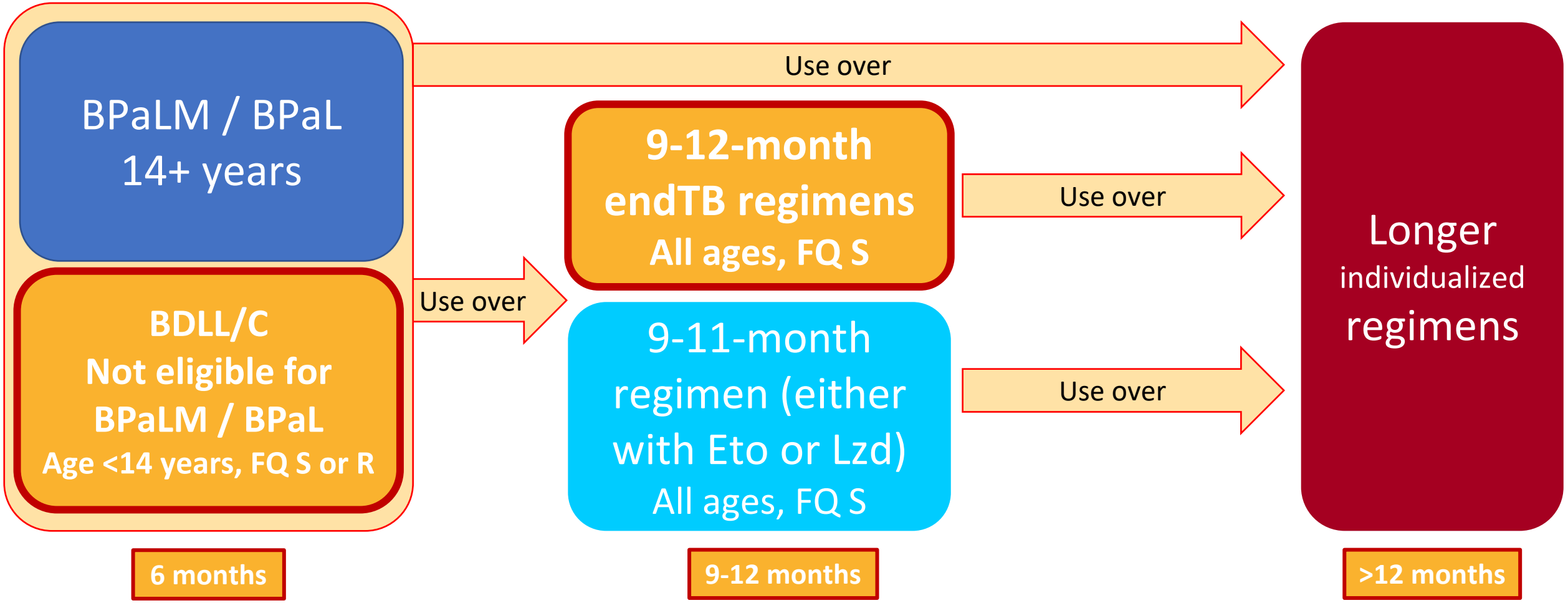


World Health Organization

Rapid communication: https://www.who.int/publications/i/item/B09123

END TB

Updated mapping of DR-TB regimens – children & adolescents

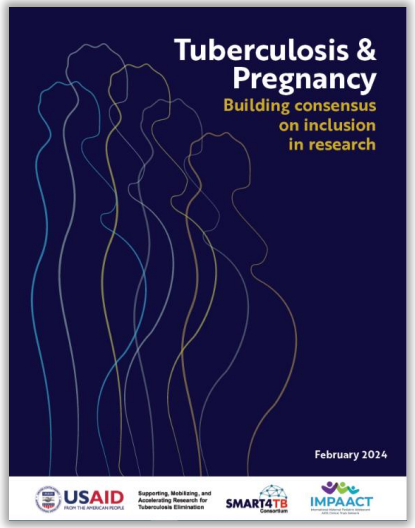


World Health Organization

END TB

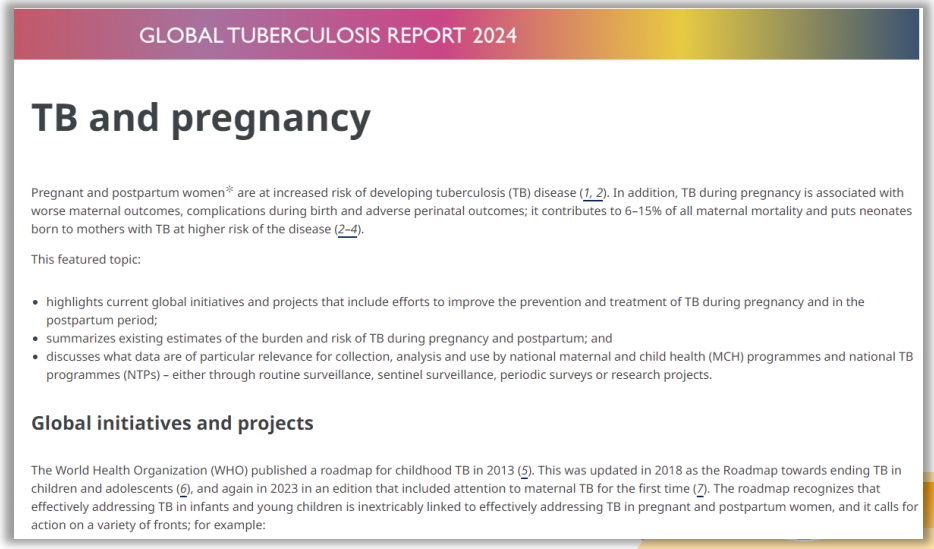
Work on TB and pregnancy

- **Consensus process** on inclusion of pregnant/lactating women in TB research in collaboration with SMART4TB project
  - Establishment of 5 working groups: preclinical, therapeutics, maternal TB surveillance, vaccines, advocacy
  - Development of working papers to feed into consensus statement
  - 3 evidence reviews in progress
  - Final consensus meeting planned for February 2025 (hybrid)
  - Link with crosscutting work on inclusion of pregnant women in trials (e.g. HIV, WHA resolution on clinical trials, updated International Council on Harmonization guidance)
- **Featured topic on TB and pregnancy** in online Global TB Report



https://tbcenter.jhu.edu/wp-content/uploads/2024/02/SMART4TB-Pregnancy-and-TB-Report.pdf

https://www.treatmentactiongroup.org/wp-content/uploads/2024/02/pregnancy_consensus_statement_full_final.pdf


GLOBAL TUBERCULOSIS REPORT 2024

TB and pregnancy

Pregnant and postpartum women* are at increased risk of developing tuberculosis (TB) disease (1, 2). In addition, TB during pregnancy is associated with worse maternal outcomes, complications during birth and adverse perinatal outcomes; it contributes to 6–15% of all maternal mortality and puts neonates born to mothers with TB at higher risk of the disease (2–4).

This featured topic:

- highlights current global initiatives and projects that include efforts to improve the prevention and treatment of TB during pregnancy and in the postpartum period;
- summarizes existing estimates of the burden and risk of TB during pregnancy and postpartum; and
- discusses what data are of particular relevance for collection, analysis and use by national maternal and child health (MCH) programmes and national TB programmes (NTPs) – either through routine surveillance, sentinel surveillance, periodic surveys or research projects.

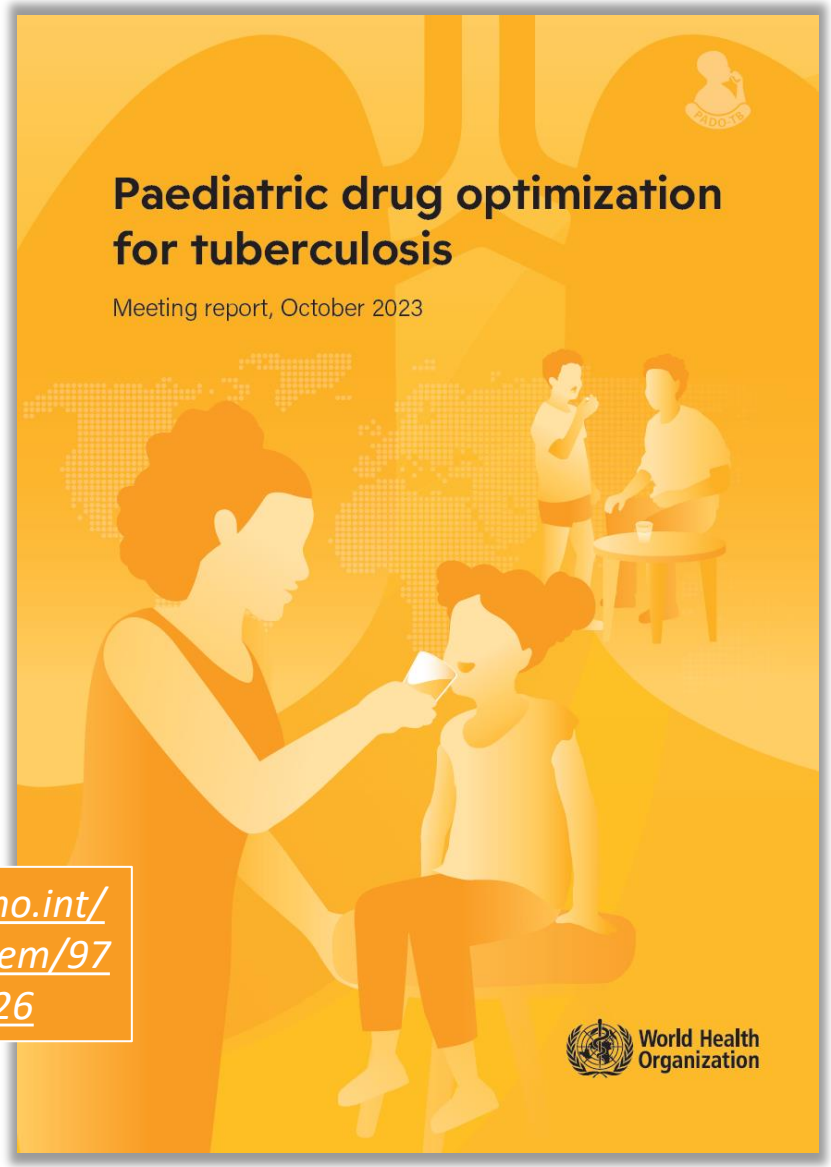
Global initiatives and projects

The World Health Organization (WHO) published a roadmap for childhood TB in 2013 (5). This was updated in 2018 as the Roadmap towards ending TB in children and adolescents (6), and again in 2023 in an edition that included attention to maternal TB for the first time (7). The roadmap recognizes that effectively addressing TB in infants and young children is inextricably linked to effectively addressing TB in pregnant and postpartum women, and it calls for action on a variety of fronts; for example:

https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024/featured-topics/tb-and-pregnancy

World Health Organization

PAediatric Drug Optimization for TB



https://www.who.int/publications/i/item/9789240094826

■ Medicines

Guidance Document
8 April 2024

22nd Invitation
to Manufacturers of Antituberculosis Medicines
to Submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit

To support national and global efforts to increase access to and the affordability of care and treatment of tuberculosis, WHO, together with UNICEF, UNAIDS, UNITAID and the Stop TB Partnership Global Drug Facility invites manufacturers of selected pharmaceutical products to submit Expressions of Interest (EOIs) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS EOI

The current Invitation is published in accordance with the *Procedure for Prequalification of Pharmaceutical Products*, adopted in 2001 by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations, and amended subsequently as part of the 45th report of the Committee, published as No. 961 of the WHO Technical Report Series in 2011.

Assessment of product(s) submitted under this Invitation for EOI includes evaluation of:

- product dossiers, which must include product data and information as specified in the guidelines for submission (see Procedures & Fees)
- manufacturing sites, which must adhere to good manufacturing practices (GMP)
- clinical sites (if applicable), which must adhere to good clinical practices (GCP).

If evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the list of medicinal products that are considered to be acceptable for procurement by UN organizations and others.

ARTICLE 2. MEDICINAL PRODUCTS INCLUDED IN THE 22nd INVITATION

The ultimate aim of this 22nd EOI is to increase the range of selected products and sources available in relation to treatment and prevention of tuberculosis (TB). These formulations are included either in the WHO Model List of Essential Medicines and/or in the WHO guidelines for treatment and prevention of TB.

https://extranet.who.int/prequal/news/22nd-invitation-manufacturers-antituberculosis-medicines-submit-expression-interest-eoi

World Health Organization

END TB

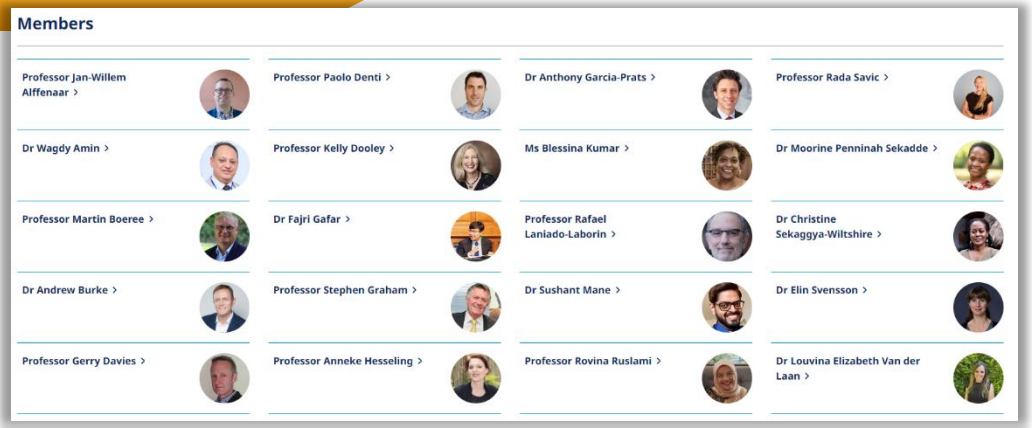
Technical Advisory Group on dosing

- Aims to complement work done by WHO Guideline Development Groups (WHO recommendations) **to inform dosing updates in WHO Operational Handbooks in a transparent, evidence-based, structured manner**

- 20 experts from geographically diverse settings and relevant technical expertise – members appointed for 3 years (eligible for reappointment)

First TAG meeting (early 2024)
reviewed new evidence on dosing of TPTregimens – published in 2nd ed. operational handbook on TPT

Second TAG meeting (TBC, 2025)
to review dosing of first-line medicines
Evidence reviews underway – updating dosing guidance to be published in relevant operational handbooks



TPT regimens and drug formulations	No. of tablets or quantity of solution by body weight band						
	3–5.9 kg (< 3 months)	3–5.9 kg (≥ 3 months)	6–9.9 kg (< 6 months)	6–9.9 kg (≥ 6 months)	10–14.9 kg	15–19.9 kg	20–24.9 kg
Three months of weekly rifapentine plus isoniazid (3HP)							
Isoniazid 100 mg dt	0.6 (6 mL[a])	0.7 (7 mL[a])	1	1.5	2.5	3	4.5
Isoniazid 300 mg tab	–	–	–	–	–	1	1.5
Rifapentine 150 mg dt	0.5 (5 mL[d])	0.7 (7 mL[d])	1.5	1.5	2	3	4
Rifapentine 300 mg tab	–	–	–	–	–	1.5	2
Rifapentine 300 mg and isoniazid 300 mg FDC tab	–	–	–	–	–	–	–
One month of daily rifapentine plus isoniazid (1HP)[e]							
Isoniazid 300 mg tab	–	–	–	–	–	–	–
Rifapentine 300 mg tab	–	–	–	–	–	–	–
Six months of daily levofloxacin (6Lfx)							
Lfx 100 mg dt	0.5	1	1	1.5	2	2.5	3
Lfx 250 mg tab	0.25 (2.5 mL[d])	0.5 (5 mL[d])	0.5 (5 mL[d])	1 (10 mL[d])	1	1.5	–
Lfx 500 mg tab	–	–	–	–	–	–	–

World Health Organization

END TB

Acknowledgements

Tereza Kasaeva, Farai Mavhunga, Katherine Floyd & other colleagues from WHO GTB

Core team members of the child and adolescent TB working group

All members of the child and adolescent TB working group

Thank you for your attention!

World Health Organization

END TB