Updates on WHO guidelines and operational handbook on Tuberculosis Preventive Treatment

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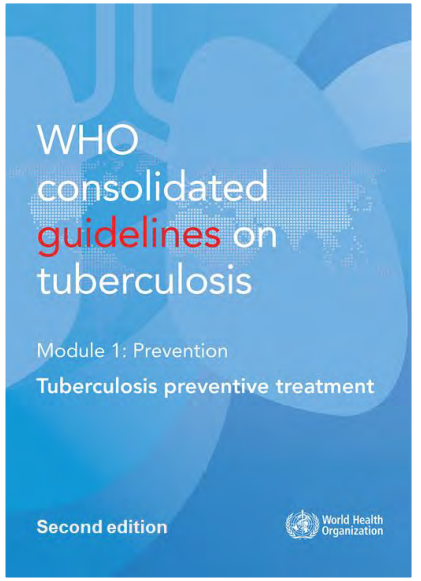
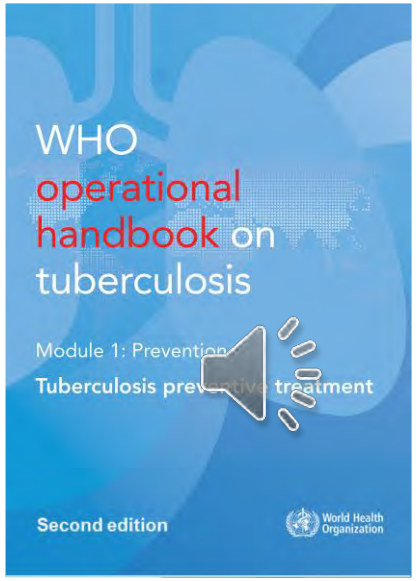
WHO Global Programme on Tuberculosis & Lung Health





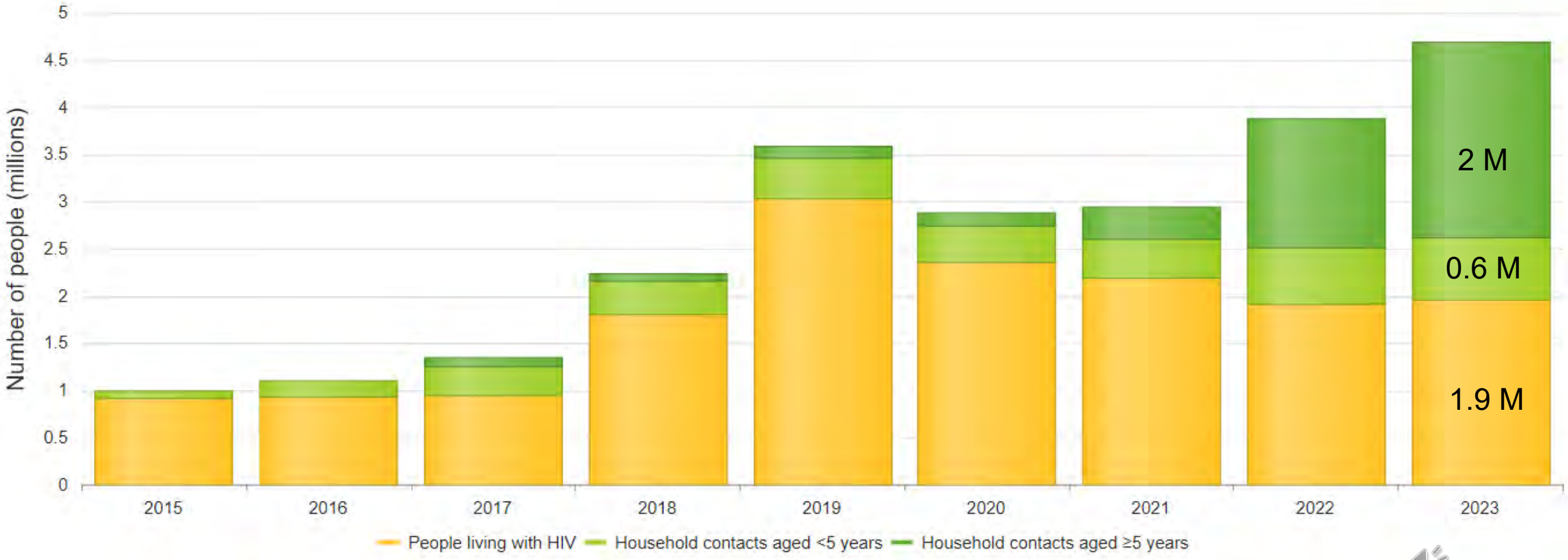
Background

The End TB Strategy – Pillars 1 & 2

TB preventive treatment (TPT) fits within a **larger framework of preventive actions** envisaged by Pillars 1 and 2 of the End TB Strategy, ranging from active TB case finding, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation.

TB preventive treatment in people with HIV & contacts

2015–2023

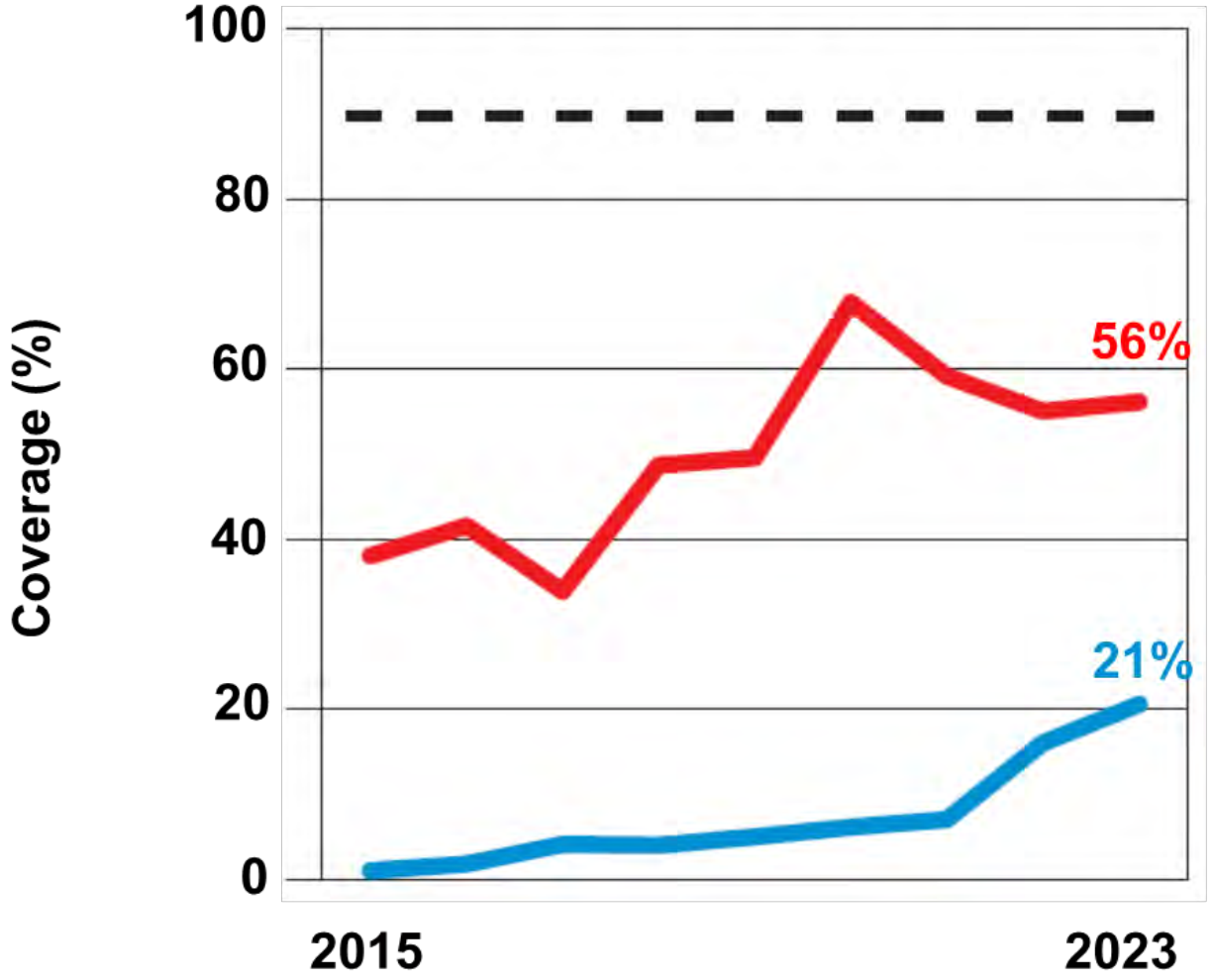


World Health Organization

END TB

Global coverage of TPT

2015–2023



90% target for 2027

People living with HIV newly enrolled on ART

Household contacts of people newly diagnosed with TB

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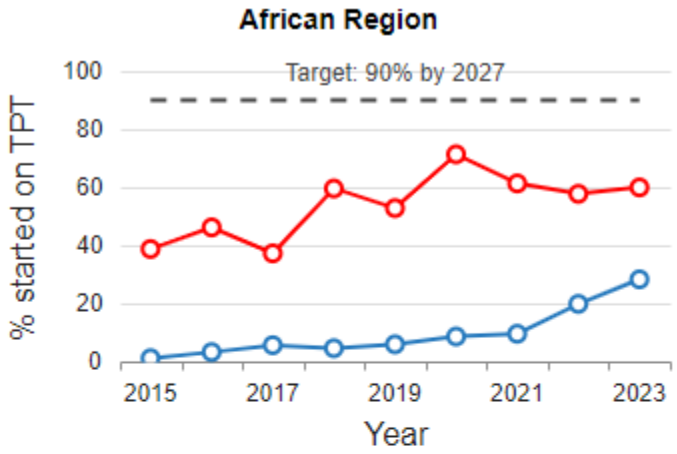
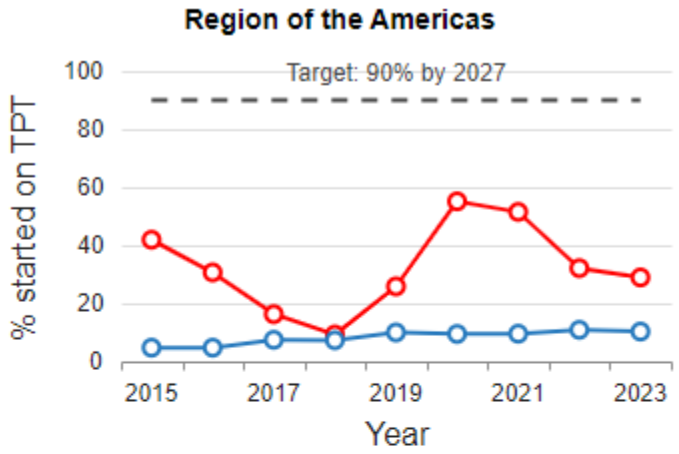
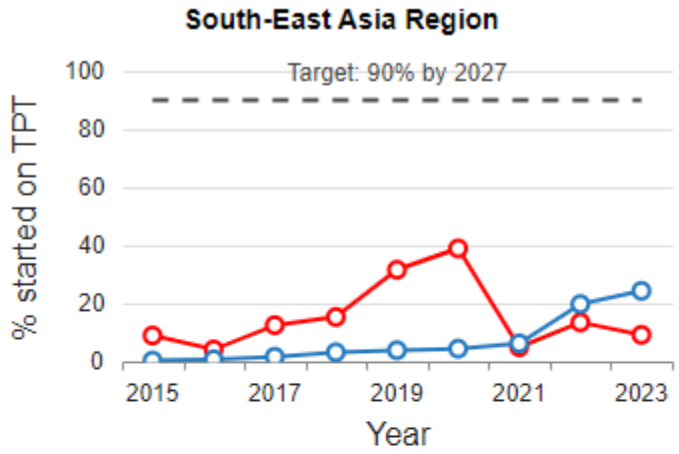
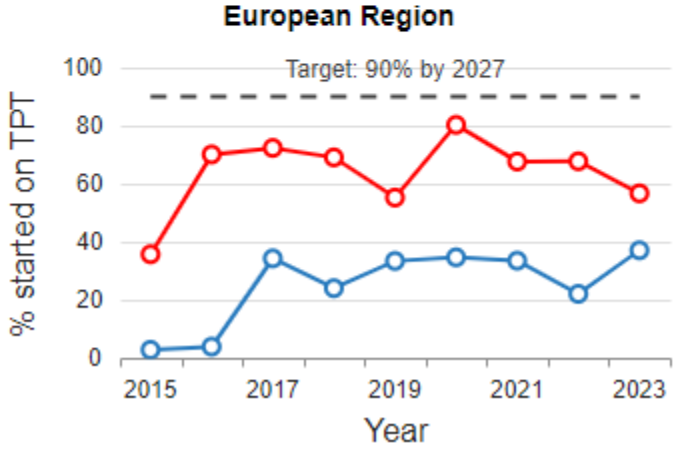
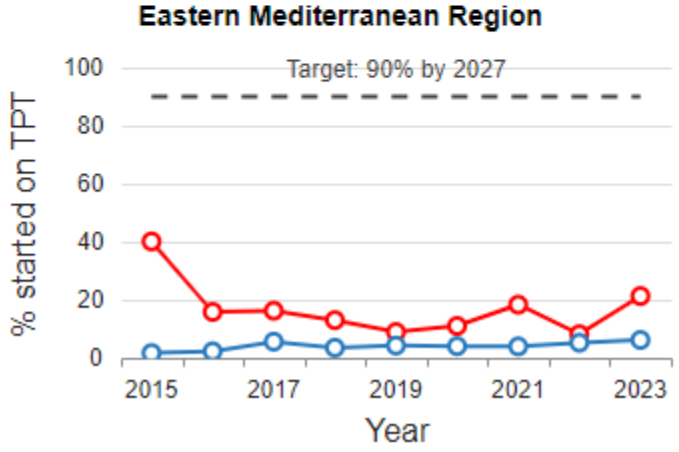
Provision of TPT to people with HIV, 2015-2023

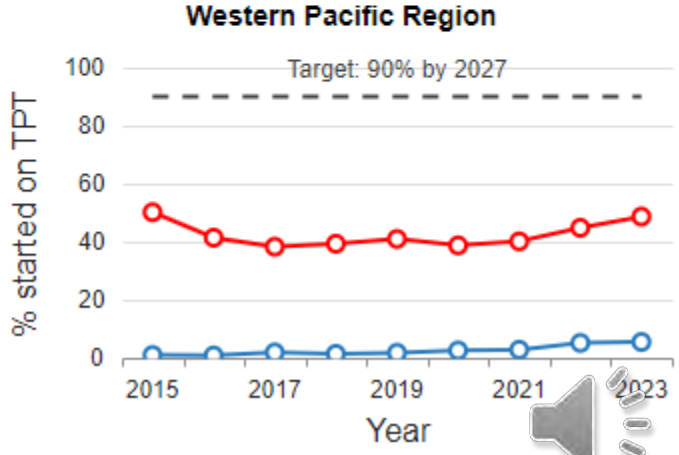












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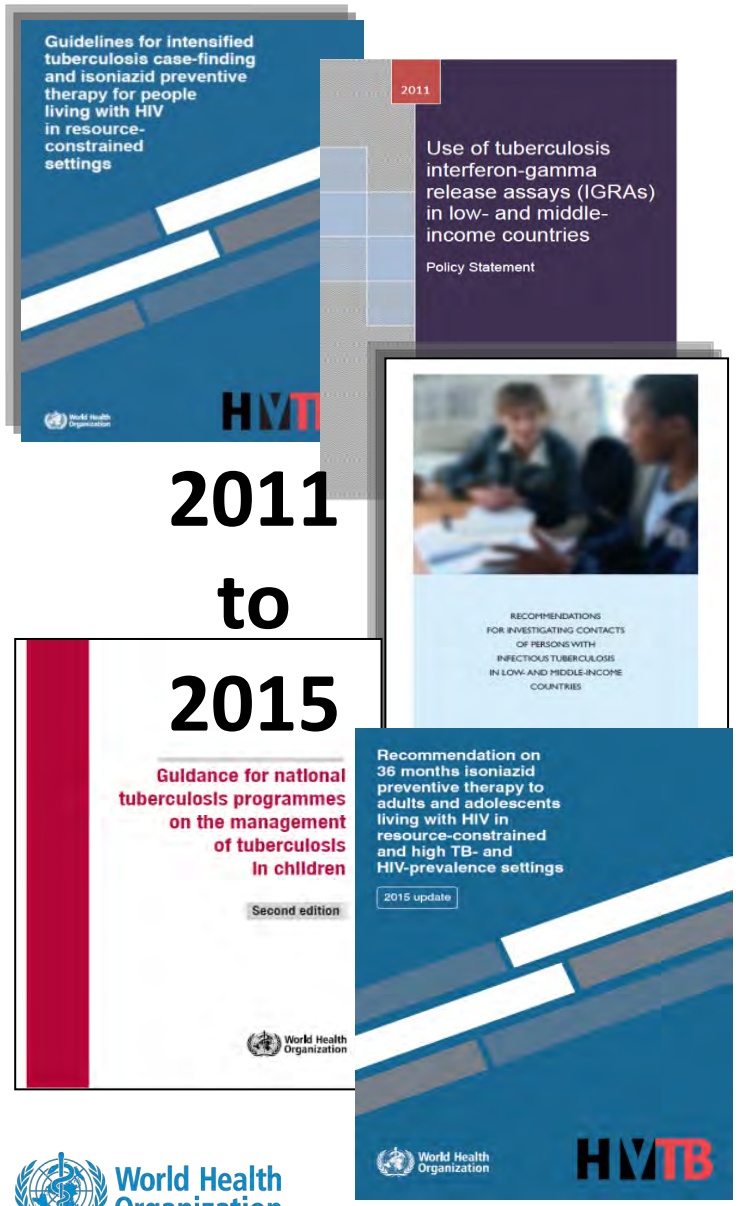
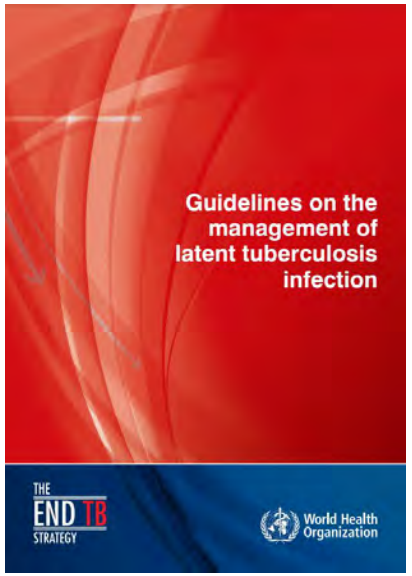
Evolution of WHO guidelines on TPT

DR-TPT

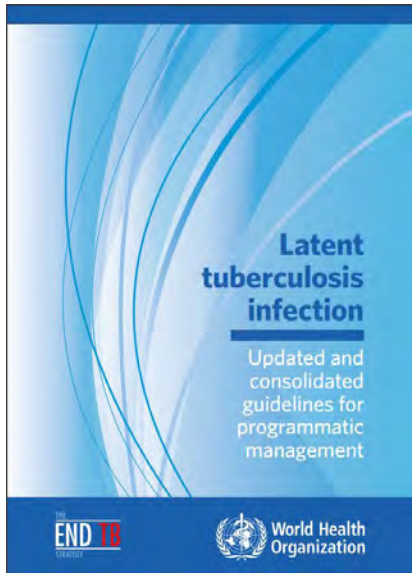


2011 to 2015

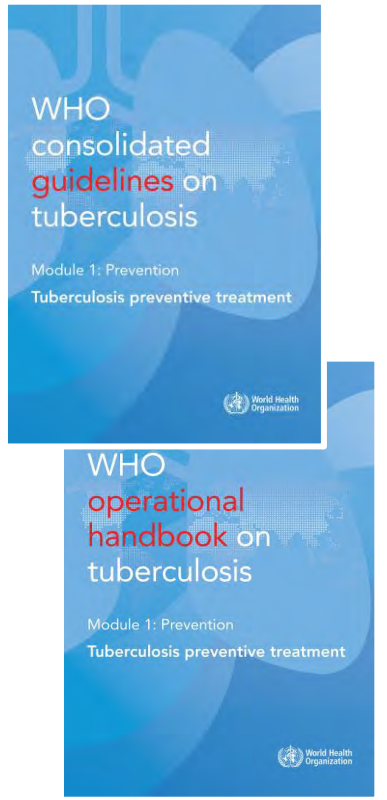
2015



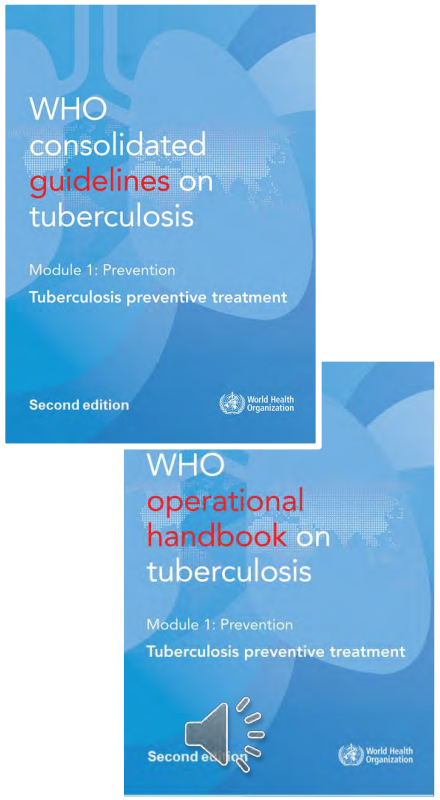
2018



2020



2024



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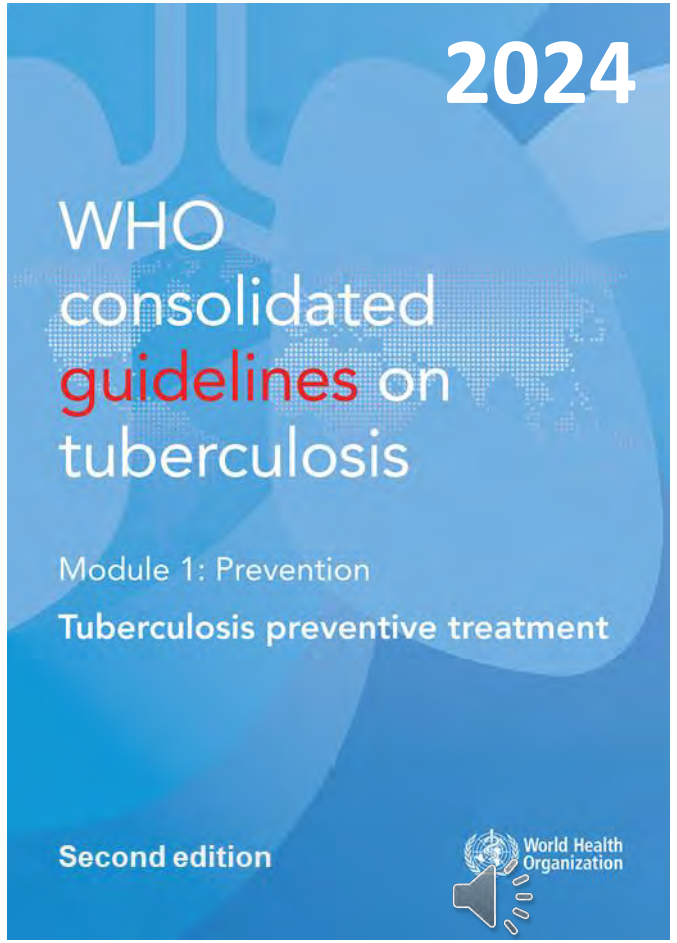
Outline of WHO guidelines on TPT

21 recommendations on 4 critical steps of the TB preventive care cascade:

1. Identify people at risk
2. Screen for TB and rule out TB
3. Test for TB infection
4. Select TPT regimen

(Research gaps)



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Recommendations (1) *Identify people at risk*

People living with HIV

- Adults and adolescents (>10y) [regardless of ARV, pregnancy, previous TB treatment, immunosuppression and availability of test for TB infection]*
- Children aged ≥ 12 months in a high TB transmission setting
- Infants aged < 12 months who are in contact with TB*
- All children who successfully completed treatment for TB disease

Household contacts of pulmonary TB (bacteriologically confirmed)

- Children < 5 years*
- Individuals aged ≥ 5 years
- Exposed to multidrug-resistant tuberculosis

Other risk indicating systematic testing & TPT

- People who have silicosis, or who are initiating anti-TNF treatment or dialysis, or preparing for an organ or haematological transplant*
- Prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use drugs

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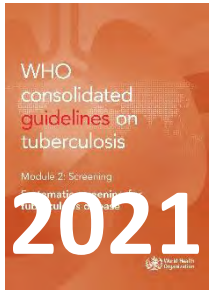
* Strong recommendation

END TB

Recommendations (2) *Screen for TB and rule out TB*



People living with HIV

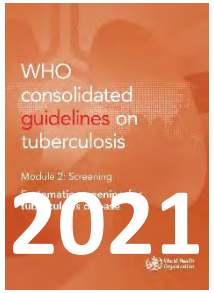
- Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age.*
- Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease. Those who report any of these symptoms may have TB and should be evaluated for TB disease and other diseases and offered TB preventive treatment if TB disease is excluded, regardless of their ART status.*
- Among adults and adolescents living with HIV, **chest X-ray** may be used to screen for TB disease.
- Among adults and adolescents living with HIV, **C-reactive protein** using a cut-off of >5mg/L may be used to screen for TB disease.
- Among adults and adolescents living with HIV, **molecular WHO-recommended rapid** diagnostic tests may be used to screen for TB disease.

* Strong recommendation

World Health Organization

END TB

Recommendations (3) *Screen for TB and rule out TB*



Household contacts of pulmonary TB and other risk groups

- The **absence of any symptoms of TB** and the **absence of abnormal chest radiographic** findings may be used to rule out TB disease among HIV-negative household contacts aged ≥ 5 years and other risk groups before TB preventive treatment.
- Among individuals **younger than 15 years** who are close contacts of someone with TB, systematic screening for TB disease should be conducted using a **symptom screen including any one of cough, fever or poor weight gain; or chest radiography; or both**.
- Among **individuals aged 15 years and older** in populations in which TB screening is recommended, systematic screening for TB disease may be conducted using a **symptom screen, chest X-ray, or molecular WHO-recommended rapid diagnostic tests**, alone or in combination.*

World Health Organization

* Strong recommendation

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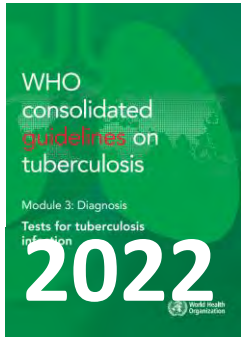
Recommendations (4) *Tests for TB infection*



- Either a TST or IGRA (QuantiFERON®-TB Gold and T-SPOT®.TB) can be used to test for TB infection*

- New antigen-based skin tests for TB infection may be used

A test for TB infection is not required to start TPT in people with HIV or contacts aged < 5 years

* Strong recommendation

List of IGRAs that meet WHO Recommendations

1. QuantiFERON TB Gold Plus (Qiagen) /ELISA-based
2. T-SPOT®.TB (Oxford Immunotec)/ELISPOT-based
3. TB-IGRA (Beijing Wantai) /ELISA-based
4. Standard E TB-Feron (SD Biosensor) /ELISA-based
5. LIAISON QFT-Plus, (Diasorin) /CLIA

Endorsed by TAG in January 2025

(under publication)

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Tests for TB infection: SIILTIBCY skin test

Stop TB Partnership
GLOBAL DRUG FACILITY

Stop TB Partnership Global Drug Facility Info Sheet: SIILTIBCY™

The SIILTIBCY skin test (marketed in India as Cy-Tb) is a new diagnostic tool for detecting *Mycobacterium tuberculosis* (Mtb) infection, using Mtb-specific antigens (recombinant proteins of ESAT-6 and CFP-10). It offers enhanced specificity over the traditional tuberculin skin test (also known as the Mantoux test), particularly in BCG-vaccinated individuals.

Technical specifications*	rdESAT-6/rCFP-10 0.5 µg/0.5 µg. Solution for injection, vial of 1 ml. Each vial contains 10 doses/tests (0.1 ml per dose/test).
Manufacturer	Serum Institute of India Pvt. Ltd. (Pune, India)
GDF price (ex-works)	$15.00 per vial of 10 doses/tests
GDF item code	rdESAT-6/rCFP-10-0.5/0.5-(V)-1 (SIILTIBCY)
Country eligibility	All countries are eligible
Minimum order quantity	To be ordered in multiples of 120 vials (1,200 doses/tests) due to specific shipping requirements
Shelf life	24 months
Storage requirements	2-8°C, in the original packaging, protect from light, do not freeze. After first opening, to be stored between 2-8°C and used within up to 28 days.

** Syringes for intradermal injection must be procured separately*

NEWS ALERT - 10 October 2024 I Geneva

BREAKING NEWS: Only $1.50 to Detect TB Infection With the Next-Generation SIILTIBCY Test

Available now in Stop TB GDF Catalog

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Recommendations (5) *TPT options*

1) 6 or 9-month, daily isoniazid (6/9H)*
2) 3-month, weekly isoniazid and rifapentine (3HP)*
3) 3-month, daily isoniazid and rifampicin (3HR)*
4) 1-month, daily isoniazid and rifapentine (1HP)
5) 4-month, daily rifampicin (4R)
6) ~~36-month, daily isoniazid (for people with HIV in high TB transmission settings)~~
7) 6-month, daily levofloxacin after exposure to multidrug- or rifampicin-resistant TB (6Lfx)*

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* Strong recommendation

END TB

Recommendations (6) *TPT for MDR-TB*

Previously **conditional recommendation** (very low certainty evidence):

- ~~*In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.*~~

Now **strong recommendation** (moderate certainty evidence):

- *In contacts exposed to multidrug- or rifampicin-resistant tuberculosis, six months of daily levofloxacin should be used as TB preventive treatment*

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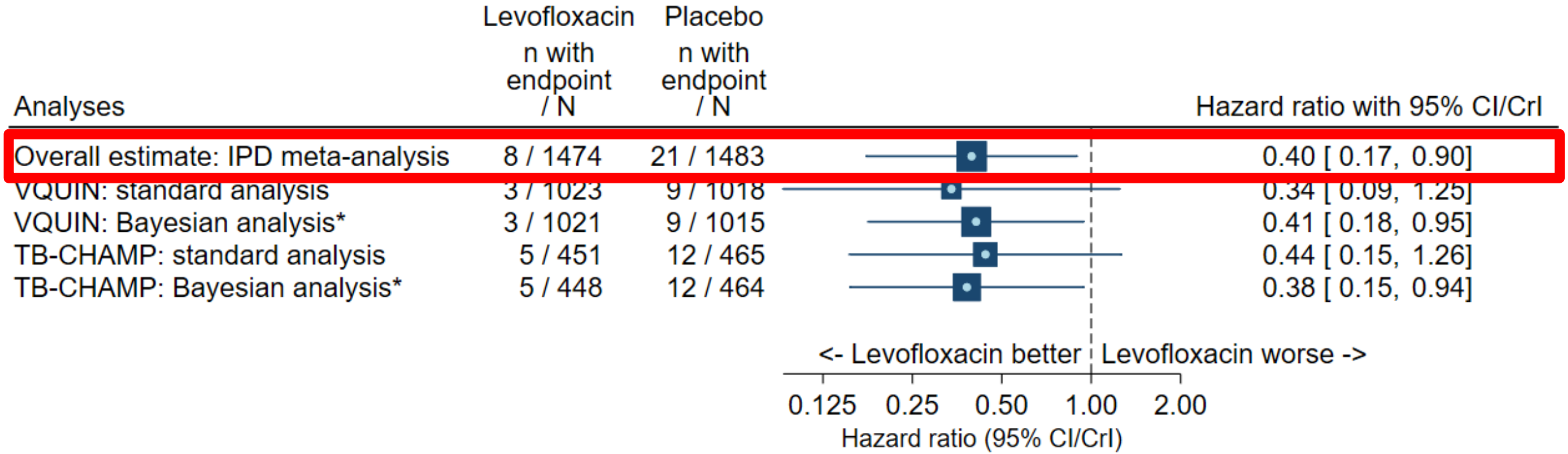
Efficacy of levofloxacin

Estimated treatment effect across different analyses: TB disease by 54 weeks



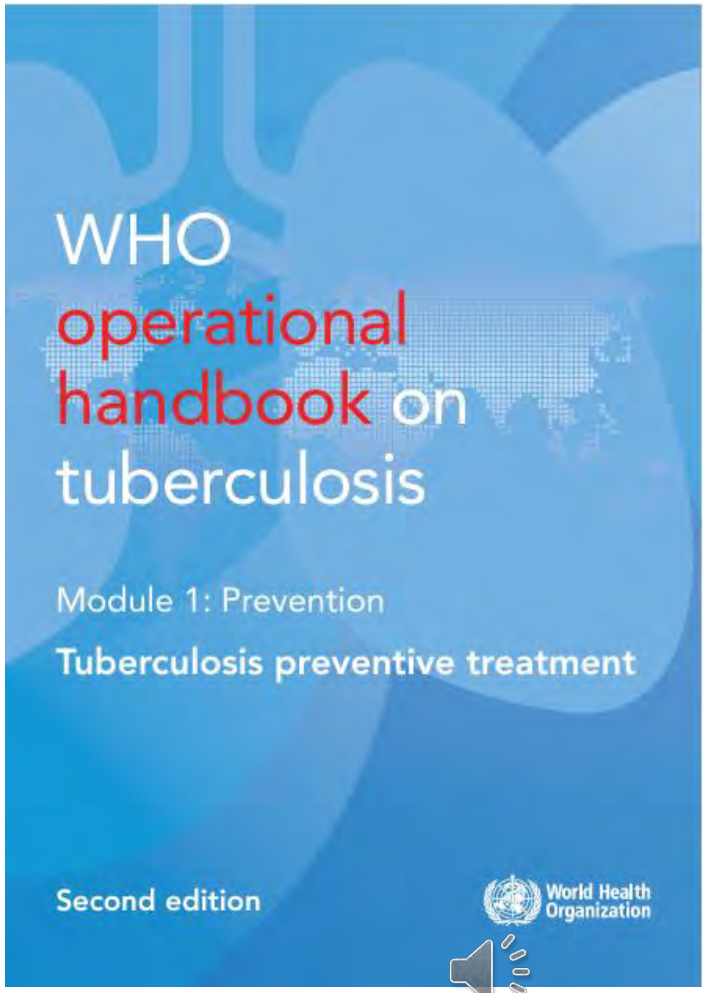
- Posterior probability that levofloxacin is superior to placebo in VQUIN population=98%
- Posterior probability that levofloxacin is superior to placebo in TB-CHAMP population=98%

Countries reporting use of levofloxacin for TPT: 2023

	AFR	AMR	EUR	EMR	SEA	WPR
1	Congo	Chile	Georgia	Somalia	**Indonesia**	**Australia**
2	Eritrea	Colombia	Kazakhstan		**India**	**Guam**
3	Mozambique	Dominican Republic	Portugal			**Mongolia**
4	Namibia	Guatemala	Serbia			**Malaysia**
5	Eswatini	Haiti	Slovakia			**Singapore**
6	South Africa	Mexico	Turkiye			
7	Zimbabwe	Nicaragua	Ukraine			
8		Peru	Uzbekistan			
9		Paraguay				
10		Venezuela				

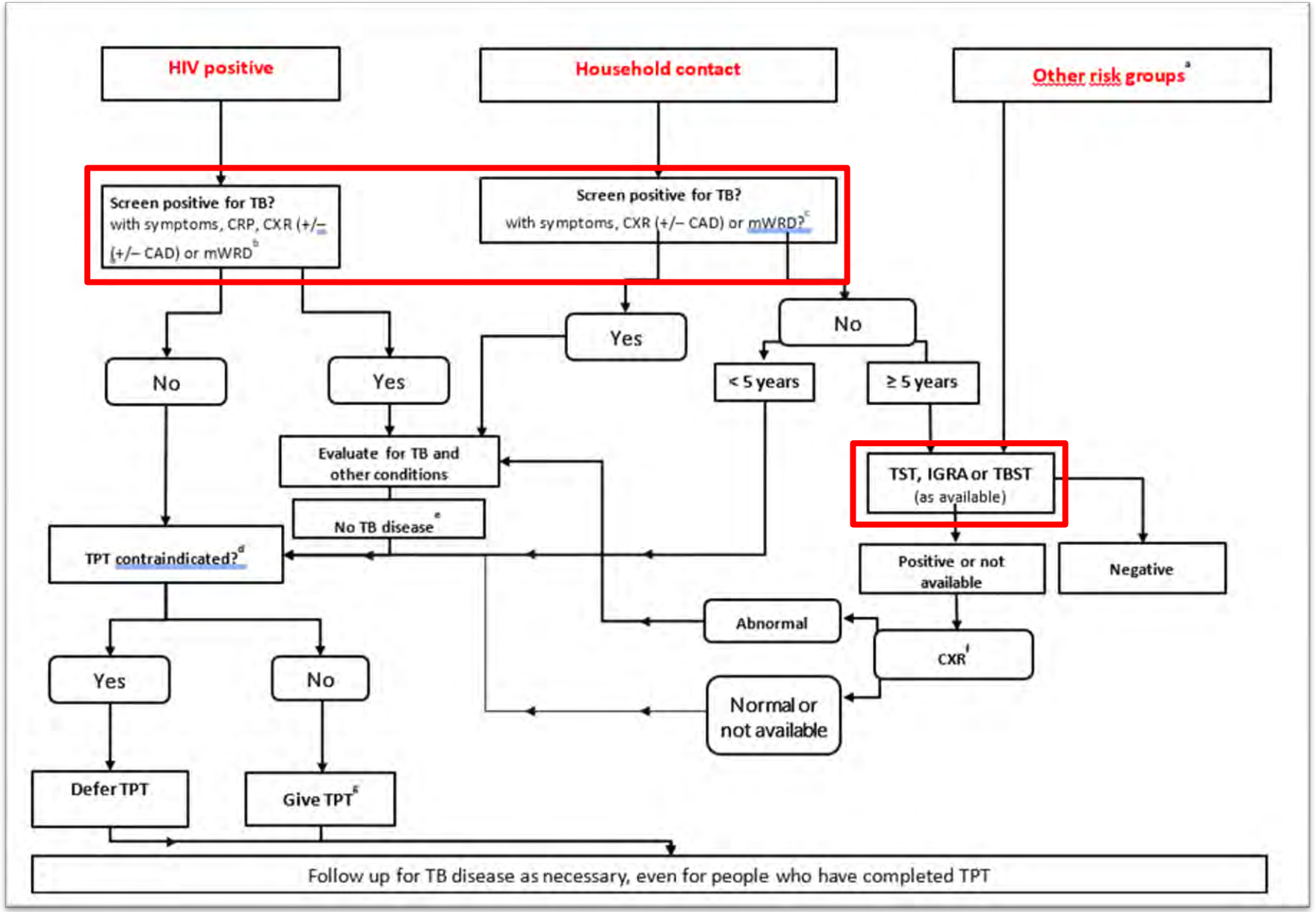
TPT operational handbook

- Evidence to address FAQs
- Provides **complementary details** on TPT critical to the implementation of different elements of PMTPT
  - contact tracing
  - drug dosages
  - drug-drug interactions
  - safety monitoring/ management of adverse events
  - management of TPT interruptions
  - adherance monitoring
  - programme indicators



https://www.who.int/publications/i/item/9789240097773

Combined algorithm for screening and testing before TPT



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Drug dosage for TPT according to body weight band

	Amount of tablets or solution by body weight band (in kilograms)												
	3 – 5.9 <3 months	3 – 5.9 ≥3 months	6 – 9.9 <6 months	6 – 9.9 ≥6 months	10 – 14.9	15 – 19.9	20 – 24.9	25 – 29.9	30 – 34.9	35 – 39.9	40 – 44.9	45 – 49.9	≥50
Three month of weekly rifapentine plus isoniazid (3HP)													
Isoniazid 100 mg dt	0.6 (6 ml)	0.7 (7 ml*)	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)	0.7 (7 ml)	1.5	1.5	2	3	4	4	5	6	6	6	6
Rifapentine 300 mg tab	-	-	-	-	-	1.5	2	2	2.5	3	3	3	3
Rifapentine 300mg and Isoniazid 300mg FDC tab[c]	-	-	-	-	-	1	1.5	2	2.5	3	3	3	3
One month of daily rifapentine plus isoniazid (1HP)													
Isoniazid 300 mg tab	-	-	-	-	-	-	-	1	1	1	1	1	1
Rifapentine 300 mg tab	-	-	-	-	-	-	-	2	2	2	2	2	2
Six month daily levofloxacin (6Lfx)													
Levofloxacin 100 mg dt	0.5	1	1	1.5	2	2.5	3	3.5	-	-	-	-	-
Levofloxacin 250 mg tab	0.25 (2.5 ml)	0.5 (5 ml)	0.5 (5 ml)	1 (10 ml)	1	1.5	1.5	2	2	2	2	2	3
Levofloxacin 500 mg tab	-	-	-	-	-	-	-	1	1	1	1	1	1.5

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Secondary safety analyses

	LfX (n=1412)	Placebo (n=1431)	Risk ratio (95% CI)	P	P for test of heterogeneity
Grade 3 or above adverse event*					
VQUIN	29 (3.0%)	19 (2.0%)	1.55 (0.87 , 2.76)		
TB-CHAMP	14 (3.1%)	23 (4.9%)	0.67 (0.34 , 1.31)		
Overall	43	42	1.07 (0.70 , 1.65)	0.75	0.06
Grade 3 or above adverse event at least possibly related to study drug					
VQUIN	10 (1.0%)	2 (0.2%)	5.26 (1.16 , 23.95)		
TB-CHAMP	4 (0.9%)	8 (1.7%)	0.53 (0.16 , 1.70)		
Overall	14	10	1.46 (0.65 , 3.26)	0.36	0.02
Grade 3 or above SAEs*					
VQUIN	20 (2.1%)	12 (1.3%)	1.72 (0.85 , 3.49)		
TB-CHAMP	8 (1.8%)	7 (1.5%)	1.23 (0.45 , 3.35)		
Overall	28	19	1.54 (0.87 , 2.74)	0.14	0.59

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Included participants who took at least one study drug dose.

** Up to 21 days after last study drug dose.*

END TB

Secondary safety analyses

	LfX (n=1412)	Placebo (n=1431)	Risk ratio (95% CI)	P	P for test of heterogeneity
Discontinuation of study treatment due to AE(s) of any grade					
VQUIN	71 (7.4%)	11 (1.1%)	6.43 (3.42 , 12.09)		
TB-CHAMP	6 (1.3%)	1 (0.2%)	5.25 (0.64 , 43.13)		
Overall	**77**	**12**	**6.32 (3.43 , 11.63)**	**<0.001**	**0.86**

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Secondary safety analyses

	LfX (n=1412)	Placebo (n=1431)	Risk ratio (95% CI)	P	P for test of heterogeneity
Musculoskeletal AE of any grade during overall study follow-up (arthritis, arthralgia, or tendinopathy)					
VQUIN	**220 (22.9%)**	32 (3.3%)	7.02 (4.67 , 10.56)		
TB-CHAMP	6 (1.3%)	4 (0.9%)	1.35 (0.36 , 5.06)		
Overall	226 (16%)	36 (2.5%)	6.36 (4.30 , 9.42)	<0.001	0.01

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Levofloxacin adverse events in V-QUIN and TB- CHAMP

- Important difference in risks between children and adults, **good tolerance in children**
- One or more adverse events of **any grade reported in about 32% adolescents and adults** in V-QUIN trial, most grade 1 or 2.
- **Serious adverse events infrequent**, about 1% grade 3 or 4 events not statistically significantly different from placebo arm
- Lfx associated with more **musculoskeletal events** (arthritis, arthralgia or tendonitis) in adolescents and adults, mostly grade 1 or 2.
- **Treatment discontinuation is uncommon**, more frequent among adolescents and adults
- Common adverse events are **dizziness, headache, nausea and abdominal pain**

Cost of DR-TPT

- **Adult**: US$ 9 (Lfx-500 mg)
- **Child**:
  - US$ 5 (Lfx-250 mg non-dispersible)
  - US$ 44 (Lfx-100 mg dispersible)

(*although dispersible is more expensive, TPT is still cost-effective and in long-term net cost savings: TB CHAMP*)

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DR-TPT in settings with high-quinolone resistance

- DR-TPT should be considered
- **Drug-susceptibility testing** of presumed source patient encouraged
- **If resistant to quinolones**, alternative TB drugs (e.g., ethionamide, ethambutol) may be considered per DST profile (less effective than 6Lfx).
- Results from the **PHOENIx trial**, in which 26 weeks of **delamanid** compared with isoniazid for household contacts (all ages) of MDR-TB patients expected in mid-2025.

Recording and reporting for the monitoring of PMTPT

1. **How many people are at risk** and could benefit from **TPT/DR-TPT**?
2. How many at-risk people were **evaluated** for TB disease or infection?
3. How many of those eligible **started** TPT/DR-TPT?
4. What were the main reasons for those eligible **who did not initiate** TPT?
5. How many of those initiating TPT/DR-TPT **completed** it?
6. For those who did not complete TPT/DR-TPT what were the main **reasons** (e.g., adverse drug reaction monitoring and management) ?

Prevent TB application

Prevent TB facilitates evaluation of TB contacts at both healthcare settings as well as at the community level. The system supports continuous monitoring of registered individuals across for tuberculosis screening and e treatment, capturing data from the initial rget population, registration, clinical ning, testing for tuberculosis infection, and e treatment. The platform also generates iders when any implementation gap is rehensive performance indicators to

Prevent TB Smart Setup

The national programme/project coordinators can use the smart setup to create a new progra captured at the stage of registration, service delivery and also create context specific alerts, a application in local context. The platform also allows the upload of historic data on index case the management of users and health facilities.

Link to Smart Setup | User manual | Video

Prevent TB Application

The application has two different interfaces which cater to healthcare providers and registere

Healthcare provider module

Healthcare workers can use this module to register new individuals from target populations a screening, test results or referral for tuberculosis preventive treatment. The different sections of the interface enable users to monitor the progress of their clients through the cascade of care for tuberculosis screening and preventive treatment.

Link to web application | Link for Android | Link for iOS |

Client module

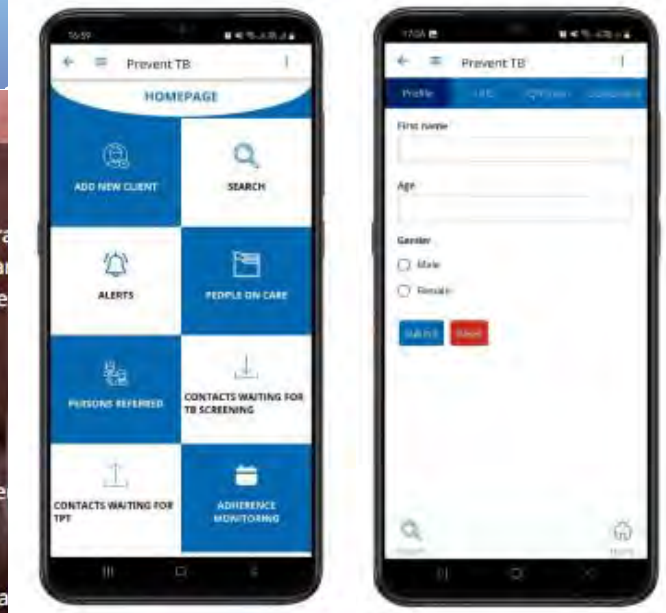
Individuals registered on the platform can use this module to a adherence and drug adverse events. Users can also communica

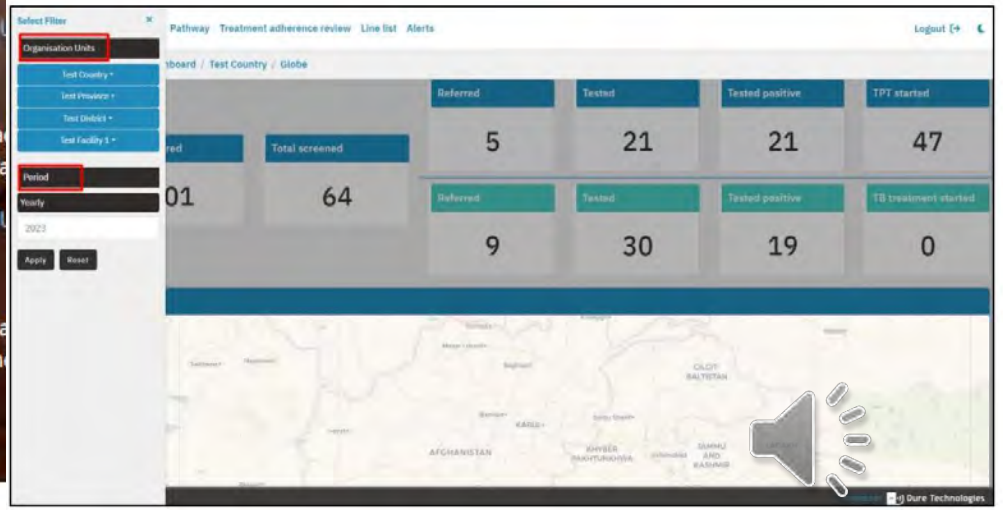
Link to web application | Link for Android | Link for iOS |

Prevent TB Dashboard

The dashboard allows data visualization through interactive cha programme managers in monitoring and evaluation of implem

Link to dashboard | User manual | Video





https://www.who.int/activities/preventing-tb#app

World Health Organization

Consolidated Guidelines | Operational Handbooks | Training Catalogue | Research and Innovation | English | Log in

WHO TB Knowledge Sharing Platform

Access the modular WHO guidelines on tuberculosis, with corresponding handbooks and training materials.

BETA Version

Ask TB KaSPar, the AI search assistant

Search the WHO TB KSP | AI Search

Drug Dosage Finder

Download WHO TB Knowledge Sharing Platform Application

Desktop Version | Mobile Version

Consolidated Guidelines

WHO guidelines provide the latest evidence-informed recommendations on TB prevention and care to help countries achieve the Sustainable Development Goals (SDGs) and the targets of the End TB Strategy.

Learn more →

Operational Handbooks

The WHO Operational Handbooks on tuberculosis provide users with practical "how to" guidance, with details essential for the proper implementation of the corresponding WHO guidance.

Learn more →

Training Catalogue

The WHO Training Catalogue on tuberculosis consists of online eLearning courses and other training materials to help users implement the corresponding WHO guidance.

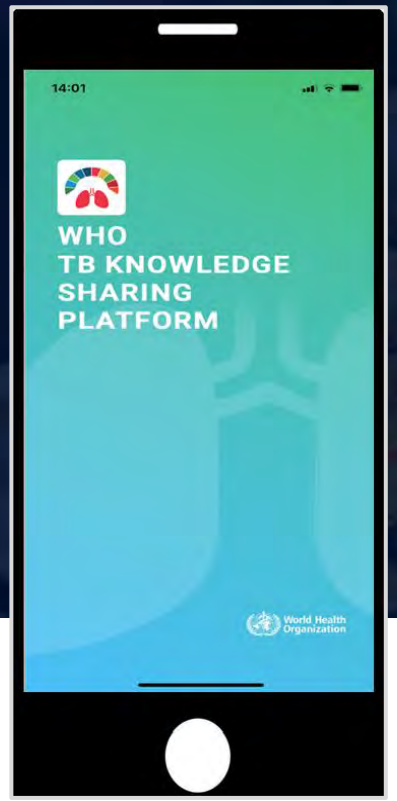
Learn more →

Research and Innovation

WHO normative guidance on tuberculosis research and innovation seek to shape the research agenda and innovation landscapes to better detect, prevent and respond to tuberculosis.

Learn more →

Feedback



https://tbksp.who.int/en

Programmatic implementation of DR-TPT- Health system costs

1. Develop/update **national guidelines** to incorporate DR-TPT
2. **Resource allocation** for scaling up DR-TPT
3. **Capacity building**, protocols for screening, baseline assessments, TPT, and management of adverse events
4. **Identification** of all contacts of DR-TB patients and systematic listing
5. **Rule out TB disease-** Symptom screening and clinical evaluation (Chest X-ray, CRP, mWRD)
6. **Testing** for TB Infection
7. **DST of the source case** especially in areas with high fluoroquinolone resistance
8. **Baseline assessment**: contraindications (tendon disorders, CNS conditions, pregnancy, known hypersensitivity)
9. Regular clinical **follow-up** (adverse event reporting)
10. **Adherence support**: counseling and support
11. **Monitoring/evaluation**: track patient outcomes, adherence rates, and adverse events

Acknowledgements

People affected by TB

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