World Health Organization

END TB

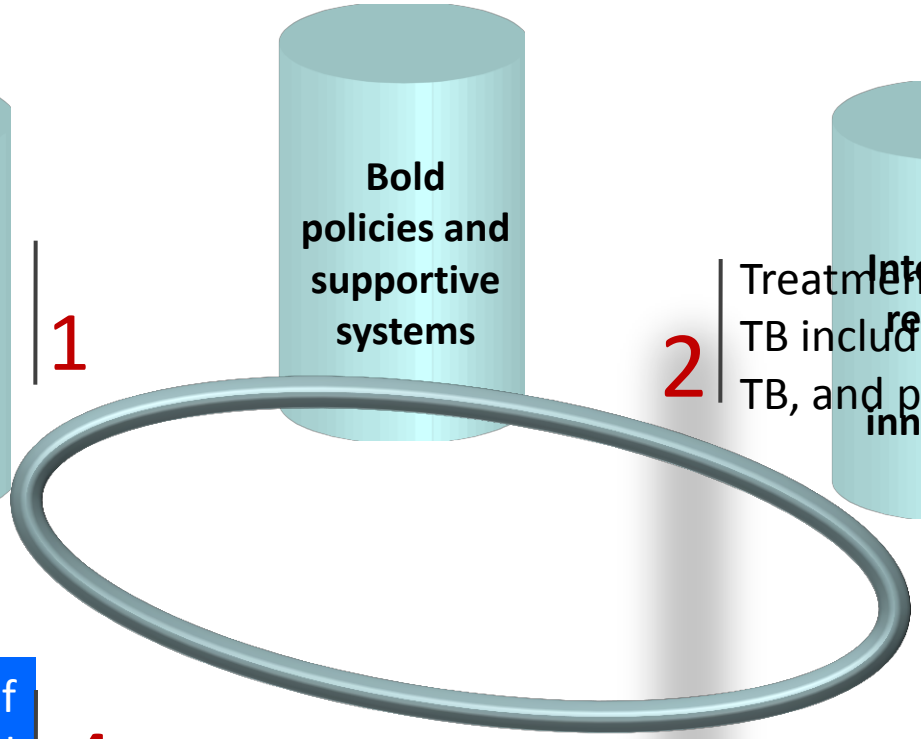
Time to implement: WHO guidelines on TB Preventive Treatment

GLOBAL TB PROGRAMME

HIV TREATMENT

WHO End TB Strategy

TARGETS: 90% reduction of deaths and 80% reduction in incidence by 2030



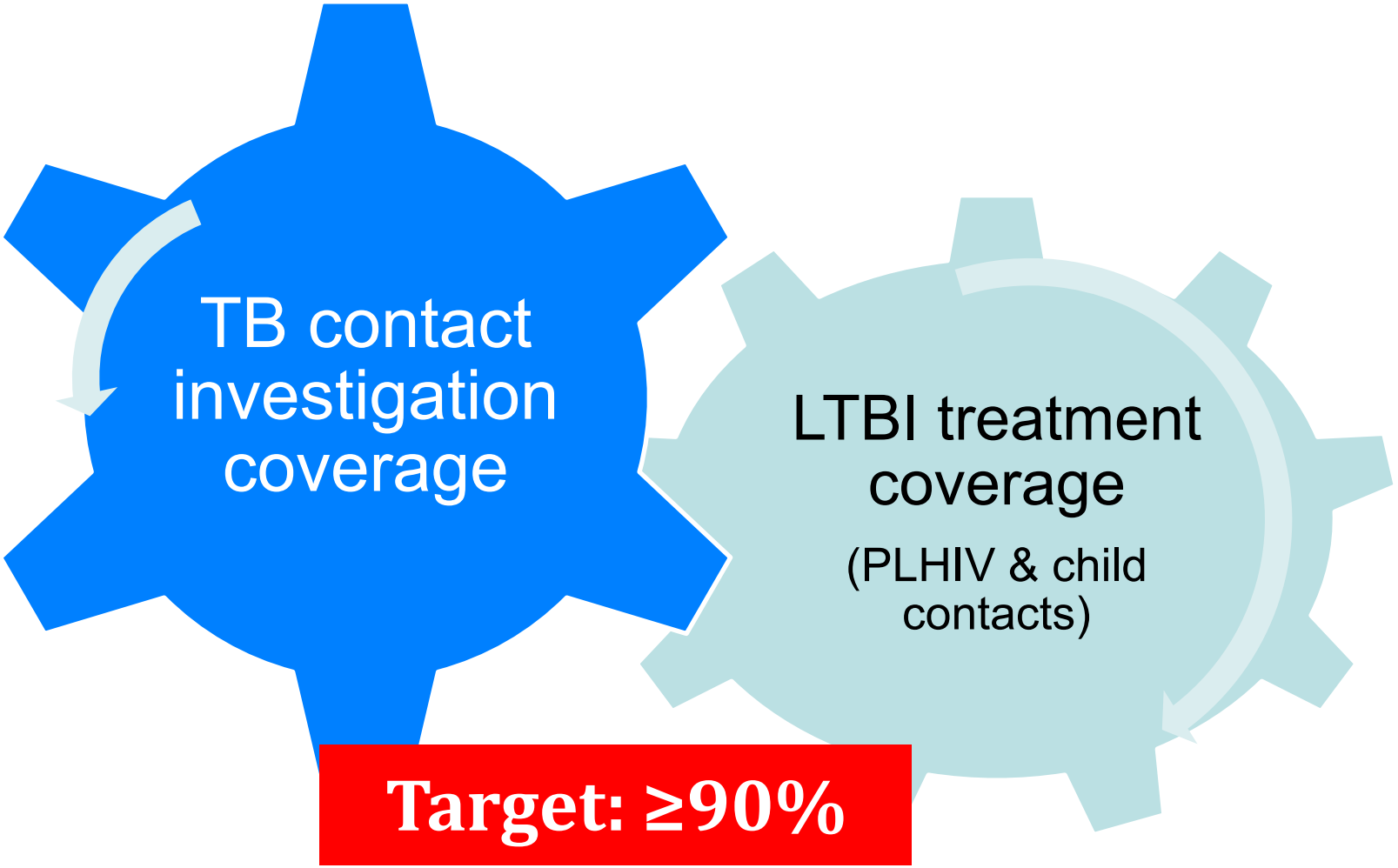
1 Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high risk groups

2 Treatment of all people with TB including drug-resistant TB, and patient support

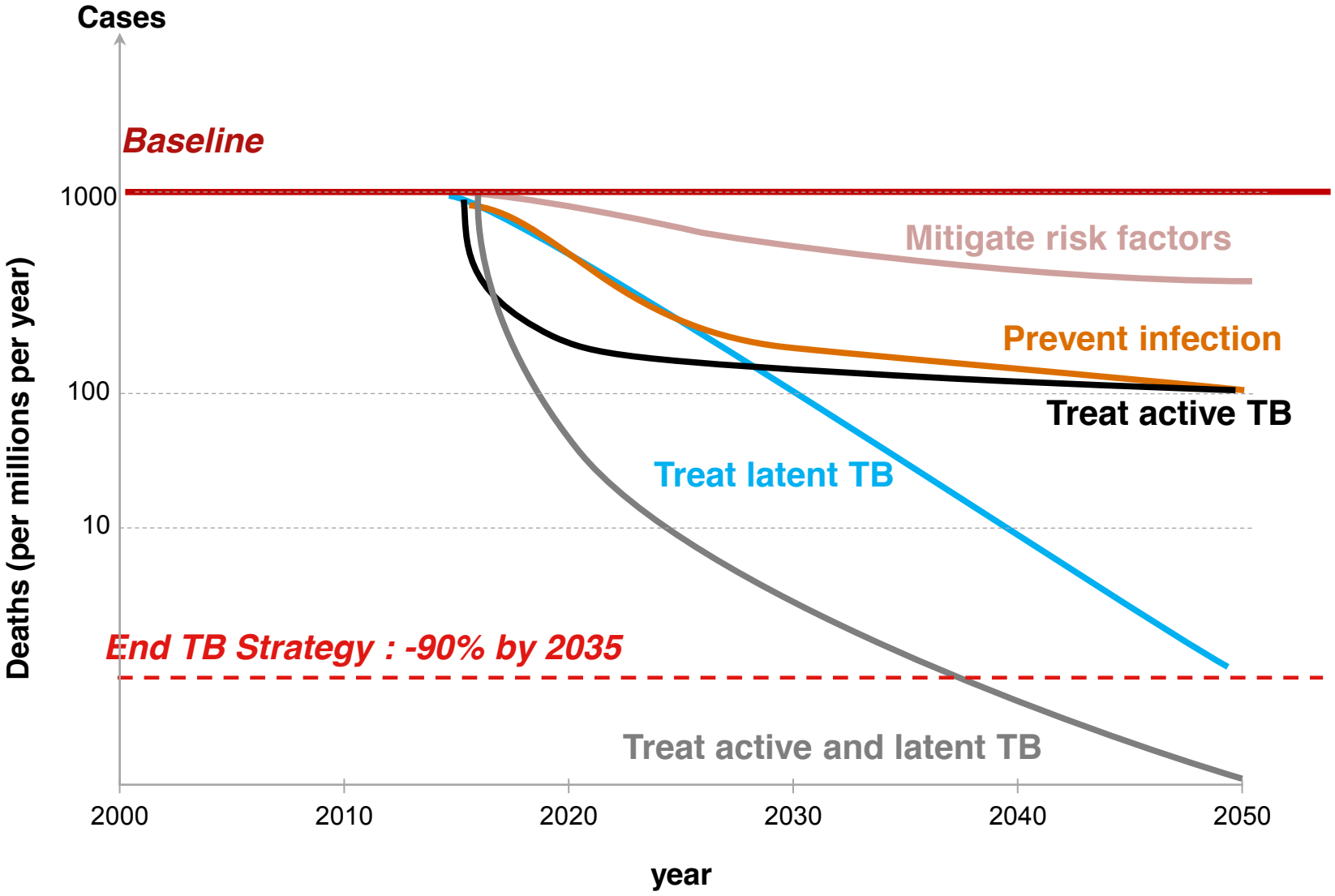
3 Collaborative TB/HIV activities, and management of co-morbidities

4 Preventive treatment of persons at high risk and vaccination of children

Two of 10 indicators to monitor the implementation of the End TB Strategy

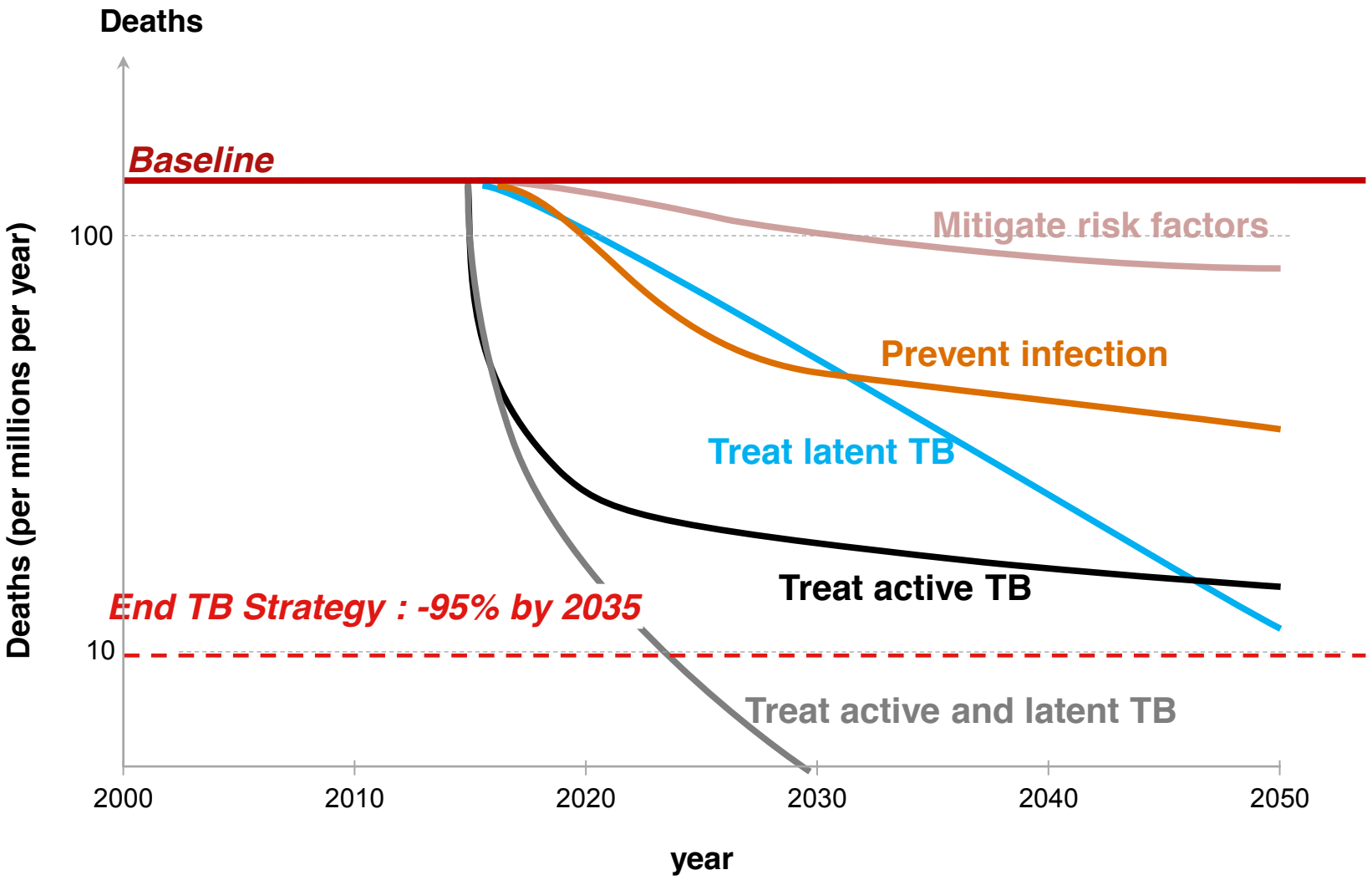


LTBI management contributes to the End TB Strategy targets (Incidence of TB)



Dye C et al., Prospects for Tuberculosis Elimination. Ann Rev Public Health 2013. 34:271-86

LTBI management contributes to the End TB Strategy targets (Deaths)

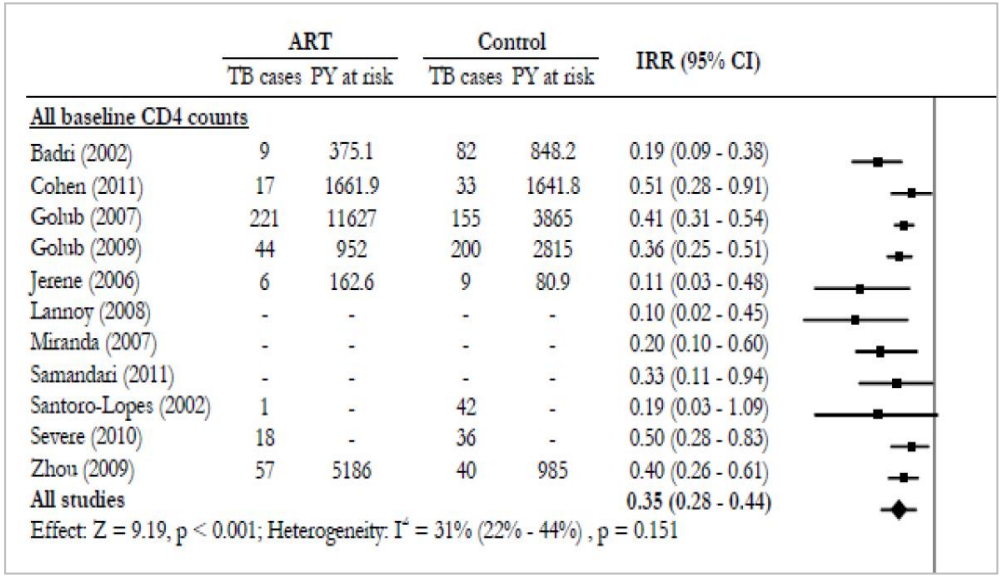


Dye C et al., Prospects for Tuberculosis Elimination. Ann Rev Public Health 2013. 34:271-86

Early ART and the Three I's

>6 million lives saved 2005-16 through scale-up

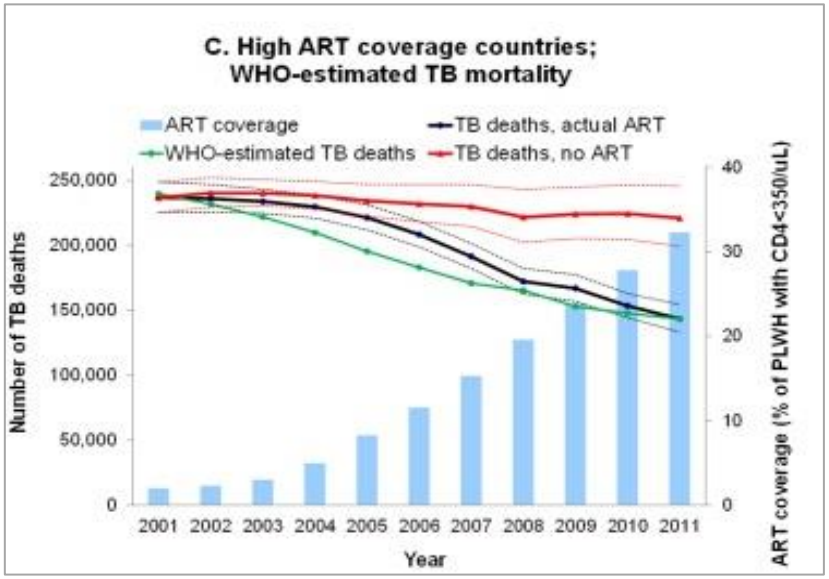
Impact of ART on TB



	ART		Control		IRR (95% CI)
	TB cases	PY at risk	TB cases	PY at risk	
All baseline CD4 counts					
Badri (2002)	9	375.1	82	848.2	0.19 (0.09 - 0.38)
Cohen (2011)	17	1661.9	33	1641.8	0.51 (0.28 - 0.91)
Golub (2007)	221	11627	155	3865	0.41 (0.31 - 0.54)
Golub (2009)	44	952	200	2815	0.36 (0.25 - 0.51)
Jerene (2006)	6	162.6	9	80.9	0.11 (0.03 - 0.48)
Lannoy (2008)	-	-	-	-	0.10 (0.02 - 0.45)
Miranda (2007)	-	-	-	-	0.20 (0.10 - 0.60)
Samandari (2011)	-	-	-	-	0.33 (0.11 - 0.94)
Santoro-Lopes (2002)	1	-	42	-	0.19 (0.03 - 1.09)
Severe (2010)	18	-	36	-	0.50 (0.28 - 0.83)
Zhou (2009)	57	5186	40	985	0.40 (0.26 - 0.61)
All studies					**0.35 (0.28 - 0.44)**

Effect: Z = 9.19, p < 0.001; Heterogeneity: I^2 = 31% (22% - 44%) , p = 0.151

Suthar et al, PLOS Medicine 2012



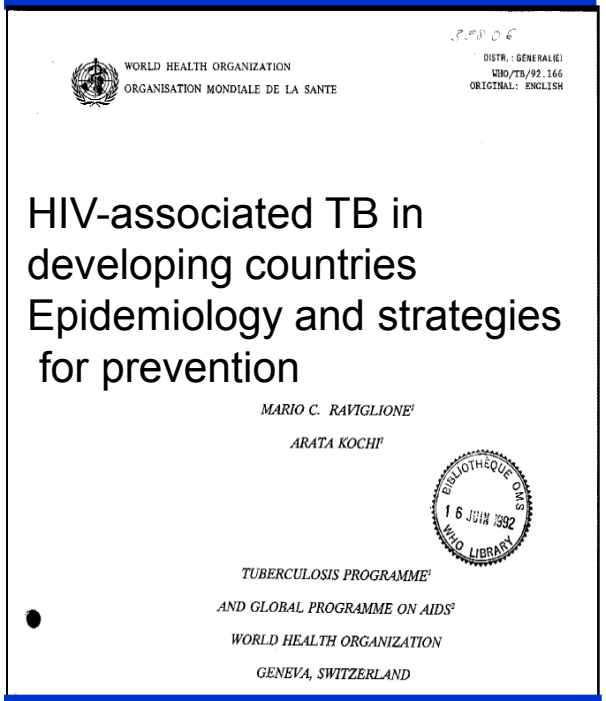
Yan et al Plos One 2016 Aug

65% TB prevention from ART

1% ↑ in ART coverage
1% ↓ in TB mortality

Isoniazid preventive therapy has been recommended for PLHIV and child contacts for ages

WHO



WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

DISTR.: GENERAL(E)
WHO/TB/92.166
ORIGINAL: ENGLISH

HIV-associated TB in developing countries Epidemiology and strategies for prevention

MARIO C. RAVIGLIONE[1]

ARATA KOCHI[1]

BIBLIOTHEQUE OMS
16 JUIN 1992
WHO LIBRARY

TUBERCULOSIS PROGRAMME[1]

AND GLOBAL PROGRAMME ON AIDS[2]

WORLD HEALTH ORGANIZATION

GENEVA, SWITZERLAND

1992

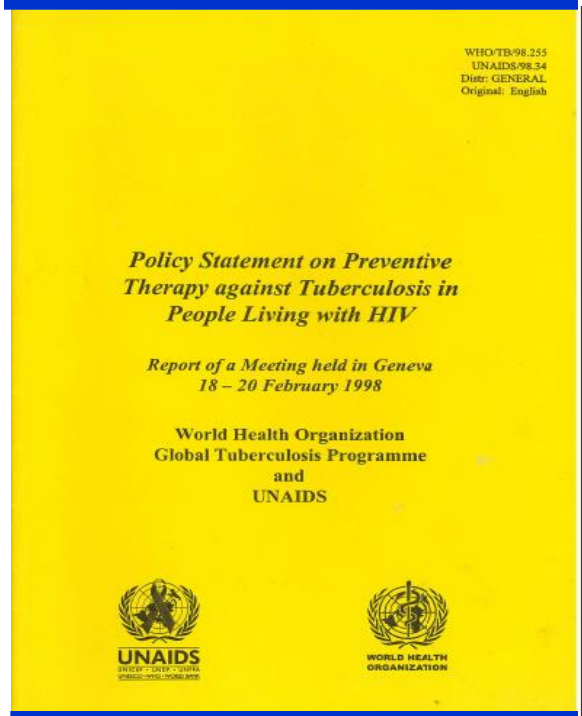
WHO & Union

Tuberculosis preventive therapy in HIV-infected individuals. A Joint Statement of the WHO and IUATLD

Wkly Epidemiol Rec 1993,68:361-364.

1993

WHO & UNAIDS



WHO/TB/98.255
UNAIDS/98.34
Distr: GENERAL
Original: English

Policy Statement on Preventive Therapy against Tuberculosis in People Living with HIV

Report of a Meeting held in Geneva 18 – 20 February 1998

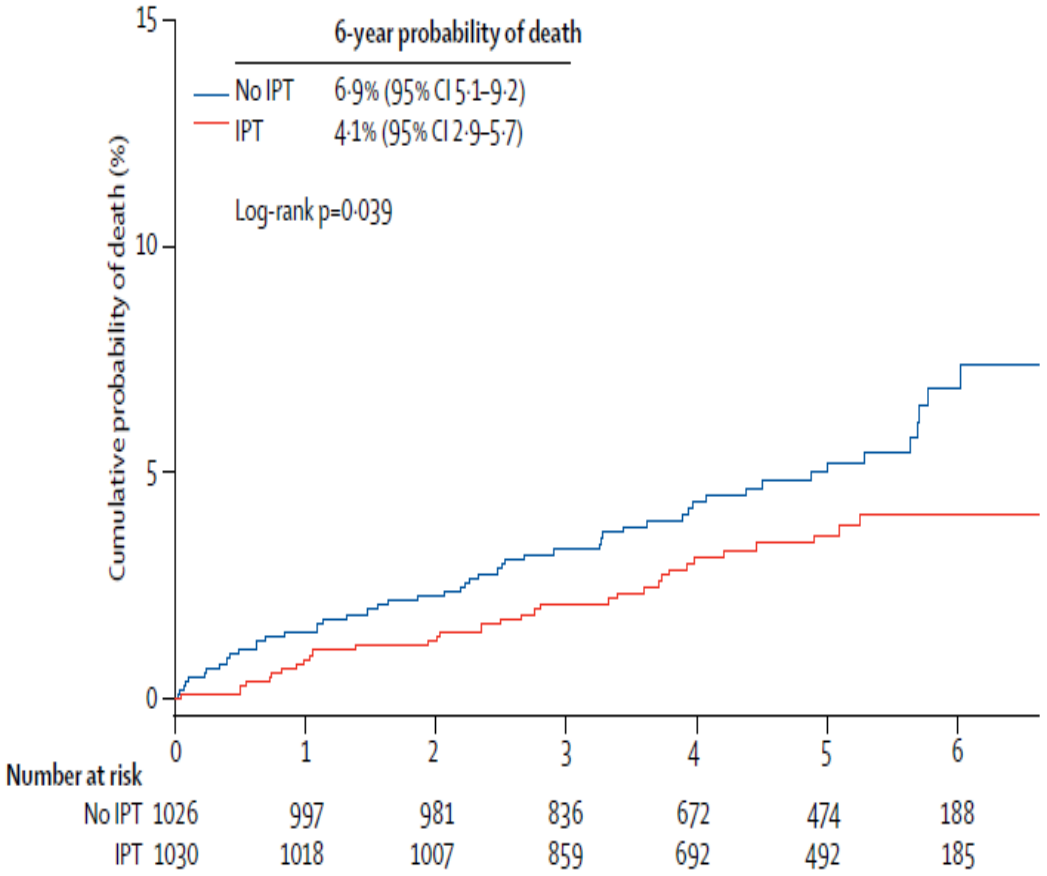
World Health Organization
Global Tuberculosis Programme
and
UNAIDS

UNAIDS

WORLD HEALTH ORGANIZATION

1998

Impact of TB preventive treatment on AIDS-related Mortality

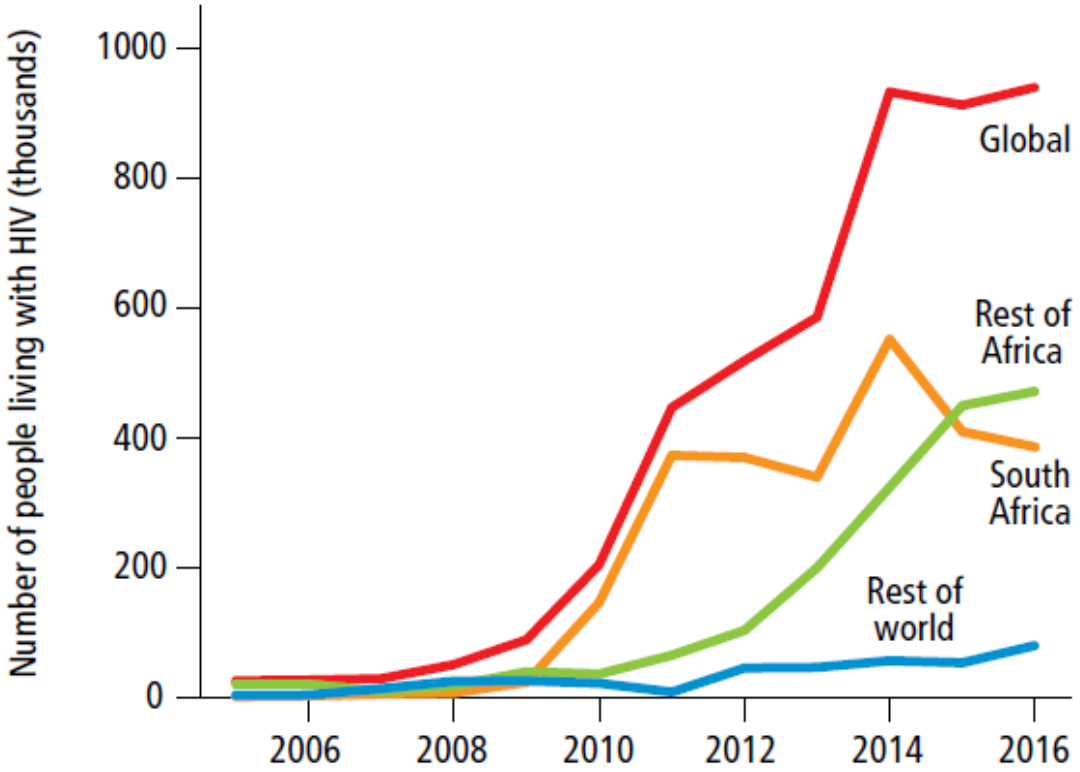


Temprano Trial
Long Term Follow-Up

37% reduction in TB mortality in PLHIV *with high CD4 counts*, after 6 months of IPT, *independent of ART*

Badje et al, Lancet Glob Health 2017; 5: e1080–89

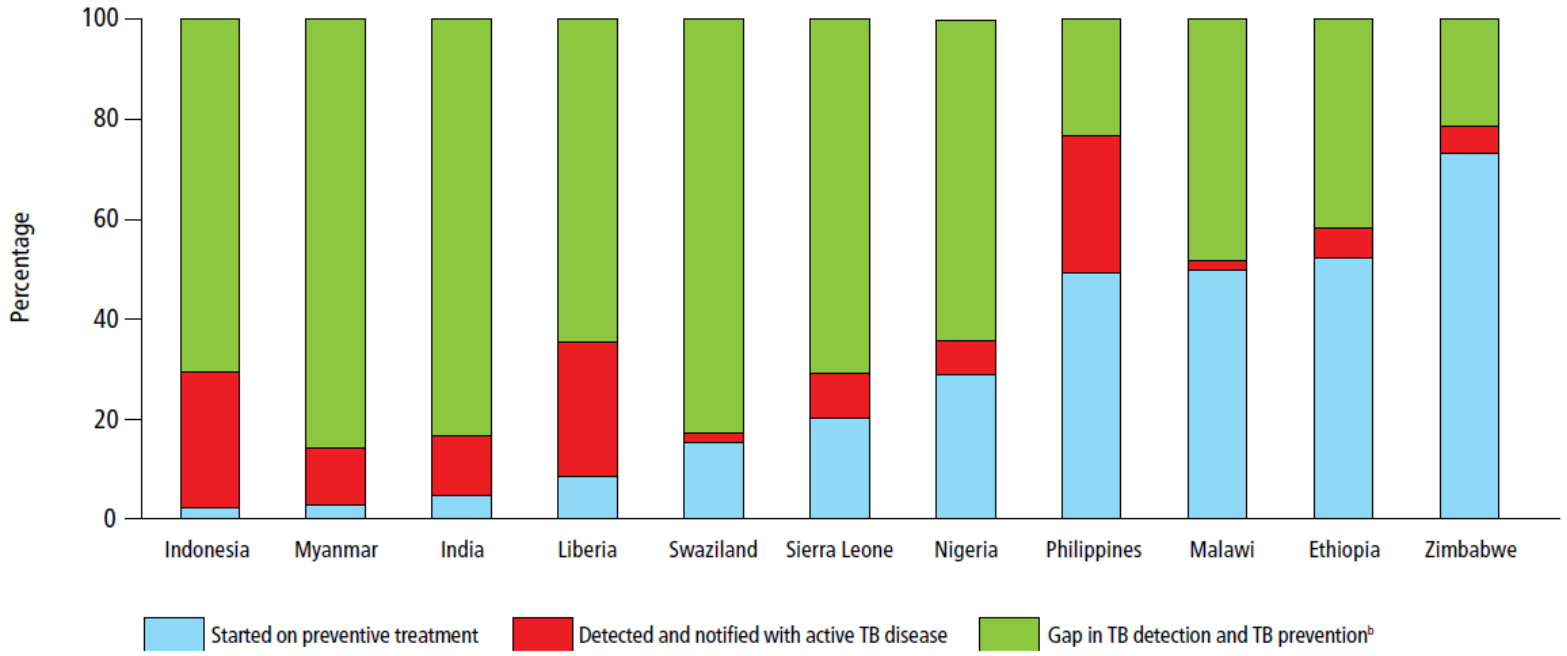
Provision of TB preventive treatment with Isoniazid to people living with HIV, 2016



WHO Global TB Report 2017

Out of 860,000 started on IPT in AFRO in 2016, only 3,300 were from Francophone African countries

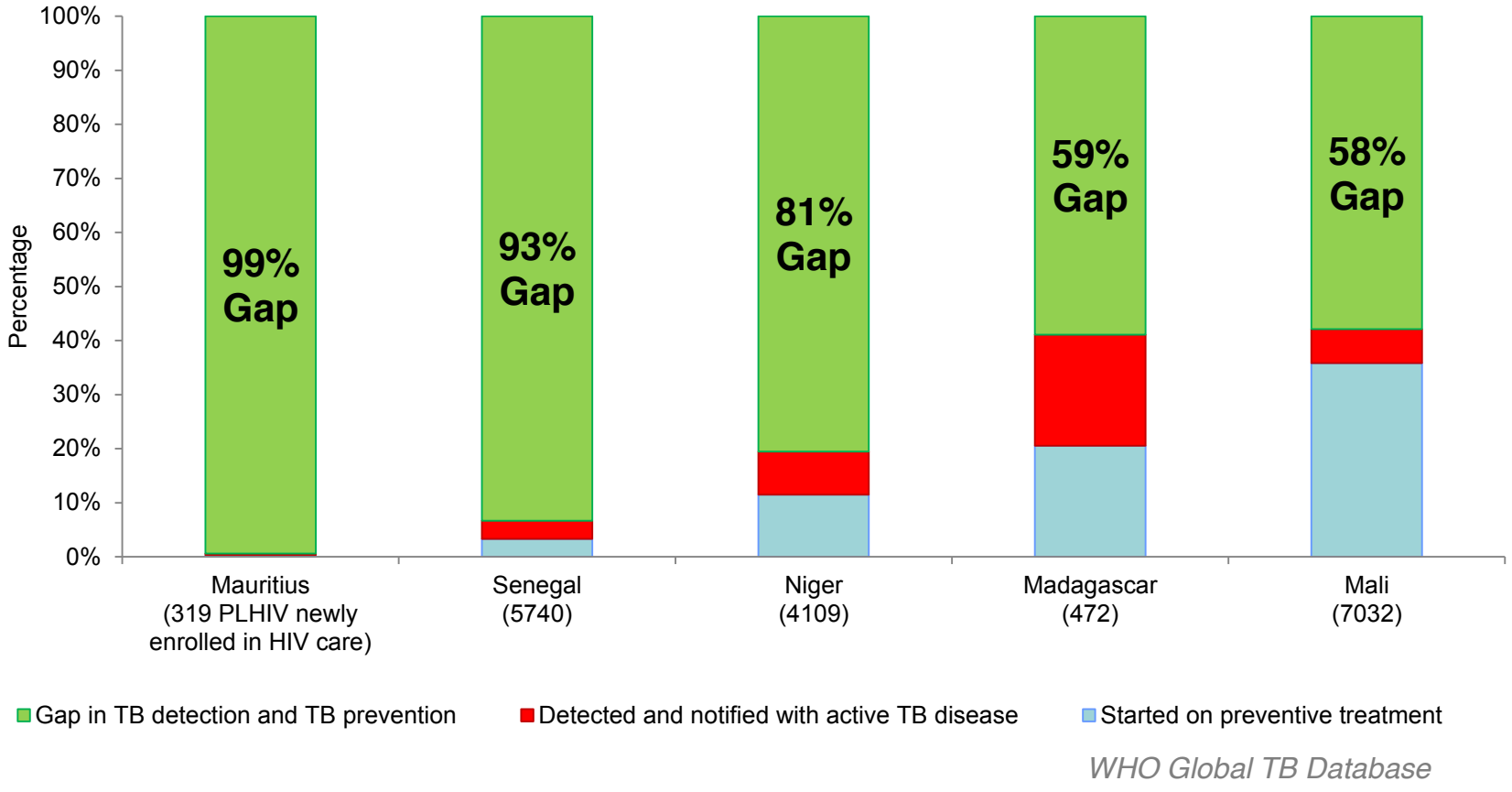
Gap in TB detection and TB prevention among people newly enrolled in HIV care in reporting high TB/HIV burden countries, 2016



WHO Global TB Report 2017

18/30 high TB/HIV burden countries did not report on IPT in 2016

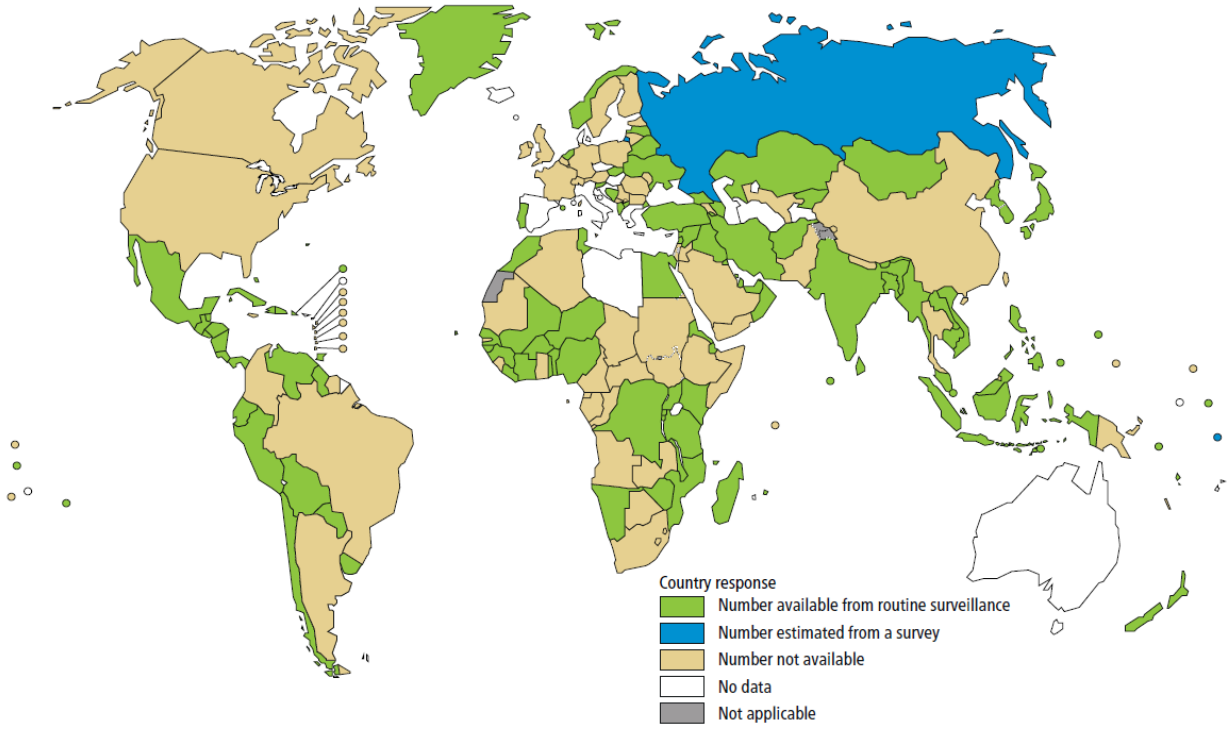
Gap in TB detection and TB prevention among people newly enrolled in HIV care in reporting Francophone African countries, 2016



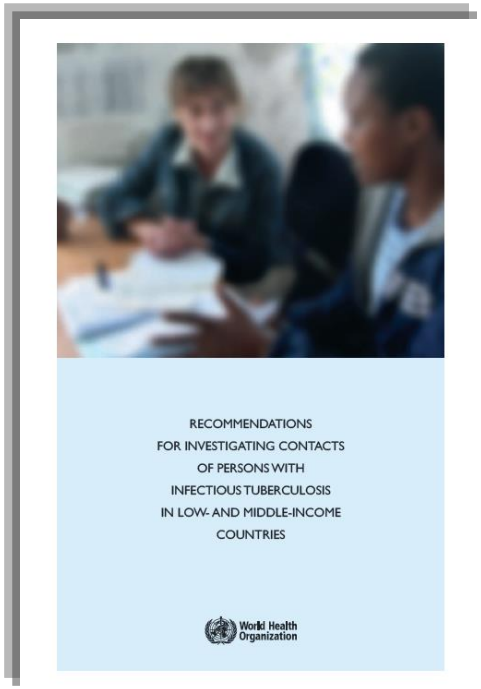
WHO Global TB Database

18/23 francophone African countries did not report on IPT in 2016

Preventive treatment for child household contacts<5yrs



Availability of data on preventive treatment among child household contacts< 5years, 2016



WHO Global TB Report 2017

162,000 (13% of estimated eligible) in 110 countries received PT

Challenges

Implementation of isoniazid preventive therapy for people living with HIV worldwide: barriers and solutions

Haileyesus Getahun[a], Reuben Granich[b], Delphine Sculier[a], Christian Gunneberg[a], Leopold Blanc[a], Paul Nunn[a] and Mario Raviglione[a]

AIDS 2010, **24** (suppl 5):S57–S65

INT J TUBERC LUNG DIS 20(12):1566–1571

http://dx.doi.org/10.5588/ijtld.16.0241

Policies and practices on the programmatic management of latent tuberculous infection: global survey

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*Global TB Programme, World Health Organization (WHO), Geneva, Switzerland; †WHO Regional Office for Europe, Copenhagen, Denmark; ‡WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; §WHO Regional Office for the Americas, Washington DC, USA; ¶WHO Regional Office for the Western Pacific, Manila, The Philippines

Key barriers for TB prevention scale up

- Does it really work?
  - Reluctance of programme managers and health workers
  - Are we not doing harm?

- Difficulty to exclude active TB and drug resistance fear
  - Inadvertent mono-treatment

- Operational barriers
  - Poor adherence of clients
  - Access to INH and who owns it
  - Challenges in recording and reporting

Four symptom algorithm identifies those eligible for IPT
(current cough, fever, night sweats or weight loss)

Getahun et al. PLoS Medicine 2011

Variable	Sen (%)	Spe (%)	NPV (95% CI) 5% TB prevalence
Community setting	67	63	97.3 (96.9-97.7)
Clinical setting	90	30	98.3 (97.5-98.8
CD4 < 200	95	23	98.9 (95.8-99.5)
CD4≥ 200	76	39	96.9 (95.1-98.0)

PLHIV with none of the symptoms should receive IPT

Risk of drug resistance following LTBI treatment

GRADE evidence profile for INH resistance after LTBI treatment with INH vs no treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis with 6 to 12 months INH	No prophylaxis	Relative (95% CI)	Absolute		
INH resistance (assessed with: Definition A for the Greenland study: >=1 colony growth at >=0.32 µg/mL INH)												
13	randomised trials[1]	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/18095 (0.17%)	28/17985 (0.16%)	RR 1.25 (0.75 to 2.1)[5]	0 more per 1000 (from 0 fewer to 2 more)	⊖⊖⊖O MODERATE	CRITICAL
								0.05%		0 more per 1000 (from 0 fewer to 1 more)		
								5%		13 more per 1000 (from 13 fewer to 55 more)		
INH resistance (assessed with: Definition B for the Greenland study: growth equal to control tube at >=0.32 µg/mL INH)												
13	randomised trials[1]	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/18095 (0.17%)	24/17985 (0.13%)	RR 1.45 (0.85 to 2.47)	1 more per 1000 (from 0 fewer to 2 more)	⊖⊖⊖O MODERATE	CRITICAL
								0.05%		0 more per 1000 (from 0 fewer to 1 more)		
								5%		23 more per 1000 (from 7 fewer to 73 more)		

[1] 12 RCTs and 1 observational study. Results were not reported separately for the observational study.

[2] Blinding: 10/13 studies used a placebo, 8/12 RCTs were double-blind (though 1 study may have different numbers of pills in INH and placebor group). Similar proportions of culture-positive TB patients underwent DST in each group.

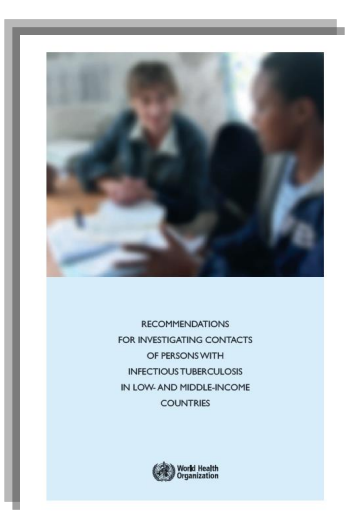
[3] Randomization: reported in 5/12 RCTs: 2 used computer-generated random numbers, 2 used random number tables, and 1 assigned by odd or even hospital number (which is not considered appropriate randomisation).

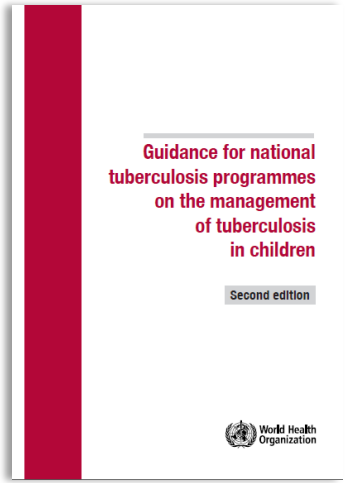
[4] Loss to follow-up: reported in 11/12 RCTs, in 6 it was <20%. In 2 studies of HIV-infected patients LTFU was noticeably higher in the INH group than for controls.

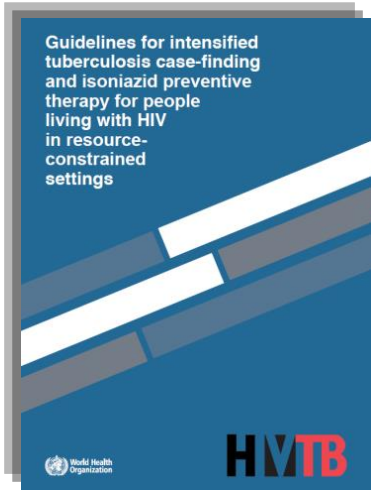
[5] In either a random or fixed effects model. Little evidence of heterogeneity (p=0.789).

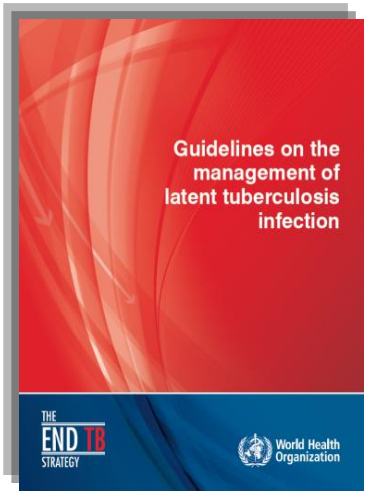
RR (95% CI) = 1.45 (0.85, 2.47)

Updates









Consolidated WHO LTBI guidelines to be released early next year

Opportunity: Fixed dose formulations

INH+RIF- child friendly FDC

INH+Co-Tx+ViB6-scored tablet

INH+RPT-under development

unicef

World Health Organization

Statement on the use of child-friendly fixed-dose combinations for the treatment of TB in children

In December 2015, the World Health Organization (WHO) and the Global Alliance for TB Drug Development (TB Alliance), with support from UNITAID, launched child-friendly fixed-dose combinations (FDCs) for the treatment of drug-susceptible tuberculosis (TB) in children weighing less than 25 kg.

The formulations available are as follows:

- **For the intensive phase of treatment.** 3 FDC (rifampicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg).
- **For the continuation phase of treatment.** 2 FDC (rifampicin 75 mg + isoniazid 50 mg).

The child-friendly FDCs were developed in line with the revised dosing to achieve the appropriate therapeutic levels, which was published in the WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, second edition (2014) (see table below).

Medicine	Dosage (mg/kg)[a]
Isoniazid (H)	10 (range 7–15)
Rifampicin (R)	15 (range 10–20)
Pyrazinamide (Z)	35 (range 30–40)
Ethambutol (E)	20 (range 15–25)

[a]As children approach a body weight of 25 kg, adult dosages can be used.

WHO Model List of Essential Medicines **20th edition**

lamivudine + zidovudine	**Tablet:** 30 mg + 60 mg **[c]**; 150 mg + 300 mg.
6.4.2.5 Medicines for prevention of HIV-related opportunistic infections	
isoniazid + pyridoxine + sulfamethoxazole + trimethoprim	**Tablet (scored):** 300 mg + 25 mg + 800 mg + 160 mg

Conclusions

- TB preventive treatment is essential for eliminating TB deaths among PLHIV;
- Identifying and addressing challenges in implementation and recording and reporting is crucial for scale-up;
- 90:90:90 and scale-up of ART for all present an immense opportunity for scale-up of TB preventive treatment;
- Exciting new opportunities offer hope for catalyzing the TB prevention response.

GLOBAL TB PROGRAMME

World Health Organization

HIV TREATMENT