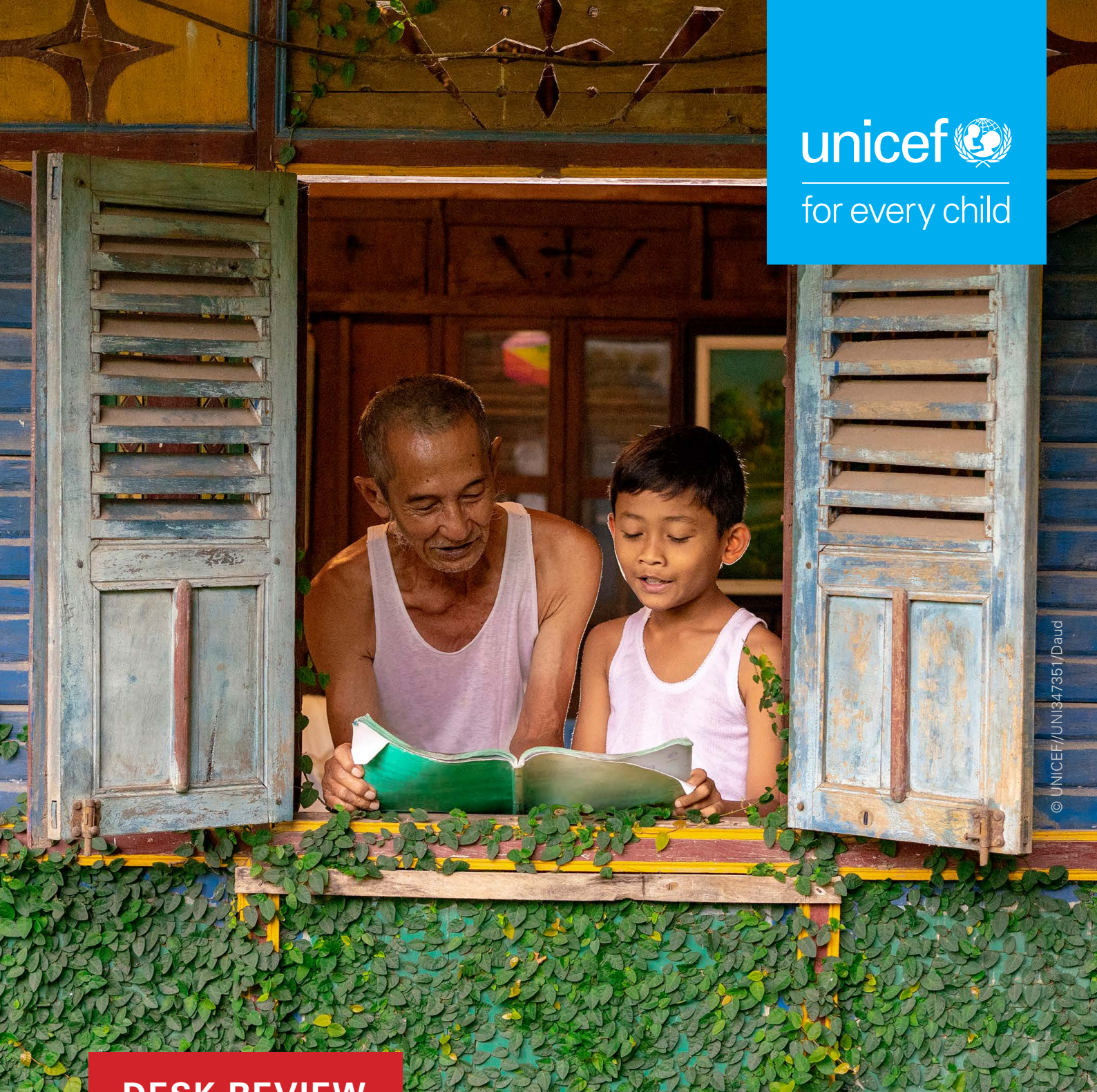




DESK REVIEW

Pediatric Tuberculosis with a Focus on Indonesia

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Abbreviations and Definitions

3HP	short-course TB Preventive Treatment (TPT) regimen for 15 years and older; once-weekly isoniazid-rifapentine for 12 weeks
3RH	short-course TB preventive treatment (TPT) regimen for children aged less than 15 years; daily isoniazid-rifampicin for 12 weeks
6H, 9H	standard TPT regimen for children aged less than 15 years; isoniazid monotherapy daily for 6 or 9 months
AFB	acid-fast bacilli
ART	antiretroviral therapy
Bappenas	<i>Badan Perencanaan Pembangunan Nasional</i> , National Development Planning Agency (Indonesia)
BCG	Bacillus Calmette-Guérin (vaccine)
BDQ	bedaquiline, MDR-TB oral treatment
BMI	body mass index
BPaL	MDR-TB treatment regimen of BDQ, pretomanid and linezolid
Cadres	health volunteers working in local Indonesian communities who connect and train families on basic health services
CBNAAT	cartridge-based nucleic acid amplification test
CDC	United States Centers for Disease Control and Prevention
CLHIV	children living with HIV
DHO	district health office (Indonesia)
DOT	directly observed therapy for the treatment of tuberculosis
DS-TB	drug-susceptible TB
EMPATI-TB	information system to assist monitoring, recording, reporting, and mentoring of TB patients to ensure patients complete treatment, developed by KNCV Indonesia
FDC	fixed dose combinations
GoI	Government of Indonesia
HBC	high burden country for TB
HCP	health care provider
HIV/AIDS	Human Immunodeficiency Virus infection/Acquired Immunodeficiency Syndrome
IGRA	interferon-gamma release assay, diagnostic method for TB
IMCI	integrated maternal, neo-natal and child illnesses
IPT	isoniazid preventive therapy
JEMM	Joint External Monitoring Mission (multi-partner, led by WHO)
KNCV	KNCV Tuberculosis Foundation
LMICs	low- and middle-income countries
LTBI	latent tuberculosis infection

Malnutrition	deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients
MAM	moderate acute malnutrition
MDR-TB	multidrug-resistant tuberculosis, a form of TB resistant to rifampicin and isoniazid
MNCH	maternal, neo-natal and child health
MNCI	maternal, neo-natal and child illnesses
NAAT	nucleic acid amplification test
NTP	National Tuberculosis Program
PHO	Provincial Health Office in Indonesia
PLHIV	people living with HIV
Posyandu	<i>Pos Pelayanan Terpadu</i> , integrated health services post in Indonesia
PMTCT	prevention of mother-to-child transmission of HIV
Pre-XDR-TB	pre-extensively drug resistant tuberculosis, a form of MDR/RR-TB resistant to fluoroquinolone
Puskesmas	<i>Pusat Kesehatan Masyarakat</i> , government (public) community health centre in Indonesia
RR-TB	rifampicin-resistant tuberculosis, a form of TB that is resistant to rifampicin
SAM	severe acute malnutrition
SITRUST	<i>Sistem Informasi Treking Untuk Spesimen Transport</i> , tracking information system for sputum specimen transport developed by KNCV Indonesia
SOBAT TB	<i>Solusi Online Berbagai Informasi TBC</i> , Online Solution for TB Information Sharing, created by KNCV Indonesia
SOP	Standard Operating Procedure
TB	tuberculosis (<i>Mycobacterium tuberculosis</i>)
TPT	tuberculosis preventive treatment
TST	tuberculin skin test
Underweight	among children under 10 years of age refers to a weight-for-age less than -2 Z-scores
UNHLM	United Nations High Level Meeting on Tuberculosis (2018)
WHO	World Health Organization
XDR-TB	extensively drug resistant tuberculosis, a form of MDR/RR-TB resistant to fluoroquinolone and at least one Group A drug
Xpert MTB/RIF	Automated, rapid molecular assay that detects <i>Mycobacterium tuberculosis</i> complex and rifampicin resistance simultaneously
Xpert MTB/RIF Ultra	Automated, rapid molecular assay that detects <i>Mycobacterium tuberculosis</i> complex and rifampicin resistance that has a faster time to results, is more sensitive in PLHIV and people with paucibacillary disease

1. Executive summary

The World Health Organization (WHO) estimated that in 2018 approximately one quarter of the world's population (1.8 billion people) to be infected with *Mycobacterium tuberculosis* (TB), of these, 70 million are children aged 0-14 years. WHO estimated that 7.5 million children aged 0-14 years are infected with TB each year (latent tuberculosis infection, LTBI), and 1-1.2 million children progress to active TB disease, more than half of whom are aged under 5 years [1]. Thirty-two thousand children are infected with multidrug-resistant TB (MDR-TB) each year. In high incidence settings, 20 per cent of the total TB burden is estimated to be in children [2].

Tuberculosis is a leading cause of child morbidity and mortality globally, responsible for 233,000 child deaths in 2017 [1]. Mortality is highest in children aged under 5 years, with malnourished children particularly affected [3]. The WHO regions of Southeast Asia and Africa account for 70 per cent of child under 5 mortality. An estimated 22 per cent of children who develop drug-resistant TB (multidrug-resistant or rifampicin-resistant TB, MDR/RR-TB) will die [4].

The WHO END TB strategy aims to eliminate preventable child deaths from TB by 2030, and the UN High-level Meeting (UNHLM) on TB in 2018 set ambitious treatment targets for children for the 2018-2022 period:

- 3.5 million children (0-14 years) treated,
- 1.5 million people with drug-resistant TB, including 115,000 children (0-14 years), treated,
- 4 million children under 5 years of age who are household contacts of people affected by TB provided with TB preventive treatment, TPT [5].

Countries endemic for TB are not on track to meet pediatric global goals. Significant challenges remain with detecting and diagnosing children with active TB and initiating treatment or with LTBI and initiating TB preventive treatment (TPT) to prevent progression to active disease. Globally, 69 per cent of children aged under 5 years with TB and 40 per cent of children aged 5-14 years are missed, either under-diagnosed or under-reported [1]. In 2014, twenty-five thousand children 0-14 years were estimated to have had MDR-TB (to which children are more vulnerable than adults), but fewer than 10 per cent were diagnosed and had access to treatment [1].

Recent advances in diagnostics and child-friendly treatments have lessened two operational barriers to reaching children with TB, but challenges remain and could threaten TB elimination efforts [6] [7] [8]. As children and adolescents have a unique care pathway, WHO guidance to National Tuberculosis Programs (NTPs) has increasingly called attention to the importance of pediatric-specific TB strategies at country level to achieve global goals [5] [9] [1].

In recognition of the criticality of the detection and diagnosis steps in the care continuum for pediatric TB, WHO guidance now advocates for locally contextualized approaches that engage both the vertical NTP and other health services that operate at the primary care level where young children typically present for care, such as maternal, neo-natal and child health (MNCH), nutrition and HIV for that high-risk group [1] [5] [9]. High burden countries for TB (HBC) are developing and piloting new approaches for pediatric TB, and an evidence base for programmatic models is emerging from their successes.

The Indonesia NTP is interested in developing an implementation model for pediatric TB—possibly linked to an ongoing, high reach child health or HIV program—to increase detection, diagnosis and treatment rates of pediatric TB in the country.

Indonesia is classified by the WHO as one of [10 HBCs for TB, HIV-associated TB and drug resistant TB](#) [10]. Indonesia has the second highest incidence of TB in the world (312 per 100,000 population) and accounts for 8.5 per cent of global cases, with high rates of drug-sensitive TB, MDR-TB and TB/HIV co-infection [11]. In 2019, 29,153 cases of TB in children aged 0-14 years were reported to the NTP [12].

Indonesia has made substantial progress towards the WHO's END TB 2030 targets but has not been as effective at identifying and screening children exposed to, at high risk of or with TB and treating them for active disease or with TPT [11]. In 2019, 35 per cent of TB cases in children aged 0-14 years were not notified to the NTP, and only 9.3 per cent of children aged under 5 years who were household contacts of bacteriologically confirmed TB cases were on TPT [11]. Fresh approaches to detecting, diagnosing and treating children are urgently needed to reduce preventable child deaths and to reach END TB 2030 targets.

In an effort to make a recommendation for a pilot pediatric TB implementation model, this document:

- Provides overviews of the pediatric TB landscape globally and in Indonesia,
- Synthesizes learnings from approaches to pediatric TB from other high burden countries that could be applicable to the Indonesian setting.

The desk review ends with questions for consideration by Indonesian stakeholders as they develop a pilot pediatric TB model for implementation in one district. If a pilot implemented in one geographic area increases the numbers of children screened, diagnosed and treated, it could inform broader scale up, particularly in high burden areas of the country.

2. Background

2.1 Global tuberculosis (TB) overview: Etiology and pathogenesis, transmission and risk factors

Tuberculosis is a communicable disease caused by *Mycobacterium tuberculosis* that is spread when people expel bacteria into the air through breathing and coughing [13]. New research has highlighted breathing as a significant mechanism for transmission of TB by demonstrating that routine inhalation and exhalation by a TB-infected person can expel over 90 per cent of TB in a day compared to 7 per cent by coughing [14] [15]. *M. tuberculosis* typically affects the lungs (pulmonary TB) but can affect other sites in the body (extrapulmonary TB). TB is prevalent in overcrowded conditions with poor ventilation.

Following exposure, a minority of people develop active TB disease (primary progression). About 50 per cent of exposed people are latently infected (latent TB infection, LTBI), and 5 per cent of these will develop TB during their lifetime (reactivation) [16]. People with recent TB infection and with medical conditions that weaken their immune system are at high risk for developing TB disease.

In the majority of patients (80 per cent in adults), TB is curable with a 6-month drug regimen [17]. First line drugs are isoniazid and rifampicin. Drug resistance to TB bacteria can develop when TB drugs are not used as indicated [18]. Drug-resistant forms of TB also can be transmitted person-to-person (primary resistance). Multidrug-resistant TB (MDR-TB) is defined as TB that does not respond to at least two TB drugs: isoniazid and rifampicin. Rifampicin-resistant TB (RR-TB) is TB that does not respond to rifampicin. Pre-Extensively drug-resistant TB (pre-XDR-TB) is MDR/RR-TB with resistance to fluoroquinolone, estimated to be 20 per cent of MDR/RR-TB patients. Extensively drug resistant TB (XDR-TB) is MDR/RR-TB with resistance to fluoroquinolone and at least one Group A drug [19].

Tuberculosis is curable and preventable but remains highly stigmatized as a disease of poverty.

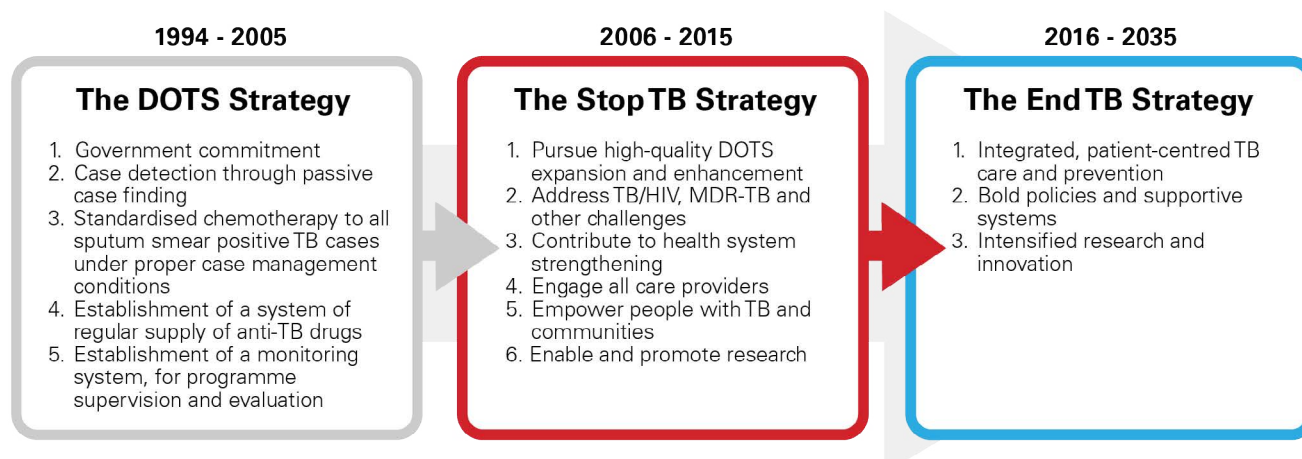
2.2 Global epidemiology and disease burden

One-quarter of the world's population (1.8 billion people) has LTBI. Thirty high-burden countries account for 86-90 per cent of global incidence [10]. In 2020, 10 million people fell ill with TB; 5.8 million people were newly diagnosed and reported, 470,000 with MDR-TB. In 2020, 1.5 million people died from TB (180,000 from MDR-TB), making TB the 13th leading cause of death globally and the second leading cause of death from a single infectious agent after COVID-19 [11]. The COVID-19 global pandemic has reversed years of progress in TB, and negative trends in numbers of people diagnosed and reported are expected to continue for the next two years [20].

2.3 Global strategy, goals and targets

Since WHO introduced the DOTS strategy in 1994, the global strategy for TB has evolved into a more patient-centered approach [21].

Evolution of global anti-tuberculosis (TB) strategies,
DOTS: directly observed therapy, short course: MDR: multidrug resistant.



The current WHO END TB Strategy envisions a world free to tuberculosis and has established ambitious targets to be achieved by 2035 [5].

VISION	A WORLD FREE OF TB - Zero deaths, disease and suffering due to TB			
GOAL	END THE GLOBAL TB EPIDEMIC			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	2030	2035
Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of TB-affected households facing catastrophic costs due to TB (level in 2015 unknown)	0%	0%	0%	0%

2.4 Current WHO guidance for National TB Programs (NTPs)

The WHO Consolidated Guidelines on Tuberculosis are a set of comprehensive recommendations in four areas that provide programmatic guidance for NTPs. They are published with accompanying operational handbooks. The guidelines and complementary operational handbooks are regularly updated. A summary by focus area (module) is provided below:

Module 1: Prevention (2020 update) [22]: For people suspected of LTBI, the WHO recommends testing using the Mantoux Tuberculin Skin Test (TST), an intradermal injection whose reaction is interpreted by a trained health worker [23], or interferon-gamma release assay (IGRA), and provision of TB preventive treatment (TPT or isoniazid preventive treatment) if positive for LTBI. TB preventive treatment for three months has been shown to reduce reactivation in infected contacts by up to 90 per cent and is an important strategy for elimination [24].

For all people living with HIV, household contacts of bacteriologically confirmed TB cases, or other people at risk of TB, TPT is recommended with the following regimens:

- 6 or 9 months of daily isoniazid
- 3 months of weekly rifapentine plus isoniazid
- 3 months of daily isoniazid plus rifampicin,
- Or, 1-month daily rifapentine and isoniazid regimen or 4-month daily rifampicin regimen

Module 2: Screening (2021 update) [25]. Systematic screening is recommended using symptom screens, chest X-ray or molecular rapid diagnostic tests recommended in these target populations:

- General population in areas where TB prevalence is 0.5 per cent or higher,
- High-risk subpopulations,
- People living with HIV,
- Household or close contacts of individuals with TB disease,
- Prisons and penitentiary populations,
- Workers with silica exposure,
- In TB high prevalence settings, among people with a risk factor for TB.

Module 3: Diagnosis (2021 update) [26]. In adults with clinical signs and symptoms of pulmonary TB, a bacteriologically confirmed diagnosis of active TB disease is recommended to initiate treatment. Historically, symptomatic adults who presented at a health facility were assessed for exposure and risk factors and by clinical examination, including chest radiography. If TB was suspected, a definitive diagnosis was made through the identification of *M. tuberculosis* bacteria in a bodily secretion, fluid or tissue, typically using the TST, or with a sputum acid-fast bacilli (AFB) smear analyzed by microscopy [27].

WHO guidance updated in 2020 now recommends rapid, automated, sensitive molecular assays using sputum. For adults suspected of pulmonary TB, the Xpert MTB/RIF for TB and RR-TB is recommended. In adults with signs and symptoms of pulmonary TB, with no or remote history of TB, Xpert Ultra is recommended. Traditional diagnostic methods such as smear microscopy, culture and Drug Sensitivity Test (DST) of sputum specimen, as well as diagnosis by clinical signs and TST or chest radiography, are additional options.

Module 4: Treatment (2020 update) [28]. Powerline and well-tolerated first-line drugs in shorter treatment regimens are available for drug-susceptible TB. If treatment regimens are strictly adhered to, treatment outcomes are good. The majority of adults can be cured with a 6-month drug regimen (globally 80.1 per cent) [17]. A four-month regimen of rifapentine, isoniazid, pyrazinamide and moxifloxacin is recommended. Most people with active TB who are treated appropriately for two weeks are no longer contagious.

For DR-TB (MDR/RR-TB, pre-XDR-TB, XDR-TB), there are fewer treatment options, longer regimens and a higher cost of care [11]. However, drug-resistant forms of TB are associated with poorer treatment outcomes globally [11]:

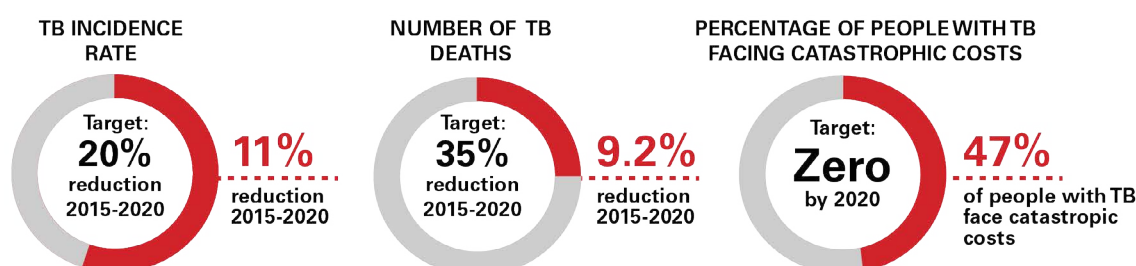
- MDR/RR-TB: 56 per cent success
- XDR-TB (20 per cent of MDR/RR-TB): 39 per cent success

New shorter, all-oral treatment regimens are now available, and there is an increased focus on providing decentralized care for DR-TB. For MDR/RR-TB, a 9-12 months regimen with bedaquiline (BDQ) is recommended. For MDR-TB with fluoroquinolone resistance, 6-9 months with BPaL (BDQ, pretomanid and linezolid) or 18-20 months all-oral, individualized treatment is recommended. Monthly monitoring of patient response to treatment using sputum culture is recommended for all DR-TB patients.

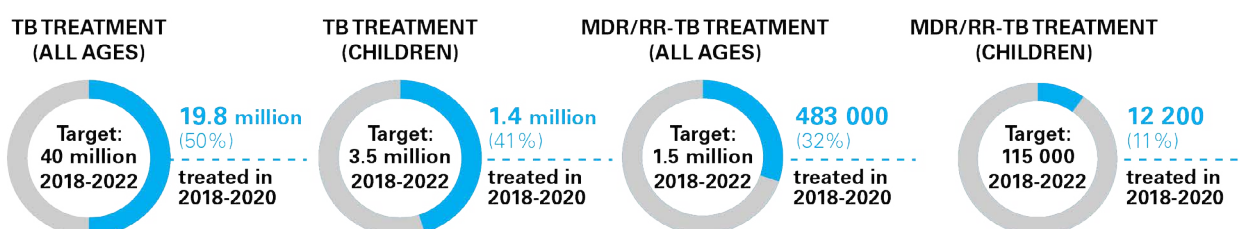
2.5 Progress towards global goals and targets

Despite some bright spots of country and regional success, the Global TB program did not meet 2020 milestones as set out in the UN High-Level Meeting on TB in 2018 and is not on track to meet its treatment or preventive treatment targets. The COVID-19 pandemic has reversed years of progress made by NTPs. For the first time in more than a decade, the number of deaths from TB globally increased. The number of patients who were newly diagnosed also went in the wrong direction, dropping from 7.1 million in 2019 to 5.8 million in 2020. Negative trends are expected to continue in 2021 and 2022 [20].

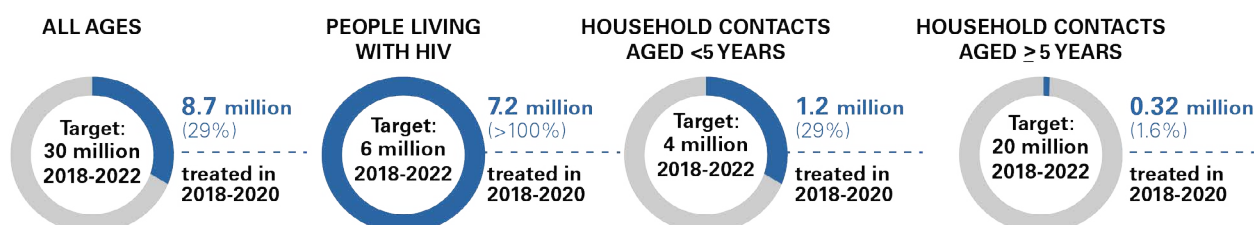
WHO End TB Strategy: 2020 milestones



UN high-level meeting on TB: Treatment targets



UN high-level meeting on TB: TB preventive treatment targets



3. Global pediatric TB overview

3.1 Importance of reaching children within the global TB strategy

Why do children deserve special attention within TB strategy?

- **High mortality and morbidity.** Tuberculosis is among the top 10 causes of child mortality globally despite available and effective treatments. Mortality is highest in children aged under 5 years, with malnourished children particularly affected [3]. Undernutrition, inadequate absorption of one or more nutrients, increases the risk of serious health outcomes, including death, and relapse in people with active TB disease [29]. Risk of mortality from TB also increases in children living with HIV (CLHIV) who have lower immune function and in children with MDR-TB [30] [4]. Children also have a higher risk than adults of TB dissemination and extrapulmonary disease, and this contributes to the morbidity in this population.
- **Infected but untreated children threaten the achievement of TB elimination.** Infected but untreated children can act as a reservoir of infection in a community and sustain TB transmission.
- **Can be a substantial proportion of the total TB burden.** Globally, children compose 10-11 per cent of the total TB burden, but this can be as high as 20 per cent in high incidence settings.
- **Require specialized programmatic approaches.** Due to the nature of TB in this population and differences in care seeking behavior, the care pathway differs meaningfully from adults and necessitates tailored tools and methods.

3.2 Pediatric TB etiology and pathogenesis, transmission and risk factors

Children have a higher risk than adults of TB dissemination and extrapulmonary disease. TB in children also presents different than in adults. Children often have nonspecific, broad clinical symptoms that are similar to other pediatric diseases [7].

Pediatric TB infection is acquired predominantly through exposure in the household to an adult infected with TB and reflects recent transmission in the community [31]. In settings of high TB prevalence in adults, there is a high likelihood of TB in children [32]. Regular and close contact with infected adults increases the likelihood of infection in children. A meta-analysis on TB transmission in households and communities found that children exposed to TB in the household were 3.79 times more likely to be infected than children without household exposure [33]. Children have a lower risk than adults of developing drug-resistant forms of TB due to in appropriate treatment.

Children with LTBI, particularly children under 2 years, are at high risk of progressing to active TB disease [34]. Progression to active TB disease depends on a number of factors, but several comorbidities increase the risk. Children aged under 5, malnourished children, CLHIV and children who are not BCG-vaccinated are at high risk of progressing from LTBI to active TB disease [35].

Children living with HIV have a higher risk of progressing from LTBI to active TB disease, of reactivating after LTBI, and of developing more serious disease [36]. Studies have shown that a higher risk of TB exists for children of HIV-positive mothers, even if these children are uninfected themselves [37] [38]. Children living with HIV who have severe immune suppression have a 5-fold higher risk of TB compared to children with mild immune-suppression [39].

There are multi-directional and causal links between nutrition and tuberculosis: there is an evidence base showing that low weight for height is a risk factor for TB and having active TB leads to weight loss [29]. Undernutrition is a significant risk factor for TB and is believed to contribute to an estimated 26 per cent of incident TB worldwide [40] [41]. In one modelling study in India, it was estimated that around 50 per cent of TB cases could be attributed to undernutrition [42]. A systematic review of six studies has shown that there is a strong and consistent log-linear relationship between BMI and TB incidence in different TB burden settings [43]. Studies have shown that 4-20 per cent of children with SAM have active TB [44] [45] [46]. In TB and HIV/AIDS patients, comorbid malnutrition increases mortality [30].

3.3 Global pediatric TB epidemiology and disease burden

Of the 1.8 billion people estimated to have LTBI, 70 million are children aged 0-14 years. Each year, more than 15 million children are exposed to TB, and an estimated 7.5 million children are latently infected. Of the children with LTBI each year, 1-1.2 million are estimated to progress to active disease, more than half of whom are under 5 years [11]. Due to a combination of immunological, environmental and behavioral factors, children under 5 years have the highest incidence and a greater risk of progression from LTBI to active disease than adults [47]. Thirty-two thousand children are estimated to fall ill from TB each year [4]. In high incidence settings, as much as 20 per cent of the total TB burden is estimated to be in children, with a global average of 10-11 per cent [2].

The numbers of children with LTBI and active TB disease are believed to be underestimates given challenges with case finding, diagnostics and reporting that are particular to this population [11] [48].

TB is a leading cause of child mortality. In 2017, 233,000 children aged 0-14 years with active disease were estimated to have died from TB. Eighty percent of these deaths were in children aged under 5 years (70 per cent from the WHO regions of Southeast Asia and Africa), 17 per cent were in children living with HIV (CLHIV), and 96 per cent were in children who never accessed TB treatment [1] [39]. An estimated 22 per cent of children who develop MDR-TB will die [4].

3.4 Global pediatric TB strategy and goals

In recognition of TB's contribution to child mortality and morbidity, there has been renewed global attention to pediatric TB in the last 15 years. Since 2006, WHO has been publishing child and later adolescent-specific technical and operational guidance for NTPs, but its advocacy for children within the global TB agenda gained momentum in 2012. That year, children were put at the center of World TB Day, and for the first time the Global TB Report featured estimates of the number of TB cases and deaths in children [20]. This was followed in 2013 by the publication of the first edition of WHO's *Roadmap towards ending TB in children* and in 2014 by the [Guidance for NTPs on the management of TB in children](#).

The rising priority of pediatric TB was apparent in the release of the [END TB Strategy](#) in 2014, which put forth a goal of eliminating preventable child deaths from TB by 2030, and at the UN High-level Meeting (UNHLM) on TB in 2018, when ambitious near-term (2018-2022) treatment targets for children were set:

- 3.5 million children treated,
- 115,000 children with drug-resistant TB treated,
- 4 million children under 5 years of age who are household contacts of people affected by TB provided with TB preventive treatment, TPT [5].

To support NTPs to reach these targets, WHO has continuously updated its guidance documents, as described in Table 1, with the latest update slated for publication by the end of 2021 (third edition of [Guidance for national tuberculosis programmes on the management of tuberculosis in children](#)).

It is worth noting that in recent years, WHO increasingly has highlighted the need for more holistic approaches to tackle the complexity of pediatric TB at country level. More recent guidance documents advocate for the use of a combination of locally contextualized approaches that connect both with the vertical NTP and with other child health services that operate at the primary care level where young children typically receive care, such as MNCH, nutrition, or at HIV clinics for that at-risk population [1] [5] [9]. The WHO also has underscored the need for MDR-TB-specific policies and actions for the pediatric population.

WHO also works closely with global stakeholders to catalyze the innovations, evidence generation and funding needed to improve pediatric TB care.

Table 1. WHO pediatric TB policies and advocacy since 2006

Year	Author	Target age	Name	Purpose
2006	WHO	Children (0-10 years)	Guidance for national tuberculosis programmes on the management of tuberculosis in children, first edition	Operational guidance for NTPs
2010	WHO	Children (0-10 years)	Rapid Advice: Treatment of Tuberculosis in Children	Revision of treatment guidance from the 2006 Guidance based on new evidence concerning the correct dosages of 4 antituberculosis medicines
2012	WHO	Children (0-14 years)	Global TB Report	Includes first estimate of pediatric TB
2012	WHO	Children (0-14 years)	World TB Day	Focus is children
2013	WHO	Children (0-10 years)	Roadmap towards ending TB in children: towards zero deaths, first edition	Operational guidance for NTPs to reach and treat children <10 years
2014	WHO, approved by the 67 th World Health Assembly	All ages	END TB Strategy	Global strategy and targets TB treatment, care and control after 2015; includes children-specific targets
2014	WHO	Children (0-10 years)	Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition	Operational guidance for NTPs
2017	WHO	All ages	WHO Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update	Recommendation of 6-month treatment regimen composed of 4 first-line TB medicines: isoniazid, rifampicin, ethambutol and pyrazinamide for DS-TB
2018	WHO ¹	Children (0-10 years) and adolescents (10-19 years)	Roadmap towards ending TB in children and adolescents, second edition	Updated operational guidance for NTPs and with the addition of adolescents (10-19 years)
2018	WHO	Children (0-10 years) and adolescents (10-19 years)	Best Practices in Child and Adolescent Tuberculosis Care	Describes best practices and lessons learnt against the original 10 key actions of the 2013 Roadmap
2020	WHO	All ages	WHO Consolidated Guidelines on Tuberculosis, 2020	Four modules: 1) Prevention; 2) Screening; 3) Diagnosis; 3) Treatment

¹ With UNICEF, Stop TB Partnership, The Union, TAG, KNCV, The Global Fund, EGPAF, USAID, and Unitaid, and released with UN High Level Meeting on TB

Year	Author	Target age	Name	Purpose
2020	WHO	Children (0-14 years)	Paediatric HIV & TB: Rome Action Plan	Calls for acceleration of research, development, registration, introduction and uptake of HIV & TB diagnostics and medicines for CLHIV
2021	WHO	All ages	WHO Consolidated Guidelines on Tuberculosis, Module 2: Screening	2021 update to Module 2
2021	WHO	All ages	WHO Operational Handbook on Tuberculosis. Module 2: Screening	Accompaniment to consolidated guidelines, Module 2, to facilitate implementation of the recommendations
2021	WHO	All ages	WHO Consolidated Guidelines on Tuberculosis, Module 3: Diagnosis, 2021 update	2021 update to Module 3: Diagnosis, to improve access to rapid molecular tests for the detection of TB and DR-TB
2021	WHO	All ages	WHO Operational Handbook on Tuberculosis, Module 3: Diagnosis – Rapid diagnostics for tuberculosis detection 2021 update	Accompaniment to consolidated guidelines, Module 3, to facilitate implementation of the recommendations
2021	WHO	12 years and older	Treatment of drug-susceptible tuberculosis: rapid communication	Update to the 2017 DS-TB treatment guideline recommending a 4-month regimen of rifapentine, isoniazid, pyrazinamide and moxifloxacin, for treatment of DS-TB
2022	WHO	12 years and older	WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug-Susceptible Tuberculosis Treatment, 2021 update	Policy update on treatment following the 2021 Treatment of drug-susceptible tuberculosis: rapid communication
2022	WHO	All ages	WHO Operational Handbook on Tuberculosis, Module 4: Treatment – Drug-Susceptible Tuberculosis Treatment	Accompaniment to WHO consolidated guidelines on tuberculosis, Module 4: Treatment, 2021 update, to facilitate implementation of recommendations
2022	WHO	Children (0-10 years) and adolescents (10-19 years)	WHO Consolidated Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children and Adolescents, third edition	Uptake to the 2014 Guidelines to incorporate new evidence and knowledge
2022	WHO	Children (0-10 years) and adolescents (10-19 years)	WHO Operational Handbook for National Tuberculosis Programmes on the Management of Tuberculosis in Children and Adolescents, third edition	Accompaniment to the WHO updated Guidance for NTPs on the management of TB in children and adolescents, 3 rd edition, to facilitate implementation of the recommendations

3.5 Current WHO guidance on TB in children for NTPs

As part of its Consolidated Guidelines on Tuberculosis (a set of programmatic recommendations for NTPs), the WHO provides pediatric-specific guidance. Full guidelines by programmatic area (five modules) can be found on the WHO website and at links in Table 1 on pages 14-15, as well as in summary by module, below:

Table 2. Key recommendations by module

Module 1: Prevention [49]	Module 2: Screening [50]	Module 3: Diagnosis (2021 update) [51]	Module 4: Treatment (2021 update) [52]	Module 5: Management of TB in children and adolescents (2021) [53]
A single dose of Bacille Calmette-Guérin (BCG) Vaccine to all infants at birth or shortly thereafter for prevention against disseminated and pulmonary TB	Risk assessment questionnaire	Bacteriological: Xpert MTB/ RIF Ultra rapid, automated, sensitive molecular assay	DS-TB: Child-friendly, fixed-dose combination. Standard regimen: 4-months of rifapentine, isoniazid, pyrazinamide and moxifloxacin	Children known to be living with HIV should not receive BCG vaccination because they are at increased risk of developing disseminated BCG disease. However, if they are receiving ART, are clinically well and immunologically stable they should be vaccinated.
Infection Control measures	Symptom screening using WHO's 4-symptom screen	Bacteriological: Microscopy, culture, DST of sputum specimen	MDR/RR-TB: All oral (no injectables), shorter course (9-11 months) regimen • Bedaquiline-containing regimen (>5 years) • Delamanid + 18-24 months treatment regimen in children and adolescents (6-17 years)	TB may present in atypical ways, such as acute severe pneumonia (more common in children aged under 2 years and children living with HIV) Bacteriological confirmation is even more important for children and adolescents who: have suspected DR-TB; are living with HIV; have complicated (e.g. airway obstruction, pneumothorax, empyema) or severe TB disease; have an uncertain diagnosis; have been treated previously.
TPT: • Contact tracing and case finding of child < 15 years household contacts of bacteriologically confirmed adult TB cases; • Testing and provision of TPT to children with LTBI or under 5 years (*children aged under 5 years do not have to be tested for LTBI before receiving TPT); children with active TB treated per protocols • TPT Regimens: short-course, daily isoniazid-rifampicin for 12 weeks (3RH); standard, isoniazid monotherapy for 6 or 9 months (6H, 9H)	Contact tracing of close/household child contacts of bacteriologically confirmed adult TB cases	Clinical signs and: Tuberculin Skin Test, chest radiography *MDR/RR-TB: Second-line drug sensitivity testing (DST) should be performed to exclude XDR-TB		The following options for TPT are recommended by WHO for use in children and adolescents: • 6 months or 9 months of isoniazid daily (6H or 9H) (all ages); or • 3 months of isoniazid plus rifapentine weekly (3HP) (age 2 years and over); or • 3 months of isoniazid plus rifampicin daily (3HR) (all ages). 1 month of daily isoniazid plus rifapentine (1HP) (aged 13 years and over) or 4 months of daily rifampicin (4R) (all ages) may be offered as alternative regimen

3.6 Overview of TB care for children within national TB programs

3.6.1. Policy-practice gaps for pediatric TB

Despite the availability of comprehensive strategic and operational documents for pediatric TB, in many high burden countries there are “persistent policy-practice gaps in developing, implementing and scaling up evidence-based pragmatic approaches” that threaten the achievement of global goals [1].

Implementation challenges have been noted in several areas:

Prevention (TPT). The standard of care for preventive TB treatment (TPT) for children exposed to adult pulmonary TB at home has been a six-monthly daily isoniazid regimen (isoniazid preventive therapy, IPT). Preventive TB treatment with IPT has been shown to be very effective at preventing progression from LTBI to active TB disease [54] [55]. In one study from Uganda, 99 per cent of child contacts of TB patients who were started on IPT did not develop TB [56]. Recent WHO guideline updates on eligibility for preventive therapy to treat at-risk children, regardless of HIV status, reflect the urgency of treating this population and now recommend TPT for:

- children aged less than 5 years, who are in the same household and close contacts of bacteriologically confirmed TB cases who are found not to have active TB disease after clinical examination or according to national guidelines even if LTBI testing is not available, and
- children aged 5 years and older, who are in the same household and contacts of a bacteriologically confirmed pulmonary TB case but who are found not to have active TB by clinical evaluation [22].

Despite the health benefits and WHO recommendation, uptake of TPT, especially in high burden countries, has been suboptimal. Treatment completion rates and adherence have improved in the last ten years, but challenges remain [57] [58]. Health care workers, even those with a knowledge of and positive attitude about TPT, have noted challenges with additional reporting and work burden, and difficulties screening to exclude active TB, as well as patients’ adherence to 6-month daily IPT and management of side effects [59] [60] [61]. In Indonesia, two small studies investigating adherence to TPT (IPT) therapy in children found low adherence to IPT and completion rates of less than 50 per cent due to a combination of financial, knowledge, health service and medication related barriers [62] [63]. A systematic review completed in 2014 highlighted the need for further research to assess different IPT delivery interventions, particularly in high-burden settings [64].

Children with HIV are at high risk for opportunistic TB infection, but as of 2018, UNAIDS was reporting that TPT was not being fully implemented as part of comprehensive HIV care for children and adolescents [65], partly due to operational challenges related to screening and diagnosing this population.

Diagnosis. One of the most significant challenges for pediatric TB has been establishing an accurate diagnosis of TB—especially a bacteriologically confirmed one [66]. Until recently, there was no rapid, sensitive and accessible diagnostic test for children. Standard diagnostic methods for adults are sub-optimal for use in children, particularly in high-burden settings or settings where child mortality is high, due to a number of factors related to TB disease in this population [66]:

- **Children have difficulty producing sputum** sufficient to allow for a bacteriologically confirmed diagnosis by microscopy, culture and assay,
- **Children have paucibacillary disease** which cannot be diagnosed using microscopy as there are too few bacillary [67] [68] [69],
- **Lower sensitivity of immunological and microbiological tests** for this age group.

At the sub-district level health facilities where symptomatic children typically first present for care, capacity challenges also complicate getting to a bacteriological diagnosis [70]:

- **Children have nonspecific clinical symptoms that are similar to other common pediatric diseases.** Since symptoms of active TB disease in children are broad, TB can be mistaken for other common pediatric respiratory illnesses such as pneumonia [71]. Young children typically present at a primary health care clinic, where awareness of TB is often limited, making a clinical diagnosis even more challenging,
- **A hospital setting can be required to obtain a sputum specimen:** gastric aspiration (in which a tube is brought into the child's stomach via their nose) is required for children under 5 and needs to be conducted in a hospital setting [69],
- **Malnourished children are not good candidates for the TST.** The TST has been shown to be less reliable in malnourished young children, for example, with wasting [72] [32],
- **Chest radiography is sub-optimal for children with extrapulmonary disease.** Children can have extrapulmonary TB, which cannot be diagnosed by radiography. For children with pulmonary TB, lower-level health facilities often lack radiography equipment.

Social and health system capacity challenges. National TB Programs in high burden countries have reported difficulties with²:

- **Community and parental lack of awareness** of TB disease risk and symptoms, treatment and TPT
- **Stigma around TB as a disease of poverty and fear and misconceptions about treatment side effects** and sometimes based on adult experience of TB treatment
- **Sub-optimal household contact tracing and initiation of TPT,** despite child household contacts of a confirmed adult TB case being a priority group for TPT as they are more vulnerable to developing severe forms of TB and at high risk of mortality
- **Inadequate training** of non-TB specialist health care providers (HCPs) on screening, diagnosis, and management
- **Cumbersome screening process**
- **Insufficient supervisory support** for HCPs
- **Lack of diagnostic capability** at (particularly lower level) health facilities

As a result, there is:

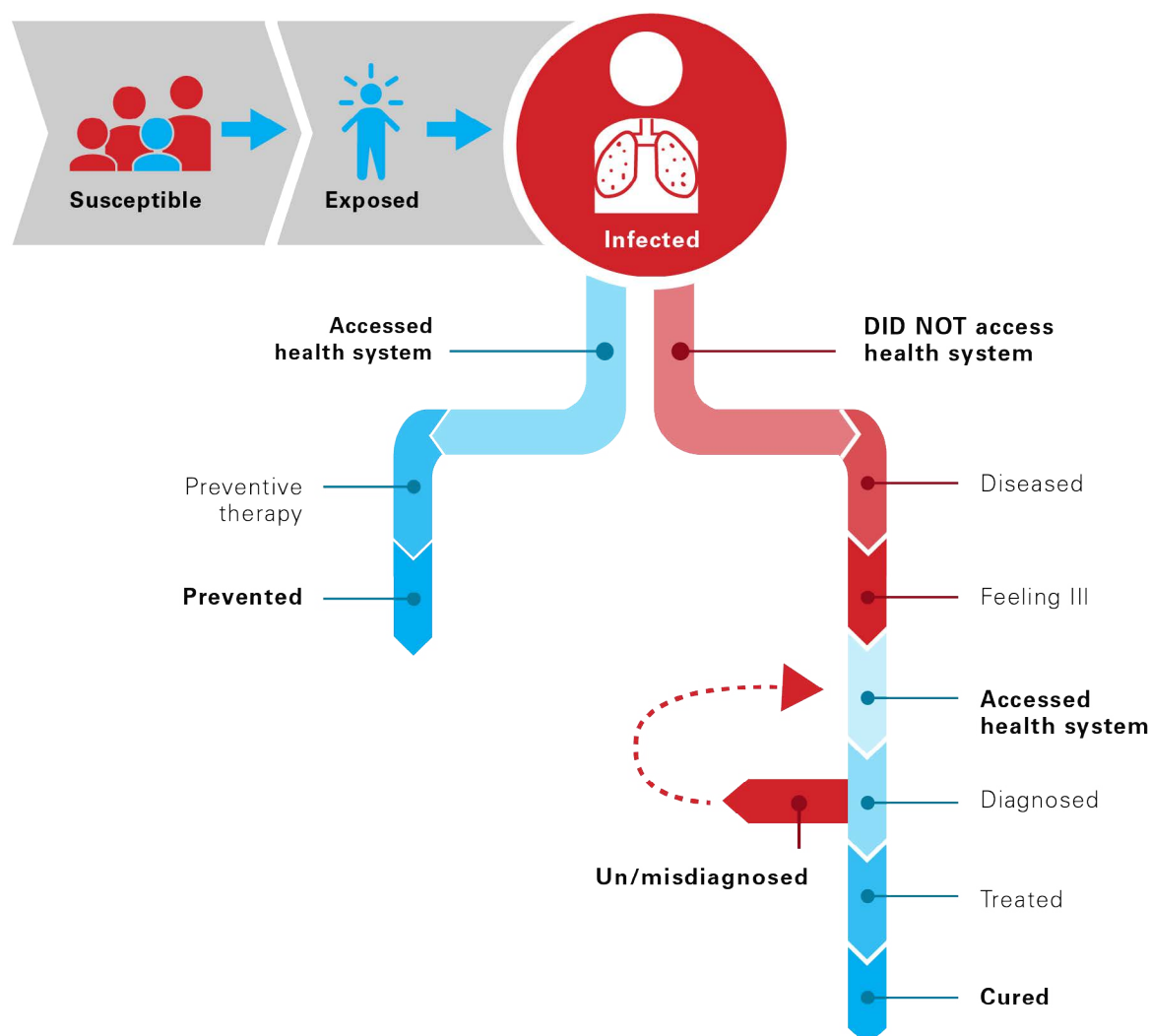
- **Delay in care-seeking** by parents of children at risk of or with TB symptoms
- **Children exposed to TB in the household are not identified and put on TPT**
- **Children at high risk are not screened for TB at health facilities where they present** (with or without TB symptoms)
- **If screened at a health facility, children are misdiagnosed or do not receive a diagnosis** due to broad spectrum symptoms and insufficiently trained or experienced HCPs; lack of confidence of HCPs in making clinical diagnoses or conducting invasive diagnostic procedures; lack of appropriate diagnostic equipment at primary care level.

2 Lists not intended to be exhaustive

3.6.2 Illustrative TB care pathway for children

A study from West and Central Africa on Best Practices on TB Case Finding and Treatment developed a child TB pathway that well illustrates the gaps experienced by children in many HBC [73]:

Figure 1. Gaps along the TB pathway



3.7 Progress towards pediatric TB global goals

The operational challenges and gaps in the TB care pathway for children are evident in the data being reported each year by TB endemic countries, especially HBC. The case detection gap is enormous: globally 55 per cent of children estimated to have TB are not reported to national TB programs. Sixty-nine per cent of children aged under 5 with TB and 40 per cent of children aged 5-14 years are missed, either under-diagnosed or under-reported [1]. In 2014, twenty-five thousand children 0-14 years were estimated to have had MDR-TB, but fewer than 10 per cent were diagnosed and had access to treatment [1].

Over 90 per cent of pediatric TB cases never receive treatment. In 2017, over 75 per cent of eligible household contacts aged under 5 years did not access preventive TPT to prevent progression from LTBI to active TB disease [1]. As a result, TB endemic countries are not on track to meet the UNHLM targets for 2018-2022:

- In 2018 and 2019, 1.04 million children were treated for TB, **30 per cent of the target** of 3.5 million children,
- In 2019, 8,986 children were treated for MDR-TB, **8 per cent of the target** of 115,000 children,
- By 2019, 782,952 children aged under 5 years who were household contacts of people with TB were reached with preventive TB treatment, **less than 20 per cent of the target** of 4 million children aged under 5 years [11].

To reach the “zero deaths” from pediatric TB target set forth in the 2014 END TB Strategy and affirmed in the 2018 *Roadmap*, NTPs’ attention must turn now to overcoming implementation challenges through more localized, integrated approaches to the entire pediatric care continuum [68].

3.8 Recent advances in key areas for pediatric TB

Recent advances in the critical areas of diagnostics and treatment for active disease and TPT to prevent progression from LTBI to active TB disease provide new optimism for country-level action.

Prevention (TPT). In 2018, the WHO updated its guidelines on TPT for children aged < 15 years to recommend a shorter course regimen, 3RH (isoniazid-rifampicin daily for 3 months) that could mitigate some of the challenges with the 6H regimen, such as adherence to treatment [22]. A 2018 study in Ethiopia showed that 3RH was safe, with better compliance, adherence and completion rates than 6H or 9H isoniazid monotherapy in children aged < 15 years [74]. An additional shorter-course TPT regimen for adults, 3HP, is also in use in low burden countries and is being piloted for use in high burden countries and in high-risk groups such as children aged < 5 years and PLHIV³.

The 2018 WHO guideline update also reflects the urgency of scaling up TPT to children exposed to TB in the household and now recommends providing TPT to:

- children under 5 years who are household and close contacts of bacteriologically confirmed TB cases who are found not to have active TB disease after clinical examination or according to national guidelines even if LTBI testing is not available, and
- children aged 5 years and older who are household and contacts of a bacteriologically confirmed pulmonary TB case but who are found not to have active TB by clinical evaluation [22].

Diagnosis. The complexity of obtaining a bacteriologically confirmed diagnosis has hampered efforts to diagnose children, particularly in primary care and outside of hospital settings. As a result, historically TB in children has been underdiagnosed, with the majority of diagnoses made presumptively based on clinical symptoms [7] [66].

3 3HP is a single pill combination of isoniazid and rifapentine taken once weekly for 12 weeks. It has fewer side effects than IPT and could improve treatment completion rates. In 2018, the US Centers for Disease Control and Prevention (CDC) updated its LTBI treatment guidelines to recommend 3HP for the treatment of LTBI in adults, in persons aged 2-11 years, and in PLHIV including AIDS. [90] There are no published data yet on 3HP’s use in children < 2 years old. Though not yet widely available in low-and middle-income countries (LMIC), a cost of ~US\$15 for 3HP recently has been negotiated for these countries. (By comparison, a six-monthly daily isoniazid regimen costs US\$9.) The Unitaid-funded [IMPACT4TB project](#) (Increasing Market and Public health outcomes through scaling up Affordable Access models of short-Course preventive therapy for TB) is piloting 3HP preventive TB treatment in 12 priority countries, including Indonesia, this year. The four-year IMPACT4TB project, a \$59 million investment by Aurum Institute, aims to reduce TB incidence and deaths among People Living with HIV (PLHIV) and child contacts through sustainable implementation of affordable, quality-assured 3HP. It prioritizes treatment for children under 5 years, PLHIV, and people in close contact with TB patients. [Indonesia is participating in pilot implementation of 3HP](#) beginning in Q2 2021 with KNCV as the implementing partner.

The development and launch in 2017 of Xpert MTB/RIF® Ultra, a rapid, automated molecular testing that is more sensitive for children with paucibacillary disease, was a major breakthrough and should lead to increased testing and bacteriologically confirmed diagnosis of the child population, even at the primary care level [7]. Like the original Xpert MTB/RIF, the Xpert Ultra is a nucleic acid amplification test (NAAT) that can detect *M. tuberculosis* complex and resistance to rifampicin in less than two hours, but it is more sensitive for people with paucibacillary disease, making it ideal for use in children. Xpert Ultra is becoming more widely available, particularly in high burden countries [75], and is recommended as the initial diagnostic test in children with signs and symptoms of pulmonary TB in the 2021 WHO Consolidated Guidelines on Tuberculosis, Module 3: Diagnosis [76].

For children living with HIV, better diagnostics are still needed. This population must have a bacteriologically confirmed diagnosis to initiate treatment as the disease can present atypically in this population [77]. In November 2020, [the Paediatric HIV & TB: Rome Action Plan](#) called on global HIV & TB stakeholders to commit to reducing morbidity and mortality in CLHIV by increasing research, development, registration, introduction and uptake of HIV & TB diagnostics and medicines for CLHIV.

Treatment. A lack of drug formulations in the correct doses for children had long been a barrier to effective treatment of this population. Before 2015, children had to be treated using adult pills that were crushed or broken to get to the WHO-recommended child dose. This resulted in wastage and incorrect dosing. The adult pills also were bitter tasting and off putting to children. In 2013, Unitaid granted the TB Alliance \$17.6 million to develop child-friendly formulations for TB through [STEP-TB](#), a partnership between TB Alliance, the WHO Global TB Programme, and Department of Essential Medicines and Health Products [78].

In 2016, new child-friendly medicines were introduced by STEP-TB and prequalified by the WHO [79]. These were fixed dose combination (FDC), soluble pills in the recommended doses and with a pleasant taste of fruit [79]. The new formulations were quickly endorsed by WHO as the first-line treatments of pediatric TB and made available through the [Stop TB Partnership's Global Drug Facility \(GDF\)](#) and the product's manufacturer, Macleods Pharmaceuticals. They are now widely used by 116 countries [79]. The first-line treatment is a 4-month regimen of rifapentine, isoniazid, pyrazinamide and moxifloxacin. The most recent, full treatment recommendation can be found in the [WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment](#). This guidance will be further updated later this year [28].

In 2019, Unitaid increased funding for pediatric TB research into child-friendly formulations for MDR-TB. In its 2020 treatment guidance, the WHO also updated its treatment recommendation for MDR-TB to a shorter course (9-11 months), all oral regimen and noted that the guidance could be extrapolated to children aged < 15 years [28]. Prior to 2020, WHO had recommended regimens containing injectable medications with serious side effects such as hearing loss. The new all oral regimen is a significant improvement over the regimens containing injectables and also is expected to improve adherence with its shorter course.

Since 2018, cycloserine in its 125mg capsule form also has been a treatment option for national programs treating children with rifampicin-resistant forms of TB.

3.9 Near-term priorities for TB care in children in TB high-burden countries

Improve case detection through active case finding and contact tracing of child household contacts of adults with confirmed TB.

- **Active case finding.** Due to widespread underdiagnosis of TB in children, active case finding is considered an essential program component of a pediatric TB strategy [7]. There are several models of active case finding that are used by NTPs: screening of household contacts of index cases, door-to-door screening in areas of presumed high TB prevalence (e.g., areas of urban poverty, with little access to health facilities), targeted screenings (e.g., of children, of older populations) either in or at health facilities. Passive case finding—where children present at clinics—is sub-optimal due to factors discussed earlier in this document, but case finding in primary health care and other innovative approaches will be discussed in a latter section of this document (examples from other HBC).

The involvement of both the private and public health sectors in reaching people with TB who are not identified or linked to the health system for care will be critical to reaching TB targets, particularly in high-burden countries such as Indonesia where the private sector contribution to health care is substantial but not connected to the NTP [11]. How to effectively engage the private sector needs more research and consideration as part of an overall pediatric TB strategy.

- **Contact tracing.** Contact tracing of household contacts of adults with diagnosed TB is a pivotal strategy to identify children at high-risk of TB and initiate them on TPT, particularly in high-burden settings [1] [56] [80]⁴. Treatment of persons at high risk of developing TB decreases progression to TB disease and improves survival [81] [82].

The WHO has published contact tracing standard operating procedures (SOPs), and most countries' SOPs reflect the WHO guidance. The recommended protocol states that all child household contacts of confirmed TB cases should be screened for TB. In practice, household contact tracing is fraught with logistical challenges, and most children are reached with preventive therapy and contact tracing too late to prevent disease [34].

Initiate TPT for all child household contacts of adult TB patients. Testing for LTBI is recommended using either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Children who have clinical symptoms of active TB disease should start treatment. Child household contacts without active TB disease symptoms should be placed on TB preventive treatment (isoniazid preventive therapy, IPT, or 3HP) without being tested further [83]. For child household contacts aged < 5 years, TPT is recommended even if testing for LTBI is not available [22]. In high TB transmission settings, adolescents living with HIV with an unknown or positive LTBI test who are unlikely to have active TB disease should be provided with at least 36 months of daily IPT.

Initiate treatment for active disease as soon as possible after diagnosis. Though there are widely available and affordable child-friendly formulations available, in many HBC, there are delays from diagnosis to initiation of treatment. WHO consolidated guidelines on tuberculosis, Module 3: Screening, note that a positive screening test carries a risk of stigmatization and uncertainty for the family and should be handled by HCPs with this mind to ensure a successful treatment path from diagnosis [25]. One qualitative study from Peru identified “burden on families” and “perceptions of disease severity” as drivers of delayed start of treatment for children diagnosed with TB [84]. Another study from India confirmed that stigma associated with a TB diagnosis contributed to treatment delays [70].

4 In low-burden countries, the Tuberculin Skin Test (TST) is the preferred test for LTBI for children younger than 5 years old (American Academy of Pediatrics Red Book, for under 2 years old), and Interferon-Gamma Release Assays (IGRAs) can be used to confirm the results of the TST. Because IGRAs are more specific for children who have received the BCG vaccine, they are the preferred test for this population.

4. Indonesia TB overview

4.1 TB epidemiology and disease burden

Indonesia is classified by the WHO as one of [10 high-burden countries for TB, HIV-associated TB and drug resistant TB](#) [10]. Indonesia has the second highest incidence of TB in the world (rate of 312 per 100,000 population) and accounts for 8.5 per cent of global cases, with high rates of DS-TB, MDR-TB and TB/HIV co-infection [11]. WHO Joint External Monitoring Mission estimated that in 2018, there were 845,000 people who developed active TB, with 24,000 cases of MDR-TB, but only 570,000 people were notified to the NTP [85]. The report also reported that there were 98,300 death from TB, and in 2018, treatment coverage was 67 per cent for DS-TB and 46 per cent from DR-TB. Smoking, under-nutrition, diabetes are the top three risk factors for TB in the country [85].

Among people living with HIV, in 2018 an estimated 21,000 new TB patients also had HIV, with a 69 per cent treatment success rate, and only 12 per cent of PLHIV received TPT in 2019 [85].

Two-thirds of the TB burden is in Java and Bali, with more cases in urban than rural areas and among the poor [85], though there is TB transmission in every province in the country.

4.2 Overview of TB strategy, goals and progress towards goals

Indonesia has high-level support (presidential, gubernatorial and mayoral) for its national tuberculosis elimination agenda, with ambitious goals of accelerating elimination efforts by 2030 and eliminating TB nationally by 2050. As a global TB priority country, the National TB Program receives annual Global Fund funding for programmatic activities and partners with a multitude of international and local organizations in both the public and private sectors for a programmatic and research agenda.

The Indonesia END TB Strategic Plan from 2020 – 2024 has six pillars:

- 1) Strengthening Leadership in the District Level Management,
- 2) Improving Access to quality TB services,
- 3) Control of Risk Factors,
- 4) Utilization of research results and technology innovation for screening, diagnosis, and treatment of Tuberculosis
- 5) Engaging Communities in TB Control, and Enhancing TB Partnership,
- 6) Health System strengthening.

The NTP has made substantial progress towards the achievement of WHO's END TB 2030 targets and its own country-level targets:

- **Increase in number of reported cases.** The number of reported cases increased by 75 per cent in 4 years, from 330,729 in 2015 to 578,987 in 2019, due to implementation of active case finding, implementation of district-based PPM, mandatory notification and strengthening of surveillance, increased contact tracing and promotion of family health approaches

- **Doubling of treatment coverage.** Treatment coverage nearly doubled between 2010 and 2018 from 35 per cent to 67 per cent. Factors influencing this increase include optimized management of integrated TB services (HIV, DM, nutrition, smoking, elderly etc.) and syncing with National Insurance System
- **Decline in annual deaths.** Annual deaths declined between 2010 and 2018 from 112,000 to ~93,000
- **Implementation of specialized DR-TB services.** Now available in 292 referral hospitals
- **Increase in molecular diagnostic capacity.** 916 GeneXpert machines are available in 478 districts and conducted over 900,000 tests in 2019, 35 per cent of all case notifications

The emergence of the COVID-19 pandemic threatened the gains of recent years, and there has been a substantial negative COVID-19 impact on TB progress in the past year [87]:

- **Deprioritization of TB activities** within the health system,
- **Decreased access** to TB services,
- **Decreased collection and processing of sputum samples** for TB testing due to a lack of PPE for healthcare workers,
- **Decreased sputum transport services** due to disruptions to the postal service,
- **Absence of policies and SOPs for simultaneous screening of TB and COVID-19,**
- **Decreased case notifications:** 42 per cent decline for DS-TB and 13 per cent decline in DR-TB case notifications from 2019 to 2020,
- **Reduced active case finding and contact investigations.**

On balance, there has been a positive COVID-19 impact in increased funding for integrated chest X-ray screenings among high-risk populations to identify TB patients, testing of household contacts of confirmed TB cases, delivery of medicines to patients' homes, and support to patients on treatment to promote treatment adherence and completion. There also is a \$5.5 MTB recovery plan funded by USAID that is expected to contribute to 380,000 TB case notifications and 7,700 DR-TB case notifications in 2021 [87].

5. Indonesia pediatric tuberculosis overview

Pediatric TB is estimated to make up 12 per cent of the total number of cases in the country [39], with 87,000 children estimated to develop TB each year. The country has been less effective at identifying children at high risk of TB and screening and treating them for active TB disease or with IPT for LTBI [11]. In 2019, approximately 65 per cent of TB cases in children aged 0-14 years were notified to the NTP [12] [85], and only 9.3 per cent of children aged under 5 years who were household contacts of bacteriologically confirmed TB cases were on TPT [11]. The proportion of pediatric TB to total TB nationally is 11 per cent, ranging from 23.8 per cent in Papua province to 2.3 per cent in Gorontalo province.

A Republic of Indonesia Joint External Monitoring Mission for Tuberculosis (JEMM) co-organized by the NTP and WHO in 2020 identified six significant challenges for pediatric TB [85]:

- 1) **Under diagnosis in primary health care** in line with the lack of confidence of primary health clinicians to diagnose TB in children. The TB scoring system which was originally designed for primary health clinicians was difficult, and impractical to follow
- 2) **Over diagnosis in the private sector**: Many children, especially those aged below 5 years seek treatment from private clinicians, where they tend to over-diagnosis using chest Xray only. Some of the clinicians are not well-informed on the new algorithm and updated guidelines
- 3) **Under-reporting in the private sector**. This is in line with findings in adult cases
- 4) **Increasing numbers of DR-TB in children**, with low enrolment rates. Also in line with adults
- 5) **Lack of awareness of TB in the community**: parents are sometimes in denial that their children could have TB or are afraid that their children will be unfairly treated, or stigmatized, at school, if their TB status is known. Schools are generally not very supportive of children or families with TB
- 6) **Limited engagement of community organizations**, although contact investigations have been carried out by some CSOs, they have not yet focused on pediatric TB case finding or adherence

In light of these challenges, the JEMM made thirteen recommendations for priority action by the NTP:

- 1) The NTP and the Indonesia Pediatric Association (GRID) should **review the current diagnostic algorithm**, especially the child TB scoring chart, and update the guideline accordingly
- 2) The NTP should develop a plan to conduct **comprehensive training on pediatric TB** for primary health care clinicians including GPs, nurses, and midwives; and an online course on child TB management for clinicians in the private sector
- 3) The NTP should **engage more with pediatricians** in order to **improve performance on TB in the hospital system**, and in their private practices; and assist in capacity building to Puskesmas and GPs on management of TB in children under 5, including sputum induction, and pediatric EPTB without complications, and excluding active TB for those being considered for preventive treatment
- 4) The NTP, together with the communication bureau, MoH, should develop a **communication strategy and education material for pediatric TB**
- 5) The NTP, through **communications campaigns**, CSOs and trained cadres, should aim to improve community awareness of TB symptoms in children and adolescents and the need to prevent disease in children in contact with TB at home, through evaluation and preventive treatment
- 6) The NTP should provide **child friendly formula medications** for DR TB and preventive therapy

- 7) The NTP, together with the BPJS, should ensure the **fees for sputum induction are covered** by insurance
- 8) The NTP should **make full use of the 360 DRTB hospital** to provide DR TB in children services. One designated room for DR-TB in children might be needed in these hospitals. A workshop on management of DR-TB in children for the clinical expert team needs to be provided
- 9) The NTP should ensure that **TB CSOs**, such as Aisyiyah and LKNU, also **play a role in finding and accompanying child TB patients and their families**
- 10) The NTP should facilitate dialogue with the Ministry of Education to provide **TB education material in school** and set mechanisms to protect children with TB from stigma, but at the same time, limit TB transmission in school
- 11) The NTP should engage a psychologist to develop **counselling tools for children with DR TB** and ensure that there are counselling modules available as part of the training materials
- 12) The NTP should, together with the PHO and DHOs, have **more focused supervision and mentoring** on TB in children
- 13) The NTP should **improve WIFITB** to ensure that notification for children with TB from the private sector can be reported

6. Synthesis of learnings from other TB high-burden countries on addressing gaps in TB care for children

Guidelines and tools are in place, and recent diagnostic methodology breakthroughs should facilitate pediatric TB diagnosis at the primary care level. There are numerous programmatic examples and case studies from high-burden TB countries that are building an evidence-based of best practices for pediatric TB programs. To ascertain whether there were learnings from pediatric TB programs in other TB HBCs that could inform a pilot in Indonesia, 23 pediatric TB case studies or programmatic examples from 12 TB HBC (sub-national level only) were reviewed. Results were synthesized to understand successes, challenges and relevance to the Indonesia context, with a focus on case detection, screening and diagnosis as these areas have been identified as weaknesses in the Indonesian pediatric TB landscape.

Many HBCs aim to address three gaps in the child TB care pathway:

Table 3. Interventions to strengthen gaps in child TB care

Gap	Intervention
Children exposed to TB in households or through close contact to an adult with TB or at high risk are not identified and put on TPT or treated for active TB disease	• Contact tracing • Community-screening / active case finding • Treatment or TPT
Infected children who do not visit the health facility, are not screened, diagnosed, do not receive treatment or TPT	• TB screening of children at the health facility when children visit for another, non-TB-related reason • Diagnosis • Treatment or TPT
Infected children who do visit the health facility, but are misdiagnosed or not diagnosed, do not receive treatment or TPT	• Increased training for health care workers • TB screening of children at the health facility when children visit for TB-related complaints • Diagnosis • Treatment or TPT

The master country case study list is attached to this document as [Appendix 1](#). In reviewing the studies, five distinct implementation models for pediatric TB were identified:

- 1) Hospital-based screening and diagnosis
- 2) Nutrition centres or IMNCI/MNCH clinic-based screening and diagnosis
- 3) Primary health center-based screening
- 4) Community-based screening campaigns
- 5) HIV/AIDS ART-clinic-based

Table 4. Comparison of models

 Implementation model	 Location	 Child reach		 Symptom screening		 Diagnosis		 Staffing and training		 Treatment	 Investment
		Ability to reach at-risk children	Age reached	Capacity	Screening cadence	Capacity (clinical)	Capacity (advanced)	HCW staffing needs	HCW training needs	Accessibility	Financial, HR, time
Hospital-based	Urban	High	0-14 years	High	Routine	High	High	Low	Medium	On-site	Low
Nutrition or IMNCI/MNCH clinic-based	Both	High	0-5 years	High	Routine	High	Low	Low	High	Referral to higher level	Medium
Primary health center-based	Both	Low	0-14 years	High	Routine	Low	Low	High	High	Referral to higher level	High
Community-based campaigns	Rural	High	0-14 years	High	Campaign	Low	Low	High	High	Referral to higher level	High
HIV/AIDS ART-clinic-based	Both	High	0-14 years	High	Routine	High	Medium	Low	High	Referral to higher level	Medium

Hospital-based screening and diagnosis

All children aged 0-14 years already visiting pediatric outpatient departments, not with TB-related complaints

What works	Potential challenges
• Demonstrated ability to reach at-risk children 0-14 years. Hospitals receive sick children; those in urban settings see children living in overcrowded conditions, a TB risk factor • Less training required for some clinicians: Some clinicians already have a base knowledge of TB and experience treating TB patients. • Availability of advanced diagnostics on site facilitates a definitive diagnosis Molecular testing (Xpert® MTB/RIF Ultra), x-ray and/or sputum smear microscopy equipment are available in many hospital settings. • Ongoing screening of at-risk children. Provides a regular method for case detection as there is a constant flow of children visiting the hospital. • Treatment can be initiated on site and immediately upon diagnosis	• Likely more successful in urban settings where pediatric patients first present at hospitals. • Depending on sub-national TB epidemiology, may not be situated in high burden areas. • Training on childhood TB screening, diagnosis and treatment required for IMCI screeners, EPI workers other clinicians. For clinicians unfamiliar with TB, training will be required. • Current workload and number of hospital staff. This would add a routine screening for all patients that could be onerous for current hospital personnel. • Not recommended for MDR-TB more decentralized models of care are recommended

Nutrition centres or IMNCI/MNCH clinic-based screening and diagnosis

Identified malnourished children aged 0-5 years visiting nutrition centres or IMNCI/MNCH clinics

What works	Potential challenges
• Demonstrated ability to reach high-risk malnourished children, a vulnerable population with high mortality rates. Opportunities for screening upon admission and if unresponsive to treatment • Young children have regular contact with Nutrition and MNCH clinics, usually located in the communities where children live. • Clinicians enthusiastic about its practicability and acceptability. • Efficiencies and strengthened quality of care	• Training required for health care workers unfamiliar with TB. Extensive training on diagnosis guidelines could be needed, and clear protocols for referrals needed. • Limited diagnosis capabilities. Lack of availability of advanced diagnosis Health care worker reluctance to perform invasive procedures, performance of TST on malnourished children is challenging. • Limited to younger children. Nutrition centers target under 5s.

Primary health center-based screening

All children aged 0-14 years visiting primary health clinics at sub-district level.

What works	Potential challenges
• First health system contact for most children so a natural point to screen children. This could be particularly true in rural areas. • Screens all ages of children (0-14 years), not only young children. • Could facilitate follow up at household level of suspected TB cases. • Could be added and standardized as an intervention to the existing package of primary care level interventions.	• More extensive training and supervision of health care workers required. Existing health care workers may be unfamiliar with TB. • Insufficient number of personnel to handle additional workload. Existing health care workers may already have a full workload that does not accommodate additional tasks. • Limited or diagnosis capability on site. Molecular testing (Xpert® MTB/RIF Ultra), chest x-ray and/or sputum smear microscopy equipment likely unavailable at primary care level, necessitating clinical diagnosis only or referral to higher levels of care for confirmed diagnosis

Community-based screening campaigns

Children aged 0-14 years screened in households or at central community sites. Expansion to adults possible.

What works	Potential challenges
• Potential high reach. To screen large numbers of children of all ages quickly. • Capacity to improve TB care If linked with health facilities. • Could be expanded to screen adults. This could be important as many children who are reached with preventive therapy are reached too late to prevent disease. Earlier diagnosis of adults is important.	• Large investment of human resources, finances and time required. • Extensive training required of screeners on TB and referral pathway. • No capacity for diagnosis if cared out by community or non-medical personnel. • Potential to be unsustainable and not integrated into standard of care.

HIV/AIDS ART clinic-based screening

All children aged 0-14 years visiting HIV/AIDS Anti-Retroviral Therapy clinics.

What works	Potential challenges
• Demonstrated ability to reach children living with HIV, a vulnerable, high priority, high risk population with high mortality rates • Proven to increase case numbers • Potential to strengthen both services and connections to the community	• Extensive training for HCPs required due to more complicated TB disease presentation and development in children with HIV comorbidity • More complicated screening and diagnosis protocols • Limited diagnosis capacity • Overloaded health workers

Table 5. Context in which each model works
High-level summary

Implementation model	Symptom screening	Diagnosis	Ability to reach at-risk children	Age reached	Rural	Urban	What works
Hospital-based	✓	✓	✓	✓		✓	- Reaches all children < 15 years - Highly trained clinicians with advanced diagnosis and treatment capabilities - Urban settings/higher level facilities - Treatment available on site
Nutrition center or IMNCI/IMNCH clinic-based	✓		✓		✓	✓	- Reaches young children at high risk of mortality - Leverages ongoing high reach programs - Community-based at the level where children access care
Primary health center-based	✓		✓	✓	✓	✓	- Community-based at the level where children access care - Reaches all children < 15 years - Treatment available on site
Community-based campaigns	✓		✓	✓	✓		- Community-based at the level where children access care - Reaches all children < 15 years - Potential to reach at-risk adults in the community - Engagement of community in TB care
HIV/AIDS ART-clinic-based	✓	✓	✓	✓	✓	✓	- Reaches high-risk population at high risk of mortality - Reaches all children < 15 years

Training and ongoing local supervision are critical to the success of every model. Simplified, locally contextualized training materials and a system for regular training and mentorship will be the linchpin of any model. Training issues were identified across all models and jeopardized effective screening and diagnosis (list not exhaustive):

- HCPs who were not TB specialists did not receive adequate training on disease-specific screening and diagnostic SOPs and protocols, some of which were complicated and/or ambiguous, and so did not follow guidelines
- Insufficient supervision and mentorship, so no expert to turn to with questions
- Trainings were not tailored to the correct level of HCP or community work
- No continuous or regular training in spite of high staff turn-over
- Ineffective teamwork
- Insufficient training on data management and reporting

7. Considerations for an Indonesian pediatric tuberculosis pilot

7.1 Considerations for the Indonesian context

The guidelines and tools are in place. Now it is a question of figuring out what works on the ground. Are screening and diagnosis the intervention points that will have the largest impact? The strategic plan has noted challenges with community engagement (e.g., lack of knowledge of TB symptoms and available services, limited coverage of civil society organizations and other stakeholders, socio-economic barriers to access) that affect case notification that should be explored further within the context of a pilot project. Other questions to consider are:

- Does what is known about the sub-national TB epidemiology support one approach over another?
- What is the right balance of available infrastructure vs intended investment? What are the corresponding possible limitations of reach?
- Is integration with an ongoing successful child health program practically feasible? Do these programs have the capacity to take on the addition of TB screening?
- Given the importance of HCP training to any model's success, could a training curriculum be developed and tested before committing resources to a full model (rapid prototyping)?

7.2 Proposed next steps

- 1) Partners agree on objectives and intervention point(s) of interest
- 2) Support an Indonesia-based research institution to undertake formative research to understand the current capacity of the health system to provide effective TB care for children in four TB high burden districts.

In each district:

- i) Assess community attitudes towards TB disease, transmission, treatment
 - ii) Assess current capacity of public and private health facilities at all levels
 - iii) Assess current child health services (e.g. IMNCI, nutrition, posyandu) that could be leveraged for TB care
 - iv) Understand capacity of schools for screening and referral
 - v) Develop innovative method for capacity strengthening of health workers
 - vi) Make recommendations for prioritising childhood TB interventions appropriate for the local community context
- 3) Pilot a full package approach to optimizing TB care in children in selected district and measure outputs and outcomes

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Appendix 1. Case studies from TB high-burden countries

Author(s)/ program & year	Country of origin	Title of Paper/ Program	Objective(s)	Target population	Methodology	Outcomes/Results	Summary of findings
TB screening and diagnosis at primary care level clinics (primary care, nutrition, IMNCI/MNCH)							
Bhat et al. (2012)	India	Intensified Tuberculosis Case Finding among Malnourished Children in Nutritional Rehabilitation Centres of Karnataka, India: Missed Opportunities	To assess use of a new India NTP diagnosis algorithm for TB in children under 5 with SAM presenting at NRCs	Children under 5 with Severe Acute Malnutrition (SAM) who present at Nutrition Rehabilitation Centers (NRCs) in 6 tehsils (sub-districts) of Karnataka state	Cross-sectional study involving review of records of identified SAM children at NRCs	72 per cent of children with SAM who reached the NRC evaluated for TB - New TB diagnosis algorithm was used: 37 per cent of the 72 per cent for 37 per cent of the 1,173 children - Of the remaining children, TST was conducted in 41 per cent - More children were found to have TB when evaluated using the new diagnosis algorithm	- Nearly 30 per cent of children identified in communities as having SAM did not come into a NRC - TB screening was sub-optimal: children were either not evaluated for TB or were sub-optimally evaluated - Several operational issues identified: - Lack of full-time pediatricians at NRCs - Often not enough electricity at NRCs to operate radiography machine - HCPs had difficulties following diagnosis algorithm: 1) requires demonstration of AFB in sputum specimens or from bronco-alveolar or gastric lavage, difficult procedures in this setting, 2) requires serial investigations, often on multiple days, increasing chances of loss to follow up - Performance of TST was a challenge on malnourished children

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Singh et al. (2021)	India	Poor adherence to TB diagnosis guidelines among under-five children with severe acute malnutrition in central India: A missed window of opportunity?	- To estimate the yield of and adherence to TB diagnosis guidelines among children under 5 with SAM admitted to NRCs - To explore challenges in screening from the HCPs' perspective	Children under 5 with Severe Acute Malnutrition (SAM) who present at Nutrition Rehabilitation Centers (NRCs) in Sagara and Sheopur districts, Madhya Pradesh state	Explanatory mixed methods: record review, key informant interviews, focus group discussions with NCR and TB programme staff	- Testing of admitted children: - TST: 83 per cent - Physical exam: 75 per cent - Asked about TB symptoms: 70 per cent - Chest radiography: 38 per cent - Asked for recent TB contact: 15 per cent - Gastric aspirate for CBNAAT: 7 per cent - Gastric aspirate for smear microscopy: 10 per cent 7 per cent of children were diagnosed with TB - Treatment outcomes for more than 50 per cent of children were not available	- Utilization of this opportunity for screening for TB is sub-optimal - Poor adherence to diagnostics guidelines - Suboptimal initial assessment - Barriers for poor screening identified: - Poor record keeping - Lack of training - Reluctance to perform invasive procedure (take gastric aspirate) - Poor team skills - Ambiguity in the diagnostic algorithm: Xpert RIF® was not available in all facilities, guidelines were not explicit about what should be done when tests/facilities were not available or feasible
Pathak et al. (2016)	India	Can intensified tuberculosis case finding efforts at nutrition rehabilitation centers lead to pediatric case detection in Bihar, India?	To assess whether intensified case finding strategies can lead to pediatric TB case detection and linkage to TB treatment	440 children under 5 with SAM at seven district-level NRCs in Bihar, India	Retrospective cohort study that included medical record reviews of SAM children registered for TB screening and RNTCP care from July-Dec 2012	39 (8.8 per cent) were diagnosed with TB - Of these, 87 per cent initiated treatment and 53 per cent were registered with the RNTCP	- Feasible to integrated screening, BUT, there are diagnostic challenges among children with SAM - Very few clinicians followed TB diagnosis guidelines

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Arscott-Mills et al. (2014)	Botswana	Yield of Screening for TB and HIV among children Failing to Thrive in Botswana	To investigate the hypothesis that TB and HIV screening of children presenting with Failure to Thrive (FTT) would detect new cases of both TB and HIV	Children aged 0-5 years attending the Lapologang 'well child' clinic, Francistown, Botswana, during one month in 2010	Two-phase cross- sectional design: 1) screening of all children for height and weight, 2) children with FTT returned after 6 weeks for a pediatric assessment: feeding history, anthropometry, HIV risk, TB screen; follow up for 6 mos.	- Of 919 children screened, ~20 per cent had TFF; more common in children aged > 12 mos. - Of the 20 per cent with TB, 6 per cent of cases who completed evaluation were diagnosed with TB	74 per cent of cases considered TB suspected were lost to follow up before TB was excluded - Only one half of children with an unknown HIV status were tested - Overall follow-up and HIV testing of children have to be strengthened
Ketema et al. (2020)	Ethiopia	Evaluating the integration of tuberculosis screening and contact investigation in tuberculosis clinics in Ethiopia: A mixed methods study	To evaluate the integration of TB screening into IMNCI clinics and contact investigation into TB clinics	180,896 children from 30 randomly selected IMNCI clinics and TB clinics in Addis Ababa from Aug 2016-Nov 2017	Mixed methods with stepped- wedge design	- IMNCI clinics: 145 444 children were screened for TB (80.4 per cent of children who attended), compared to 60 per cent pre-intervention - TB clinics: 559 under 5 contacts identified and 80.1 per cent screened, compared to 66.2 per cent screened pre-intervention >95 per cent of health providers indicated that integration of screening and contact investigation is acceptable and practical	- TB screening was highly successful - Clinicians gave positive feedback about the addition of TB screening

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Kizito et al. (2018)	Uganda	Quality of care in pediatric tuberculosis diagnosis at primary care clinics in Kampala, Uganda	To assess the quality of routine pediatric tuberculosis (TB) evaluation in urban primary care clinics	24 566 children aged < 15 years attending 6 government-run urban clinics in Kampala from Nov 2015 to Dec 2016	Cross-sectional study	- Proportion of children screened for TB symptoms was 55-65 per cent - Of children with symptoms suggestive of TB, 20.6 per cent were referred for sputum evaluation at the on-site lab - Of those referred, 44 per cent were tested initially using sputum smear microscopy instead of the recommended first line Xpert testing	- Quality of care was poor, particularly for children aged < 5 years - Only half of all children were fully screened for symptoms and TB contact history; only 20 per cent who screened positive were referred for sputum exam; none of the children who met the clinical criteria for TB diagnosis started treatment - Recommended diagnostics were not used: Poor adoption of national guidelines stating that Xpert testing is the first line even at facilities where Xpert testing was available
Frieze et al. (2018)	Cambodia	Examining the quality of pediatric tuberculosis in Cambodia: a cross-sectional study	To quantitatively assess the quality of clinician performance and the availability of diagnostic tools for diagnosing pediatric TB in high-burden districts	40 clinicians and 104 parents at referral hospitals and villages in the 24 highest burden districts	Cross-sectional study between August and Sept 2015; qualitative interviews using a structured questionnaire	- Limited availability of advanced diagnostic tools at the clinics - Lack of confidence in clinicians to make diagnosis based on clinical factors	- Recommendation to provide training to clinicians to diagnose pediatric TB to emphasize how to conduct a clinical exam, assess symptoms and diagnose without advanced diagnostic tools - Lack of capacity generally for diagnosis

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Cranmer et al. (2017)	Kenya	Integrating tuberculosis screening in Kenyan Prevention of Mother-To-Child Transmission programs	To inform future scale-up of TB screening and prevention services within PMTCT programs	Data from HIV-infected women and their infants from the National PMTCT-MCH Survey and the PMTCT-Nyanza Survey (from 141 MCH clinics, 498 women,	Assessment of the prevalence and correlates of postpartum TB symptoms and TB exposure among HIV-infected mothers at 6-week and 9-month infant immunization visits from two surveys of the PMTCT program	- Postpartum HIV-infected mothers frequently reported TB exposure and had a positive TB symptom screen, but few received IPT - Maternal positive TB symptom screen was associated with infant HIV and nonspecific infant TB symptoms - Older infants were more symptomatic at 9 months compared to infants screened at the 6-week immunization visit	- Integration of maternal TB symptom screening into MCH immunization programs could prompt infant TB and HIV screening and prevention - Opportunity to prevent TB in infants through early maternal diagnosis and IPT administration to TB-exposed infants
Screening and diagnosis at hospitals							
Indus Hospital TB Programme (2016-present) Amanullah et al. (2015)	Pakistan	<u>Indus Hospital Screening Project for Pediatric TB at Tertiary Care Hospitals</u>	To detect TB in children who are either missed or in early disease stages at large public and private tertiary care urban hospitals	Children aged 0-14 years already visiting pediatric OPDs at tertiary hospitals in 4 cities, but not necessarily with TB-related complaints	Active screening by rapid symptomatic and risk factor screening among child (0-14 years) OPD patients by trained IMCI screeners and EPI workers	583,744 children screened 17,978 children tested 8,102 diagnosed 7,911 put on treatment	- In Peshawar, reported pediatric TB cases in 2018 increased by 113 per cent compared to 2016 - In Karachi, reported pediatric cases in 2018 increased by 59 per cent compared to 2016

Author(s)/ program & year	Country of origin	Title of Paper/ Program	Objective(s)	Target population	Methodology	Outcomes/Results	Summary of findings
Indus Hospital TB Programme (2014-present) Amanullah et al. (2015)	Pakistan	<u>Indus Hospital Mass Screening to Combat Pediatric TB Underdiagnosis in Rural Jamshoro</u>	To increase the number of children reached, screened, tested, detected and put on anti-TB treatment in a rural district	Children aged 0-14 years in Jamshoro district	- Active case finding through mass screening of all child contacts of newly diagnosed TB patients from two outpatient clinics by trained young community members - Drs and HCPs trained in child TB diagnosis and management - Free testing	In first 12 months, 844 children identified and started on TB treatment	187 per cent increase in case notifications in the district in the first 12 months
Malik et al. (2018)	Pakistan	Improving pediatric tuberculosis detection and treatment through facility-based screening in rural Pakistn	To show the impact of systematic verbal screening and contact tracing with appropriate management services on TB case finding in pediatric populations	160,600 children aged 0-14 years and adults presenting at 4 public health hospitals in Jamshoro district (intervention) and 11 health centers in Hyderabad district (control) between Oct 2014 and Mar 2016	- Facility-based screening - Household contact tracing Capacity building for medical personnel - Provision of free diagnostics	1,448 additional pediatric TB notifications in the intervention area (+299.8 per cent from expected notifications) - Treatment success rate in children was >94 per cent in intervention district compared to 83 per cent in control district	3-fold increase in pediatric TB notifications in the intervention district - Relatively higher proportion of children with TB found in the 0-4 years age group

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Van Brusselen et al. (2020)	D R Congo	Improving pediatric TB diagnosis in North Kivu (DR Congo), focusing on a clinical algorithm including targeted Xpert MTB/RIF on gastric aspirates (GAs)	To evaluate whether the introduction of an adapted MSF pediatric TB diagnosis algorithm influenced the number of children started on TB treatment	Diagnosed pediatric TB cases (children aged 3 month- 15 years) started on treatment in the inpatient therapeutic feeding centre (ITFC) and the pediatric ward at the General Reference Hospital in Masisi, North Kivu	Retrospective analysis of the pediatric TB register from before (Jul-Dec 2016) and after (July-Dec 2017) introduction of the new diagnosis algorithm	• # of GAs performed increased to 94 in 2017 from 0 in 2016 • 68 children started TB treatment in 2017 compared to 19 in 2016 • Overall pediatric fatality rate decreased from 42 to 25 per cent after the introduction of the algorithm (not statistically significant)	• Significant increase in number of children on TB treatment after the intro of a new diagnosis clinical algorithm • Biggest increase in diagnoses in 2017 was in patients with a negative Xpert MTB/RIF result, but clinically highly suggestive of TB according to the new diagnosis algorithm • Increased clinician awareness believed to have played a role in the higher number of diagnoses in 2017
Screening / intensified case finding in communities							
Oshi et al. (2016)	Nigeria	Does intensified case finding increase tuberculosis case notification among children in resource- poor settings? A report from Nigeria	To improve detection of pediatric TB through intensified case finding strategies at out- patient clinics, ART clinics and through household contact tracing	6 states in southern Nigeria from July 2013 to June 2014	Prospective, community- based and hospital-based intervention package: awareness materials, health worker training, hospital screening	• 1,590 pediatric TB cases detected, • 0-4 years: 39.2 per cent of cases • 5-14: 60.8 per cent of cases • Children screened in outpatient clinics: 36,214, 648 confirmed cases • 1,303 children screened through contact tracing; 25 confirmed • 2,686 children screened at the ART clinics; 45 confirmed cases	• Increased the number of pediatric TB cases detected during the intervention period • Increased the number of cases detected in ART clinics • Improved the capacity of the health facilities for TB care

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Joshi et al. (2015)	Nepal	Impact of intensified case-finding strategies on pediatric TB case registration in Nepal	To assess the difference in pediatric TB registrations and case registration rates in 10 intervention districts where a package of intensified case finding had been implemented and 7 control districts	Children aged –14 years in 10 intervention districts and 7 control districts	Retrospective record review using routinely collected data	- Significant increase in pediatric TB case registrations between Years 1 and 2 (from 2.9 per cent to 5.0 per cent) in the intervention districts, no difference in the control districts - Percentage difference was significant in ages 0-4 years but not in ages 5-14	Of the various case-finding strategies, household contact screening, private-public mix of services and mobile health chest camps produced the highest yield of TB
Marks et al. (2019)	Vietnam	Community-wide screening for tuberculosis in a high-prevalence setting	To evaluate the effectiveness of active community-wide screening using the MTB/RIF assay compared to standard passive case detection for reducing the prevalence of TB over a four-year period	Community members in Ca Mau Province	RCT	10 per cent reduction in TB prevalence each year with a nearly 50 per cent reduction in TB infection rates among children over the study period	Effective intervention, but resource intensive to implement
USAID (2020)	Vietnam	NTP Pilot to advance TB detection in children/USAID Infectious Disease Detection and Surveillance (IDDS)	To expand the use of stool-based testing with GeneXpert by integrating its use into active case finding and increase presumptive TB patients' access to quality diagnosis services at national, provincial and peripheral levels	Children in Nghe An province			

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PROPER CARE	Vietnam	Pilot of active case finding (ACF) in one urban district	To pilot the use of full-time CHWs paid for ACF and case management	Community members in Go Vap district, Ho Chi Minh City			
Vo et al. (2020)	Vietnam	A comparative impact evaluation of two human resource models for community- based active tuberculosis case finding in Ho Chi Minh City, Viet Nam	- To scale up the ACF activities under the PROPER CARE project, - to measure changes in TB case notifications resulting from ACF - to compare the relative changes in TB case notifications between ACF implemented by incentivized volunteers and salaried employees	All household contact, close contacts and urban priority groups with clinical symptoms for whom in 12 districts of Ho Chi Minh City	Controlled intervention study over 2 years; verbal screening of household contacts of TB patients by CHWs; testing	- ACF: 321 000 people screened, 70,439 were a household contact of a TB patient or had symptoms of TB - Notification: 14.5 per cent increase of notifications in the intervention area (pre/post) - Number of people screened by salaried employees was 121 per cent higher compared to volunteers - Number of patients started on TB treatment in the salaried employee districts was 19 per cent lower than those started on treatment on the volunteer districts	- Both HR models were effective - Key success factors: - expansion of screening coverage to vulnerable population, - enabling access to more sensitive Xpert diagnostic - leveraging existing healthcare structures - community engagement complementary to facility-based case finding - Strong community linkages
TB Net (Tuberculosis Neighborhood Expanded Testing)	South Africa	Increase case detection in communities	To improve access to TB testing and treatment	Khayelitsha, Cape Town	Four campaigns (each lasting 2-3 days) for neighborhood-based TB screening focused on high-risk households in the vicinity of identified index patients	1,600 sputum jars distributed 151 samples returned and sent to lab 140 tested successfully 12 tested positive; all 12 successfully linked to care	- Practically feasible - Establishes care linkages, esp between HIV and TB - Allows for self-testing - Some challenges with stigma (households refusing TB education), sputum testing

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Treatment							
Speeding Treatments to End Pediatric TB (STEP-TB) Project (2013-17)	Global, led by TB Alliance with WHO	Speeding Treatments to End Pediatric TB project	Reduce market barriers to bring optimized products to market, make products available through a global mechanism, mobilize demand for products in country	Global	Active collaboration with pharmaceutical partners		- New child-friendly formulations brought to market and rapid uptake facilitated - Policy changes implemented - Registration strategies developed and implemented
Optimization of existing services							
Breath for Life (2016-present)	Vietnam	Optimization of pediatric TB services to reduce pediatric TB morbidity and mortality in one high TB burden province	Accelerate pediatric TB case detection, treatment and prevention in public and private sector	Four districts of Nghe An province, a province with high incidence of TB and HIV	- Activate the NTP system at all levels - Partnership with PATH and J&J - Mobilize public -private mix networks - Engage communities and families	- In one year, the number of children diagnosed with TB in four districts was doubled from 74 to 148 - Overall case detection increased - From 2015 to 2017, the number of children enrolled in IPT increased from 49 to 244	Overall increase in cases. In 2016, the largest number of new pediatric TB cases diagnosis was in Nghe An
IMPAACT4TB (2017-2021)	12 HBC: Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi	Increasing market and public health outcomes through scaling up affordable access models of short-course preventive therapy for TB	Promote the use of the shorter-course regimen 3HP for preventive TB therapy among PLHIV and children aged under 5 years	12 HBC	- Support new manufacturers - Assist countries with procurement, registration, importation of rifapentine - Develop tools to identify eligible individuals	Ongoing	Ongoing

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CaP TB (EGPAF) (2017-2021)	Cameroon, Cote d'Ivoire, DRC, Kenya, Lesotho, Malawi, Tanzania, Uganda, Zimbabwe, India	Catalyzing Pediatric Tuberculosis Innovations (CaP TB): Implementation and Integration of New TB Care & Treatment Models	• Bring new child-friendly formulations to improve diagnosis • Improve capacity to diagnose pediatric TB and improve uptake of new FDCs • Increase access to preventive TB therapy • Develop innovative models of care	Multiple communities and health facilities in 9 countries in Africa and India	• Integration of TB screening, diagnosis, treatment initiation into MNCH, pediatric inpatient and outpatient, nutrition and HIV entry points • In India, integration into private sector • CHWs trained to conduct household contact tracing, screen identified pediatric contacts, monitor treatment adherence • Ensure availability of fixed-dose formulations • Support intro of 3RH for LTBI treatment • Support Xpert Ultra intro and Omni tech	• Ongoing	• Ongoing

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