SCALING UP INTERVENTIONS TO FIND CHILDREN WITH TB

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STOP TB FIELD GUIDE

Stop TB Partnership

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StopTB Field guide 5: Scaling Up Interventions to Find Children with TB

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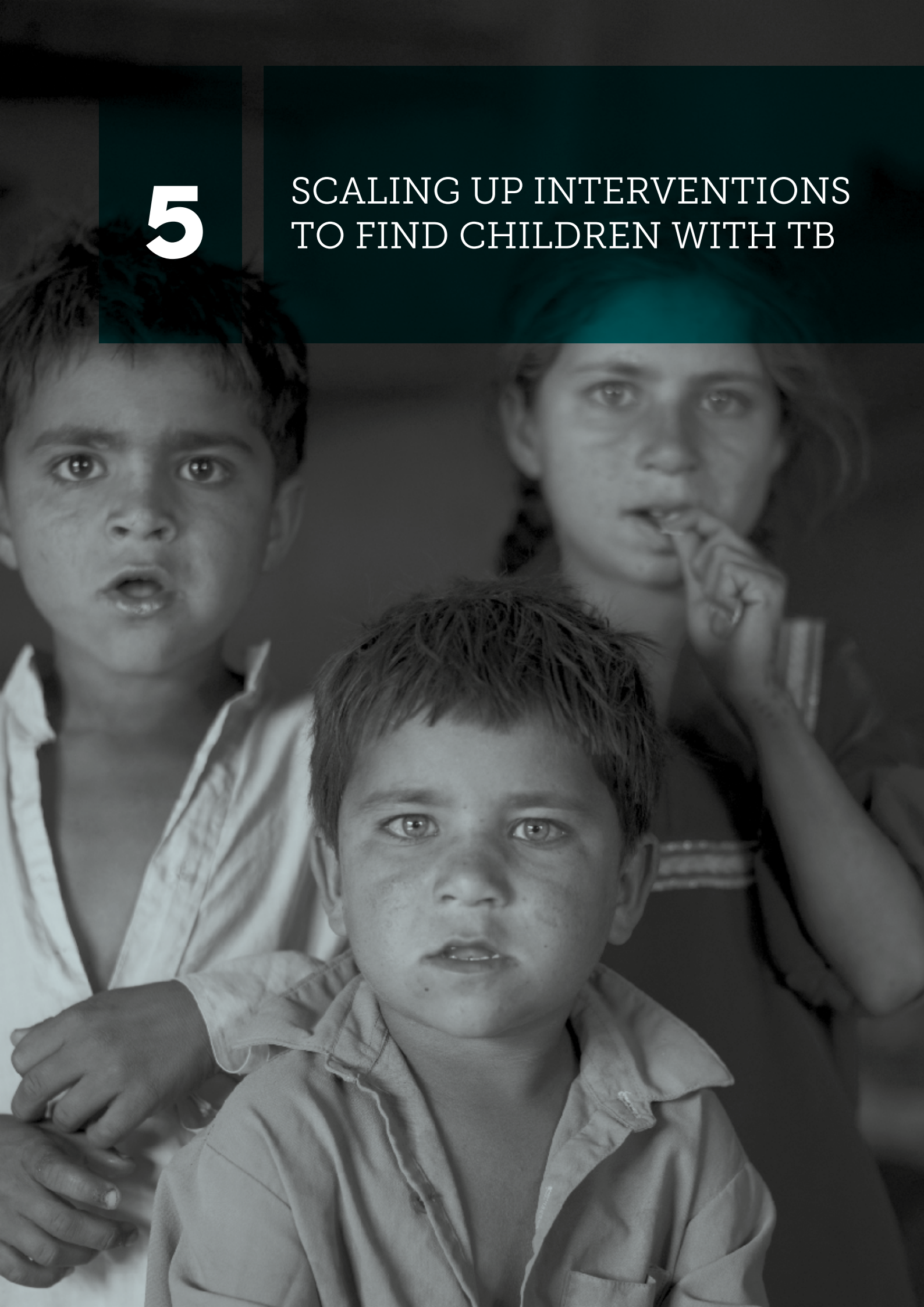

PURPOSE OF THIS DOCUMENT

This document is one in a series of 11 field guides produced by Stop TB Partnership in collaboration with the Global Fund to Fight AIDS, Tuberculosis and Malaria, Interactive Research and Development Global (IRD), KIT Royal Tropical Institute, and multiple global experts and implementation partners. The field guides rely on practical experiences and expertise of implementers and are meant to help national TB programmes and other TB programme managers to identify the best strategies for finding people with TB who are missed by routine health services.

This document is not to be treated as guidance, but rather as a collection of considerations, tools, experiences and examples that highlight successes and challenges in implementing effective TB case-finding interventions and may assist in their planning. This field guide addresses childhood TB and attempts to support TB programme implementers in rolling out and contributing to effective interventions to find missing children with TB.

This field guide went through extensive peer review by the agencies and individuals acknowledged below. It presents a range of examples from peer-reviewed literature and implementation practice. Where not cited, examples are provided by TB REACH.

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The production of these field guides represents a significant effort, bringing together more than 60 experts from over 30 different institutions globally in the spirit of partnership to help address a major barrier in the TB response: the fact that millions of people with TB are still missed by the current routine health systems.

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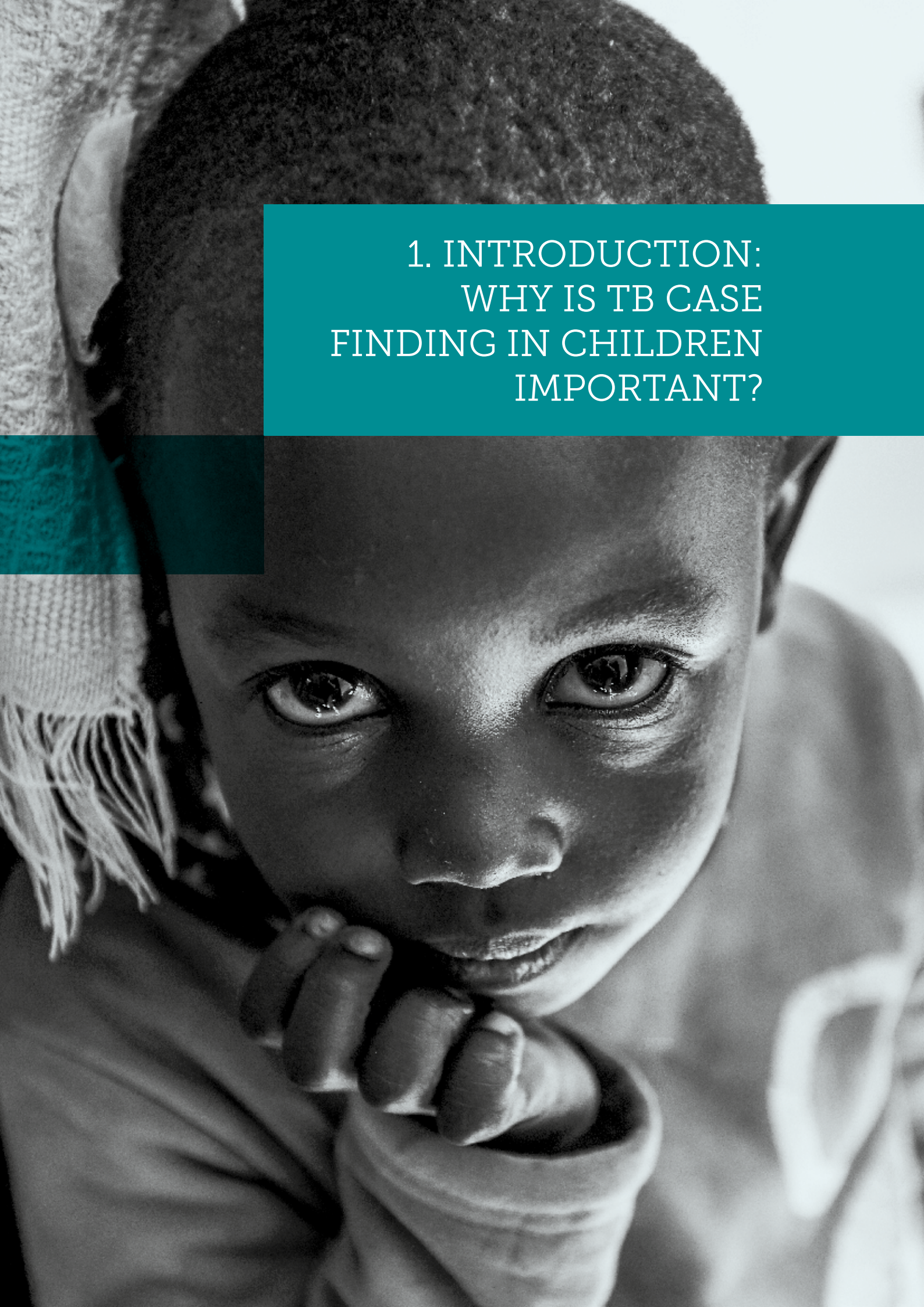
Abbreviations

ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guérin vaccine
CHW	Community health worker
CT	Computed tomography
CXR	Chest X-ray
DR-TB	Drug-resistant tuberculosis
DST	Drug-susceptibility testing
EPTB	Extrapulmonary tuberculosis
FDC	Fixed-dose combination
GA	Gastric aspiration
HCW	Health care worker
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
IMCI	Integrated Management of Childhood Illness
INH	Isoniazid
IPT	Isoniazid preventive therapy
LAM	Lipoarabinomannan
MDR-TB	Multidrug-resistant tuberculosis, defined as resistance to rifampicin and isoniazid
M&E	Monitoring and evaluation
MNCH	Maternal, newborn and child health
M.tb	Mycobacterium tuberculosis
NGO	Nongovernmental organization
NPA	Nasopharyngeal aspiration
NTP	National TB programme
SLD	Second-line drug
TB	Tuberculosis
TBI	Tuberculosis infection
TPT	Tuberculosis preventive treatment
TST	Tuberculin skin test
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Xpert	Xpert MTB/RIF assay, a cartridge-based nucleic acid amplification test (NAAT) for rapid tuberculosis diagnosis



1. INTRODUCTION: WHY IS TB CASE FINDING IN CHILDREN IMPORTANT?

Every day almost 700 children die from tuberculosis (TB). Childhood TB is an emergency and represents a moral and ethical failure in the global response to a preventable and curable disease.

In 2016, over 1 million children were estimated to have TB, but only 430,470 (43%) were notified (1). While the overall global TB notification gap is reported to be 39% (1), a larger gap exists for children, likely due to a combination of under-diagnosis and poor reporting. The rates of detection and treatment of childhood TB are low as a result of a combination of factors:

- Overall lack of clinical suspicion among health care providers who serve children and families, even in areas of high TB incidence;
- Lack of capacity on the part of lower level health care workers (HCWs) and reluctance on the part of the more advanced health care workforce to act on clinical diagnosis;
- Low sensitivity of most diagnostic tests in the microbiological confirmation of TB, and the paucibacillary nature of active TB, especially in children under 5 years of age;
- Failure to perform contact investigation for children living in households with adult TB patients;
- Lack of capacity among HCWs to conduct gastric aspiration, nasopharyngeal aspiration, sputum induction, etc.

Estimates also suggest that as many as 2 million children globally have multi-drug-resistant (MDR-) TB and 30,000 children develop MDR-TB every year (2). The gaps in MDR-TB diagnosis and treatment in children are immeasurably amplified, with only 2–10% of estimated MDR-TB cases among children being diagnosed and reported (2); even fewer children with extensively drug-resistant (XDR-) TB are diagnosed and commenced on appropriate treatment (3).

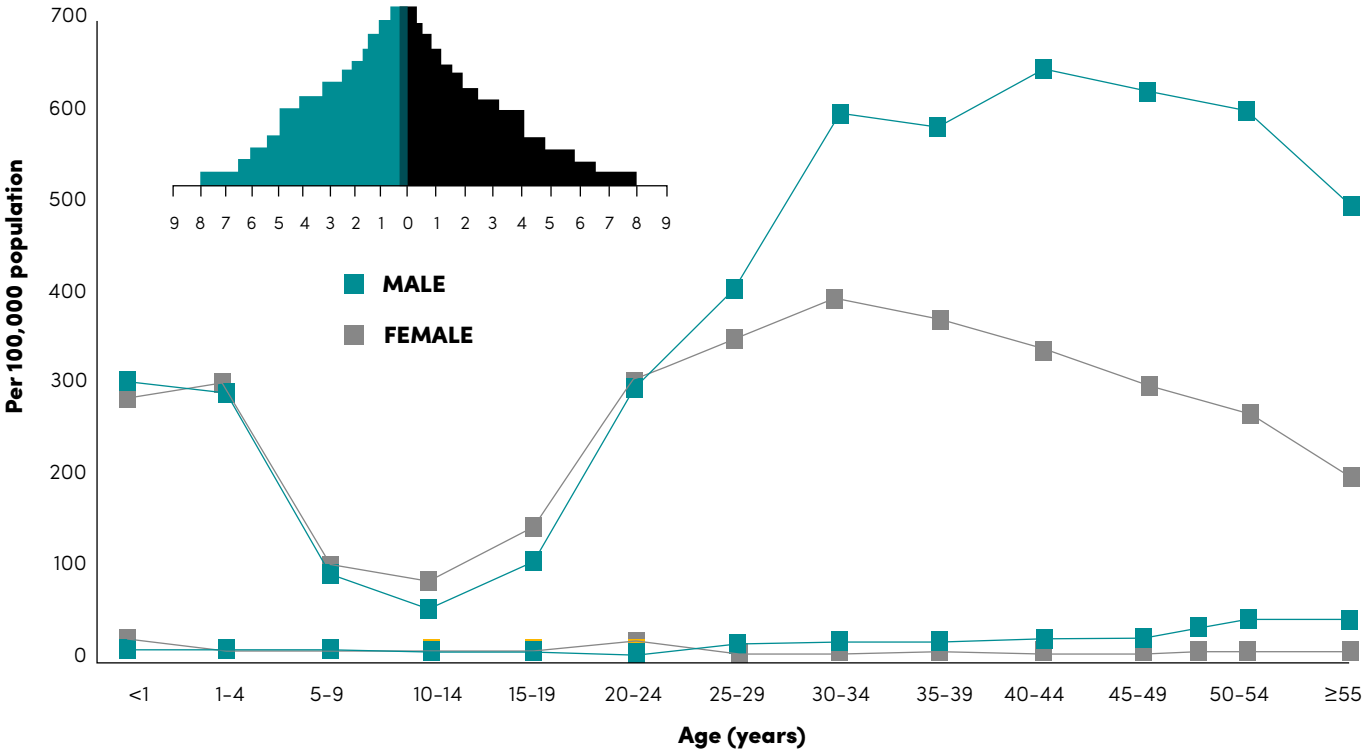
The diagnosis and treatment of MDR- and XDR-TB in children is further complicated by:

- Lack of drug-susceptibility testing (DST), which can only be performed on bacteriologically-confirmed cases;
- Lack of clinical trials on the treatment of children with drug-resistant (DR-) TB;
- Lack of access to child-friendly second-line formulations;
- Fear of side effects of second-line drugs (SLDs).

In 2016, only 161,740 children under 5 (13% of the 1.3 million children eligible) were reported to have received preventive therapy, despite well-established WHO recommendations (1). Although poor reporting may result in an underestimate, the inadequacy of household contact investigation and failure to provide lifesaving TB preventive treatment (TPT) are undeniable.

The diagnosis of TB in a child under 5 is considered an important sentinel event in the community, as it signifies a recent transmission most often from an adult with active TB. Diagnosing and managing TB in children efficiently will not only reduce child sickness and death, but can also have a marked impact on a TB epidemic in the community. Until recently, many national TB programmes (NTPs) believed that addressing TB in children was not a critical component of the national TB response. However, an estimated 97 million children are infected with Mycobacterium tuberculosis (M.tb) and are at risk of progressing to TB disease, which may be life-threatening (4). Furthermore, children under 5 are at greater risk of developing severe life-threatening forms of TB (such as TB meningitis and disseminated TB), while older children contribute to the infectious pool and propagate TB transmission in the community. Finally, children under 5 contribute significantly to the TB burden in high incidence settings, as illustrated in Figure 1.

Figure 1. **Distribution of TB burden by age and gender in different settings**



Age- and gender-related differences of tuberculosis incidence in hypothetical high and low tuberculosis incidence populations.
Notes: Reproduced with permission of the International Union Against Tuberculosis and Lung Diseases. Copyright © The Union. Donald PR. Chilhood tuberculosis: the hidden epidemic. Int. J Tuberc Lung Dis. 2004;8(5): 627-629. 8

There are multiple barriers (societal, health systems, economic) that prevent children from accessing TB diagnosis and treatment. TB diagnosis in children remains a critical challenge, as evidenced by the large case detection gap. The research community and funders must work to develop new diagnostics, specifically point-of-care tests that are capable of rapidly detecting TB in children. In the meantime, a shift in NTP policies, focusing both on community awareness and optimizing health staff knowledge and insight, will help to advance case finding among children.

There is a wide range of factors contributing to the worldwide under-diagnosis of TB in children:

- Children are dependent on their caregivers to access health care, but caregivers and communities often have limited awareness of TB in children, resulting in children presenting late or never presenting to TB services, even where these services are available.
- Not all cadres of health care providers have adequate awareness, training and mentorship to diagnose childhood TB; there is a lack of capacity and confidence among health care providers to diagnose clinical TB or appropriately interpret diagnostic testing where it is available.
- There is a need for more sensitive diagnostic tools that are child-friendly and capable of collecting specimens without invasive procedures, particularly to improve the microbiological confirmation of diagnosis and to enable TB drug-resistance testing.
- Active contact investigation among children living in households with TB is not routinely implemented.
- TB prevention is often not prioritized by public health authorities, resulting in a lack of commitment and resources to support the delivery of TPT.
- Childhood TB diagnosis and treatment is often confined to specialized centres, with complex referral systems and limited integration into routine TB care and routine child health platforms.
- Childhood TB care and treatment is inadequately integrated or linked with other programmes, such as maternal, newborn and child health (MNCH) and Integrated Management of Childhood Illness (IMCI) service platforms, HIV care programmes, immunization and nutrition clinics.
- Lack of clear monitoring frameworks within NTPs and non-TB programmes, particularly with regard to clinically diagnosed TB.
- Recording and reporting are incomplete and poorly standardized, especially in the area of documenting treatment outcomes, leading to low childhood TB notifications.

2. DESIGNING A CHILDHOOD TB CASE-FINDING PROJECT

2. DESIGNING A CHILDHOOD TB CASE-FINDING PROJECT

There are a number of important components that need to be in place for a TB case-finding project targeting children to be successful. These include:

- Educating caregivers and raising awareness in the community;
- Implementing contact and symptom screening and diagnostic approaches that differ according to age group;
- Ensuring that appropriate staff are in place and capacitated through training and ongoing mentorship to deliver high-quality services.

2.1 Educating caregivers and raising awareness in the community

One of the first steps in identifying childhood TB is raising awareness in parents, caregivers and communities, as well as providing education and support to health care providers. Children are dependent on their caregivers to access health care; it is therefore very important to understand and address barriers originating within the family, the broader community and the health care workforce that may reduce children's access to TB care.

Table 1. Examples of barriers to TB diagnosis among children (family, community and health systems)*

Family Barriers	Community Barriers	Economic barriers	Health systems
Child health may not be prioritized; particularly if several working family members have TB, their health concerns might be addressed first.	TB might be stigmatized in the community and having a child with TB may point to other family members living with TB.	Cost of travel and the multiple visits required for diagnosis might be prohibitive.	Paediatric TB services may not be fully integrated into overall services, causing families to travel farther or on several days to access diagnosis.
Women who assume child care-giving roles might be unable to travel to health facilities with the child without the permission of a husband and/or unaccompanied.	In some communities, adolescent women with TB might have reduced marriage prospects.	Distance from health care facilities may be great.	HCWs are inadequately trained and mentored to care for children with TB.
When the index patient is not the primary caregiver (usually the mother), the information regarding the need for screening may not be communicated clearly within the household.	TB remains stigmatized in many high coinfection regions, where a diagnosis of TB may suggest a diagnosis of HIV.	Although TB care is free, often contact investigation and child evaluation are not.	Paediatric diagnosis outside of contact investigation often requires multiple diagnostic tests such as chest radiograph or tuberculin skin test (TST) that are not readily available.
The rationale behind taking a child who is well and without symptoms (contact investigation) to the health centre for evaluation and medication is not clearly understood.			

**For every community there may be a different set of barriers, e.g. young mothers, no family support. Therefore, prior to starting activities, implementers should identify the specific barriers within the communities where the programme will operate and work to address them.*

What to focus on in awareness activities?

Family members need to be aware that TB can occur in children, even if they have received the BCG vaccination.

- It is essential in caregiver education for there to be clear messaging around the BCG vaccine's ability to provide protection against complications such as meningitis and disseminated TB, but not other forms of TB (5). This education may begin in antenatal settings as appropriate. There is also emerging evidence that BCG vaccination in children may be protective against exposure to primary TB infection; however, more practical guidance is needed on how this can impact messaging and/or programming (5).
- Caregivers need to know that TB symptoms are different in children compared to adults, and may not include a cough. Rather, symptoms could be failure to thrive and/or reduced playfulness. Furthermore, multiple medical visits may be required to obtain an accurate diagnosis of TB and to obtain multiple specimens via collection procedures that may be perceived as invasive yet are safe.
- Where TB has been diagnosed in a family, the importance of comprehensive screening, disease evaluation, preventive or curative treatment, and infection control cannot be overemphasized and communicated throughout the household.

When educating communities and health workers, campaigns should emphasize that contact investigation has to begin in the clinic. Discussing with index patients the risks that TB may present to their children is part of contact investigation; investigations are not carried out solely in the community or within the home.

Raising awareness in the community

Community awareness can increase the detection of childhood TB. In Bangladesh, a package of community sensitization coupled with HCW training increased childhood TB case finding from 3.8% to 12% of those referred to the centre. Settings that provide opportunities for community awareness activities include schools, religious meetings, community societies e.g. Girl Guides and Boy Scouts, and village governance meetings. Meetings for other health-related issues, such as quarterly district meetings, nutrition programmes and immunization programmes, can also be used. TB educational materials should be available at every paediatric outpatient department. TB survivors can provide motivation to promote TB case finding and treatment adherence. Posters and handbills distributed in communities have also been shown to be successful (6,7).

In many countries, caregiver consent is required for TB screening and testing in children. This needs to be considered when designing programmes, e.g. mass screening campaigns at schools. It is important to understand local legislation and cultural customs in order to ensure that caregivers are engaged and the required permissions are obtained.

2.2 Considerations for different age groups

TB programmes usually define "children" as individuals who are under 15 years of age (1). However, TB disease epidemiology varies as age increases, and different screening and diagnostic approaches are needed for different paediatric age groups.

Children under 5

Children with TB between 0 and 4 years of age may have no complaints, may be unable to voice their complaints, and/or often present with non-specific acute or chronic symptoms. They also have difficulty spontaneously producing sputum specimens for diagnosis. Pulmonary TB in children of this age is also often paucibacillary (low bacillary load). For these reasons, TB in this age group is difficult to confirm bacteriologically and to differentiate from other conditions such as pneumonia, malnutrition, sepsis and meningitis. However, because infants and young children are at higher risk of developing severe forms of TB disease that may be fatal (e.g. TB meningitis and disseminated TB), it is particularly important to pay attention to this age group. Diagnosis is often based on history of TB exposure and the presence of clinical signs and symptoms, even without bacteriological confirmation. Furthermore, decisions regarding treatment initiation may have to be made quickly, since disease progression may be rapid and the family might not be available later for follow-up.

The first step to diagnosis in children in this age group is to comprehensively ask about potential TB exposure, particularly within households but also in any setting of prolonged contact, e.g. daycare, extended family, including exposure to adults with a chronic cough (who may not yet have confirmed TB). When history of exposure is understood (particularly within the household), a high index of suspicion for TB is critical. If there is no household exposure, TB should still be considered in the child who is failing to improve with routine care (e.g. routine antibiotics for pneumonia), is falling off their growth curve, or whose activity levels have drastically declined.

Older children

The period of time from age 5 to puberty is considered the "golden age for TB in children", as the incidence of TB seems to fall in this age group (see Figure 1). However, the same non-specific symptoms described above may apply, although a prolonged cough is more common in this age group.

As age increases, the presentation of TB begins to clinically mimic that of an adult, with prominent pulmonary symptoms. In addition, the ability to produce sputum improves with age, enabling older children to provide samples. Experience shows that children over 8 years of age with pulmonary TB are generally capable of producing a sample (6), and every effort needs to be made to collect sputum for microbiological confirmation and susceptibility testing before starting any treatment. This is because, due to fewer organisms, even a few doses of any TB treatment can make it very difficult to isolate an organism for bacteriological diagnosis.

Access to education: In multiple settings, stigma and lack of knowledge on the part of both the parents and education system officials may interrupt school attendance for prolonged periods of time for children and adolescents with TB (8). This lag in education needs to be minimized, as it further fuels stigma, may delay diagnosis and has a serious negative impact on affected children.

Adolescents

A recent global analysis estimates that 1.78 million adolescents and young adults (aged 10–24 years) developed incident TB in 2012, representing 17% of all new TB cases globally (9). Adolescents are more likely to have M.tb infection and adult-type TB. They may also be more infectious than younger children. Increased prevalence of other comorbidities and behaviours, such as diabetes, HIV, and substance, alcohol and tobacco use, potentially contributes to the increase in incidence. Coupled with stigma, peer pressure and low care-seeking behaviour, these characteristics make it important for programmes to consider adolescents and young adults – a historically neglected group.

Selection of the population in which to target case-finding efforts should be informed by local epidemiology within the community being served. Children under 5 and adolescents have an increased risk of TB, and therefore rigorous case-finding programmes targeting these age groups are more likely to find children with TB. Specific campaigns targeting adolescents are likely to be more effective than general campaigns targeting all children. Similarly, programmes tailored to age are required to support children through to treatment completion.

Gender: Higher rates of TB have been reported in adolescent women than in adolescent men (10), in contrast to other age groups in which males typically have higher rates of TB. Recognition of the increased risk in adolescent women may be of relevance as screening programmes are planned, particularly in settings where young women face gender-specific barriers to accessing TB care. In addition, in areas with high rates of adolescent pregnancy, the risk of perinatal TB makes it imperative to design appropriate screening and diagnostic programmes for adolescent women to ensure the health of both the mother and baby.

2.3 Staffing considerations

Training and mentorship

Health care providers across the spectrum – from community health workers (CHWs) to specialist physicians – may feel unprepared to address TB in children. Therefore, implementers may need to consider various training modalities prior to and during the intervention. A combination of

- Didactic training;
- On-the-job experience;
- Sustained mentorship; and
- Clear referral mechanisms

can provide a platform to significantly increase childhood TB diagnosis and treatment. As health care providers are empowered to feel more comfortable with diagnosing and treating childhood TB, fewer children with TB will be missed.

In South Kivu, a poorly resourced province in the Democratic Republic of the Congo (DRC), a lack of clinical skills was shown to result in under-detection of childhood TB: Only 18.1% of children had a bacteriologically-confirmed diagnosis and a correlation was drawn between rates of sputum smear- negative TB notified among adults and cases identified among children in different health facilities (11). Health facilities with more advanced skills and assisted by a nongovernmental organization (NGO) were able to identify more children with TB and adults with sputum smear-negative TB. This demonstrates the importance of ongoing monitoring, training and mentorship in order to ensure that clinicians have the capacity and confidence to diagnose childhood TB when bacteriological results are negative or when appropriate tests are unavailable or inaccessible.

Didactic training

Basic training on childhood TB prevention, screening, diagnosis and treatment is required for all levels of staff as a precursor to instituting or scaling up a programme and building the necessary capacity. In Bangladesh, in addition to the community awareness activities mentioned above, field workers and government health workers were taught how to utilize a flow sheet for diagnosis as a part of didactic training for TB; a separate training for private sector physicians was also held. These interventions increased the diagnosis of both sputum smear-negative TB and extrapulmonary disease (6). Similarly, in a TB REACH project in Nigeria, a combination of awareness raising and didactic teaching for medical officers/ paediatricians, nurses, general health workers, and private medicine vendors improved the notification of childhood TB (7). The training covered symptom screening and included an overview of how to use various tools, including score charts, flip charts, flowcharts, and growth-monitoring charts.

A TB REACH project in Afghanistan[1] focused on training clinicians in public and private specialist hospitals on the diagnosis of TB in children. This training resulted in a three-fold increase in all-form notifications, while a TB REACH project in Cambodia[2] reported increased diagnosis of extrapulmonary TB (EPTB) in children as a result of training.

[1] *TB REACH Wave 3. Innovation towards zero TB deaths among children in Kabul City of Afghanistan. ACREOD.*
[2] *TB REACH Wave 4. Innovating mobile diagnostics for active case finding for TB within high-risk populations in urban and rural Cambodia. Sihanouk Hospital Center of HOPE.*

POSSIBLE TRAINING TOPICS INCLUDE:

- How the presentation of and susceptibility to TB changes throughout childhood and adolescence;
- Screening algorithms and appropriate use of scoring charts such as Keith Edwards (12);
- Role of and specific interpretation of paediatric chest X-rays (CXRs);
- Diagnosis of other respiratory illnesses and comorbidities;
- Paediatric TB medication preparations, dosages, safety profiles and delivery strategies tailored to age in order to improve completion of therapy goals;
- DR-TB in children;
- Role of testing for infection: TST and interferon-gamma release assay (IGRA);
- Management of TB contacts, including screening, testing and TPT;
- Specimen collection techniques (practical exercises);
- Integration of TB and HIV care and treatment;
- Understanding and facilitating local referral mechanisms;
- Use of reporting tools to efficiently capture accurate notification data;
- Effective monitoring and evaluation (M&E) to inform and refine ongoing programme roll-out;
- Importance of operational research to fill large existing gaps in the evidence.

Training for CHWs and screeners should include instruction on how to recognize the signs and symptoms of TB, administer the initial verbal screening questionnaire (including asking for contact history) and link children to appropriate care. In addition to training on the recognition of the signs and symptoms of TB, HCWs require education on the safety profile of TB medications and TPT in children. Fear of side effects should not prevent treatment (for either TB disease or infection), particularly in children under the age of 2 for whom TB treatment can be lifesaving. However, didactic training alone may have little effect on HCW practices unless it is accompanied by on-the-job training, mentorship and ongoing support.

On-the-job training

On-the-job training can be provided by job shadowing and clinical rotations that deliberately include paediatric TB. This practical experience should likely include a module dedicated to CXR quality and reading in children. In the Kingdom of Eswatini (formerly Swaziland), the Baylor clinic, which sees over 100 children per day, offers comprehensive services and functions well as a training hub. Nurses from surrounding clinics visit for a week at a time and receive peer mentoring on various topics, including TB screening and diagnosis.

Ongoing mentorship

Mentorship enables HCWs to translate training into practice. Ongoing training and mentorship are the cornerstones of building staff confidence and competence. Different platforms have been used successfully to connect less experienced physicians with specialist support. Remote support through web platforms such as Skype and WhatsApp enables front-line providers to share CXR images and test results with specialists in real-time, thereby facilitating prompt decision-making. The Butimba project in Eswatini effectively used a hotline that received calls and texts. Patient confidentiality issues must be taken into account when using these platforms.

Creating opportunities for learning and information exchange: Creating an informal "community of clinicians" with interest and experience in TB clinical and programmatic issues facilitates shared learning and referrals. This community can also be very useful in advocating for reduced diagnostic costs and in facilitating patient referrals and access to existing diagnostic services.

An example of such a community is TB Project ECHO® (Extension for Community Healthcare Outcomes)[3], which is a virtual case-based collaborative model of medical education that leverages videoconferencing to bridge geography and includes a combination of interactive and didactic training sessions that occur between once per week and once per month. Learning sessions are built around standardized case histories presented by participants for group discussions that are led by more experienced TB clinicians. These clinical education and problem-solving sessions include short didactic presentations and focus on the skills needed or problems faced by participating clinicians. Locally relevant best practices emerge from the discussions through peer-to-peer sharing and empower participants in their day-to-day work. Participants are able to join these 1–2 hour learning sessions using easily accessible video conferencing technology.

Clear referral mechanisms with feedback

Having clear referral mechanisms will enable all cadres of staff to seek support from more experienced colleagues and access ongoing learning. For example, community screeners need to know where to refer children with possible TB; in turn, the feedback they receive can both encourage them and increase their efficiency. Experience has shown that front-line workers are far more likely to engage with the complexities of childhood TB if they know that their patients will ultimately receive a final diagnosis with the support of a more experienced physician. In effect, the more experienced physician provides a "safety net" for the less experienced clinician (13). In addition, specialist units can serve as a clinical monitoring mechanism and as the hub for training and mentoring.

[3]*More information on TB ECHO can be found here. https://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/Tuberculosis/HealthcareProfessionals/TBECHO)*

Optimizing human resources

Diagnosing the majority of children with TB is relatively straightforward when HCWs are:

- Sensitized and trained regarding when to suspect TB;
- Alerted to how to recognize key history, signs and symptoms;
- Able to understand the relative safety of TB treatment in children; and
- Confident in the use of algorithms for the diagnosis of TB in children (including clinical diagnosis).

Bacteriological confirmation of childhood TB can be more difficult given the limitations of existing tests. These limitations should, however, never dissuade the sensitized clinician from moving forward with diagnosis and treatment. With training, task-shifting (i.e. entrusting diagnosis to lower cadres of health workers) has been very successful in increasing both TB case detection and TPT initiation in children. All cadres of HCWs can contribute to raising awareness and finding children with TB, e.g. nutritionists, adherence supporters, pharmacists and traditional healers.

Community health workers (CHWs)

CHWs are very effective in raising awareness about childhood TB at the community level and in sensitizing other HCWs and family members on the importance of screening, early diagnosis and contact investigation for contacts of both adult and child index patients. CHWs can be trained to provide initial verbal TB screening, but require a clearly structured screening algorithm and access to a predefined referral process. In Pakistan, a TB REACH project trained CHWs to verbally screen children. During the project, 105,000 children in four paediatric outpatient departments in rural facilities were screened; children with possible TB were referred to trained physicians in the facility and 1,417 children (prevalence: 1.3%) were diagnosed with TB (14).

Nurses

Nurses are often at the front line of managing TB patients. With mentorship, nurses can be utilized to the full scope of their practice to provide TB care to children and their families. With appropriate referral systems in place for complex decisions, nurses can effectively manage many patients with TB. In South Africa, clinics that adopted an approach to MDR-TB that involved task-sharing between doctors and nurses demonstrated higher treatment success rates than the national average; this model may optimize the use of scarce human resources and improve access to care (15).

General physicians

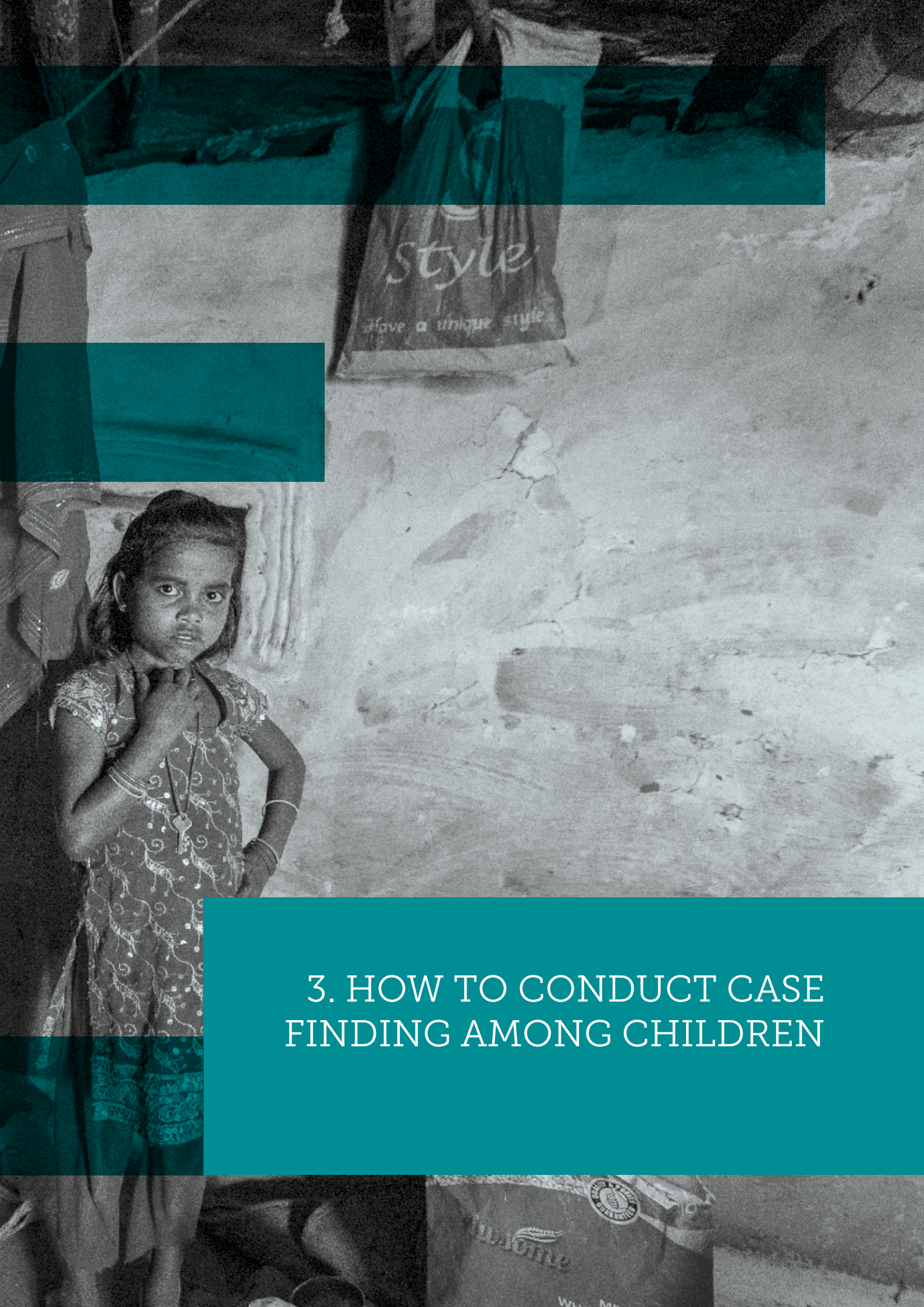
General physicians play a large role in the diagnosis and treatment of TB in children. In some settings, general physicians provide a TB diagnosis with referral for management, while in others, general physicians perform case management of both drug-sensitive (DS-) and drug-resistant (DR-) TB.

Specialist paediatricians

Specialist paediatricians may not always be available, but in well-resourced settings can assist with complicated TB, such as abdominal TB, spinal or meningeal TB, and DR-TB. In addition to clinical management, specialist paediatricians can also provide ongoing mentorship, didactic teaching and overall programme support.

Caregivers

A complicating issue around childhood TB is the confidence parents/caregivers have in the diagnosis and treatment. Depending on the community context, caregiver confidence in non-specialist TB diagnosis may need to be built and sustained. These non-specialist interactions may also serve as an opportunity to find TB among other family household contacts, including adults. Lessons from HIV models for engaging and educating caregivers may be reviewed and utilized by implementers (16).



3. HOW TO CONDUCT CASE FINDING AMONG CHILDREN

3. HOW TO CONDUCT CASE FINDING AMONG CHILDREN

3.1 Contact investigation

Opportunities and challenges of contact investigation

Contact investigation is a basic component of the package of care for all TB patients and should be routine. It is a very important mechanism for both identifying and preventing TB in children. Although contact investigation is a part of most national guidelines, it is generally poorly implemented. The rate of development of TB disease in household contacts under 5 has been reported to be between 15% and 20%. This rate is very high and makes contact investigation a preferred and highly efficient methodology for implementers aiming to find children with TB (17,18).

Challenges that preclude national programmes from effectively conducting contact investigation include:

- Lack of political will and appropriate resource allocation to emphasize that contact investigation is part of the expected national standard of care;
- Poor awareness and lack of information on the value of contact investigation to save children's lives by detecting and treating or preventing TB;
- Lack of capacity among staff to take on the additional burden of work;
- Fear on the part of health care providers regarding the safety of TB medications in children;
- Misperceptions that TPT may cause drug resistance;
- Fear of stigma and consequences, as well as an uneven gender power balance within households, may dissuade index patients from disclosing their TB status to other household members;
- Lack of financial resources may stop contacts from visiting facilities for screening;
- Issues of confidentiality may prohibit household visits in cases where children cannot come to facilities;
- Misunderstanding on the part of health workers that contact investigation is carried out solely in the field. Contact investigation starts with a discussion about the risk to children in the clinic with the index case, preferably immediately following diagnosis, and continues with contact invitation to bring the children into the clinic for screening;
- Household contact investigation is a labour-intensive process, requiring multiple visits to a household outside of working hours to ensure that all household members are reached;
- Mothers/caregivers may also be reluctant to start or continue TPT while children are perceived to be healthy.

Note on household contact investigation: Research studies tend to report higher yields from screening household TB contacts than are seen in implementation projects. This is likely due to dedicated resources being allocated and interventions being closely monitored over a defined research period. In practice, case yield may be low when contact investigation is carried out over multiple sites with inadequate resources, which may be discouraging for HCWs, policy makers and implementers. However, efficient and effective contact investigation activities may be performed with limited resources. Contact investigation is a route to providing TPT to the millions of children exposed to TB at home.

More information on contact investigation can be found in the relevant field guide in this series. Implementers should consider this to be one of the key approaches to finding children with TB.

Opportunity for addressing TB infection: Household contact investigation presents an opportunity not only to detect TB, but also to initiate TPT for all contacts, regardless of age or HIV status, who are eligible and do not have TB disease (19).

TB infection (TBI) is defined as a state of persistent immune response to stimulation by M.tb antigens, without evidence of clinically manifested active TB. Children are exposed to TB through inhalation of aerosolized droplets. Children then follow three possible routes:

1. Some children, particularly those under the age of 2, may progress directly to TB disease, even before tests for TBI can become positive.
2. Some children may contain the original infection, have evidence of TBI by testing, and go on to develop TB disease.
3. Some children may contain the original infection, not become ill for a significant period of time, but test positive for TBI. This third category has been referred to as "latent" TBI.

However, the term "latent" may be misleading, as it may imply that no treatment is required. Therefore, the term "TB infection" is more accurate in conveying the risk and need for treatment. Mathematical modelling studies estimate that 97 million children currently have TBI worldwide (4), and each year, about 1 million children progress to TB disease (1). Addressing TBI in children should be a key part of any case-finding intervention and is a cornerstone to turning the tide on childhood TB. Considerations for addressing TBI are described in a "Focus on" section of this field guide on page 17.

Considerations for contact investigation in children

Step 1

Ensure that there is adequate awareness, education and support available:

- To assist index patients in disclosing to their family that they have TB; and
- To convey the importance of TB screening and prevention for their family members.

This awareness also needs to be present on the part of the providers, as they need to establish rapport with index patients who might be feeling overwhelmed, guilty or otherwise too distressed about their own diagnosis to consider their children. This process starts with having a patient-centred discussion with the index patient at diagnosis.

Step 2

Analyse and attempt to eliminate the barriers that may prevent children from accessing screening. Programmes need to have mechanisms in place to overcome such issues, e.g. cost of transport and diagnostic testing and long waiting times, through innovations such as:

- Providing transport and/or CXR vouchers;
- Allocating designated times for screening children or combining child screening with the index patient's follow-up visit (index patient and child return together);
- Visiting the household outside of working/school hours;
- Offering differentiated models of care so that families may choose facility- or community-based evaluation of child contacts.

Programmes may explore different models for contact investigation:

- Contact investigation paper slips have been used to bring patients into facilities in South Africa. People with TB were asked to give these slips to their contacts to encourage them to follow through with TB screening. While some people with TB had difficulty presenting the slips to their contacts, others said it was sometimes easier than holding an "emotionally charged" conversation (20).
- Not all contacts may be able to come to facilities due to time and resource constraints. An active contact investigation project must have a system in place to identify these contacts and conduct follow-up home visits. An initial household visit can be used to counsel household members on TB and the importance of early diagnosis, TPT and infection control. Initial symptom screening and sputum collection can take place at this first household visit, which may remove the need for the family to attend the clinic. Further visits should focus on contacts who were not available/did not reach the health facilities. In Eswatini, a TB REACH Wave 3 project utilized a mix of household visits and clinic referrals to perform household contact investigation in remote areas. The project screened over 12,000 contacts with a programme yield of 1.6%. This project demonstrated that contact investigation prioritizing children is not only feasible in a high TB/HIV burden setting, but can also contribute to overall case detection (21).
- In some settings, extending contact investigation to other close contacts beyond the household may increase yield. In the Republic of the Gambia, 78% of diagnosed children were found in the immediate household; the remaining 22% were diagnosed within the same compound. Sometimes childcare is provided by grandparents or other relatives with TB for prolonged periods of time; these family dynamics need to be taken into account during contact investigation.
- Children who are close contacts of TB patients residing in congregate settings, e.g. Madrasahs, Buddhist monasteries, orphanages and other close living conditions, should also receive contact investigation.

Focus on: Treating TBI in children

As implementers consider the previous steps in planning contact investigation interventions among children, the following steps should guide child contact management. Figure 2 provided below visually emphasizes the importance of completion the TBI treatment.

Figure 2. The IPT Journey [4]

[4] *Figure 2 was developed at the Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University to aide patient and provider education.*

Identifying whether the child might have been exposed to TB involves defining the contacts that will be targeted to complete screening. Some definitions that have been used in projects include:

- **Household contacts:** all persons who share living, eating and sleeping spaces within the same building as the index patient
- **Household contacts:** as locally defined, according to customs and practices
- **Household contacts and close social contacts:** may include all persons who have been in close proximity with the index patient for at least 8 consecutive hours on a single day, or for a total of at least 15 hours per week for multiple weeks; can include contacts outside of the household (e.g. in workplaces or schools)

Once the definition of "contact" is chosen, programmes need to decide how to:

Triage the contacts

Depending on resources and national algorithms, this should include at a minimum symptom screening and clinical evaluation with CXR as clinically indicated. All contacts may either be eligible for TPT or require further evaluation for active disease, but this step is especially crucial for children.

Ruling out active TB and prescribing TPT is often perceived as the most complicated step for health care providers who work with children due to a range of factors.

CONSIDERATIONS FOR MANAGING CONTACTS WHO ARE CHILDREN

- ☐ Practitioners in programmes to find missing children with TB must establish a concrete timeline for initiating TB treatment and TPT in children, remembering that TPT is protective. Prolonged delay in child contact management programmes can allow for development of disease in the child or even death before diagnosis can occur. Children under 2 require urgent evaluation and treatment.
- ☐ There may only be a narrow window of opportunity for treating both TB and TBI during household contact investigation with the family being accessible. Once TB treatment is initiated in index adults, the sense of urgency often fades and contact with the child's caregiver might be lost.
- ☐ Use of tools, such as a child contact register, may assist in tracking whether children exposed to TB have been brought to the clinic or evaluated in the home. In a busy clinic, it is difficult to track whether an index patient has undergone child contact management screening without some sort of tracking tool in place.

DIAGNOSTIC AND TREATMENT CONSIDERATIONS

- ☐ Lack of symptoms and a normal physical examination effectively rule out active TB disease; therefore, a routine history and physical examination is essential.
- ☐ TPT is much better tolerated than TB treatment, is safe and carries lifesaving potential for many children.
- ☐ Caregivers must be educated about TPT and its lifesaving potential.

Initiate TPT and monthly support for adherence coupled with monitoring for adverse events

TPT also depends on the index TB patient's resistance pattern. If the index patient has known DS-TB (or has at least been Xpert-diagnosed with rifampicin-susceptible TB), the WHO-recommended options for treating the index patient's child contacts are detailed in Table 2.

Table 2. Recommended medicine dosages for the treatment of DS-TB infection in children (19)

Drug regimen	Child dose per kg body weight (maximum)
Isoniazid alone, daily for 6 or 9 months	10 mg (range: 7–15 mg)
Daily rifampicin alone for 3–4 months	15 mg (range: 10–20 mg)
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: 10 mg (range: 7–15 mg) Rifampicin: 15 mg (range: 10–20 mg)
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥12 years: Isoniazid: 15 mg Individuals aged 2–11 years: Isoniazid: 25 mg Rifapentine: • 10.0–14.0 kg = 300 mg • 14.1–25.0 kg = 450 mg • 25.1–32.0 kg = 600 mg

In some countries, the recommendation for a specific TPT regimen may be based on country epidemiological data rather than on individual drug susceptibility data.

For contacts of DR-TB patients, TPT depends on the resistance pattern of the index patient. In the case of isoniazid (INH)-susceptible and confirmed rifampicin-resistant patients, 6H can still be used; in the case of INH mono-resistance (susceptible to rifampicin), 4R can be used. For treatment of contacts with INH-resistant and RR-TB, randomized clinical trials are underway. In the meantime, expert consensus is to use a later-generation fluoroquinolone (levofloxacin or moxifloxacin) along with a second medicine to which the TB strain is susceptible for a duration of 6 months (22).

Contact investigation and TPT require thought and effort. However, with dedicated resources, counselling and support, and the newer regimens, TPT uptake and completion rates can increase. An ongoing project in Karachi, Pakistan has shown uptake rates of 70%, with 75% treatment completion rates.[5] Another intervention in Nghe An, Viet Nam resulted in a 22% increase in TPT initiation over a period of 2 years for eligible children (23).

[5] *Indus Hospital Network, Global Fund Implementation Project, 2017.*

M&E of process measures

M&E is critical throughout and should be paired with standardized reporting. Careful M&E is an important part of addressing TBI treatment and follow-up in children over time, enables documentation of successes, provides adverse event monitoring and facilitates additional diagnoses if issues persist.

Special considerations for TBI diagnosis

Guidelines on TPT in HIV-affected children are rapidly changing in line with new evidence and new regimens. At present, TPT options for children living with HIV are limited due to concerns regarding drug–drug interactions between rifamycin-based medicines and standard antiretroviral therapy (ART), but implementers should keep up to date with the latest evidence in order to ensure optimal treatment. At the time of publication, the following WHO recommendations apply for TPT in children living with HIV (19):

- **Infants <12 months** who are in contact with a contagious TB index patient and TB disease is ruled out should receive 6 months of isoniazid preventive therapy (IPT).

- **Children >12 months** in settings with high TB prevalence who have no TB symptoms and no TB contact should receive 6 months of IPT.
- **All children living with HIV** who have successfully completed TB treatment may receive INH for an additional 6 months.

Skin and blood tests for diagnosis of TBI

Both TST and IGRA are indirect tests to detect TBI. Although a TST is performed on the arm and an IGRA is a blood test that is sent to a laboratory, both tests operate in a similar manner: They test for the body's immune response in order to detect previous exposure to (and thus presumably infection with) the TB organism. Both tests therefore depend on an intact immune system and may produce a false-negative result in children with decreased immunity (e.g. due to HIV infection, recent fever or viral illness, malnutrition, etc.)

A **TST** is considered positive (indicating TBI) when read at 48–72 hours after application if it is

- ≥10 mm irrespective of BCG immunization; or
- ≥5 mm in children living with HIV or children who are severely malnourished (24).

Although it is a test for TBI, TST can sometimes be used as an adjunct in diagnosing TB when used in combination with a history of contact, signs and symptoms of TB, and other diagnostic tests. At the time of diagnosis, 30% of individuals with active TB will have a negative TST result; therefore, a negative TST result does not exclude TB disease. Furthermore, a positive TST result does not distinguish between TBI and active disease; therefore, when a TST is being used to find TBI, TB disease must be ruled out with a history and examination at the minimum.

TST has significant limitations. A functional cold chain is needed to preserve the test prior to use, and training is required to ensure application of the correct intradermal technique and consistent reading. The need for patients to return for reading within 48–72 hours may also be a barrier. Recently, increased international demand has also led to global stockouts.

IGRA is not widely used in children (especially in those under 2 years of age) due to limited evidence of use in high TB burden settings, lack of consensus regarding sensitivity, and uncertainty over the body's immune response at such a young age. High costs and the need for blood draws are additional barriers. The most recent WHO recommendations indicate that either IGRA or TST can be used as the first-line diagnostic test for infection, but it is not required for initiating TPT in people living with HIV or child household contacts under 5. In BCG-vaccinated children, IGRA has improved specificity over TST for the detection of TBI. However, at this time, guidance is lacking on the operationalization of broad-based IGRA in resource-constrained settings.

CRITICAL TAKEAWAY POINTS REGARDING TST AND IGRA:

- Neither TST nor IGRA differentiates between TBI and active disease.
- Negative TB or IGRA results do NOT rule out infection or disease.
- Neither test is required for TB diagnosis, and final decisions regarding TB disease and its treatment initiation should not rely on TST availability.
- It is important that diagnostic algorithms make it clear that a TB diagnosis can still be made and TPT initiated in the absence of TST or IGRA.
- When available and affordable, tests for infection (TST and IGRA) can be useful adjunct tools to help clinicians improve the confidence in the diagnosis of both TBI and active disease. This can be useful for motivating some families to adhere to treatment.

3.2 TB case finding as a part of antenatal and postnatal care

Perinatal TB is defined as TB in the mother and/or child during the time of pregnancy or between birth and 4 months. It is a high-risk condition for both the mother and the child (25).

The risks of perinatal TB transmission are higher if the mother:

- is living with HIV and is not yet on ART;
- has advanced or disseminated TB disease early in its treatment at the time of delivery;
- has "primary" TBI, pleural effusion, EPTB or disseminated TB without lung cavities, as all of these patients may have a bacillary phase in which bacilli spread to other sites such as the endometrium;
- is on TB treatment for <2 months before delivery;
- is not on TB treatment at the time of delivery or post-partum;
- is not sputum culture negative at the time of birth and contact with the neonate.

Antenatal TB

In the **antenatal period** (i.e. before the baby is born), TB may be difficult to diagnose in the mother, as TB symptoms such as loss of appetite and tiredness may overlap with those experienced during pregnancy and may be overlooked as independent symptoms. In addition, the adaptations of the mother's immune system that allow for pregnancy to occur may dampen some of the typical symptoms of TB disease, such as cough and fever. Static weight or lack of weight gain needs to be documented and monitored as a possible warning sign of TB. Any TB symptom, regardless of duration and past TB history or contact history, requires careful examination and investigation, particularly in high-burden settings. CXR with abdominal shielding may be performed at any time during pregnancy. HCWs need to be aware that the risk of exposure for the foetus during a shielded CXR is extremely low, whereas undiagnosed TB in the mother is a risk to the health of the foetus; health cadres at all levels need to be able to discuss this issue and counsel pregnant women when radiography is indicated.

All antenatal services should include an HIV counselling and screening component. Mothers living with HIV should receive i) ART, ii) TB screening and iii) TB treatment for active TB if diagnosed or TPT for 6 months if there are no other contraindications (19).

Postnatal TB

In the **postnatal period** (i.e. once the infant is born), there are two circumstances in which to consider TB in the neonate: i) the mother has TB and either has not received adequate treatment or is still smear-positive at the time of birth; or ii) the neonate is ill at birth, with TB being included as one of the possible diagnoses. Signs of neonatal TB may include low birth weight, small for gestational age, or pre-term delivery. Non-specific signs include pneumonia, no improvement on antibiotics (respiratory distress syndrome in severe cases), lymphadenopathy, abdominal distension due to ascites and/or hepato-splenomegaly. Less commonly, the neonate may present with jaundice, meningitis, seizures, and/or ear discharge. A high index of suspicion must

therefore be maintained, and TB must be considered as part of the differential diagnosis in endemic areas.

Placental examination and biopsy of necrotic areas to send for histology and TB culture may be useful if TB in the mother is known at the time of delivery and specimen collection and processing is possible.

The most recent BCG guidance from WHO also makes the following recommendations with regard to the use of the BCG vaccination in neonates (5):

- Neonates born to women of unknown HIV status should be vaccinated, as the benefits of BCG vaccination outweigh the risks.
- Neonates of unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether or not the mother is receiving ART.
- Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant has been confirmed to be immunologically stable (CD4 >25%).
- Neonates born to mothers with pulmonary TB: Asymptomatic neonates born to mothers with bacteriologically-confirmed pulmonary TB should receive TPT if TB disease has been excluded, and should be regularly followed up to verify the absence of TB. If an infant remains asymptomatic, has no immunological evidence of TB at the end of preventive treatment, and is HIV-negative, BCG vaccination should be provided using a normal infant dose.

3.3 Child TB case finding in HIV care

Paediatric HIV clinics need to integrate TB screening, diagnosis and prevention into the routine care they provide to children living with HIV. Interventions for children and adolescents living with HIV are particularly important in high TB burden settings.

For this group, TB symptom screening should be performed at every clinic visit, including visits for renewal of ART prescriptions. The following differences in children living with HIV (vs. HIV-negative children) should be considered (see Table 3):

- Clinical symptoms may be common and lack specificity for TB.
- Disease is usually paucibacillary regardless of age; the vast majority of cases are clinically diagnosed and bacteriological confirmation is challenging.
- TST >5mm is considered positive.
- Acute and chronic lung diseases other than TB are more common.
  - » There may be an overlap in radiological findings.
  - » More than one lung disease may be present at any one time, which may delay or mask response to treatment.

Table 3. Impact of HIV on recommended approach to diagnosis of TB in children (24)

Recommended approach to diagnosis of TB in children	Impact of HIV infection
Careful history, including history of TB contact	Especially important because of the poor sensitivity of TST for identifying TB infection
Careful history of symptoms consistent with TB	Lower specificity: clinical overlap between symptoms of TB and HIV
Clinical examination, including growth assesment	Lower specificity: malnutrition is common with TB or HIV
Tuberculin skin testing	Lower sensitivity: TST positivity declines with increasing immunosuppression
Bacteriological confirmation whenever possible	Important regardless of HIV status
Investigations relevant for suspected pulmonary and extrapulmonary TB	Wider range of diagnostic possibilities becasue of other HIV-related disease
Chest X-ray findings	Lower specificity: overlap with HIV-related lung disease

Please see additional recommendations on treating TBI in children living with HIV in the special "Focus on" section on page 17.

In some settings, particular attention should be paid to girls and young women who are living with HIV and might also have TB, as they comprise one of the most vulnerable groups often with the most limited access to services.

3.4 Child TB case finding in other settings

Every contact with the health system should be used as an opportunity to detect possible TB exposure and TB in children; these include

- **General paediatric outpatient clinics,** where children may present with non-specific complaints. These clinics should perform a TB screen that includes a discussion of risk factors, most importantly household exposure;
- **Immunization clinics** in facilities or communities;
- **Nutrition clinics,** where children come to be screened for nutritional deficiencies, or to receive nutritional support. These clinics are ideally situated to screen children who may be at particularly high risk for TB.
- **Private providers.** In settings where parents prefer to take their children to private providers for care rather than to public sector providers, private providers should be included in training. In a Pakistan-based private sector initiative, the use of lay people combined with mobile phone software, incentives and communication campaigns resulted in a 7-fold increase in childhood TB notifications (26). In Nepal, a successful project engaged private practitioners by covering the costs of diagnosis in private facilities under a TB REACH grant. Children were then referred to the NTP for treatment (27). (Please see field guide on private provider engagement in this series.)
- Opportunities where children may accompany their parents, e.g. at **community outreach camps**, may be useful, particularly in high-risk communities;
- **Pharmacies** may provide TB screening for children when parents present scripts for chest complaints;
- **Schools**. TB screening and referral programmes have been introduced in schools. However, experience has been varied, not consistently showing high yields compared to other settings (27,28,29). These lower yields may be because children who are able to attend school are generally healthy. In addition, given that the presentation of TB disease varies with age, screening strategies at primary school level should differ from screening at secondary school or college level. Obtaining parental consent and ensuring referral of children with possible TB are also potential obstacles that need to be carefully considered before embarking on a school-based screening campaign.

4. HOW TO DIAGNOSE TB IN CHILDREN

4. HOW TO DIAGNOSE TB IN CHILDREN

Signs and symptoms of TB in children may vary, and it is important to note that these may be non-specific, as denoted in Figure 3.

Figure 3. Signs and symptoms of TB in children

TB symptoms in children	TB signs in children
• Chronic unremitting cough ≥2 weeks • Fever • Weight loss • Drenching night sweats • Failure to thrive • Fatigue/decreased playfulness • Reduced appetite may not be reliable	• Non-painful enlarged lymph nodes that may be asymmetrical (with or without fistula formation) mostly in the cervico-facial region • Non-painful swollen joints, usually single, weight-bearing joint • Respiratory distress with/without cough • Meningitis not responding to antibiotic treatment with onset of symptoms >2 days • Pleural effusion (especially in children >3 years of age and adolescents) • Pericardial effusion • Distended abdomen with ascites • Spinal gibbus

ASSESSING TB CONTACT HISTORY*

- Is there anyone of any age on TB treatment in the house?
- Is anybody coughing and looking sick in the house?
- Did anybody die recently? If yes: was s/he coughing, having fever or night sweats, or was s/he diagnosed with TB?
- If someone has TB, when did s/he start treatment? For how long has s/he been living in the household?

  NB: A "household" can include an extended community wherein children are cared for, e.g. by grandparents or neighbours, outside of school/while parents work.

Please note, these questions are just suggestions to elicit a history. They are not intended as a "risk assessment", and any child with any suggestion of exposure must be investigated; this includes e.g. visiting child family members, children of house help.

**Please note, these questions are just suggestions to elicit a history. They are not intended as a "risk assessment", and any child with any suggestion of exposure must be investigated; this includes e.g. visiting child family members, children of house help.*

TB must be considered in any child with:

- any of the signs or symptoms described in Figure 3;
- a history of contact with a TB patient (currently or in the past 2 years).

Signs and symptoms of TB will differ according to the age of the child. Children under 5 are the age group most likely to be missed (see Figure 1).

4.1 Clinical diagnosis

Scoring systems are used to SCREEN for TB. However, validation of such systems has been difficult, and specificity and sensitivity vary widely, especially in populations with high rates of TB/HIV coinfection (30). In a South African study, the sensitivity of a scoring system decreased to 51–56% when children under 3 and HIV positive children were included (31). In some instances, not all components included in a defined scoring system are available, e.g. a scoring system lists TST but TST is not available locally. The absence of some elements in the scoring system then becomes a barrier to diagnosis for clinicians who feel unable to score the child completely. For all of these reasons, there is no paediatric scoring system that is validated or endorsed by WHO.

However, scoring systems do serve to focus attention on important issues that may be forgotten in routine care, such as TB contact history, weight monitoring and documentation of symptom persistence, as found in Bangladesh and exemplified earlier in the chapter (6). Scoring systems should therefore only be used as a TB screening tool. They may be useful in guiding front-line HCWs' initial screening and subsequent referral of children for more comprehensive evaluation. Although there are examples of scoring systems that have been better validated, such as those developed by the Brazil Ministry of Health for TB and TB/HIV coinfection (32), no scoring system serves as a reliable diagnostic tool for childhood TB.

As microbiological confirmation is rare, the diagnosis of childhood TB depends on careful consideration of a combination of history, symptoms, clinical examination and CXR, which can be augmented by other diagnostic tests if available. The certainty of diagnosis increases as more positive findings are collected. This requires clinicians with training and experience to ensure that health care providers have the confidence to either initiate TB treatment or rule out TB disease in order to commence TPT. Although the challenge of under-diagnosis is generally associated with childhood TB, the risk of over-diagnosis remains, particularly when projects are focusing specifically on childhood TB and raising awareness and suspicion around the disease. When weighing the balance between under-diagnosis and over-diagnosis, the child has less risk of an adverse outcome in systems that over-diagnose than in those that under-diagnose. Children die of untreated TB, not overtreated TB. The issue of over-diagnosis is a programmatic one and should be considered when evaluating the context of a programme. The algorithms presented in Figures 3–4 reflect those implemented by programmes in the field (33).

Figure 4. Diagnosis of children not living with HIV

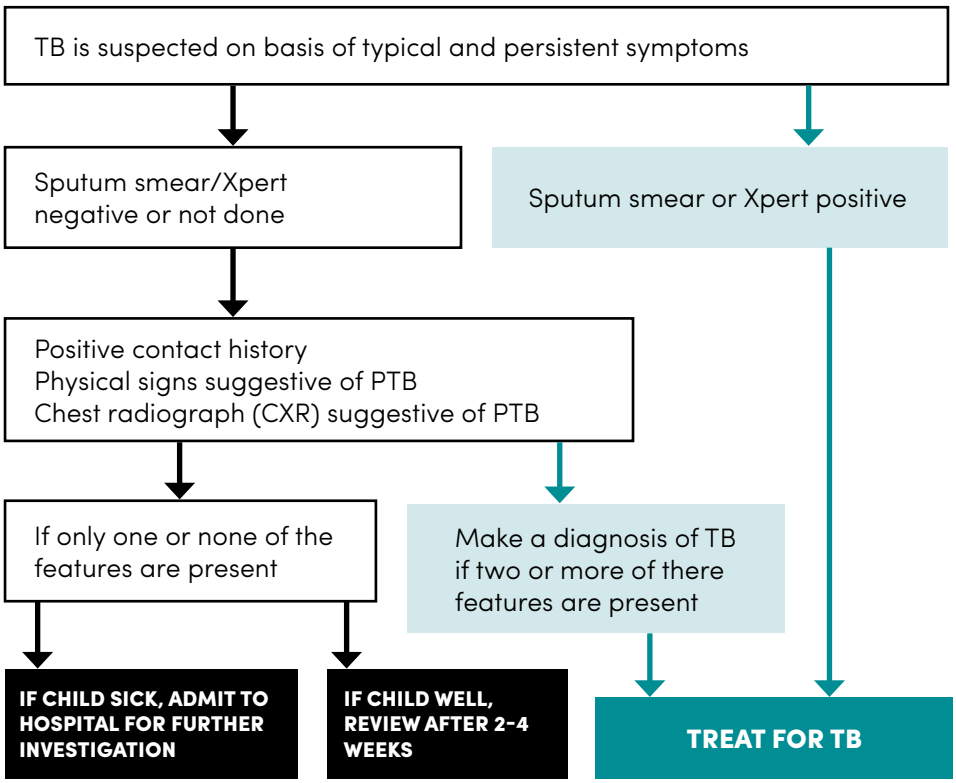
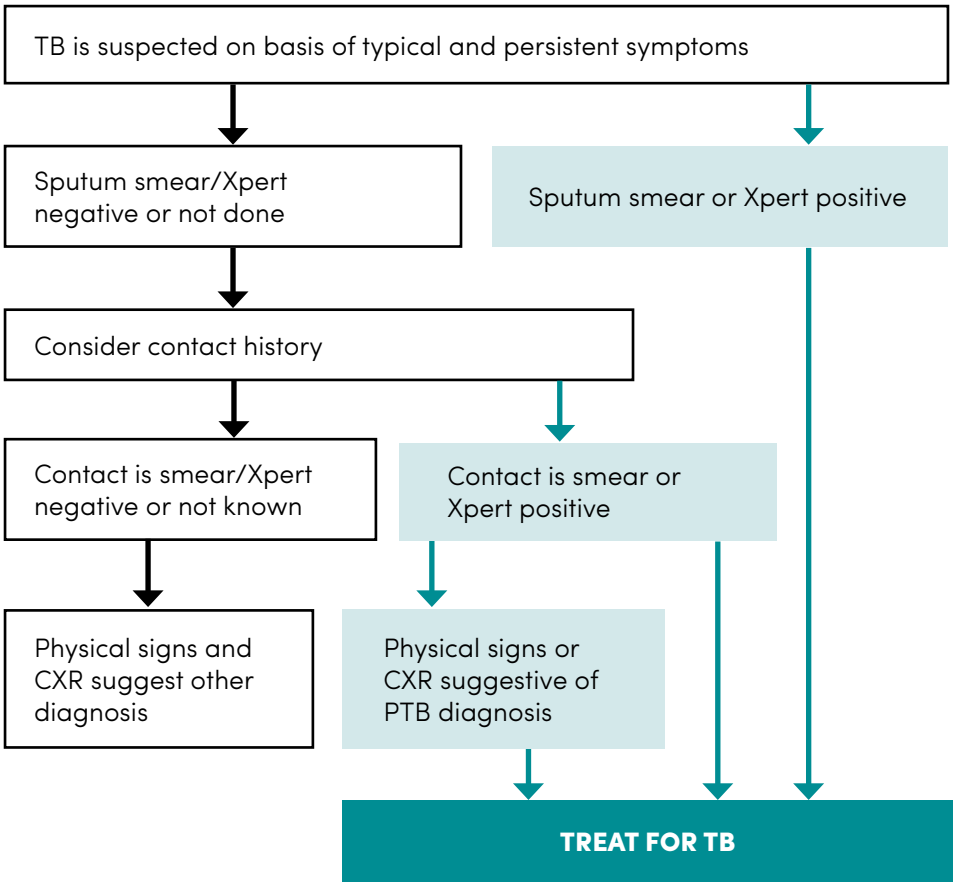


Figure 5. Diagnosis of children living with HIV



Often the only confirmation of a clinical diagnosis of TB disease is that the child's symptoms disappear and the child gains weight on appropriate TB treatment. Meanwhile, failure to improve on treatment may suggest the presence of HIV or other comorbidities, DR-TB, poor adherence, or that another diagnosis should be considered. Hence, it is imperative to closely monitor children after TB treatment is initiated.

As there are no standard objective criteria with which to validate the diagnosis of clinical TB, regular monitoring of programme performance is required, with particular emphasis on the ratio of "clinical" TB to microbiologically-proven TB. This ratio will vary with HIV prevalence and depending on which diagnostic tool is deployed. Regular clinical audits can be particularly helpful in assessing individual provider performance as described in Section 5 below.

4.2 Bacteriological confirmation

Children with TB generally become ill with lower bacillary burdens than adults and, before the age of 8, may not have the tussive (coughing) force to re-aerosolize the organism. Therefore, while bacteriological confirmation of TB is considered to be the gold standard for diagnosis in adults, it is inappropriate to hold clinicians to this standard when caring for children. Even if sputum can be obtained, it may contain few bacilli and thus be negative on smear and/or by Xpert testing. In some high TB burden countries, childhood TB notification rates are falling disproportionately compared to those of adults, suggesting that clinicians may be erroneously relying on Xpert testing rather than on clinical judgment when evaluating children for presumptive TB. Culture is the only test that can allow for full DST if positive and if available. If neither Xpert nor culture is available, sputum smear examination can still be used; however, smear is only positive in 5–10% of children with confirmed TB (34). Clinicians must be empowered to accurately and clinically diagnose TB in children (35).

Programmes must continue with training and mentoring of clinicians who care for children, and monitor changes in notification as new diagnostics and algorithms are rolled out.

When DR-TB is a consideration, such as in a contact of a DR-TB patient, the importance of trying to obtain bacteriological confirmation is heightened and every effort should be made to obtain a specimen. However, the lack of bacteriological confirmation should not stop the decision to provide treatment, and regimens can be designed based on the index patient's drug-susceptibility patterns.

The following strategies for specimen collection can assist programme implementers in obtaining specimens from children. The different types of specimen are not listed in order of recommendation. The choice of specimen will depend on multiple factors, including the age of the child, the expertise and level of training of the clinician, and the availability of laboratory services.

Respiratory specimens*

- Children over the age of 8 should be able to understand instructions for **routine expectorated sputum specimen collection**. The older they are, the more likely they will be able to produce spontaneous sputum. Studies have found that **sputum induction** is safe and effective in children of all ages (36). Emergency equipment should be available wherever sputum induction is performed.
- **Gastric aspiration (GA)** using a nasogastric feeding tube may be performed in young children (usually under the age of 6––8 years) who cannot follow directions for sputum sampling. It is traditionally performed in young hospitalized children for whom the most likely specimen to be positive is a gastric aspirate obtained in the morning before they have eaten or left their bed. Smear positivity is low due to the low bacillary load in children. Culture positivity can be influenced by specimen handling, with delay in culture negatively affecting yield. The diagnostic yield of a set of three gastric aspirates is 25–50% using TB culture. Specimens obtained via GA may be subjected to Xpert testing with yields similar to culture. This method is therefore helpful for ruling in but not ruling out TB disease in children.
- **Nasopharyngeal aspiration (NPA)** is performed by placing a small catheter through the nose to the back of the nasopharynx, rapidly instilling 3–5 cc of saline and quickly suctioning material into the attached syringe as the child coughs. NPA can be conducted in outpatient and even home settings; a second sample can be collected 4 hours after the first.

Extrapulmonary specimens

- **Lumbar punctures** are useful to distinguish between TB and bacterial and other meningitis, e.g. cryptococcal meningitis in children living with HIV. TB meningitis remains a diagnosis often missed and leads to high morbidity and mortality. Biochemistry that shows lymphocytosis, high protein, and normal or lowered glucose is suggestive of TB and fluid should be sent for Xpert testing and culture if available. However, cerebral spinal fluid (CSF) findings vary widely. Any child with meningitis who has been ill for >2 days, has a history of TB contact, is showing weight loss/failure to thrive or has new onset of neurological deficit should be started on TB treatment for meningitis. CT scan should be arranged where possible. If not available, repeat serial lumbar punctures may be helpful.
- Samples from **lymph nodes** may be obtained by fine needle aspiration and examined by microscopy, Xpert or culture. Histopathology can be consistent but not diagnostic.
- An **ascitic, pleural tap or pericardial aspirate** can also be analysed. Typical findings include straw-coloured fluid, and high protein (exudates) and white blood cells (mainly lymphocytes). Again, microscopy, Xpert and/or culture may be helpful in supporting a diagnosis, but are often not positive.
- Sending **stool samples** for Xpert testing has been shown to have similar performance to sputum/gastric aspiration in detecting TB in both children living with HIV and those who do not have HIV (37,38); however, the laboratory requirements for stool Xpert testing are very specific, and this should not be the investigation of choice for those who can produce sputum.
- **Urinary lipoarabinomannan (LAM) test** is a point-of-care test that checks for one of the components in the cell wall of TB that at times can be filtered into the urine. WHO has recommended urinary LAM for TB diagnosis in adults with advanced HIV (CD4 count <100) (39). This is the first TB diagnostic test that has demonstrated a reduction in deaths when used in clinical trials. Although not yet endorsed by WHO for children, one recent publication from Kenya demonstrated the same benefit for children presenting with advanced HIV as for adults (40).

** Please refer to WHO's 2014 guidance on the management of TB in children for a detailed description of how to perform expectoration, gastric aspiration and sputum induction (24).*

4.3 Using imaging tests to aid diagnosis in children

CXR is very useful in the diagnosis of TB in children. Availability of the chest radiograph should include the ability to assess the quality of CXR and to have the radiograph interpreted by someone with experience in doing so. Radiographic patterns in children mirror the patterns of disease that occur in that child's age range. Therefore, it is always useful to know the child's age so as to look for that pattern. In children under the age of 2, the patterns to consider are hilar adenopathy (primary TB), miliary pattern of disease, and focal consolidation with or without collapse (if primary TB is not detected). The second stage is that the enlarged lymph nodes impinge on the small central airways and cause post-obstructive pneumonia or collapse. These patterns can extend up to 5–6 years of age, although a miliary pattern becomes less common. Once the child goes through puberty, the radiographic patterns mirror those of adults with focal infiltrates or cavities or pleural effusions. Miliary disease is much less likely unless the older child is HIV positive and not on ART. The chest radiograph in a child may also be normal and the symptoms not due to TB at all, e.g. chronic cough in an untreated asthmatic. Consequently, the ability to distinguish a normal chest radiograph is also important. In EPTB, the chest radiograph (lung parenchyma) is generally normal and does not contribute to the diagnosis.

Other radiographic methods can be used to evaluate for specific forms of childhood TB. **Ultrasound** may be used to identify nodes in the neck or abdomen or to evaluate for pericardial effusions or ascites. Mediastinal lymphadenopathy has been used to assist in diagnosing TB (41). Expert opinion from high TB burden countries suggests that ultrasound may be helpful in diagnosing neonatal TB by looking for the presence of ascites in the newborn. Emerging evidence also supports use of ultrasonography in HIV-associated clinically diagnosed childhood TB (42). Bone radiographs may be helpful in delineating Pott's disease (TB of the spine), especially if the disease is advanced and has resulted in a gibbus deformity.

Computed tomography (CT) scans may also be useful, but tend to be less available, more expensive and require more expertise to read. Chest CT may be helpful in delineating mediastinal or hilar adenopathy. They may also be used to try to exclude congenital abnormalities or to evaluate post-TB complications such as bronchiectasis. CT of the brain can be used to look for tuberculomas and may also be used to delineate early TB lesions of the bones, particularly the spine. Abdominal CT may be helpful in finding intra-abdominal pathology such as nodal disease, intestinal wall thickening or ascites, although, as noted above, ultrasound is a more accessible method.

4.4 Linkage to diagnosis and treatment

Robust referral and follow-up mechanisms, including assuring appropriate drug supply, need to be in place before commencing a childhood TB screening campaign. In all circumstances, regardless of where initial screening takes place, it is imperative that both the screeners and the caregivers are clear on the nearest available centres for diagnosis. It is important to ensure that families will be able to access these services. Where transport costs may be a barrier, families may be provided with transport support, e.g. vouchers. The screening programme should ensure that the child with possible TB reaches the referral centre and commences TB treatment or TPT where appropriate. Information about the cost of care also needs to be understood by the programme. In most countries, TB treatment is free in the public sector, whereas the diagnostic testing required, particularly for children, may not be. In designing screening programmes, it is critical to pay attention to these costs and advocate for the removal of these financial barriers.

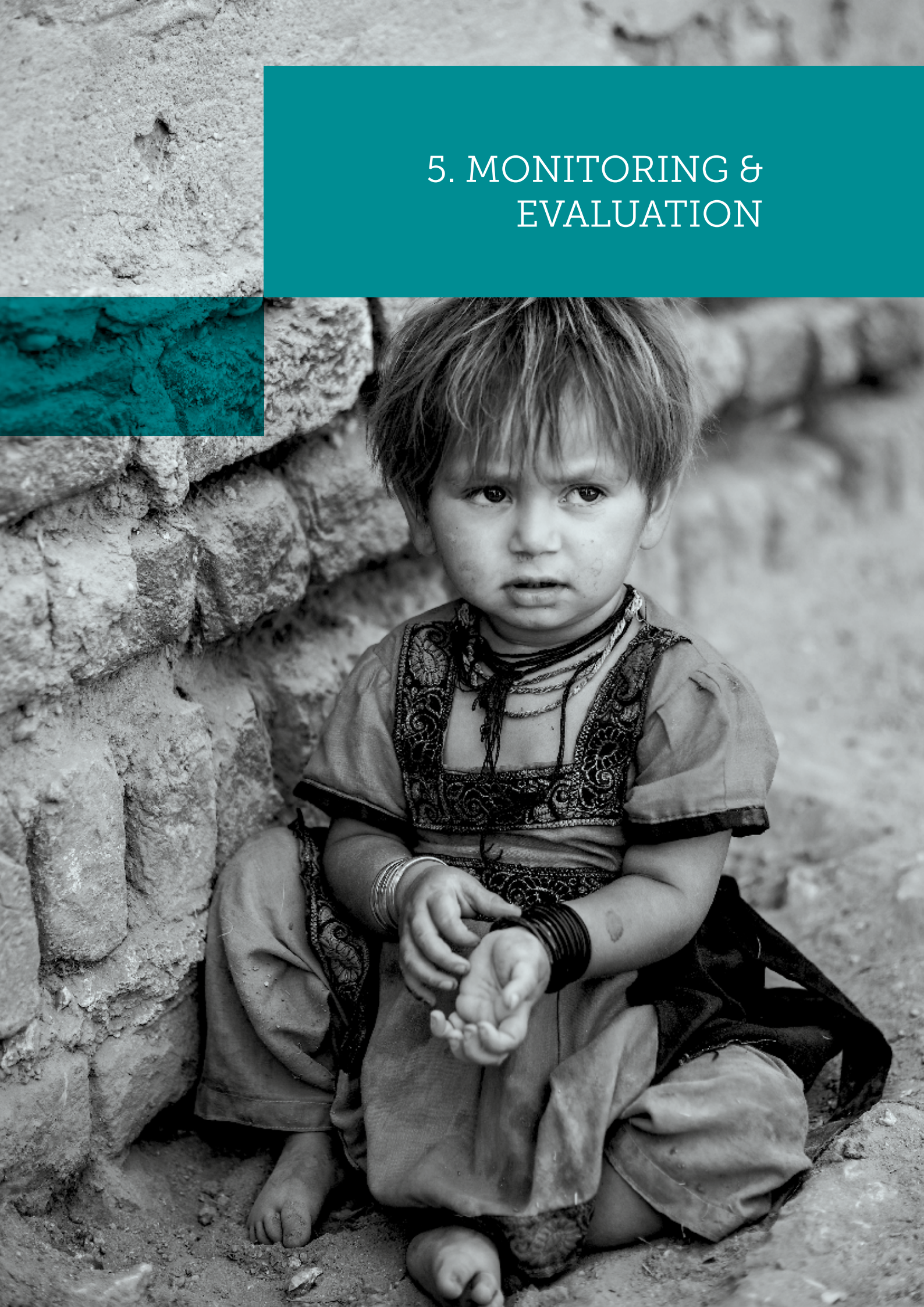
CHWs must ensure that children and their caregivers understand the importance of adhering to daily TB treatment and completing the course for both treatment and TPT. To facilitate treatment adherence and completion, national programmes should implement the new child-friendly dispersible fixed-dose combinations (FDCs) for children weighing less than 25kg. Problems with the previous formulations, such as suboptimally dosed FDCs or adult formulations that had to be crushed, included under- or over-dosing. The new FDCs are water-dispersible with a more pleasant taste and are likely to lead to improved adherence and treatment completion. Forecasting and stock management are also easier, as there are fewer tablets. WHO and UNICEF have recently recommended the use of the new continuation-phase child-friendly FDCs to improve adherence to TPT (43).

Table 4. Child-friendly FDCs: Dosage based on children weighing <25kg* (43)

	Numbers of tablets	
Weight band	**Intensive phase: RHZ 75/50/150[a]**	**Continuation phase: RH 75/50**
4–7 kg	1	1
8–11 kg	2	2
12–15 kg	3	3
16–24 kg	4	4
≥25 kg	Adult dosage recommended	Adult dosage recommended

**It is important to note that tablets are scored so that half a tablet may be used to increase dosage accuracy.*
[a]Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.

5. MONITORING & EVALUATION



TB programmes usually define "children" as people under 15 years of age, further disaggregated into two groups: 0–4 years and 5–14 years (1). All data points should be disaggregated by age and gender. At minimum, age should be disaggregated by 0–4 years and 5–14 years to meet WHO and international reporting standards. However, further breakdown could be considered, depending on the programme and beneficiaries. For example:

- Neonatal TB: <28 days
- 29 days–1 year
- 2–4 years
- 5–10 years
- 11–14 years

Given the increasing evidence of TB in adolescents and young adults (9), the size of this age group globally, and the fact that 90% of this population lives in low-income countries (44), programmes may consider further disaggregating "adult" data as

- 15–18
- 19–24
- >25 years

This disaggregation may also be useful as interest grows in vaccines for this age group (45). The age distribution may differ in children and adolescents in terms of gender, as discussed in Section 2.2. Monitoring this trend will be important for programme evaluation and for ensuring that appropriate interventions are deployed.

Clinical audits are essential for monitoring a childhood TB programme. They are particularly important because not all patients will have microbiological confirmation at the start of treatment, making it difficult to have "empiric" case definitions and challenging to monitor progress on treatment. Growth charts are particularly helpful in the follow-up of paediatric TB and are easy to use. The ultimate measure of treatment success is "disease-free 1 year after treatment conclusion" (46). This measure is especially useful when bacteriological confirmation of cure is not obtained – as is often the case in childhood TB – and should be considered as part of routine programme follow-up.

Innovative monitoring methods may be deployed, as demonstrated by a TB REACH project in South Kivu, a poorly resourced province in DRC, where it was shown that a lack of clinical skills resulted in under- detection of childhood TB (11).

5.1 Measuring success

The ultimate success of programmes aiming to find children with TB should be assessed in terms of the number of children who commence TB treatment (either for TB disease or TBI), achieve treatment completion and are disease free. In most programmes, the expected target for notifications should be for 10–13% of case notifications to occur in the paediatric age group. Local epidemiology is also helpful in guiding programme evaluation. In a TB REACH project in western Kenya, it was found that for every two TB index cases, there was one child under 5 identified in contact interviews as living within the household. Using estimates such as these provides some indication as to how well a programme is finding children with TB/TBI.

National notifications may be influenced by a variety of factors, including different recording and reporting practices and the introduction of new systems, and thus

may be challenging to monitor and evaluate. For these reasons, collecting and reporting data at the facility level and then collating them at each subsequent level will provide more granular information and allow for detailed interrogation. For example, a study in Java showed that only 1.6% of child TB patients diagnosed in hospital were reported to the NTP (47). Training and supporting facility staff to review and use their own data is essential to assist in performance management and to promote quality improvement. TB Data for Action, developed by the Zimbabwe NTP and recently adopted in Kenya, is an example of a training and supervision programme empowering facilities to use their own data to discover and correct gaps in the TB care cascade. Where specific case-finding projects are introduced, it is important to assess the additional yield of the project, that is, the number of children found by the project (with active disease and with TBI placed on TPT) who would not otherwise have been detected. While assessing additional yield can be difficult, pre- and post-project statistics can be compared in intervention versus control areas.

5.2 Process indicators

Accurate recording, regular evaluation and rapid course correction of process indicators can significantly increase the efficacy of an intervention and optimize resources. The programme can use two possible approaches to collecting data on these cascades: collecting data on groups of individuals moving through the cascade (individual-level cohort data), or collecting the number of people who complete each cascade step during a certain time period (aggregate data). Individual-level cohort data are more robust. To collect individual-level data, it is necessary to have data systems that allow for the tracking of individuals over time. Both registers and electronic health records can be used to track the patient. Records held by patients themselves (e.g. paper treatment cards) or mobile apps that do the same thing are other options. If it is not possible to track individuals through all the steps of a cascade, programmes can use aggregate data to fill in the missing steps. If large numbers of patients are assessed, then the indicators calculated using aggregate cross-sectional data can be comparable to what would be found using individual-level data.

It is important to note that not only children who are bacteriologically-confirmed with TB, but also children with presumptive TB (all children treated for TB), those with EPTB, and those who die in hospital with TB should be recorded and reported.

Process indicators for a childhood TB programme include:

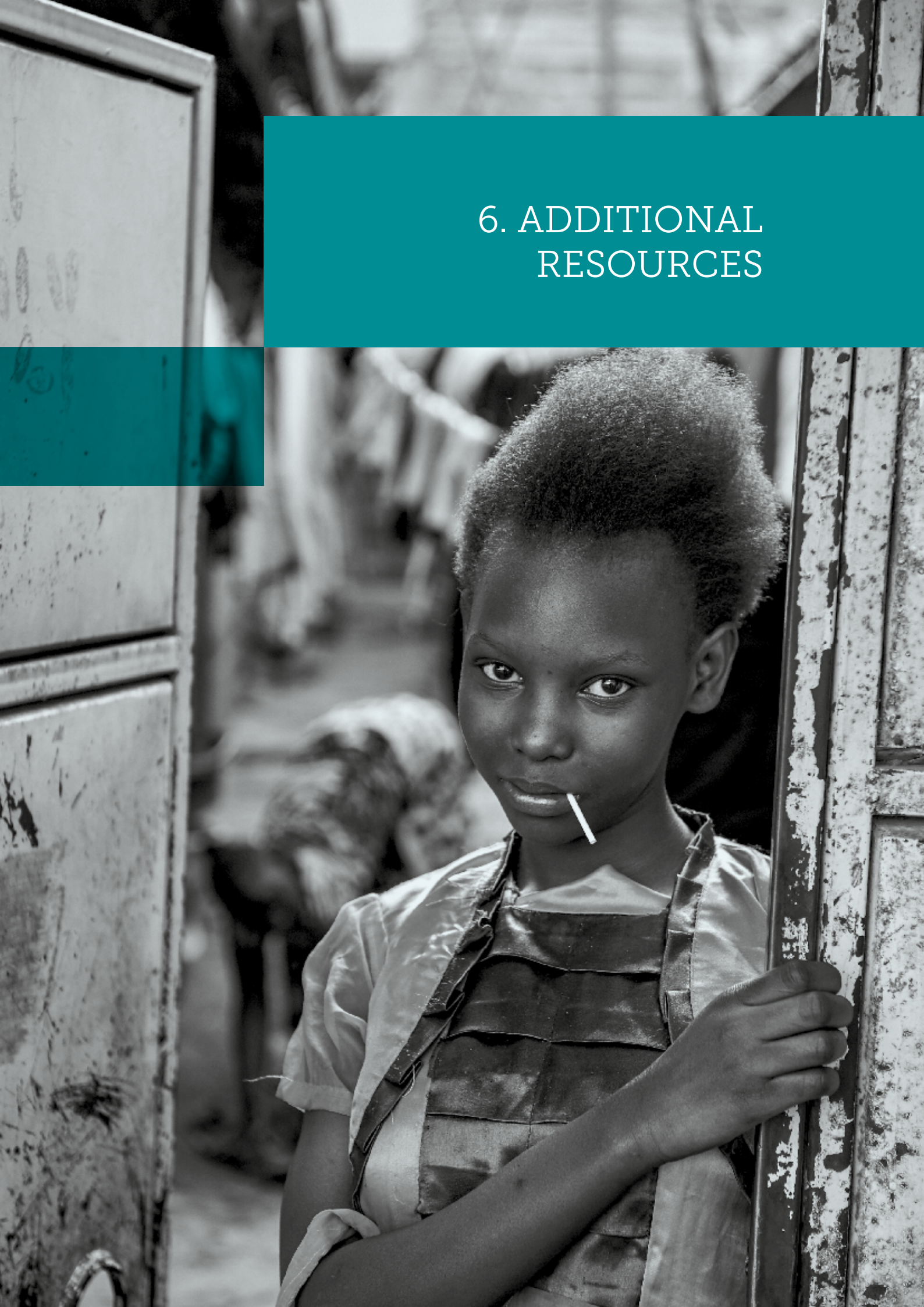
- Number of children screened
  - » Site
  - » Staff cadre
  - » Initial screening tool
- Number of children with presumptive TB
- Number of children with diagnostic tests performed (by different diagnostic test)
- Number of diagnostic test results
  - » This ensures tests are done and results are received (e.g. sputum may be inadequate/contaminated or CXR may be done but not read)
- Number of children diagnosed with TB
  - » How the final decision was made (e.g. microbiological, CXR, clinical examination, or a combination)
- Number of children diagnosed with rifampicin resistance
- Number of patients diagnosed who initiate treatment
  - » Include linkage to treatment for DR-TB as appropriate

TB contact investigation and preventive treatment are critical components in ending the childhood TB epidemic, and indicators must be collected and monitored. This M&E framework mentions sets of process indicators corresponding to contact investigation and prevention. Each is presented as a "cascade" of steps, with indicators measuring the proportion of people moving from one step to the next. People being treated for TB disease have contacts that should be screened for TB disease, and those free from TB disease should receive TPT to treat TBI. The process of evaluating these contacts and giving them TPT can be monitored using the following indicators:

- Number of TB index patients
  - » Number of contacts identified
    - Contacts evaluated
      - » Diagnosed with TB or
      - » No TB but not eligible for TPT or
      - » Eligible for TPT
        - Prescribed TPT (describe regimen)
          - » Started TPT
            - Completed TPT
            - Developed TB disease
            - TPT course not completed
              - » Reasons for non-completion, e.g. side effects, non-adherence, doctor stopped, stockouts

Additional considerations with respect to M&E include, for example, the importance of having standardized "case" definitions. Children should represent at least 10–13% of all TB cases and may represent an even higher proportion in some countries. It is important to note that children may be diagnosed in "general" hospital settings, and it is important to ensure that these children are linked to the TB system. However, according to WHO, in 2016 only 6.9% of the total TB notifications were children, reflecting considerable under-diagnosis and likely also under-reporting (1). In 2010, Bhutan reported 14% childhood TB (50% EPTB), indicating a high level of TB awareness, childhood TB screening and integration of TB diagnosis into the public health system (48).

6. ADDITIONAL RESOURCES



- WHO. Guidance for national programmes on the management of TB in children, 2nd edition (2014) (24)
- WHO. Childhood TB training toolkit (2014)
- IUATLD (The Union). The Union's desk guide for diagnosis and management of TB in children (2016) (33)
- WHO, UNICEF, CDC, The Union, Stop TB Partnership, USAID. Roadmap for child tuberculosis (2013)
- The Union, WHO. Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in children living with HIV: Recommendations for a public health approach (2010)
- Online training course on child TB for health workers (2015): The Union's six-module curriculum covers how to diagnose, treat and prevent childhood TB, including how to perform contact screening. The modules are interactive and ask participants to make decisions about patient care in various settings through case examples. The self-paced course, which takes six to eight hours to complete, is designed for HCWs at the secondary and primary level of the health care system and is available in English, French and Spanish. The content is based on WHO's 2014 Guidance for national tuberculosis programmes on the management of tuberculosis in children, as well as The Union's desk guide for diagnosis and management of TB in children, and focuses on the clinical management of childhood TB. One full module is dedicated to TB prevention, focusing on household contact screening and provision of preventive therapy.
- TB CARE II, The Sentinel Project. Management of MDR-TB in children: a field guide (2012)
- MAP-IT web-based tool: "The model for assessment of pediatric interventions in TB"
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