OUT OF THE DARK:

MEETING THE NEEDS OF CHILDREN WITH TB

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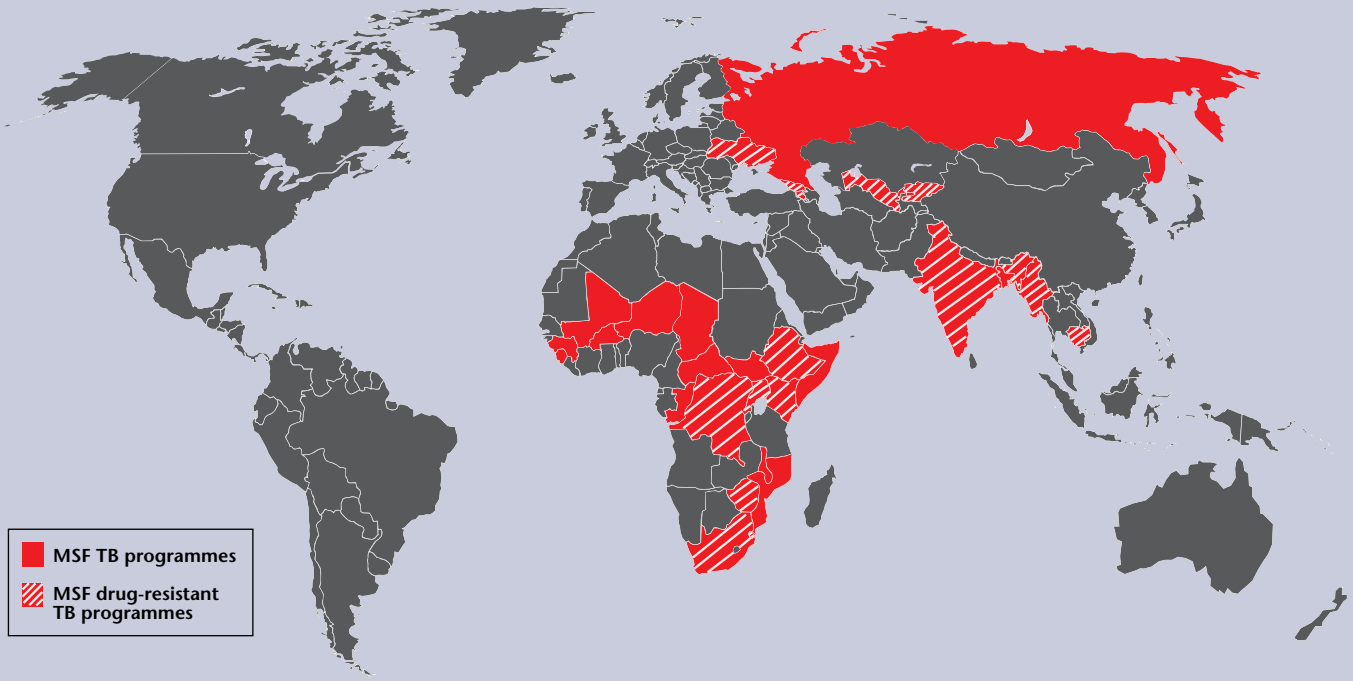
MSF TB TREATMENT PROGRAMMES



MSF provided TB treatment to 30,000 people in 29 countries in 2010. That included 3,300 children under the age of 15 and 1,000 people receiving treatment for drug-resistant TB.

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Though curable, tuberculosis (TB) kills at least 130,000 children each year,[1] making it one of the top ten causes of death in children. There are also rising numbers of children who are infected with drug-resistant forms of TB which require complex treatment.

Paediatric TB is a neglected disease. Insufficient research and development attention has led to a lack of diagnostic methods adapted for children's needs and a lack of appropriate drug formulations for children. This, in turn, has contributed to a situation in which TB programmes often under-diagnose, under-treat, or omit altogether children with TB.

Despite the difficulties in diagnosing and treating children with TB, children can be cured, and it is imperative to make the best use of the tools that are available today to ensure that children with TB do not remain in the dark. This report will outline the current state of paediatric TB care, looking at current practices, new developments and research needs – in paediatric TB diagnosis, treatment and prevention. It intends to act as a support to treatment programmes for implementation of the best standard of care currently available to children with TB, and to raise awareness of the need to continue to push for improvements in the management of childhood TB.

Paediatric TB treatment has also been neglected as a strategic priority. Until recently, the World Health Organization's (WHO) Global Tuberculosis Control strategy has focused on identifying and managing the most infective causes of TB (primarily smear-positive pulmonary TB). However, children with TB, especially those under ten years of age, tend to have a form of the disease that is difficult to diagnose, as it reveals very few bacteria in the lungs (paucibacillary smear-negative disease). Because paediatric TB is an indicator for the current control of TB in the general population, and also acts as a future reservoir for TB disease, any successful TB control programme should include a paediatric focus.

Children with TB differ from adults in their disease progression in ways that have important implications for the prevention, diagnosis and treatment of TB. Young age, and co-morbidities such as malnutrition and HIV, all further worsen the mortality and morbidity in children with TB. However, when started promptly, the outcome of TB treatment in children is generally good, even in those that are young and immuno-compromised. Some studies suggest that compared to adults, children appear to experience fewer adverse events associated with use of the recommended treatment regimens.[2]

While critical gaps in research and development for paediatric TB remain and must be filled, there is much that can be done today to reduce the number of children dying from the disease each year.

Diagnosis

"It's really difficult sometimes for one person to make a decision where the case is not straightforward. So you always consult each other, you share. You can go to the next room, present the case, show the person the x-ray. Then you can have a small discussion in relation to the x-ray and the previous history. Then you can take a collective decision, it's not just one person who decides who is to start in difficult cases. So I think that has really assisted us, sharing information and consulting each other when we get stuck."

Hussain Kerrow, MSF Clinical Officer, Kenya

Outdated tools and enormous practical challenges make the diagnosis of paediatric TB very difficult, especially in resource-poor settings. Poor diagnostic capacity in many parts of the world means that many children die without ever being diagnosed or treated; others are diagnosed only long after they have developed active disease, making treatment more complicated and less likely to succeed.

While most of these problems also apply to TB in adults, diagnosing TB in children is far more problematic.

The most commonly used TB test is sputum smear microscopy to confirm the presence of TB mycobacteria. A positive culture is however considered the "gold standard" definitive result, although the technique can take weeks or months to give results. But most children, especially the youngest ones, cannot produce enough sputum for these tests. And even when they can, sputum-based tests do not detect paucibacillary or extrapulmonary TB that occurs more frequently in children. Only 15% of paediatric TB cases are sputum smear-positive, and only 30 to 40% yield mycobacteria-positive cultures;[3] for children who are co-infected with HIV, the figures are even lower.

Other diagnostic methods, such as chest x-ray and tuberculin skin testing, do not involve detecting the presence of TB bacteria directly, but each of these non-microbiological methods also has major limitations.

More research is needed for a simple diagnostic tool that can give on-the-spot results. Yet despite these challenges, physicians usually can make a TB diagnosis, based on the cumulative evidence from several approaches along with clinical findings, with enough confidence to justify initiating treatment. The following section describes the main tools available for diagnosing paediatric TB and summarises how to optimise their use in deciding on whether to start treatment.

CURRENT PRACTICES

Current WHO guidelines[4] focus on gathering evidence from the following range of approaches:

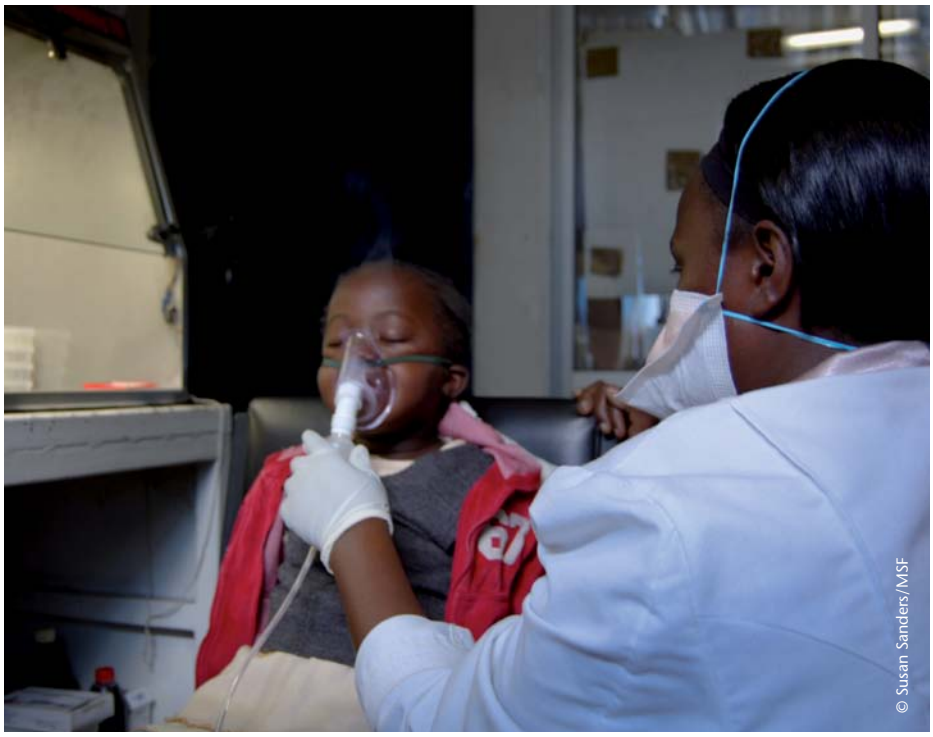
Clinical	Careful history (including TB contact; symptoms consistent with TB) Physical examination (including growth assessment) HIV testing (in high HIV prevalence areas)
Non-microbiological	Tuberculin skin testing (TST) Other investigations relevant for pulmonary or extrapulmonary TB (e.g., x-rays)
Microbiological	Bacteriological confirmation whenever possible

CLINICAL APPROACHES

In the absence of a definitive "gold standard" test, clinical findings and judgement are especially important in diagnosing TB.

The key components to consider are:

- Careful history, including history of TB contact and symptoms consistent with TB. Contact history is particularly important, especially in very young children with suspected TB.
- Clinical examination for symptoms consistent with suspected pulmonary or extrapulmonary TB, plus growth assessment. Beyond looking for classical symptoms of TB in adults, extra vigilance is essential since children are more likely than adults to present with atypical symptoms. In addition, symptoms for extrapulmonary TB vary widely, depending on where in the body the infection is located.
- HIV testing (in high prevalence areas). Children with HIV are more susceptible to TB, at increased risk of disease progression, but are more likely to have smear-negative disease.



Charity Achieng lives with her mother in Mathare, a slum on the edges of Kenya's capital, Nairobi. Charity is suspected of having TB but is finding it hard to cough up the necessary sputum sample from deep inside her chest required to attempt a diagnosis through miscroscopy. For that reason, Charity is having an induced sputum test which consists of breathing a saltwater mist through a mask which makes her cough deeply from her lungs and will hopefully help her produce an adequate sample for analysis.

NON-MICROBIOLOGICAL APPROACHES

- **A chest x-ray (CXR)** can be useful for diagnosing TB, but presents several challenges. An x-ray machine is not always readily available, especially in resource-limited settings. Obtaining quality films is difficult, and trained personnel are needed to interpret the x-ray appropriately and to ensure maintenance and safety of the machine. If these difficulties can be addressed, possibly by using novel techniques such as teleradiology for interpretation, then CXR is a helpful addition to the diagnostic toolkit.
- **Tuberculin skin testing (TST)**. Although a positive TST has been considered as evidence supporting a TB diagnosis, the utility of TST in endemic countries is severely limited by some shortcomings. Chief among these: an inability to distinguish between latent and active TB, high proportions of both false negative and false positive results, and particular unreliability in HIV-infected and malnourished children.
- **Other tests**. Diagnostic tests based on detection of interferon-gamma production (interferon-gamma release assays, IGRA's) have not been shown to have major advantages over TST in terms of sensitivity and specificity.[5]

  Thus, while these tests can play a role in diagnosing latent TB in high-income, non-endemic countries, their utility in diagnosing active TB in children in high-burden countries is very limited. WHO advises against the use of IGRA in middle- and low-income countries.[6] This is the second negative policy issued by WHO this year following strong recommendation against serological tests for diagnosis of active TB.[8]
- **"Score charts"** that weigh the findings from these different diagnostic measures have long been used in various contexts as aids in reaching a final diagnosis; more than 16 such tools have been developed. However, their performance varies widely across different settings and is poorest in children with pulmonary TB and those who are HIV-infected.[9]

MICROBIOLOGICAL CONFIRMATION

Although obtaining mycobacteriological confirmation of TB in children poses significant challenges, it should nevertheless be attempted whenever and wherever possible, and especially in suspected DR-TB cases, to ensure that a decision to initiate DR-TB treatment is correct. However, initiation of treatment should not be delayed for specimen collection if there is clinical suspicion of TB.

One major constraint in obtaining bacterial confirmation is that most young children cannot produce adequate sputum – instead, they produce only saliva. Several procedures are currently being used or studied to improve the collection of sputum from children or to test the usefulness of alternative non-respiratory specimens (see Table 1) so that more paediatric TB cases can be confirmed microbiologically.

"If we are lucky enough to be able to access better facilities, for instance in a local hospital, there are a few techniques we can use to get hold of a sputum sample. But access to even these less than perfect procedures is a luxury for most of our patients who don't live near a hospital. So most of the time you make a decision based on your clinical observation – should I or should I not treat this child for TB. And making that decision you're talking about the life of a child, so it is not something to be taken lightly."

Dr Bern-Thomas Nyang'wa, MSF TB Implementer

TABLE 1: OVERVIEW OF SPECIMEN COLLECTION METHODS[10]

SPECIMEN COLLECTION METHOD	DESCRIPTION & CHARACTERISTICS
Gastric aspiration[42]	Tube inserted into stomach to extract gastric fluids which may contain swallowed sputum • Difficult, invasive procedure • Requires hospitalisation or repeated visits on three consecutive days • Must be performed by trained nurses • Highly uncomfortable for children; poorly accepted
Lymph node fine needle aspiration	• Minimally invasive • Can be safely performed on outpatient basis[43] • Yields specimens suitable for smear microscopy, culture and drug-sensitivity testing • Yield for bacteriological culture (to confirm TB diagnosis) might be higher than with sputum • Potentially under-utilised diagnostic option
Sputum induction[44]	Child breathes into nebulizer containing gases which irritate lungs & induce coughing • Can be performed on most children. Requires some basic equipment and infection control measures • Requires trained nurses. Highly operator dependent • One sputum induction provides same yield of bacteriological confirmation as three gastric aspirations[45] in hospitalised children; incremental yield with a second sputum induction • Useful in hospital settings; limited data currently available on the use of this method in primary healthcare facilities
String test	Child swallows gelatin capsule containing coiled nylon string, capsule recovered later by pulling string • Most appropriate for older children, who tolerate procedure well[46] • Yield of bacteriological confirmation similar to sputum induction in HIV-infected adult population[47] • Limited by cost, lack of widespread availability • Younger children have difficulty swallowing the capsule • Not yet widely used; additional studies needed[48]
Nasopharyngeal aspiration	• Relatively non-invasive • Variable performance, but some studies suggest similar yield to culture of sputum induction[49,50] • Not yet widely used; more data needed[51,52] to assess usefulness of samples obtained
Stool	• Easily obtained; can be done at primary health facilities • Contains TB bacteria from swallowed secretions • Specimen requires stringent decontamination procedures, thus culture from stool specimens has proven insensitive so far • More studies needed to assess usefulness, feasibility

NEW DEVELOPMENTS

The most significant recent advance in TB diagnosis is Xpert MTB/RIF, an automated system that identifies TB bacteria (by detecting its DNA) from sputum samples in less than two hours and also detects mutations which confer resistance to rifampicin, a key TB drug. Although it uses expensive machinery and requires a laboratory infrastructure with trained personnel, Xpert MTB/RIF could potentially mean major increases in diagnostic capacity where implemented.

A first evaluation of this technology for diagnosing paediatric pulmonary TB was recently published.[11] It found that Xpert MTB/RIF has a higher detection rate than smear microscopy; however, sensitivity for smear-negative TB was lower on samples from children compared with those from adults.

Furthermore, Xpert MTB/RIF was less sensitive than standard culture methods in diagnosing childhood TB, although much faster (one day vs 12 days). While this shows that Xpert MTB/RIF can support much more rapid diagnosis of paediatric TB, it also reveals diagnostic challenges and limitations that still need to be overcome – not least a reliance on sputum samples, which limit its utility to a minority of paediatric cases.

In general though, emerging methods and technologies for diagnosing TB are rarely evaluated in samples from children, leading to a paucity of information on the performance of new tests in paediatric patient populations. For example, of five promising new methods – microscopic-observation drug-susceptibility assay (MODS), nitrate reductase assay (NRA), colorimetric redox indicator assay (CRI), line-probe assay (LPA) and loop-mediated isothermal amplification (LAMP) – studies are either limited or completely lacking in children. Evidence for the performance of these methods on extra- pulmonary samples is even weaker.[12]

The ideal TB diagnostic test would be one that works with specimens other than sputum, so that microbiological confirmation of paediatric TB would no longer be limited by a child's inability to cough up sputum. One exciting approach involves attempts to diagnose TB in urine, by detecting the presence of a fatty molecule (lipoarabinomannan, or LAM) found in the cell wall of TB bacteria and secreted into the urine by active TB. Current work is focused on evaluating this urinary test for diagnosing TB in HIV-infected adults.[13] Such a test is potentially also ideal for children, since urine is a plentiful, easily collectable sample. However, to our knowledge there are no studies assessing the performance of this test in paediatric populations.

Several obstacles have hindered such studies. One is the lack of a gold standard test to use in evaluating the performance of new tests in children; another is the lack of standardisation in study design. However, consensus on the methodological approaches to follow for evaluating new diagnostic tests in children has recently been reached,[14] eliminating a critical barrier in paediatric TB diagnostics research and development. These new approaches should be implemented rapidly so that the rate of progress can be accelerated.

TREATMENT

Treatment

Children diagnosed with TB in a timely manner and started on appropriate treatment usually have successful treatment outcomes–anti-TB drugs are generally better tolerated in children than in adults.[2]

But achieving treatment success in children relies not only on prompt diagnosis and treatment initiation, but also on the administering of appropriate treatment regimens, accurate dosing of the child based on its weight, and support for treatment adherence. Making sure children's caregivers receive appropriate education, counselling and support is therefore critical. Securing a continuous supply of quality-assured drugs is an additional prerequisite for successful paediatric TB treatment.

Despite common practice in a number of countries, there is no evidence that routine hospitalisation of children with TB results in better outcomes and it should be required for specific circumstances only. Policies of routine, prolonged hospitalisation that persist in many countries need to be urgently reviewed in light not only of their potentially negative psychosocial impact on individual children and their families, but also in consideration of the risk of hospital-acquired transmission.

An important development for paediatric TB treatment has been the review of anti-TB drug dosages for children with drug-susceptible TB. In 2009, the World Health Organization released revised dosage guidelines for TB in children that increased the dosages of each of the four drugs used in first-line TB treatment. While it is welcome that the guidelines have been changed to reflect optimal doses for children, the formulations available on the market today are not tailored to deliver the new dosages. And a slow response on the part of WHO to release recommended drug strengths and the composition of new fixed-dose combination drugs (FDC) has meant that, despite two years having passed since new dosage guidelines were issued, no new FDC drugs for children have been developed to correspond to the new doses. Until that happens, treatment providers are struggling to provide children the new doses through complex interim dosing recommendations *(see Box on page 11)*.

Children co-infected with HIV, or with drug-resistant TB are additionally problematic in relation to treatment, with limited adapted paediatric formulations available to facilitate simple management. There are several guidelines available which provide dosages for children to treat DR-TB, however for several drugs, conflicting dosages are published. The majority of drugs used for treatment of DR-TB are old, and no pharmacokinetic data is available for use in children. Therefore, dosages available today are based on extrapolation of adult dosages, expert opinion, and experience.

And while there are several promising new drugs for TB under development, only one drug in the pipeline is being studied in children. Children should systematically be included in new drug trials, so they can also benefit from advances in research and development.

While there are several promising new drugs for TB under development, only one drug in the pipeline is being studied in children.

"TB medication in general is safe. It's difficult to take so many many tablets, but in general the side effects are quite few… However we have to be careful, particularly in children to make sure that we dose them correctly and that we monitor them very closely for side effects. Because obviously children can't tell us, like an adult can tell us, what's wrong with them or if they're in pain or if they're not feeling well."

Dr Marianne Gale, MSF Medical Advisor for Paediatric TB & HIV

CURRENT PRACTICES

TREATMENT REGIMENS

The treatment of drug-sensitive TB in children follows the same principles as that of adults. Four drugs – isoniazid, rifampicin, pyrazinamide and ethambutol – are taken for a two-month intensive phase, followed by a four-month continuation phase of rifampicin and isoniazid.

At the end of 2010, WHO released new guidelines for the management of childhood TB. These guidelines clarified the role of ethambutol in childhood TB which for several years had been questioned due to its toxicity profile, and also advised against the use of streptomycin in children.

Ethambutol is a drug which has been shown to be safe in children of all ages when dosed within the recommended range (15-25mg per kg). The risk of optic neuritis (inflammation of the optic nerve) with this dosage is extremely low.[15] WHO recommends the inclusion of ethambutol in the intensive phase of treatment in children, in any region where there is high HIV prevalence or isoniazid resistance. Furthermore, it should be given to children who have extensive or severe disease, including smear-positive TB.[16]

Streptomycin has long been used to treat TB re-treatment cases in children, as well as TB meningitis. However, there is little evidence of its added value in treatment regimens, while its adverse effects on hearing (which can be catastrophic, especially for children) and the distress resulting from giving children a daily injection are well known. WHO no longer advises the use of streptomycin in any first-line treatment regimen for children.[17] Children with TB meningitis, as well as children with osteo-articular TB (TB of the joints and bones), should now be treated with a twelve-month regimen (a two-month intensive phase of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a ten-month continuation phase of rifampicin and isoniazid).

Cases of apparent treatment failure in children in settings of low DR-TB prevalence are most often due either to poor adherence, incorrect dosing, or simply a wrong diagnosis of TB. In such cases, these factors should be looked for and corrected if found.

If genuine treatment failure is suspected, every attempt must be made to obtain appropriate specimens for culture and drug-sensitivity testing (DST), or where this is not possible, a decision about what treatment to give can be made on the basis of treatment regimen of the source case, and the likelihood of the case being DR-TB.

NEW TB DRUG DOSAGES FOR CHILDREN

In 2009, the WHO released revised dosages for children of the first-line drugs isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E).[18] Unlike the old dosages, the current recommendations take into account the physiological differences between adults and children, with larger doses required to achieve optimal serum concentrations.

This is a welcome advance. However, the change in the guidelines means that the currently available FDCs are not tailored to deliver the new doses. In parallel to the release of the new doses, WHO issued interim guidance to help treatment providers to prescribe the existing drug formulations to attain the new doses.[19]

Unfortunately, this is complex and presents many operational challenges. It has complicated the prescribing of TB treatment in children, with several different combinations of multiple tablets needed to deliver the new target doses (using the current FDC in addition to single drug formulations). This situation is not ideal, and vigilance is required in prescribing and dispensing to minimise the risk of drug errors. The use of multiple formulations adds additional pressure to the drug supply channel to ensure all formulations are available at the point of dispensing.

The complexity of the interim dosing guidelines has delayed the implementation of new dosing guidelines in paediatric TB programmes. While complex, this can be overcome with adequate training and supervision, and every effort should be made to ensure the new guidelines are implemented so that children are treated in line with current evidence.

Meanwhile, over two years since the paediatric TB dosages were revised, WHO has still not clearly indicated to drug manufacturers what the composition of a new FDC – that corresponds to the new dosages – should be. Drug manufacturers have therefore understandably been unwilling to invest in the development of a new FDC for children. It is estimated to take three to five years for a new quality-assured FDC to be available, and this timeline will only begin with clear advice from WHO about the definitive composition of the required FDC. Urgent action is needed.

THE HARDEST CASES

Children who are co-infected with HIV or are infected with drug-resistant strains of TB have additional challenges in relation to treatment. There are limited formulations adapted for children. Nevertheless, successful treatment in these groups is possible.

CHILDREN WITH TB/HIV CO-INFECTION

TB is a major cause of illness and death in children living with HIV – almost half of all paediatric TB cases are in children who are co-infected with HIV.[20] Due to particular difficulties in diagnosing TB in HIV-positive children, many die undiagnosed and untreated. Even when these children are diagnosed, they are still at great risk of death, particularly during the first two months of treatment.[21] Immune suppression, other co-morbidities, poor adherence that may result from the high pill burden, and risk of immune reconstitution inflammatory syndrome can all contribute to poorer TB treatment outcomes in HIV-positive children. Intermittent TB regimens are no longer recommended for the treatment of children in HIV-endemic settings.[22]

Randomised controlled trials conducted in adults infected with both TB and HIV show a clear benefit in early antiretroviral treatment (ART) initiation, within eight weeks of the start of TB treatment, compared with delayed initiation.[23, 24, 25] Current WHO guidance therefore extrapolates adult evidence to children, recommending ART initiation between two to eight weeks after the start of TB treatment.[26]

Children under three years old who are co-infected with both TB and HIV are particularly vulnerable to poor TB treatment outcomes, and clinical vigilance is very important. This is due to their high risk of severe TB disease, combined with compromised treatment options resulting from key antiretroviral drugs not being approved for this young age group, and significant drug interactions with antiretrovirals and rifampicin.

For children on second-line antiretroviral regimens who develop TB, the treatment regime is complicated further by drug interactions which require more medications, which can be difficult to procure as well as unpalatable to take. Significant pill burdens play an important role not only in poor adherence, but also make potentially serious drug errors more likely to occur. Careful attention when dispensing drugs and clear explanations to the caregiver are essential.

CHILDREN WITH DRUG-RESISTANT TB

There is a paucity of evidence to support current treatment recommendations for DR-TB in children. Guidance is based on extrapolations from adult recommendations and expert opinions drawing on data from case series and small cohort studies. The general principles of DR-TB treatment are the same as for adults.[27]

Observational data suggest that even though second-line anti-TB drugs are known to be more toxic, they are generally well-tolerated in children. Given the serious nature of DR-TB, no drug is absolutely contraindicated. Some of the major side effects of concern in children include hearing loss and renal impairment from long-term use of the injectable drugs (kanamycin, amikacin and capreomycin) and hypothyroidism, which is associated with the use of ethionamide and/or para-aminosalicylic acid (PAS). Education of caregivers on these side effects, as well as regular and careful monitoring of children on treatment, is essential.

Among the commonly-used second-line TB drugs, paediatric formulations exist for only one of the oral drugs (levofloxacin), which is not widely available. The manipulation of adult formulations for the treatment of children with DR-TB is therefore necessary, but this is a complex process that is far from ideal, requiring careful attention, as there are considerable risks of over- and under-dosing.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Unlike the recent review by WHO of the drug dosages for treatment of drug-sensitive TB, the dosages of second-line drugs to treat DR-TB in children are extrapolated from adults and based on experience and expert opinion in light of the limited pharmacokinetic (PK) data available. There are some researchers currently looking into PK studies for drugs for DR-TB in children.[28] This is welcome, and once available, there will be a need to develop age-appropriate formulations to support treatment of these children.


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NEW DEVELOPMENTS

There have been recent developments in TB treatment for adults, with several new drugs currently in the final stages of development.

There is a clear need for these new drugs to undergo trials in children, or have a paediatric component incorporated in ongoing trials, so that when they become available to the adult population, children do not have to wait before they can benefit from them. There also needs to be research conducted into where these new drugs could fit in current regimens, or indeed whether they might allow shortening of the TB regimen in the future. Of the new drugs in the pipeline, only TMC207 (bedaquiline) currently has a paediatric implementation plan in place.

The paediatric population should not be left without access to these new drugs once they become available for adults.

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PREVENTION

Prevention

Active screening and proper management of child contacts of TB cases has the potential to greatly reduce the burden of TB in children.

Whereas adults can carry TB for years or decades without developing disease, TB disease in children is mostly the result of recent disease transmission. Therefore, the starting point of TB prevention in children is the scale up of prompt diagnosis and treatment of TB cases in the general community.

At the same time, active screening and proper management of child contacts of TB cases has the potential to greatly reduce the burden of TB in children and is an activity that must be reinforced.

Ultimately, an effective vaccine is the critical tool needed for prevention, but as yet, no breakthroughs are on the horizon.

CURRENT PRACTICES

CONTACT TRACING, SCREENING AND PROPHYLAXIS

Despite the fact that tracing, screening and isoniazid preventive therapy (IPT) for eligible child contacts of drug-sensitive patients has long been recommended,[29] they have not been systematically or effectively performed, as many TB programmes have not considered them priority activities. A recent study of children with culture confirmed TB in South Africa found that opportunities for preventive therapy were missed in 71% of cases.[30] Furthermore, IPT is frequently perceived to be unfeasible, with the potential to create drug-resistance if given to a child with active TB. These myths must be overcome to address the needs of child contacts that can benefit hugely not only from prophylaxis but from intensified case finding through the tracing and screening process.

To improve contact tracing:

- All patients with TB (especially if smear-positive) must be routinely asked about close contact with any child under five years old or any HIV-infected child regardless of age. The reason and importance of bringing these individuals for TB screening must be explained to the patient.
- Staff should be trained on the importance of contact tracing, and perhaps a focal person nominated.
- Simple, systematic data collection should be performed to monitor the volume and quality of contract tracing activity as well as enable measurable outcomes to be reported.

To improve contact screening:

- Symptom-based screening must be adopted. This has been shown to be a safe and feasible alternative to the use of chest x-rays and tuberculin skin testing to rule out active TB[31] and has long been recommended. Chest x-rays and tuberculin skin testing are neither readily available nor easily performed in many TB-endemic settings and constitute a barrier to preventive therapy.
- Children who have a 'positive' symptom screen should go on to be investigated for TB.
- Children who have a 'negative' symptom screen should be prescribed prophylaxis with six months of isoniazid – a regimen with proven efficacy following TB exposure/infection. The risk of generating drug-resistance in children by inadvertently giving isoniazid to a child with active TB is minimal given the generally paucibacillary nature of childhood TB (in contrast to adult type TB disease).

Interferon Gamma Release Assays (IGRAs) do not have a place in the screening of contacts of TB in resource-limited TB endemic settings.[32]

For children in contact with DR-TB, the strategy for prophylaxis is far less evident, making this subject a critical area for research. WHO currently recommends close follow-up for a period of at least two years.[33,34]

PREVENTION OF TB IN CHILDREN WITH HIV

Children living with HIV should undergo routine symptom-based screening for TB at each contact with health services. All who are contacts of a TB case, but with no evidence of active TB disease, are eligible for IPT regardless of age (in other words, not only if they are under five years old).

Furthermore, WHO recommends that HIV-infected children older than 12 months of age who are unlikely to have active TB (on symptom-based screening), and have no known contact with a TB case should receive six months of IPT as part of a comprehensive package of HIV care.[35, 36]

In contrast, children less than 12 months of age who are unlikely to have active TB and have had no known contact with a TB case should not receive IPT. This recommendation is based on evidence that where there is early ART initiation for infants and vigilance for TB exposure, IPT has no benefit.[37]

Lastly, WHO makes a conditional recommendation (on the basis of adult evidence) that all children with HIV who have successfully completed treatment for TB disease should receive isoniazid for an additional six months.

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VACCINATION

BCG is the only currently licensed vaccine for TB and is usually standard for children at birth or shortly after in high-burden countries. Studies place its efficacy between 0-80% with its main protective effect being against disseminated forms of TB in young children. It offers little, if any, protection against pulmonary forms of TB.[38]

The BCG vaccine is not recommended for children with HIV due to the well-described risk of disseminated BCG disease (a form of mycobacterial disease caused by the modified mycobacterium used in the BCG vaccine).[39] However, given that children's HIV status is usually unknown at birth when BCG is given, the current advice is to continue to give BCG at birth to all infants in settings where TB and HIV are highly endemic until it is feasible to implement policies of delayed, selective vaccination.[40]

INFECTION CONTROL

Good infection control is an important part of preventing TB in children. This encompasses a wide range of interventions, some of which are costly and complex. However there are some simple practical measures to protect children that are often not taken.

These include:

- Educating TB patients regarding cough hygiene in the home as well as in the clinic environment.
- Advising patients to avoid sleeping in the same bed or room as children at least until they become smear-negative.
- Minimising the presence of relatives on TB wards and in particular not permitting children on the ward. Well-ventilated outdoor spaces should be available for visitors and patients to meet.
- Ensuring well-ventilated clinic waiting areas, especially where children are present.

For further infection control practices and advice see:

http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf

THE WAY FORWARD

The way forward

The prevention, diagnosis and treatment of paediatric TB have been neglected for many years. However, the recent rise in awareness of paediatric TB combined with new advances in adult TB care mean that there is now the potential to change this.

Although many gaps remain with regard to the existing tools and treatment for children with TB, there are existing recommendations that can be adopted, tools that should be implemented and research questions that are waiting to be answered. These can all be addressed today.

This booklet has highlighted what can be done to improve the services available for children with TB. However, the work must continue, not only for the paediatric world to catch up with adult TB services, but also to ensure that children are included from the outset in all advances in TB care.

There are existing recommendations that can be adopted, tools that should be implemented and research questions that are waiting to be answered. These can all be addressed today.

DIAGNOSIS – WHAT CAN BE DONE?

...at the clinical level

- Train health staff on the diagnosis of childhood TB.
- Include paediatric-specific diagnostic advice in clinical guidelines adapted to the resources of the context.
- Improve the availability, quality and interpretation of chest radiography in children.
- Encourage health staff to treat based on careful clinical assessment, even if TB is difficult to confirm.
- Encourage taking detailed contact history, especially in areas of high DR-TB prevalence.
- Maximise the use of existing tools for obtaining appropriate specimens in children, such as sputum induction and lymph node biopsies, especially in contexts of high DR-TB prevalence, or for children in contact with a case of DR-TB.

...by the research and diagnostic development community

- Ensure timely evaluation of diagnostic methods and technologies in paediatric populations.
- Ensure wide endorsement and implementation of the consensus on standardised methodological approaches for evaluation of new diagnostics in paediatric populations).[41]
- Ensure there is a specific focus on childhood TB in the search for TB diagnostic biomarkers that could lead to the development of a point-of-care test for TB in children.
- Prioritise R&D efforts on diagnostics that use samples other than sputum (i.e. urine or capillary blood).

...by national and international policy makers

- Raise awareness in the community about childhood TB.
- Make childhood TB a public health priority.
- Ensure that children have access to faster diagnosis provided by new technologies such as Xpert MTB/RIF.

TREATMENT – WHAT CAN BE DONE?

...at the clinical level

- Implement new WHO-recommended treatment strategies for children with careful attention to correct drug dispensing and dose adjustment according to weight.
- Ensure that children with TB/HIV receive integrated care and are initiated on ART between two to eight weeks after TB treatment has commenced.
- Treat children with confirmed or suspected DR-TB with careful dosing and close monitoring. Record and report treatment outcomes and adverse events.
- Give education, counselling and support to the caregiver, as well as to children old enough to understand their disease.

...by the research and drug development community

- Develop new fixed-dose combinations for drug-sensitive TB based on new WHO recommendations.
- Continue to explore existing and new drugs to optimise a therapeutic strategy for HIV/TB co-infected children under three years old.
- Study the pharmacokinetics and safety of second-line TB drugs in children.
- Optimise treatment strategies for children with DR-TB.
- Include children early in clinical trials of new anti-TB drugs.

...by national and international policy makers

- WHO to provide clear guidance to drug developers on needed fixed-dose combinations of first-line drugs to support implementation of the new WHO-recommended dosages. Donors to support development of such formulations.
- Include up-to-date recommendations on treatment and monitoring of children in national TB guidelines.
- Ensure that quality-assured, paediatric formulations of anti-TB drugs are continuously available.
- Review existing policies on routine hospitalisation of children with TB and support outpatient-based treatment strategies.

PREVENTION – WHAT CAN BE DONE?

...at the clinical level

- Undertake child contact tracing in TB programmes.
- Ensure all HIV infected children are screened for TB at every visit.
- Use symptom-based screening to rule out active TB and start eligible children on INH prophylaxis.
- Use simple data collection to document, monitor and report activity related to contact management.
- Ensure good infection control practises are initiated and maintained throughout TB services.
- Ensure all pregnant women, especially those with HIV, are screened for TB, as a measure for both the health of the mother and infant.

...by the research and product development community

- Identify and initiate studies on potential prophylactic strategies for child contacts of DR-TB that are safe and effective, including with new TB drugs.
- Study the operational barriers to contact tracing, screening and prophylaxis in routine settings.
- Continue to investigate optimal strategies for prophylaxis especially for HIV infected children: including the possibility for a shortened regimen by the use of new drugs or combination therapy.
- Continue research into new TB vaccines.

...by national and international policy makers

- Make the management of TB contacts a priority component of TB programmes and require the reporting of measurable outcomes.
- Include up to date recommendations on the management of contacts in national guidelines.
- Continue to invest in the development of an effective TB vaccine that is safe for HIV infected infants.

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