FACT SHEET

UNCOUNTED AND UNTREATED: CHILDREN WITH TUBERCULOSIS

Tuberculosis (TB) is estimated to kill more than 64,000 children every year, making it one of the leading causes of death in children worldwide. But that number is acknowledged to be an underestimate: because of ineffective diagnostic tests, many more children go undiagnosed and therefore uncounted and untreated. Even when children are diagnosed, they face a lengthy and often complicated treatment course. This is a situation that is not likely to change anytime soon unless significant changes are made to existing programs and tools – children are routinely excluded from the research and development activities that might provide access to better paediatric diagnostic tests and treatment in the future.

DIFFICULT DIAGNOSIS

Because children's immune systems aren't as well developed as those of adults, TB often progresses more quickly and affects organs other than the lungs, such as the brain. Thus, rapid and correct diagnosis of TB is even more critical in children.

But the standard TB tests used in adults are not well-adapted for diagnosing TB in children. This means most children have to be diagnosed through a clinical exam and symptoms. But medical staff find it difficult to reach a final diagnosis because the most familiar signs associated with TB – including fever and weight loss – are not always apparent in children. Clinical diagnosis is also complicated by the fact that it is hard to rule out many other common childhood diseases, because the symptoms are shared equally with TB.

Médecins Sans Frontières (MSF) has been treating TB for 25 years. In 2011, 26,600 TB patients were treated in MSF-supported projects in 39 countries. Half of these projects involved treating multidrug-resistant TB (MDR-TB) – a total of 1,300 patients in 21 countries. MSF is now one of the biggest NGO providers of MDR-TB care worldwide.

> *"When you're only detecting TB in one out of ten children, you can be sure that many are falling through the cracks simply because they're not being diagnosed, resulting in unnecessary deaths and the disease spreading to others."*
>
> **Dr. Philipp du Cros,**
> **Head of MSF's Manson Unit**

THE MOST COMMONLY-USED DIAGNOSTIC TOOL MISSES NINE OUT OF EVERY TEN CHILDREN

The primary TB test used today – called *sputum smear microscopy* – uses a microscope to identify the TB mycobacteria in a sample of sputum (phlegm) coughed up from deep in a person's lungs. Most children are not able to cough up sputum, instead only producing a watery saliva sample that won't yield good results. This makes it necessary to use extreme methods to obtain sputum samples from children (see box overleaf).


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Further, TB in children is often located outside the lungs, showing up instead elsewhere in the body – this is known as extra-pulmonary TB. For these reasons, examining sputum from a child's lungs under a microscope only manages to diagnose around 15% of cases of TB in the children tested, leaving 85% undetected.

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ALTERNATIVE TOOLS ARE ALSO INADEQUATE

Other tools like tuberculin skin tests and chest X-rays to diagnose TB all have strong limitations that make it difficult to reliably diagnose TB. X-rays for example can be a helpful tool, but the equipment and trained staff required to interpret the results are often not available in resource-limited settings.

Today's best practice or 'gold standard' tool to diagnose TB is based on *culture* techniques, which involve seeing if the TB bacteria are present in a sputum sample by letting them grow over a period of weeks. While this method is more accurate than microscopy, it still only manages to diagnose TB correctly in about 30-40% of paediatric patients and can take up to eight weeks to get a result.

The delay before a confirmed diagnosis is obtained is also a problem, as it means children go untreated and risk getting even more ill.

A new test is being rolled out in some developing countries, including in MSF projects, that can deliver quicker results – in under two hours. The Xpert MTB/RIF test is based on molecular technology. Although this still requires some laboratory infrastructure, the test can be used outside of highly sophisticated laboratory settings. An additional benefit of the new tool is that it can detect resistance to one of the most commonly used drugs, rifampicin. Although studies have shown that Xpert MTB/RIF has higher detection rates of TB in children than microscopy and provides an equally rapid diagnosis, this test is not as good at identifying TB cases in children as the culture method.

However, both culture and the Xpert MTB/RIF test are still mainly reliant on sputum or other respiratory samples, so the problems noted with smear microscopy also apply here. There is an urgent need for affordable and easy-to-use TB tests that do not rely on respiratory specimens, but instead work with samples that are easier to obtain like blood, urine or stool.

The situation is further complicated if a child is also infected with HIV. Children tend to have fewer TB bacteria in their sputum, a condition called pauci-bacillary TB. This makes it even harder to spot the presence of TB under the microscope.

DIAGNOSING DRUG-RESISTANT-TB IN CHILDREN: MORE COMPLEX YET

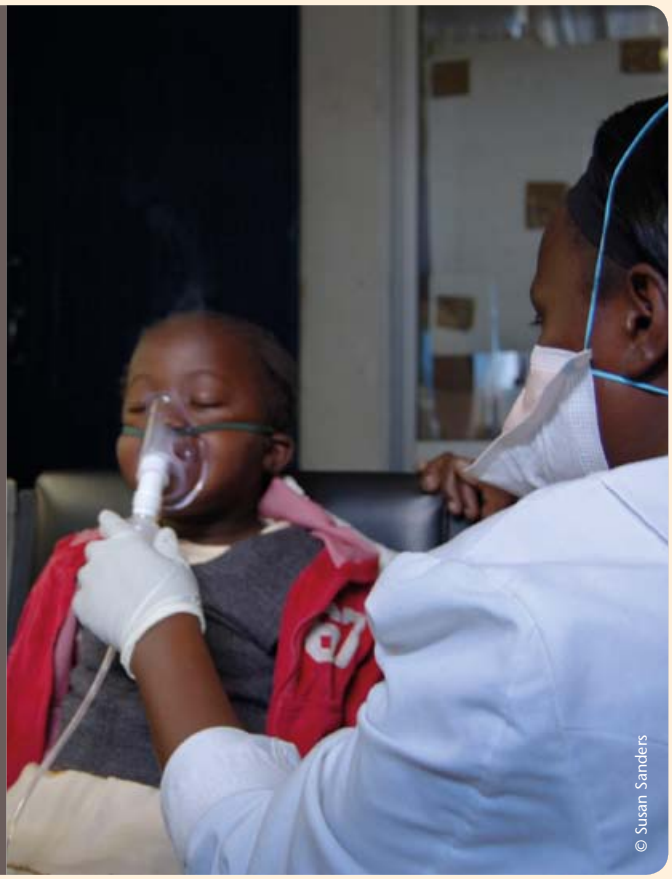
As with adults, the complexities of diagnosing and treating TB are multiplied when children are affected by drug-resistant forms of the disease. In addition to confirming the presence of TB mycobacteria, those suspected of having drug-resistant strains of the disease should also undergo drug sensitivity testing to establish exactly which drugs their TB strain is resistant to – but few labs in low- and middle-income countries have the capacity for this testing. Additionally, this process adds further time to the diagnostic process, leaving more patients without timely treatment.

INVASIVE TESTS

Several invasive methods need to be used to get sputum samples from children. These procedures are not well-tolerated by children, involve hospitalisation, and require trained personnel and attention to infection control. This means they are not well-suited to resource-limited settings.

> *"One technique we use involves getting the child to breathe in vapour so their lungs get irritated, helping them to cough up sputum. Or if it's a small child, we then suck out the sputum from the back of the throat. Another way to get sputum is to try to remove it from the stomach. It feels pretty hard doing all this as a doctor with a sick child. But you don't have a choice. You can't do anything else if you want to find out what's wrong with the child."*
>
> **Dr Bern-Thomas Nyang'wa, MSF TB Advisor**

A somewhat better tolerated method for improving sputum collection (the string test) has shown promising results in adults, but there is not yet enough evidence about its performance in children.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TOUGH TREATMENT

When diagnosed quickly and accurately, children respond well to TB treatment. But the treatment course is long – six months for those with drug-sensitive TB and up to two years for those with drug-resistant forms of the disease.

CHILDREN GOING UNDER-DOSED

For drug-sensitive TB, there are combination tablets that allow children to take the four-drug regimen in one pill. These facilitate treatment as they reduce the pill burden for patients, and they make dispensing easier, too.

However, since these were developed, the World Health Organization (WHO) has increased the recommended dosages for children, which means the existing pills no longer correspond to the newly-recommended dosages. TB treatment providers therefore have been given guidance to use the existing combination drugs together with additional individual tablets of the four drugs in order to reach the new dosages. As this is quite complex, many countries have not incorporated this guidance into their national TB programmes, and children are therefore going under-dosed.

And this situation may take a while yet to change, as it may take as many as three years to develop new child-friendly combination pills (because the market for TB medicines for children is small, manufacturers see little incentive and therefore urgency in investing in producing these).

> *"It's frustrating because you want to get it right and get the child on treatment, and yet you hesitate, because in diagnosing TB, you are then asking the child and the parents or caregiver to enroll in a six-month course of treatment – or up to two years if the child has drug-resistant TB."*
>
> **Dr. Grania Brigden, TB Advisor, MSF Access Campaign**

A GUESSING GAME: TREATING CHILDREN WITH DRUG-RESISTANT TB

There is no guidance from WHO on the best way to treat children with drug-resistant TB, and currently only three of the medicines used to treat the disease in adults have been specifically formulated or adapted for children.

To work around this, caregivers have to break up adult tablets to reach an estimation of the amount a child needs. Some small children cannot physically swallow large tablets so the pills have to be ground up and added to liquid. This carries significant dangers of under- or over-dosing.

As with adults, children also have to endure a painful daily injection for several months and experience side-effects from the drugs (although encouragingly, most children do not suffer the severe side-effects caused by the existing medicines to the same degree as adults). Because it can be hard for children to express themselves, caregivers cannot always tell the impact these side effects have on them.

As with many diseases affecting developing countries, the pharmaceutical industry does not see a lucrative market in return for investing in research and development. With TB being so difficult to diagnose in children, the market appears deceptively small. This holds true even more so for drug-resistant TB in children. While two new drugs that will be active against drug-resistant TB are expected to come to market in 2013, neither has been studied in paediatric patients, which means any advances they offer will not be available for children.

SWAZILAND: TAILORED REGIMENS FOR DR-TB

MSF's programme in Swaziland has treated more than 30 children for DR-TB, the youngest just 12 months old. Despite the difficulties of obtaining microbiological confirmation in children, we were able to get adequate samples to perform culture tests and to ensure that they were on exactly the right drugs they need. We've found it particularly challenging that DR-TB medicines are not adapted for children. Despite this, the children have done well and appear to tolerate the difficult treatment with fewer severe side effects than those endured by adults. The monitoring and follow-up of these children is further being improved to ensure that the long, toxic treatment is as safe and effective as possible.

> *"You need to measure out the amount of medicines you give a child according to their weight, so we had to break one of the tablets into quarters, that's as exact as you can get. It's so difficult with such a young baby; they are still teething and so they are in pain and they don't want to eat. Then if you force her to drink the crushed tablet in the milk, because she needs to have her drugs, she's going to vomit. She was getting the same side effects as me because we were on the same drugs. As a mother, you feel really caught in the middle. It was not good at all."*
>
> **Busiwe Beko**, whose one-year-old baby daughter was the youngest child to be treated for DR-TB in Brooklyn Chest Hospital in South Africa.

TB-HIV CO-INFECTION: MULTIPLYING THE CHALLENGES

TB is a major killer of children who are also infected with HIV. Children with HIV younger than one year old have an up to 24-fold higher risk of developing TB than their HIV-uninfected peers. Diagnosing TB in children co-infected with HIV is even more difficult, because children with HIV very often exhibit non-specific signs and symptoms such as fever and failure to thrive that may be due to the HIV itself, co-infections with tuberculosis or another opportunistic infection.

> *"The lack of new diagnostics and new drugs means that innovative approaches are needed to deliver the best medical care possible to the greatest number of affected children. There are many children who do not have even the chance of survival because they are not even diagnosed, let alone treated. It is an ongoing challenge for us to develop these new approaches and share our experience and knowledge widely with other actors."*
>
> **Dr Marianne Gale, MSF Medical Advisor for Paediatric TB & HIV**

Co-infection with HIV has also been shown to decrease the yield of induced sputum or gastric fluid samples as compared with children who do not have HIV.

MSF's experience has shown that children co-infected with TB and HIV are more than twice as likely to die as those that are HIV-negative, making it all the more critical to get them on treatment as quickly as possible. Further, it can be particularly difficult for children co-infected with HIV to adhere to their treatment because of the large number of pills they have to take each day. Combined, these factors explain the poor outcomes for very young children co-infected with TB and HIV.

WHAT NEEDS TO HAPPEN:

Paediatric TB has been neglected for too long. However, with increased attention on the epidemic and new drugs in the pipeline, there is real potential for change.

PAEDIATRIC TB DIAGNOSIS:

- The research and development (R&D) community should develop new tests that are not based on respiratory samples like sputum, but instead use samples that are easier to obtain, such as blood, stool or urine.
- Wherever Xpert MTB/RIF is available, children should have prompt access to the test in order to ensure a more rapid diagnosis
- If a child cannot provide an adequate sample to confirm diagnosis, then clinicians should use all other clinical means available (including chest X-ray if possible) to diagnose and start treatment.

MSF in 2012 began the first treatment programme for children with DR-TB in Tajikistan, outside the capital Dushanbe.

PAEDIATRIC TB TREATMENT:

- Combination pills, based on the new WHO dosing guidelines, should be developed by drug manufacturers as soon as possible.
- Drugs to treat TB should be studied in children so they are developed as child-friendly formulations. Additionally, new drugs coming out of the drug development pipeline should be routinely studied in children as early as possible.
- As the last comprehensive paediatric TB guideline was published in 2006, there is an urgent need for WHO to publish a new comprehensive guideline incorporating all elements of paediatric TB care, including the treatment of DR-TB in children.

SENTINEL PROJECT:

UNITING RESEARCHERS, CAREGIVERS AND ADVOCATES ON PAEDIATRIC DR-TB

A global partnership comprised of leading paediatric researchers, advocates, and treatment providers – including MSF – was launched in October 2011. The Sentinel Project gathers knowledge and data for the optimal diagnosis, management, and prevention of DR-TB in children. For more information, visit: http://sentinel-project.org

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