

# Tuberculosis: New Faces of an Old Disease





# Tuberculosis under control? Definitely not

Many people in rich countries think of tuberculosis as a disease of the past. Indeed well into the 1980s, experts thought that tuberculosis (TB) could be eliminated in a matter of decades.<sup>1</sup> TB was seemingly under control.

Antibiotics, developed from the 1940s on, appeared to be effective in treating the disease. And as long as the strategy introduced by the World Health Organization (WHO), known as DOTS (Directly Observed Treatment, Short-Course), was correctly and efficiently rolled out, policy makers were convinced that TB would one day be a scourge of the past.

But now the international community recognises that with around nine million new cases appearing every year, TB is far from defeated. TB is a deadly killer, responsible for 1.7 million deaths in 2006 – that is almost four lives claimed every single minute. The vast majority of TB cases occur in developing countries, with 22 high burden countries (mostly low and middle income countries) carrying approximately 80 percent of the global burden. Two billion people – one third of the world's population – are infected and carry the tubercle bacillus.<sup>2</sup>



Busiwe Beko and daughter. Both mother and child were infected with MDR-TB and have now both recovered, South Africa



Worse, this ‘disease of the past’ has returned with **new faces** that are stretching our capacities to breaking point. The rapid spread of TB among people living with HIV, coupled with the emergence and spread of strains of TB that are resistant to the most common and effective drugs used to treat the disease, have led to a situation where far from being contained, TB is in fact spiralling out of control.

After calling victory too early, the world is waking up to the fact that TB has re-emerged as a major threat to global health.

### Fuelled by the HIV pandemic

People living with HIV are particularly vulnerable to developing TB. For that reason, TB incidence rates have shot up dramatically in the wake of the HIV epidemic, in particular in sub-Saharan Africa.<sup>3</sup>

In countries characterised by high HIV prevalence, the

number of TB cases has almost tripled in the last 15 years. In South Africa, 44 percent of newly detected TB cases are estimated to be HIV positive. Globally, the figure stands at eight percent.<sup>4</sup> In developing countries, TB is the leading cause of death among people who are HIV infected.<sup>5</sup>

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*In just one generation we have become witnesses to the ravaging of the African continent by the deadly combination of HIV and TB (...). At the same time, in Eastern Europe, multi-drug-resistant strains have been created by bad control practices and disseminated all over the former USSR and beyond (...). The global TB incidence rate continues to rise.*

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**Dr. Mario Raviglione,**

Director of WHO Stop TB Department



Joseph Ramokoatsi, MSF “lay counsellor” and HIV/TB patient, Lesotho

## Drug-resistant strains spreading globally

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*We should understand that TB spares no one – there's no single image today that represents the face of this disease. People think of TB as a disease primarily of men, of older people, of prisoners, but we have all sorts of people being treated here, all ages and from all walks of life, including a number of very young women.*

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**Dr. Juliet Melzer,**  
MSF, Uzbekistan

The emergence and geographical spread of strains of TB that are resistant to treatment by the standard anti-TB drugs is a second major concern. Resistance to any one drug is the result of naturally occurring genetic mutation within the *Mycobacterium*, but resistance to multiple drugs emerges through incorrect, interrupted or frequently repeated treatment.

The WHO estimates that there are now almost 490,000 new cases of multidrug-resistant (MDR) TB every year, and that the amount of drug resistance has been ever-increasing in countries as diverse as Peru, South Africa, China and India.<sup>6</sup> An estimated 120,000 people die annually from multidrug-resistant TB.<sup>7</sup>

### Challenges multiplied

Diagnosis, treatment and prevention of drug-susceptible TB is difficult enough. But when it comes to tackling the disease in patients who are also infected with HIV or those with resistant strains of the disease, the medical challenges are multiplied.

In this document, through our work in Africa, the Caucasus and Asia, we illustrate our encounters with the

new faces of TB and the tough challenges that we face in treating patients with drug-resistant TB and those infected with both TB and HIV. We also shed light on the limits of our capabilities, specifically linked to the continuing neglect of research into the development of newer and better vaccines, diagnostics and drugs to prevent, detect and treat tuberculosis.



Ulbosin, MDR-TB patient, Uzbekistan

### What is TB?

Tuberculosis is a contagious airborne disease and spreads like a common cold. It is caused by a bacterium called *Mycobacterium tuberculosis* (or *M. tuberculosis*) which usually infects the lungs.

Only one in ten people infected by the bacterium will actually develop the disease, since a healthy immune system will keep the infection dormant. But these infections can be reactivated years, even decades later, if the immune system is weak. This explains why people living with HIV whose immune system has been suppressed by the virus are so vulnerable to TB.

**The pulmonary form of TB** is characterised by a persistent cough, shortness of breath and chest pain. Each person with the infectious form of TB, if untreated, will go on to infect between ten and 15 other people each year.

The *Mycobacterium* can also infect almost any part of the body, such as the lymph nodes, the spine or bones. This is **the extra-pulmonary form of TB**, and is more common in HIV infected patients and children. Although extra-pulmonary TB may not be contagious, it is equally vital to diagnose and treat it rapidly, as all forms of the disease can be deadly if adequate treatment is not given.



DR-TB patient, Russia

## Médecins Sans Frontières (MSF) and TB

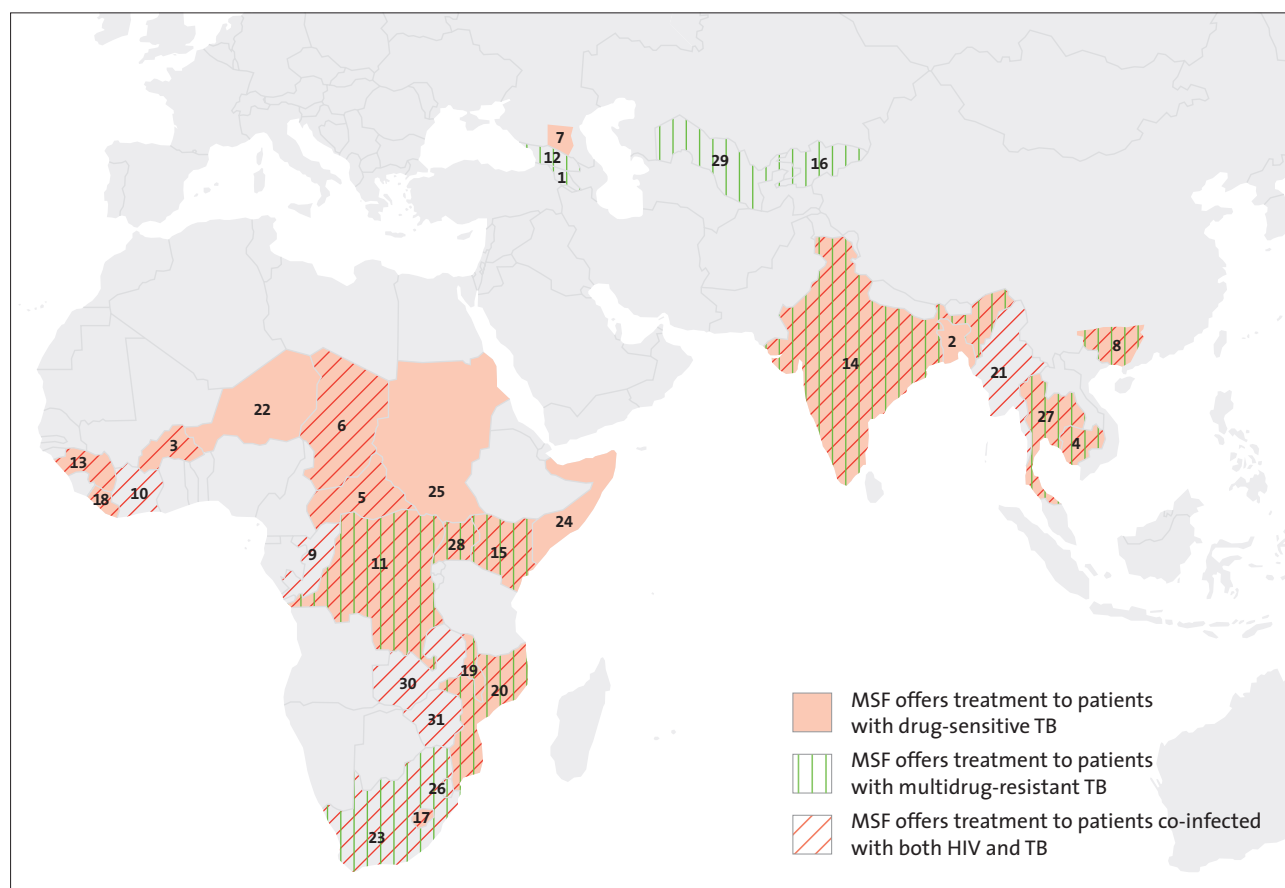
We have been treating tuberculosis since our first day of operations more than 30 years ago. Today, MSF – often working alongside national health authorities – treats patients in 31 countries in a wide variety of settings, ranging from urban slums to rural areas, prisons or refugee camps.

MSF has been working to integrate care for patients with TB and HIV infection across many of its projects.

MSF has also increased the numbers of people it treats with multidrug-resistant tuberculosis from 11 patients in 2001 to 574 patients in 2007 in 12 different

projects in countries including Uzbekistan, Georgia, Armenia, Kenya and South Africa.

In the period between 1999 and 2005, 52 percent of patients with drug-resistant TB under MSF's care in projects in the Caucasus, Central Asia and Thailand either completed their treatment or were cured. 12 percent died and 18 percent defaulted on their treatment due to its length and toxicity. For the remaining 18 percent, treatment either failed or patients had yet to complete their treatment. These figures illustrate the difficulties of treating drug-resistant TB even when this treatment is provided with considerable support and resources.



- |                                 |                             |                 |
|---------------------------------|-----------------------------|-----------------|
| 1 Armenia                       | 11 Democratic Rep. of Congo | 22 Niger        |
| 2 Bangladesh                    | 12 Georgia                  | 23 South Africa |
| 3 Burkina Faso                  | 13 Guinea                   | 24 Somalia      |
| 4 Cambodia                      | 14 India                    | 25 Sudan        |
| 5 Central African Republic      | 15 Kenya                    | 26 Swaziland    |
| 6 Chad                          | 16 Kyrgyzstan               | 27 Thailand     |
| 7 Russian Federation (Chechnya) | 17 Lesotho                  | 28 Uganda       |
| 8 China (Guangxi)               | 18 Liberia                  | 29 Uzbekistan   |
| 9 Congo Brazzaville             | 19 Malawi                   | 30 Zambia       |
| 10 Côte d'Ivoire                | 20 Mozambique               | 31 Zimbabwe     |
|                                 | 21 Myanmar                  |                 |



# HIV/TB co-infection: Fighting a Losing Battle?

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*Mortality in co-infected patients is much higher than in patients only suffering TB. There's no time to waste here: it may be only a matter of a few weeks before patients die.*

**Dr. Eric Goemare,**  
MSF, South Africa

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People living with HIV/AIDS, whose immune systems are suppressed, are particularly susceptible to TB. Not only are they much more likely to develop active TB, but the disease also progresses much more rapidly in HIV positive patients. TB causes up to half of all deaths of people with HIV.

This vulnerability caused by weakened immune systems explains why TB has been ripping through the populations in sub-Saharan Africa where there is a high prevalence of HIV.

In the past 15 years, new TB cases have tripled in such countries.<sup>8</sup> In Lesotho, for instance, where MSF runs an HIV care project in a rural health clinic, of the 221 patients started on TB treatment in 2006, 92 percent were also infected with HIV.

© Dieter Telmians



Patients at HIV/TB clinic, Cambodia

## Diagnosis: Falling through the net

People infected with both TB and HIV often present unclear clinical symptoms and are frequently missed by existing diagnostic tools.

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*I remember one young man who was very sick. He had HIV but I couldn't diagnose TB. He was not coughing but he was losing weight fast. We did the TB tests: both sputum test and X-ray were negative. The only thing that made me suspect he had TB was his swollen and fluid-filled abdomen. I wanted to start treating him for TB but because the tests were negative, I wasn't able to put him on treatment. Eventually, he went to the big city and got a correct diagnosis there. The lack of the right diagnostic tools that could work in our setting caused a treatment delay of two months.*

”

**Dr. Charles Ssonko,**  
MSF, Zambia

The most widely used technique for diagnosing TB in developing countries is no more sophisticated than examining a suspected patient's sputum sample under a microscope to assess whether it contains *TB mycobacteria*. This method, called **sputum-smear microscopy**, was developed well over a century ago.

Although relatively fast and easy to implement in resource-limited settings, the method has significant limitations: it detects less than half of all TB cases, and it is, by definition, not able to identify TB in people, such as children or many people living with HIV, who either have difficulties producing enough sputum from their lungs for a sample for analysis, or don't have sufficient or any *mycobacteria* in their sputum to be detected under the microscope.<sup>9</sup> It also completely misses the extra-pulmonary form of TB.



Monica, HIV/TB patient, Kenya

The other possibility is to X-ray the patient's chest. But for people living with HIV/AIDS, the X-ray often doesn't show up the typical changes in the lung associated with TB infection. The result is that TB infection in many patients who are HIV positive goes undiagnosed – they are falling through the net.

### The need for speed

We therefore desperately need better diagnostic techniques. Currently, a technique known as **culture** is considered the best alternative to microscopy. Culture consists of incubating (or 'growing') a sputum sample in a reagent or medium to see whether it contains live *TB mycobacteria*. It gives results that are far more accurate than microscopy. But as the *mycobacteria* are

such slow-growing organisms, it can be up to eight weeks before a result comes through.

Swift diagnosis of tuberculosis is crucial – not only so that the patient can be put on appropriate treatment as soon as possible, but also to prevent the spread of the disease in the community.

Faster culture techniques do exist: one technique, known as MGIT (Mycobacterium growth indicator tube), is based on a liquid culture rather than the usual solid culture medium. Liquid culture methods have been endorsed by WHO since 2007.<sup>10</sup> MGIT, however, requires very skilled staff, a constant power supply and high safety standards to protect the laboratory staff handling the samples from contamination – things that simply do not exist in many of the more remote settings where we work. Getting hold of the component parts – new tubes and liquid reagent – also requires a reliable supply-chain which cannot always be assured.

In a pilot project in Kenya, where up to 80 percent of TB patients are co-infected with HIV, MSF is working with another improved culture medium. Called thin layer agar (TLA), it shortens the time to diagnosis down to eight to ten days and shows similar accuracy to that achieved by MGIT. TLA is cheaper and less logistically challenging than the MGIT culture technique. Yet although these factors combine to make TLA potentially a very interesting tool for the



Culture test for TB



sustainable scale-up of TB diagnosis, it is still a rather complex technique that has to be carried out in a laboratory with proper staff training and protection.

### As close to the bedside as possible

Many of today's existing tools are excessively complex. The use of culture as the main diagnostic tool – though it gives more accurate results than microscopy – still presents serious drawbacks in many of the settings where we work: access to culture remains very limited as the vast majority of TB patients (an estimated 85 percent) seek care in small clinics and health posts where either no test or only sputum-smear microscopy is available. Only the remaining 15 percent is seen at better equipped health structures, where it is possible to perform TB diagnosis using culture techniques.<sup>11</sup>

Current diagnostic methods thus need improving – we need tools that give better results, but are also faster, and we need tools that are as low-tech as possible.

### Treatment: two diseases, one patient

Current TB treatment is complex and long-lasting, involving a combination of antibiotics that were developed more than 35 years ago. Lengthy treatment timelines (six or eight months of antibiotics therapy) and drug side effects make it difficult for patients to adhere to treatment through to its completion. Currently, the recommended strategy to maintain adherence is Directly Observed Treatment (DOT), where a health worker or a community volunteer supervises the patient taking his or her medication. While this can improve cure rates, it remains highly labour intensive for health staff, and places considerable strain on patients who sometimes have to travel several kilometres, every day for several months, to a health centre in order to receive treatment.<sup>12</sup>

Treating patients who are infected with both TB and HIV is even more difficult. When the drugs for the two diseases are taken in combination, there can be drug interactions, which may lead to increased side effects or reduce the effectiveness of treatment. For example, one of the main TB drugs, rifampicin, lowers the efficacy of one of the most common anti-retrovirals used to treat AIDS, nevirapine. As a result, a more complicated treatment regimen is required. The patient must take a vastly increased number of pills every day, which when taken together can have toxic effects, notably on the liver.



Dr. Pheelo Lethola, MSF doctor, Lesotho

### Integrating HIV and TB treatment

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*The drugs for these two diseases interact. In integrated HIV/TB programmes, we can follow this interaction more easily and we know exactly what drugs the patients are on, so if necessary we can take patients off drugs that aren't working for them.*

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**Dr. Gilles Van Cutsem,**  
MSF, South Africa

Given the high risks of co-infection in places where large numbers of people with HIV live, it has become increasingly clear that treatment for the two diseases should be integrated. Treatment integration would allow patients to benefit from early diagnosis of either disease and ensure effective monitoring of the combined treatments.

MSF has worked on setting up 'one stop shops', in effect clinics where people are treated for both diseases in one place. This brings benefits to both health care staff and patients – patients are assured swifter diagnosis of the two diseases, and staff can effectively monitor them for both treatments at the same time.

However, despite the clear statement from WHO and others of the importance of implementing an integrated approach,<sup>13</sup> in most places TB and HIV programmes continue to operate in isolation from each other. In 2006, worldwide less than one percent of people living with HIV/AIDS were reported to be also screened for tuberculosis.<sup>14</sup>

## Living with two diseases: HIV/TB co-infection

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*It's not easy taking all the drugs. I take two tablets for my TB every morning at 6 am and then for my HIV I take one in the morning and three at night. I get pains in my legs and headaches and sometimes I just don't want to take the drugs, but I do my best.*

**Margaret,**

40 years old, Nigeria. She is co-infected with TB and HIV.

”



© Sophie Scott

**Bharat Terde, HIV/TB patient, India**

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*After being diagnosed as having both diseases, Alison died within six months. She was already too sick for the medicine to help her. When she died, they took five litres of liquid out of her chest. It was a terrible way to die. I think if Alison had been diagnosed earlier and gone to the clinic to get treatment, she would have been alive today. Alison was a good person, I miss her very much. She left behind four children.*

**Sarah,**

speaks about her sister Alison, 29 years old, Zambia.

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“

*I am fine now. I have had some tough times, but I survived. When I meet other patients who are reluctant to take a TB or HIV test, I always try to convince them. I give myself as an example. I was once also very sick, but now I am as strong as a horse. I would like to say to other co-infected patients that life is worth living, you should get treatment. You only have one life, you should take this opportunity and get some treatment. Without it you will die. And that is completely unnecessary.*

”

**Masautso,**

37 years old, Voluntary Community Worker, Zambia.

Masautso helps detect and take care of TB and HIV

patients. He was previously co-infected with TB and HIV.

“

*I had diarrhoea, fever, and my lymph nodes were swollen. I thought it would pass. So I did nothing. But I became weaker and weaker. I suspected it was TB but I could not afford treatment. Then I heard about the MSF clinic where you get treatment for free. The diagnosis was TB and I started treatment. In the beginning I felt a bit giddy and my fingers tingled. When they told me I was also HIV positive, I was in pieces. Every month now I come to the clinic for my pills. If I take my pills it will go fine. I don't want to think about death. If I take my pills carefully I can do things and care for my children.*

”

**Lucy,**

32 years old, Myanmar. She is taking antiretrovirals for her HIV infection and finished her TB treatment a month prior to being interviewed.

© Chris de Bodie



**HIV/TB patient with his wife, Myanmar**

# Drug-resistant tuberculosis: entering the mainstream

## What is drug resistance and how does it develop?

In the case of TB, resistance to drugs – when the effectiveness of a drug against a pathogen is reduced – develops through a mutation of genes in the bacteria. Although this is a natural phenomenon resistant bacteria will only multiply in the presence of the drug in question.

Resistance can also develop if the bacteria are under-exposed to drugs, because of under-dosing or if the treatment is interrupted or not continued for long enough. In all of these cases, treatment is likely to fail and the disease will re-emerge in a more resistant form, meaning that fewer drugs will be effective against the bacteria.

But direct infection with resistant strains is also possible. Because TB is an airborne disease, a patient can contract drug-resistant TB directly through contact with another person already ill with the drug-resistant strain. There are concerns that the number of those directly infected this way is rapidly increasing.

For instance in Tashkent in Uzbekistan, 15 percent of TB cases who have never been previously treated for TB have MDR-TB, that is to say the resistant strain was caught directly from another person with MDR-TB.<sup>15</sup>

## Diagnosis: establishing which drugs work, and which don't

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*Basically with drug-resistant TB, whenever you look for it, you find it. And when you try to deal with it, you inevitably run up against the shortcomings of the available diagnostic tools and treatment. What we are also finding is that more and more patients we see have drug-resistant TB and they come to us with ever more resistant forms of the disease.*

”

**Dr. Juliet Melzer,**  
MSF, Uzbekistan



MDR-TB patient, Lesotho





MDR-TB patient, Cambodia

Many countries in the developing world are not aware of the incidence of drug resistance among their populations affected with TB. A major factor is the difficulty associated with diagnosing drug-resistant strains.

Detecting drug resistance means finding out not only whether a person has TB or not, but just as importantly establishing to which drugs the patient's TB strain has become resistant. For each individual patient, there will be a different pattern of resistance. Some programmes provide a standard drug combination to all patients with MDR-TB but to ensure a patient is given the best possible treatment, doctors need to get an accurate profile of the specific drug resistance for each of their patients.

The diagnostic processes that allow medical workers to establish which drugs will work against the particular TB bacilli in a patient, and which won't, are known as **drug sensitivity testing** – or DST. Results cannot be achieved with microscopy or by looking at chest X-rays but they can be obtained through certain culture methods.

A sputum sample is cultured a first time to grow the *TB mycobacteria* – as described in the previous chapter. The bacteria are then exposed to various TB drugs. After a period of time, the bacteria are then re-examined to see which drugs have had an effect. If the *mycobacteria* have continued to grow then we can conclude that they are resistant to the effects of the drug. If, however, the *mycobacteria* have been killed, we can conclude the drugs are still effective.

This might allow caregivers to determine a patient's resistance patterns, but the method comes with all the problems associated with culture described above: it relies on sputum samples, so the technique is of limited use to those unable to produce sputum or with extra-pulmonary TB. It is complex, relying on a well-equipped laboratory and skilled staff, so much so that it is rarely available in developing countries, and not at all in more remote settings. And it is lengthy, taking up to eight to 12 weeks – time that patients needing to start treatment can ill-afford.

More modern techniques that work on analysing the DNA of the *Mycobacterium* do address the last problem at least, in that they can give results in less than 48 hours. But they demand highly sophisticated pieces of equipment, meaning that we are still very far from a TB diagnostic tool that can be used as close to the patient's bedside, however remote the setting, as possible.

### Treatment: a terrible burden

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*I get terrible headaches, dizziness and loss of appetite. It is better now, but there were times in the past when I just wanted to die, I felt so low and depressed. Maybe it was the drugs, or maybe the length of treatment, but it all just seemed too much.*

”

**Sarsenbai Menglibaev,**  
MDR-TB patient, Uzbekistan



Sarsenbai Menglibaev with his family, Uzbekistan

© Donald Weber

Treating drug-resistant TB is notoriously arduous for patients and presents huge difficulties for health programmes. Most of the second-line TB drugs used to treat drug-resistant TB are known for their relative ineffectiveness against the bacilli, meaning a lengthy treatment of up to two years. Patients must receive daily injections for up to six months and take a handful of different drugs once or twice a day for a further eighteen months or more. Treatment is also fraught with numerous side effects which require additional medical management.<sup>16</sup>

Such intense treatment places very big demands on patients. Many have to give up work in order to see their treatment through. Some patients who are hospitalised for periods of their treatment are isolated from their families, which can again give rise to psychological problems and major loss of income.

The toxicity of the drugs is perhaps the most striking feature of drug-resistant TB treatment (see box “The grim reality of DR-TB treatment”). Indeed, the severity of the side effects has been compared to cancer chemotherapy, with the difference that MDR-TB therapy is not administered in cycles, but in a continuum over two years. With a long list of commonly experienced side effects added to such a lengthy treatment, it is not surprising that many patients give up, some considering the treatment worse than the disease.

“*We explain to patients that to treat MDR-TB, you have to use medicines that will work like a bomb and clean everything out once and for all. That takes time because the bacteria responsible for TB are vicious and can hide anywhere in the body. When they re-emerge, they are even more vicious. But sometimes nothing helps. Inevitably, there will be people who give up treatment. It's a source of enormous frustration for us.*”

**Dr. Adrien Marteau,**  
MSF, Georgia

MSF project data from Georgia, Armenia, Uzbekistan and Thailand show a patient defaulter rate of 18 percent. Faced with these challenges, MSF has tried to improve the situation by introducing ambulatory and outpatient methods of treatment together with offering psychological and some economic support to patients. We have learned that we can often help

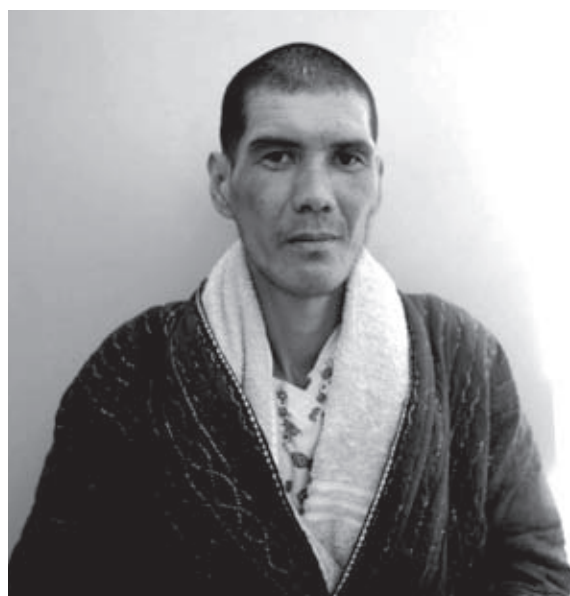
patients overcome the social and economic barriers to continuing treatment.

Other caregivers experience similar difficulties. The proportion of patients cured and completing their treatment remains below 50 percent in many programmes, especially when the patient is HIV/TB-co-infected.<sup>17</sup> However, success rates of up to 66 percent have been reported in some programmes.

What is particularly concerning is that even when the best treatment is available, some drug-resistant patients will go on to develop yet further resistance to their drugs. Data from our project in Sukhumi, Georgia, show that 13 percent of MDR-TB patients went on to develop extensively drug-resistant TB, or XDR-TB despite all of MSF's efforts to provide the highest standards of care. Similarly, in Uzbekistan, the analysis of an MSF cohort of MDR-TB patients revealed that six percent of patients developed XDR-TB while under treatment.<sup>18</sup>

### **Practical difficulties make expanding treatment challenging**

For healthcare programmes, there are also logistical difficulties to contend with. Very often there is only one supplier of the second-line drugs used to treat drug-resistant TB. This can mean that caregivers often have to wait for new supplies of a drug and stocks can actually run out – any treatment interruption bringing disastrous consequences for patients and further fuelling resistance.



Kairat, MDR-TB patient, Uzbekistan

© Donald Weber

The financial cost of treating drug-resistant TB is also very high compared to treating a patient with drug-susceptible TB. Because the number of drug-resistant patients actually receiving treatment is still quite low, pharmaceutical companies manufacturing the drugs face low demand and do not get the advantage of cutting costs through large volume production. In addition, these drugs are complicated to produce and use expensive raw ingredients.

Some treatment programmes have access to quality-assured drugs at discounted prices through a WHO-hosted initiative known as the Green Light Committee (GLC). For them, the average cost of a two-year treatment stands at around US\$2,000.<sup>19</sup> Drugs purchased outside this procedure cost a great deal more: in Cambodia, for example, MSF has paid around US\$7,300 for a single patient's treatment course.

Donor funding is available in principle through the Global Fund to Fight AIDS, TB and malaria but countries need to make the scale-up of MDR-TB treatment a priority.

These factors, taken together, explain why only ten percent of the estimated new MDR-TB cases are treated each year, and less than two percent are receiving verifiable, quality-assured, second-line anti-TB drugs through WHO's Green Light Committee mechanism.<sup>20</sup>

### DR, PDR, MDR, XDR: the many faces of resistant TB

The term **drug-resistant TB, or DR-TB** is used to describe those strains of TB which show resistance to one or more of the common first-line drugs.

Patients infected with strains of TB that are resistant to (at least) the two most powerful first-line antibiotics used to treat TB, namely rifampicin and isoniazid, are said to have **multidrug-resistant TB, or MDR-TB**.

Patients who have MDR-TB and also show resistance to second-line drugs, including at least one from the class known as fluoroquinolones and one of the injectable drugs, are described as suffering from **extensively drug-resistant TB or XDR-TB**.

All forms of resistance to more than one of the first-line antibiotics and which are neither MDR- nor XDR-TB are defined as **polydrug-resistant TB, or PDR-TB**.

There are thus a wide range of resistance profiles - the drugs that work for one patient will not necessarily work for another. But beyond the different categorisations of DR-, PDR-, MDR- or XDR-TB, this is the same disease, albeit one that may require different combinations of drugs in order to treat different people effectively.



TB patient at HIV/AIDS medical facility, Cambodia





MDR-TB drugs

## The grim reality of DR-TB treatment

Below are some of the side effects that accompany second-line TB drugs – note that not all of these drugs will be taken at once by DR-TB patients.

### Para-aminosalicylic acid

Developed in 1946.

Two sachets of granules a day taken with acidic liquid drink.

Para-aminosalicylic acid or PAS is one of the drugs most hated by MDR-patients. Many patients experience nausea and vomiting so severe that it can lead to anorexia. In some places, there have been so called 'PASer strikes' where patients simply refuse to take the drug.

### Cycloserine

Developed in 1952.

Two to three capsules a day for a minimum of 24 months.

Cycloserine frequently causes headache and dizziness. But on rare occasions it can even cause changes in personality and lead to aggressive behaviour or depression or it may provoke psychotic disturbances. Some patients say they hear voices and hallucinate. On rare occasions, treatment has to be interrupted for fear that a patient may commit suicide.

### Kanamycin

Developed in 1952.

One intramuscular injection each day for at least six months.

Kanamycin injections are often painful. This is particularly true when the patient is emaciated by their illness and little muscle remains available, a factor which also increases the likelihood of infection from the injection. Occasionally, patients using the drug can also suffer from dizziness and vertigo. Most alarmingly, kanamycin is capable of sending patients irreversibly deaf.

### Ethionamide

Developed in 1956.

Two to three tablets a day for the whole course of the treatment.

Ethionamide has been known to give patients nausea, diarrhoea, vomiting, splitting headaches as well as mouth and gum infections. Taken in combination with PAS, patients can suffer from low blood pressure, leading to feelings of total lethargy, fatigue and weakness. The drug can also lead to occasional bouts of psychotic disturbance.

### Capreomycin

Developed in 1963.

One injection a day for at least six months.

An alternative to kanamycin that is administered by a painful daily injection, capreomycin can provoke potentially allergic reactions. It can also lead to a loss of hearing resulting in either partial or total deafness.

***“If you want to live,  
you have to finish the whole regimen.”***  
**MDR-TB treatment in Armenia**

The Caucasus region has one of the highest rates of MDR-TB worldwide, as indicated in WHO’s 2008 drug resistance surveillance report. In September 2005, MSF and the Armenian Ministry of Health opened a treatment programme for drug-resistant TB, the first and only one in the capital, Yerevan.

N.L. was the first patient to complete treatment which lasted almost two years.

*“At first, I couldn’t imagine how difficult it would be,” says N.L. “I just wanted to be treated and return home to my family. But it was a long, slow process.”*

N.L. had been in and out of TB treatment for nearly 15 years. After years of failed attempts to comply with a strict and demanding treatment regimen, the TB bacilli in his system had gradually developed resistance to drugs. Fearing that he might infect his wife and son, N.L. moved out of home. And because of the fierce stigma associated with TB, he didn’t tell his neighbours about his illness. Meanwhile, his condition went from bad to worse.

Still, N.L. was one of the lucky few who were able to start treatment through the MSF programme in October 2005.

Treatment at the special drug-resistant TB (DR-TB) unit in the outskirts of Yerevan involves taking a combination of up to 20 pills every day, accompanied by a painful injection in the morning for up to six months.

*“When I was three months into the hospital treatment, I began to suffer side effects,” says N.L. “Feelings of weakness, dizziness, nausea, fatigue, mood changes, shortness of breath. It was so intolerable that just looking at the drugs was enough to make me nauseous.”*

There were nearly 20 more months of treatment ahead, and already N.L. was in constant agony. His daily struggle started to overshadow any benefits that treatment could bring.

*“N.L.’s main visitor was his son, who helped him a lot to cope with the sense of isolation at the hospital,” says an MSF volunteer. “Our team too - social workers, psychologists, doctor and nurse - encouraged him in different ways, and wherever possible.”*

After seven months in hospital, N.L.’s sputum smears finally became negative. TB bacilli were no longer

detected in his body and N.L. was discharged from the hospital. He was not yet cured, but he could now go home, back to his family, and continue ambulatory treatment –or outpatient treatment – at a clinic in Yerevan. However, this was not the end of the story: N.L. started outpatient treatment with great difficulty.

*“I was happy to leave the hospital and be reunited with my family. But on top of the side effects going to the clinic every day for many more months, throughout the hot summer and harsh winter was not easy. I thought I would never be able to get through it.”*

MSF, with the help of N.L.’s son, continued to encourage and emphasise the importance of adherence to the treatment. The MSF team also offered N.L. social support. They provided him food parcels to ensure a balanced diet, transportation allowance to cover the costs of getting to the clinic every day, firewood for the coldest months of winter, and psychological counselling when needed. After months of strenuous effort on both sides, N.L. started to believe in the effectiveness and benefits of treatment. His attitude changed over time.

*“I very much wanted to finish my treatment so I continued to take the drugs regularly. If you want to live, you have to finish the whole regimen.”*

Right up to the end of his treatment, N.L. visited the clinic every day and never missed a dose.

In Armenia, where health care resources remain among the most limited in former Soviet Union countries, MSF covers the entire cost of treatment. Second-line drugs for treatment of drug-resistant TB alone cost over 9,000 euros per DR-TB patient. MSF has to date enrolled over 160 people with polydrug-resistant, multidrug-resistant or extensively drug-resistant TB in treatment programmes in the capital, Yerevan. 20 patients have successfully completed the treatment, 11 have died, and 21 have defaulted on treatment. The rest are still undergoing treatment.



MSF doctor, Armenia

# “The Perfect Storm”: When TB drug-resistance and HIV/TB co-infection collide

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*Treating MDR-TB and HIV simultaneously is incredibly frustrating because of drug interactions and the potential for many strong side effects, let alone the number of pills patients have to take every day. With the tools we have today, we're fighting a losing battle in places where we see a lot of HIV/AIDS. The risk of MDR-TB spreading like wildfire is a terrifying but all too likely prospect.*

**Dr. Liesbet Ohler,**  
MSF, Kenya

When drug-resistant TB emerges in vulnerable populations also infected with HIV the elements of a “perfect storm” are created. The results are catastrophic. The world woke up to this threat in 2006 after a hospital in KwaZulu-Natal in South Africa reported that 52 out of 53 patients co-infected with HIV and extensively drug-resistant strains of TB had

died before their diagnosis could be confirmed and they could be put on treatment.<sup>21</sup>

MSF first encountered drug-resistant TB in eastern Europe and the former Soviet Union, where the problem of MDR-TB first emerged and the medical infrastructure was already in place for treating TB.

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However, with the spread of TB across increasing numbers of HIV positive populations in sub-Saharan Africa, the picture is now completely different. The medical infrastructures in these countries – already swamped by HIV (for instance the estimated 5.5 million people living with HIV in South Africa),<sup>22</sup> let alone other diseases – are ill-equipped to cope.

## **Patient isolation – a counterproductive strategy**

Some countries – such as South Africa – have adopted the policy of isolating DR-TB patients from the community as the national strategy. Diagnosed patients are admitted to regional, specialised treat-



MDR-TB patient and MSF staff, Uzbekistan





© Henrik Glette

Khayelitsha TB campaign, South Africa

ment centres for at least six months, usually into congregate wards. The main argument is around the need to reduce community transmission by ‘isolating’ patients. However, there is little evidence that prolonged hospitalisation improves adherence and prevents transmission, and there are even indications to the contrary. In addition, this policy raises difficult ethical questions. There are several reasons why isolation cannot continue to be the norm for all patients.

Firstly, under-resourced and overburdened health services can’t provide the required facilities, with the result that many patients are kept waiting without treatment.

Secondly, there is now evidence that patients within the confines of such health facilities will actually pass on the disease to their fellow in-patients and health staff, even while they are receiving second-line therapy.<sup>23</sup>

But the overwhelming reason for not pursuing this

blanket policy of hospitalisation is that so many patients will simply not be able to tolerate the isolation in far-away specialised hospitals. They may lose their economic livelihoods and separation from their normal support networks makes treatment unbearable. This could result in many patients defaulting from such hospitals with dire consequences for themselves and with the risk of spreading infection back in the community. Furthermore, isolation could discourage people from being diagnosed and therefore drive the epidemic underground, leading to increased community transmission.<sup>24</sup>

#### **Out in the community: MSF pilots integrated care project**

For these reasons, in Khayelitsha, a township outside Cape Town in South Africa, MSF and local health authorities have been developing a community-based approach to treatment of patients infected with drug-resistant TB – most of whom are also infected with HIV.

This model of care brings with it its own challenges including the need to train local health staff, give peer adherence support to patients, adapt patients’ housing conditions to reduce transmission risks for family members, boost the rapid tracing of patients who default on treatment, and raise awareness more widely about the disease, how it can be treated and its spread limited.

It is hoped that through this model of care more patients will be diagnosed and successfully treated if they are supported to follow treatment in their homes and communities. In addition, building treatment capacity at the primary care level will allow more patients to access care.



© Brendan Bannon

Dr. Liesbet Ohler, MSF doctor, Kenya

**Dr. Cheryl McDermid is the team leader for MSF's drug-resistant TB pilot project in Khayelitsha, South Africa**

Once a patient is diagnosed with TB, we offer counselling so that the patient understands the disease. We educate patients about TB, make them aware that they can be cured, and explain how they can prevent transmitting the disease to others. An MSF counsellor and a peer educator provide this support. Both are former DR-TB patients themselves, and are therefore able to counsel patients based on first-hand experience.

A second counselling session ideally takes place at the patient's home with family members present. Again, we explain the disease, its transmission and treatment and how the risk of transmission at home can be reduced. Sometimes MSF assists the family by providing a separate sleeping space for the patient or installing a window. Ironically, many of the corrugated iron shacks in Khayelitsha provide adequate ventilation because of the gaps left in the buildings as a result of poor construction.

All patients are invited to join a support group which meets weekly. These groups are excellent for encouraging patients just starting on treatment – they can

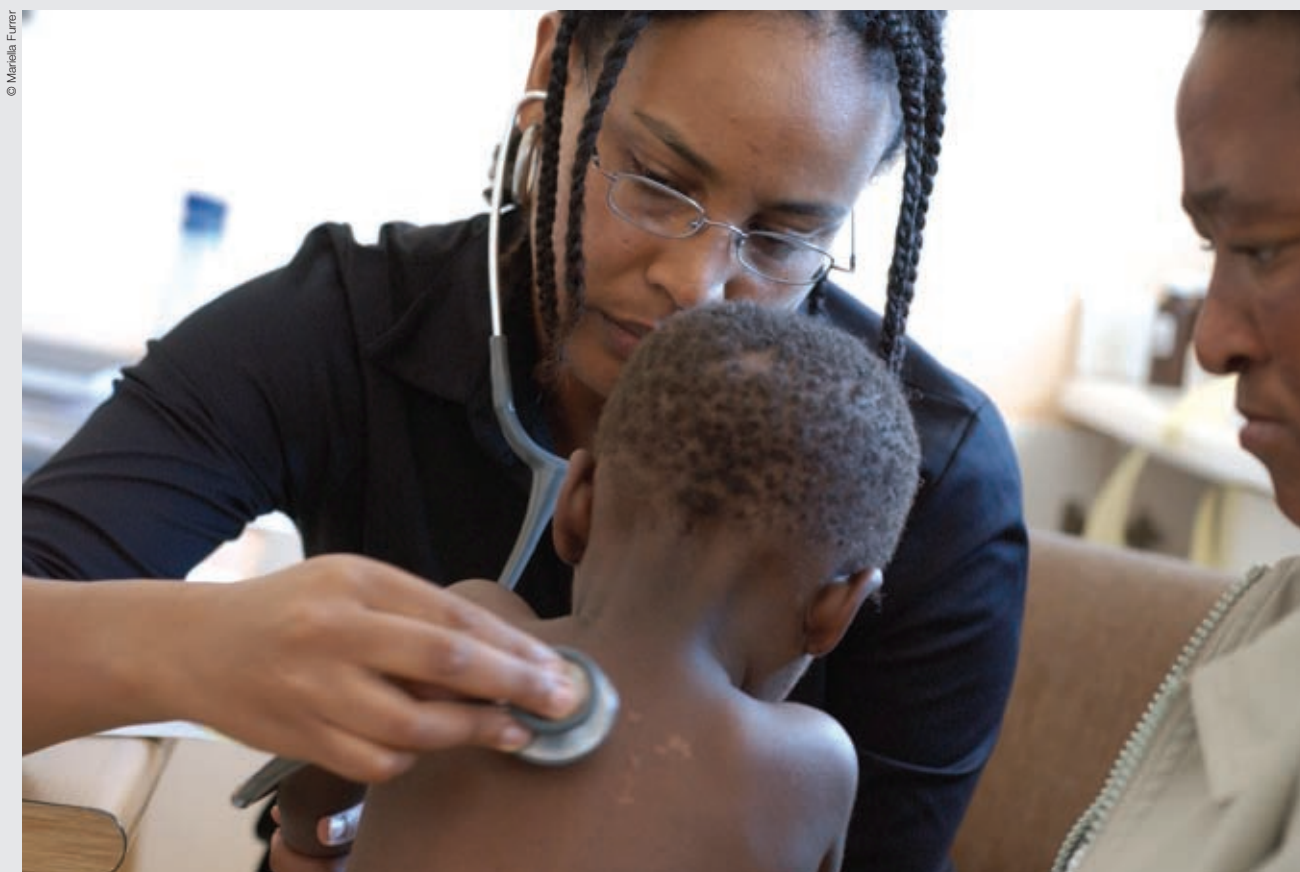
meet people who have been on treatment for much longer, and learn how others cope with taking their TB drugs.

An MSF counsellor visits patients in hospital at least once every fortnight. These visits reduce feelings of abandonment and neglect and the counsellor acts as a link between patients and families.

Most patients with DR-TB do not need complex hospital care. To provide an alternative to sub-acute care, we are establishing a small inpatient facility with 12 beds. This will offer outpatient services but also allow us to treat inpatients for several weeks at a time in a healthcare environment that is closer to patient's family and friends. For patients whose treatment options have run out, the facility will give them the option to receive palliative care and spend the end of their lives close to loved ones.

Our approach aims to allow patients to stay in or near their own homes and, to the greatest extent possible, to maintain a normal, autonomous life.

*Of the nearly 6,000 people diagnosed with TB in Khayelitsha in 2008, 196 have been diagnosed with DR-TB to date. 74 percent of patients with DR-TB were also infected with HIV.*



© Mariella Furer

HIV/TB clinic, Khayelitsha, South Africa

# Conclusions and recommendations

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*We're still simply not seeing the necessary urgency and major investment into research and development that is needed to make sure the basic science of TB gets translated into newer drugs that can shorten and improve treatment, and diagnostic tests that can be used in resource-poor settings.*

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**Dr. Tido von Schoen-Angerer,**

MSF Campaign for Access to Essential Medicines

## **MSF calls for increased access to treatment**

We need a massive effort to ensure more patients have access to appropriate treatment. This means:

### **Boosting access to better diagnostic methods**

Until a new easy-to-use and sensitive point-of-care

diagnostic test for TB is developed, there is no alternative but to boost access to existing diagnostic tools. Additional TB culture facilities must be set up wherever possible. Significant international and national efforts to build the capacity of laboratory facilities will also be necessary if the WHO recommendation to screen patients at risk of DR-TB for drug resistance is to be implemented successfully. MDR-TB rates in many areas of the world are high enough to justify routine DST testing in all new TB patients. For people living with HIV, DST should be performed at the start of TB treatment, as far as possible, to avoid mortality due to unrecognised DR-TB. Rapid DST methods should be used whenever feasible for the initial screening of DR-TB.<sup>25</sup>

### **Prioritising TB and scaling-up drug-resistant TB treatment programmes**

Current scale-up of TB treatment programmes is far too slow to achieve the global target to treat 1.6



Muynaq, TB patient, Uzbekistan





Murat Eidergetsov, MDR-TB patient, Uzbekistan

million MDR- and XDR-TB patients by 2015.<sup>26</sup> What's more, this global target does not even include all new patients with MDR-TB: with more than one million people already with MDR-TB today and an additional 490,000 new cases emerging each year, many more will need treatment. The goal of treatment scale-up is unrealistic with the tools at our disposal today. Greater efforts are needed to accelerate scale up.

Like tobacco control, MDR-TB requires an international response. An international agreement on TB with a specific focus on control and treatment of MDR-TB could strengthen the WHO's role towards countries that are not on track to control the MDR-TB epidemic. It would also draw the attention of policy makers to the MDR-TB problem.

New treatment models, including patient follow up at community level, are needed in particular in high burden MDR-TB / HIV contexts. The current centralised, hospital-based model will not be replicable in many health systems.

### **Removing the barriers preventing the supply of second-line drugs**

To reduce drug costs and improve the supply of second-line drugs, it is necessary to identify more than one quality-assured producer for each of the drugs needed in a second-line regimen. A global scale-up of MDR-TB treatment should increase volumes sufficiently to attract further drug producers and to reduce the price thanks to economies of scale and competition.

WHO leadership is needed to ensure that the drugs it recommends for second- and third-line treatment continue to be delivered to MDR-TB programmes, even when no regulatory indication for TB treatment exists.



MSF staff, Kyrgyzstan

### **Integrating TB and HIV care**

TB treatment is falling dramatically behind where it matters most: Africa. Routine HIV testing and care must be made available to TB patients and all HIV patients must be screened and have access to early diagnosis and treatment of TB.

### **MSF calls for an end to the neglect of TB research and a new framework for innovation and access**

Many of the formidable obstacles we face in treating and detecting TB today are due to the inadequacy of the tools at our disposal.

Not enough is being done. Despite the presence of new actors and initiatives working in the field of TB diagnosis research, current research and development efforts are still woefully insufficient to deliver the diagnostic tests that answer the most urgent medical needs. We need tests that are more accurate than culture or microscopy, that give results fast and are simple enough to be used in remote settings.

Although the situation has significantly improved in the last decade, the TB drug pipeline is also relatively weak. About 40 compounds are currently in the global TB drug pipeline.<sup>27</sup> This might sound promising, but if we compare it to the 171 and 371 drugs currently in clinical development respectively for pain management<sup>28</sup> and cardiovascular diseases<sup>29</sup> and developed only by US pharmaceutical companies, the size of neglect for TB research and development becomes evident.

Furthermore, 'attrition' rates mean that this is in fact falling far short of what is needed – on average only one compound out of 20 makes it through the development stages, while the other 19 are abandoned.<sup>30</sup>

TB vaccine research has made progress and today we have some candidate vaccines in the pipeline. However, they are all in the early stage of development and clinical testing will not be completed before the next seven to eight years. Moreover, after the vaccines are tested singularly, further clinical research will need to be conducted to identify the most effective combination of priming and boosting vaccines. Therefore, an effective vaccine for TB is still years away and sustained funding will be necessary to reach this goal.

We need a massive push to get new tools for TB.

This means:

### **New tools that respond to needs**

Currently many different research agendas co-exist, and the most urgent needs don't necessarily attract the most investment. For diagnostics, for example, the needs of patients that are falling through the net must be prioritised. We need tools that work for children, for HIV positive patients, for all forms of active TB, and that can determine drug resistance. This may mean using samples other than sputum, which is so problematic for many patients.

### **Looking at the peripheral level**

Diagnostic developers need to focus on the periph-

eral level. They must concentrate on developing tools that can be used as close as possible to a patient's bedside. This would allow diagnosis to be carried out at the places where the majority of patients are seen and ensure that patients are immediately enrolled into appropriate treatment, avoiding the spread of disease.

### **Boosting clinical trial capacity**

More clinical trials are needed for the validation of tests and new drugs. Yet only US\$20 million is spent annually worldwide for clinical trials for TB drugs compared to around US\$300 million for HIV drugs in the US alone.<sup>31</sup> In order to get more clinical trials done, funding needs to be fast tracked, and building of clinical trial capacity in endemic countries must become a priority. This requires a concerted effort of its own.

### **Boosting clinical trials for MDR-TB drugs**

Improvements in MDR-TB treatment are critically urgent not only because of the current desperate situation in MDR-TB treatment but also because an entirely new first-line regimen for TB that would also address the problem of drug-resistant TB is many years away. New drugs that are developed for TB should undergo trials in MDR-TB patients. A series of trials will be necessary to identify the best regimens and to integrate any new compound in the MDR-TB

© Donald Weber



Svetlana Pralieva, TB patient, Uzbekistan

treatment regimen. A new initiative, Research Excellence to Stop TB Resistance (RESIST-TB) has been created to address this gap, but lacks crucial funding. This must change.

### **Ensuring access to knowledge**

Cooperation among different research projects must be encouraged, and access to knowledge and others' research facilitated, for example through promising open source initiatives.

### **Spending more money now**

TB predominantly affects developing countries. As a result, TB research has been neglected through a lack of market incentives for pharmaceutical companies to invest in this area. The shortfall is colossal. Funding needs are estimated at around US\$2 billion,<sup>32</sup> yet barely US\$400 million is spent today. European countries' contributions are particularly weak.<sup>33</sup>

### **Supporting alternative mechanisms to finance research and development and support access**

The current system for stimulating and rewarding research into and development of medicines, diagnostics and vaccines relies predominantly on the high prices that can be secured for health products developed, notably through granting monopoly and other intellectual property rights.

It is no secret that the system is broken. Alternative mechanisms that stimulate research and development into neglected diseases, but also ensure that any products developed remain affordable and accessible to those in need, must be explored.

We need a combination of larger and more sustainable 'push' funding through grants to researchers and academics, and 'pull' funding, through mechanisms such as a prize fund.

### **Backing a TB diagnostic test prize fund**

Prize funds that separate the cost of research from the price of the finished product mean that any developed drug or diagnostic test can be priced more affordably for developing countries. They also allow donors to steer research towards areas of priority needs by determining in advance what medical innovation deserves to be rewarded.

In April 2008, at an expert roundtable discussion convened by MSF, TB researchers, economists and campaigners showed considerable interest in a proposal for a prize fund that would encourage the development of an easy-to-use, point-of-care TB diagnostic test.



MSF lab technician, Uzbekistan

The governments of Barbados and Bolivia subsequently made such a proposal to WHO. They suggested exploring multiple prizes: for the development of a low-cost rapid diagnostic test for TB; for new treatments for Chagas disease; for a priority medicines and vaccines prize fund; and for new cancer treatments in developing countries.

### **Putting patents into a patent pool**

The idea behind a patent pool is that different patent-holders, such as companies, universities and research institutes, make their patents and other relevant intellectual property available to others on a voluntary basis through the pool. The pool then acts like a one-stop patent shop and allows other companies and researchers to access those patents in exchange for a fair royalty payment to the patent-holders.

UNITAID is currently setting up a medicines patent pool. The pool will initially focus on HIV and seek to boost access to new antiretroviral drugs in developing countries and to stimulate follow-on innovation such as the development of fixed-dose combinations or paediatric formulations. Once established, the patent pool could be extended to TB. Companies should collaborate with UNITAID with a view to voluntarily contribute their patents.



# Glossary of terms

**Active tuberculosis.** A form of TB characterised by active growth and multiplication of bacteria in the infected part(s) of the body, leading to the destruction of infected tissues and organs. As opposed to latent TB it needs immediate treatment.

**Adherence.** A patient is fully adherent to a treatment if the drugs are taken at the right dose, at the right time for the whole duration of the treatment course; if no doses are missed; if no appointments for follow up are missed; and if the patient feels co-responsible for his or her treatment. For TB, one patient out of two will have difficulties in following the treatment course. Poor adherence may lead to treatment failure, the development of drug resistance, and increases the threat of transmitting the disease to others.

**Ambulatory treatment.** Also called outpatient treatment, ambulatory treatment for TB is delivered and directly observed by a caretaker (see DOT), but without keeping the patient hospitalised. Patients living near a health centre will go to the centre on a daily basis to collect their treatment. Patients living further away will be visited by a community health worker who will deliver treatment to the patients' home.

**Combination therapy.** Therapy characterised by the simultaneous administration of two or more drugs.

**Completion.** A type of treatment outcome used to determine the success (or lack of success) of treatment for individual patients. Treatment completion applies to patients who have undergone a whole treatment course but for whom there is no confirmation of cure. This can either be because the absence of *M. tuberculosis* from the patient's sputum was not correctly verified or because the patient was not able to produce sputum. This definition will also be used for patients who initially enrolled as smear negative, as in their case a negative sputum sample is not a confirmation of a specific response to treatment.

**Culture.** Bacterial culture is a laboratory method to multiply bacteria in order to assess their presence or not in a patient's sample. This is done by letting the bacteria grow in predetermined culture media under

controlled laboratory conditions, outside the natural environment where they usually grow (e.g. for TB, the human body).

**Culture medium.** A liquid or solid substance with a composition that supports the growth of micro-organisms or cells outside the natural environment where they usually grow.

**Default.** A patient who defaults has interrupted treatment for over two months. Defaulters who eventually return to access healthcare will usually be re-started on treatment, but the treatment regimen used will be stronger, with initially five (instead of four) drugs, as the patient might have developed resistance by virtue of defaulting.

**DNA.** Deoxyribonucleic acid. This is the molecule that encodes the genetic information that determines the development and functioning of living organisms and some viruses.

**DOT.** Directly-Observed Treatment. As opposed to self-administered treatment (SAT), DOT involves a patient taking medication in front of a healthcare or community worker, in order to ensure that the lengthy regimen is taken in full by the patient.

**DOTS.** Directly-Observed Treatment, Short-course is WHO's recommended strategy for detection and cure of TB. DOTS combines five elements: political commitment, access to microscopy services for diagnosis of TB, reliable drug supplies, surveillance and monitoring systems and use of highly efficacious regimes with direct observation of treatment.

**Drug resistance.** When a drug used to treat tuberculosis is in fact ineffective against a strain of *M. tuberculosis*, the bacteria is said to be resistant to the drug (as opposed to drug-susceptible or drug-sensitive).

**Drug sensitivity testing.** Sometimes also called anti-biogram, Drug Sensitivity Testing, or DST, is a technique to determine which drugs work and which don't. It is done by exposing the TB bacilli to a culture medium enriched by the antibiotic: if the bacteria are able to

grow, the antibiotic is ineffective and the bacteria are resistant to the drug. If there is no growth, the antibiotic is proven to be effective, and the bacteria are sensitive or susceptible to the drug.

**Drug-susceptible TB.** Bacteria are said to be sensitive to a drug when the drugs are effective in killing or stopping the multiplication of bacteria in the body and can therefore clear the infection. The strains of TB which are sensitive to all first-line drugs are called drug-susceptible.

**Extra-pulmonary TB.** Form of TB where *M. tuberculosis* infect parts of the body other than the lungs. This is most commonly the lymph nodes, bones, central nervous system, cardiovascular and gastrointestinal systems.

**First-line drugs.** The drugs used as the first resort to treat a disease. In the case of TB, the following five drugs are usually chosen: isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z) and streptomycin (S). These drugs are highly effective in drug-susceptible TB and patients usually tolerate them well.

**Latent TB.** A form of TB characterised by the presence in the body of *M. tuberculosis* in a “dormant” state. In other words, they are not actively growing or multiplying. This form of the disease is not contagious. As opposed to active TB, most of the time, no treatment is needed.

**MGIT.** MGIT stands for *Mycobacterium* Growth Indicator Tube. A diagnostic technique that contains a liquid medium releasing fluorescence when *Mycobacteria* are growing. The fluorescence is detected by a machine. The huge benefit of MGIT is the shorter time lag until a positive result can be obtained (8-10 days compared with 4-6 weeks for conventional culture media). But MGIT requires a well equipped laboratory, constant power supply and well trained staff.

**Microscopy.** Microscopy is currently the most commonly used technique to diagnose TB. Two to three sputum samples are taken from the patient and the sample will be stained and later read under the microscope. If TB bacilli are present, they occur in the form of small red rods, while the rest of the sample is blue.

**Mycobacteria.** Types of bacteria, of the genus *Mycobacterium*, that cause diseases such as TB and leprosy.

***Mycobacterium tuberculosis* or *M. tuberculosis*.** A pathogenic bacterial species of the genus *Mycobacterium* and the causative agent of most cases of TB. First discovered in 1882 by Robert Koch.

**Outpatient treatment.** See ambulatory treatment.

**Pathogen.** Any disease-producing agent (e.g. virus, bacteria, fungi).

**Peripheral level.** In the organisation of health systems, the peripheral level represents the first point of contact of a person who is unwell with the health services. In low- and middle-income countries, peripheral health facilities are often located in rural and remote areas.

**Point-of-care testing.** Testing at the point-of-care means that diagnosis is carried out as close as possible to the site of patient care. The driving notion behind point-of-care testing is having a test as convenient to the patient as possible and giving immediate results that can lead to prompt initiation of treatment.

**Pulmonary TB.** Form of TB where *M. tuberculosis* bacteria are infecting the lungs.

**Push and pull mechanisms.** ‘Push’ financing mechanisms are those that invest upfront in research to stimulate the development of new products. ‘Push’ programmes provide direct funding through, for example, grants to universities or government laboratories. In contrast, ‘pull’ mechanisms are economic devices designed to create or secure a market, thereby improving the likelihood of a return on financial investments and thus making such investment more attractive.

**Reagent.** A chemical agent used for chemical reactions. Reagents are used in medical laboratories to facilitate reactions which then can confirm or reject a diagnosis.

**Second-line drugs.** Second-line drugs are used when the first-line drugs are no longer effective to cure a patient. They are less effective against *M. tuberculosis* and have many more side-effects than first-line drugs.

**Sputum smear-positive or smear-negative TB.** We speak about sputum smear-positive TB when *M. tuberculosis* bacteria can be identified in the sputum of patients through examination with a microscope. Sputum smear-negative TB, on the contrary, is when bacteria can not be identified in the sputum of patients.

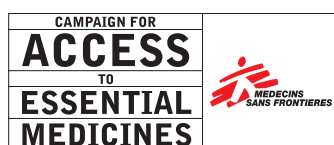
**TLA.** Thin layer agar. A solid culture medium used to facilitate the rapid culturing of *M. tuberculosis*. The TLA method is cheaper and easier to handle than MGIT and therefore a promising technique for more remote settings.

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