Treating drug-resistant TB:

What does it take?

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Abbreviations

DOT	directly observed therapy
DOTS	directly observed treatment, short-course
DST	drug susceptibility testing
DR-TB	drug-resistant tuberculosis
GDF	Global Drug Facility
GLC	Green Light Committee
MDR-TB	multidrug-resistant tuberculosis
PAHO	Pan American Health Organization
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
SRA	Stringent Regulatory Authority
TB	tuberculosis
UPDP	United Nations Development Programme
UNOPS	United Nations Office for Project Services
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Glossary

Rapid molecular diagnostic techniques: Rapid molecular diagnostic techniques: Techniques used to diagnose TB drug-resistance through identification of the presence of gene mutations in the TB bacilli that are associated with drug-resistance. The results can be available in two hours. Examples of commercialised rapid molecular diagnostic tests include the Cepheid GeneXpert MTB/RIF and Hain Life Sciences GenoType MTBDRplus.

Primary resistance: TB drug-resistance documented before a patient's first anti-TB treatment. This signifies infection by a strain that is already drug-resistant.

Acquired resistance: This is when the strain acquires resistance after infecting the patient.[1]

Second-line drugs: In the traditional classification of anti-tuberculosis drugs, this refers to anti-TB drugs other than the first-line drugs rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin.

Editorial committee

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Table of contents

DEFINING TB

Drug-resistant tuberculosis (DR-TB) is used to describe all those strains of TB that show resistance to one or more of the common first-line drugs. The term is used in this booklet to include all of the possibilities listed below.

Monodrug-resistant tuberculosis describes TB that is resistant to any one first-line drug.

Polydrug-resistant TB (PDR-TB) is defined as strains that are resistant to more than one first-line TB drug, but not to both isoniazid and rifampicin.

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to isoniazid and rifampicin, the two most powerful TB drugs. Isolates that have multiple resistance to any other combination of TB drugs – but not to isoniazid and rifampicin – are not classed as MDR-TB.

Extensively drug-resistant tuberculosis (XDR-TB) is defined as TB that is resistant to the first-line drugs isoniazid and rifampicin, and also to second-line drugs, including at least one from the class of antibiotics known as fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin).

HOW DO DRUG-RESISTANT STRAINS DEVELOP AND SPREAD?

Resistant strains develop in a number of ways:

Drug-resistant TB can spread in the same manner as drug-sensitive TB and is spread as readily: TB germs are released into the air when a person with TB of the lungs or throat coughs, sneezes, speaks or sings. People become infected when they breathe in the germ.

DR-TB also develops during the treatment of drug-sensitive TB when patients fail to complete their full course of treatment; when healthcare providers prescribe the wrong treatment, the wrong dose, or the wrong length of time for taking the drugs; when the supply of drugs is interrupted; and when the drugs are of poor quality. DR-TB transmits more readily in poorly-ventilated and crowded settings and, as a result, outbreaks in hospitals and prisons have been reported. DR-TB is of particular concern for people with weakened immune systems, such as people living with HIV/AIDS.

Under optimal conditions, standard TB treatment for drug-sensitive TB is effective in 90 to 100 percent of patients who take the medication, with less than 3 percent post-treatment relapse. However, these results are seldom achieved by TB programmes, with many programmes struggling to achieve sustained cure rates of 80 percent.[2]

In resource-limited settings, strategies for the large-scale management of DR-TB should be monitored regularly to check on their effectiveness. In 2010 the World Health Organization (WHO) announced that there would be universal access to treatment by 2015. The WHO also introduced new guidelines (in 2008, updated in 2011) on drug sensitivity testing (DST) for TB, and on the treatment of DR-TB. However, despite these apparent advances, the majority of patients with drug-resistant TB continue to have poor access to care or to receive sub-standard treatment. The result is that the number of cases of DR-TB is growing, while cases with increased resistance (extensively drug-resistant TB) are becoming more common.

1. Introduction: The specific challenges of DR-TB as part of tuberculosis care

Tuberculosis (TB) is a curable disease that kills nearly 1.45 million people across the globe each year and is the main cause of death for people living with HIV/AIDs. Of the 8.8 million new tuberculosis cases each year, 440,000 are forms of the disease that are multidrug-resistant,[3] meaning they cannot be treated with the two primary antibiotics used to treat TB. The four countries with the largest number of estimated cases of drug-resistant TB (DR-TB) in 2008 were China, India, the Russian Federation and South Africa. By July 2010, 58 countries and territories had reported at least one case of extensively drug-resistant TB (XDR-TB), which is resistant to both first and second-line drugs. It is widely acknowledged that the global response to this public health disaster barely touches the problem. In the high-burden countries for DR-TB and XDR-TB (those with data on treatment outcomes for DR-TB cases), a reported 24,511 people were enrolled on treatment, and success rates of 25 to 82 percent were reported among patients who started treatment in 2007.[4]

The treatment of drug-resistant strains of TB is difficult for a number of reasons. Major barriers include the high cost and limited availability of quality-assured second-line drugs; extensive laboratory and monitoring requirements; the adverse side effects of second-line drugs; inadequate support for adherence, as well as inadequate psychosocial and palliative care; and insufficient international funds to support the scale-up of treatment. While it is possible to cure drug-susceptible TB within six months, DR-TB requires extensive chemotherapy for up to two years with drugs which have toxic side effects, are less effective and are 50 to 200 times more expensive.

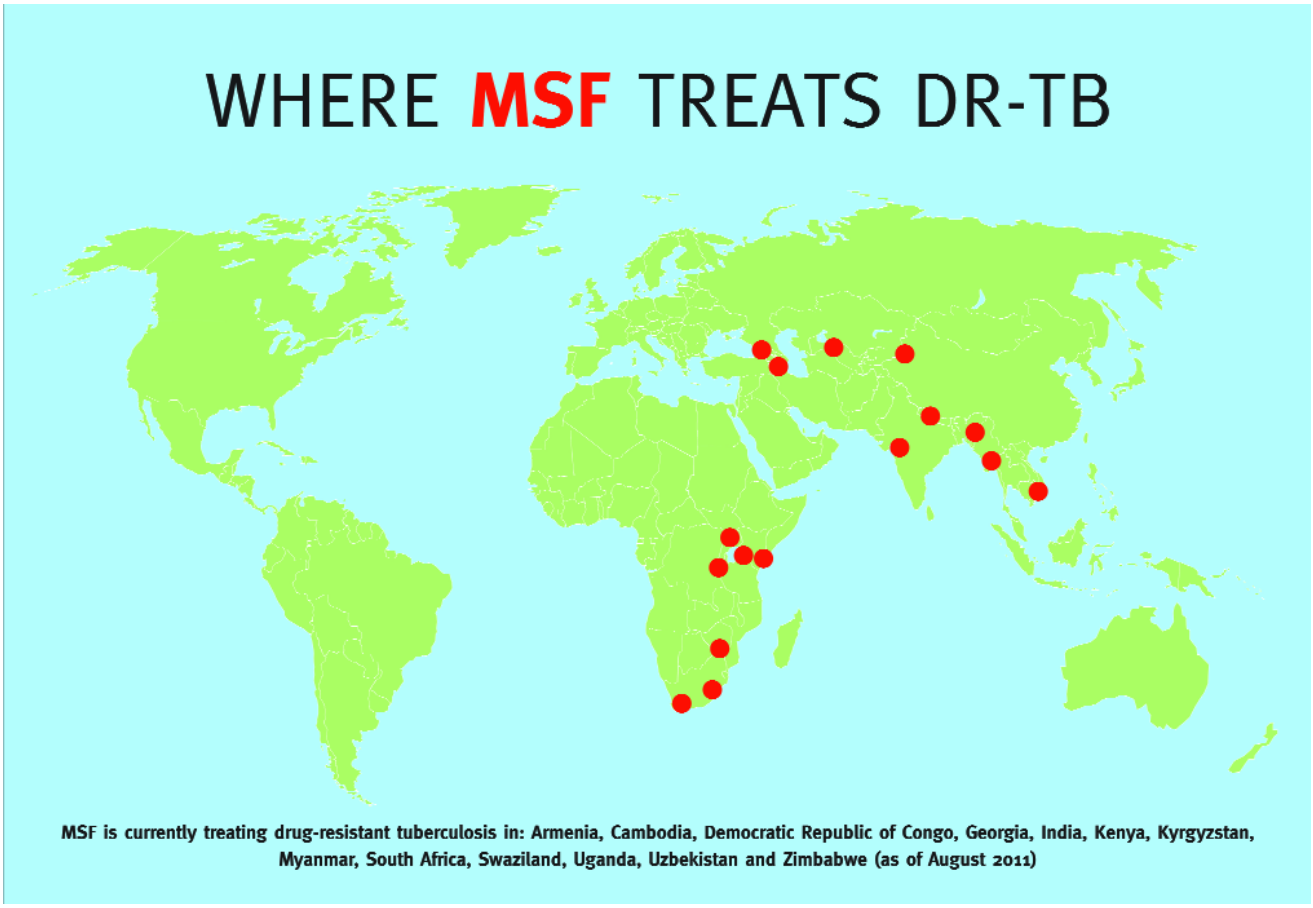
MSF is keen to demonstrate that high-quality care *can* be delivered to patients suffering from drug-resistant TB despite the challenges of the settings in which we work. This booklet aims to share some practical examples and potential solutions to the very specific challenges of DR-TB care.

From 2001 to 2010, MSF enrolled 3,692 patients with drug-resistant TB, with a success rate of 52 percent, a default rate of 22 percent, a failure rate of 9 percent, and a death rate of 11 percent in the 2001-07 cohort. This is in keeping with results of other stakeholders providing DR-TB care.[5]

For the purpose of this booklet, 14 MSF projects in 12 countries around the world have been reviewed, in contexts ranging from post-conflict insecure environments, through urban slums and townships, to remote rural populations. This booklet describes the imaginative solutions and innovative practices that are being used in these very different contexts. It is intended as a practical resource: to help overcome the obstacles to starting treatment programmes, and to help develop ways to scale up existing programmes. We do not underestimate the challenges involved, nor do we advocate a single, standardised approach for all locations and patient groups – the specific context and requirements for each situation require their own tailored approaches. Rather this booklet aims to bring together the experience garnered by MSF teams and partners, to document country-adapted flexible strategies that have enabled health providers to overcome the difficulties and develop treatment programmes for DR-TB.

The booklet is organised into two main sections. The first section describes practical examples that illustrate all components of patient care, while the second section gives data and commentary on the most recent research and development.

We hope that the experiences shared here will inspire you to get started, whether you are considering how to treat just one patient in your care, or wondering how to develop an approach that can be replicated at national level.


WHERE MSF TREATS DR-TB
MSF is currently treating drug-resistant tuberculosis in: Armenia, Cambodia, Democratic Republic of Congo, Georgia, India, Kenya, Kyrgyzstan, Myanmar, South Africa, Swaziland, Uganda, Uzbekistan and Zimbabwe (as of August 2011)

1. Practical solutions

1.1 Finding patients

1.1.1 Improving case-finding criteria

Universal access to TB treatment is best realised through effective case detection. The early diagnosis and treatment of TB is vital in preventing the spread of the disease.[6] TB, in both its drug-sensitive and drug-resistant forms, is transmitted easily from person to person. The major risk of infection by TB patients to family members and other contacts is from exposure prior to diagnosis. By limiting the criteria for testing patients, it is easy to miss cases and allow the disease to spread.

Ideally all TB patients in all situations should have access to timely drug sensitivity testing. In reality, however, financial and logistical issues – such as budget allocation, available drugs, staff numbers and laboratory capacity – too often influence case-finding strategies for DR-TB, leading to cases being missed. In places where adequate diagnostics have only limited availability, it may be necessary to adapt diagnostic strategies in order to respond to the priority needs. Each context where MSF operates differs in its strategy for case-finding criteria based on general morbidity, HIV prevalence and the risk of illness and mortality.

Gathering reliable data is an important first step for any change in policy with regard to case detection criteria. Even when programmes start with initially limited testing criteria, it is important to plan for gathering local data and expanding the testing criteria in the future.

With the advent of an increase in numbers of HIV patients, and the rise of drug-resistant TB, we aim to scale up TB care. As better tools are developed, the challenge will be to treat appropriately all new and re-treatment cases as soon as possible, in particular the contacts of confirmed DR-TB patients and all people living with HIV/AIDS who are TB suspects.

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SOUTH AFRICA: Raising awareness

In MSF's project in Khayelitsha, an important component of the case detection strategy has been the education of clinic staff. By training them to promote increased awareness of DR-TB among patients and other health staff, it has enabled TB to be diagnosed and treated more effectively and promptly at the primary healthcare level. This, together with programmatic data,[i] has prompted the case detection strategy in the programme to be changed, so that all TB cases are now screened for drug resistance, allowing early diagnosis and treatment, and preventing the further spread of DR-TB.

SWAZILAND: Intensified case finding

In Swaziland, a drug resistance survey carried out in 2009 revealed 7.7% of DR-TB in new cases and 35% in retreated cases. Of all detected DR-TB patients, 70% are new cases. Swaziland has a TB incidence (for all forms of TB) of 1,275/100,000. All of these new cases would have been missed if the DR-TB detection strategy had only included retreatment cases. Intensified case finding has now been adopted in the programme with screening for TB of all people living with HIV/AIDS at each consultation, and the offer of culture and DST to all identified patients.

[i] In 2009, 231 patients were diagnosed with DR-TB, giving a case notification rate of 45 per 100,000 people per year (for an estimated population in Khayelitsha of 500,000). This represents an estimated detection rate of 54% when compared to the DR-TB prevalence estimated in previous surveys (2008/09). Until now, only 29% of DR-TB cases diagnosed in Khayelitsha have been new cases.

UZBEKISTAN: Changing criteria

MSF commenced DR-TB treatment in Karakalpakstan in 2003 and by the end of 2010 had enrolled 1,495 patients. The number of patients enrolled per year increased from 23 patients in 2003 to 373 patients in 2010. The registration group of enrolling patients changed over time. Between 2003 and 2005, the majority of patients enrolled were those who had failed two or more previous TB treatments. In 2006, the criteria for DST was changed to test all smear-positive TB patients, and then in 2008 to test all TB suspects. The category of "new" patients with DR-TB, who have not previously received TB treatment, has been rising, and since 2008 totals about 30% of enrolled patients.

1.1.2 High-risk groups

High-risk groups for DR-TB vary according to the context, and certain groups should always be considered as at an increased risk of contracting the disease. These include people living with HIV/AIDS, especially children, because they are immunocompromised; prisoners living in overcrowded conditions, where the disease can spread easily; and healthcare workers, because of the likelihood of cross-infection from patients in overcrowded and poorly ventilated hospitals and health clinics. Studies have found healthcare workers have rates of DR-TB several times higher than in the general population.[7] Examples of other high-risk groups seen in MSF programmes include migrants working in the mining industry and patients who have been incorrectly prescribed TB drugs for other conditions.

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KYRGYZSTAN: Prisoners at risk

MSF's project on the outskirts of the capital, Bishkek, provides TB care within the penitentiary system, where TB incidence is estimated to be 25-30 times higher than in the general population, and where 30 percent of those with TB have a drug-resistant strain of the disease. In this programme an active case-finding policy requires that all new inmates are screened upon arrival and all patients are screened every six months. Staff and prisoners are also trained to recognize TB symptoms. All patients diagnosed with TB have sputum sent for culture and DST, as all are considered high-risk for DR-TB.

INDIA: HIV-positive patients

MSF runs a dedicated home-based treatment for HIV and DR-TB in Mumbai which serves people living with HIV/AIDS who have been excluded from the public health system for social reasons. All of MSF's HIV-positive patients are screened for TB on each visit; if TB is suspected, then sputum is sent for culture and DST. The programme demonstrates that it is not only important to provide treatment but also to influence positive access for all patients at risk.

UZBEKISTAN: Healthcare workers

Four percent of all DR-TB patients in MSF's project in Karakalpakstan between 2003 and 2010 were healthcare workers (defined as anyone who works in the health system, including cleaners and guards). Healthcare workers were also more likely than other patients to default from treatment. The risk of transmission means that healthcare workers who are diagnosed with TB are often barred from work, which may cause health workers to present late. As they are a high-risk group, there should be effective policies in place for their own protection, as well as for the protection of patients. Consideration must be given as to when it is safe for healthcare workers with TB and DR-TB to return to work, particularly if they have contact with immunocompromised patients. Alternative work duties should be identified, or temporary disability payment schemes put in place.

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1.1.3 Contact tracing

People who have been in close proximity to DR-TB patients need to be traced and screened for the disease, as they are at high risk of infection. Contact screening is therefore an important method of improving case detection and thus reducing the risk of future transmission.

The ongoing monitoring of household contacts is relatively simple in situations where home-based care is provided for DR-TB patients and where health staff visit patients on a regular basis. Where care is provided away from a patient's home, it may be more difficult to monitor contacts. While patients are widely encouraged to refer relatives for screening, this has generally had poor outcomes, and in practice the process of getting contact cases screened for TB is haphazard. Most successful has been when teams of social workers or adherence counsellors and strong networks of outreach workers have gone out into the community to trace contacts and identify suspects, as happens within the MSF projects in Georgia and in Homa Bay, Kenya. When family members live far away, they can be encouraged to attend the clinic for screening by reimbursing transport costs, as happens in MSF's programmes in the Democratic Republic of Congo and Swaziland.

It is particularly important to include children in contact tracing. A study conducted in South Africa of children under five who were contacts of adults with DR-TB found evidence that 51% were infected and 12% had active disease.[8] It is essential that DR-TB programmes ensure good contact tracing systems, otherwise a large number of cases, especially children, will be missed.

SOUTH AFRICA: Tracing child contacts

The Khayelitsha programme has implemented a system of enhanced contact screening in which household contacts of DR-TB cases are identified and recorded at both the time of diagnosis in the clinic and at the subsequent home visit. Home visits are possible through a strong network of community health workers and peer supporters. Symptomatic contacts and all children under five years old or who are HIV-positive are given a letter stating that there has been contact with a confirmed case of DR-TB and encouraged to go to the clinic. Screening of close contacts yields a significant number of DR-TB cases. Programmatic data from 2009 show active TB diagnosed in 12% of 84 screened children under five years of age.

1.1.4 Diagnosis

Early diagnosis is vital for DR-TB patients. A delayed diagnosis can result in progressive lung destruction, higher bacillary loads, a worsening clinical condition and ongoing transmission.[9] Late diagnosis of DR-TB results in lower treatment success and failure rates.[10,11] The speed with which it is possible to obtain an accurate and specific profile of the different TB drugs to which the TB bacillus is resistant varies from context to context. Molecular line probe assays (LPAs) for the rapid detection of DR-TB were endorsed by the WHO in 2008,[12] while the Cepheid Xpert MTB/RIF test was endorsed by the WHO in December 2010.[13]

The time taken to diagnose DR-TB and start treatment depends as much on the process used for prompt diagnosis and treatment as on the diagnostic tools available. Further challenges are presented by laboratory quality and the turnaround time for results. There is still a need for reliable and efficient laboratories. In many places, sending specimens to Antwerp remains the only reliable option, as well as being the fastest. Other factors that can contribute to delays in the diagnosis of DR-TB include difficulties in locating and recalling patients to clinics in order to discuss their results and start treatment. The aim to shorten the time it takes to get a result must include the time it takes for the result to reach the patient and appropriate treatment to start.

MSF now plans to implement the Xpert MTB/RIF in a variety of different settings, with plans to order 27 of the analysers by the end of 2011. To date, 16 are already in the implementation phase in 16 countries. Diagnostic algorithms, registers and monitoring tools have also been developed to help with the improvements needed in clinical processes. It is anticipated that introducing the Xpert MTB/RIF will help integrate DR-TB care into general TB care in MSF projects. However, whilst these new tools mark significant improvements in TB diagnostics, neither are suitable for all patients or in all contexts.

UGANDA: Increased laboratory capacity and quality

In order to emphasise the need for good quality control, the MSF teams in Kitgum commenced DR-TB diagnosis by sending samples to the laboratory in Antwerp, with a turnaround time of approximately eight weeks to get DST results for first and second-line TB drugs. Uganda has since increased its laboratory quality, and the project is now able to send samples for culture and rapid genetic testing to the Kampala National Tuberculosis Reference Laboratory.

UZBEKISTAN: Timely uptake of new tools

Due to the implementation of line probe assays, the diagnosis of rifampicin resistance is possible in one day, and a full resistance profile is available within one month. The programme in Karakalpakstan has started to concurrently test drug sensitivity and resistance to first and second-line drugs for samples using line probe assay, which reduces the turnaround time for full DST results by around 14 days per sample in this high DR-TB context.

SOUTH AFRICA: New diagnostic tools

In Khayelitsha, the implementation of new diagnostic tools, as well as improvements to clinical processes, has resulted in the reduction of turnaround time from sample collection to DR-TB treatment initiation. For example, sending samples to the reference lab where the line probe assay diagnostic is used resulted in a 50 percent reduction, from 72 days in 2005 to 35 days in 2009. Similarly, in 2010 with the WHO endorsement of the Cepheid GeneXpert MTB/RIF test for the rapid detection of rifampicin resistance,[14] implementing the test within the project showed the feasibility of rapidly screening TB suspects for rifampicin-resistant forms of DR-TB in a high-burden setting, giving a result within just two hours.[ii] On that basis, the South African Department of Health, like many national TB programmes around the world, has since decided to introduce the GeneXpert diagnostic tool across the country.

[ii] Multicentric study including Médecins Sans Frontières (MSF), Cape Town University (UCT), the Foundation for Innovative New Diagnostics (FIND), the National Health Laboratory Service (NHLS) and the Provincial Administration of the Western Cape (PAWC).

1.2 Patient-centred care

1.2.1 Adapting approaches to treatment delivery models

MSF's experience suggests that, for case detection and treatment outcomes to be improved, a patient-centred and decentralised approach is necessary. The Beijing ministerial meeting of high M/XDR-TB burden countries in April 2009[15] identified that ministries of health often rely on models of care – such as long-term hospitalisation – that are not suited to the needs of patients, are not in line with WHO guidance,[16] reduce the impact of treatment, and are not cost-effective.[17] By contrast, successful outpatient treatment of DR-TB has been demonstrated in Peru and Lesotho by Partners In Health (PIH), using trained, supervised and paid treatment supporters.[18]

In all of the programmes where MSF treats DR-TB, there is a consensus that, to achieve optimal treatment outcomes, the model of care must be adapted according to patients' needs and the local context. There are many examples of projects having expanded DR-TB care into the community, either through home-based interventions or through health facilities close to where patients live. Several programmes use a combined approach that includes both community and hospital-based care, which can be essential for managing severe cases, adapted according to patients' needs.

In countries where a high percentage of TB patients are co-infected with HIV, integration of TB and HIV care is recommended, including integration of DR-TB care. Integrated care results in improved adherence to treatment, improved treatment outcomes and a more efficient delivery of healthcare services, which is especially important in places where there are inadequate numbers of healthcare workers.

UGANDA: Home-based care

In MSF's programme in Kitgum, treatment for DR-TB patients is managed predominantly in the home. Hospital referral is reserved for those patients with severe adverse drug side effects, for those with severe clinical conditions requiring more intensive care, or for those unable to care for themselves and lacking adequate support at home. The home-based approach is very positive for patients, who generally feel more comfortable being cared for in familiar surroundings with their families and friends nearby. This makes it easier for them to manage stress-related conditions and cope with minor side effects. Patients' families are protected with infection control measures including renovations to homes and the use of natural ventilation and sunlight. So far, all patients receiving home-based care have shown good tolerance to their DR-TB treatment.

GEORGIA: A flexible approach

MSF and the Georgian Ministry of Health started to adapt their approach in 2007 to DR-TB cases in an attempt to reduce the proportion of patients who either refused treatment or defaulted during the course of treatment. The approach is flexible and multi-disciplinary, with the possibility of home-based care. Patients are discharged from hospital after an average of five weeks, following a change in the discharge criteria from being culture-negative to being sputum smear-negative.

In order to improve access to treatment near patients' homes, MSF has started to expand the network of DR-TB services to available primary healthcare centres. Clinical staff at these centres have been trained, and infection control measures introduced. Specific care for HIV/TB co-infected patients is dealt with through the regional HIV centre. Patients' incomes are also assessed so as to provide compensation for their loss of earnings from being unable to work.

KENYA: A combined approach

In the urban slum of Mathare, Nairobi, a combined health facility and community-based model is being used. During the intensive phase, patients on twice-daily doses go to the nearest health facility to receive the injectable drugs and their 'morning' dose of oral drugs. The 'evening' oral drugs are administered in the patients' homes by trained community health workers who also supervise DOT throughout the continuation phase. The health facility has a daycare clinic where patients can spend the day and receive a meal.

SOUTH AFRICA, SWAZILAND, KENYA: One-stop services

Extremely high rates of HIV and DR-TB co-infection in South Africa, Swaziland and Kenya (of between 60% and 85%) have resulted in MSF setting up 'one-stop services' where these co-infected patients can be treated for both diseases at the same time. The focus is on integration, antiretroviral initiation and strong psychosocial support, due to the increased risk of adherence problems associated with a very high pill burden and potentially unpleasant side effects.[19] Infection control within such services is implemented according to current transmission research and knowledge.

Recent studies in Khayelitsha, South Africa,[20] and in Homa Bay, Kenya,[21] contrasted outcomes for integrated and non-integrated care. They concluded that providing a one-stop service for TB and HIV resulted in a significant reduction in time from the start of TB treatment to the initiation of antiretroviral treatment, without negatively affecting TB treatment outcomes. Integration also resulted in improved clinical skills and record keeping, and was broadly supported by staff and patients.

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1.2.2 Children

Diagnosing and treating children is a significant challenge. TB in children is difficult to diagnose bacteriologically as it has a low culture yield (due to pauci-bacillary disease).[22] While the basic principles of treatment regimens are the same as for adults, many of the medications do not come in paediatric formulas. Field teams report difficulties in cutting tablets and dividing the content of capsules accurately to get correct dosages. Guidelines are available that offer some limited advice on paediatric DR-TB management,[23] including a literature review of treatment and monitoring for possible adverse side effects of paediatric drug-resistant therapy in high-resource, low-burden settings. At the correct dose, the drugs are generally well tolerated by children,[24] and success rates as high as 95% have been reported.[25]

ARMENIA: Following up child contacts

Despite the large burden of DR-TB in Armenia and the numerous adults detected and treated since 2005, when MSF began supporting the National Tuberculosis Control Programme in December 2010, it found that very few children had been treated for DR-TB due to the difficulties of diagnosing this disease in children.

However, positive efforts have been made since then to improve the baseline screening and careful follow-up of child contacts, as well as to improve the quality of diagnosis, including work on the implementation of sputum induction, and the training of clinicians on paediatric TB diagnostic issues. As a result, in the first three months of 2011, four children were diagnosed and started on DR-TB treatment. In coming months, the programme plans to undertake new operational research into the follow-up of child contacts with the aim of improving detection rates amongst children.

SWAZILAND: Tailored regimens

The MSF programme in Swaziland has treated more than 15 children for DR-TB, the youngest just 18 months old. Despite the difficulties of obtaining microbiological confirmation in children, the team were able to get individual drug sensitivity results for the majority of children, allowing the treatment regimen to be tailored for maximum effectiveness.

The team has struggled with second-line drug formulations that are not adapted to children but, despite these challenges, children have done very well and seem to tolerate the difficult treatment regimen with less 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 as effective as possible.

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1.2.3 Adherence

Adherence to DR-TB treatment is a challenge for a number of reasons, but it is essential in order to lower death rates, stop further resistance developing and halt the emergence of extensively drug-resistant TB. In MSF's DR-TB programmes, default rates range from zero to 39%.[26] The danger is that default rates can increase as scale-up occurs, so successful strategies must be employed to support patients effectively and help them adhere to what is always, for patients, an extremely challenging treatment regimen. The causes of poor adherence include the burden of having to take so many pills at once; the often debilitating side effects of the drugs; the length of time for which the drugs need to be taken; the unpleasantness and pain of repeated injections; the social isolation and intense boredom caused by long hospital stays; the perception, midway through treatment, of feeling better and having made a full recovery; a lack of family support; financial instability from being unable to hold down a job; inadequate or inappropriate support from health workers; and the social stigma frequently associated with the disease.[27]

As well as the internationally agreed standard of direct observation of treatment for patients, MSF promotes patient-centred support for DR-TB treatment, as patients often have difficulties tolerating treatment due to side effects. Patient-centred support emphasises regular monitoring of patients for the timely identification and management of adverse side effects. This in turn promotes adherence.[28]

Ongoing counselling and support is essential, as is education and information about TB and what TB treatment involves. This information needs to be presented in a clear way that both the patient and the patient's family can understand. Health literacy should also be targeted at patients already undergoing treatment.

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KENYA AND INDIA: Flexible support

In the Mathare project, in Nairobi, patients generally live nearby so are able to attend the local health facility on a daily basis and take their medication under the supervision and support of trained nursing staff. In the project in Manipur, by contrast, patients often live far from the health facility, and travel is difficult due to insecurity in the region, so a mobile team of trained nurses and counsellors visits patients in their homes to give support, provide the treatment and promptly recognise the potential development of side effects.

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CAMBODIA: Sharing guidelines

Supporting patients through continuing education and counselling is of paramount importance in improving adherence to treatment and reducing default from treatment, and so in Cambodia the MSF team has developed comprehensive guidelines, with an educational and psychological focus, for the counselling of DR-TB patients. The guidelines have been shared with all partners involved in DR-TB care in the country.

SWAZILAND: Treatment supporters

In the rural Shiselweni region, where the population is scattered over a large area, 'treatment supporters', who are trained, supervised and compensated, provide support to patients for the entire duration of their treatment.

MYANMAR: Solving problems in advance

The programme in Myanmar has a strong emphasis on the education and psychosocial support of patients during treatment. Both DR-TB suspects and patients starting treatment are provided with information about DR-TB by doctors, nurses and counsellors, with the use of flip charts and educational brochures, which can be taken home to read. A popular cartoonist was recruited to draw the pictures, and all the materials were pre-tested with focus groups to ensure that the messages and diagrams were clear.

In pre-treatment assessments, counsellors identify personal factors that may help patients cope with their treatment, as well as factors that might interfere with their adherence to it. Patients are supported to solve problems in advance and think about how to deal with difficulties that may arise in the course of the treatment.

KENYA: Community support network

The project in Homa Bay has a community network of health workers and dedicated DR-TB counsellors who have developed effective materials for information, education and counseling. Community health workers provide treatment support and transport is reimbursed for clinic or hospital visits. The decentralised, home-based model makes care more accessible for patients and allows them to stay in their homes, reducing the need for financial support and helping to reduce the stigma associated with hospital treatment of TB.

1.2.4 Social factors

Many of the factors associated with poor DR-TB treatment adherence are related to the difficult social and economic circumstances in which so many patients live. A review of counselling and clinical records in programmes in South Africa and Uzbekistan suggests that significant factors associated with default are the stigma associated with DR-TB, lack of family support, and difficulties associated with not having a stable home life. Other factors include: excessive alcohol use, either by patients or by close household members, which can contribute to a chaotic home life; the difficulties of staying in hospital for long periods; and the need to work and provide financial support to others.
In Homa Bay, Kenya, MSF has an active policy of engaging with local and international NGOs involved in poverty alleviation to help support their patients.

To increase health literacy levels in communities, MSF staff run public awareness campaigns, take part in radio shows, and produce newsletters targeting community centres, schools, universities, health facilities and community groups. As well as educating people about DR-TB and potentially improving case detection, these activities help to reduce the stigma associated with the disease and with regularly attending clinics, which in turn can ease patients' feelings of shame and isolation.
To increase the provision of social support to patients, MSF trains lay counsellors to provide individual counselling. Some run support groups, which involve family members and staff in addition to patients. To tackle the problems of boredom and stigma, MSF provides activities and entertainments to keep patients busy and to encourage them to interact, make friends and form mutually supportive relationships. In the inpatient facility in Baraka, in DRC, for instance, MSF provides radios and playing cards for patients along with an outside gazebo for passing time with family or friends.

To help patients through treatment, social support should include both incentives (such as money or household food parcels) and enablers (assistance with transport, and nutritional support for malnourished patients). In Georgia, for example, patients receive both material and financial support to rehabilitate their houses for infection control, whilst in Armenia, patients are provided with food parcels and allowances for heating and transport.

UGANDA: Treatment buddies

In response to the difficulties faced by patients in adhering to treatment, MSF provides incentives to DR-TB patients including money and food. Patients also have a 'treatment buddy' who helps to keep them entertained, for example by listening to the radio or reading newspapers together. This helps to keep them engaged in the world outside and to stave off boredom.

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INDIA: A place to stay

Patients in Manipur who need to attend the MSF clinic but live far away are provided with accommodation for the duration of their treatment in a house rented by MSF. They also receive social support from trained lay counsellors, while clinic staff provide local newspapers to read, and fruit juice to disguise the taste of the pills. A support group brings together patients, staff and family members, and close professional relationships are encouraged between patients and all levels of the DR-TB team.

1.2.5 Travel difficulties

Patients may experience difficulty accessing hospitals and clinics for a number of reasons, including long distances, high travel costs and political insecurity. Such difficulties need to be taken into account when deciding on which model of care will work best for patients. For example, the Mathare project, in Kenya, is situated in a densely populated urban slum, and asking patients to attend the clinic on a daily basis for directly observed therapy is not an issue, due to the short distances from home and the absence of transport costs. In Swaziland, by contrast, attending the clinic may mean five hours of travelling each way – so the availability of supervised treatment supporters based in villages is an important consideration. In many low-resource settings where the cost of public transport to health facilities is a major barrier to treatment, MSF reimburses travel costs.

Political insecurity may result in patients having difficulties reaching hospitals. In Manipur, in northeast India, roadblocks are common and travel is severely restricted. In this situation, it is easier for MSF staff to travel to patients' homes than for patients to make daily journeys to clinics, and the care delivery model has been adapted accordingly. In the Democratic Republic of Congo, by contrast, providing TB treatment support is impractical for MSF staff due to security issues and the difficulties of travelling long distances on extremely poor roads. In addition, the dilapidated state of the health service after years of conflict means that the clinical status of many patients is severe, and so care in this context has been adapted to involve longer hospital stays.

1.2.6 Referral to hospital

In contexts where care is provided in outpatient clinics or in patients' homes, there is a need for adequate referral mechanisms to be in place in case patients have severe adverse effects, struggle to cope with adherence, or are too sick to manage treatment at home. The referral and admission process into hospital is much easier for patients if they are accompanied by known staff. It is also good for patient morale and adherence if patients have continued contact with known staff after being admitted to hospital. In some instances, small inpatient facilities have been established as an alternative to hospital care, so that patients can receive inpatient or palliative care close to their homes and families. These requirements could also be fulfilled through use of district hospitals, or more effective use of existing TB hospitals.

INDIA: Accompanying nurses

To make hospital admission easier for patients in Mumbai, an outreach nurse accompanies patients to hospital, and does follow-up through regular visits and contact with the doctor in charge of their care. Clinical back-up is available for critically ill patients.

SOUTH AFRICA: Close to home

Most DR-TB patients in Khayelitsha do not require acute hospital care, though they do sometimes require admission for support with taking their medication, with managing side-effects, or with overcoming other barriers to receiving treatment at home. To provide sub-acute care, a small 12-bed inpatient facility has been established in Khayelitsha which offers care to patients in an environment close to their homes and families. It also has the capacity for appropriate supported end-of-life care.

1.2.7 Infection control

Most transmission occurs among undiagnosed patients. For this reason, the best way of tackling infection control is to identify DR-TB patients, commence treatment with an effective DR-TB regimen and support patients to complete every dose of treatment.

TB can spread easily in a hospital environment. However, measures to prevent transmission of TB in healthcare facilities were largely neglected in both policy and practice until 2005, when outbreaks of MDR-TB and XDR-TB in a hospital setting in southern Africa brought it to public attention.[29] There is evidence that cough prevalence, sputum smear-positivity and crowded, poorly-ventilated living conditions have a significant impact on transmission rates.[30] The infection risk associated with hospital admission to a large congregate ward is up to 50 percent within 24 hours.[31] In 2009, the WHO updated its policy on TB infection control.[32] This provides guidance on how to prioritise elements of TB infection control under four main headings:

managerial activities; administrative activities; environmental controls; and personal protective equipment. Key control actions include:

- **Early and rapid diagnosis and correct treatment**
- **Decentralised and ambulatory treatment (community-based)**
- **Separation/isolation by status**
- **Shorter inpatient stays**
- **Comprehensive TB care**
- **Occupational health screening**

Infection control teams can ensure that infection control procedures are followed, both in healthcare facilities and in patients' homes.

Despite the infection risk associated with hospitals, there is a prevailing lack of confidence that transmission is controllable in the community, which is one of the main obstacles to adapting care to the community level. Once patients are diagnosed and have started treatment, the potential for them to infect others reduces substantially, even for DR-TB patients. So in order to reduce transmission, early case detection and treatment initiation are essential. Staff protection also needs to be considered. It is important that health workers are screened for TB and HIV and offered appropriate care, support and treatment if found to be infected. Staff members suspected of having TB should have access to rapid molecular diagnostic techniques for identification of DR-TB and screening for their own household members if they are found to have TB. In addition, staff who are suspected of TB should have paid time off work until the diagnosis is either confirmed or excluded, to reduce the risk of transmission within facilities.

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SWAZILAND: Equipment and etiquette

In Swaziland, appropriate measures are taken for safe sputum collection, and for cough triage to identify patients in the clinic and fast-track them to see a doctor. Safety equipment is provided for laboratory technicians, and staff working in close contact with patients wear N-95 respirators. Infection control in households is managed by expert clients who provide education on home infection control techniques, including cough etiquette, sleeping in separate rooms, and improving ventilation.

SOUTH AFRICA, SWAZILAND, UGANDA: Community campaigns

In Khayelitsha, MSF actively promotes infection control within the community by targeting community leaders, traditional healers, schools, social groups, shebeens (local bars) and local non-governmental organisations. It also runs a weekly radio phone-in and campaigns at train stations and taxi ranks.In Swaziland, the psychosocial coordinator organised an awareness campaign aimed at passengers at kombi stands, and handed out 'Open the Window' stickers to kombi drivers. In Uganda, MSF has a radio talk show which tackles health topics including DR-TB. In addition, World TB Day and HIV/AIDS awareness days have both been used as platforms for promoting greater understanding of DR-TB.

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KYRGYZSTAN: Making changes in prisons

In Bishkek, where MSF provides DR-TB treatment to prisoners, the importance of infection control is often underestimated, both by the prison services and by the National Tuberculosis Programme. MSF is the only organisation to supply masks for prisoners. Prisoners are transported in poorly ventilated vehicles, and prison cells remain extremely crowded, with inmates often non-compliant with infection control measures. However, extensive renovations, which include environmental infection control measures, are being carried out in the prisons where MSF is working. Improvements have also been made to the earlier detection of TB and DR-TB and to providing effective treatment. Patients are now separated according to their resistance profile, and MSF provides ongoing education for staff and inmates, as well as a TB newsletter which targets inmates, the prison administration, doctors and nurses in the civilian healthcare system, and new generations of medical students at the university.

1.3 Resources

1.3.1 Human resources

In a survey of the 22 high-burden countries for TB, 17 national treatment programme managers identified inadequate human resources as the most important constraint for reaching TB control targets.[33] The WHO estimates the global deficit of doctors, nurses and midwives as at least 2.4 million.[34]

To recruit and then retain staff, training is crucial at the initiation phase of any programme, helping to alleviate health workers' fears and concerns, as well as to provide them with ongoing clinical support. In one MSF programme, there was a high resignation rate from staff after only a few months of the programme due to their being stigmatised by other staff members in the clinic. This situation was addressed by ensuring that TB and infection control training was done for all medical staff, including those who were not directly involved in TB patient care.

1.3.2 Task shifting

Task shifting is the process of delegation, whereby tasks are distributed, where appropriate, to lower cadres of trained health workers. By reorganising the workforce in this way, task shifting can make more efficient use of the human resources available.[35] In DR-TB care, national shortages of doctors in many countries mean that task shifting is essential. It is particularly important where a decentralised approach is used to DR-TB care. Some specific tasks

can be shifted from doctors to nurses, and from nurses to employed community health workers, who are trained in infection control, directly observed therapy, and the identification and treatment of side effects. Delegating such tasks is a key step towards unburdening existing health staff and increasing access to patient-oriented DR-TB services. However, the management of DR-TB requires strong back-up and regular supervision by skilled medical doctors .

However, in some contexts there are restrictions on what can be achieved. In many countries, lay people are not authorised to give injections, so that patients in the intensive phase of treatment have no choice but to travel to the health facility every day. This is the situation in Kenya and Swaziland; MSF is challenging this, but has failed so far to achieve a change in policy. With appropriate training and supervision it is possible for lay staff or lower-level healthcare workers to safely and effectively give injections and directly observed therapy for DR-TB, as has been shown by Partners In Health in Peru.[36] The effectiveness of community health workers or lay people as treatment supporters has been demonstrated for a range of infectious diseases, including HIV and drug-sensitive TB,[37] and should be further elaborated for DR-TB.

When shifting tasks to other cadres of staff, it is essential to ensure staff are accredited and fully trained, feel confident in their new roles, can make good clinical decisions, are well supervised and supported, and are able to provide a high standard of patient care. The use of *aide-mémoires* for nurses or community health workers to support checking patients for the development of side effects has been found to improve staff confidence and task competence. The ability to refer to higher-level healthcare workers is essential, and defining when this is required is important. The higher-level healthcare workers should have an ongoing role providing supervision and mentoring.

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SWAZILAND: Community nurses identify DR-TB suspects

In MSF's programme in Shiselweni region, task-shifting activities have played an important part in increasing the level of coverage needed to tackle the enormous health burden of the duel HIV/TB epidemic. With an estimated case detection rate of 86 percent (based on an incidence rate of 1,257/100,000 and an estimated population of 208,454 in Shiselweni region), task shifting to nurses for the case detection of TB suspects, used alongside a diagnostics algorithm within the peripheral clinics, is key to detecting DR-TB.

1.3.3 Flow of drugs

The aims of TB treatment are to cure the patient, restoring their quality of life and productivity, to reduce transmission to others, and to prevent the development and transmission of drug-resistance. To achieve these aims, treatment providers must have an uninterrupted supply of quality-assured medicines. Managing the drug supply channels to ensure continual access is an essential component of any TB treatment programme, though this is rarely simple due to the number of stakeholders involved. Regulatory issues – including lengthy registration procedures and restrictions on the importation of quality-assured drugs – can result in negative patient outcomes, no matter how well managed the drug supply in a particular programme.

MSF centralises the procurement of second-line TB drugs through its procurement centres. To alleviate some of the complexities and ensure that stock is continually available, over the past few years a minimum-level security stock has been implemented, based on expected patient numbers. This decision has been beneficial and has allowed MSF to minimise the impact of global stock ruptures for some of the injectable drugs.

See also 'DR-TB drugs under the microscope', MSF and International Union Against Tuberculosis and Lung Disease, 2011.

Supply channels

Patients' access to TB drugs is generally through the public sector (national TB programmes), or through the private sector or NGOs. For DR-TB programmes, recent changes as a result of the review and restructuring of the Green Light Committee (GLC) Initiative mean that all countries (and, in theory, all treatment providers) will be able to approach the Global Drug Facility (GDF) direct for the procurement and supply of quality-assured second-line drugs. Additional reforms include the regionalisation of technical support for the scale-up of DR-TB care. It is not clear what impact these changes will have on the structure of GDF, which is currently under review.

Supply chains

Stakeholders involved in the supply chain:

- Manufacturers
- National Drug Regulatory Agency (NDRA)
- National TB programmes
- Donors
- Procurement agents
- Distributors
- Purchasers – NGOs or international organisations (eg PAHO, UNOPS, UNDP)
- Clinicians/Prescribers
- Pharmacies/Dispensers

Quality Assurance

Quality assurance is the concept that overarches all systems and processes involved in the manufacture and development of a product, which together result in medicines that are safe, effective and do no harm. Quality assurance for medicines should be to the same standards regardless of the disease or in which part of the world the patient lives. Today there are several mechanisms to evaluate drugs to ensure that quality standards of a drug are compliant with internationally recognised standards. These include: WHO prequalification; registration or marketing authorisation by a Stringent Regulatory Authority (SRA); and time-limited approval by the Expert Review Panel of the Global Drug Facility/Global Fund.[iii]

Rational use of drugs

Even if quality-assured drugs are available, inappropriate prescribing practices may result in interruptions in drug supply, in patients taking inadequate regimes, defaulting from treatment or selectively purchasing only part of the prescribed medications due to financial constraints, all of which will result in negative patient outcomes. In many developing countries, TB drugs are readily available from private pharmacies without a prescription. This is a cause for concern, as short-course treatment (or monotherapy) of TB drugs has been shown to be a key factor in the development of resistance. In many settings there is a lack of legislation or, if the legislation exists, there is no capacity to enforce it.

1.3.4 Partnerships

All MSF programmes describe the early involvement of the Ministry of Health and other partners as essential in the scale-up of DR-TB treatment. In Uzbekistan, Armenia, Georgia and South Africa, the Ministry of Health is responsible for implementation. All components – from case detection to adherence strategies and resource constraints – need to be absorbed into the Ministry of Health system to ensure continued quality of care. Laboratory and treatment capacity, and the use of available rapid diagnostic tests, need to be increased and strengthened to cope with growing numbers of TB and DR-TB patients requiring diagnostic testing and follow-up monitoring. Context-specific components such as task shifting need to be agreed on and integrated into health policy, as does psychological care, which is an essential component, regardless of the model of delivery.

Partnerships with other organisations also have an important role to play. In prisons in Kyrgyzstan, for example, MSF manages the diagnosis of PDR-TB, while the International Committee of the Red Cross (ICRC) provides the treatment for MDR-TB. In MSF's programmes in India, social support for patients is provided through an NGO network in Mumbai, while in Manipur MSF is investigating the possibility of the World Food Programme providing food support for patients.

A very successful collaboration has been in place for years with Partners In Health and other partners, with a number of international workshops and symposiums being held involving Ministries of Health, experts in DR-TB management, and doctors working with DR-TB in the field. Recent events were held in Swaziland in 2009, in Mumbai and Cape Town in 2010, and in Uzbekistan in 2011.

[iii] See <http://www.stoptb.org/gdf/> and <http://www.theglobalfund.org/en/>

2. Research and development

2.1 Diagnosis

Priorities for research and development into diagnostics for DR-TB include:
• Flexible and cost-effective scale-up of the rapid diagnostic test.
• A simplified system of monitoring patients for follow-up.
• The development of a non-sputum based point of care test (POC) for the diagnosis of DR-TB, especially for groups who are currently neglected or difficult to diagnose, including those with suspected extra-pulmonary DR-TB and paediatric DR-TB.
• Rapid diagnosis of XDR-TB.

2.2 Drugs

Having been at a virtual standstill for the last 40 years, the TB drug pipeline has seen encouraging progress in recent years.[38,39] There are currently ten new or re-purposed compounds in the clinical development stage, and it is hoped that some of these will be part of a future single treatment regimen, active against both drug-sensitive TB and all forms of drug-resistant TB.[40] A series of trials will be necessary to identify the best regimens and to integrate any new compound into the DR-TB treatment regimen. Dedicated funding will need to be allocated to make this happen. The two most advanced compounds in the TB drug pipeline are currently undergoing trials (OPC-67683, Otsuka; and MC207, Tibotec/J&J, which has completed phase 2b and will soon start phase 3 clinical trials). Finally, a large number of new drug candidates with novel mechanisms of action need to be available, so as to allow for the selection of optimum regimens and meet the goal of a single therapeutic regimen effective against both drug-sensitive and drug-resistant TB with a shorter duration of treatment and with fewer side effects than current DR-TB treatment.

Drug discovery efforts need to be scaled up in order to have a healthy pipeline which can deliver an optimal treatment regimen. However, although the development of such a regimen is a long-term goal, it is not clear how long it will take to achieve this objective, and we cannot afford to sit back and wait. The urgency of the problem means that we need to continue to scale up treatment now, and improve the outcomes of DR-TB treatment with the tools that are currently available.[41]

Summary

As the examples in this booklet show, treatment for drug-resistant tuberculosis has been implemented in MSF projects in a variety of different contexts across the world, with the result that many more patients now have access to effective treatment. As contexts change, as new challenges are addressed, and as scale-up brings about increasing involvement from other partners, the approach to treating DR-TB has evolved. There is no doubt that it takes time to build capacity, train staff, improve infrastructure and develop diagnostics. But rather than waiting for the perfect system to be in place, we need to work with what we have, and get as many people as we can on treatment as soon as possible. As international awareness about the disease increases, there is a growing momentum to stop it in its tracks. Now is the time to act, to build on this momentum, and to prove that DR-TB really can be beaten.

TB&ME

MSF has recently launched a new blogging platform, called TB&ME, related to the importance of developing more patient-centred services and the need to listen to the patients's perspective. Here, DR-TB patients from around the globe blog their experiences of living with the disease and discuss the issues that affect their lives. The site currently features patients from Armenia, South Africa, Uganda, Swaziland, India, Australia and the Philippines. It aims to highlight the fact that DR-TB is a global problem. Most importantly, TB&ME aims to give people with DR-TB a chance to tell the world what they think is needed to improve their care and services. Readers have the chance to leave comments and questions, to which the patients can respond. Visit: **http://msf.ca/blogs/tb/**

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