

# „COMPREHENSIVE TB CARE FOR ALL“

## THE KARAKALPAKSTAN EXPERIENCE

The “Comprehensive TB Care for All” programme is a collaboration between the Ministry of Health of the Autonomous Republic of Karakalpakstan and Médecins Sans Frontières.

MEDECINS SANS FRONTIERES

# Executive summary

Médecins Sans Frontières (MSF)[1] has been working with the Ministry of Health of the Republic of Uzbekistan (MoH) since 1998 to battle the growing threat of tuberculosis, including drug-resistant tuberculosis (DR-TB), in the country.

The epidemiological data on Uzbekistan shows that TB is an alarming problem in the country and justifies the increasing priority being attached to control efforts within the country. Estimates of the disease prevalence in the country put the total number of people with tuberculosis at 63,000 people, equivalent to a rate of 227 per 100,000 population. Within the World Health Organization's (WHO) European region, only three countries (Tajikistan, Kyrgystan and Moldova) have a higher prevalence.

Of major concern is the rate of multi-drug resistant tuberculosis (MDR-TB) infection. According to WHO, 14% of new TB cases are multidrug-resistant; this is the seventh-highest rate of infection in new cases in the world. But the proportion of new TB smear positive cases that are MDR-TB seems to be rising in our programme.

The Government of Uzbekistan recognizes the problem of tuberculosis in the country, and is a signatory to the Berlin (2007) and Beijing (2009) Declarations on TB, committing itself to strong action against the "alarming threat" posed by the disease.

Initially MSF was involved in three projects implementing the Directly Observed Treatment Shortcourse (DOTS) strategy in collaboration with the MoH. Following high rates of failure to first line treatment in DOTS project sites, in 2003 a DOTS-plus pilot project was commenced in Nukus City and Chimbay rayon within the Autonomous Republic of Karakalpakstan by MSF in collaboration with the MoH. The day-to-day management of this project was resumed by the MoH at the end of 2010. From the start of MDR-TB treatment in 2003 until 2010, the project had enrolled 1495 patients. Of these, 1017 patients had completed treatment by the end of 2010. The success rates were fairly stable at about 60% each year. Failure rates decreased from 19% in 2005 to 5% in 2008. Rates of death have remained stable and below 8%. Defaulter rates were 12% in 2005 and 16% in 2006, but increased significantly in 2007 to 25%, and have then levelled off with 25% also defaulting in 2008. Clearly, adherence to treatment is the principal issue that needs to be addressed.

The MoH and MSF have now started a new project in Karauzyak and Takhtakupir, in Karakalpakstan. The project aims to provide comprehensive TB care, including rapid diagnosis and integrated DOTS and DOTS-plus treatment, for all patients in all districts in Karakalpakstan.

The present programme includes clinical management of patients including through ambulatory treatment, state-of-the-art TB and MDR-TB laboratory services allowing rapid diagnosis and sensitivity testing, tight infection control practices, psychosocial counseling and adherence support to patients, health education and health system strengthening measures.

On the basis of its experience diagnosing and treating tuberculosis in the Republic of Uzbekistan, MSF can identify the following three key recommendations.

- Tuberculosis is an alarming threat to public health in Uzbekistan: Existing coverage, case detection and cure rates are not high enough to show any promise of containing the disease in the medium term. Urgent action is therefore needed, led by the Government of Uzbekistan and with the assistance of international actors including MSF, to confront this serious threat to public health.
- Comprehensive TB diagnosis and treatment needs to be scaled up: Not even 10% of the country's population has access to adequate drug-resistant treatment and diagnostics. MSF and MoH in collaboration have established the various components for TB diagnosis and treatment in the course of the Karakalpakstan project. There is now an urgent need for a roll-out plan and scaling up TB care and diagnostics so that every individual has immediate access to drug resistance (DR) testing at the time of TB diagnosis and can start on the correct drugs immediately, regardless of where they live.
- Ambulatory treatment from Day One can expand numbers and improve outcomes: Ambulatory treatment should generally be preferred to hospital-based treatment because it reduces the chance of cross-infection of hospitalized patients with drug-resistant strains, and because it could possibly reduce adherence problems related to prolonged hospital stays, such as the isolation of the patient from their social environment. Ambulatory treatment also has the advantage of reducing the capacity constraint in the hospital system, allowing for much greater numbers to be treated.

The Government of Uzbekistan is aware of the threat posed by TB and is strengthening its commitment to confronting the disease, using a wide range of means and resources. MSF is likewise committed to assisting the Government and people of Uzbekistan to face this threat, and we stand ready to provide whatever support, advice and expertise we can.

Further, MSF would like to extend its thanks to the Government of Uzbekistan, in particular the health authorities nationally and in Karakalpakstan, for the strong collaboration and good relations over the fourteen years of MSF's work in the region.

[1] For a glossary with the most common abbreviations used in this report please refer to p.19.

# Introduction

MSF has been working with the Ministry of Health of the Republic of Uzbekistan since 1998 to battle the growing threat of TB, including DR-TB in the country.

MSF's objective is to impact on the TB epidemic in Uzbekistan by reducing morbidity and mortality from the disease and by restricting its spread. We seek to do this in two ways: firstly, by supporting the MoH to build a high-quality treatment programme in Karakalpakstan which can effectively diagnose and treat patients from the region; and secondly, by using that programme as a model, advocating that it be spread to other regions of Uzbekistan and other Central Asian countries facing similar problems.

This report outlines what has been done so far in Karakalpakstan, including the project design and medical outcomes. On the basis of that experience, it draws out the lessons learnt for the future. In particular, it advances a more patient-centred approach to the care of tuberculosis patients.

Further, this report seeks to contribute to growing discussion across the Central Asia region, as various countries step up their efforts against the disease.

**TB threatens the whole Central Asia region**
It is not only in Uzbekistan that tuberculosis constitutes an alarming threat to public health.

All five Central Asian nations have very high TB prevalence: Kazakhstan (198 per 100,000), Kyrgyzstan (236), Tajikistan (374), and Turkmenistan (82, although most likely significantly under-reported) all compare to Uzbekistan (227).

Death rates likewise are all elevated throughout the region: Kazakhstan (20 per 100,000), Kyrgyzstan (22), Tajikistan (48), Turkmenistan (20) and Uzbekistan (19).

Numbers under treatment and cure rates show some variation: Kazakhstan (6167 in patient cohort, 64% cured), Kyrgyzstan (1640, 80%), Tajikistan (2057, 76%), Turkmenistan (1331, 83%) and Uzbekistan (5117, 75%).

Clearly, strong leadership exercised by governments in the region will not only assist their own populations, but will also push forward the regional control effort. Further, this indicates that exchange and mutual learning between the countries will have very beneficial effects in improving patient treatment quality, numbers and outcomes.

Source: World Health Organization (2010), World Tuberculosis Report. WHO: Geneva. [Available online at: http://www.who.int/tb/publications/global_report/2010/en/index.html.]

# Background


A nation of 26.4 million people located in Central Asia, the Republic of Uzbekistan became a nation on August 31, 1991, when it declared independence from the former Soviet Union.[2]

Stable since independence, the country is making advances towards its development goals: it is considered on track to achieve Millennium Development Goals on primary education and women's empowerment; it is making some progress towards eradicating extreme poverty, reducing childhood mortality and improving maternal health.[3] Uzbekistan ranks 102 in the Human Development Index, out of 169 countries, and is likewise considered a middle-income country in terms of gross domestic product per capita. Its life expectancy at birth is 68.2 years, its under-five mortality is 38 per 1000 live births, and it spends 2.3% of GDP on health.[4]

Nevertheless, the country faces important threats to its public health, including rising rates of infection of tuberculosis. The country's health care system reflects the legacy of the former Soviet Union. TB case management is centralized in specific TB facilities, with a legally required and lengthy inpatient phase. Infection control is in need of strengthening in both in- and outpatient settings and laboratory services are under-equipped.

The Government of Uzbekistan recognizes the problem of tuberculosis in the country, and is a signatory to the Berlin (2007) and Beijing (2009) Declarations on TB, committing itself to strong action against the "alarming threat" posed by the disease.

[2] Government of Uzbekistan (2011), Governmental Portal of the Republic of Uzebkistan. [Online.] [Available at: http://www.gov.uz/en/.]

[3] MDG Monitor (2011), Tracking the Millennium Development Goals: Uzbekistan Progress by Goal. [Online.] [Available at: http://www.mdgmonitor.org/country_progress.cfm?c=UZB&cd=860.]

[4] United Nations Development Program (2010), Human Development Report. UNDP: New York. {Available online at: http://hdr.undp.org/en/reports/global/hdr2010/.]

There are, in effect, parallel systems in place for the treatment of tuberculosis. DOTS is available throughout Uzbekistan. However, other treatments such as self-administered treatment, seasonal treatment and "anti-relapse" treatment are also found. First and second line TB drugs can be purchased over the counter in local pharmacies. The six-point Stop TB Strategy is starting to be introduced[5]. However, at this point, DOTS-plus treatment, for DR-TB patients, can only be accessed by the population residing in the capital Tashkent and in parts of Karakalpakstan (Nukus, Chimbay, Karauzyak and Takhtakupir rayons) where the MoH and MSF have expanded DR-TB care services.

# Epidemiology

The epidemiological data on Uzbekistan shows that TB is an alarming problem in the country and justifies the increasing priority that the government is attaching to control efforts within the country.

WHO estimates of the disease prevalence in the country put the total number of people with tuberculosis at 63,000 people, equivalent to a rate of 227 per 100,000 population[6]. Within the WHO's European region, only three countries (Tajikistan, Kyrgystan and Moldova) have a higher prevalence, although it should be noted that under-reporting of TB is common in the region[7]. Incidence is estimated at 35,000 people per year, or 128 per 100,000 people. Mortality from TB (excluding HIV-related deaths) is likewise elevated. It is estimated that some 5100 people died of the disease in 2009, a rate of 19 per 100,000. The rates for prevalence, incidence and mortality have remained more or less stable over the last 20 years.[8]

There were a total of 21,453 notified cases of TB in 2009, comprising 16,569 new cases and 2451 re-treatments. When compared to the incidence of the disease, this indicates a case detection rate of 50%, with an additional 35,000 people per year undiagnosed and untreated.[9]

Of major concern is the rate of multi-drug resistant tuberculosis infection: According to WHO, 14% of new TB cases are MDR. This is the seventh-highest rate of infection in new cases in the world. There is an estimated number of 4,700 MDR cases among total TB cases in the country per year.[10] The vast majority of these patients (90%) remain undiagnosed and untreated.

In the Autonomous Republic of Karakalpakstan, incidence and prevalence rates are among the highest in the whole region: 136 and 454 per 100,000 population per year[11] respectively.

A drug resistance survey conducted by MSF in 2001 found that MDR-TB infection accounted for 13% of all new TB cases, and for 40 percent of all TB patients already under treatment[12]. The survey has not been repeated to allow an analysis of the trend over time. In our programme, we are now seeing that the proportion of MDR-TB cases amongst those classified as new smear positive cases is greater than 40%. This is sentinel laboratory data and as such is vulnerable to bias. However, it does give an indication of the scale of drug resistance we are encountering and highlights the critical importance of screening all TB patients for drug resistance.

The appearance of extensively drug-resistant forms (XDR-TB), caused by bacteria resistant to the most effective second line drugs, further complicates the situation. XDR-TB is brought about by the development of resistance to second-line anti-TB drugs, usually through the mismanagement of MDR-TB treatment. The development of XDR strains raises great concerns about a future TB epidemic with restricted treatment options. The increasing prevalence of HIV including especially amongst intravenous drug users is also of concern, although it is not yet evident amongst the TB patient cohort in Karakalpakstan.

[5] "The Stop TB Strategy is WHO's recommended approach to reducing the burden of TB in line with global targets. The six major components of the strategy are: pursue high-quality DOTS expansion and enhancement; address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations; contribute to health system strengthening based on primary health care; engage all care providers; empower people with TB, and communities through partnership; and enable and promote research." In World Health Organization (2009), World Tuberculosis Report. WHO: Geneva. [Available online at: http://www.who.int/tb/publications/global_report/2009/key_points/en/index.html.]

[6] World Health Organization (2010), World Tuberculosis Report. WHO: Geneva. [Available online at: http://www.who.int/tb/publications/global_report/2010/en/index.html.]

[7] See, for example: Médecins Sans Frontières (2010), Turkmenistan's Opaque Health System. MSF: Berlin. [Available online at: http://www.msf.org/msf/fms/article-images/2010-00/turkmenistan_health_system.pdf .]

[8] World Health Organization (2010), World Tuberculosis Report. WHO: Geneva. [Available online at: http://www.who.int/tb/publications/global_report/2010/en/index.html.]

[9] Ibid.

[10] World Health Organization (2010), Multidrug and extensively drug-resistant TB (M-XDR-TB): 2010 global report on surveillance and response. WHO: Geneva.

[11] AK Khamraev (2008), Drug Resistant Tuberculosis Control in Karakalpakstan. [Presentation.]

[12] Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, et al. (2006) "Tuberculosis recurrence and mortality after successful treatment: Impact of drug resistance". PLoS Medicine. 3(10): e384. DOI: 10.1371/journal.pmed.0030384

# Project evolution

**From implementing DOTS...**
Médecins Sans Frontières has been involved in the treatment of tuberculosis in Uzbekistan since 1998, working alongside and in partnership with the Ministry of Health of the Republic of Uzbekistan.

Initially MSF was involved in three projects implementing the DOTS strategy in collaboration with the MoH in the Autonomous Republic of Karakalpakstan, the Khorezm region in Uzbekistan and the Dashoguz region in neighbouring Turkmenistan. The MoH resumed the day-to-day management of DOTS implementation in these locations upon the conclusion of the projects in July 2004.

**...to treating Drug-Resistant TB...**
Following high rates of failure to first line treatment in DOTS project sites, the MoH approved a request by MSF to conduct a drug resistance survey. The outcomes revealed a very high level of DR-TB, including among new patients. Therefore, to treat these patients, in 2003 a DOTS-plus pilot project was commenced in Nukus City and Chimbay rayon within Karakalpakstan by MSF in collaboration with the MoH. The project received approval from the Green Light Committee (GLC), an expert review and advisory panel, validating its quality and capacity to treat appropriately.

The main site of the project has been TB2, a 75 bed health facility, renovated by MSF specifically for MDR-TB patients. It is located 30 minutes outside Nukus city centre and functions as part of the established MoH inpatient facilities, including the rayon's main TB dispensary and the wider DOTS system. A high-quality mycobacteriological laboratory was also established in Nukus (at the TB1 hospital), to allow for the timely diagnosis of DR-TB.

There is a legally required inpatient phase initially. Following that, in an approach piloted in this programme by the MoH and MSF, patients receive treatment as outpatients from the hospital's outpatient department and from DOTS-plus corners located within MoH-run polyclinics in Nukus, and also from the DOTS-plus corners and rural health posts in Chimbay.

The project started as a pilot to treat 100 patients from Nukus city and Chimbay rayon and later in 2005 was expanded to treat 750-800 patients. On project handover, on December 31, 2010, 1495 patients had been admitted since 2003. By the end of 2010, 1017 outcomes have been declared (that is, patients were either cured, completed treatment, failed treatment, died, defaulted or were transferred). The success rates are fairly stable at about 60% each year, which is an acceptable result. Ambulatory treatment was integrated in the existing network of DOTS corners in the polyclinics in Nukus town in spring 2009. Clinical inpatient and ambulatory management was fully resumed by the MoH from MSF in Nukus and Chimbay in December 2010.

**...to providing comprehensive TB care.**
In January 2010, the MoH and MSF have started a new project in Karauzyak and Takhtakupir, which are north of Nukus and Chimbay rayons in Karakalpakstan. The project aims to provide comprehensive TB care, including rapid diagnosis and integrated DOTS and DOTS-plus treatment, for all patients in all districts in Karakalpakstan, so as to have a significant impact on controlling the local TB epidemic. The project strategy rests on introducing rapid testing of drug resistance and expanding ambulatory treatment.

# Project activities


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**Clinical Management**

The project has established a high quality of clinical services for TB, following WHO guidelines:

- Care is provided in inpatient facilities (TB2, now handed over) and through outpatient departments (principally DOTS and DOTS-plus corners in primary health care centres).
- Ambulatory and home-based care has been developed, shortening the length of stay in the inpatient facilities. This is now being extended from Nukus and Chimbay rayons to the rayons of Karauzyak and Takhtakupir.
- Community TB doctors and nurses working in the DOTS corners of the health centres are now fully involved in care provision and are responsible for daily pill distribution, treatment evaluation and side-effect management.
- Treatment approaches have been standardized and simplified. The introduction of new drugs and approaches has especially helped the capacity to manage the frequent and debilitating side effects of the MDR-TB treatment.
- In initial phases, MSF supplied all drugs and most medical supplies. Now, this is provided through the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and UNITAID, although MSF still provides third-line drugs, and occasionally fills gaps. Approval of the GLC for second-line drugs at reduced prices has been obtained.

**Diagnostic services**

The project has been based on sophisticated new technologies to allow for more rapid diagnosis and initiation of treatment:

- State-of-the-art TB and MDR-TB laboratory services were established in the mycobacteriological laboratory located in Nukus as well as high-quality clinical laboratory services.
- The use of MGIT technology (donated by FIND), alongside conventional culturing and drug sensitivity testing techniques, has contributed significantly to reducing the time period needed for detection of MDR-TB as well as the processing of a higher number of samples.
- A new rapid molecular genetic assay (the GenoType MTBDR-plus assay from Hain Lifesciences, donated by FIND) has now been introduced which allows the diagnosis of MDR-TB after a one-day laboratory procedure, in contrast to six to eight weeks with conventional culture methods and two to four weeks with liquid media techniques. This technology was approved for use in Karakalpakstan by the MoH and was introduced in October 2010.
- The Borstel supranational reference laboratory in Germany supports the laboratory with quality control.

**Infection control**

Strong infection control practice has been a key component of the project, to limit the possible contacts between TB and non-TB patients as well as between sputum smear positive and negative patients:

- MSF is assisting the MoH to put in place all aspects of infection control (administrative, environmental and personal protection) in the health facilities and to closely monitor compliance to the guidelines. New guidelines have been drafted and are presently being reviewed by the MoH.
- Physical separations like separate rooms or partitions are being introduced: 10 polyclinics in Nukus have been renovated, as well as two primary-level clinics, with more underway.
- Other methods have included ultraviolet (UV) lamps and respirators for medical personnel.
- A considerable effort was conducted to ensure that waste management was of a good standard, such as safe destruction of sputum samples.
- The major challenge is to provide infection control for ambulatory patients at home, such as proper ventilation and a separate room for patients; this needs to be designed on an individual base. All patients will need to be instructed about infection control at home and have access to individual masks and sputum containers.
- New guidelines are needed detailing the measures to be taken at each level. Stronger measures need to be taken

on: proper masking protocols, UV lamps, ventilation, and health education for all health staff, patients, caregivers and families. This applies to polyclinics and primary-level clinics just as much as hospitals.

**Psychosocial, psychological and adherence support**

The provision of support to the patient, as well as the affected family, before and during the whole treatment period, has been at the centre of the project and key to increase patients' treatment adherence:

- The majority of (DR-)TB patients suffers from side effects of their medication. Some of them are quite potent and long lasting, such as nausea, headaches and sleep disturbances. Overall, side effects can be considered one of the major obstacles to treatment adherence.
- Individual, group and family counseling is being carried out by specialized MSF staff to help them deal with managing these side effects, as well as the social implications of the disease.
- Diagnosis and treatment of psychiatric problems, either pre-existing, latent or attributed to the strong side effects of the drugs, is also carried out on a routine basis in cooperation between treating doctors, specialist psychiatrists and the mental health team under supervision of a mental health specialist.
- Psychological support in the palliative care of patients, who are failing treatment and are in a terminal stage of the disease, is provided on a continuous basis.
- Social support, in the form of income supplementation, is also provided to patients without income, or who are very poor.
- There are two different types of support. "Enablers" are forms of assistance which are required for the patient to continue treatment; they are mandatory parts of any high-quality TB treatment project. Important enablers are covering patients' transport costs, and ensuring patients get adequate food. "Incentives" are introduced in recognition that treatment is difficult and that some further assistance can help improve adherence (an example is food packages given to all patients).
- The decentralization of treatment to the rayons will make adherence and psychosocial support more complicated. To manage this, the project is putting in place a psychosocial counselor for each rayon, who will provide counseling to patients and support to a network of "patient support workers."
- Active case finding, adherence counselling and defaulter tracing programme components, like a one-day defaulter tracing system for those who don't return for treatment, need to be put in place in each rayon. Patients under treatment and lay members of the community also need to be trained to provide appropriate peer support at the community level.


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**Health education and public health activities**

Health education and TB awareness activities are an important component of the project in order to reduce the considerable stigma against TB patients in the general public, to restore the dignity of patients as well as to reduce the barriers to access to adequate TB treatment:

- Project activities have included charity concerts, puppet shows for schools, mobile exhibits, presentations at schools and colleges and public activities on World TB Day.
- There is a need for legislative and regulatory steps to restrict the spread of DR-TB by controlling access to TB drugs. The sale and distribution of TB drugs outside the national treatment programme as well as advertisement for TB drugs should be banned. Prescription of TB drugs should be restricted to only clinicians registered by the national programme, and only after proper registration and formal diagnosis.

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**Assisting the building of stronger systems**

MSF has sought to support the work of the Ministry of Health in building its capacity to provide quality care to TB patients:

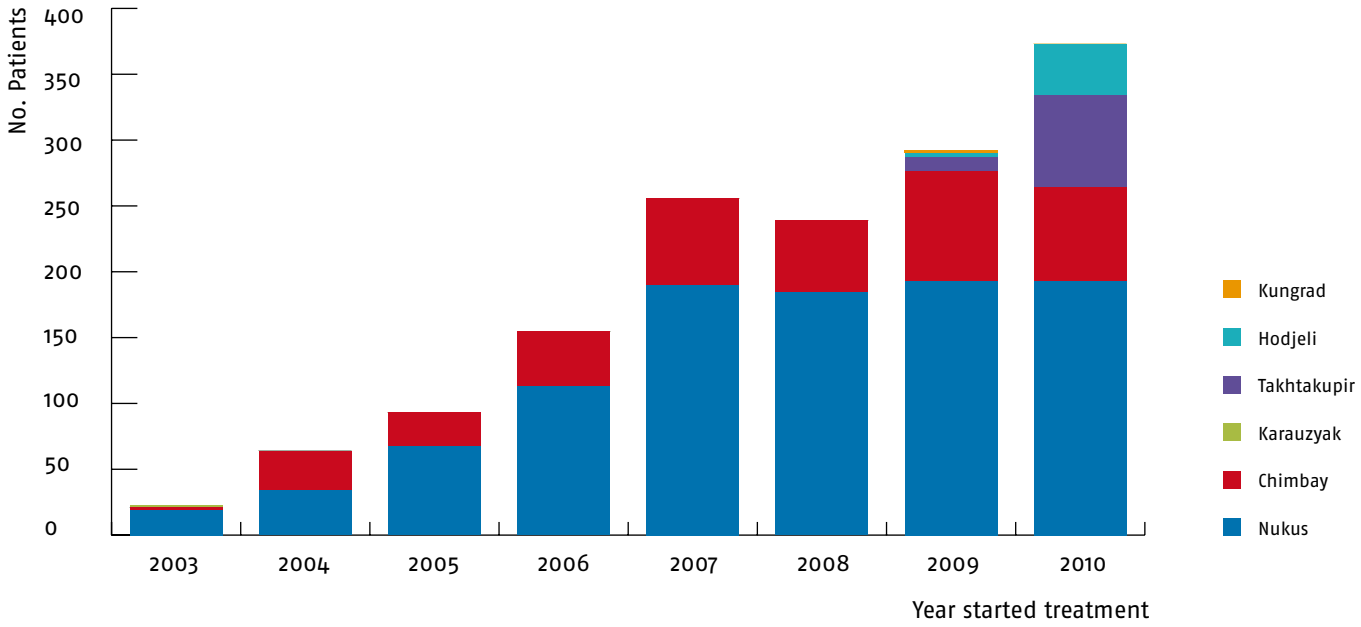
- The Government of Uzbekistan has sought and received support from the Global Fund for its tuberculosis programme. MSF has fully supported this effort, providing advice when requested and serving as a Global Fund Sub-Recipient. The Global Fund's assistance provides the basis for longer-term financing for TB care in the country. In Uzbekistan, at present, most TB drugs are procured through funding from the Global Fund to fight AIDS, Tuberculosis and Malaria.
- Extensive provision of training to medical staff has contributed significantly to the capacity and sustainability of the project. Several internationally-led trainings have been conducted, and project staff has been supported to undertake study abroad. There are also very frequent locally-organized trainings held, along with training on the job for less experienced staff.
- All relevant data, such as data on treatment, side effects and outcomes, are recorded in a computerized database based on epidemiological information which is supervised and maintained by a team of database managers and an epidemiologist. The database is designed to allow for a range of operational research issues. The MoH and MSF jointly own the data and publications emerging from the operational research. All operational research undergoes ethical review by MSF and is approved for publication by the MoH.
- To cater to the expansion of the project, a new and more sophisticated epidemiological database is due to be installed during 2011.
- Developing quality supply line management has been a major priority, in order to prevent the threat of ruptures. Of specific importance is the presence of adequate buffer stocks. There have been a number of ruptures of TB medications. In some cases, MSF has been able to fill gaps, but in other cases, it has led to patients missing part of their treatment: in December 2010, 116 patients missed pyrazinamide for an average of 2.3 days. At several points, the MoH and MSF have had to suspend or restrict new admissions because of lack of drugs.

*"I had a lot of fears. I was so afraid of the disease. Well, I got good treatment, but what if it happened again? What are people saying when they find out I am sick? Will society accept me? Can I have a family? Will I be a mother? I was afraid of all the things that might never be."* former patient, Nukus

# Medical results

**Cohort description**
By the end of 2010, the project had enrolled 1495 patients since 2003. The number of patients admitted per year has continued to increase, from 23 patients enrolled in 2003 to 373 patients enrolled in 2010 (Figure 1).

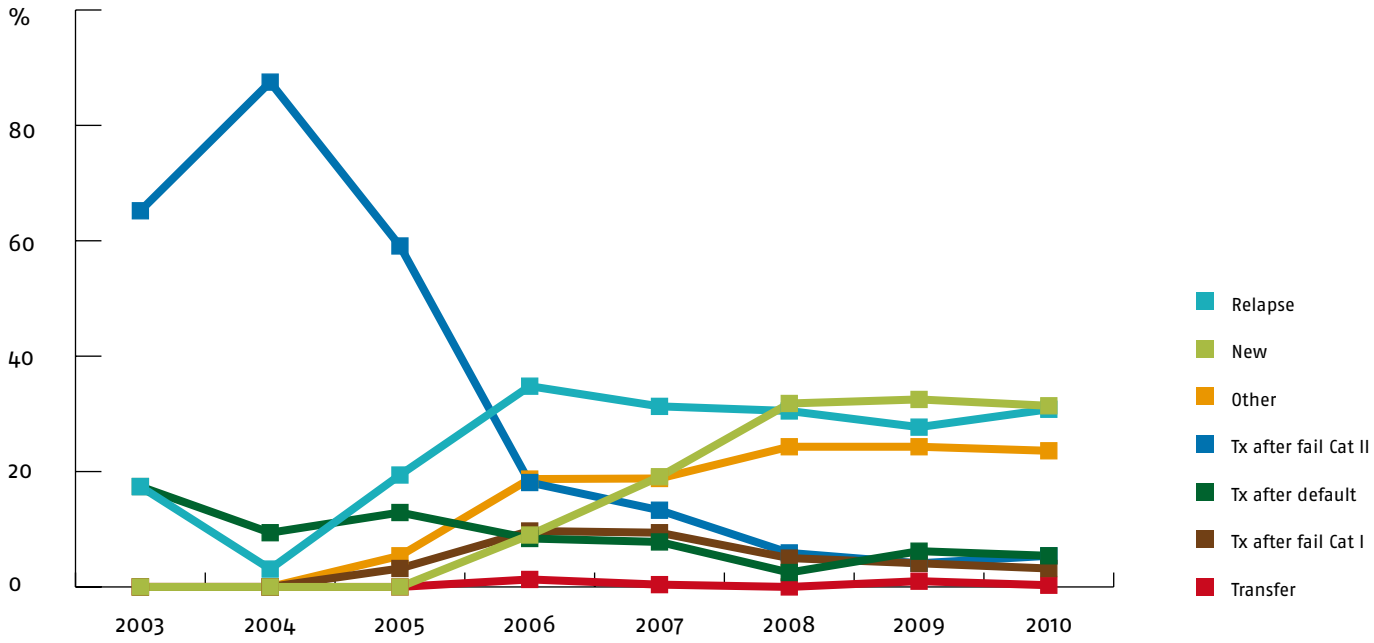
**Figure 1: Number of patients starting treatment by year and district**




The registration group of enrolling patients changed over time. Between 2003 and 2005, the majority of patients that enrolled were those that had failed category II treatment. Since 2006, new, relapse and "other" patients form the majority of enrolling DR-TB patients. The category of "new" patients has been rising and since 2008 totals about 30% of enrolled patients (Figure 2).

*"Thank God I can now take my drugs in the outpatients phase, close to my house. Compared to the time in hospital, my present condition is much better. At the hospital you always see the same people. The place where you have to go is the same. In the outpatient phase, you take the drugs looking at the guys, looking at cars, you look at the girls and after that, the burden of the drugs disappears."* patient, out-patient phase

**Figure 2: Incoming patients starting treatment by registration group and year**




During 2010, 261 patients from Nukus and Chimbay were admitted to the program and 264 had started treatment[13]. In comparison, 109 patients were admitted and started treatment in the newly-supported Karauzyak and Takhtakupir rayons. Our plan for the new rayons also includes drug-sensitive TB patients.

**Table 1: Enrolment during 2010**

| | Jan-10 | Feb-10 | Mar-10 | Apr-10 | May-10 | Jun-10 | Jul-10 | Aug-10 | Sep-10 | Oct-10 | Nov-10 | Dec-10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **New** | 15 | 16 | 15 | 10 | 15 | 20 | 3 | 5 | 16 | 17 | 11 | 6 |
| **Relapse** | 10 | 13 | 6 | 11 | 8 | 10 | 4 | 9 | 8 | 12 | 7 | 17 |
| **Tx after default** | 5 | 1 | 0 | 4 | 1 | 1 | 2 | 2 | 0 | 0 | 3 | 1 |
| **Tx after fail Cat I** | 2 | 1 | 0 | 0 | 0 | 3 | 0 | 1 | 1 | 1 | 0 | 3 |
| **Tx after fail Cat II** | 3 | 3 | 0 | 1 | 1 | 2 | 0 | 6 | 1 | 1 | 2 | 0 |
| **Other** | 4 | 5 | 2 | 4 | 3 | 6 | 3 | 5 | 6 | 5 | 7 | 6 |
| **Transfer** | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | 39 | 39 | 23 | 30 | 28 | 43 | 12 | 28 | 32 | 36 | 30 | 33 |

13 In some cases, there may be a short time lag between a patient being enrolled and a patient starting treatment, hence the differing figures.

**Cohort treatment**

At present, all patients diagnosed with DR-TB receive hospitalization in either of the two main TB treatment centres in Nukus, TB1 or TB2. Patients spend from one to 10 months there, until their sputum smear becomes negative (and therefore considered non-contagious). After that, they continue their treatment in ambulatory settings which could be at a polyclinic in Nukus or at primary-level clinics in the rayons. There is also a group of patients hospitalized, for various reasons, in the negative wards of TB1 or Chimbay TB hospital.

The project has treated a total of seven patients who were diagnosed on admission as XDR-TB, of which two have successfully completed treatment. (There have been other patients enrolled in the programme with MDR-TB who have later developed XDR-TB.) Further, there have been three patients confirmed to also have HIV; unfortunately, two of them died.

**Table 2: Patients currently on treatment, by location**

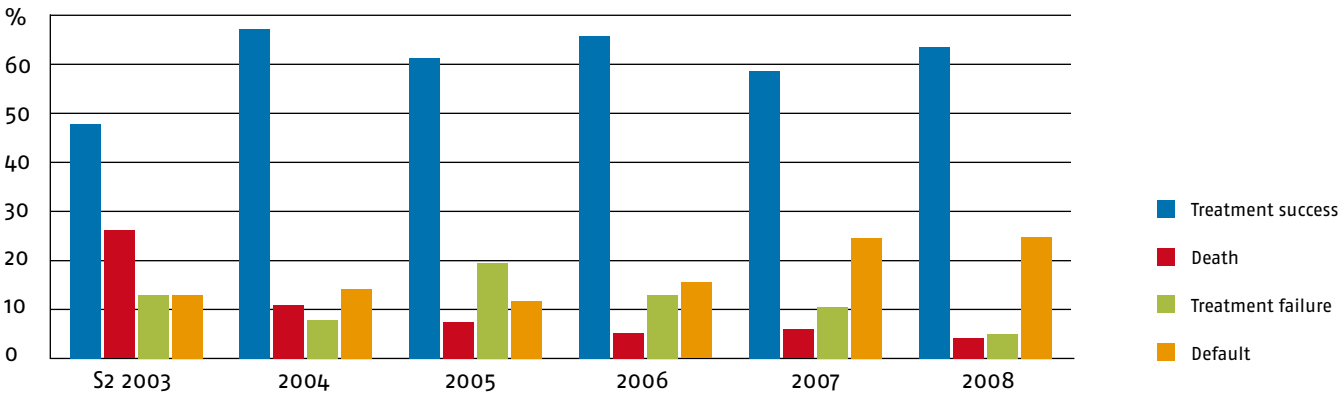
| | Nukus | Chimbay | Takhtakupir | Karauzyak | Total |
|---|---|---|---|---|---|
| **Inpatient TB2** | 24 | 12 | 5 | 6 | 47 |
| **Outpatient** | 214 | 95 | 31 | 63 | 403 |
| **Inpatient TB1** | 17 | 5 | 0 | 5 | 27 |
| **Other** | 1 | 0 | 0 | 0 | 1 |
| **Total** | 256 | 112 | 36 | 74 | 478 |

**Cohort outcomes**

By the end of 2010, 1017 outcomes had been declared. The success rates are fairly stable at about 60% each year. Failure rates have decreased from 19% in 2005 to 5% in 2008. Rates of death have remained stable and below 8%. Defaulter rates were 12% in 2005 and 16% in 2006, but increased significantly in 2007 to 25%, and have then levelled off with 25% also defaulting in 2008.

*"I am wishing for health for myself, without missing any drugs. That's a big thing, no? I can picture that I will be cured, discharged from hospital, that I will have gained weight. If you are not healthy, everything is useless. My children would be left alone. Who would take care of them? That's why I am taking these drugs."* patient, out-patient phase

**Figure 3: Overall treatment outcome indicators**

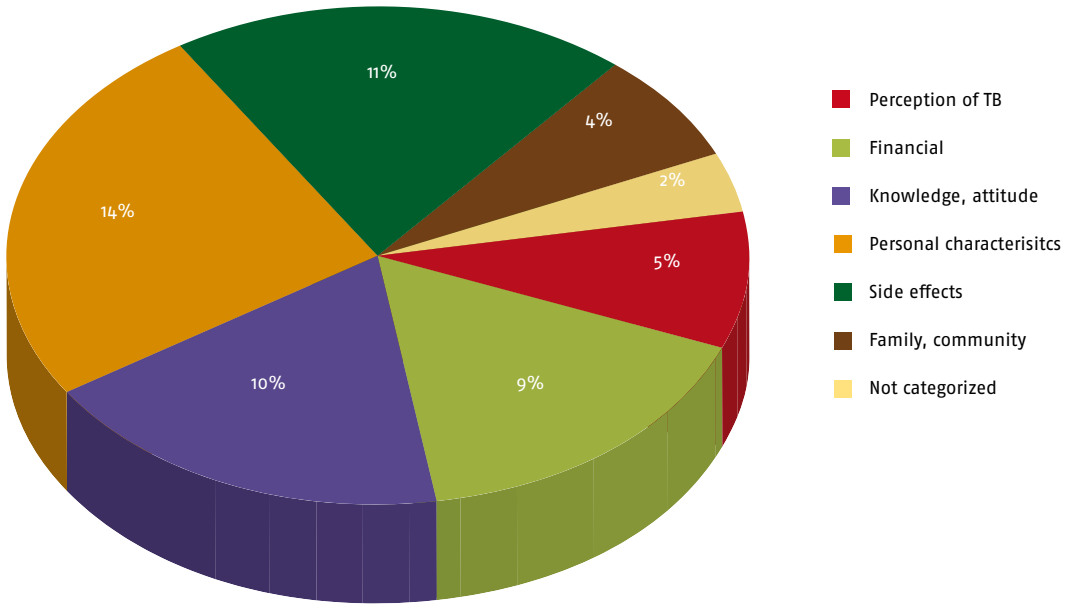



**Reasons for default**

Reducing the high proportion of defaulters is one of the major challenges the project faces. An analysis of the reasons given by patients for defaulting (see Figure 5, n = 55) shows that the most significant reasons are: side effects (11 cases), personal characteristics (such as alcoholism) (14), financial pressures (9) and knowledge, attitudes and beliefs about treatment (10).

There is also the phenomenon of "cryptic defaulters", that is, patients who do not formally default but who are not adherent to treatment (e.g. they miss treatments, or refuse to take a specific drug). Of 109 patients in Karauzyak and Takhtakupir for whom we have data, 31 (or 28.4%) took a drug at less than 80% of the prescribed dose for two or more months of treatment follow-up. Reasons for this appear varied: for example, in some cases, patients choose not to take a particular medication that they associated with strong side effects.

**Figure 4: Reasons given by patients for defaulting, Dec 2009-Nov 2010**



# Recommendations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On the basis of its experience diagnosing and treating tuberculosis in the Republic of Uzbekistan, MSF can identify the following three key findings.

**Tuberculosis is a serious and alarming threat to public health in Uzbekistan**

The spread of TB infection constitutes a serious and alarming public health threat to the country. Existing coverage, case detection and cure rates are not high enough to show any promise of containing the disease in the medium term. Given the prevalence of drug resistant forms of the disease, there will be an unacceptably high level of mortality from the disease for the foreseeable future.

Urgent action is therefore needed, led by the Government of Uzbekistan and with the assistance of international actors including MSF, to confront this serious threat to public health.

Clearly, the political commitment of the central government will be a crucial factor, as will be the management exercised at each level by the MoH.

Commitment is strong and is growing within the country for the adoption of best international practice in TB control. Presently, the Government of Uzbekistan is showing strong recognition of the problem of TB infection and is actively seeking ways to strengthen control efforts. In 2010, the Prime Minister requested evaluations to be conducted by the MoH and by the WHO to identify ways to optimize and rationalize resources. While the MoH's TB programme requires strengthening at all levels in order to carry out the six essential components of WHO's Stop TB Strategy[14], much progress has been made in the last few years. Currently, a new national TB plan and the reunification of all prikazes are underway and are planned for 2011.

**Comprehensive TB diagnosis and treatment needs to be scaled up**

The biggest bottleneck Uzbekistan faces is the lack of access to drug-resistant tuberculosis care and diagnostics. Only in four districts of Karakalpakstan, where MSF's tuberculosis project is located, and in Tashkent City do people have access to drug-resistant TB care. Not even 10% of the country's population has access to adequate drug-resistant treatment and diagnostics.

MSF and MoH in collaboration have established the various components for TB diagnosis and treatment in the course of the Karakalpakstan project, such as the mycobacteriological laboratory, psychosocial support, nutrition, transport and drug supply. There is now an urgent need for a roll-out plan and scaling up TB care and diagnostics so that every individual can be properly diagnosed and adequately treated.

[14] See footnote 4, above.

On diagnosis, sensitivity testing and diagnosis of DR-TB needs to occur at the earliest possible moment. Through new molecular biological tests, which have been successfully introduced in Nukus in 2010, the results can be made available quickly.

The country-wide availability of the newest generation of rapid diagnostic tests such as GeneXpert would have several advantages: it would speed up the diagnostic process, and thus avoid delays in having TB patients start their treatment, and it would avoid that all patients initially get treated with first line drug which are inappropriate for patients with DR-TB and bear the risk of amplification of resistances. Further, it would allow for the segregation of patients according to resistance class and therefore serve to reduce cross-infection in health facilities.

On treatment, it is important to simplify treatment protocols as far as possible for the majority of cases. This has been done already with the drug regimens, and has now also been done with the side effect management protocols, to allow for both a strong targeting of side effects and for the decentralization of side effect treatment to the lower levels.

Paediatric case detection rates are extremely low given the prevalence of TB and DR-TB in both rayons and dedicated inpatient facilities. There are several factors that contribute to that. For one, diagnosis of paediatric TB is more difficult in general because it is less often possible to isolate the bacteria in children, which makes it often impossible to test children for any resistances. Several steps should be taken to improve the outcome of TB in children: all paediatric TB suspects should receive TB culture and DST if positive; and there should be a low threshold to put children that are close contacts of confirmed DR-TB patients on DR-TB treatment.


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In terms of programme design, all future TB programmes should integrate all types of TB, rather than segregating or focusing solely on MDR-TB. Further, all patients should receive drug sensitivity testing (DST). This will ensure that effective, good-quality treatment should be accessible to all who need it, both drug sensitive (DS) and DR cases.

MSF's projects in Karakalpakstan focused first on DOTS implementation, then on treatment of MDR-TB. The new approach, starting in 2010, is more comprehensive than both. Disconnecting the DR-TB project supported by MSF from the wider MoH DOTS programme caused a number of problems. MoH TB facilities became overwhelmed with patients starting DOTS treatment. As diagnosis was sometimes weak, many of these new patients should likely have been enrolled in the DR-TB project but were not. Providing comprehensive care to all TB patients, regardless of sensitivity profile, would address these problems.

**Ambulatory treatment from Day One can expand numbers and improve outcomes**

Ambulatory care should be offered to all patients from the very start of treatment, unless there are specific medical indications requiring admission. Ambulatory treatment should generally be preferred to hospital-based treatment because it reduces the chance of cross-infection of hospitalized patients with drug-resistant strains, and because it could likely reduce

**Expanding access to new technologies**

In its TB projects in Uzbekistan, MoH and MSF have sought to innovate and pioneer new technologies and new solutions to the problems of TB treatment:

In 2006, MoH, MSF and the Foundation for Innovative New Diagnostics (FIND) introduced the Mycobacteria Growth Indicator Tube (MGIT) assay into Uzbekistan via a demonstration project, procured at reduced prices from the originator company. The technology allows for quicker detection and greater sensitivity in identifying drug susceptibility profiles.

In 2008, MSF lobbied the innovator company, Bayer, in support of a Green Light Committee request to supply at concessional rates the drug moxifloxacin, which it eventually did. Moxifloxacin is relatively new for TB use, and is considered one of the more powerful and effective drugs.

In 2010, MoH, MSF and FIND again collaborated to introduce the GenoType MTBDR-plus assay into the country. This was obtained from Hain Lifesciences at reduced price. The test allows for significantly quicker drug sensitivity testing.

Presently, MSF is seeking to promote the concept of "compassionate use" which, if contained in national legislation and regulations, would allow greater access of patients to certain drugs. In particular, it would allow the entry into Uzbekistan of TMC 207, a new anti-TB drug which is currently still in development.


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adherence problems related to prolonged hospital stays, such as the isolation of the patient from their social environment. Ambulatory care should also reduce waiting times prior to the start of treatment.

The evidence is mounting that ambulatory care for TB offers good outcomes. For drug sensitive TB, it has been demonstrated[15] that there are no more household contact conversions after the start of TB treatment, so there is no risk of further infection during outpatient treatment. For drug resistant TB, experience from community-based models from Peru[16] and South Africa[17] show that 90% of MDR-TB cases can be safely treated as outpatients from treatment initiation. From an infection control viewpoint, the risks to the community of admitting patients are often greater than keeping patients where they are – where contacts have already been exposed to their strain of TB, and they will now be on effective treatment.

Ambulatory treatment also has the advantage of reducing the capacity constraint in the hospital system, allowing for much greater numbers to be treated.

The Ministry of Health has already progressed on the work of providing a firm legal and administrative footing for ambulatory care from day one, including by issuing new prikazes. In February 2011, the Ministry of Health in Karakalpakstan issued a prikaz formally allowing treating smear-positive patients in ambulatory settings; it is hoped that this can serve as a model for a national prikaz as well.

Hospitalization rates can and should be reduced. In principle, DOTS patients and smear negative patients should not be hospitalized. A recent WHO review of the national treatment programme recommended ending the practice of excessive and over-long hospitalization of certain categories of patients ("chronic", "disability", "anti-relapse"). This will significantly reduce the risk for the patient of being infected with drug-resistant strains while in hospital. Admission should remain available for severe side effects and patients severely ill at initiation.

Presently, health system financing in Uzbekistan is based on bed occupancy, on the "per number of beds" principle. This creates incentives for keeping patients in hospital for longer than is necessary, which is exactly the opposite of the desired situation. Instead, a system needs to be introduced, with advice from appropriate experts in health-system financing, which provides a proper mix of incentives for good-quality treatment.

[15] Kamat SR, Dawson JJ, Devadatta S, Fox W, Janardhanam B, Radhakrishna S, et al (1966). "A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India". Bulletin of the World Health Organization. 34:517-32.

[16] Shin S, J Furin, J Bayona, K Mate, JK Kim and P Farmer (2004). "Community-based treatment of multidrug-resistant tuberculosis in Lima, Peru: 7 years of experience." Social Science and Medicine. Oct; 59(7):1529-39.

[17] Heller T, RJ Lessells, CG Wallrauch, T Bärnighausen, GS Cooke, L Mhlongo, I Master, ML Newell (2010), "Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa." International Journal of Tuberculosis and Lung Disease. Apr; 14(4):420-6.

# Conclusion

Uzbekistan faces many challenges in controlling the threat of tuberculosis. Future efforts in TB prevention and control will require extensive commitment and investment from all actors, including the Government of Uzbekistan and all relevant international actors including MSF.

Scaling up drug-resistant tuberculosis care and diagnostics services is one of the most urgent tasks to be tackled. But DOTS or DOTS-plus alone are not the sole answer either. Diagnosis and treatment should be provided as part of a wider package, including infection control, psycho-social support and public health measures. Reducing the hospitalization rate, and increasing the numbers who are treated in ambulatory services, should also allow not only for better patient adherence and outcomes, but also allow for the expansion of the number of patients treated.

The results of the collaboration in Karakalpakstan, between the MoH and MSF, show that good treatment outcomes can be accomplished. It further shows that new technology, new ideas and new systems can be introduced and can work well in Uzbekistan. Already, the new model of patient-centred care, decentralized and simplified and expanded to the districts, is showing promise.

Médecins Sans Frontières is strongly committed to assisting the Government and people of Uzbekistan to face this threat of tuberculosis, and we stand ready to provide whatever support, advice and expertise we can.

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Médecins Sans Frontières is an international medical humanitarian aid organisation. We offer medical assistance to populations in distress, to victims of epidemics, natural or man-made disasters and to victims of armed conflicts, without discrimination and irrespective of race, religion or political affiliation.

## Abbreviations

DR: drug resistant
DS: drug sensitive
DST: drug sensitivity testing
MSF: Médecins Sans Frontières
MoH: Ministry of Health
DOTS: Directly Observed Treatment Short course
DR-TB: drug-resistant tuberculosis
FIND: Foundation for Innovative New Diagnostics
GLC: Green Light Committee, an international expert review and advisory panel
MDR: multi drug-resistant
NTP: National TB Programme
TB: tuberculosis
Tx: treatment
WHO: World Health Organization
XDR-TB: extensively drug-resistant

**IMPRESSUM**

Published by:
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