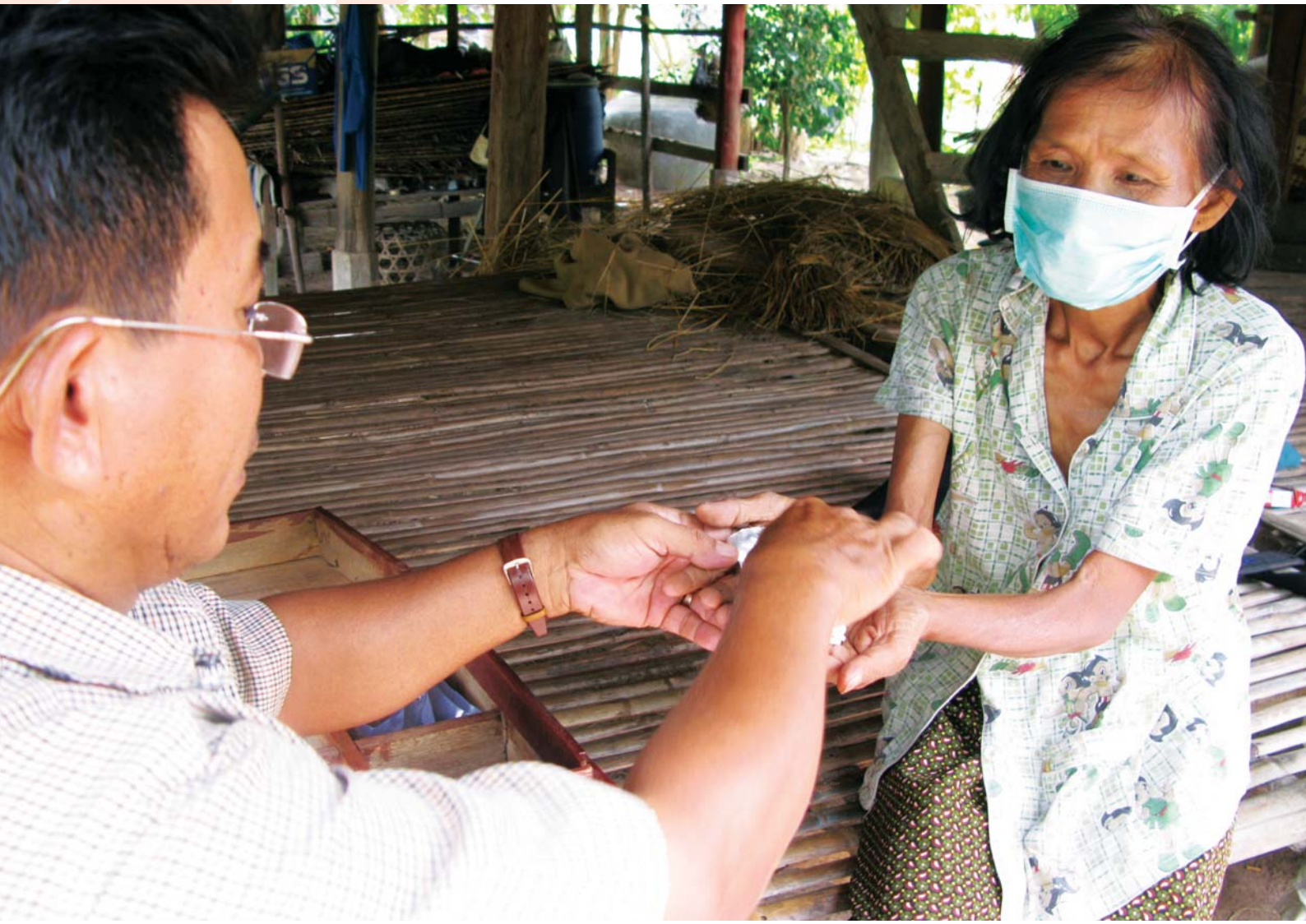
Care and Treatment for Drug Resistant Tuberculosis:

a pilot project in Takeo province, Cambodia,

2007-2009



MEDECINS SANS FRONTIERES
ក្រុមពេទ្យគ្មានព្រំដែន

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Contributors

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Acknowledgments

The design and implementation of the drug resistant TB pilot project in Cambodia and its evolution was made possible through the efforts of a number of individuals, teams of MSF international and expatriate staff and with the cooperation of various actors.

These include the Ministry of Health of Cambodia, CENAT, Provincial Health Department, Referral Hospital of Takeo, Cambodian Health Committee, Médecins Sans Frontières France, and the health care staff working in the referral hospitals and health centers.

We acknowledge our patients and their families for their constant efforts to overcome the challenges they face living with drug resistant tuberculosis. Their voices are documented in this report, through interviews collected at their welcoming homes.

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List of Abbreviations

Am	Amikacin
BK	Bacillus Koch
CENAT	Centre National de Tuberculose
CHC	Cambodian Health Committee
Cm	Capreomycin
Cs	Cycloserine
DM	Diabetes Mellitus
DOT	Directly Observed Therapy
DST	Drug Susceptibility Testing
E	Ethambutol
EP	Extra Pulmonary
Eto	Ethionamide
GIT	Gastrointestinal Tract
H	Isoniazid
HC	Health Center
IPC	Institut Pasteur du Cambodge
Km	Kanamycin
Lfx	Levofloxacin
MDR	Multi Drug Resistant
MoH	Ministry of Health
MoU	Memorandum of Understanding
Mox	Moxifloxacin
MSF-B	Médecins Sans Frontières Belgium
OD	Operational District
Ofx	Ofloxacin
NTM	Non Tuberculosis Mycobacteria
PAS	P-Aminosalicylic acid
PDR	Poly Drug Resistant
PHD	Provincial Health Department
Pto	Prothionamide
RH	Referral Hospital
TB	Tuberculosis
Z	Pyrazinamide

DR-TB in Cambodia and MSF's involvement

The overall TB prevalence in Cambodia is extremely high. In 2007, the estimated prevalence of all forms of TB was 664 per 100 000 population, with a smear positive incidence of 219 per 100 000 making Cambodia among the 22 highest burden countries for TB in the world. The TB mortality rate was 90 per 100, 000 population.

A survey was conducted by CENAT in 2001-2002 in Cambodia and revealed a prevalence of 3.1% MDR-TB among previously treated cases. Treatment outcomes of drug-resistant tuberculosis (DR-TB) are known to be significantly worse than in first-line treated TB patients. Moreover, outbreaks of DRTB in populations cause alarmingly high mortality rates that require a prompt and coordinated response by health officials and health-care providers.

MSF has been operating a Chronic Diseases Clinic in Donkeo Referral Hospital, Takeo Province (with 199,424 inhabitants), since 2003. The clinic has offered comprehensive care and treatment to patients with HIV/AIDS, diabetes and hypertension.

At the same time MSF became an active member of the Multi-Drug Resistant Tuberculosis Technical Working Group (TWG), based at the National TB Program, CENAT. MSF-Belgium and MSF-France, as well as CHC, a local NGO partner, greatly contributed to the establishment of this working group and received encouraging comments for bringing to the group technical expertise, as well as field experience, from the first treatment DR-TB programs in the country.

I discovered that I had TB 18 years ago. Back then I was a soldier fighting against the Khmer Rouge and often had to go to the jungle towards the Thai border. This meant that I could not take my medication correctly and would interrupt the treatment before I got cured. It was also very expensive for me to buy the medication. I feel that this is my last chance to get well.

P. V. 48 years old, Takeo

Project Description

Project location

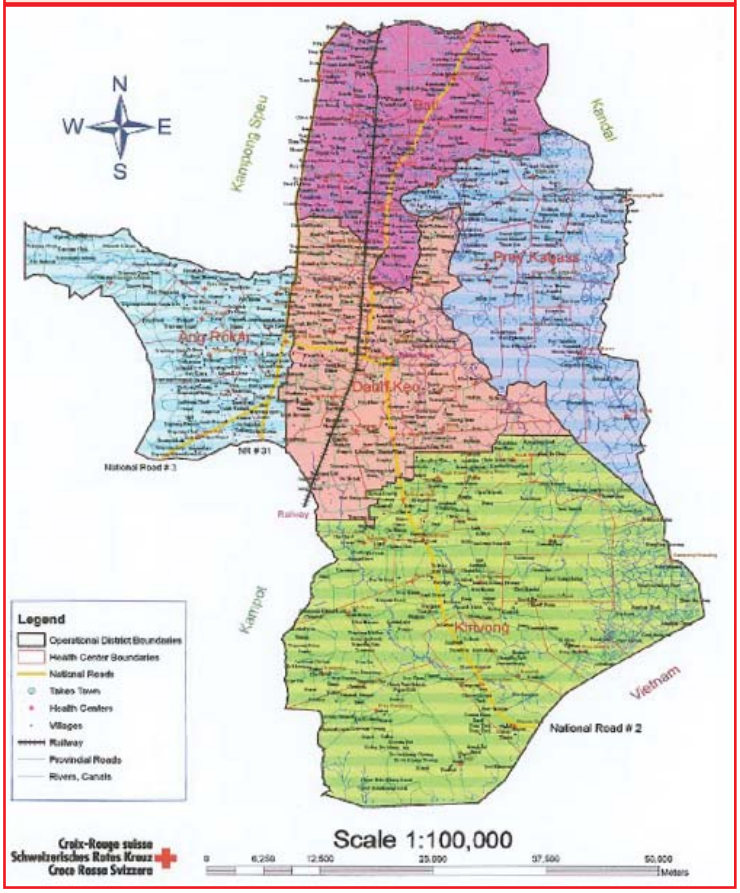
Takeo province (3,563 square kilometers) is located in the south of Cambodia, bordering on Kandal, Kampong Speu and Kampot provinces and to the south with Vietnam. The current population is about 924,800 or 6.4% of the country's total (14,363,519 in 2007). The population density is 259.5 people per square kilometer.

Project Objectives

Overall objective:

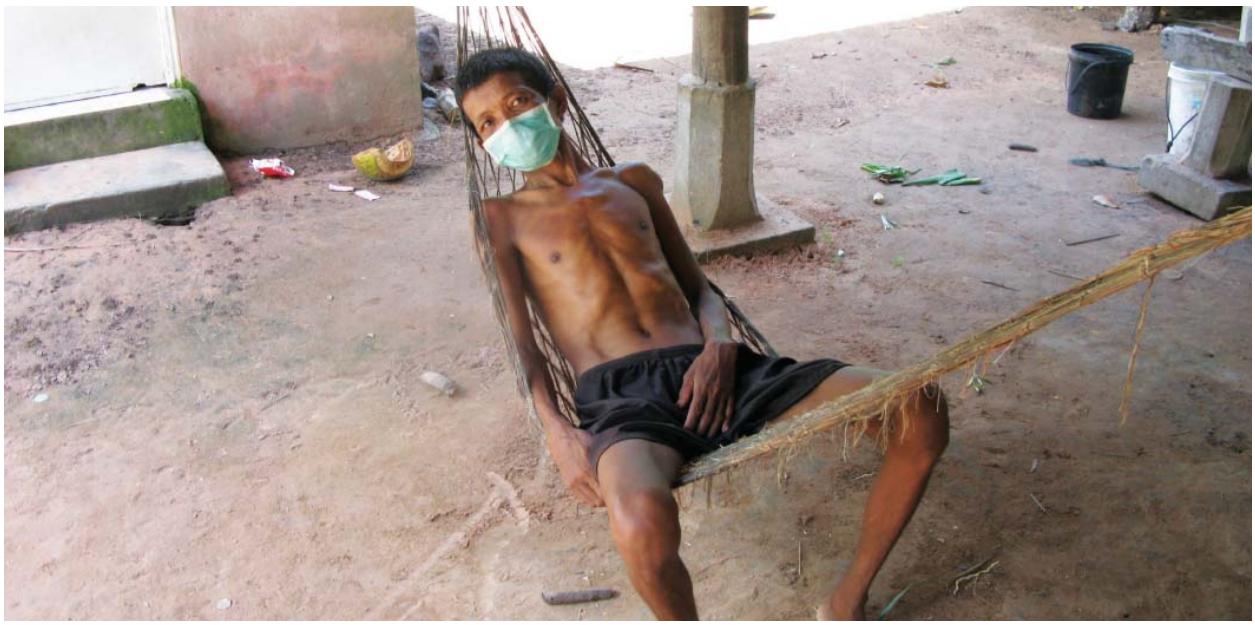
The overall objective of the project was to provide quality care to all patients suffering from DR-TB in Takeo province and to develop a model of care that would be applicable to other similar settings .

Takeo Province
Operational Districts and Health Centers



Before I was treated by MSF, I was given treatment six times. I bought drugs myself and spent a lot of money, but I kept on coughing blood. Now that I feel better I want to look for a job, perhaps as a mototaxi-driver. When I was sick, my daughter and her husband supported me, but I want to be able to support myself. However I am very worried that I will start coughing blood again if I take a job that is too exhausting.

M.S., 55 years, Takeo



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Specific objectives included:

1. to improve the diagnosis of DR-TB
2. to improve treatment outcomes
3. to decrease DR-TB transmission in the community

Case finding strategy

The aim of the case finding strategy was to identify patients with DR-TB and to initiate adequate treatment in a timely manner. Timely identification and prompt initiation of treatment prevent acquisition of further resistance, progression to permanent lung damage and spread of the disease to others.

Only patients who were confirmed smear positive BK with the following criteria were sent for culture and DST:

1. patients failing Cat 2 or known as chronic cases
2. patients with smear positive TB entering Cat 2 regardless of the previous TB history (Cat 1 failure; Defaulter; Relapse, etc…);
3. close contacts of MDR-TB smear positive patients

The selection of patients eligible for DR-TB case finding was done in two ways:

1- through consultation of the TB register of patients registered since 2006 (active case finding)
2- through referral of suspected patients detected by TB staff (passive case finding)

To confirm the diagnosis of DRTB, smear sputum positive specimens were sent to Pasteur Institute in Phnom Penh for standard culture and Drug Susceptibility Testing (DST). If the culture was positive, then DST for 1st line anti-TB drugs was done at Pasteur and DST for 2nd line TB-drugs was done in Supra National Reference Laboratory in Hong Kong, for all MDR-TB cases. Growth detection and identification of M. tuberculosis took on average 3–8 weeks and DST of an M. tuberculosis isolate took additional 2–4 weeks. The costs for culture and DST for 1st and 2nd line were 48 US$ and 430 US$ respectively.

The final responsibility for enrolment of patients to MDR-TB treatment (DOTS plus program) was with the physician in charge for the TB ward at Donkeo referral hospital in cooperation with the MSF Medical doctor.

Treatment strategy

All patients found to have DR-TB, were initially started on a standardized treatment regimen that was then modified to an individualized treatment regimen based on the patient's DST results. Every treatment regimen initially consisted of at least four drugs that were likely to be effective. The dosage was determined by body weight. Efforts were made to recognize and treat adverse drug effects in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality. An injectable agent (an aminoglycoside or capreomycin) was used for a minimum of six months (intensive phase) and at least four months past culture conversion. The minimum length of treatment was 18 months (continuation phase) after culture conversion.

Drugs used by MSF-B included: Pyrazinamide (Z), Capreomycine (Cm), Levofloxacin (Lfx), Ethionamide (Eto), Cycloserin (CS) and PAS Paser (PAS). When second line resistance results became available, often up to two months into treatment, the treatment regimen was modified to provide at least three drugs to which the infecting strain was found to be susceptible.

Case holding strategy

A case presentation for each patient was organized before treatment initiation in order to discuss the medical history, review baseline lab results and other investigations, plan a treatment regimen, and identify any other special problems. These case discussions involved the MDR-TB doctors, TB nurses, counselors, social workers, and the project coordinator.

At the beginning of the program in 2007, patients were hospitalized until smear conversion occurred. DOT was performed twice a day, six days per week by health staff in the TB ward and the TB doctor examined patients daily.

Later in the program (2008) the time of hospitalization was reduced. Patients were then treated on ambulatory basis with monthly visits to the hospital for medical follow up. Treatment was taken at home by directly observed the rapy (DOT) with three DOT watchers for each patient. The first DOT watcher was a health professional who gave the prescribed medicines in the morning (injection and pills), and the 2nd and 3rd DOT watchers were villagers in the same

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community who volunteered to give medicines every evening. The DOT Watchers had a one-day training on TB/MDR drugs, doses and identification of adverse events and were supervised by the MSF TB nurse and by the 1st DOT Watcher.

Long hospitalization was never well accepted by patients who complained of isolation, boredom, homesickness and loneliness. It was found that drop-out rates were higher in the hospitalization phase than in the ambulatory phase.

Patient support and counseling

Treatment for DR-TB is long and difficult for patients. Many of the second-line anti-tuberculosis drugs have significant side effects. Some are common and, although debilitating, are relatively manageable, such as nausea and vomiting, while others are more severe and lifelong, such as deafness. Taking these drugs continuously for up to two years requires an enormous commitment from patients and their families. Supporting patients through education and counseling is of paramount importance in improving adherence to treatment and reducing default from treatment.

In Takeo, DR-TB patients and their care givers were offered counseling on the diagnosis day by a dedicated MSF DR-TB counselor supported by the TB Nurse supervisor.

The aims of this counseling session were threefold:

1. to educate patients and families about DR-TB and its treatment
2. to assess the risk of transmission of DR-TB in the household and develop strategies to minimize this risk
3. to counsel household members and close contacts about the need for screening other family members

The DR-TB counselor was always available to In addition, the DR-TB counselor was always available to counsel patients who were having difficulties adhering to treatment or who had missed clinic appointments.

A comprehensive guideline for the counseling of DR-TB patients was soon developed by the MSF team as it was found that there was a lack of specific material and a protocol for the support of patients with such a long and challenging treatment. The guidelines were shared with all partners involved in DRTB care in the country.

Home Visits

Home visits were made by counselors and nurse supervisors at least once a month to provide medical follow up, emotional support to improve adherence and advice on infection control measures. During the visit the team also supervised and coached the DOT Watchers, and supplied drugs and medical materials.

The medication that I take makes my eyes blurry. Sometimes I have trouble finding my way back to my house, so the neighbours will have to help me. I wish that my family would support me more, and I often feel lonely. But I am happy that there are neighbours who come every day to help me take my medication.

T.P., 60 years old, Takeo

Treatment follow up and monitoring

Patients underwent an extensive evaluation before treatment initiation that included the following medical review and tests performed by MoH/MSF-B TB doctors or nurses:

- sputum smear microscopy, culture and DST to both first and second-line drugs
- TB disease and treatment history
- past medical history
- documentation of suspected MDR-TB contacts
- physical examination
- chest radiograph
- lab tests
- psychiatric evaluation

During the hospitalization phase the MoH/MSF-B attending physician saw the patient on a daily basis. In the continuation phase the patient was seen as often as needed but at least once a month. Patients were monitored closely for signs of adverse events and for treatment failure. The timely and appropriate management of side effects was considered critical to treatment adherence. Special attention was put at each visit to evaluate for:

- respiratory distress
- GI intolerance of medications
- progression of hearing loss or tinnitus
- depression or psychotic symptoms.

At each visit, a physical exam was done and lab tests were prescribed according to a written protocol.

This is the fifth time that I am on treatment. Sometimes I feel that I don't want to live anymore, because the side effects are so strong. I can't eat my rice, and find it difficult to hold or carry things. When it gets really bad, I want to stop taking the medication. But my wife tells me to continue and really supports me. God bless me.

Y. H., 66 years old, Takeo

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Nutritional support

IIn addition to causing malnutrition, DR-TB can be exacerbated by poor nutritional status. Thus, without nutritional support, patients can become enmeshed in a vicious cycle of malnutrition and disease. The second-line antituberculosis medications can also decrease appetite, making adequate nutrition a greater challenge.

For relatively non-malnourished patients, general and therapeutic food items were provided by MSF-B social workers to encourage the patients to have a balanced nutritional diet. For malnourished patients, therapeutic foods (Plumpy'nut, BP-100, Soy Milk) were provided by MSF-B social workers under close follow up.

Infection Control

Reducing the risk of transmission of drug-resistant strains of TB in both health care facilities and at home is a vital concern. Infection control (including administrative, environmental, and personal protection measures) is therefore important to implement in patients' homes, in health care facilities, and in the community at large.

The implementation of the IC measures included:

- improvement of natural ventilation in the hospital and houses
- use of respiratory protectors, N95, by the health professionals
- provision of surgical masks for all clients sitting in waiting areas

During the hospitalization phase, patients and family received infection control health education before and during the treatment. Masks were provided to all patients, staff, and care takers.

During the ambulatory phase, a patient-centered approach to DR-TB treatment allowed patients to be in their own homes and, as much as possible, resume a normal, autonomous life. In order to minimize the risk to other household members, an initial home assessment was conducted which considered the vulnerabilities of household members – young children, people with HIV and other chronic illnesses, along with an assessment of space available and ventilation in the home. From this, a risk-reduction plan was drawn up that included education about TB transmission, the need for cough hygiene, separate sleeping arrangements for the patient and strategies to reduce contact with vulnerable household members. Paper masks were also distributed to the patients.

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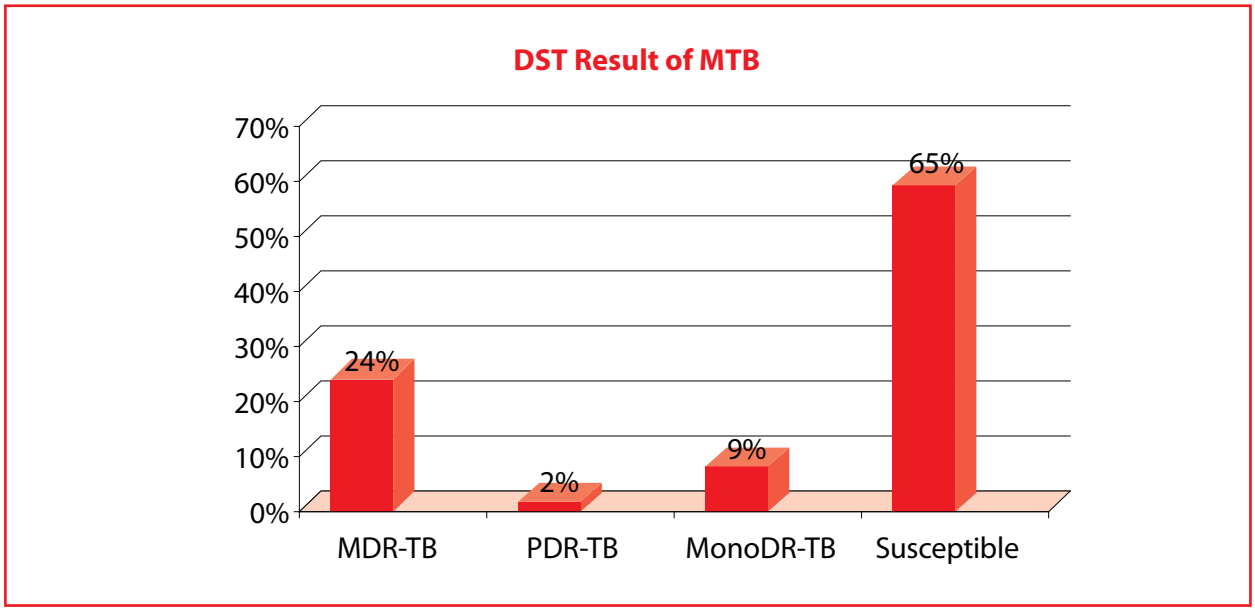
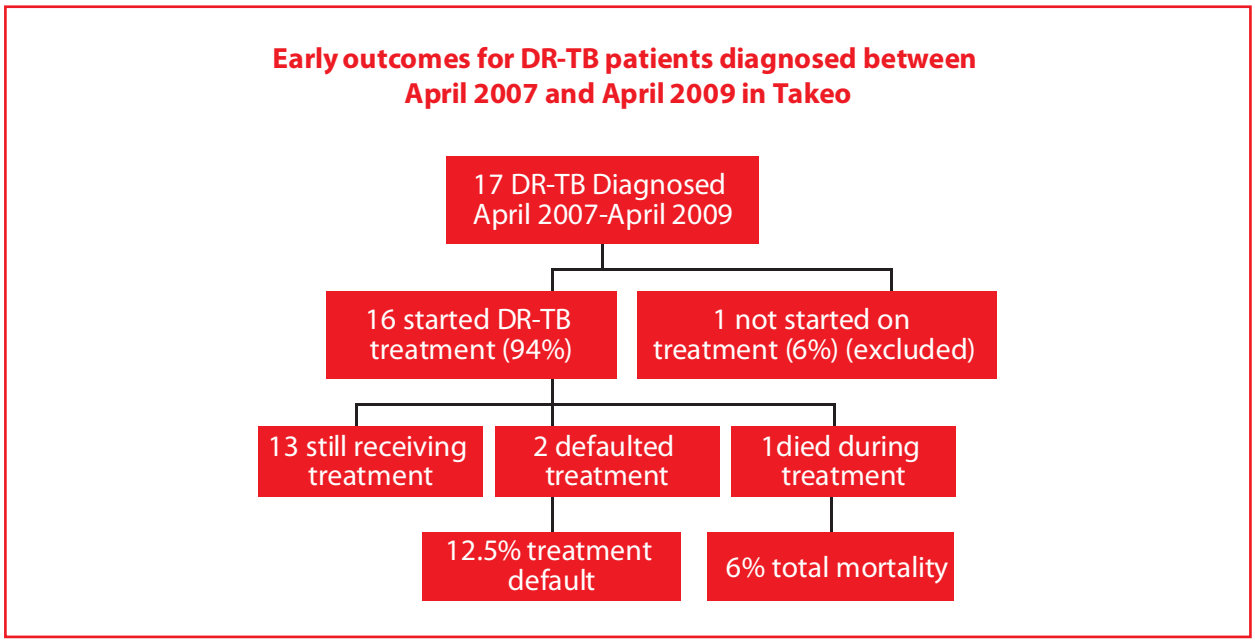
Program Outcomes

DST results for confirmed MTB

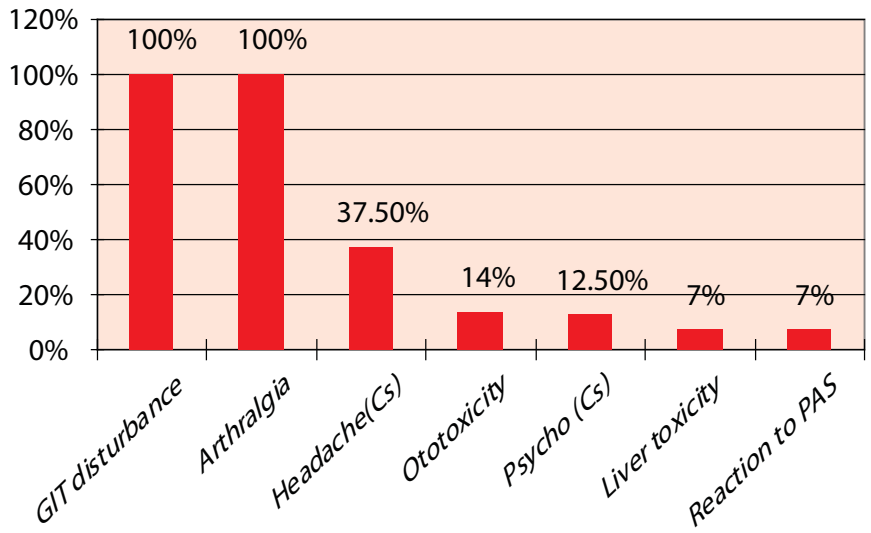
DST revealed that 65% of patients were susceptible to first line TB drugs, while 24% suffered from MDR-TB, 9% from MonoDR-TB and 2% from PDR-TB. The high susceptibility of MTB to first line drugs was likely due to the low prevalence of MDR-TB among patients previously treated and the wide inclusion criteria.



DR-TB Treatment Outcomes



Side effects with DR-TB treatment



Eight patients had their treatment regimens modified. Reasons for modification of the regimen included:

- *severe side effects*
- *drug toxicity*
- *drug intolerance*
- *lack of ancillary drugs*
- *second line DST results*
- *no clinical improvement and suspicion of treatment failure*

The side effects from my medication are so strong that I cannot do anything until 1-2 PM. I vomit every morning, and have strong headaches and diarrhoea. I try to get on with my normal life but the medicine makes me feel very weak, and I sometimes have difficulties even standing up. My life has really changed a lot since I started taking this medication.

Y. C., 48 years old, Takeo

Hand over of DR-TB activities

All DR-TB program activities were successfully handed over to CHC, CENAT, and MoH in Takeo in April 2009.

Challenges and Lessons Learned

- *Reliable DST, access to a quality controlled laboratory and a short delay between specimen collection and DST results are important factors for adequate patient management*
- *Long hospitalization was not well accepted by patients*
- *Managing side effects was challenging for clinicians*
- *Cold chain requirements need to be checked before shipping samples and before supplying facilities and homes with cold chain drugs*
- *Intensive and supporting counseling, including emotional and social support are paramount for patient empowerment and treatment adherence*
- *Infection control measures, especially administrative ones, are challenging to maintain.*

Recommendations

- *New, rapid diagnostics should be introduced as soon as possible to ensure early detection of DR-TB*
- *Hospitalization should be as short as possible*
- *Training of clinicians on early recognition and management of side effects should be continuous*
- *An expanded formulary of auxiliary drugs should be readily available*
- *The cold chain should be in place for sample transportation and drug supply*
- *Patient and family counseling should be introduced at the earliest possible time in MDR-TB programs.*
- *One person should be in charge of supervising infection control measures in each health facility. Attention should be given to the care takers who tend to stay with the patients in the same wardroom, in a supportive and compassionate manner.*

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