Photo: John Freeman

Scaling up diagnosis and treatment of drug-resistant tuberculosis in Khayelitsha, South Africa

An integrated, community-based approach, March 2011

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We also acknowledge the many individuals suffering from drug resistant tuberculosis in Khayelitsha and their strength in dealing with this difficult disease.

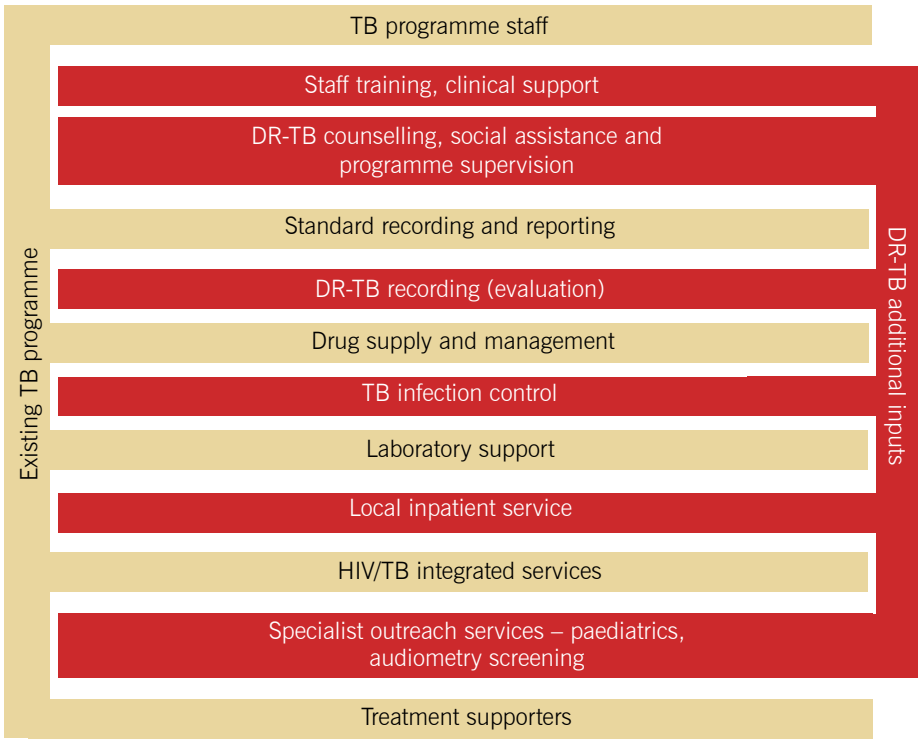
Executive Summary

Since 2007, in response to the growing epidemic of drug-resistant tuberculosis (DR-TB) in Khayelitsha, Médecins Sans Frontières (MSF), the City of Cape Town and the Provincial Government of the Western Cape are carrying out a pilot project to provide treatment to DR-TB patients at the primary care level. Khayelitsha is a township with one of the highest burdens of HIV infection and tuberculosis across South Africa and globally.

The Khayelitsha DR-TB Programme demonstrates how a patient-centred, decentralised model of care can increase case detection and improve treatment outcomes; thereby reducing further DR-TB transmission. The model is based on the understanding that the majority of DR-TB is transmitted by patients who are not on treatment. Consequently, the major objectives are to increase case detection, decrease time to diagnosis and treatment initiation, improve treatment outcomes and optimise infection control. The programme has been gradually implemented over three years, based on increasing experience, monitoring of outcomes and continuous re-evaluation.

In order to integrate DR-TB care and treatment into the existing TB programme at primary care level, a range of additional supports have been provided (see diagram). Although the model of care in Khayelitsha has been developed specifically for this setting, the majority of these interventions are likely to be feasible and sustainable across a range of different settings with minimal adaptation.

While a number of challenges remain, the successes of the programme may guide efforts to increase access to treatment and improve outcomes for DR-TB patients elsewhere.



Key successes include:

- **Improved case detection;** the number of cases diagnosed in Khayelitsha has increased from 118 in 2006 to 231 in 2009. This is the result of intensive training of health care workers promoting increased awareness of DR-TB and enabling more effective management of DR-TB patients at primary care level
- **Improved initiation of treatment;** more than 80% of patients diagnosed in 2009 and 2010 were started on treatment. The median time to treatment initiation has decreased from 71 days in 2007 to 33 days in 2010
- **Improved treatment regimens;** the treatment regimen in Khayelitsha has been strengthened by the inclusion of moxifloxacin (instead of ofloxacin) and terizidone for all patients. Ongoing treatment is guided by the availability of second-line drug susceptibility results in close to 90% of patients, increased from only 35% in 2007. Twenty percent of patients found to have initially undetected second-line resistance in 2009 and 2010 were able to receive an effective regimen from the outset, preventing the development of further resistance while awaiting second-line drug susceptibility results
- **Ambulatory treatment;** in 2010, 71% of patients were able to start treatment at their local clinic, 15% started treatment in the community-based sub-acute inpatient facility in Khayelitsha and only 14% were admitted to the centralised DR-TB hospital; thereby reducing the demand for scarce hospital beds and allowing clinically stable patients to remain in their communities with support from their families
- **TB infection control;** measures to reduce the risk of nosocomial TB transmission have been implemented in all primary health care facilities and the sub-acute inpatient facility in Khayelitsha. In addition, activities to increase community awareness and provide information on infection control are provided to the general community at taxi ranks, churches and shopping malls
- **Improving patient support;** patients are receiving initial one-on-one counselling, ongoing adherence support at weekly support groups, as well as dedicated home visits to support and educate the family, assess infection control measures and trace contacts
- **Improved survival;** Among patients diagnosed with DR-TB in 2008, 62% were alive at 18 months after diagnosis. Given that 76% of all DR-TB patients are HIV infected, this represents a significant improvement from that reported elsewhere

Many of the challenges faced in Khayelitsha are common to programmes aiming to scale up DR-TB treatment globally; especially the lack of access to rapid diagnosis of drug resistance for all TB patients, long and difficult treatment regimens that lead to high rates of default from treatment as well as the lack of new drugs to improve treatment outcomes and reduce the risk of treatment failure.

In Khayelitsha, and indeed in many other parts of South Africa, increased access to newer and more rapid diagnostic tools will enable case detection to be improved dramatically. Currently, it is estimated that approximately only half of DR-TB cases in Khayelitsha are diagnosed. Although this is a dramatic success when compared to the barely 3% that have access to appropriate treatment globally, this will need to be increased substantially if we are to ultimately control the DR-TB epidemic.

Simple measures such as the introduction of DR-TB registers in all primary health care facilities will enable a more accurate assessment of the DR-TB burden in the community, and therefore more accurate reporting at a national level.

In addition, new approaches to reducing the proportion of patients who fail treatment through earlier identification and access to a wider range of drugs are needed. Providing care for patients in whom treatment has failed and who remain infectious will require balancing the individual's rights to care and treatment with protection of the community.

The successes demonstrated in the Khayelitsha DR-TB programme show that diagnosing and treating drug resistant TB through the primary health care system is essential if the thousands of prevalent cases throughout South Africa are to be offered treatment and a chance of cure. Decentralisation of treatment will, however, require the commitment of resources to the primary care level, away from expensive hospital-based programmes. Given the high cost of treating just one patient for drug resistant TB, prevention through treatment of existing cases should be of the highest priority.

Introduction

Khayelitsha is the largest township in South Africa's Western Cape Province. It lies 40 kilometres from Cape Town and is home to at least 500,000 people, over half of whom are unemployed. Khayelitsha has one of the highest burdens of HIV infection and tuberculosis (TB) both in the country and globally. In 2009, antenatal HIV prevalence was 30% and the case notification rate for TB was at least 1,500 per 100,000 people per year – among the highest estimated TB incidence rates in the world [1].

Médecins Sans Frontières (MSF) started working in Khayelitsha in 1999 supporting a pilot programme to prevent mother-to-child-transmission of HIV. In 2001, the first patient in Khayelitsha received antiretroviral therapy (ART) through a pilot programme supported by MSF that has been subsequently integrated into the Western Cape Province ART programme. By the end of 2010, more than 15,000 people had been successfully started on life-saving ART in Khayelitsha. Successes have also been seen the in the treatment of TB; in 2009, 81% of new sputum smear positive cases and 65% of retreatment smear positive patients were successfully treated. The proportion of new smear positive patients not completing treatment was 7.7%, and 17% for retreatment smear positive patients [1].

Despite these successes, Khayelitsha has a growing epidemic of drug-resistant TB (DR-TB), an epidemic that threatens both the success of the National Tuberculosis Programme and the gains made through expanding access to antiretroviral treatment for HIV. Given this emerging threat, it is necessary to rapidly diagnose and effectively treat as many DR-TB cases as possible in order to prevent further progression of the epidemic. In light of national policy to centralise treatment through hospitalisation of all DR-TB patients, Khayelitsha was one of the early pilot sites for decentralised care and expanded access to effective treatment for DR-TB in South Africa. This report describes the DR-TB model of care as it has developed in Khayelitsha, along with the key achievements to date and the challenges that remain.

The Burden of DR-TB in Khayelitsha

South Africa has one of the highest burdens of DR-TB globally, with close to 10,000 patients diagnosed with multi-drug resistant (MDR) TB in 2009 [2]. In Khayelitsha, there is a particularly high level of DR-TB. A survey carried out at two sites in Khayelitsha conducted by MSF, the City of Cape Town and the National Health Laboratory Service (NHLS) in 2008/09 found that 5.2% of new TB cases and 11.1% of previously treated TB cases were due to rifampicin-resistant strains [3]. If applied to the actual number of TB cases diagnosed in 2008, these figures indicate that if all TB cases in Khayelitsha were to be screened for DR-TB, close to 400 would be diagnosed each year, leading to an estimated incidence of close to 80 per 100,000/year (Table 1). More than half of these cases occur among TB patients who have not previously received TB treatment, indicating that most DR-TB in Khayelitsha is transmitted, rather than acquired through inadequate TB treatment. This ongoing community transmission of DR-TB, especially among the vulnerable HIV infected population, is highly likely to be driving this epidemic.

Earlier diagnosis and treatment will both reduce transmission and improve treatment outcomes. The Khayelitsha pilot project is based on the premise that, in a high TB/HIV prevalence setting, the burden of DR-TB may best be reduced by:

- a community-based approach
- improved case detection strategies
- increased access to quality-assured medications in robust combinations

Table 1: Results of a drug resistance survey conducted in Khayelitsha in 2008/2009 [3].

	New TB cases	Previously treated TB cases
Number of culture positive TB cases in survey	269	261
Susceptible	236	211
Rifampicin mono-resistance	5 (1.9%)	9 (3.4%)
Isoniazid mono-resistance	19 (7.1%)	21 (8.0%)
MDR-TB	9 (3.3%)	20 (7.7%)
Any rifampicin resistance	14 (5.2%)	29 (11.1%)
Any isoniazid resistance	28 (10.4%)	41 (15.7%)
Number of TB cases diagnosed in Khayelitsha in 2008	4279	1542
Estimated % of rifampicin-resistant TB (from survey)	5.2%	11.1%
Estimated number of rifampicin resistant TB cases if all screened for DR-TB	223	168
Total estimated rifampicin resistant TB cases in 2008	391	

- shortening the time to both diagnosis and treatment initiation
- prioritizing TB infection control in health facilities
- intensified patient support to ensure adherence.

Of the estimated 391 cases of DR-TB in Khayelitsha in 2008, only 211 (54%) were diagnosed. In such a high DR-TB burden context as this, every TB patient should be tested for drug resistance to achieve the necessary coverage. However current guidelines only recommend testing for DR-TB in patients who were previously treated for TB or who are not responding to TB treatment.

Drug-resistant tuberculosis definitions:

In this report, DR-TB refers to infection with *Mycobacterium tuberculosis* bacteria that are:

- Resistant to the two most important first-line anti-tuberculosis drugs (rifampicin and isoniazid), therefore defined as 'multidrug resistant' or MDR
- Resistant to rifampicin alone, therefore defined as 'rifampicin mono-resistant'
- Resistant to rifampicin, isoniazid and two of the most important classes of second-line anti-tuberculosis drugs, namely a fluoroquinolone (such as ofloxacin) and an injectable drug (either amikacin, kanamycin or capreomycin), therefore defined as 'extensively drug-resistant' or XDR
- Resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as either one of the fluoroquinolone drugs OR any of the three injectable second-line anti-TB drugs (amikacin, kanamycin or capreomycin), therefore defined as pre-XDR

Given that all DR-TB patients require second-line anti-tuberculosis treatment and that patients can be infected with strains of TB bacteria having a wide range of possible combinations of resistance to different drugs, we use the term drug resistant TB (DR-TB) throughout this report

The Khayelitsha Model of Care for DR-TB

Principles of the Khayelitsha Model

The Khayelitsha DR-TB programme has been implemented based on principles of respect for individual patient rights as well as public health protection, integration into existing TB services, the need for intensified TB infection control measures at all levels, an understanding that the majority of community transmission occurs prior to initiation of treatment and that ambulatory treatment can be implemented without posing an increased risk for community transmission (see box).

The model of care now being implemented in Khayelitsha has developed in a progressive manner since late 2007. Not all components were implemented initially; rather, changes and new initiatives were introduced as the programme developed and lessons were learned.

The aim of this report is to offer the experience in Khayelitsha as an example of how this model of care may be adapted and developed within the context of a particular setting, rather than as a 'prescription' of what should be done in any situation. Other settings will be different, both in terms of existing resources and further requirements needed to provide quality care to patients with DR-TB. The main focus should be on the actual services that are needed to provide decentralised patient care. Many of the activities may be carried out through existing support structures in primary health care clinics and therefore other settings may not require all of the additional resources described in this model. There may already be the capacity to expand existing activities to meet the objectives described, e.g. DR-TB data monitoring by existing TB data managers, use of a sub-acute step-down facility or hospital isolation unit for admission of patients when necessary, or training of lay clinic staff to perform audiometry screening.

BASIC PRINCIPLES OF IMPLEMENTATION:

- Use of a patient-centred approach that places the patient at the centre of their treatment and respects human rights, paired with constant consideration for public health protection
- Integration of DR-TB diagnosis and treatment into the routine TB programme and primary health care infrastructure
- An understanding that the majority of DR-TB transmission occurs before patients are diagnosed and started on appropriate treatment
- Acute awareness of the need for airborne infection control in all health facilities, as well as in patients' homes and within the community in general
- With appropriate support, ambulatory treatment can be implemented without increased risk of community transmission
- The realisation that in high HIV/TB burden, low resource settings, centralised DR-TB programmes (i.e. mandatory hospital admission) have failed to contain the rise of DR-TB
- A willingness to learn from the experience of TB programmes and ARV programmes, where decentralisation of nurse-based, integrated care and standardised protocols have resulted in increased access to care, high levels of adherence to treatment, and shorter delays between diagnosis and treatment initiation

Figure 1: The diagnostic and treatment process in Khayelitsha.

Khayelitsha primary care clinic:

- DST result received in clinic
- Medical Officer assessment and decision – clinic-based treatment vs hospital admission (direct referral)
- Start DR-TB treatment (if clinic-based) using a six-drug strengthened standardized regimen: kanamycin, moxifloxacin, terizidone, ethionamide, ethambutol, pyrazinamide
- First counseling session at time of treatment start in clinic
- Second counseling and infection control session in home (allowing for identification of ALL contacts)
- Contact screening
- Patient attends weekly support group meetings

Receive second-line DST, adjust treatment accordingly, ongoing monitoring:

- Routine monitoring (clinical and laboratory)
- Early identification and management of any side effects
- Psychosocial and financial support (access to government and community support services)
- Early defaulter tracing
- Re-screen contacts

Additional services in Khayelitsha:

- Clinical patient review meetings
- Audiometry screening
- Lizo Nobanda sub-acute inpatient facility
- Paediatric outreach clinic
- Infection Control support for facilities

Initial Evaluation of the Setting

Implementation of the programme began in late 2007 with a review of the status of DR-TB diagnosis and treatment at that time. The key findings of this review included: long waiting times for hospital admission in order to initiate DR-TB treatment, high numbers of patients failing to be initiated on treatment or subsequently defaulting from treatment and inconsistent DR-TB screening or contact tracing.

Health care workers at primary care level had limited knowledge and understanding of DR-TB, leading to fear of infection and negative attitudes toward patients. Once patients were diagnosed with DR-TB based on a laboratory result, a referral was simply sent to the specialist TB hospital without proper counselling or follow-up of the patient to ensure that they had commenced on or completed treatment. Poor understanding of TB and DR-TB transmission led to inconsistent implementation of airborne infection control measures in Khayelitsha clinics.

Monitoring and evaluation of DR-TB was also initially sub-optimal. There was a lack of data at primary care level regarding the numbers of patients diagnosed and their outcomes. Many diagnosed patients were never admitted to the specialist hospital for treatment, and therefore were never recorded as being diagnosed with DR-TB. This situation resulted in a significant under-estimate of the DR-TB burden.

Phased Implementation

One of the first steps to improve the situation was to introduce DR-TB registers into each clinic. The maintenance of this monitoring and reporting system is one of the cornerstones of the Khayelitsha programme, as it is used to assess progress towards the programme objectives.

Another essential component of the programme was to provide extensive DR-TB training for health care workers in the clinics. Ongoing training and support of clinic staff and other stakeholders (e.g. other NGOs and community organisations) has enabled the gradual development and integration of the treatment process for DR-TB patients to be implemented at the primary care level. Figure 1 details the components of this process, from increased case detection through to provision of additional patient support services, which have been introduced gradually over the past three years.

Increasing Diagnosis of DR-TB

As of December 2010, 989 individual patients with DR-TB had been diagnosed in Khayelitsha (Figure 2). Since there is often a significant delay from the time patients give a sputum sample to receipt of the diagnostic sputum result in the clinic, total numbers for 2010 are expected to increase. In 2009, 231 patients were diagnosed with DR-TB, giving a case notification rate of 45 per 100,000 people per year (using an estimated population of 500,000 in Khayelitsha). This number represents an estimated case detection rate of 54% when compared to the DR-TB prevalence as estimated by the survey done in 2008/09 [3]. Although this is a noteworthy achievement of the programme so far, further improvement to increase detection of DR-TB in Khayelitsha is still necessary and possible.

Education and training of clinic staff was necessary to raise awareness of the case detection strategy to increase diagnosis of DR-TB, by requesting sputum culture and drug susceptibility testing (DST) for TB patients at risk of DR-TB. Under current South African policy, only certain groups of patients are screened for drug resistance. These groups include:

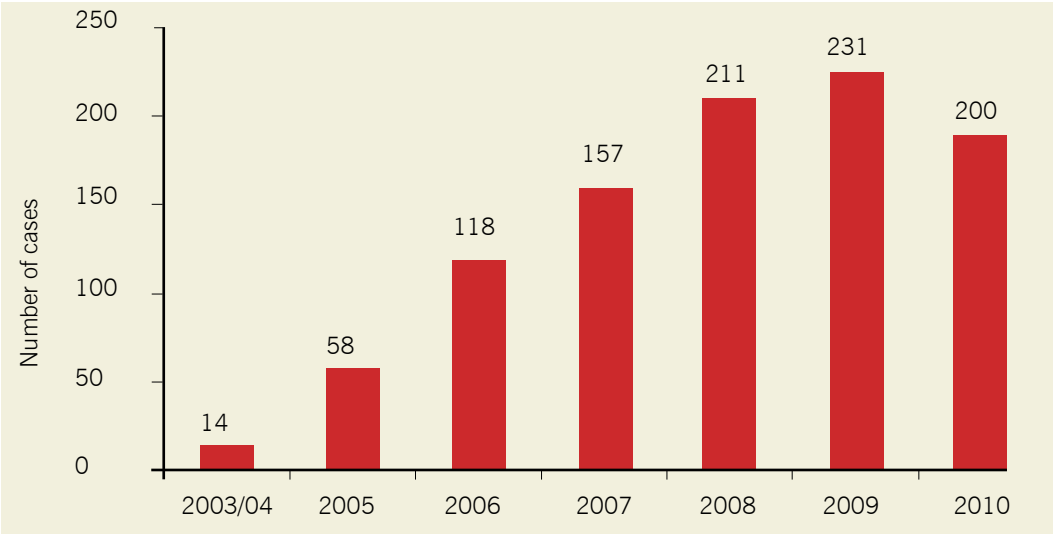
- TB patients who have received TB treatment previously
- close contacts of confirmed DR-TB patients
- high risk groups (health care workers, miners, prisoners)
- patients who have a poor clinical response to TB treatment

- patients who do not smear or culture convert after 2 months of treatment or who re-convert after 5 months of TB treatment.

HIV positive patients are at higher risk of developing any form of TB compared to HIV negative patients, and ideally all HIV-infected patients should be screened for DR-TB. However the high burden of HIV in Khayelitsha means that this would place massive demands on the current laboratory service if the current screening method of TB culture and drug susceptibility testing were to be used for such a large number of samples.

In 2009, only 29% of DR-TB cases diagnosed in Khayelitsha were new cases. However, based on the 2008/09 survey, more than half of all DR-TB cases in Khayelitsha should be in this category. It is likely that we are missing a large proportion of new DR-TB cases using the current case detection strategy. These data highlight the need to screen all TB cases for TB drug resistance, in order to allow for early diagnosis and treatment, and prevention of further spread of DR-TB. This requires improved access to more rapid diagnostic techniques, which would allow a larger number of samples to be screened.

Figure 2: Number of DR-TB cases diagnosed in Khayelitsha by year (2003–2010).



RAPID DIAGNOSTICS – CEPHEID XPERT MTB/RIF

During 2010 and continuing into 2011, a new rapid molecular test for TB and drug resistance (CEPHEID Xpert MTB/RIF, also known as 'GeneXpert') has been undergoing testing in Khayelitsha. This is being carried out as part of a multi-centric trial in collaboration with the University of Cape Town (UCT), the Foundation for Innovative New Diagnostics (FIND), the National Health Laboratory Service (NHLS), and the Provincial Administration of the Western Cape (PAWC) and City of Cape Town Departments of Health [4]. Initial results from the study conducted in one Khayelitsha clinic are promising, and for the first time allow for the potential to rapidly screen all TB suspects for DR-TB in a high burden setting such as Khayelitsha. Efforts are currently underway to allow much wider access to this technology. If the Xpert MTB/RIF diagnostic could be used to test all TB suspects in Khayelitsha for DR-TB, we would expect to see dramatically increased case detection initially, followed by reductions over time as community transmission is reduced.

Improved case detection has also been demonstrated by the increasing proportions of DR-TB patients who are HIV infected (Figure 3). Among the 200 people diagnosed with DR-TB to date in 2010, the HIV status is known for 187 (94%), of which 142 (76%) were found to be co-infected. This figure is now similar to that for drug-susceptible TB, whereas previously the percentage of HIV-infected DR-TB cases was lower. This suggests that HIV infected people most likely had died before a diagnosis of DR-TB could be made, as HIV-positive patients with DR-TB clinically deteriorate more quickly. This achievement also reflects improved HIV Counselling and Testing (HCT) coverage through greater integration of HIV and TB services in Khayelitsha. The increased proportion of co-infected patients suggests improved survival of HIV-infected DR-TB patients.

Initiating DR-TB Treatment at the Primary Care Level

As DR-TB case detection increases, it is necessary to train and empower clinic administrative and health care staff to manage cases appropriately. When a laboratory result showing at least rifampicin resistance is received in any of the 10 primary care clinics in Khayelitsha, staff are required to register patients' results in the DR-TB register, to rapidly recall the patients to clinic (using existing processes for follow-up of any other TB patients) and to ensure that they are referred to a doctor for clinical assessment. In some clinics, the doctor might only attend the clinic once or twice weekly, while in other larger clinics, a full time medical officer is available. At least one doctor per clinic in Khayelitsha has been trained in management of DR-TB patients through a number of dedicated DR-TB training workshops and ongoing monthly clinical review meetings.

Once the patient has been assessed and counselled by the doctor, a decision is made as to whether or not the patient requires hospital admission or is able to receive treatment through directly observed therapy (DOT) at the clinic on a daily basis. Experience has shown that the majority of patients diagnosed with DR-TB in Khayelitsha do not require hospitalisation based on their clinical condition – they are often well enough to attend the clinic daily to receive their second-line TB treatment on an ambulatory basis. This becomes particularly noticeable as clinic practices improve and patients are diagnosed with DR-TB earlier. This is not to say that hospitalisation is not necessary at all for DR-TB patients. As with drug sensitive TB, some DR-TB patients do become clinically unwell and may require hospitalisation at some point in their treatment. Therefore it remains necessary to maintain good communication links with tertiary services and to establish appropriate referral pathways between facilities.

In 2010, only 14% of cases from Khayelitsha were admitted to the centralised specialist DR-TB hospital at the time of treatment initiation. A further 15% of patients had their treatment started in the dedicated DR-TB sub-acute in-patient facility in Khayelitsha (see page 24), while 71% were able to start their treatment through their local primary care clinic (Figure 4).

Figure 3: Percentage of diagnosed DR-TB cases who are co-infected with HIV.

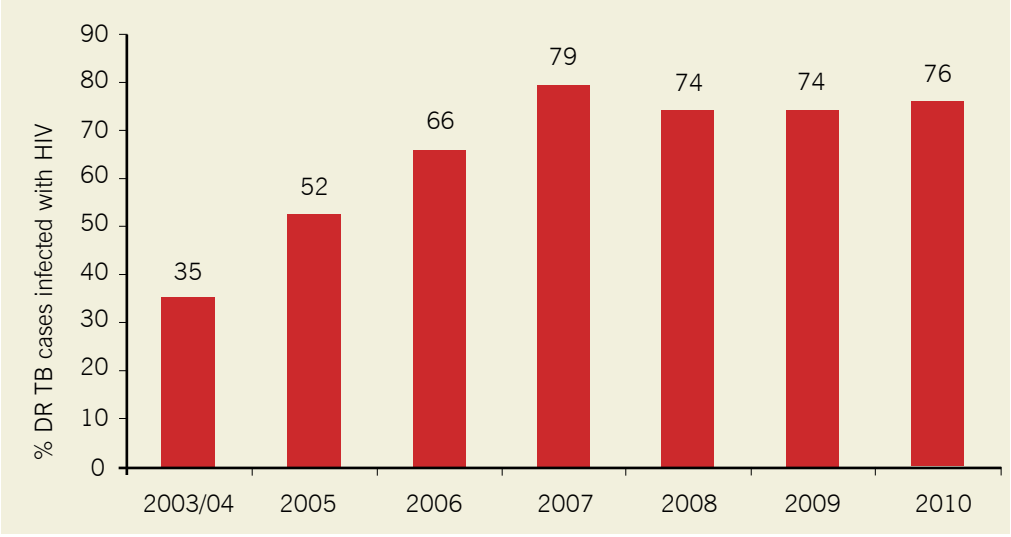
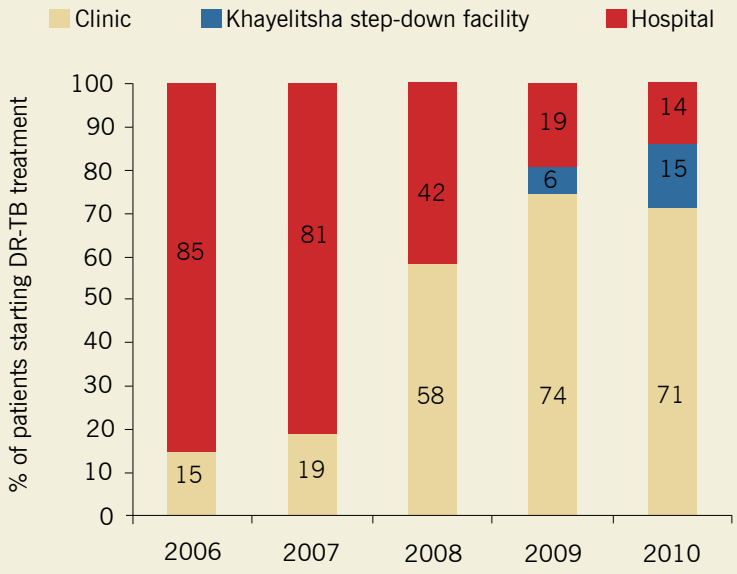


Figure 4: Site of DR-TB treatment initiation in Khayelitsha 2006–2010.



Managing XDR-TB at Primary Care Level?

Under current national policy, it is not possible to initiate treatment for extensively drug resistant (XDR) TB patients in their local clinics. Capreomycin is used to treat patients with demonstrated aminoglycoside (kanamycin or amikacin) resistance. While kanamycin is accessible as part of the standard regimen for MDR-TB in primary care clinics in Khayelitsha, capreomycin is currently only available for use in specialised DR-TB centres in South Africa. Therefore all patients requiring capreomycin have to be hospitalised in order to receive this medication. Due to the high demand for beds in the centralised TB hospital (which also serves many other surrounding sub-districts), an agreement was reached with them in early 2010 that patients in Khayelitsha may receive capreomycin if they are admitted in the sub-acute inpatient facility located in the community, (called Lizo Nobanda), provided the prescription is approved by a doctor from the TB hospital. Admissions to Lizo Nobanda for this reason are only intended to be for a short period in order to allow patients to commence treatment while they wait for a bed to become available at the specialist centre. While some patients with XDR-TB do require hospitalisation (as is the case for all TB), many are stable enough to attend their clinic daily to receive treatment; therefore a blanket policy to restrict access to capreomycin (and also PAS) in the community means that an unnecessary proportion of patients are admitted who could be managed in their local clinic. Indeed, given the delay in receiving second-line DST results, there are a number of patients who have already begun to receive clinic-based treatment for MDR-TB but who are then subsequently found to require capreomycin and have to be admitted to receive this treatment.

THE NEED FOR CAPREOMYCIN AT CLINIC LEVEL

Zyanda, a 35-year-old HIV-positive woman, presented at her local clinic in Khayelitsha with a persistent cough and night sweats and was started on regular TB treatment. Her sputum smear was negative, but her brother had been diagnosed with DR-TB the year before and had died in hospital, so the clinic staff sent her sputum for culture and DST. Apart from her symptoms, she was fairly well and was able to walk to the clinic daily to receive her treatment. She had no children and lived in a shack with her mother and her uncle, and was able to sleep in a separate room. After 3 weeks, the DST results on the positive MTB culture revealed that she had XDR-TB and required capreomycin as part of her treatment regimen because of demonstrated aminoglycoside resistance.

Due to the policy of hospitalising all patients requiring capreomycin, a bed was requested at the specialist TB hospital, and in the meantime, Zyanda was admitted to the sub-acute inpatient facility in Khayelitsha to receive her DR-TB treatment, including the capreomycin injections. She remained in this community facility for a total of three months until a bed became available in the hospital. During that time she was monitored by the nurses according to the same protocol as that used in the primary care clinics in Khayelitsha. She saw a doctor once a week. She tolerated her treatment well and occasionally worked in the garden or helped the nurses to care for the other patients. After two months of treatment, her sputum cultures converted to negative, but according to the treatment protocol she was required to continue capreomycin for another four months. She was still only able to access capreomycin while admitted in the sub-acute facility or in hospital, despite remaining clinically stable and no longer posing an infection risk to others.

When a bed became available in the TB hospital she was transferred there to complete the remaining three months of capreomycin injections before being discharged back to her clinic to receive oral medications for the remaining months of her treatment regimen. With the adequate clinical monitoring and support provided through the Khayelitsha decentralised DR-TB programme, Zyanda could have been managed well in her clinic, reducing the demand on beds in the TB hospital and allowing her to remain at home with her family.

Table 2: Number of diagnosed DR-TB patients who were started on second-line TB treatment and the number who are known to have died before treatment could be started.

Year	Diagnosed DR-TB	Started on treatment (%)	Died before starting treatment
2003/04	14	14 (100%)	0
2005	58	52 (90%)	0
2006	118	85 (72%)	10 (8%)
2007	157	106 (68%)	21 (13%)
2008	211	159 (75%)	24 (11%)
2009	231	195 (84%)	20 (9%)
2010	200*	164 (82%)	16 (8%)
Total	989	775 (78%)	91 (9%)

* Note that some of these patients may still start treatment.

Increasing the Number of DR-TB Patients Starting Treatment

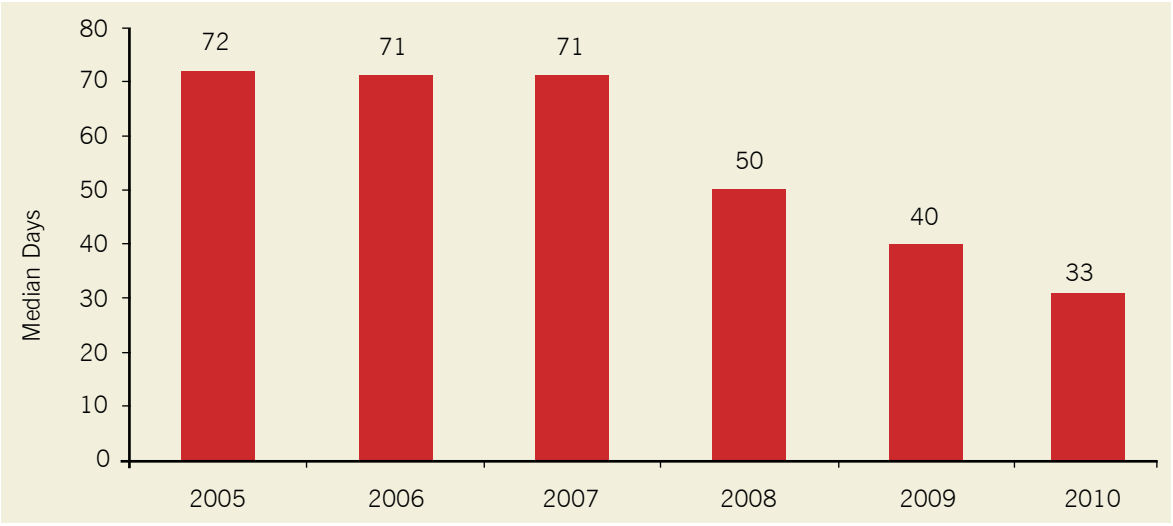
Improved case detection and early initiation of appropriate treatment, primarily through the provision of clinic-based ambulatory treatment, are key factors in reducing overall mortality and preventing further ongoing transmission of DR-TB. Since 2007, the number of patients initiating DR-TB treatment has increased dramatically in Khayelitsha (Table 2). These are patients that would otherwise remain untreated and therefore infectious, potentially spreading DR-TB in the community and in health facilities.

Prior to 2007, the registration and reporting of DR-TB cases in Khayelitsha was inconsistent and incomplete; patients who were initiated on treatment were more likely to be registered at a centralised DR-TB centre called Brooklyn Chest Hospital (BCH), compared to those diagnosed but not started on DR-TB treatment (a survivor effect). Therefore, the percentage of recorded patients in whom treatment was initiated declined as reporting improved in 2006/07 and has now stabilised at around 80% in the last two years.

Currently, the most common reason patients are not started on treatment is that they die between sputum sampling and the time that the result is reported from the laboratory, the patient located and treatment started. Pre-treatment mortality remains at approximately 10% of all diagnosed patients. This highlights the need to diagnose and start patients on DR-TB treatment as soon as possible.

In 2007, it took a median of 71 days between sputum sampling and treatment initiation (Figure 5). Although the time taken for TB to grow in culture is variable, the routine use of a molecular test, the Hain Line Probe Assay, for detecting resistance to rifampicin and isoniazid in the National Health Laboratory Service (NHLS) has reduced the delay in obtaining first line

Figure 5: Median Days between sputum sampling and treatment initiation by 2005–2010.



susceptibility results on positive smears and cultures. In addition to the use of the Hain LPA, efforts to maximise the efficiency of existing processes have also helped to reduce the time from sputum sampling to DR-TB treatment initiation. These efforts include:

- prompt delivery of sputum samples to the laboratory
- timely reporting and delivery of results to the relevant clinics
- rapid recall of patients to the clinic to see the doctor

Although the time between sputum sampling and treatment initiation declined to 33 days in 2010 it is still too long to avoid mortality in a significant number of cases. Among the 36 patients diagnosed with DR-TB in 2009 and 2010, who died before treatment could be initiated, the median time between sputum sampling and death was 25 days [5]. Expanded use of a rapid diagnostic test for DR-TB such as the Xpert MTB/RIF (GeneXpert) offers an excellent opportunity to dramatically reduce early mortality.

RAPID DRUG RESISTANCE TESTING FOR ALL TB CASES

Asanda, a 46-year-old HIV-positive man, was diagnosed clinically with sputum smear-negative pulmonary TB in October 2010 and was started on the standard first-line TB treatment in his local clinic. He was commenced on antiretroviral therapy (ART) two months after TB treatment had been established. A month later he became clinically unwell with increased cough, fever and a worsening chest X-ray. His sputum was again tested and had subsequently become smear-positive for TB. The sample was sent for further testing by culture and DST, and further antibiotics were added to his treatment to cover other non-TB infections.

The sputum culture results came back a few weeks later demonstrating resistance to isoniazid and rifampicin; however by this stage Asanda had been admitted to hospital due to further deterioration of his condition. He was started on the standard treatment regimen for DR-TB, however he died a few days later. Had he been eligible for DR-TB screening initially, this man could have been correctly diagnosed from the beginning. More rapid diagnostics, available to all patients suspected of TB, would have meant Asanda could have started DR-TB treatment earlier and his death may have been prevented.

Strengthening the DR-TB Treatment Regimen

Unlike antiretroviral drugs used in HIV treatment, there is no third-line treatment available for TB. Once the tuberculosis bacteria have developed resistance to first-line drugs, there is only a limited range of second-line drugs available to cure DR-TB. Many of these drugs have little evidence for efficacy and have a considerable risk of side effects. Once resistance has developed to second-line drugs, the chances of cure are severely limited [6]. As a result, when DR-TB is detected and treatment initiated, all efforts should be made to cure the patient using all available second-line drugs – there is essentially one chance of cure [7]. The use of a weakened regimen (i.e. with less than 4 active drugs) for any reason, either due to concerns over cost or attempts to reserve certain drugs, risks the creation of additional second-line resistance during treatment, thus severely limiting the patient's chances of cure.

In Cape Town, resistance to isoniazid and rifampicin is tested using a rapid molecular test (line probe assay) on positive sputum cultures [8]. To determine how many of these cases have second-line drug resistance, further conventional, culture-based drug susceptibility testing (DST) is also conducted. Results for second-line resistance are often received some time after the patient has initiated treatment, and in some cases not at all. In Khayelitsha, the proportion of MDR-TB cases that have second-line DST results available from the time of diagnosis has increased dramatically from only 35% in 2007 to 88% in 2009 (Table 3). This improvement was brought about initially by efforts to remind clinic staff to routinely request second-line DST on any positive cultures showing first line TB drug resistance, while more recently it has become standard procedure for the laboratory service to routinely carry out second-line testing on all samples resistant to isoniazid and rifampicin. Additional efforts to encourage staff to obtain a confirmatory sputum sample at treatment initiation, on which second-line DST can also be conducted, have also contributed to this increase.

While the increased availability of second-line susceptibility results at clinic level is laudable, the data demonstrate alarmingly high levels of second-line resistance, prior to initiation of second-line treatment. In 2009 and 2010, among the

Table 3: Number of MDR-TB cases diagnosed in Khayelitsha, number with second-line DST results available, and number with additional resistance detected to ofloxacin and/or an injectable.

Year	MDR-TB*	2nd line DST results available (% of MDR-TB)	Ofloxacin resistance (% of 2nd line available)	Injectable resistance (% of 2nd line available)	XDR-TB (% of 2nd line available)
2007	126	43 (35%)	17 (40%)	17 (40%)	13 (30%)
2008	159	115 (74%)	20 (17%)	18 (16%)	11 (10%)
2009	169	145 (88%)	19 (13%)	17 (12%)	12 (8%)
2010†	161	123 (80%)	15 (12%)	23 (19%)	7 (6%)
Total	615	426 (69%)	71 (17%)	75 (18%)	36 (9%)

*Laboratory confirmed MDR-TB cases (not all DR-TB cases)
†Data for 2010 incomplete due to time taken for culture and DST

ONE CHANCE OF CURE – THE NEED FOR A STRENGTHENED REGIMEN

In June 2009, Nosisi, a 47-year-old lady with TB symptoms, presented at a Khayelitsha clinic. She gave a sputum sample which was sent for culture and DST as she had been treated for TB two years previously. Three weeks later, laboratory results confirmed smear positive MDR-TB (resistance to both isoniazid and rifampicin using the line probe assay). Three days later, she was started on the standard DR-TB treatment regimen used at the time: kanamycin, ofloxacin, ethambutol, ethionamide and pyrazinamide.

After she had been on treatment for 6 weeks, second-line DST results became available, showing resistance to ofloxacin but susceptibility to amikacin, ethambutol and ethionamide. Given that DST for both ethambutol and ethionamide is often unreliable [9, 10] and DST is not conducted for pyrazinamide, Nosisi may well have been receiving monotherapy with kanamycin for the first 6 weeks of treatment.

Although the treatment regimen was modified after the second-line DST results became available, and new drugs were added (including moxifloxacin and ethionamide), a culture taken at 5 months of treatment was positive and displayed resistance to amikacin. It is likely that this resistance developed during the first six weeks of treatment, while Nosisi was receiving an inadequate regimen.

268 MDR-TB cases with available second-line DST, 13% were infected with strains having ofloxacin resistance, 15% with resistance to an aminoglycoside and/or capreomycin, and 7% were infected with XDR-TB strains. Overall, 20% of MDR-TB patients have resistance to either ofloxacin or an injectable or both.

These figures suggest that a large proportion of DR-TB cases in Khayelitsha will not be effectively treated if a regimen that contains a limited number of second-line drugs to which the organism is susceptible is used in the initial treatment regimen. Instead, this has the potential to create further resistance (see box).

In response to this risk, the Khayelitsha project has strengthened the initial drug regimen for DR-TB; the regimen now includes moxifloxacin and terizidone for all patients starting DR-TB treatment. This will enable the 20% of patients with initially undetected second-line resistance to receive an effective regimen from the outset. Until recently, the standard regimen in South Africa included kanamycin, ofloxacin, ethambutol, ethionamide and pyrazinamide. In April 2010, the Western Cape Province provided terizidone for all DR-TB patients, replacing ethambutol in the standard regimen. Moxifloxacin has been used in Khayelitsha since 2008; initially only for patients with demonstrated resistance to ofloxacin, but expanded to include all patients starting DR-TB treatment as of September 2009. At that point, cycloserine was also added to the starting regimen, but was replaced by terizidone (a similar drug to cycloserine) in April 2010, when terizidone was provided for all DR-TB patients in the province. Therefore the initial treatment regimen for suspected and confirmed cases of DR-TB in Khayelitsha currently consists of kanamycin, moxifloxacin, terizidone, ethionamide, ethambutol, and pyrazinamide

The necessity of a strengthened regimen is even further emphasised if widespread roll-out of the Xpert MTB/RIF (GeneXpert) test is to occur. This will mean that the gap between treatment initiation and receipt of second-line DST results will widen further.

Rationale for Use of Moxifloxacin

Although all fluoroquinolones have activity against *Mycobacterium tuberculosis*, the newer generation fluoroquinolones, including moxifloxacin, appear to be particularly efficacious [11-13]. Currently, therapeutic options for treating MDR-TB are extremely limited and treatment outcomes are particularly poor when fluoroquinolone resistance has developed [14,15]. Moxifloxacin, a newer fluoroquinolone with greater anti-TB activity than ofloxacin, has considerable potential to improve the treatment of drug resistant TB, and is recommended by the World Health Organization for MDR-TB treatment [16]. In addition, moxifloxacin may be effective against a significant proportion of isolates phenotypically resistant to ofloxacin or ciprofloxacin [17,18] and is potentially less likely to promote fluoroquinolone resistance compared to the older fluoroquinolones [19-21].

Despite these benefits, moxifloxacin use is almost entirely restricted to resource-rich settings – its prohibitive cost has forced many to recommend the use of levofloxacin, the S-isomeric form of ofloxacin, for MDR-TB treatment in resource-limited settings despite these countries bearing the greatest disease burden. While levofloxacin is likely to be an improvement over ofloxacin [22,23], its molecular similarity suggests a high degree of cross-resistance with ofloxacin [24]. Preliminary data from Latvia suggests good treatment outcomes are achievable for XDR-TB patients treated with a moxifloxacin-containing regimen [25]. Therefore, moxifloxacin most likely offers the best chance of cure for patients with MDR-TB and those with undetected fluoroquinolone resistance and XDR-TB.

Currently, MSF are working internationally to improve access to moxifloxacin for DR-TB patients. The use of moxifloxacin in Khayelitsha, while improving outcomes for individual patients, also serves to provide evidence for global advocacy efforts regarding moxifloxacin access and affordability.

Patient Adherence Support

Second-line treatment for DR-TB is long and difficult. Patients receive painful injections for at least 6 months and several of the second-line drugs are associated with significant and potentially debilitating side effects. Patients are often required to attend clinics each day and are occasionally hospitalised to receive treatment, making it difficult to continue working or to support families. A diagnosis of MDR-TB or XDR-TB is also associated with stigma and is often perceived as a death sentence by patients. For these reasons, counselling and treatment literacy are essential components of the Khayelitsha programme.

Once a patient has been diagnosed with DR-TB and a decision made on where treatment is to be initiated, the patient is then counselled by one of three counsellors dedicated for DR-TB patients. This requires an appropriate system of referral and good communication between the doctor or TB nurses and the counsellors. The first counselling session takes place in the clinic, preferably on the same day as the patient receives the diagnosis, and the counsellor explains what DR-TB is, how it is treated and what the patient will need to do to complete treatment and be cured. The counsellors use lay terms and culturally appropriate language, often repeating what has been explained to them by the doctor. Among the 409 patients starting DR-TB treatment in 2009 and 2010 in Khayelitsha, 301 (73%) were counselled by a dedicated DR-TB counsellor at the time of treatment initiation.

For ambulatory patients who receive treatment through the clinic, a home visit is conducted as soon as possible after the patient has received the initial counselling session and started treatment. One of the DR-TB counsellors along with one other person, either the social worker, nurse or peer educator, go together into the community to visit the patient in their usual place of residence. The aims of this visit are several-fold:

- to re-emphasise some of the issues raised in the first counselling session and discuss any further questions
- to involve other family or household members in supporting the patient to take treatment
- to provide education and support to both the patient and the household members to enable them to minimise the risk of DR-TB transmission
- to initiate screening for DR-TB among close household contacts, particularly children

Patients are also encouraged to attend weekly DR-TB support groups, which are run by an adherence counsellor together with a peer educator. Support

groups have been set up in each of the Khayelitsha clinics to provide a forum for discussion and peer support for patients throughout the duration of their DR-TB treatment. The peer educators are members of the support groups who are identified by the counsellors as being particularly adherent to treatment, with a good understanding of their disease and able to support other patients. They receive an incentive and assist the counsellors on a daily basis to run each of the support groups in the different clinics; this position is replaced by different support group members every three months. The DR-TB counsellors are also available throughout treatment for ongoing advice and counselling, particularly for those patients with problems adhering to treatment. The counsellors also regularly visit and provide support to patients during admission in the TB hospitals and in the sub-acute inpatient facility, Lizo Nobanda, which is located within the community in Khayelitsha.

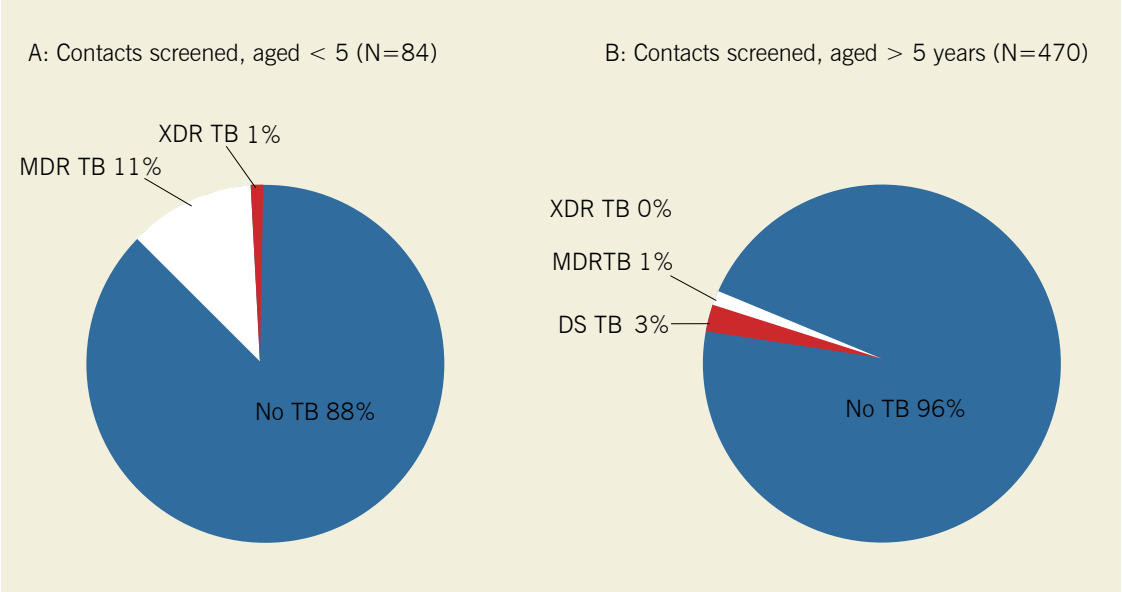
Patients with DR-TB are severely limited in their capacity to work, both directly due to the impact of their illness and sometimes due to the risk of further disease transmission. While all DR-TB patients in South Africa qualify for a State Disability Grant, many patients have trouble accessing it for a variety of reasons, and receipt of the grant often takes at least 4 months from the time treatment is initiated. These first months of treatment are often the most difficult, when patients are ill and receiving daily injections as part of their regimen. A dedicated social assistant is available in Khayelitsha to assist patients in accessing grants, in addition to referring patients to other support services, such as those available for people with substance abuse problems or hearing impairment.

In Khayelitsha, patients attend clinics daily to receive treatment under direct observation (DOT) throughout the full regimen. During the intensive phase of treatment, the clinic visit enables patients to receive the injection and also allows clinic staff to assess patients' clinical status, monitor adherence and detect potential side effects early. A standardised monitoring chart was introduced to guide doctors and nurses in managing DR-TB patients, and summarises the parameters necessary to monitor adverse events and guide treatment duration. This chart has been distributed for use in clinics in other sub-districts outside of Khayelitsha.

Beyond the intensive phase, when patients are stable, culture-converted (i.e. no longer sputum culture positive) and only receiving oral drugs, daily attendance at the clinic is demanding and perhaps unnecessary to ensure adherence. For these reasons, a network of community treatment supporters for patients on continuation phase was established in one clinic in November 2009 to assess the feasibility of further roll out across Khayelitsha. Each patient is allocated a treatment supporter who lives nearby and who goes to see the patient in their own house every day to watch them taking their tablets. The treatment supporter reports back to one of the counsellors each month with a record of the patient's adherence and any problems encountered. Although only a small number of patients have been enrolled into this pilot project, all of them have been adherent and have not defaulted thus far throughout their 12 – 18 month continuation phase of treatment. It is hoped that this initiative may be expanded to other clinics in 2011.

In order to monitor patients' attendance at clinics, a 'tick sheet' was introduced whereby the TB nurses tick next to a patient's name each day when they administer their injection and observe them swallowing their pills. These 'tick sheets' are reviewed weekly by the TB staff, who then inform the counsellors if a patient is starting to default treatment. The counsellors trace defaulters through phone calls or home visits to identify the reason for default. Although intensive defaulter tracing was attempted throughout 2009, its limited success suggests that resources invested in this activity may be better utilised in providing stronger support at the time that patients are diagnosed with DR-TB,

Figure 6: TB diagnosed among contacts of DR-TB index cases diagnosed in 2009.



and during the initial phase of treatment. Less intensified efforts are still being made to contact patients if they start to default treatment in order to identify those patients who might benefit from further assistance.

Contact Screening

Close contacts of DR-TB cases (i.e. those living in the same household) have a higher risk of developing DR-TB than do those in the general community [26]. Contact screening is therefore an important method for improving case detection and to diagnose infectious cases within households, thus reducing the risk of future transmission. Enhanced contact screening was implemented in Khayelitsha from late 2008 through identification and recording of household contacts of DR-TB patients both at the time of diagnosis in the clinic and at the subsequent home visit. Symptomatic contacts and all children less than 5 years or who are HIV-positive are given a letter stating their contact with a confirmed DR-TB patient and are advised to attend their local clinic for screening. In 2009, 144 patients who were diagnosed with DR-TB had their close contacts screened. In total 574 individuals were screened, either by asking about symptoms or through bacteriologic testing of sputum. Of available results (n = 554), children aged 5 years or less made up 84 of the contacts, while 470 contacts were aged above 5 years. Significant numbers of active TB cases were diagnosed among these contacts (Figure 6).

As the diagnosis of any TB in children is difficult and there is limited evidence regarding prophylaxis and treatment of children with DR-TB, a specialist paediatrician has conducted a monthly outreach clinic in Khayelitsha since November 2008 to assist local medical officers in managing children who are exposed to DR-TB. Overall, screening of close contacts yields a considerable number of DR-TB cases, particularly among children aged less than 5 years old. It is, however, important to note that while efforts are made to screen all paediatric contacts, the figures quoted in figure 6 are amongst children who attend the specialist clinic. This selected sample are likely to be at higher risk of TB and so are not necessarily representative of all paediatric contacts of DR-TB patients. Additionally, the majority of DR-TB diagnosed in very young children is presumed to be DR-TB based on the drug resistance profile of the index case and an assessment of the exposure between the index case and the child. Efforts are currently underway to improve diagnosis through conducting sputum induction in Khayelitsha clinics.

Most index cases will have been infectious for some time prior to diagnosis and treatment initiation. Therefore, the majority of transmission to household contacts undoubtedly takes place prior to diagnosis of DR-TB. It is important to note that drug-sensitive (DS) TB was diagnosed more often than DR-TB among older close contacts of DR-TB index cases. Therefore it cannot be assumed that all close contacts developing active TB will have DR-TB.

Table 4: Interim treatment outcomes for patients initiated on DR-TB treatment by year.

	2007	2008	2009
Started treatment	96	164	211
Treatment success*	30 (31%)	23	8
Still on treatment	3 (3%)	37	114
Died	27 (28%)	34 (21%)	36 (17%)
Default	31 (32%)	59 (36%)	38 (18%)
Treatment failure	2 (2%)	1	1
Transfer	3 (3%)	10	14

*Treatment success = 'cure' or 'treatment completion'

Improving Treatment Outcomes and Reducing Mortality

Treatment for DR-TB requires a minimum of 18 to 24 months and often even longer. As a result, analysis of treatment outcomes can only be conducted 2 years after patients initiate treatment. Given that the Khayelitsha programme was only initiated in late 2007, with staged implementation, its impact on treatment outcomes for patients starting treatment in 2008 or later cannot yet be definitively determined. However, there are some interim outcomes that have been assessed, particularly the impact of the programme on reducing mortality and improving survival.

Treatment outcomes are determined based on the WHO recommended definitions [27]. However, these definitions were primarily developed based on data from the treatment of DR-TB patients without HIV co-infection. Given the high and often rapid mortality among HIV-positive patients, the definition of treatment failure, whereby a patient must remain culture positive for at least one year, may not be a true reflection of patients in whom treatment is failing. Patients often die or default treatment before this time.

Although it is still too early to assess improvement in treatment success, the absolute number of patients accessing DR-TB treatment and being given a chance of cure is increasing each year (Table 4). However, the proportion of patients defaulting treatment remains very high. One of the reasons for this is that more people start DR-TB treatment, among them patients who would previously have not started due to refusing to be hospitalised (Table 4). To date, 36% of patients who started treatment in 2008 have defaulted, i.e. interrupted treatment for at least 2 months. Further investigation of these patients revealed that 30% had subsequently died, and 23% had been re-registered to start treatment again. The outcomes for the remaining 47% patients are unknown. The median time on treatment before default was 6.4 months (range 0.4 – 18 months).

Clearly the level of treatment default in Khayelitsha remains concerning. Based on a review of counselling and clinic records, the most significant factors associated with default were:

- stigma associated with DR-TB
- difficulties associated with the lack of a stable home and consequent travel back and forth from the Eastern Cape
- lack of family support

Other relevant factors included:

- excessive alcohol use by either patients or close household members leading to household instability
- poor rapport with clinic staff
- difficulties with staying in hospital for long periods
- the need to work and financially support others
- patients starting to feel better and therefore discontinuing treatment

This preliminary review suggests that the factors associated with DR-TB treatment default in Khayelitsha are often related to the difficult social and economic circumstances in which patients

live. Complex interventions to reduce default rates are required to address these issues in an holistic manner.

Mortality among people with DR-TB in Khayelitsha, although remaining high, appears to be improving over time (Figure 7). Of those diagnosed with DR-TB in 2008, 62% were still alive 18 months after diagnosis (defined as the date that sputum was taken in which DR-TB was first identified). This means that overall mortality is 38% (including patients not started on treatment), which compares favourably with reports from elsewhere in South Africa. For example, mortality at approximately one year among patients with MDR-TB in KwaZulu Natal is reported at 71% [28]. It is important to note, however, that active surveillance has not yet been done in order to follow up each patient and determine whether they are alive or not, so mortality may be somewhat higher than this, particularly among patients who have defaulted treatment.

Figure 7: 18-month survival of patients diagnosed with DR-TB in Khayelitsha in 2008.

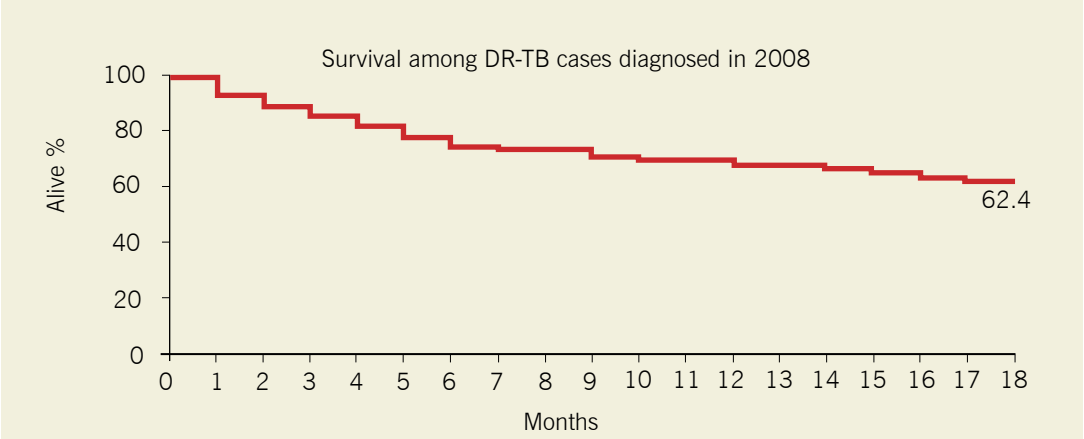
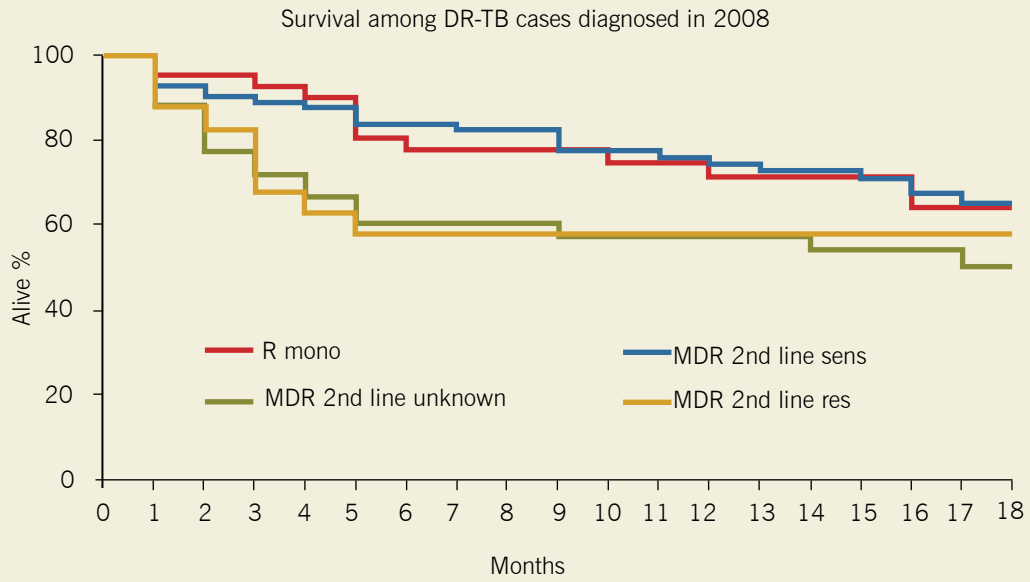


Figure 8: Survival among DR-TB cases diagnosed in 2008 by drug resistance profile.



R mono = rifampicin mono-resistance

MDR 2nd line sens = MDR-TB with no resistance to the second line drugs

MDR 2nd line unknown = MDR-TB with unknown 2nd line DST

MDR 2nd line res = MDR-TB with either resistance to a fluoroquinolone or a second-line injectable or both.

Preliminary data also suggests that survival among patients infected with TB strains having resistance to second-line drugs may be poorer (Figure 8). Those in whom no second line DST is available also appear to have poorer survival; these are often patients who die before treatment can be started.

Although survival among DR-TB cases overall appears to be improving, mortality is much poorer for the subgroup of patients who are diagnosed with XDR-TB at the outset. Of the 31 patients diagnosed from 2008 to 2010 with XDR-TB, 17 (55%) are known to have died as of January 2011. It was hoped that outcomes would be better for these patients than for those in whom XDR-TB develops at some point during treatment (for whatever reason, such as poor adherence or an inadequate regimen). Although this has not yet been demonstrated, the strengthened initial regimen has only been in place since late 2009 and therefore it may still be too early to draw any conclusions.

Supporting Health Staff

In order to empower existing TB/HIV clinic staff to manage DR-TB patients at primary care level, a three-day DR-TB training course was developed to educate health care professionals on important aspects of DR-TB management. This course has now been taken over by the City of Cape Town Department of Health and is run by doctors, nurses and counsellors who routinely manage DR-TB patients in the clinics.

Doctors responsible for managing DR-TB patients in Khayelitsha are supported in a number of ways. Since October 2008, all new DR-TB cases diagnosed and initiated on treatment in Khayelitsha

are presented and discussed at a monthly patient review meeting attended by all clinicians and supporting staff. This forum also provides an opportunity to discuss more complicated cases and learn from the experience and expertise of others. Expert opinion from clinicians outside Khayelitsha is also sought when necessary, either through requesting their attendance at the monthly meetings, or by the clinic doctors taking time out to attend clinical discussion meetings with senior doctors in the specialist TB hospital or elsewhere. In a similar way, the monthly specialist outpatient clinic for paediatric DR-TB also aims to build local capacity to diagnose and manage paediatric DR-TB patients through transfer of skills.

Monitoring Hearing Loss Among DR-TB Patients

The second-line injectable agents (amikacin, kanamycin and capreomycin) are key drugs in the treatment of DR-TB, but carry a significant risk of side effects. Among these is the risk of ototoxicity (hearing loss and dizziness), which can be extremely debilitating for individuals and may become irreversible if injections are continued. The percentage of patients suffering hearing loss with use of these drugs is reported to range between 7% and 33%, although data is scarce, especially for HIV-infected individuals being treated for DR-TB [29-31].

In the initial stages, the injectable agents may only affect the higher frequency wavelengths, without the patient actually noticing any change in hearing. Further damage may be prevented by adjusting the dose and/or frequency of the injectable agent, before the hearing loss becomes irreversible. In order to identify earlier those patients suffering ototoxicity and to more accurately define the risk of hearing loss with DR-TB treatment, an audiometry screening service has been established in a centrally located clinic within the community in order to improve access for Khayelitsha patients. A small, sound-proof booth was built in the clinic, with a hearing screening machine which requires annual calibration. A lay staff member was trained by an audiologist from the University of Cape Town (UCT) to conduct this hearing screening and to recognise abnormal test results necessitating earlier referral back to the doctor.

Since the clinic audiometry service was set up in August 2009, over 700 audiometry screenings have been conducted as part of the DR-TB programme in Khayelitsha. This includes screening of 140 patients at the time of treatment initiation (i.e. baseline screening), with monthly follow-up screening throughout the injectable phase. Among these patients, 42% showed a significant level of baseline hearing loss; this hearing loss may be due to previous streptomycin treatment, or other non-TB related factors. As yet there is insufficient data to assess the proportion of patients whose hearing deteriorates with DR-TB treatment, but it is thought to be significant. Quality assurance for this service in Khayelitsha is being carried out in collaboration with the UCT audiology department and has been excellent for the Khayelitsha service to date.

Inpatient Care

While the majority of patients can be started on second-line treatment through their local clinic, there will always be a need for facilities to hospitalise certain patients at treatment initiation if they are clinically unwell or at some point during their treatment (e.g. for a significant adverse event). The specialist TB hospitals in Cape Town that provide treatment for DR-TB patients are located a considerable distance from Khayelitsha and public

Effective Utilisation of Hospitalisation for DR-TB Treatment

The Lizo Nobanda facility is an example of how hospitalisation can be used within a DR-TB programme. While a separate stand-alone facility for DR-TB is not always necessary, there are some key requirements for hospitalisation suggested by the experience in Khayelitsha:

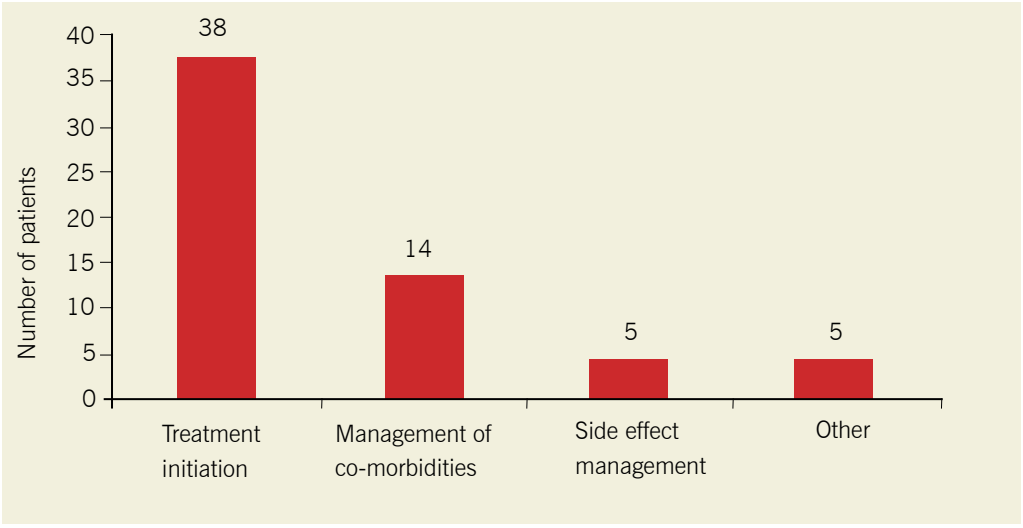
- Capacity to hospitalise clinically unwell patients to start treatment without delay
- Access to appropriate medical care (nurse-led with weekly doctor visits), and good referral system to higher level health services when necessary
- Effective infection control measures to protect both staff and other patients from infection
- Proximity to the community in which patients reside, to allow ongoing family and community support
- Provision of counselling and support with access to social services for admitted patients
- Capacity for appropriate supported end-of-life care

These requirements could be fulfilled through use of district hospitals, or more effective utilisation of existing specialist TB hospitals.

transport is poor. As a result, patients admitted to hospital in these centres often feel isolated from their families and community, particularly if they are hospitalised for unnecessarily long periods of time (i.e. until culture conversion or the end of the intensive phase of treatment).

In response to this situation, a small, 12-bed inpatient facility was established within the community of Khayelitsha. This facility, the Lizo Nobanda TB Care Centre, can admit patients who may be suffering side effects of medication, or having trouble with adherence. It can also be used for short, 2–3 week hospitalisations in order to initiate treatment, particularly for HIV-infected patients, who additionally need to start antiretroviral treatment (ART). The facility was opened in April 2009 and to date 111 patient admissions have been recorded; including 62 in 2010. As the facility is staffed and run by nurses, the clinic doctors in their respective clinics remain responsible for the care of any of their patients admitted to Lizo Nobanda, and are required to review them least once a week.

Figure 9: Reason for patient admission to Lizo Nobanda TB Care Centre (Khayelitsha) in 2010.



The most common reasons for admission in 2010 were: short-term stay for treatment initiation (61%), management of co-morbidities such as diabetes and other HIV-related conditions (23%) and medication-related side effects during DR-TB treatment (8%); see Figure 9.

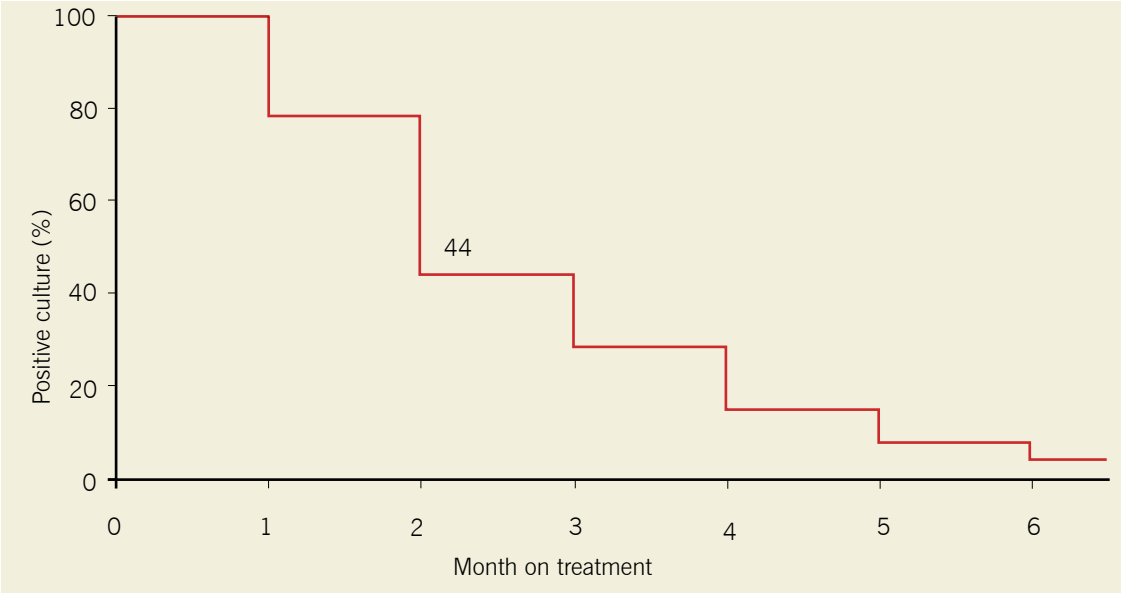
The remaining patients were admitted for a variety of reasons including infection control issues at home, socio-economic problems, adherence support or palliative care. The median length of stay for those patients admitted for treatment initiation was 23 days, 26 days for management of co-morbidities, and 30 days for management of side effects of DR-TB medication.

Reducing DR-TB Transmission and Infection Control

The most effective activity in reducing the transmission of DR-TB, and indeed tuberculosis in general, is to diagnose as many cases as possible, as early as possible and to start them on appropriate treatment. To this end, all of the activities in Khayelitsha related to improving case detection and treatment initiation are aimed at reducing transmission and curbing the DR-TB epidemic.

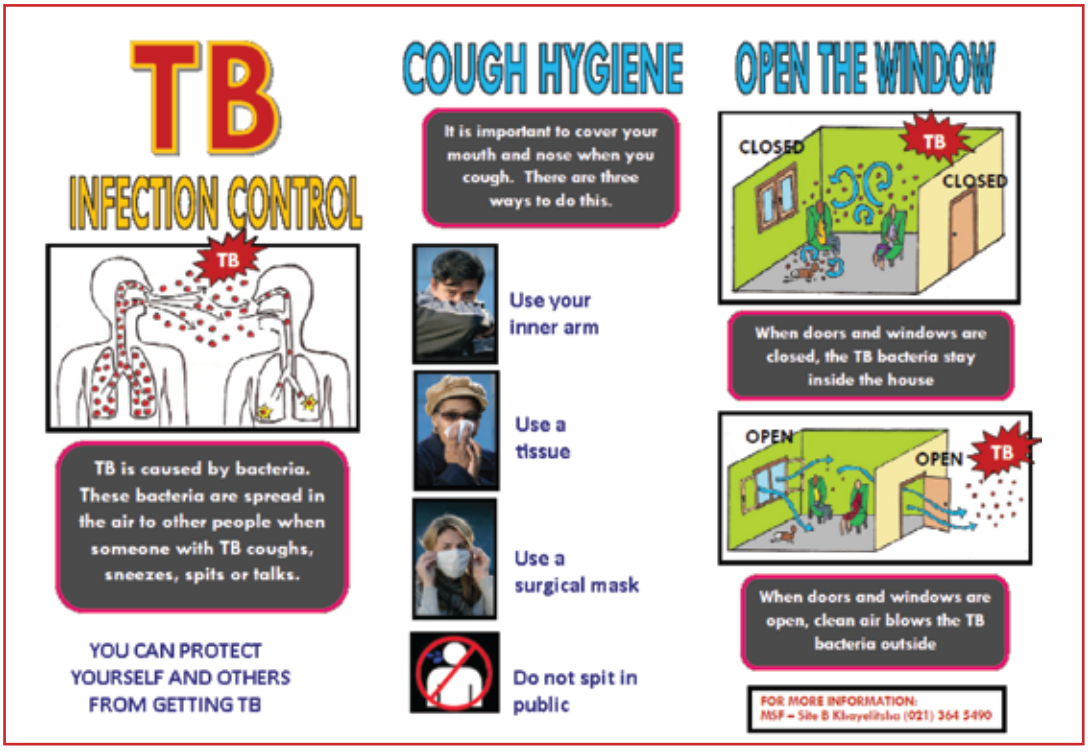
Patients initiated on appropriate second-line treatment for DR-TB will have reduced infectiousness even before culture conversion. This results from both the action of the drugs, and from improved cough hygiene and other behaviours such as improving ventilation in the home, resulting from patient education and counselling. Culture conversion is defined for initially culture-positive cases as the date of the first of two negative cultures at least one month apart. Culture conversion appears to be rapid in Khayelitsha; by 2 months of treatment, more than half (56%) of patients have converted an initially positive sputum culture to negative (Figure 10). This is based on an analysis of more than 300 culture-positive cases who started treatment in 2008 and 2009. By 6 months of treatment, very few patients remain on

Figure 10: Culture conversion by month of treatment among 303 culture positive patients starting DR-TB treatment in 2008 and 2009.



treatment with positive cultures; the majority of those in whom sputum cultures fail to convert to negative have died during the first 6 months of treatment, most likely indicating treatment failure.

Specific infection control (IC) measures are also initiated in the homes of DR-TB patients, health care clinics and in the community. A dedicated Infection Control officer has been employed in Khayelitsha since 2007 (although with a considerable gap through 2010). This individual works closely with the staff in health care facilities to ensure that proper administrative, environmental and personal protection measures are in place to reduce the spread of infection between patients, visitors and staff inside the facilities. In 2007, each health care facility in Khayelitsha underwent a formal IC assessment; these were repeated in 2010 and necessary recommendations were made. The IC officer works closely with existing clinic administrative and medical staff to maintain the IC committees which had initially been identified in 2008 in each of these facilities. She provides ongoing support to ensure that each of the committees continue to meet regularly, firstly to design and implement individualised Infection Control Plans and then to ensure supervision and monitoring of IC activities and interventions within each facility. Structural modifications to improve patient flow and ventilation within the facilities have been carried out in some clinics and recommendations made for others. In addition, separate sputum collection booths have been constructed to allow privacy for patients while reducing the risk of transmission to health care staff and others. In the homes of DR-TB cases, the emphasis is on counselling and education to change behaviour in order to reduce the risk of transmission. This includes, for example, cough hygiene education to reduce the spray of infectious particles when a patient coughs or sneezes. Patients and families are also empowered to reduce the transmission risk in their homes through improving ventilation and changing sleeping arrangements to allow the DR-TB patient to sleep separately. The DR-TB counsellors provide this



education, advice and support, with input from the IC officer when needed.

Although efforts are made to reduce the risk of transmission in the homes of DR-TB patients after they have been diagnosed, the majority of transmission to household contacts has most likely occurred before this time. However, the emphasis on developing an understanding of how TB is transmitted, how it is diagnosed and how it is treated, is fundamentally important in empowering household members and allowing for rapid diagnosis of further contacts should they develop active TB disease.

There have also been efforts to reduce the risk of TB transmission in the community at large in Khayelitsha. Public meeting places, such as churches, local drinking establishments (i.e. shebeens) and taxi ranks have been targeted. In particular, a campaign to raise awareness of the risk of TB transmission in crowded taxis was started in March 2009, with education sessions for taxi drivers and the distribution of stickers for display in taxis (see page 26). Two DR-TB counsellors also attend a weekly session at the local radio station where they have an hour long slot to discuss any DR-TB issues with local people calling in to ask questions.

Programme Management and Human Resources

The DR-TB programme in Khayelitsha is run in collaboration between MSF, the City of Cape Town and the Western Cape Province Department of Health. The aim is to utilise existing services and staff wherever possible, in order to develop a model of care that is both cost-effective and feasible for expansion elsewhere.

The programme is overseen by a 'task team' that meets monthly to discuss issues around implementation, assess progress, and deal with difficulties as they arise. The task team is comprised of key staff in the DR-TB programme including health care workers treating DR-TB, patient support staff, MSF management staff, the Khayelitsha manager of health services for the City of Cape Town, representatives from DP Marais (DPM) and Brooklyn Chest Hospitals (BCH), representatives from the Provincial DR-TB review panel, district and provincial policy makers, managers and stakeholders, and various other experts and visitors from outside of Khayelitsha. The monthly task team meeting also serves as a forum to give feedback related to ongoing operational research projects in Khayelitsha such as the study on the feasibility of implementing the Xpert MTB/RIF rapid diagnostic test for DR-TB and studies on improving natural ventilation for TB infection control in clinics. This forum is also used to discuss particularly difficult or problematic cases which raise important issues; external experts are often invited to join these discussions on particular issues, such as human rights of DR-TB patients, DR-TB in children or diabetes in TB/HIV patients.

The numbers of staff involved in providing each of the services listed in Table 5 has changed considerably throughout the implementation of the programme in Khayelitsha as the programme has evolved, and very much depends on the DR-TB burden. It is therefore possible that if case detection increases substantially with the introduction of rapid testing of all TB suspects, the numbers of staff may also need to increase.

Table 5: List of services and providers that form the DR-TB programme in Khayelitsha.

Service	Service Provision
Diagnosis of DR-TB	TB staff in primary care clinics (City of Cape Town and Western Cape Province) Green Point laboratory, National Health Laboratory Service
Medical management	Medical officers and TB nurses working in clinics (City of Cape Town, Western Cape Province and MSF) TB nurses and auxiliary staff working in Lizo Nobanda (MSF) Medical staff at BCH and DPM (Western Cape Province)
Counselling	Three dedicated DR-TB counsellors (City of Cape Town, TB/HIV Care and MSF) Two peer educators (MSF)
Social assistance	Dedicated Social Assistant (MSF)
Audiometry service	Dedicated hearing screener (MSF)
Drug supply	All drugs besides moxifloxacin are supplied by the City of Cape Town and Western Cape Province Departments of Health. Moxifloxacin is supplied by MSF. Drug management by the City of Cape Town
Inpatient services	Patients admitted to BCH or DPM (Western Cape Province) Lizo Nobanda TB care centre, Khayelitsha (MSF and City of Cape Town)
Data collection and management	Data manager (MSF), facility-based DR-TB registers completed by TB staff (City of Cape Town)
Programme supervision	Two professional nurses (City of Cape Town and MSF)
Programme management	Medical Officer (MSF) Manager Health Services Khayelitsha (City of Cape Town)
Infection control	Infection control officer (MSF)
Evaluation and operational research	Epidemiologist and two research assistants (MSF) and collaboration with the University of Cape Town and the University of Stellenbosch
Training	Collaboration between MSF and City of Cape Town
Transport of staff to clinics, home visits and for patients admitted to Lizo Nobanda	Two drivers (MSF)

Challenges

While there have been major successes in Khayelitsha over the past 3 years, there are a number of challenges remaining. Many of these are common to DR-TB treatment internationally. Over the last decade an estimated 1.5 million people have died globally from DR-TB, and barely 0.5% of the 5 million who developed the disease had access to appropriate treatment [32]. There is therefore an urgent need to scale up DR-TB treatment globally if we are to mitigate the impact of this epidemic. Addressing these challenges requires continued funding, resources, and especially political commitment.

Fundamental to improving access to treatment is increasing access to diagnosis. Drug susceptibility testing is not currently available for all TB suspects, thereby limiting the capacity to increase case detection given that more than 50% of cases will be 'new' and not considered 'high risk'.

The reasons for treatment default are numerous and complex, and cannot be addressed by counselling alone. Patients have complex socioeconomic situations and require good psychosocial support to address these issues in an holistic manner. Shorter treatment regimens and the use of drugs with fewer side effects would considerably aid patients' adherence to treatment.

There is a small proportion of patients whose sputum remains culture-positive despite a prolonged course of treatment with second-line DR-TB drugs. In 2008, 172 patients were started on DR-TB treatment, and of these, 17 (10%) were considered to have failed treatment; just under half of these patients died. The remaining patients subsequently defaulted, continued treatment or had treatment withdrawn. There is currently much debate regarding the optimal management of patients in situations where continuing treatment is unlikely to result in cure. Some patients require hospital admission at this point due to their deteriorating clinical status; however many patients remain stable and ambulant for many months following treatment withdrawal and would like to remain at home with their families. It is necessary to put systems in place to ensure that these patients continue to have access to medical care, as well as to provide psychosocial support to the patient and their families in order to optimise their quality of life and to reduce the risk of DR-TB transmission to others.

Failure to monitor patients regularly may lead to situations where it is too late to intervene with additional drugs. Patients may begin to show signs of failing treatment before they reach this stage; these patients should be targeted to try more options with other available drugs. However, access to new drugs and Class 5 drugs (those with unproven efficacy for DR-TB) is currently limited for these patients.

Current reporting systems for DR-TB rely on paper registers at the facility level, however registration of patients on the sub-district electronic database remains centralised at the specialist TB centres, leading to problems with transfer of data between facilities and incomplete data reported. It is necessary to put systems in place to ensure that these patients continue to have access to medical care, to provide psychosocial support to the patients and their families to optimise their quality of life, and also to ensure that the risk of infecting others is reduced.

A TREATMENT FAILURE PATIENT MANAGED IN KHAYELITSHA

Neliswa, a 49-year-old patient, was considered to have failed DR-TB treatment after a long process including a number of courses of second-line TB drugs. Despite good adherence and a strong personal conviction to finish treatment, her sputum remain culture-positive. The decision was made to withdraw treatment, and the patient was informed that she would unlikely to ever be cured of DR-TB. She survived for a year after treatment was withdrawn, and eventually moved out of her home due to her fear of infecting her family members. She moved into the sub-acute inpatient facility in the community (Lizo Nobanda) where she required very minimal nursing care right up until the last few weeks of life, at which point she also received palliative input from local hospice nurses. She died peacefully at home while out on a 'weekend pass'.

Conclusions

Preliminary results suggest that the Khayelitsha DR-TB model of care is improving case detection, decreasing time to treatment initiation, and through a more patient-centred approach, improving patient retention and clinical outcomes. A large number of individuals and organisations have contributed to this preliminary success – without their motivation and commitment, such success would not be possible.

The process of learning what works and what doesn't work is ongoing in the Khayelitsha DR-TB programme. It is hoped that lessons learned in Khayelitsha will inform policy and practice not just in South Africa but also in other settings internationally.

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