

**A COMPARISON OF DIRECT OBSERVATION OF TREATMENT METHODS
USED FOR TREATING PULMONARY TUBERCULOSIS IN DURBAN
(ETHEKWINI), KWAZULU-NATAL**

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ABSTRACT / SUMMARY

Introduction

Tuberculosis (TB) causes approximately 2 million deaths every year. The problem is escalating explosively in sub-Saharan Africa and is directly related to the increase in the prevalence of Human Immunodeficiency Virus infection. South Africa was ranked as having the fourth highest global incidence of TB in 2006.

In 1993, the World Health Organization introduced the Directly Observed Treatment Short-Course strategy to increase efficiency of national TB programmes. The Direct Observation of TB therapy element of the strategy has been contentious. An ideal method of direct observation remains elusive and its role in improving adherence is questionable.

Aim

The purpose of this research is to determine the most effective directly observed method for pulmonary TB offered in an urban area of South Africa.

Methods

A retrospective cohort analysis was conducted at the Prince Cyril Zulu Communicable Diseases Centre in Durban, KwaZulu-Natal. The study population consisted of adult patients who commenced a course of TB therapy between July 2005 and June 2006. The effect of clinic based, family member, community health worker, lay community health volunteer and workplace based direct observation on TB treatment outcomes, and frequency of recurrence was determined. A sub analysis was performed of the effect of the different methods of direct observation in employed patients.

Results

Workplace based direct observation resulted in a higher frequency of successful treatment outcomes than the other methods of Direct Observation ($p < 0.001$). Being a re-treatment patient was the only significant factor associated with recurrence, both for the entire study population and for those who were employed.

Discussion

The findings of this study are generalizable to other developing countries where challenges in implementation of an effective TB programme such as poverty, high burden of HIV infection, a migrant population with strong rural ties and reliance on traditional practices to cure illness play a major role.

Recommendations

There is often no best treatment observer. Every case has to be individually evaluated and the most acceptable and accessible treatment observer chosen. The findings of this study strongly suggest that workplace Direct Observation can have a significant impact in improving TB treatment outcomes.

(Word count = 351 words)

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ACRONYMS AND ABBREVIATIONS

PTB- Pulmonary tuberculosis

MDR TB – Multi drug resistant tuberculosis

XDR – Extreme drug resistant TB

DO – Direct Observation of TB therapy

HIV infection- Human Immunodeficiency Virus infection

Communicable Diseases Centre – Prince Cyril Zulu Communicable Diseases Centre

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Table 1: Tuberculosis treatment outcome indicators for KwaZulu-Natal and South Africa.

	<i>WHO target</i> ⁵	<i>South Africa 2005</i> ⁵	<i>KwaZulu - Natal 2005</i> ⁵
Cure rate	85%	58%	45%
Successful treatment completion rate for new smear positive cases		71%	64%
Interruption rate for new sputum positive cases		10%%	15%

South Africa, is regarded as being one of the 27 countries with a high burden of multidrug resistant TB (MDR TB) with a prevalence of 1.6% in new TB patients and 6.6 % in retreatment TB cases.² The Medical Research Council survey conducted in 2001 and 2002 revealed a strong association between previous treatment failure, defaulting therapy and the development of MDR TB.²

Prior to 1993, there was no standardization in terms of a definition for a positive diagnosis of TB, the drugs to be utilized for successful treatment of TB and the duration of TB treatment. In addition, a constant and consistent supply of TB drugs was not always available and laboratory services needed to confirm a TB diagnosis were both inadequate and inefficient. The result was that in poorly resourced settings, TB programmes proved ineffective in controlling the epidemic.⁸

As a result, in 1993, the World Health Organization (WHO) introduced the Directly Observed Treatment Short-Course (DOTS) strategy to increase efficiency of national TB programmes. The goal of the programme was to identify 70 % of infectious cases and to cure 85 % of the cases identified. South Africa adopted the World Health Organisation DOTS strategy in 1996.² Direct Observation (DO) of the ingestion of TB drugs, for the initial 2 months of therapy (intensive phase) forms one component of WHO's DOTS

strategy to improve adherence and thus decrease the period of infectiousness and the risk of the development of MDR TB.

WHO has reported that the DOTS strategy has proved very successful, with the proportion of patients cured being greater than 80% and less than 10% thereof defaulting therapy.⁷ However, in South Africa, the experience of direct observation of TB treatment has not been as successful, with more than 10% of patients reported to have defaulted treatment in 2006.²

Treatment supporters, who have included clinic nurses, lay community health workers, family members, school and crèche teachers, shopkeepers and workplace supervisors, have all been involved in Direct Observation of TB treatment.

1.1.1 What needs to be known?

Since 1993, different methods of Direct Observation (DO) have been utilized to enhance adherence to TB therapy. The choice of who observes the taking of therapy (treatment supporter) often depends on a negotiation between the health care worker and the patient. Insight into the most practical and acceptable method of this key element of the Directly Observed Therapy strategy is vital if the proportion of TB patients completing treatment is to be improved and global, national and provincial TB outcomes targets are to be achieved. Ultimately, an increase in the number of patients adhering to prescribed TB therapy ought to occur, with a decrease in the incidence of the major public health challenges of MDR TB and extreme drug resistant TB (XDR TB).

1.1.2 What is the importance of this study?

Studies have evaluated two or three methods of TB Direct Observation in different communities with varying results. Some of these studies have supported Direct Observation whilst others have indicated that it may be irrelevant in ensuring adherence to treatment and, ultimately, the control of the TB epidemic. There is a paucity of data on the outcomes of workplace Direct Observation of TB treatment. Anecdotal evidence

suggests that employed individuals may regard clinic based Direct Observation as unacceptable because of the pressure experienced to absent themselves from their employment for the purposes of the supporter observing them taking their medicine on a regular basis.

1.1.3 How the study will solve the problem?

By evaluating several methods of Direct Observation, during a period in time, in one community recording a high prevalence of HIV infection in a resource-limited setting, the study will contribute to new knowledge. Furthermore, it will compare workplace Direct Observation with the more traditional methods of TB treatment supervision.

1.2 STATEMENT OF THE PROBLEM

1.2.1 Research Hypothesis

Different models of Direct Observation, including that provided by workplace supervisors, family members, community health workers and lay community volunteers is superior to supervision provided by primary health care nurses in a resource constrained setting and results in better TB treatment outcomes being achieved.

1.2.2 Research Questions

- 1) Will Direct Observation by workplace supervisors, family members, community health workers, lay community volunteers and primary health care nurses achieve better TB treatment outcomes?
- 2) Does an association exist between new and retreatment patients, patient gender, age, employment status and type of direct observation of TB therapy, and TB treatment outcome?
- 3) Is there an association between new and retreatment patients, patient gender, age, employment status and type of observation of therapy being taken, on the recurrence of TB in patients who have had an initial successful treatment completion for PTB.

1.3 PURPOSE OF THE RESEARCH

The purpose of this research is to determine the most effective method of Direct Observation of Tuberculosis therapy for Pulmonary Tuberculosis (PTB) offered from July 2005 to June 2006, at the Prince Cyril Zulu Communicable Diseases Centre, in an urban area of Durban, South Africa with high a HIV/TB prevalence in order to be able to influence policy and improve PTB treatment outcomes.

1.4 SPECIFIC OBJECTIVES OF THE RESEARCH

OBJECTIVE 1:

To describe the demographic characteristics of the patients who commenced a course of TB therapy between July 2005 and June 2006.

OBJECTIVE 2:

To compare the effect of different methods of Direct Observation on PTB treatment outcomes in the patient sample in conjunction with selected variables namely gender, age, employment and re – treatment status.

OBJECTIVE 3:

To compare the effect of different methods of Direct Observation on PTB treatment outcomes amongst employed patients in conjunction with selected variables namely gender, age, employment and re – treatment status.

OBJECTIVE 4:

To describe risk factors for recurrence of pulmonary or extra pulmonary TB in the sample within the subsequent two years, that is up to August 2008.

1.5. ASSUMPTION UNDERLYING THE STUDY

It is assumed that patients did indeed receive Direct Observation by the observers/ treatment supporters to whom they were allocated, as there is no way to verify this other than patient self-report.

1.6 SCOPE OF THE STUDY

The research addresses the various methods of Direct Observation of TB treatment utilized by TB patients and the effect that each method has on TB treatment outcomes.

1.7 ORGANIZATION OF THE REPORT

The body of the report is in the following format:

Chapter 1 provides background information on the TB epidemic globally and in South Africa. The WHO DOTS strategy, which includes Direct Observation of TB treatment, is described in this chapter. The aim and objectives of this research are listed in addition to the definition of terms that will be used in the following chapters.

Chapter 2 focuses on the scope and the purpose of the literature reviewed. The impact that previous studies have had on the study question, as well as the limitations and strengths of these studies are discussed.

Chapter 3 presents research methods used in collecting the data, the study design, research population, data sources and statistical methods employed.

Chapter 4 presents the results in appropriate tables and graphs as well as describing the findings.

Chapter 5 contains the section where the findings and outcomes of the research are discussed. Limitations of the study as well as factors contributing to bias and confounding are addressed.

Recommendations and conclusions in Chapter 6 highlight areas for policy change and further research based on the outcomes of this study.

1.8 SUMMARY

In spite of the reality of the global burden of TB decreasing, the problem continues to escalate in South Africa. The WHO DOTS strategy, encompassing direct observation of therapy, has proven effective in many developing countries with high TB burdens. In order to improve TB outcomes by improving adherence to TB therapy, it is vital to evaluate different methods of Direct Observation of therapy and to both inform, and facilitate policy change.

2 CHAPTER II: LITERATURE REVIEW

2.1 INTRODUCTION

2.1.1 DIRECTLY OBSERVED THERAPY SHORT - COURSE (DOTS) STRATEGY

“It is not the responsibility of the patient, but the moral and legal obligation of the health system to ensure that an individual is cured of TB and that drug resistant strains are not passed onto the community”.⁷

In response to the burgeoning TB epidemic and the failure of national TB programmes, globally, to address the crisis adequately, the World Health Organization introduced the Directly Observed Therapy Short-Course strategy in 1994 to increase efficiency of national TB programmes.⁸ The goal of the programme was to identify 70 % of infectious cases of tuberculosis and to cure 85 % thereof.

The failure of national TB programmes to control the TB epidemic was largely due to the absence of standardization in the programmatic management of this curable infectious disease. This included the lack of a standard definition for a positive diagnosis of TB, unavailability of a standard drug regimen for utilization in the successful treatment of TB and no universally accepted duration of TB treatment. In addition, a constant supply of TB drugs was not always available and inadequate laboratory services to confirm a TB diagnosis existed.⁶

The DOTS strategy aimed to address all of the above shortfalls and the following five components constitute the basis of this strategy.⁸

- 1) Political commitment to ensure sustained TB control activities;
- 2) Case detection by sputum smear microscopy;
- 3) Standardized short course chemotherapy with patient support and directly observed therapy (DOT) during the intensive phase of therapy, the continuation phase of rifampicin containing regimens and the whole re treatment regimen;

- 4) A regular, uninterrupted supply of all essential anti TB drugs; and
- 5) A standard recording and reporting system to monitor the treatment outcomes for patients and programmes.

2.1.2 DIRECT OBSERVATION (DO) OF TUBERCULOSIS THERAPY

There is consensus that four elements of the DOTS strategy are self-explanatory and implementation has been successful in most settings. However, the Direct Observation of TB therapy component of the strategy, has often been labelled as contentious. This controversy is most often related to interpretation of what “Direct Observation of therapy” means and to challenges in its implementation.

The World Health Organization definition of Direct Observation stipulates that every dose of TB treatment must be ingested under direct observation by an observer who is **not a family member**, at least during the intensive phase of treatment.¹⁰ The Direct Observation supporter must be trained by and must be accountable to the health system. The definition is applicable for all regimens containing rifampicin, the single most important drug in modern TB therapy which served to decrease the treatment period from between 12 to 18 months to between 6 to 8 months. The rifampicin containing regimen has proven to be highly effective in decreasing the TB bacterial load dramatically, rendering the patient non-infectious early on in treatment and improving the well being of the patient. Direct Observation was recommended to ensure that the drug is used effectively, in order to prevent the emergence of rifampicin resistance, which may arise because of non-adherence to TB therapy.

The aim of Direct Observation is two fold, namely, to promote adherence by directly observing (at least during the intensive phase of treatment) that every scheduled dose of TB treatment is ingested. The second function of Direct Observation is to provide a supportive environment to patients who are initially often ill and are confronted with the additional burden of prolonged pill taking, which often has unpleasant side effects. However, it has been noted that Direct Observation is often used to “root out” possible

defaulters who may have a negative impact on a health facilities' performance. The judgmental attitude of health care workers serves as a deterrent for patients to re-enter the system and continue with treatment following short intervals of treatment interruption.

Despite the adoption of the DOTS strategy, the proportion of treatment interruption in 2002 in the WHO Africa region was reported to be 11%.¹¹ In response to the large proportion of defaulters in 2002, the WHO DOTS strategy was revised, to provide more flexibility in terms of patient support and supervision and to improve access to TB treatment. It was advocated that Direct Observation of TB Treatment be more "context specific" and "patient sensitive". Where previously family member support was not considered as Direct Observation, it was now recommended as an acceptable method of Direct Observation.¹²

2.2 PURPOSE OF THE LITERATURE REVIEW

The purpose of the literature review is to assess the current knowledge of Direct Observation of TB treatment. Does the current knowledge support Direct Observation of treatment in comparison to self-supervision? Does it work effectively in resource-constrained settings and is it acceptable to all role players? If direct observation of TB therapy is generally effective and accepted, does the type or method of Direct Observation have an impact on TB treatment outcomes? A review of the literature will allow an evaluation of the advantages and disadvantages of the various methods of Direct Observation.

2.3 SCOPE OF THE LITERATURE REVIEW

In this literature review, both studies that have supported direct observation and those that have concluded that it has no positive outcome on TB treatment outcomes have been reviewed. In addition, studies that have evaluated and compared the different methods of Direct Observation are discussed.

The literature review has focused on studies evaluating Direct Observation in circumstances similar to those described in this study. There is a focus on Direct Observation in developing countries, where traditional methods of treating disease play a major role and the study populations are migratory with strong rural ties and commitment. In this study, the Direct Observation supporters were not offered any incentives, therefore an attempt was made to include, as far as possible, studies in which no incentives or enablers were offered to improve adherence to therapy.

Studies have shown that Direct Observation has been successful in improving adherence in countries including India, Senegal, Nepal and South Africa, whilst other studies have demonstrated no significant effect on adherence to TB therapy in South Africa, India and Pakistan.

2.4 SOURCES OF LITERATURE REVIEWED

A Pubmed search for relevant articles was conducted using the University of KwaZulu-Natal library electronic database. The key words used initially in the search were “Direct Observation of TB therapy.” In order to access articles on workplace Direct Observation of TB therapy, the following key words were used: “workplace supervision of TB treatment” and “public – private partnerships and TB”. Additional studies were identified through back tracing of reference lists from journal articles reviewed.

2.5 CURRENT UNDERSTANDING OF THE QUESTION IN THE STUDY

The studies included in this literature review range from observational to experimental study designs that have been used to evaluate various methods of Direct Observation in low resourced and developing countries. The results thereof have provided no clear evidence of the most effective method for Direct Observation of therapy for TB patients.

Studies implemented amongst the same population and by the same research team have produced conflicting evidence on the value of Direct Observation.

2.5.1 SELF SUPERVISION OF TB THERAPY

Three randomized controlled trials that reported on the efficacy of self-supervision (that is no direct observation of TB therapy by a third party) compared to other methods of Direct Observation of TB therapy found self supervision to be equally efficacious or superior to the other methods of Direct Observation.^{13,14,15}

The first of these studies, a randomized controlled trial evaluating the efficacy of Direct Observation was conducted by Zwarenstein *et al.*¹³ in Cape Town, South Africa between May 1994 and September 1995. The study evaluated the efficacy of Direct Observation of TB therapy by volunteer lay health workers, clinic based health workers and self-supervision.¹³ The study showed that there were no statistically significant differences in the success of treatment between the three options for Direct Observation of TB therapy (p 0.136). The risk difference for lay health worker versus clinic Direct Observation was 17, 2% (95 % CI: 0.1 to 34.5). The risk difference for lay health worker versus self-supervision was 15% (CI: 3.7 to 33.6). However, the study did not achieve statistical significance because of the small sample size (n = 156).

The second randomized controlled trial alluded to was also conducted amongst a similar patient population in the Western Cape Province in South Africa by the same principal investigator from 1994 to 1995.¹⁴ This study demonstrated that self supervision was superior to clinic based Direct Observation in ensuring adherence to TB treatment, amongst new TB patients, although the WHO target of 85% being cured was not achieved. The proportion of patients that successfully completed treatment in self-supervision arm was 60% versus 54% in clinic based Direct Observation group. The risk difference obtained was 6% for self-supervision versus clinic based Direct Observation (90% CI: 5, 1 to 17). As in the above study, the limitation of this study was the small sample size of 216 patients a factor that did not allow the study to achieve statistical significance.

The third randomised controlled trial was conducted between September 1996 and June 1998, in Pakistan, prior to the implementation of a national tuberculosis control program

in that country.¹⁵ The study, conducted in a setting with poor health infrastructure, demonstrated that there was no statistically significant difference in treatment success for patients receiving health worker Direct Observation (clinic based or community health worker Direct Observation) versus family member Direct Observation (2% difference; 95% CI- 8.6 to 11.9, p 0.75). The comparison between health worker Direct Observation and self-supervision (-3 % difference; 95% CI: 12.8 to 8.0; p 0.65) also did not reveal any significant difference on TB treatment outcomes. Overall, 60% cure was achieved, markedly below WHO targets.¹⁵

The limitation of this study is that a larger proportion (16%) of patients randomized to health worker Direct Observation compared to family member Direct Observation (2%), were unable to comply with Direct Observation allocation. The authors suggested that this could have been due to a larger number of rural patients having been randomized to health worker Direct Observation resulting in bias.

The strength of this study resides in that it was performed under field conditions and thus results should be generalizable to other settings in developing countries.

FACTORS ASSOCIATED WITH UNSUCCESSFUL DIRECT OBSERVATION OF TB THERAPY

The apparent failure of Direct Observation of TB therapy has prompted further investigations into possible contributing factors for this poor performance. A study using qualitative and quantitative methods in Delhi, India has investigated reasons for the failure of clinic based Direct Observation of therapy.¹⁶ The findings and recommendations can be extrapolated to any method of Direct Observation used in an urban setting and has therefore been included in this literature review.

In this study, 2676 patient records were reviewed and 40 in depth interviews were conducted amongst patients who had defaulted TB treatment whilst receiving clinic based direct observation of TB therapy, between 1996 and 1998.

The article highlights the issue that all role players need to accept responsibility for adherence to TB treatment. It is not the responsibility of the patient alone. Patients have responsibilities that extend beyond merely completing their TB treatment. They often have obligations and responsibilities to their families to provide an income and obligations to their employers to provide a service. Therefore, the method of Direct Observation must be easily accessible and acceptable to the patient, allowing him/her to continue functioning as a productive member of society.

The acceptability of Direct Observation of therapy presents challenges for both patients and providers. According to the authors, a high proportion of defaulters is an indication of the failure of the TB control programme as a whole. A programme is likely to exhibit successful treatment outcomes if the model of Direct Observation used is acceptable and user friendly. From their evaluation, Jaiswal *et al.*¹⁶ have demonstrated that four factors affect treatment outcomes in clinic based Direct Observation of therapy, namely, programme factors, provider factors, the disease process issues and patient factors.

PROGRAMME FACTORS

Programme factors include the location wherein Direct Observation of therapy is actually conducted. The site needs to be easily accessible to the poor and the sick. In addition, the study showed that adherence to Direct Observation was higher if patients were assured of a consistent supply of anti TB drugs.

PROVIDER FACTORS

Provider factors, including the attitude and behaviour of health care workers, had an impact on adherence to Direct Observation. It was noted that providers often lacked communication skills, appearing rude and unapproachable to patients. Patients often lost confidence in health care workers who failed to manage adverse events appropriately. The authors found that treatment interruption increased, because re- entry into the system was difficult once a patient had been temporarily non-adherent. Non-adherent patients were labelled “non-compliers” and unreliable and were viewed as a group that would have a negative impact on the facility’s performance.

DISEASE FACTORS

TB disease related factors included drug side effects and the failure of health care workers to deal with these effectively. The high pill burden of TB treatment also increased non-adherence. The perceived response of the disease to treatment also affected adherence. A large number of patients defaulted because they felt that there was no improvement in their condition. Others defaulted because they became asymptomatic soon after treatment initiation. Patients with co morbid illnesses, which affected their ability to travel to the Direct Observation site, were also likely to default on treatment.

PATIENT FACTORS

Patient factors identified as important were the migratory nature of the population with TB, the extent of alcohol abuse and the patients' obligations to their employers. Many patients in this study were migrant workers with strong rural ties, who sought employment in the city to support extended families in rural areas.

The TB control programme workers tended to view certain obstacles to Direct Observation as insurmountable and non-negotiable. Patients who could not adhere to Direct Observation for a period often became treatment interrupters because no provision was made for them to continue with TB treatment whilst they were away in rural areas attending to family crises.

Employed patients did not adhere to TB treatment because clinic hours coincided with work hours – there was a conflict between the demands of employment and the inflexibility of the programme. Alcohol abuse amongst TB patients affected adherence as well as the relationship with health care workers and family members.

A chart review of 96 patients in California, USA, conducted between 1994 and 1997 by Mac *et al.*¹⁷ evaluated the effect of Direct Observation on treatment outcomes amongst Vietnamese immigrants suffering from TB. The study, undertaken in a well-resourced setting by public health clinics and private doctors, demonstrated that other patient

factors such as their cultural background and health beliefs and practices could constitute a barrier to adherence. Cultural backgrounds may propagate misconceptions about treatment. The patients understanding of illness, the need to complete treatment and the consequences of not completing treatment may affect adherence negatively.

Among the Vietnamese, there is a common belief that treatment for an ailment is usually symptomatic and, as soon as the patient felt better, it was common practice for interruption of treatment to occur. Herbal medication and other alternative practices to cure ailments were relied upon and were considered a factor in non-adherence to TB therapy.

Allopathic medicine was not considered as a suitable option for many Vietnamese people. It was sometimes perceived as being too “strong”, with the result that the patient adjusted dosage or duration of treatment. Anecdotally, similar challenges exist in our study site at eThekweni (Durban) as well.

2.5.2 CLINIC BASED DIRECT OBSERVATION OF TB THERAPY

The three randomized controlled trials evaluating clinic based Direct Observation,^{13,14,15} discussed earlier in the chapter, have concluded that this method of Direct Observation is not inherently superior to self-supervision or other methods of Direct Observation in improving TB treatment outcomes.

In contrast to the above, a chart review conducted in Kerela, India by Balasubramanian *et al.*¹⁰ found that clinic Direct Observation improved successful treatment completion rates to well above the WHO target of 85% (from 55% to 95%). However, implementation of the Direct Observation strategy was challenging (about 26 % of patients and health workers did not comply with Direct Observation). Two hundred patients were included in this retrospective study, which entailed chart review and interviews, conducted between February 1995 and February 1996. The 27 % of patients

who were allocated to Direct Observation but who did not receive it were more likely to exhibit treatment failure (45% versus 3%, relative risk 17; 95% CI: 6 to 46; $p < 0.001$).

The limitation of this study, based on a retrospective chart review and interviews, is the increased likelihood of recall bias. In the event of treatment failure, patients and health workers were far less likely to admit to non-adherence to Direct Observation. The value of this study is that it demonstrated that some kind of supervision is superior to no supervision of treatment at all, and that other methods of Direct Observation of TB therapy must be explored.

A retrospective chart review conducted by Mac *et al*¹⁷ in California, USA also demonstrated that Direct Observation by facility based health workers had a favourable response on TB treatment outcomes. In this study with a sample size of 50 patients of Vietnamese origin, the completion of TB therapy was 16% higher and relapse was 8% lower in the Direct Observation group. However, the statistical significance of these findings may be questionable, as the authors did not report confidence intervals or p values.

Although the results of the chart review conducted by Balasubramanian *et al*.¹⁰ displayed statistical significance, the findings are not as significant as the results of the randomized controlled trials conducted by Zwarenstein *et al*.^{13,14} and Walley *et al*.¹⁵ because of study design (the randomized controlled trial is the gold standard in terms of study design).

FACTORS ASSOCIATED WITH FAILURE OF CLINIC BASED DIRECT OBSERVATION OF TB THERAPY.

According to the Zwarenstein *et al*.¹³ clinic, based Direct Observation could be ineffective because it is often unacceptable to the patient. It is often equated to surveillance, and may therefore appear authoritarian and demoralizing to the patient. It robs the patient of autonomy and can be degrading. It places the burden of responsibility to ensure patient adherence on the clinic health worker and, in this regard,

may have a negative impact on the relationship between the patient and provider. In addition, there is the additional financial burden to both the health system and the patient (indirect costs associated with time away from work and travel costs).¹³

Balasubramanian *et al.*¹⁰ also explored reasons for non-compliance with Direct Observation and, as in the studies undertaken in South Africa, conflict with health worker; inconvenience and financial constraints were some of the obstacles identified. Age and infirmity posed an obstacle to patients presenting for Direct Observation to a health facility. The investigators found that women were less likely to participate in Direct Observation because of the social stigma associated with having TB, lack of confidentiality and fear of rejection from the community.

FACTORS ASSOCIATED WITH SUCCESS OF CLINIC BASED DIRECT OBSERVATION OF TB THERAPY.

Mac *et al.*¹⁷ demonstrated that, in spite of differences in culture, health beliefs and practices, facility based Direct Observation of TB Therapy amongst Vietnamese immigrants in the USA is effective in ensuring successful treatment completion when compared to self-supervision. This positive impact on TB treatment outcomes is attributed to facility based Direct Observation offering more support to the patient to complete TB treatment, allowing more frequent monitoring of clinical response to TB treatment and patient tracing in the event of missed doses.

2.5.3 FAMILY MEMBER DIRECT OBSERVATION OF TB THERAPY IN COMPARISON TO COMMUNITY HEALTH WORKER DIRECT OBSERVATION OF TB THERAPY.

In a randomized cluster trial conducted in Senegal, West Africa between June 2003 and January 2005, with a sample size of 1522 patients, Thiam *et al.*¹¹ demonstrated that family member supervision was superior to supervision by community health workers and clinic nurses. Family member supervision achieved cures of 88%, compared with

77% in the other two groups (RR 1.18; 95% CI: 1.03 to 1.34). The treatment interruption was also much lower in this group (3, 9% versus 7, 9%; RR 0.43; 95% CI: 0.21 to 0.89).

However, the aim of this trial was to evaluate far more than merely the effect of choice of Direct Observation of TB treatment supporter under standard of care conditions as advocated by the National TB Control Program of Senegal, on TB treatment outcomes.

The authors recognized that Direct Observation alone was not effective in ensuring adherence and that the degree of adherence was dependent not only on patient characteristics, but on provider and disease factors, as demonstrated in previous studies.

¹⁶ The aim of this trial was to evaluate the effect of an intervention package designed to increase acceptability and accessibility of Direct Observation. Health personnel received training on effective TB management and on counselling and negotiation skills, which proved to be effective in promoting an interactive, cordial relationship between patient and provider. Decentralization of TB services occurred, with involvement of community health workers. Patients chose their TB supporters and this served to strengthen the Direct Observation strategy. Central supervision of the peripheral clinic staff by the district health team was encouraged and, therefore, health workers possessed the necessary knowledge to cope with any adverse events due to TB drugs.

The study design is a strength of this study. Bias was reduced because it is a randomized controlled trial and, further, because it is a cluster-randomized trial, which would reduce bias associated with individuals (personality-associated factors).

The limitation acknowledged by the authors is that they failed to consider the confounding effect of HIV co- infection on TB treatment outcomes.

However, it has been noted that this trial is not generalizable and would be difficult to duplicate under field conditions in under resourced areas because supervisors received enhanced training and monitoring throughout the study and this does not occur under normal programme conditions although it would be ideal and should be part of good TB management practice. ⁷ In addition, the authors failed to evaluate relapse/recurrence rates,

an outcome which is considered an important measure of the efficacy of TB treatment following successful cure. ⁶

A cluster randomized trial conducted by Newell *et al.* ⁹ set in Nepal between July 2002 and July 2003 compared the efficacy of family member Direct Observation and community worker Direct Observation on TB treatment outcomes. The outcome was that family supervision and community worker supervision resulted in similar outcomes (family supervision exceeded the WHO target cure rate of 85% and community worker supervision met the WHO target). The odds ratio of success of community Direct Observation relative to family member Direct Observation was 0.67 (95% CI: 0.41 to 1.10; p =0.09).

FACTORS ASSOCIATED WITH SUCCESS AND FAILURE OF FAMILY MEMBER DIRECT OBSERVATION OF TB THERAPY.

There are several reasons why family member supervision of Direct Observation should be effective. Family members are genuinely concerned with the well-being of the patient and this method of Direct Observation is easily accessible to the patient. However, in a review article, Frieden *et al.* ⁷ were of the opinion that this method of Direct Observation could have a negative impact on adherence for the following reasons. In some cultural settings, it would be unacceptable for a family member to exert pressure on the head of the household to modify behaviour. If the issue of TB treatment supervision created discord within a household, the practice would most likely be abandoned in order to preserve harmony. Furthermore, there exists a risk of family members having little confidence in “western medicine” or not understanding the importance of ingesting TB treatment every day.

FACTORS ASSOCIATED WITH SUCCESS AND FAILURE OF COMMUNITY HEALTH WORKER DIRECT OBSERVATION OF TB THERAPY.

There are advantages associated with using community health workers as Direct Observation supporters. They are accepted members of the community, share the same cultural values, are always available and identify with the community. In addition, they

have received basic training on TB and are aware of the obligations of all role players in the TB programme to improve TB treatment outcomes. However, there are disadvantages. The issue of stigma still remains. At the community level, there is an assumption that all individuals with TB are HIV co infected. For this reason, patients may choose clinic supervision as it may be perceived as being more discrete.¹⁸

2.5.4 LAY COMMUNITY VOLUNTEER BASED DIRECT OBSERVATION OF TB THERAPY

A prospective cohort study conducted by Barker *et al.*¹⁹ in a rural area in South Africa demonstrated that community volunteer based direct observation of TB Therapy (Direct Observation mainly by shopkeepers) was as effective as direct observation provided by professional health workers (OR= 1.32; 95% CI: 0.82 to 2.13). In total, 1476 patients were included in this study conducted between January 1997 and June 1999. Three quarters (77%) of the patients TB treatment was supervised by unpaid community volunteers.

FACTORS ASSOCIATED WITH SUCCESS AND FAILURE OF LAY COMMUNITY VOLUNTEER DIRECT OBSERVATION OF TB THERAPY.

The advantages of lay community volunteers as Direct Observation of TB therapy supporters resides in the fact that they are aware of the challenges faced by the community and can thus bridge the gap between the health system and the community.¹⁸

The disadvantages associated with using lay community volunteers as Direct Observation supporters is that they do not receive any formal training on TB and they are not accountable to the health system and therefore may not realize the value of adherence to TB therapy.¹⁸

2.5.5 WORKPLACE BASED DIRECT OBSERVATION OF TB THERAPY

Studies evaluating the effect of workplace Direct Observation of TB Therapy have focused on public-private partnerships in TB management rather than on Direct Observation alone.

Studies conducted in Asia, namely India, Philippines and Nepal have demonstrated that public-private partnerships have a positive impact on improving TB treatment outcomes. However, there is a paucity of data on the effectiveness of the above partnership on TB treatment in Africa.²⁰

A study, employing both qualitative and quantitative methods to evaluate the effectiveness of workplace, non-governmental organization and public sector management of TB in South Africa (Free State, North West and Western Cape provinces) found that workplace management proves to be superior to the other two models.²⁰ In the workplace, Direct Observation was provided by nurses in the occupational health clinics and those patients whose TB was managed by the non-governmental organization received Direct Observation by community volunteers. The records of 1268 patients, who commenced treatment between January and June 2001 from six sites, were evaluated. Although the WHO target of 85% cured was not achieved, private workplace TB management achieved higher proportion of cure and successful treatment completion in addition to lower proportion of defaulting and failure of TB treatment. Of the three models, public sector management of TB had the poorest outcomes. The quality of the study is doubtful as the authors failed to present measures of association and comment on whether statistical significance was achieved.

Another limitation of this study is that sites were chosen in a “purposive”, non-randomized manner with differing HIV prevalence, which could have influenced TB treatment outcomes. The authors also acknowledge that selection bias could have occurred. Thus, sites with better previous treatment outcomes may have been preferentially selected.

FACTORS ASSOCIATED WITH SUCCESS AND FAILURE OF WORKPLACE BASED DIRECT OBSERVATION OF TB THERAPY.

The authors attribute the poor performance of the public sector in TB treatment outcomes to poor quality of care offered which is linked to dwindling human resources and failure to take into account patient demands and preferences.

The superior outcome in the workplace arena is attributed to the high degree of motivation amongst both employers and staff. Staff motivation is linked to job security and the shame of being “paraded” if treatment is not taken. Employers or management is motivated to ensure adherence to treatment because of loss of productivity associated with non-adherence and the consequent deterioration in health status of workers.

2.6 SUMMARY

The studies reviewed have ranged from retrospective chart reviews to randomized controlled trials of varying quality and generalizability and have produced conflicting evidence on the value of Direct Observation of TB therapy. However, the lesson learnt is that the method of Direct Observation needs to be negotiated between patient and provider so that issues related to acceptability and accessibility are considered.

3 CHAPTER III: METHODS

3.1 INTRODUCTION

The purpose of this research was to assess the effectiveness of different methods of Direct Observation of TB Therapy offered to patients at a large TB facility in Durban, KwaZulu-Natal.

3.2 TYPE OF RESEARCH

The study is epidemiological research.

3.3 STUDY DESIGN

The study design is an observational, analytic, retrospective cohort study.

3.4 TARGET POPULATION/STUDY SITE

The study was conducted at the Prince Cyril Zulu Communicable Diseases Centre in Durban, KwaZulu- Natal. The Prince Cyril Zulu Communicable Diseases Centre is the designated clinic for the diagnosis and treatment of TB cases from north and south central Durban, in the province of KwaZulu-Natal and experiences a large TB caseload. In 2004, 5192 patients presenting with a new episode of TB were managed in this facility.²¹. This facility serves mainly the black communities who live and work in the catchment areas of the clinic. The majority of the patients are unemployed and indigent.

The facility was chosen for this study because a high case load of TB patients sought health care at this clinic and it is easily accessible because of its central location and close proximity to a taxi rank (Taxi services are the most popular and affordable mode of transport for the majority in the community). As part of municipal health services, treatment at this facility is free and patients need to reside in or work in the central Durban area to qualify for care in this centre.

Apart from management of TB this centre also offers management of sexually transmitted infections and offers voluntary counseling and testing for HIV infection.

Direct observation of TB therapy is strongly recommended for all patients diagnosed as having TB at the Prince Cyril Zulu Communicable Diseases Centre and is either supervised by clinic staff, workplace based supporters, family members, lay community volunteers or community health workers. Self supervision is not a recommended option at this site. The choice of Direct Observation supporter is negotiated and agreed to by the patient together with the clinician. Direct Observation of TB Therapy occurs for the entire duration of TB treatment period (intensive phase and continuation phases of treatment for both new and retreatment cases of TB).

Diagnosis of PTB is based on sputum microscopy, clinical presentation and/or chest radiography. Following the positive diagnosis of TB, the patient presents to a Direct Observation of TB therapy nurse who provides information on dosing and common side effects of TB medication. Patients also receive health education, which includes information on appropriate diet and investigation of household contacts, especially, children under 5 years of age, to exclude TB.

The Direct Observation of TB therapy nurse supervises the first dose of TB treatment and TB treatment is dispensed for a short period, dependent on the method of direct observation chosen.

Patients are reviewed twice during the duration of treatment to assess response to treatment. These review visits occur at the end of the intensive phase and continuation phases of therapy. Each assessment includes sputum microscopy for detection of acid-fast bacilli. Chest radiography is part of the clinical evaluation only if sputum is not available for examination or if the patients' clinical response to treatment is suboptimal. Therefore, the decision to commence the patient on the continuation phase of treatment or to discharge the patient is based on sputum examination, clinical response to treatment and/ or chest radiography.

TREATMENT REGIMEN USED.

Treatment at the Prince Cyril Communicable Diseases Centre is in accordance with the South African National Tuberculosis Control Programme guidelines.²² New cases of TB receive 6 months of TB treatment (2 months of intensive phase of therapy in a fixed dose combination of rifampicin, isoniazid, ethambutol and pyrazinamide and 4 months of continuation phase of therapy, a combination of rifampicin and isoniazid. (Treatment is prescribed to be taken for 5 days per week, Monday to Friday for both the intensive and continuation phases). Re treatment TB cases receive 8 months of treatment in total, consisting of 3 months of fixed dose combination of 4 drugs and 2 months of streptomycin as part of the intensive phase of therapy and 5 months of a fixed dose combination of two drugs and ethambutol as part of the continuation phase of treatment.

3.5 DEFINITION OF TERMS

CLINIC BASED DIRECT OBSERVATION OF TB THERAPY

Clinic Direct Observation of treatment, at the Prince Cyril Communicable Diseases Centre or at a local/peripheral clinic, comprises either daily or weekly supervision. Patients on the retreatment TB regimen, which includes streptomycin injections present for daily Direct Observation of TB treatment. Those patients undergoing weekly supervision of treatment receive a one-week's supply of medication to take home and treatment is self-supervised. In the event of missed doses, patients are traced after they have missed ten doses.

FAMILY MEMBER/ COMMUNITY HEALTH WORKER/ LAY COMMUNITY VOLUNTEER/ WORKPLACE SUPERVISION OF DIRECT OBSERVATION OF TB THERAPY

Patients receive a 2 month supply of TB treatment from the TB clinic that they are expected to deliver to the Direct Observation supporter. Direct Observation of TB Treatment by supporters other than clinic health workers occurs daily, 5 days per week (Monday to Friday). Workplace Direct Observation entails supervision by a workplace-based health professional, work supervisor or employer.

Family members and lay community health volunteer Direct Observation supporters are expected to present together with the patient for health education and information on TB to the Direct Observation TB therapy nurse at the Prince Cyril Zulu Communicable Diseases Centre or to the patients local clinic. Work place supervisors receive telephonic education on TB and the supporters' role in ensuring adherence to TB treatment. Direct Observation supporters are relied on to record ingestion of medication on a Direct Observation record card. They are also required to inform the health facility if the patient fails to take TB medication.

RECURRENCE OF TB

The recurrence of TB was defined as the onset of a subsequent episode of TB following a successful treatment outcome (either previous cure or successful treatment completion). No differentiation was made between relapse (occurrence of infection due to same strain of *Mycobacterium tuberculosis*) and re-infection (occurrence of infection secondary to a new strain of *Mycobacterium tuberculosis*).

Patients' records were reviewed and recurrence was assumed to have occurred if the patient was treated for a subsequent episode of TB. If the patient had not presented to the site for management of a subsequent episode of TB, an assumption was made that the patient had not had a recurrence.

3.6 STUDY POPULATION

The study population consisted of adult patients (older than 17 years of age) who commenced a course of TB therapy for either a first episode of pulmonary TB (PTB) or recurrence of PTB between July 2005 and June 2006.

SELECTION OF STUDY POPULATION

Exclusion Criteria

Patients who were excluded from the study included patients who suffered from MDR TB or XDR TB, who were initiated on a trial of TB therapy by the attending clinician (not confirmed PTB), who were younger than 17 years of age and those who were transferred out to other clinics and hospitals.

3.7 DATA SOURCES

Records of all patients and the TB register for the site are electronically available. Patients' demographic information, laboratory investigations, chest radiography reports and clinical findings are recorded electronically on Data Care Hospital Package. The patient information is then stored on the "Top Speed Data Base". Microsoft Excel Programme was linked to the Top Speed Data Base and the required information of consecutive eligible patients receiving a new course of PTB treatment and being allocated to one of the Direct Observation methods from 01 July 2005 was recorded on an Excel spreadsheet. Information on TB recurrence could not be accessed from the Top Speed Data Base in the manner described and was obtained by perusing through the patient records from Data Care Hospital Package. Information on recurrence was then recorded on the Excel spreadsheet.

3.8 VARIABLES

EXPOSURE VARIABLES:

- Clinic based direct observation of TB Therapy;
- Workplace / occupational direct observation of TB Therapy - that is, supervision by workplace health professional, employer or work supervisor;
- Community health worker based Direct Observation of TB Therapy;
- Family member based direct observation of TB therapy;
- Direct Observation of TB therapy by a lay community volunteer;

- Basic demographic data (race, age, gender, employment status); and
- Category of patient, that is, whether a first time episode of TB or a case of recurrent TB.

OUTCOME VARIABLES:

Treatment outcomes are defined as follows:²²

1. Cured: Patient who is smear negative at, or one month prior to, the completion of treatment and on at least one previous occasion.
2. Treatment completed: Patient who has completed treatment but without proof of cure.
3. Treatment Failure: Patient who remains or becomes again smear positive at five months or later during treatment.
4. Died: Patient who dies for any reason during the course of TB treatment.
5. Treatment Interrupted: Patient whose treatment was interrupted for two months or more.

The principal outcome “successful treatment” includes patients who were cured and those who completed TB treatment. Patients who had failed treatment, died, who were lost to follow up or had interrupted treatment were categorized as an “unsuccessful outcome”.

RELIABILITY AND VALIDITY OF DATA SOURCE.

The reliability of the data source is dependent on the clinicians managing the patients and recording findings on patients’ chart notes in the computerized record. However, as the source of the data is the electronic TB register for the site and the Data Care Hospital Package, which serves as the basis for reporting outcomes to the district, provincial and national TB offices, it is assumed that the data is generally reliable. In addition, information and outcomes recorded in Top Speed Data Base was reconciled with patient records in Data Care Hospital Package.

3.9 BIAS AND LIMITATIONS

BIAS

Information bias is likely as there was no means available to verify the extent of Direct Observation of TB therapy coverage (if Direct Observation had actually occurred according to Direct Observation agreed upon at the commencement of TB treatment). There was no way to verify if patients had switched methods of Direct Observation during the course of TB treatment, as this information is not captured in the electronic chart notes. Clinic based Direct Observation of TB therapy occurred either on a daily or weekly basis and this could have resulted in bias.

CONFOUNDERS

The extent and severity of PTB may have varied in the patients allocated to the different methods of Direct Observation. Employed patients, the majority of whom were allocated to workplace supervision, were still able to perform their workplace duties adequately, in spite of having TB, and may have had less severe TB disease and better performance scores. In order to control for this factor a sub analysis of treatment outcomes and recurrence of TB was done amongst employed patients.

- The presence of concurrent illness, for example, HIV infection, would affect the primary outcome variable as it would affect mortality.
- Concomitant medicine use for chronic illnesses such as hypertension and diabetes may affect adherence negatively as it will serve to increase pill burden.
- Alcohol and drug abuse, education level and gender are factors that could all affect adherence to TB therapy.

STRENGTHS AND WEAKNESSES OF PROPOSED STUDY

Since it is a retrospective cohort study, the Hawthorne effect would have no effect on results (being in a study /being observed would affect the behaviour of both treatment supporters and patients).

Testing the hypothesis in a randomised trial would be much more appropriate to control for confounders.

3.10 STATISTICAL ANALYSIS

SAMPLE SIZE CALCULATION

A Fisher's exact test with a 0.05 two sided significance level will have 82% power to detect the difference between a group 1 proportion, p_1 , of 0.7 and a group 2 proportion, p_2 , of 0.8 when the sample size in each group is 400.

A sample of up to 400 participants per type of Direct Observation of TB Therapy supporter was randomly drawn from a computerized database (excel spreadsheet) using SPSS in the case of more than 400 participants meeting entry criteria. Where the number of participants was limited and less than 400, all available participants were used.

STATISTICAL METHODS

SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) was used to analyse the data. A p value <0.05 was considered as statistically significant.

Bivariate associations between outcomes and exposures were assessed using Pearson chi square tests in the case of categorical exposures and independent t-tests for quantitative variables. The outcome was dichotomized into treatment success or failure and the exposures were compared between the outcome groups using logistic regression analysis with odds ratios. Odds ratios were used because the outcome and exposures were

assessed simultaneously and there was no time factor (that is, there was no time to event), although this is a retrospective cohort study.

To account for possible confounding effects in assessing the independent association between type of Direct Observation of TB Therapy support and outcomes, binary logistic regression analysis was performed. Backwards stepwise models were constructed with entry and exit probabilities set at 0.5 and 0.1 respectively, based on likelihood ratios. Odds ratios and 95% confidence intervals were reported.

ASSOCIATIONS MEASURED

The association between successful treatment outcome and recurrence of TB were measured with the following variables, method of direct observation of TB Therapy, employment status, race, age at start of treatment, sex and category of PTB patient (whether a new/ first time case of TB or a re treatment case).

ETHICS

Approval was obtained from the Ethekwini Municipality to access the medical records at the Prince Cyril Zulu Communicable Diseases Centre for the specified time period.

The ethical approval was obtained from the Biomedical Research Ethics Committee of the University Of KwaZulu- Natal South Africa, (Reference EXPO 44/06).

3.11 SUMMARY

A retrospective review was conducted to assess the efficacy of different methods of Direct Observation of TB therapy offered to PTB patients between July 2005 and June 2006 at the Prince Cyril Zulu Communicable Diseases Centre in Durban, KwaZulu-Natal.

The study population consisted of adult patients who commenced a course of TB therapy for either a first episode of PTB or recurrence of PTB.

Bivariate associations between outcomes and exposures were assessed using Pearson chi square tests in the case of categorical exposures and independent t-tests for quantitative variables. To account for possible confounding effects in assessing the independent association between types of Direct Observation of TB therapy support on TB treatment outcomes, binary logistic regression analysis was performed.

4 CHAPTER IV: RESULTS

4.1 INTRODUCTION

The chart review of patients commencing therapy for pulmonary tuberculosis between July 2005 and June 2006 at the Prince Cyril Communicable Diseases Centre yielded a sample of 1211 participants who were included in the analysis. Sample size was limited for the groups of family member DO, lay community volunteer DO and community health worker DO to 203, 147 and 61 participants respectively.

Patients who had multi drug resistant PTB, extra pulmonary TB, who were initiated on a trial of TB therapy by the attending clinician (not confirmed PTB), who were younger than 17 years of age and those who were transferred out to other clinics and hospitals were excluded from the sample population.

4.2 DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

The majority of patients were Black [1074 (88.7%)] and male [746, (62.4%)], The median age of the study population was 34.6 years when therapy was commenced (minimum age - 17.7 years; maximum age - 87.7 years) and the 25th to 75th inter quartile range was 28.3 to 44.4 years. Nearly half (46%) of the sample reported being employed although the employment status of 26% (320) of the patients on treatment for PTB was unknown.

Table 2: Demographic characteristics of the 1211 patients with pulmonary tuberculosis commenced on TB treatment at the Prince Cyril Zulu Communicable Diseases Centre from July 2005 to June 2006

<i>Demographic characteristic</i>	<i>Number (n)</i>	<i>Percentage (%)</i>
Race		
Asian	79	6.5
Black	1074	88.7
Coloured	43	3.6
White	15	1.2
Total	1211	100
Age group		
<20 years	28	2.3
20-29 years	351	29.0
30-39 years	415	34.3
40-49 years	234	19.3
50-59 years	130	10.7
60-69 years	36	3.0
>= 70 years	17	1.4
Total	1211	100
Sex		
Female	455	37.6
Male	756	62.4
Total	1211	100
Employment Status		
Employed	551	45.5
Unemployed	340	28.1
Unknown	320	26.4
Total	1211	100

An equal number of TB patients [400 (33%)] received Direct Observation of TB therapy from the workplace or from a clinic (Figure 1).

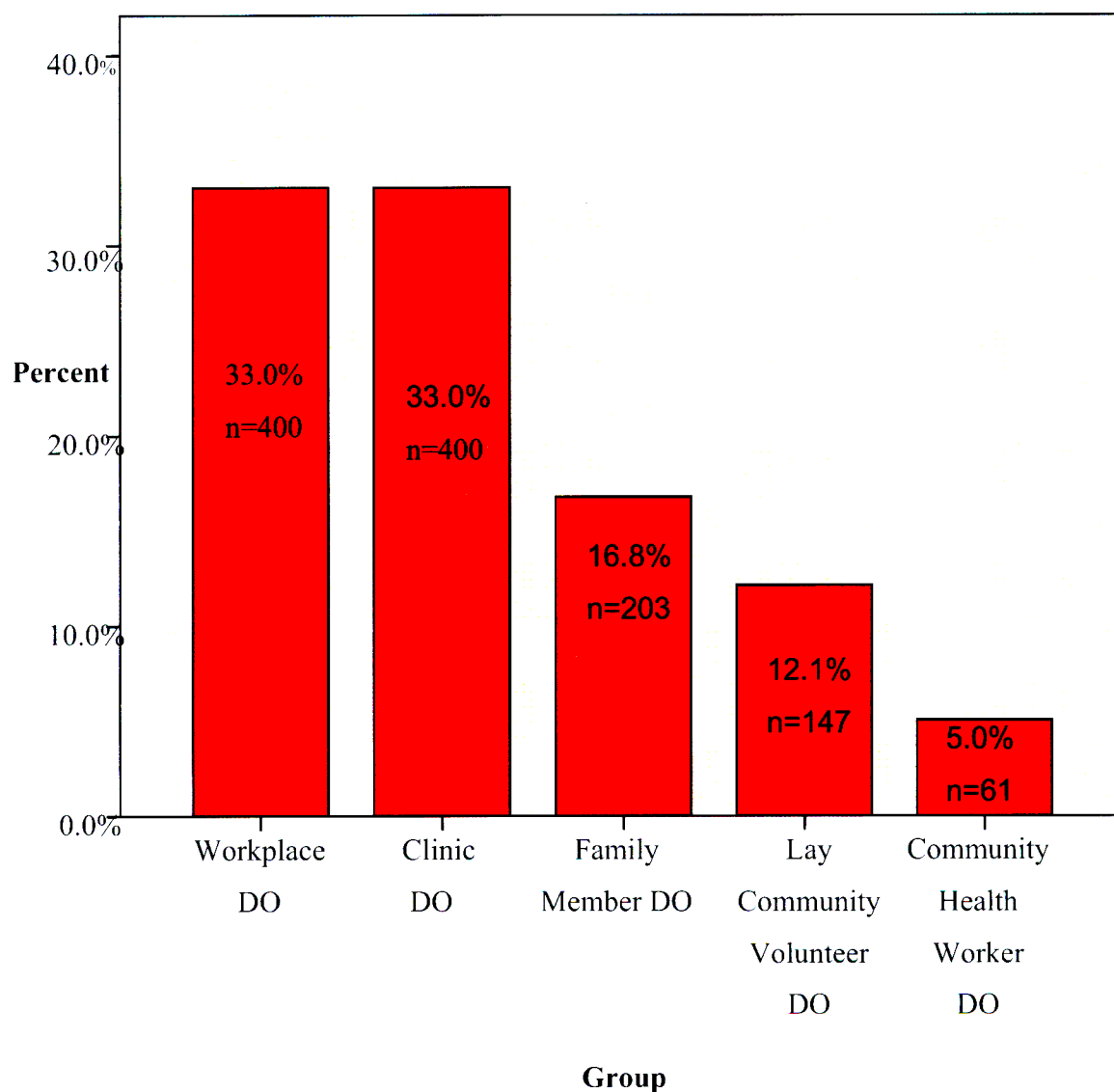


Figure 1: Method of Direct Observation of therapy (percentage - number) of 1211 pulmonary tuberculosis patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

4.3 TREATMENT OUTCOMES

A full course of TB treatment was successfully completed by 64.7% (784) of patients. The remainder [427 (35.3%)] had interrupted treatment, failed treatment, died or were lost to follow up.

Table 3: Treatment outcomes of 1211 pulmonary TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Outcome</i>	<i>Frequency</i>	<i>Percent</i>
Cured	607	50.1
Treatment completed	177	14.6
Treatment interrupted	389	32.1
Loss to follow up	16	1.3
Death	12	1.0
Treatment failure	10	.8
Total	1211	100.0

4.3.1 RISK FACTORS FOR UNSUCCESSFUL TUBERCULOSIS

TREATMENT OUTCOME:

Pearson Chi Square Test was used to check the validity of the assumptions. The association between various risk factors and the tuberculosis treatment outcomes were recalculated using logistic regression, adjusting for the following exposures of interest: category (new or retreatment TB patient), method of direct observation, race, sex, age and employment status. Method of direct observation, category of patient, employment status and gender were the only remaining risk factors following adjustment for all risk factors with backward stepwise modelling.

PTB patients who had workplace based Direct Observation had the best (73%) treatment outcomes that were statistically significantly ($p < 0.001$) better than family member supported Direct Observation (51.%) which was least successful (Table 4). Although the adjusted odds ratio (OR=2.3; 95% CI: 1.58 to 3.4; $p < 0.001$) for unsuccessful outcome of family member direct observation was lower than the crude

odds ratio (OR=2.5; 95% CI: 1. to 3.62; $p < 0.001$), family member Direct Observation was still significantly more likely to result in an unsuccessful outcome than workplace Direct observation. Clinic based Direct Observation (OR=1.4; 95% CI: 0.99 to 1.91; $p=0.057$), community health worker (OR=1.2; 95% CI: 0.64 to 2.13; $p=0.61$) lay community volunteer (OR=1.1; 95% CI: 0.69 to 1.69; $p=0.72$) were more likely to have unsuccessful treatment outcomes when compared to workplace based Direct Observation. These findings were not statistically significant (Table 4).

New patients (patients who had never had TB previously) experienced a significantly ($p < 0.001$) more successful treatment outcome (70 %) than patients who were being re-treated (55 %), (Table 4). After adjustment of all other risk factors, patients who were being treated for a subsequent episode of PTB (retreatment) were at a two times higher risk of unsuccessful treatment outcome than new PTB patients (Adjusted OR=1.98; 95% CI: 1.53 to 2.56; $p < 0.001$) (Table 4).

Employed patients (72 %) also had better treatment outcomes compared to unemployed patients (28% treatment success), ($p < 0.001$). Following adjustment for other risk factors unemployed people (Adjusted OR = 1.64; 95 % CI: 1.18 to 2.28; $p = 0.003$) and those patients of unknown employment status (Adjusted OR = 1.60; 95 % CI: 1.17 to 2.19; $p = 0.003$) had a 1.6 times higher risk of unsuccessful treatment outcome than employed people (Table 4).

The most successful treatment outcomes were seen amongst Black patients (67% treatment success), followed by Indian (61%) and Coloured patients (51%), ($p < 0.01$). However, following adjustment for other risk factors race was not a significant risk factor for unsuccessful treatment outcome (Table 4)..

Women were more likely to complete treatment successfully (68%) compared to men (63%) (Adjusted OR = 1.44; 95% CI: 1.11 to 1.87, $p = 0.005$) (Table 4).

With every one year increase in age, beyond 17 years, the risk of treatment failure increased by 1.01 times (95% CI: 1.00 to 1.02; p=0.046), before adjustment for other risk factors.

Table 4: Risk factors for unsuccessful treatment outcome for 1211 pulmonary TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Unsuccessful Treatment outcome (n=427) No. (%)</i>	<i>Treatment success (n=784) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Workplace DO (reference)	109(22.3%)	291(72.7%)	400 (33%)	1			<0.001
Family member DO	99 (48.8%)	104(51.2%)	203 (16.8%)	2.54 (1.79-3.62)	<0.001	2.33 (1.58-3.44)	<0.001
Clinic DO	148(37.0%)	252(63.0%)	400 (33%)	1.57 (1.16-2.11)	0.003	1.36 (0.99-1.90)	0.057
Community Volunteer DO	51 (34.7%)	96 (65.3%)	147 (12.1%)	1.42 (0.95-2.13)	0.091	1.08 (0.69-1.69)	0.723
Community Health worker DO	20 (32.8%)	41 (67.2%)	61 (5.0%)	1.30 (0.73-2.32)	0.371	1.17 (0.64-2.13)	0.606
Total	427(35.3%)	784 (64.7%)	1211 (100%)				
New treatment (reference)	252(30.5%)	574 (69.5%)	826 (68%)	1			<0.001
Re-treatment	175(45.5%)	210 (54.5%)	385 (32%)	1.90 (1.48-2.44)	<0.001	1.98 (1.53-2.56)	<0.001
Total	427(35.3%)	784 (64.7%)	1211 (100%)				
Employed (reference)	156(28.3%)	395(71.7%)	551 (46%)	1			<0.001
Unemployed	145(42.6%)	195 (57.4%)	340 (28%)	1.88 (1.42-2.50)	<0.001	1.64 (1.18-2.28)	0.003
Unknown	126(39.4%)	194 (60.6%)	320 (26%)	1.65 (1.23-2.20)	<0.001	1.60 (1.17-2.19)	0.003
Total	427(35.3%)	784 (64.7%)	1211 (100%)				

Table 4 (continued): Risk factors for unsuccessful treatment outcome for 1211 pulmonary TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Unsuccessful Treatment outcome (n=399) No. (%)</i>	<i>Treatment success (n=812) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Black (reference)	365(34.0%)	709(66.0%)	1074 (89%)	1			
Indian	31 (39.2%)	48 (60.8%)	79 (6.5%)	1.26 (0.79-2.00)	0.343		
Coloured	21 (48.8%)	22 (51.2%)	43 (3.5%)	1.85 (1.01-3.42)	0.048		
White	10 (66.7%)	5 (33.3%)	15 (1%)	3.89 (1.32-11.45)	0.014		
Total	427(35.3%)	784 (64.7%)	1211 (100%)				
Female (reference)	146(32.1%)	309 (67.9%)	455 (38%)	1			
Male	281(37.2%)	475 (62.8%)	756 (62%)	1.3 (1.0-1.6)	0.073	1.44 (1.11-1.87)	0.005
Total	427(35.3%)	784 (64.7%)					
Age @ commencement of treatment				1.01 (1.0-1.02)	0.046		

4.4 RECURRENCE OF TB

Of the 772 patients who successfully completed treatment and for whom data on recurrence was available, 10% (75 patients) experienced recurrence of TB within a two-year follow up period (from June 2006 to August 2008).

4.4.1 RISK FACTORS FOR RECURRENCE OF TB:

Analysis for recurrence included 772 participants who had successfully completed treatment since 12 participants were not included because of missing information on recurrence. Category of patient (retreatment versus new PTB patients) was the only remaining risk factor following adjustment for all risk factors with backward stepwise modelling. Retreatment patients were at 2.1 times higher risk for recurrence when compared to new patients (95% CI: 1.29 to 3.432; $p=0.003$) (Table 5).

Family member Direct Observation demonstrated the highest frequency of recurrence (13 %), (OR=1.12, 95% CI: 0.57 to 2.24; $p=0.739$) and community health worker Direct Observation the lowest frequency of recurrence (2.5%) but the results were not statistically significant (OR =0.20; 95% CI: 0.03 to 1.50; $p= 0.285$). Employed patients showed a higher frequency of recurrence (10.1%) when compared to unemployed patients (8.8%), (OR = 0.86; 95% CI; 0.47 to 1.55; $p= 0.872$) but again results were not statistically significant. Coloured patients were more likely to have recurrent TB disease (13.6%), (OR=1.44; 95% CI: 0.42 to 4.99; $p= 0.566$) and White patients were least likely (0.0%) to develop a subsequent episode of TB (OR = 0.00; 95% CI: 0.00; $p= 0.999$). Males were more likely to have recurrence (10.7%) than females (8.2%) (OR= 1.35; 95% CI: 0.82 to 2.24; $p= 0.241$).

Table 5: Risk factors for recurrence of TB for 1211 pulmonary TB patients commenced on a course of TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Recurrence No (n=697) No. (%)</i>	<i>Recurrence Yes (n=75) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Workplace DO (reference)	249(88.6%)	32 (11.4%)	281(36%)	1			
Family member DO	90(87.4%)	13(12.6%)	103(13%)	1.12 (0.57-2.24)	0.739		
Clinic DO	231(91.7%)	21(8.3%)	252(33%)	0.71 (0.39-1.26)	0.241		
Community Volunteer DO	88(91.7%)	8(8.3%)	96(12%)	0.71 (0.31-1.59)	0.403		
Community Health worker DO	39(97.5%)	1(2.5%)	40(5%)	0.20 (0.03-1.50)	0.118		
Total	697(90%)	75(10%)	772(100%)				
New treatment (reference)	522(92.2%)	44(7.8%)	566(73%)	1			
Re-treatment	175(85.0%)	31(15.0%)	206(27%)	2.10 (1.29-3.43)	0.003	2.10 (1.29-3.43)	0.003
Total	697(90%)	75(10%)	772(100%)				
Employed (reference)	347(89.9%)	39(10.1%)	386 (50%)	1			
Unemployed	177(91.2%)	17(8.8%)	194 (25%)	0.86 (0.47-1.55)	0.606		
Unknown	173(90.1%)	19(9.9%)	192 (25%)	0.98 (0.55-1.74)	0.938		
Total	697(90%)	75(10%)	772(100%)				

Table 5 (continued): Risk factors for recurrence of TB for 1211 pulmonary TB patients from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Recurrence No (n=697) No. (%)</i>	<i>Recurrence Yes (n=75) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Black (reference)	629(90.1%)	69(9.9%)	698 (90%)	1			
Indian	44(93.6%)	3(6.4%)	47 (6%)	0.62 (0.19-2.06)	0.436		
Coloured	19(86.4%)	3(13.6%)	22 (3%)	1.44 (0.42-4.99)	0.566		
White	5(100.0%)	0(0.0%)	5 (1%)	0.00 (0.00)	0.999		
Total	697(90%)	75(10%)		772(100%)			
Female (reference)	281(91.8%)	25(8.2%)	306 (40%)	1			
Male	416(89.3%)	50(10.7%)	466 (60%)	1.35 (0.82-2.24)	0.241		
Total	697(90%)	75(10%)		772(100%)			

4.5 SUB ANALYSIS OF EMPLOYED PATIENTS

Of the total sample size of 1211 patients, 551 (46 %) were employed and were included in the analysis. Three hundred and forty patients (28%) reported to be unemployed and the employment status for 320 patients (26%) was unknown. Seventy two percent of employed patients completed treatment successfully. The employment status for patients allocated to the different methods of Direct Observation is indicated in Table 6. The majority of employed patients opted for workplace supervision (55%) and about a quarter of employed patients were supervised at a clinic (26%). Of the patients that received workplace supervision 75% were employed, 5% had reported that they were unemployed and the employment status of 20% was not known.

Table 6: Employment status for 1211 pulmonary TB patients commenced on TB therapy from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Employment status</i>	<i>Workplace DO (n=400) No. (%)</i>	<i>Family member DO (n=203) No. (%)</i>	<i>Clinic DO (n=400) No. (%)</i>	<i>Community volunteer DO (n=147) No. (%)</i>	<i>Community health worker DO (n=61) No. (%)</i>	<i>Total</i>
Employed	302(54.8%)	52(9.4%)	141(25.6%)	25(4.5%)	31(5.6%)	551(46%)
Unemployed	20(5.9%)	88(25.9%)	143(42.1%)	74(21.8%)	15(4.4%)	340(28%)
unknown	78(24.4%)	63(19.7%)	116(36.3%)	48(15%)	15(4.7%)	320(26%)
Total	400 (33%)	203(16.8%)	400(33%)	147(12.1%)	61(5%)	1211(100%)

4.5.1 RISK FACTORS FOR UNSUCCESSFUL TB TREATMENT OUTCOME AMONGST EMPLOYED PATIENTS:

Lay community health volunteer Direct Observation of treatment had better treatment outcomes (84.0%) than workplace Direct Observation (72.8%). Workplace Direct Observation was only marginally better than clinic Direct Observation (70.9%) and family member Direct Observation had the least successful outcome (61.5%). However, the results were not statistically significant ($p=0.313$) (Table 7).

Indian employed patients had the best treatment outcomes (84%), followed by Black patients (71.3%), Coloured patients (70.0%) and White patients (33.3%). These results were not statistically significant ($p=0.252$).

Female employed patients were least likely not to complete treatment successfully (21.6%) when compared to their male counterparts (treatment failure 31.1%). These results were statistically significant ($p=0.024$).

New TB patients showed a statistically better treatment outcome (76.1%) when compared to retreatment patients (62.4%), ($p<0.001$).

After adjusting for the effect of race, sex, age at treatment start, category of patient and method of Direct Observation, the effect of method of Direct Observation was not found to be statistically significant ($p=0.11$). Family member Direct Observation was significantly more likely not to succeed when compared to workplace Direct Observation ($p=0.025$). Male employed patients were 1.7 times more likely not to complete treatment than female patients were ($p=0.018$). Retreatment was still a significant risk for unsuccessful treatment outcome when compared to new cases ($p < 0.001$).

Table 7: Risk factors for unsuccessful treatment outcome for 551 employed pulmonary TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Unsuccessful Treatment outcome (n=399) No. (%)</i>	<i>Treatment success (n=812) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Workplace DO (reference)	82 (27.2%)	220 (72.8%)	302 (55%)	1			0.110
Family member DO	20 (38.5%)	32 (61.5%)	52 (9%)	1.69 (0.90-3.17)	0.340	2.07 (1.09-3.91)	0.025
Clinic DO	41 (29.1%)	100 (70.9%)	141 (25%)	1.27 (0.81-1.99)	0.102	1.36 (0.72-1.78)	0.585
Community Volunteer DO	4 (16.0%)	21 (84.0%)	25 (5%)	0.61 (0.20-1.83)	0.377	1.08 (0.15-1.40)	0.171
Community Health worker DO	9 (29.0%)	22 (71.0%)	31 (6%)	1.31 (0.73-2.32)	0.522	1.17 (0.51-2.73)	0.694
Total	156(28%)	395 (72%)	551 (100%)				
New treatment (reference)	89(23.9%)	284(76.1)	373 (68%)	1			
Re-treatment	67(37.6%)	111(62.4%)	178 (32%)	1.71 (1.15-2.53)	0.008	1.71 (1.09-2.68)	0.018
Total	156(28%)	395(72%)	551 (100%)				
Black (reference)	147(28.7%)	366(71.3%)	513 (93.5%)	1			
Indian	4(16%)	21(84%)	25 (4%)	0.54 (0.18-1.60)	0.265		
Coloured	3(30.0%)	7(70.0%)	10 (2%)	1.21 (0.31-4.76)	0.783		
White	2(66.7%)	1(33.3%)	3 (0.5%)	5.66 (0.51-62.89)	0.159		

Table 7 (continued): Risk factors for unsuccessful treatment outcome for 551 employed pulmonary TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Unsuccessful Treatment outcome (n=399) No. (%)</i>	<i>Treatment success (n=812) No. (%)</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Female (reference)	35(21.6%)	127(78.4%)	162 (29%)	1			
Male	121(31.1%)	268(68.9%)	389 (71%)	1.62 (1.04-2.54)	0.033	1.97	0.001
Total	156(28%)	395(72%)	551 (100%)				

RISK FACTORS FOR TB RECURRENCE AMONGST EMPLOYED

PATIENTS:

Analysis for recurrence of TB included 386 employed patients who had successfully completed treatment. Nine participants were excluded because of missing information on recurrence. Recurrence of TB occurred in 10.1% of employed patients.

Workplace Direct Observation showed the highest risk of recurrence followed by family member, community volunteer, clinic based and community health worker Direct Observation in decreasing order of recurrence of TB but the results were not statistically significant ($p=0.253$) (Table 8).

Recurrence of TB was highest amongst Coloured patients, followed by Black, Indian and White patients but again results were not statistically significant ($p=0.839$). Male patients were more likely to have recurrent TB (10.4%) in comparison to females (9.5%), ($p=0.792$). Retreatment employed TB patients were significantly more likely to have a recurrent episode of TB (16.5%) than new patients were (7.6%), ($p=0.009$).

Retreatment was the only significant exposure variable for recurrence following binary logistic regression analysis with the use of backwards stepwise models utilized to assess the independent association between exposure variables and recurrence of TB (table 8). Retreatment patients were 2.4 times more likely to experience a recurrent episode of TB than new TB patients (95% CI: 1.23 - 4.74; $p=0.01$).

Table 8: Risk factors for recurrence of TB amongst 386 employed TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure variable</i>	<i>Recurrence no</i>	<i>Recurrence yes</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Workplace DO (reference)	185(87.3%)	27(12.7%)	212(56%)	1			
Family member DO	28(87.5%)	4(12.5%)	32(8%)	0.98 (0.32-3.01)	0.970		
Clinic DO	95(87.5%)	5(12.5%)	100(26%)	0.36 (0.14-0.97)	0.043		
Community Volunteer DO	19(90.5%)	2(9.5%)	21(5%)	0.72 (0.16-3.27)	0.672		
Community Health worker DO	20(95.2%)	1(4.8%)	21(5%)	0.34 (0.04-2.660)	0.343		
Total	347(90%)	39(10%)	386(100%)				
New (reference)	256(92.4%)	21(7.6%)	277(72%)	1			
Retreatment	91(83.5%)	18(16.5%)	109(28%)	2.40 (1.23-4.73)	0.010	2.41 (1.23-4.73)	0.010
Total	347(90%)	39(10%)	386(100%)				

Table 8 (continued): Risk factors for recurrence of TB amongst 386 employed TB patients commenced on TB treatment from July 2005 to June 2006 at the Prince Cyril Zulu Communicable Diseases Centre.

<i>Exposure Variable</i>	<i>Recurrence no</i>	<i>Recurrence yes</i>	<i>Total (n) (%)</i>	<i>Crude Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>	<i>Adjusted Odds Ratio (95% Confidence Intervals)</i>	<i>P value</i>
Black (reference)	321(89.7%)	37(10.3%)	358 (93%)	1			
Indian	19(95.0%)	1(5.0%)	20 (5%)	0.46 (0.06-3.51)	0.451		
Coloured	6(85.7%)	1(14.3%)	7 (2%)	1.45 (0.17-12.34)	0.736		
White	1(100%)	0(0%)	1	0.00 (0.00)	1.000		
Total	347(90%)	39(10%)	386(100%)				
Female (reference)	114(90.5%)	12(9.5%)	126	1			
Male	233(89.6%)	27(10.4%)	260	1.10	0.793		
Total	347(90%)	39(10%)	386(100%)				

SUMMARY

The majority of patients in this study were from the black community, male, with a median age of 35 years at start of treatment. Less than half of the patients were employed.

In this analysis, equal numbers of patients received workplace and clinic based Direct Observation of TB therapy. Family member based Direct Observation, community health worker Direct Observation and lay community volunteer groups did not meet the sample size requirement of 400 patients.

Sixty five percent of patients had a successful treatment outcome and, of these for whom data was, available, ten percent experienced a recurrence of TB.

Multivariate analysis to assess the independent risk of each one of the exposure variables/ risk factors demonstrated that retreatment patients were more likely to have unsuccessful treatment outcomes and recurrence. Workplace supervision of TB treatment, female gender, black, employed patients were more likely to have successful treatment outcomes.

To control for the possible confounding effect of employment status a subgroup analysis of employed patients was done. The overall effect of method of Direct Observation was not statistically significant but family member Direct Observation was the only method of Direct Observation which was significantly more likely to have an unsuccessful TB treatment outcome when compared to workplace Direct Observation. Male patients and retreatment cases of TB were more likely to fail treatment. Amongst employed patients, retreatment cases were more likely to experience recurrence of TB.

CHAPTER V: DISCUSSION

5.1 INTRODUCTION

The study evaluated the effectiveness of five different methods of Direct Observation of TB therapy (clinic based supervision, family member supervision, workplace based supervision, community health worker supervision and lay community volunteer supervision) on PTB treatment outcomes and recurrence of TB following successful treatment completion in a resource constrained setting with a high burden of Tuberculosis. The findings of this study are generalizable to other developing countries where challenges in implementation of an effective TB programme such as poverty, high burden of co morbid illnesses such as HIV infection, a migrant population with strong rural ties and reliance on traditional practices to cure illness, play a major role.

5.2 FINDINGS

The successful treatment completion rate of 65% was below the WHO target and that of 71% achieved for South Africa as a whole in 2005.⁵ It was similar to the 64% successful treatment completion rate achieved for KwaZulu-Natal achieved in 2005⁵ and thus maybe assumed that similar challenges in improving cure rates are faced by most TB facilities in the province. The sub optimal cure rates achieved in this facility could also be attributed to the migratory nature of the patient population, a factor which may have affected the level of adherence to TB treatment.

Recurrence:

Of those that had a successful outcome and for whom data on recurrence was available, 10% experienced recurrence of TB. This is similar to the recurrence range of 0% to 14% reported in other studies.⁷ Severity of disease, bacteriological response time to TB treatment and the total amount of chemotherapy taken has been identified as predictors of recurrent TB. It is reasonable to assume that patients who continue with employment and receive work place Direct Observation whilst on TB treatment have less severe disease. In addition these patients do not have the inconvenience of travelling to their treatment

supporters and should therefore be adherent to treatment and thus have lower recurrent TB when compared to the other groups. Therefore discerning the reason for the higher incidence of recurrence amongst patients receiving work placed Direct Observation, who had the most successful treatment outcome initially, is challenging.

Direct Observation of TB Therapy:

Analysis of treatment outcome by Direct Observation supervision method demonstrated that workplace based supervision had a higher frequency of successful treatment outcome than the other methods of Direct Observation ($p < 0.001$), with family member support being the least successful. The assumption that patients receiving workplace supervision of treatment had less severe disease and did not have the inconvenience and expense associated with travelling to the Direct Observation supporter would account for the more successful outcome in this group of patients.

A study based in South Africa that evaluated workplace supervision also found this method of Direct Observation to be superior to clinic based and community based Direct Observation. In the study conducted by Sinanovic *et al.*²⁰ workplace management of TB extended beyond just direct observation of TB therapy. It included the diagnosis of tuberculosis and clinical and laboratory monitoring of response to TB therapy.

In this study, family member Direct Observation was 2.3 times more likely than workplace support to result in unsuccessful treatment outcome. This is in contrast to a study where it was found to be superior¹¹ or equivalent to other methods of Direct Observation.⁹ In a randomized cluster trial conducted in Senegal, Thiam *et al.*¹² demonstrated that family member supervision was superior to supervision by community health workers and clinic nurses. Family member supervision achieved cures of 88%, compared with 77% in the other two groups. The treatment interruption was also much lower in the patients who were supervised by family members. The outcome of a cluster-randomized trial conducted by Newell *et al.*⁹ in Nepal demonstrated that family member supervision and community worker Direct Observation of TB treatment were equally as effective in ensuring adherence to TB treatment. Family supervision exceeded the WHO

target cure rate of 85% and community worker supervision met the WHO target. However, it has been commented that the findings of Thiam *et al.*¹¹ in Senegal lacked external validity, as it was not conducted under programmatic conditions (the study would be difficult to duplicate under field conditions in under resourced areas because supervisors received enhanced training and monitoring throughout the study).⁷

Clinic based Direct Observation was more likely to be unsuccessful when compared to workplace Direct Observation. The finding is in contrast to the findings of a chart review done amongst TB patients that share similar characteristics to patients at the eThekweni site. In the study conducted in India, clinic based Direct Observation increased successful TB treatment outcomes from 55% to 95%.¹⁰

Long waiting times and inconvenient hours of operation, often make clinic based Direct Observation unacceptable to patients, especially if it limits their ability to fulfil their work obligations.

Patients allocated to lay community volunteer and community health worker Direct Observation were less likely to experience unsuccessful treatment outcome when compared to clinic based, and family member Direct Observation of TB therapy. However, these results were not statistically significant which is probably related to the small sample sizes in these groups.

Patient gender:

Females were more likely to successfully complete treatment and this is in accordance with findings of other studies.^{15,19} A randomized controlled trial conducted by Walley *et al.*¹⁵ evaluating the efficacy of self supervision, health worker supervision and family member Direct Observation on TB treatment outcomes in Pakistan demonstrated that male patients were more likely to be non adherent to TB treatment when compared to female patients (38% versus 23%). A prospective cohort study evaluating the effectiveness of community volunteer Direct Observation on TB treatment outcomes in

South Africa demonstrated that males were significantly more likely to fail TB treatment (OR =1.38; 95% CI: 1.02 to 1.87).¹⁹

Employment status:

A higher proportion of employed patients (72%) had successful TB treatment outcomes when compared to the study population as a whole (65%). Unemployed people were at greater risk of treatment failure than employed people were. Unemployed patients would tend to have a lower socioeconomic status and other comorbid illnesses, which would impact on adherence and response to TB treatment.

An analysis of employed patients showed that method of Direct Observation had no overall effect on TB treatment outcomes although family member Direct Observation was significantly more risky for unsuccessful treatment outcome than workplace Direct Observation. Amongst employed patients, retreatment patients were more likely to have TB recurrence when compared to new cases of PTB.

An observed anomaly is that, of the patients that received workplace supervision 5% had reported that they were unemployed and the employment status of 20% was unknown. It has been noted by clinicians that TB patients often do not disclose their employment status correctly in order to enhance their chances to qualify for a disability grant for which employed individuals are ineligible (anecdotal evidence). This could be a possible reason for the noted anomaly of employment status amongst patients receiving workplace Direct Observation.

A little over half of the employed patients opted for workplace Direct Observation whilst a quarter chose clinic based Direct Observation. Employed patients often do not disclose that they are on TB treatment to their employers and co-workers for fear of dismissal from employment. This could account for nearly 45% of employed individuals choosing other methods of Direct Observation over workplace Direct Observation. Severe TB disease and an inability to return to employment at the time of commencement of TB treatment could also account for employed patients opting for other methods of Direct

Observation. In addition, employed patients receiving streptomycin as part of a re-treatment TB regimen would have been allocated to clinic based supervision if an occupational health facility was not accessible.

Category of TB patients:

Retreatment, patients exhibited a significantly higher risk of unsuccessful treatment outcome than new TB patients did confirming the finding in the study conducted by Zwarenstein *et al.*¹⁴ Retreatment was also the only significant risk factor associated with recurrence of TB following prior successful treatment completion. If a high incidence of MDR TB existed amongst re-treatment patients, it would explain the higher risk of unsuccessful treatment outcomes in this group of patients. A diagnosis of MDR TB is often only arrived at once sputum culture results become available about 6 weeks after a patient has been commenced on standard first line TB treatment. The incidence of MDR TB was not measured in this study.

5.3 VALIDITY

Internal validity:

A retrospective cohort study does not constitute the ideal study design to answer the research question. A randomized controlled study remains the gold standard in study design and would have improved the internal validity of the study. The current study was conducted under programmatic conditions and, thus, not all effect modifiers, confounders and bias could be controlled for or eliminated. However, to improve the internal validity of this study, binary logistic regression was conducted to control for the effect of confounders and to assess the independent effect of method of Direct Observation of TB therapy on TB treatment outcomes. Odds ratios were used as the measure of association (although unsuccessful treatment outcome is not a rare outcome so the association may be an overestimate) because the outcome and exposures were assessed simultaneously (that is, there was no time to event).

The odds ratio for unsuccessful treatment outcome was reported on instead of the odds ratio for treatment success because in logistic regression the odds ratio for the “disease” outcome (unsuccessful treatment outcome - in this study) in case control studies is traditionally calculated. The outcome indicator used by the WHO however is treatment success.

External validity:

The study was performed under programmatic conditions. As the data was collected retrospectively, providers and patients could not have exhibited a social desirability bias. They did not receive any additional intervention other than that prescribed by the South African National TB Programme and, thus, the results of this study are generalizable to managing Direct Observation of TB in other developing countries.

5.4 BIAS AND LIMITATIONS

The study was undertaken under routine programmatic conditions and maybe affected by some bias and limitations.

Clinic based Direct Observation was not aggregated into daily or weekly clinic based Direct Observation in the analysis. From personal experience at the clinic, it was observed that some patients were supported daily and others supported weekly. This is a limitation of the study.

Some patients who received workplace based Direct Observation were supervised by occupational health nurses, located in the workplace, and although supervision by occupational health nurses is considered as part of workplace Direct Observation this could have influenced adherence and TB treatment outcomes, as nurses have better counselling skills and knowledge on TB management when compared to other work place based supervisors.

The limitation associated with measurement of recurrence in this study is that passive follow up was employed to determine whether recurrence had occurred or not (patient charts were reviewed to determine whether patients had returned to the site for management of a subsequent episode of TB.) An assumption was made that patients would return to the same site in the event of developing symptoms of a subsequent episode of TB; therefore, under reporting of recurrence is likely to have occurred. In addition, it is not possible to differentiate between relapse of the same infection or re-infection by a new strain of *Mycobacterium tuberculosis*.

Misclassification bias

Studies have found that patients do not comply consistently with the original method of Direct Observation allocation. A randomized controlled trial conducted by Walley *et al.*¹⁵ in Pakistan demonstrated that 16 percent of patients allocated to health worker Direct Observation and 2% of patients allocated to family member Direct Observation did not comply with original method of Direct Observation of TB therapy.¹⁵

A chart review conducted in Kerela, India by Balasubramanian *et al.*¹⁰ found that implementation of Direct Observation of TB therapy was a challenge following allocation to a Direct Observation method (about 25% of patients and health workers did not comply with Direct Observation).

In this study, there is no means to verify that the method of Direct Observation agreed upon, was actually practiced through out the period of TB therapy. Therefore, misclassification bias may have arisen.

Documentation of employment status is dependent on patient self-report and could have resulted in misclassification bias, if employed patients had reported that they were unemployed.

5.5 EFFECT MODIFICATIONS

The severity of the preceding episode of TB disease has been independently associated with recurrence of TB (presence of cavitations and more extensive lung involvement) and this study is limited in not taking this factor into account.⁶

The presence of comorbid illnesses such as HIV infection could also affect TB treatment outcomes. Unfortunately, the prevalence of HIV infection could not be assessed in this study as patient acceptance of voluntary counseling and testing for HIV infection and the extent of disclosure of HIV status was low when this study was implemented.

CHAPTER VI: RECOMMENDATIONS AND CONCLUSIONS

6.1 INTRODUCTION

The high burden of tuberculosis results in clinic based observation not always proving feasible, both for the patient and the provider. Therefore, other effective methods of Direct Observation of TB therapy need to be considered. Studies implemented have not proven the superiority of any one method of Direct Observation.

6.2 CONCLUSIONS

For employed TB patients Direct Observation at the workplace has proved to be the most effective option in this study. This method of Direct Observation needs to be considered by other facilities to ensure that employed patients are not absent from work when they are required to report to treatment supervisors for direct observation of TB treatment. This will help to ensure that patients remain employed and in a position to fulfil the financial obligations, they have to their families and continue to be productive members of society.

6.3 RECOMMENDATIONS

Sample size limitations for family member, community health worker and lay volunteer direct observation methods do not allow for the unequivocal recommendation of workplace based supervision of TB therapy as the preferred method of observation for employed TB patients. Nevertheless, the findings of this study strongly suggest that this method of Direct Observation can have a significant impact in improving TB treatment outcomes.

There is often no best treatment observer. Every case has to be individually evaluated (taking into account patient, provider and disease factors) and the most acceptable and accessible treatment observer chosen. If family member Direct Observation forms the

only option for supervision, then family members should receive enhanced education on TB and should receive intensive supervision and home visits by a clinic based health care worker.

TB treatment is delivered to the workplace by clinic staff; at a TB clinic in the suburbs of Durban (Pinetown), for those individuals who choose workplace based Direct Observation. This contact with workplace based supervisors of TB treatment by TB clinic staff promotes a cordial relationship between the clinic and workplace staff and ensures that TB clinic staff is aware of those patients that are not adherent to TB treatment timeously. Delivery of TB treatment to the workplace, if practised by the staff of the Prince Cyril Zulu Communicable Diseases Centre, could increase adherence to TB treatment and ultimately result in more successful TB outcomes amongst employed TB patients.

6.4 RECOMMENDATION FOR FURTHER STUDY

Future studies evaluating recurrence, need to take cognisance of the severity of TB disease by taking into consideration chest radiography findings and scoring severity of disease according to radiological findings.

In addition, planned studies should take into consideration patients' HIV infection status and level of disability.

Patients and providers interviews should be implemented to determine whether there is adherence to method of Direct Observation initially agreed to. Reasons for non-adherence to method of Direct Observation may be explored during interviews. This information will be vital in improving adherence to TB treatment.

Retreatment patients demonstrated poor treatment outcomes and higher frequency of recurrence of a subsequent episode of TB; therefore, future studies are required to evaluate effective interventions to improve treatment outcomes in this group of patients.

It has been noted that Direct Observation in this group of patients is ineffective and qualitative studies involving in- depth interviews is required in this group of patients to determine the reasons for the failure of Direct Observation. ¹⁴

Ideally, a randomized trial should be considered which would increase the internal validity of this study. A randomized study evaluating the effect of different methods of Direct Observation amongst employed patients (a group in which 72% of patients had successful TB treatment outcome) may yield vital information on the ideal method of Direct Observation of TB treatment.

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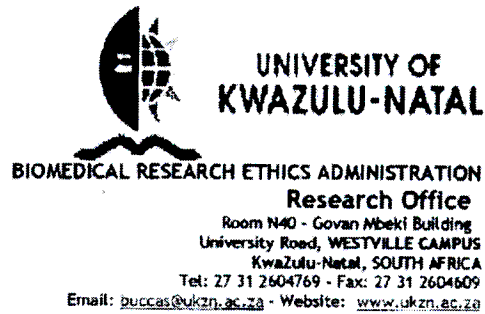
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APPENDIX 1 – DATA COLLECTION TOOL

THE PRINCE CYRIL ZULU COMMUNICABLE DISEASES CENTRE	Patient number	Date Treat Starts	Age at treatment start	Date treatment ends	Patient Category (new/re treatment	Race	Employment status	Method of DO supervision	Five month sputum result	Date of last visit	TB Treatment Outcome	Recurrence Yes/no
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APPENDIX 2- ETHICAL APPROVAL TO CONDUCT STUDY



26 March 2007

Dr G Nair
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CHATSWORTH 4030
Fax: 031-4037040

EXPEDITED APPLICATION

PROTOCOL: A COMPARISON OF DIRECT OBSERVATION OF TREATMENT METHODS USED FOR TREATING PULMONARY TUBERCULOSIS IN DURBAN, KWAZULU-NATAL. DR G NAIR, DEPT OF PUBLIC HEALTH MEDICINE. REF: EXP044/06

Dear Dr Nair

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your response received 23 March 2007 to queries raised on 24 November 2006.

We also confirm receipt of the outstanding permission letter from the hospital manager of Prince Cyril Zulu Communicable Diseases Centre.

The study is given full ethics approval and may begin as at today's date: 26 March 2007.

This approval is valid for one year from 26 March 2007. To ensure continuous approval, an application for recertification should be submitted a couple of months before the expiry date. In addition, when consent is a requirement, the consent process will need to be repeated annually.

I take this opportunity to wish you everything of the best with your study. Please send the Biomedical Research Ethics Committee a copy of your report once completed.

The sub-committee's decision will be RATIFIED at a full sitting of the Biomedical Research Ethics Committee meeting to be held on 10 April 2007.

Yours sincerely


PROFESSOR J MOODLEY
Chair: Biomedical Research Ethics Committee