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RISK FACTORS ASSOCIATED WITH TB INCIDENCE IN AN ADULT POPULATION FROM POORLY RESOURCED SOUTH AFRICAN URBAN COMMUNITIES WITH HIGH TB PREVALENCE

BY

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A RESEARCH REPORT SUBMITTED TO THE FACULTY OF HEALTH SCIENCES, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (MEDICINE) IN EPIDEMIOLOGY AND BIOSTATISTICS

SEPTEMBER 2010

DECLARATION

I, **Jabulani Ronnie Ncayiyana** declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine in the field of Epidemiology and Biostatistics in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……. .....[Signature of candidate]

…….29……..day of …September……..2010

DEDICATION

This work is dedicated to the memory of my beloved parents Philemon and Ntombizodwa Florence Ncayiyana. I am because you are.

Mr. Jabulani R. Ncayiyana

2010

“[I] urge all advocates to be captured indeed "infected" with the zeal and passion of those who are committed to this campaign to eliminate TB as a public health concern. May you all be passionate zealots. What a splendid gift TB elimination will be for humanity's Third Millennium.'

Desmond Tutu

Archbishop Emeritus of Cape Town, South Africa

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TABLE OF CONTENTS

DECLARATION iii

DEDICATION iii

ACKNOWLEDGEMENTS iv

LIST OF FIGURES vii

LIST OF TABLES viii

LIST OF APPENDICES ix

LIST OF ABBREVIATIONS x

ABSTRACT xii

CHAPTER 1.GENERAL INTRODUCTION 1

1.1. INTRODUCTION 1

1.2. PROBLEM STATEMENT 4

1.3. JUSTIFICATION 6

1.4. LITERATURE REVIEW 7

1.5. OBJECTIVES 18

CHAPTER 2.METHODOLOGY 19

2.1. STUDY DESIGN 19

2.2. STUDY POPULATION AND STUDY AREA 22

2.3. SAMPLE SIZE 23

2.4. DATA PROCESSING & MANAGEMENT 23

2.5. OUTCOME VARIABLE 24

2.6. EXPLANATORY VARIABLES 24

2.7. FOLLOW-UP 25

2.8. RESEARCH QUESTION 25

2.9. ETHICAL CONSIDERATIONS 26

2.10. PLANS FOR DISSEMINATION AND UTILISATION OF RESULTS 26

2.11. DATA PROCESSING METHODS AND ANALYSIS 27

CHAPTER 3.RESULTS 29

3.1. BACKGROUND FACTORS 29

3.2. TB INCIDENCE RATES 29

3.3. RISK FACTORS 34

3.4. LOGISTIC REGRESSION ANALYSIS 36

3.5. POPULATION ATTRIBUTABLE FRACTION (PAF) ESTIMATES 41

CHAPTER 4.DISCUSSION 42

4.1. Introduction 42

4.2. Marital status/cohabiting 42

4.3. Smoking 44

4.4. Imprisonment 45

4.5. Gender 46

4.6. Age and HIV 47

4.7. Alcohol 48

4.8. HIV 51

4.9. Limitations of the study 52

CHAPTER 5.CONCLUSION AND RECOMMENDATIONS 54

5.1. CONCLUSION 54

5.2. RECOMMENDATIONS 55

REFERENCES 57

APPENDICES 75

LIST OF FIGURES

Figure 1.1: Epidemiology of tuberculosis – factors affecting risk of exposure, infection, progression to disease and death (source: Story A. Tuberculosis – A general introduction) 3

Figure 3.1: TB Incidence rates by gender in the R/U population 31

Figure 3.2: TB Incidence rates by age group in the R/U population 32

Figure 3.3: Cumulative (5 year period) TB incidence rates by alcohol/smoking status in the R/U population 33

LIST OF TABLES

Table 3-1: Distribution of socio-demographic variables for the cohort, Cape Town, South Africa, 2003-2007. 30

Table 3-2: Proportion of new TB cases by selected factors, Cape Town, South Africa, 2003-2007. 35

Table 3-3: Logistic regression analysis for host related factors of TB. 37

Table 3-4: Logistic regression analysis for environmental related factors of TB. 39

LIST OF APPENDICES

APPENDIX 1: Variables of interest and their definitions 75

APPENDIX 2: Population Attributable Fraction (PAF) Estimates 76

APPENDIX 3: Ethics Clearance certificate 77

APPENDIX 4: Data User Agreement Form 78

LIST OF ABBREVIATIONS

AIDS Acquired immunodeficiency syndrome

BCG Bacille Calmette–Guérin

BMI Body Mass Index

DTTC Desmond Tutu TB Centre

DOTS Directly observed treatment short-course strategy

HBCs High-burden countries, of which there are 22 that account for approximately 80% of all new TB cases arising each year

HIV Human immunodeficiency virus

MDGs Millennium Development Goals

MDR Multidrug resistance (resistance to isoniazid and rifampicin)

MDR-TB Multidrug-resistant tuberculosis

NTP National tuberculosis control programme or equivalent

PAL Practical Approach to Lung Health

R/U Ravensmead/Uitsig

SADHS South African Demographic and Health Survey

STATSSA Statistics South Africa

TB Tuberculosis

UN the United Nations

WHO World Health Organisation

XDR-TB Extremely drug resistant -TB due to MDR strains that are also resistant to a fluoroquinolone and at least one second-line injectable agent (amikacin, kanamycin and/or capreomycin)

ABSTRACT

Introduction: Tuberculosis (TB) persists as a serious global public heath problem of a magnitude requiring urgent attention. The increase in new cases of TB in African countries where the prevalence of HIV is relatively low has been associated with other host and environmental factors. There is little or no comparable data on the association between host and environmental related factors and TB incidence in low HIV prevalence regions of South Africa.

Objectives: This study aims to investigate host and environmental factors associated with incident TB in one region of South Africa.

Methods: 3493 TB-free participants were recruited, and baseline data collected at the beginning of 2003 in the Lung Health Study in Ravensmead and Uitsig, Cape Town, South Africa. The TB register was used to identify new cases among the 3493 participants between 2003 and 2007.

Results: Of the 3493 study participants, 109 developed TB; i.e. 57 males and 52 females. The incidence of TB in the Ravensmead and Uitsig study population was 632 per 100 000. Cohabiting, OR= 2.09 (95% CI= 1.05 - 4.17), smoking, OR= 2.19 (95% CI= 1.48 - 4.14), and history of imprisonment

OR= 1.88 (95% CI= 1.09 - 3.23) were all statistically associated with TB incidence in multiple logistic regression models. The summary population attributable fraction for these three factors was 53.2%.

Conclusions: TB incidence was high in this community. Cigarette smoking was one of the most important predictors of TB incidence, and the proportion of smokers in this population was relatively high. TB control and prevention strategies need to focus on interventions which will reduce or limit the impact of TB risk factors.

CHAPTER 1. GENERAL INTRODUCTION

1.1 INTRODUCTION

Tuberculosis (TB) incidence rate is a key indicator for monitoring performance in TB control interventions, and an understanding of the epidemiology of TB forms the basis for implementing a successful national TB control programme (Rieder, 1999; Ward, 2004). Thus it follows that identifying those at increased risk of developing TB disease is strategic in TB control (Ward, 2004). TB control programmes aim to stop transmission by identifying and treating infectious disease, preventing infection (vaccination), and preventing disease among infected high-risk individuals (preventive intervention).

TB is ranked second to Acquired Immunodeficiency Syndrome (AIDS) as the leading cause of death globally (Raviglione, 2003). Worldwide, the number of new cases is still rising due to an increased case load in Africa, Eastern Mediterranean and South-East Asia (WHO, 2007; Story, 2004). WHO declared TB a global health emergency in 1993 (Story, 2004). Africa, home to 11% of the world's population, carries 31% of the global burden of TB cases (Story, 2004; WHO, 2007; WHO 2008a). The TB case load has continued to grow in Africa (WHO, 2007), despite the 46 countries in the WHO African

region adopted a resolution declaring TB as an emergency in the African region (WHO, 2005). WHO reported that 13 (87%) of the 15 countries with the highest estimated TB incidence rates in 2007 were in Africa (WHO, 2009).

TB persists as a serious global public-heath problem which needs urgent attention (Stop TB, 2002). Renewed global efforts to control TB started when the World Health Assembly resolution recognized TB as a major global public health problem (WHO, 1991). Later, when the United Nations (UN) adopted the Millennium Declaration in 2000, TB became one of the priorities defined in the Millennium Development Goals (MDGs). The MDG related to the TB control impact (Target 8) is not only to halt the incidence, but also to begin to reverse it by 2015 (Dye *et al*., 2005). The long term goal set by WHO and its Stop TB partners is to eliminate TB as a public health concern (i.e. to reduce TB incidence to 1 or less per million population by 2050) (Lönnroth & Raviglione, 2008).

TB is a multi-factorial disease in which the environment interacts with host-related factors to contribute to the development of the clinical disease (Lienhardt, 2001). However, the causal chain of processes influencing the epidemiology of TB is not merely of a simple linear nature as shown in Figure 1 (Story, 2004). Exposure to a potentially infectious case is a prerequisite for becoming infected. Once an individual is exposed, there are factors which determine the following:

- The risk of becoming infected,

- The probability that an infected individual will develop tuberculosis, and

- The likelihood that a diseased individual will die from TB (Story, 2004; Rieder, 1999).

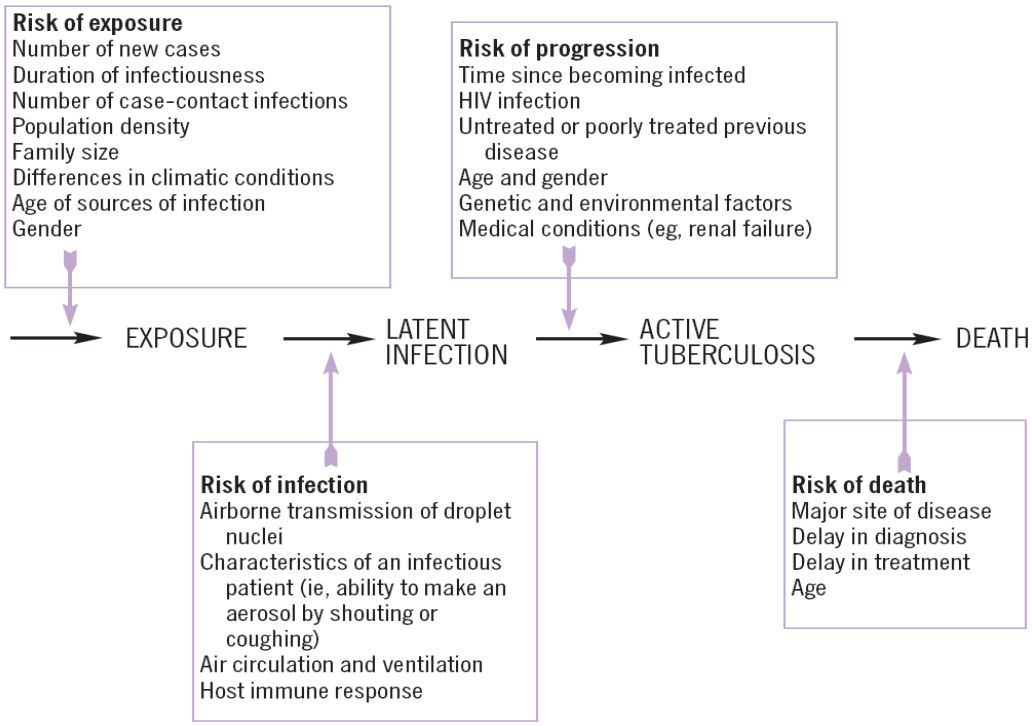


Figure 1.1 Epidemiology of tuberculosis – factors affecting risk of exposure, infection, progression to disease and death (source: Story A. Tuberculosis – A general introduction)

The World Health Organisation (WHO) estimated that 9.27 million new cases of TB occurred in 2007, compared with 9.24 million new cases of TB in 2006. Of these 9.27 million new cases, an estimated 44% or 4.1 million were new smear-positive cases. India, China, Indonesia, Nigeria and South Africa were ranked first to fifth respectively in terms of the total number of new TB cases (WHO, 2009). Approximately 80% of TB cases are found in only 22 countries[1]; with the highest incidence rate reported in Africa (WHO, 2008a; WHO, 2007). The unprecedented growth of the TB epidemic in Africa is attributable to several factors, the most important being the Human Immunodeficiency Virus (HIV) epidemic (Chaisson and Martinson, 2008).

1.2 PROBLEM STATEMENT

South Africa has a long history of high TB burden (Harling et al, 2008). WHO's estimate of national incidence of TB in South Africa was 600 cases per 100 000 persons per annum in 2005, and this increased to 940 cases per 100 000 persons per annum in

[1] 22 High-Burden Countries (in alphabetical order): Afghanstan,Bangladesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Uganda, UR Tanzania, Viet Nam, Zimbabwe.

2006; the fourth highest rate in the world (WHO, 2008a; WHO, 2007). WHO estimates the 2007 TB incidence rate to be 948 new cases per 100 000, with South Africa ranking fifth in terms of the total number of incident TB cases in the world (WHO, 2009). It was one of the reported five leading underlying causes of death among South Africans between 1997 and 2001 (Stats SA, 2006). Statistics South Africa (Stats SA), further reported TB to be a leading cause of death among African and Coloured males during the same period (Anderson & Phillips, 2006; Stats SA, 2006).

Host-related and environment-related factors have been shown to play a role in the development of tuberculosis (TB), but few studies were carried out to identify their respective roles in the developing countries (Lienhardt et al., 2005). Moreover, in most studies investigating risk factors for TB, host-related and environmental factors were usually investigated separately, using different designs, making it impossible to assess their respective effects (Rieder, 1999; Lienhardt, 2001). There is a need to re-examine the contribution of environmental and host-related factors for TB and identify factors that can influence the individual risk of development TB, in order to adjust and adapt TB control policies (Lienhardt et al., 2005).

1.3 JUSTIFICATION

There has been a reported increase in new TB cases in sub-Saharan countries or communities with a relatively low HIV prevalence (WHO, 2009; WHO, 2007; Corbett *et al*., 2003), indicating that there are factors other than HIV driving high TB incidence in these settings. The high TB incidence rates estimated for some African countries are partly explained by the relatively high rates of HIV co-infection (Corbett *et al*., 2003). The WHO reported that TB incidence rates are falling in seven of nine epidemiological sub-regions and are stable in eastern Europe. However, TB incidence rates are increasing in African countries even in places with a low prevalence of HIV (WHO, 2009).

In South Africa, few previous studies have shown a conflicting association between host and environmental factors and active TB disease (Coetzee *et al*., 1988; Schoeman *et al*., 1991; Harling *et al*., 2008). In addition, the design of previous studies has usually been case-control and cross-sectional, and their results might be biased by the limitations of these types of studies. Data are needed on the rates of disease by place and person according to the various risk factors (Lienhardt, 2001). Little or no comparable data exists about the association between host and environmental related factors and TB incidence in regions of South Africa with high TB incidence and low HIV prevalence.

This study investigates the association between host and environment related factors and TB disease in a high TB prevalence setting.

1.4 LITERATURE REVIEW

The development of TB is a two-stage process in which a susceptible person exposed to an infectious tuberculosis case first becomes infected and may later develop the disease, depending on various factors (Lienhardt *et al*, 2005). Thus the risk factors for infection are quite different from those associated with developing TB after infection (Story, 2004; Rieder, 1999).

A complex relationship exists between the host factors and environmental factors which determines who develops TB after infection (Lienhardt, 2001). Some of these factors have considerable impact because not only are they strong risk factors in themselves, but they may also be highly prevalent in the general population. Even though some factors appear to increase TB risk several-fold, they may be regarded as medical curiosities of minimal public health importance because they occur only rarely. The importance of any risk factor in public health is determined by both the strength of the association and the prevalence of the risk factor in the population (Rieder, 1999; Lönnroth et al., 2008).

In persons infected with tubercle bacilli, any factor modifying the balance established in the body between the host's immune defences and the tubercle bacilli can have an impact on the risk of developing the disease (Lienhardt *et al*, 2005). The relative importance of TB risk factors was investigated in a number of recent systematic reviews. Stevenson *et al*. (2007) estimated that 15% of adult pulmonary TB cases in India can be attributed to diabetes (Stevenson *et al*., 2007). This finding was consistent with the results of a recent review which found consistent evidence for an increased risk of TB among people with diabetes (Jeon & Murray, 2008).

Another recent review study investigated alcohol use as a risk factor for TB and found that there is a three-fold risk increase of active TB associated with consumption of more than 40g of alcohol per day, and/or having an alcohol use disorder (Lönnroth *et al*., 2008). Lin *et al*. (2009) demonstrated that tobacco smoking is associated with an increased risk of TB. They also reported that passive smoking and biomass fuel combustion also increase the TB risk (Lin *et al*., 2007). Improved understanding of the respective effects on TB risk factors on the incidence of TB will have strong implications for tuberculosis control and prevention (Lienhardt, 2001).

Studies investigating risk factors for TB have been conducted mainly in developed countries, with relatively few studies in developing countries, particularly in high TB burden countries (Lienhardt *et al*., 2005). Studies conducted in developed countries

showed immigration and HIV infection as important risk factors for TB, especially for those individuals born in high burden countries. A study by McKenna *et al*. from 1986 to 1993 found that the incidence of tuberculosis in foreign-born persons residing in the western United States was almost twice the rate among foreign-born persons in the rest of the country. The incidence of tuberculosis in foreign-born persons varied substantially according to the world region of origin. People from Asian countries other than India, Japan, mainland China, and countries of the former Soviet Union had the highest rate. Fifty five per cent of immigrants with tuberculosis had the condition diagnosed in their first five years in the United States (McKenna *et al*., 1995).

A recent study which lasted from 2001 to 2006 reported that immigrants accounted for 57% of all TB cases in the United States in 2006 (Cain *et al*., 2008). Individuals born in sub-Saharan Africa and Southeast Asia accounted for 53% of the total annual number of cases among all foreign-born persons, even though they comprised just 22% of the total US foreign-born population (Cain *et al*., 2008).

Rose reported that the increase in tuberculosis in England and Wales over 10 years in the 90s was due to an increase in the number of patients who had been born abroad (Rose *et al*., 2001). A study in Alberta Canada, reported that immigrants accounted for 56.3% of all TB cases from 1989 to 1998, and by far the highest rates were seen in immigrants to Canada from Asia, in particular HBCs (Long *et al*., 2002).

A study in Liguria Italy, reported a 30% increase in new TB cases among non-European immigrants (Crimi *et al*., 2005). In Madrid, Spain, a study from 1994 to 2004 also reported an increase of TB rates among immigrants (Inigo *et al*., 2006). It is conceivable that immigrants are more at risk, especially given that they are plagued by socioeconomic problems in their new country including homelessness, and staying at a homeless shelter or a nursing home where contact with TB patients may be increased (Romaszko *et al*., 2008).

HIV infection is purported to be the greatest single risk factor for the progression to active TB disease in adults (Frieden *et al*., 2003). The latest WHO report showed that of the 9.27 million TB incident cases in 2007, an estimated 1.37 million (15%) were also HIV-positive (WHO, 2009). This estimate is double the estimate of 0.7 million cases in 2006 (WHO, 2008a). The rise in tuberculosis in the United States in the mid-1980s was due in part to the high prevalence of HIV infection (CDC, 1992).

In US cities where studies have been performed, the prevalence of Human Immunodeficiency Virus (HIV) infection among tuberculosis patients was high (Weis *et al*., 2002). A study in King County, Washington found that HIV infection was associated with a six-fold increase in risk of developing TB (Buskin *et al*., 1994). Another 12-year-study in San Francisco went further to quantify the impact of HIV on TB epidemic. The study found that in San Francisco, the TB rates were eight times higher among persons

infected with HIV than among persons who were not infected with HIV. The study also found that the percentage of tuberculosis cases among HIV-positive patients in San Francisco that was attributable to their HIV infection during the 12-year-period was 87% (DeRiemer *et al*., 2007). Recent analysis shows that 2.6% of all new TB cases in Europe in 2000 were attributable to HIV co-infection (Corbett *et al*., 2003). Churchill *et al.,* reported an increase of HIV associated TB in adults attending three north central London hospitals (2000).

However, the impact of HIV infection as a risk factor for progression to active TB is limited by its prevalence in the population and the access to highly active antiretroviral therapy (HAART). The WHO's measurements provided strong evidence that the relative risk of developing TB in HIV-positive people as compared with HIV-negative people is higher than previously estimated (WHO, 2009).

The relative risk of developing TB in HIV-positive persons was estimated at 20.6 times (95% CI 15.4–27.5) in 2007 in countries with a generalised HIV epidemic (i.e. countries where the prevalence of HIV is above 1% in the general population), while the relative risk was estimated as 26.7 times (95% CI 20.4–34.9) in countries where the prevalence of HIV in the general population is between 0.1% and 1%, and 36.7 times (95% CI 11.6–116) in countries where the prevalence of HIV in the general population is less than 0.1% (WHO, 2009).

A few studies have also reported a decrease in TB incidence among HIV infected patients. Crimi *et al*. demonstrated a marked reduction in TB notifications among AIDS patients between 1996 and 2002 in the Italian region of Liguria (Crimi *et al*., 2005). Similar trends were reported in Madrid; the authors attributed this reduction to TB control efforts and the widespread availability of HAART (Inigo *et al*., 2006).

Several studies have been conducted to investigate factors associated with TB in the developed countries. A study conducted in Houston Texas investigating epidemiological differences between US-born and foreign-born patients, reported that among US-born patients black ethnicity, smoking, use of alcohol, use of illicit drugs, low income, lack of high school diploma, incarceration and homelessness were independent risk factors for TB (El Sahly *et al*., 2001). These findings were consistent with the results of previous studies conducted in other US cities (Small *et al*., 1994; Alland *et al*., 1994 and Barnes *et al*., 1997).

A recent study reported that substance abuse (use of illicit drugs or alcohol) is the most prevalent behavioural risk factor among patients with TB in the United States (Oeltmann *et al*., 2009). A study in London showed that homelessness, prison and problem drug use were independent risk factors for TB (Story, 2004). A study in Rotterdam demonstrated an increase of TB cases among drug addicts or homeless persons from

8.8% of total cases in Rotterdam in 1999 to 12.6% of total cases in 2001 (De Vries and Van Hest, 2005).

Numerous studies evaluating risk factors associated with TB have been conducted in developing countries; however, most of these studies were conducted in West Africa and very few were conducted in high burden countries (HBCs) in the African region (Lienhardt, 2001; Lienhardt *et al*., 2005). Furthermore, most of these studies were case-control studies, thus there are issues with generalisability and temporality (WHO, 2001).

In sub-Saharan Africa risk factors associated with TB include HIV infection, age, male gender, history of asthma, marital status, family history of TB, increasing household size, ethnicity, crowding, family structure, cigarette smoking, alcohol consumption and poor housing conditions (Hill *et al*., 2003; Gustafson *et al*., 2004; Lienhardt *et al*., 2005 & Hill *et al*., 2006). As expected earlier studies focused on investigating HIV infection as a risk factor for developing TB. In the Mwanza Region in Tanzania a population-based case-control study carried out to investigate the relative and population-attributable risk of HIV infection for developing active tuberculosis reported that HIV infection was associated with an eight-fold increase in the risk of developing active tuberculosis (Van den Broek *et al*., 1993).

The study further showed that 29% of total TB cases were attributable to HIV infection. These findings were consistent with results of previous studies conducted in other African regions (Orege *et al*., 1993; Houston *et al*., 1994; Van Cleeff & Chum, 1995). A study in rural northern Malawi showed an increase of new smear-positive TB cases attributable to HIV increased from 17% in 1988-1990 to 57% in 2000-2001. The authors conclude that without HIV the incidence of smear-positive TB would have fallen in this population (Glynn *et al*., 2004).

Although HIV infection has clearly had a profound effect on TB epidemiology, other potentially important risk factors have not been investigated extensively (Dye, 2006). Studies investigating other factors associated with TB in sub-Saharan Africa were limited to countries with low HIV prevalence and low TB incidence, especially in West Africa. A multi-centre study conducted in low HIV prevalence in West African countries, viz Guinea, Guinea Bissau, and the Gambia investigated the combined effect of both host and environmental related factors on TB, and demonstrated that TB was associated with male sex, HIV infection, smoking (with a dose-effect relationship), history of asthma, family history of TB, marital status, adult crowding, and renting a house (Lienhardt *et al*., 2005).

This finding was consistent with the results of the other studies conducted in Guinea Bissau and the Gambia (Hill *et al*., 2003; Gustafson *et al*., 2004 and Hill *et al*., 2006).

Crampin *et al*. in Karonga District in Malawi reported that TB cases were associated with HIV infection and having a family or household contact with tuberculosis. The study also found that current or recent pregnancy, smoking and cooking smoke exposure were not associated with TB (Crampin *et al*., 2004). An earlier study in this population found that age, gender, type of occupation, education and housing structure were associated with TB (Glynn *et al*., 2000).

A recent study in this population reported that close TB contact is a risk factor for developing active TB. It found that an identifiable recent contact with known smear-positive cases accounted for 12.5% of the tuberculosis burden in this population (Crampin *et al*., 2008)

Very few studies investigating other factors associated with TB have been conducted in HBCs outside of sub-Saharan Africa, yet these countries collectively account for 80% of incident TB cases globally (WHO, 2009). A study in India reported that TB was associated with a low education level, kitchen type and diabetes in south India. It also found that high income, cooking with biomass fuels, history of smoking and alcohol consumption were not associated with TB (Shetty *et al*., 2006). Another study in south India found that age, male gender, smoking and alcoholism were all independently associated with TB (Kolappan *et al*., 2007). In Russia, a study reported that the main risk factors for tuberculosis were low accumulated wealth, financial insecurity,

consumption of unpasteurised milk, diabetes, living with a relative with tuberculosis, being unemployed, living in overcrowded conditions, illicit drug use, and a history of incarceration in both pre-trial detention centres and prison (Coker *et al*., 2006). A study in Brazil reported a lower socioeconomic status as a risk factor for TB (Vendramini *et al*., 2006).

There is limited data on host and environment related factors associated with TB in South Africa. An earlier study in the Mamre community near Cape Town found no association between crowding and TB, while it reported an association between alcohol abuse and TB (Coetzee *et al*., 1988). Another study conducted in the Mamelodi community found no association between socioeconomic factors and the risk of developing TB (Schoeman *et al*., 1991). A recent study found alcohol abuse, cigarette smoking and low body mass index (BMI) were each independent risk factors for tuberculosis in the general South African population (Harling *et al*., 2008).

Other studies on risk factors for TB in South Africa have been conducted on miners where risk factors included age, mining occupation, silicosis status, and HIV infection (Kleinschmidt & Churchyard, 1997). HIV infection and silica exposure have been reported as major risk factors for TB in other studies conducted on South African gold mining populations (Corbett *et al*., 1999; Corbett *et al*., 2000).

The aim of TB control is to break the cycle of transmission, either by interrupting human transmission of infection or by protecting individuals against infection/disease (Lienhardt & Ogden, 2004). Therefore TB incidence is a critical impact measure of TB control interventions. The Directly Observed Treatment (DOTS) approach to TB control is comparatively cost-effective and its successful implementation has been associated with the decline in TB incidence rates in some places. However, a systematic review showed no difference in the cure rates in patients on DOTS therapy compared with self-administered therapy (Volmink & Garner, 2007).

The rapid decline of TB incidence rates has also been reported in many countries which have not successfully implemented DOTS (Lönnroth & Raviglione, 2008). This suggests a stronger focus on prevention interventions is needed. A better understanding of risk factors can also broaden new avenues for identifying target groups for TB control interventions (Lönnroth & Raviglione, 2008).

1.5 OBJECTIVES

1.5.1 General objective

To investigate factors associated with TB incidence in the adult population of Ravensmead and Uitsig communities from 2003-2007.

1.5.2 Specific objectives

- To calculate the TB incidence in Ravensmead and Uitsig communities from 2003 to 2007;

- To identify factors associated with the TB incidence in Ravensmead and Uitsig communities from 2003 to 2007;

- To investigate the relationship between host and environment related factors and TB incidence in Ravensmead and Uitsig communities from 2003 to 2007.

CHAPTER 2. METHODOLOGY

2.1 STUDY DESIGN

This study is a prospective cohort study through secondary data analysis of the Lung Health Survey 2002 and electronic TB register data collected from the epidemiologic field site of Ravensmead and Uitsig in Cape Town, South Africa.

2.1.1 About the 2002 LHS

The Lung Health Survey was conducted from 1st July to 15th December 2002. Two questionnaires, the children's questionnaire, and the adults' questionnaire were used for the 2002 LHS. Eight hundred and thirty nine (15%) residential addresses were randomly selected and all individuals living at these addresses were eligible for the study.

A census of the survey population was carried out by enumerating all people living in the selected households. Where the head of the household did not consent for the household to be enrolled in the survey, a replacement household at an adjacent address was selected, first to the right, and then to the left of the household. All

participants were supervised by a trained field worker and, had a pre-coded questionnaire containing questions on demographic characteristics and earlier TB treatment completed. The aim of the 2002 Lung Health Survey was to determine the prevalence of lung diseases, including asthma and chronic obstructive pulmonary disease (Den Boon, 2007).

2.1.2 Ravensmead & Uitsig TB register database

The Ravensmead and Uitsig TB patient treatment registers are kept and maintained at two primary healthcare facilities serving these communities. The electronic TB treatment register database of Ravensmead and Uitsig patients is maintained and updated at the Desmond Tutu TB Centre.

Treatment starting date, smear and outcome results were recorded in the database. Demographic data, including race, date of birth, gender, and home address at the time of treatment commencement were also recorded in the database. The TB case definitions and treatment outcomes were classified according to WHO treatment guidelines (WHO, 2003). A TB case is classified according to whether or not the patient has previously received TB treatment. This distinction is also essential for epidemiological monitoring of the TB epidemic at regional and country level.

The following definitions are used:

- **New**. A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than one month.

- **Relapse**. A patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis again.

- **Treatment after failure.** A patient who is started on a re-treatment regimen after having failed previous treatment.

- **Treatment after default.** A patient who returns to treatment, positive bacteriologically, following interruption of treatment for two months or more.

- **Transfer in.** A patient who has been transferred from another TB register to continue treatment.

- **Chronic case. A** patient who is sputum-positive at the end of a re-treatment regimen

- **Other**. All cases that do not fit the above definitions (WHO, 2003).

2.2 STUDY POPULATION AND STUDY AREA

The study population comprised adults (persons ≥15 years) living in the Ravensmead and Uitsig communities who participated in the Lung Health Survey in 2002. The study area is an established epidemiological field site in Cape Town, South Africa. It comprises two neighbouring suburbs (Ravensmead and Uitsig) with a combined population of 36 343 (Stats SA, 2003) served by two primary healthcare clinics and a tertiary university hospital, and spans an area of 3.4 km^2. Migrant workers make up a small proportion of the population, although there is a high level of mobility both within the community and to and from neighbouring areas.

The study area is unique in South Africa because it used to have a relatively low prevalence of HIV. In the whole district in which Ravensmead and Uitsig are based the HIV prevalence among mothers attending antenatal care clinics increased from 7.9% in 2001 to 15.1% in 2004 (Shaikh *et al*., 2006). The study area has an extremely high notified disease rate of TB (761/100 000 per year for all forms of TB; 238/100 000 per year for new smear positive disease) (Verver *et al*., 2004). The WHO directly observed treatment short-course strategy (DOTS) was introduced in these two communities in 1997 (Den Boon *et al*., 2007).

2.3 SAMPLE SIZE

A total of 3 971 adults from 837 randomly-selected households within the Ravensmead and Uitsig communities were eligible to participate in the Lung Health Survey. This study consisted of the cohort of the 2002 Lung Health Survey participants (3494) who met the following criteria:

- No diagnosis of TB at the time of the survey.

- Had complete data on exposure and outcome.

2.4 DATA PROCESSING & MANAGEMENT

The 2002 LHS and electronic TB register data were double entered into a Microsoft Access databases. Inconsistencies between the two entries were checked against original data and errors were corrected. The required variables for this study were extracted into two different databases; individual and environment information from the 2002 LHS and the TB cases from the electronic TB register. These databases were transferred to STATA. The data were cleaned, checked for consistency and accuracy, and duplicates and incomplete records were dropped. The two databases were then merged into one STATA flat table.

2.5 OUTCOME VARIABLE

The outcome variable for this study was a TB case; classified as a person who started on TB treatment and had at least a positive microbiological smear or culture and was registered in the TB treatment register. The source of the outcome variable was the electronic TB register dataset.

2.6 EXPLANATORY VARIABLES

Explanatory variables available for the study were as follows (see Appendix 1 for categories and definitions):

- Host related variables: age, gender, education, occupation status, marital status, smoking status, alcohol consumption and, lung health conditions..

- Environmental-related variables: silica dust exposure, prison, cooking fuel.

- The source for risk factors/explanatory variables was the 2002 Lung Health Survey database.

2.7 FOLLOW-UP

Three thousand four hundred and ninety three (3493) initially TB-free participants were recruited, and baseline data were collected at the beginning of 2003 in the Lung Health Study in Ravensmead and Uitsig, Cape Town, South Africa. Follow-up began on 1 January 2003 and continued until 31 December 2007.

Data from the TB register were reviewed to identify new TB cases among the 3493 participants. Participants were characterised as a TB case if their demographic details matched the demographic details of the 2002 LHS and a treatment starting date had been recorded in the TB treatment register database. Non TB cases were individuals who did not have follow up-data, i.e. had no TB treatment history during the follow-up period.

2.8 RESEARCH QUESTION

What are the host and/or environmental factors associated with TB incidence in the Ravensmead and Uitsig communities of Cape Town, South Africa?

2.9 ETHICAL CONSIDERATIONS

Written informed consent was obtained from the head of each household. The study was approved by the research ethics committees of Stellenbosch University and the University of Cape Town.

For this secondary data analysis, unique identifiers were removed to ensure the confidentiality and privacy of study participants. Approval and permission to use datasets was obtained in writing from the Desmond Tutu TB Centre (DTTC) and a data transfer form was completed and signed. Due care was taken to ensure that the analysis of this study was restricted to its purpose. Ethics approval for this study was granted by both University of Witwatersrand and Stellenbosch University Research Ethics Committees.

2.10 PLANS FOR DISSEMINATION AND UTILISATION OF RESULTS

The final report will be submitted to the University of Witwatersrand's library for accessibility by researchers and policy-makers. The preliminary and final results will be presented at local and international conferences. And also be published in a peer-reviewed scientific journal. Copies of the report findings will be forwarded to the both

Provincial and National Department of Health's Tuberculosis Control Programmes as a potential tool for informing policy direction.

2.10 DATA PROCESSING METHODS AND ANALYSIS

The statistical analysis was performed using SPSS version 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA) and STATA version 8.0 for Windows.

To calculate the TB incidence for the period from 2003-2007, the number of new cases over the study period was divided by the total number of the study participants and averaged over a year. This calculation has been described elsewhere (Passannante & Ahamed, 2005). To compare incidence rates, ordinary Binomial approximations of the Normal test were used.

There were three stages in the analysis of the data. These include descriptive statistics, univariate, and multiple logistic regression analysis. These stages are described below:

Frequency and percentages were reported for categorical variables, and the Chi-squared test was used to identify factors associated with TB incidence in Ravensmead and Uitsig communities. Where the observations were too small (cell size less than 5),

Fisher's exact test was used. The subjects under investigation were defined by a set of 22 variables, including age, gender, education, marital status, smoking status, alcohol consumption and basic clinical symptoms such as a previous history of TB and other chest conditions. The selected variables are presented in Appendix 1.

Univariate and multiple logistic regression models were used to investigate factors associated with TB incidence. Estimated Odds ratios were reported with 95% confidence intervals, and the statistical significance was set at the 5% alpha level, and all tests were two sided. Maximum likelihood methods were used to estimate models, and the likelihood ratio test was used to compare different models. The researcher investigated possible effect modification using multiple logistic regression.

The final multiple logistic regression model and STATA command *"aflogit"* procedures were used to obtain estimates of the population attributable fractions (PAFs) (%) of incidence of TB associated with significant risk factors and corresponding 95% confidence intervals.

CHAPTER 3. RESULTS

3.1 BACKGROUND FACTORS

The study comprised 3493 participants, and the mean age was 38 years (SD=16.13). More than half (n=1996, 57%) of the study participants were female, with 1678 (48%) reported as married; very few were either divorced (7%) or co-habiting (4%). Approximately half (n=1766, 51%) of the study participants had a primary education. The majority of study participants were unemployed (n=2004, 58%) with (n=1537, 45%) reporting a monthly household income of less than R500 (Table 3.1).

3.2 TB INCIDENCE RATES

TB incidence for the period from 2003-2007, was calculated by the number of new cases over the study period by the total number of the study participants and averaged over a year. The average annual incidence of TB in Ravensmead and Uitsig was 632 per 100 000. TB incidence rate was higher among males (773 per 100 000) compared to females (527 per 100 000). The difference in TB incidence rate between males and females was statistically significant (p=0.02) (Figure 3.1).

Table 3-1 Distribution of socio-demographic variables for the cohort, Cape Town, South Africa, 2003-2007.

Variable and category	Frequency	%
Sex		
Male	1496	42.9
Female	1996	57.1
Total	**3492**	**100**
Age groups (years)		
15-24	969	27.8
25-34	742	21.3
35-44	732	21.0
45-54	470	13.5
>=55	568	16.3
Total	**3,481**	**100**
Marital status		
Married	1,678	48.3
Single	1,285	37.0
Widowed	143	4.1
Divorced	238	6.8
Cohabiting	134	3.9
Total	**3478**	**100**
Monthly income		
<R500	1,537	44.8
R500-R999	640	18.7
R1000-R1999	624	18.2
>=R2000	517	18.4
Total	**3431**	**100**
Employment status		
Employed	1,468	42.3
Unemployed	2,004	57.7
Total	**3472**	**100**
Education status		
None	107	3.1
Primary	1,766	50.6
Secondary	914	26.2
Started tertiary	704	20.2
Total	**3491**	**100**

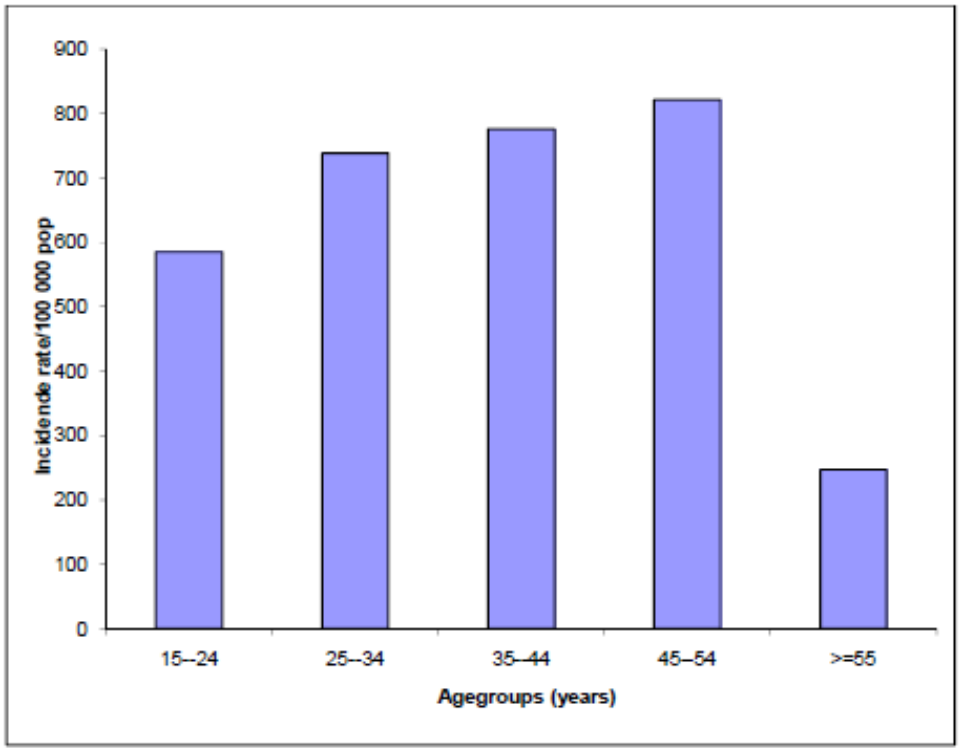


Figure 3.1 TB Incidence rates by gender in the R/U population

The TB incidence grew with increasing age until age 54 years, and then the rates fell to the lowest rate of 247 per 100 000. The rate increased from 585 per 100 000 among 15-24 age-groups to 821 per 100 000 among 45-54 age groups. There was a significant association between age and TB incidence (p=0.02) (Figure 3.2).

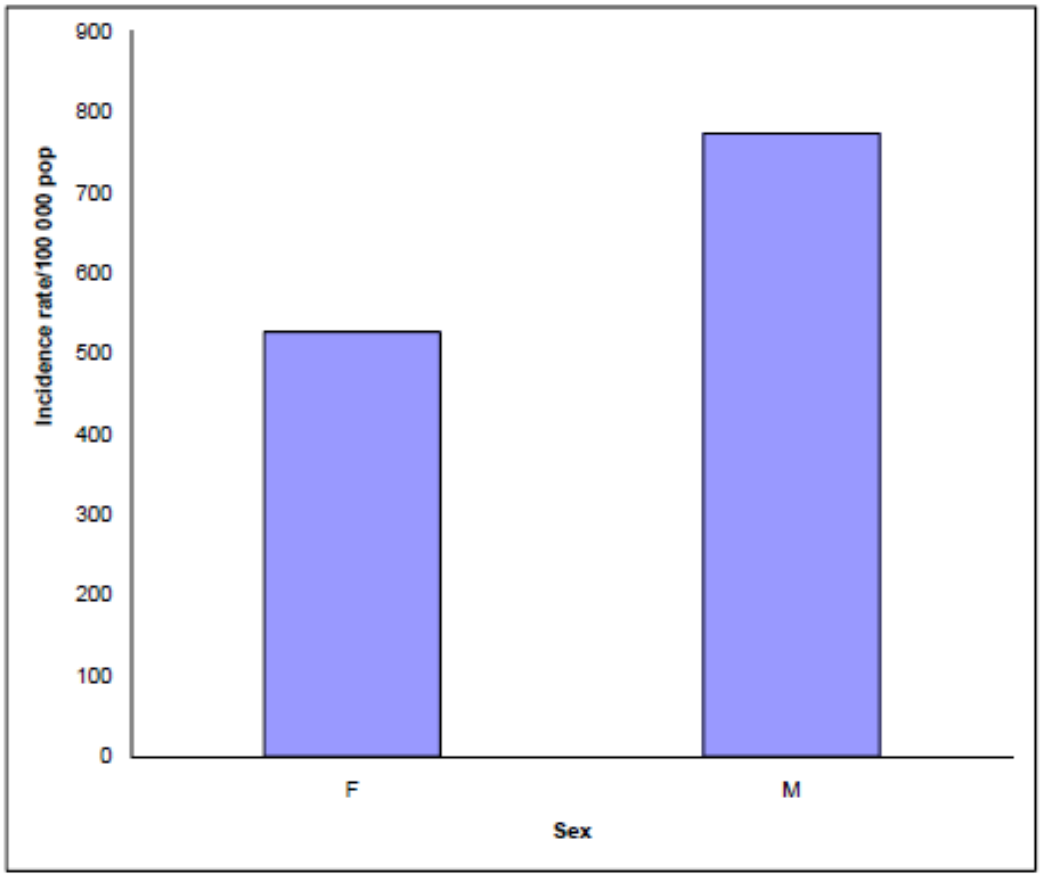


Figure 3.2 TB Incidence rates by age group in the R/U population

TB incidence also differed according to smoking and alcohol status. Smokers developed TB at a rate of 871 per 100 000 per year and non-smokers at a rate of 313 per 100 000 per year ($p<0.01$). Alcohol drinkers developed TB at a rate of 949 per 100

000 per year while non-alcoholics developed TB at a rate of 465 per 100 000 per year ($p<0.01$) (Figure 3.3).

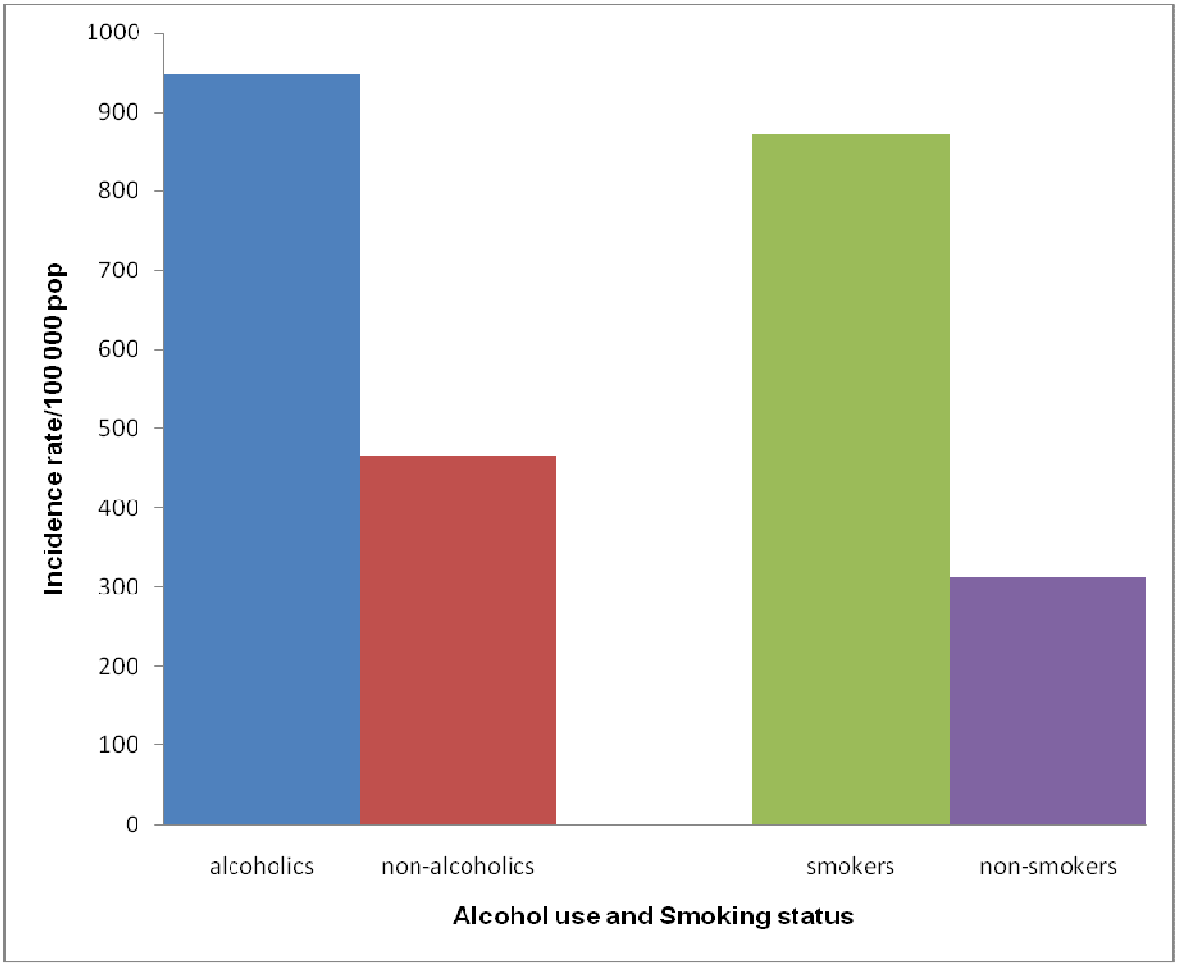


Figure 3.3 Cumulative (5 year period) TB incidence rates by alcohol/smoking status in the R/U population

3.3 RISK FACTORS

Fifty seven (3.8%) males developed TB disease compared with 52 (2.6%) of females (p=0.04). TB occurred in 86 (4.8%) smokers and 23 (2.9%) non-smokers (p<0.01). There was a higher percentage (7.6%) of TB in individuals who had spent time in prison compared with 2.7% of those who had not been in prison (p<0.01). There was a statistically significant difference in proportion for TB cases between age-groups (15-24=2.9%; 25-34=3.6%; 35-44=3.8%; 45-54=4.0%; >=55=1.2%) (p=0.04), alcohol use (Yes=4.7%, No=2.3%) (p<0.01), and previous history of chest conditions (TB=18.2%, other chest condition=2.5%) (p=0.02) (Table 3.2).

Table 3-2 Proportion of new TB cases by selected factors, Cape Town, South Africa, 2003-2007.

Variable and category	TB+ N=109 (%)	TB- N=3384 (%)	Total N	P-value (<0.05)*
Sex				
Male	57 (3.81)	440 (96.19)	497	0.04*
Female	52 (2.61)	1944 (97.39)	1996	
Age groups (years)				
15-24	28 (2.89)	941 (97.11)	969	
25-34	27 (3.64)	715 (96.36)	742	
35-44	28 (3.83)	704 (96.17)	732	0.04*
45-54	19 (4.04)	451 (95.96)	470	
>=55	7 (1.23)	561 (98.77)	568	
Previous medical history				
TB	23 (7.64)	278 (92.36)	301	<0.01*
Other chest conditions	12 (1.65)	715 (98.35)	727	
Smoking (cigarettes)				
Yes	86 (4.28)	1,922 (95.72)	2008	<0.01*
No	23 (1.55)	1,457 (98.45)	1460	
Smoking (other)				
Yes	20 (4.82)	395 (95.18)	415	<0.01*
No	89 (2.90)	2,980 (97.10)	3069	
Exposure to silica dust				
Yes	12 (4.03)	286 (95.97)	298	0.35
No	97 (3.04)	3,091 (96.96)	3188	
Exposure to other hazards				
Yes	31 (3.78)	789 (96.22)	820	0.20
No	77 (2.90)	2,579 (97.10)	2656	
Exposure to birds in a cage				
Yes	8 (1.86)	422 (98.14)	430	0.10
No	101 (3.34)	2,927 (96.66)	3028	
Alcohol use				
Yes	57 (4.66)	1,167 (95.34)	1224	<0.01*
No	52 (2.30)	2,207 (97.70)	2259	
Cooking fuel				
Electricity	100 (3.00)	3,229 (97.00)	3329	0.18
Other fuels	6 (5.22)	109 (94.78)	115	
Prison				
Yes	21 (7.64)	254 (92.36)	275	<0.01*
No	85 (2.67)	3,104 (97.33)	3189	

*Significant at p<0.05

3.4 LOGISTIC REGRESSION ANALYSIS

3.4.1 Univariate logistic regression model for risk of tuberculosis

Host related factors

The univariate analysis was done to identify significant host factors associated with TB incidence in order to inform the multivariate model. Table 3.3 presents the results (reference categories are in bold print).

In summary, the odds of developing TB were higher in males (OR= 1.48; 95% CI= 1.01-2.17). When compared with individuals 15-24 years of age, individuals of age greater or equal to 55 years had reduced odds of developing the disease (OR= 0.42; 95% CI= 0.18 - 0.97). Compared with being married, cohabiting increased the odds of developing TB (OR= 3.17; 95% CI= 1.69 - 5.97). A monthly household income of R2000 or more compared with a monthly household income of less than R500 decreased the odds of developing TB by 48% (OR= 0.52; 95% CI= 0.28 - 0.98).

The disease was associated with alcohol consumption (OR=2.07; 95% CI= 1.44 - 3.04) and cigarette smoking (OR= 2.84; 95% CI= 1.78 - 4.51) (Table 3.3). Individuals with a previous history of TB were more likely to develop TB compared to those with previous history of other chest conditions (OR= 0.20; 95% CI= 0.10 – 0.41).

Table 3-3 Logistic regression analysis for Host related factors of TB.

Variable and category	Univariate OR (95% CI)	p-value (<0.05)*	Multivariate OR (95% CI)	p-value (<0.05)*
	Host related factors			
Sex				
Female	**1**	-		
Male	1.48 (1.01 - 2.17)	0.04*		
Age group				
15-24	**1**	-		
25-34	1.27 (0.74 - 2.17)	0.39		
35-44	1.34 (0.79 - 2.28)	0.29		
45-54	1.42 (0.78 - 2.56)	0.25		
>=55	0.42 (0.18 - 0.97)	0.04*		
Marital status				
Married	**1**	-	-	-
Single	0.73 (0.47 - 1.14)	0.17	0.83 (0.48 - 1.43)	0.49
Widowed	1.07 (0.42 - 2.72)	0.89	1.07 (0.39 - 2.89)	0.10
Divorced	0.50 (0.18 - 1.41)	0.19	0.92 (0.29 - 2.93)	0.89
Cohabiting	3.17 (1.69 - 5.97)	<0.01*	2.19 (1.09 - 4.38)	0.03*
Employment status				
Yes	**1**	-		
No	1.09 (0.74 - 1.60)	0.68		
Education status				
None	**1**	-		
Primary	1.02 (0.36 - 2.84)	0.98		
Secondary	0.55 (0.18 - 1.64)	0.28		
Started tertiary	0.72 (0.24 - 2.15)	0.55		
Monthly income				
<R500	**1**	-		
R500-R999	0.74 (0.42 - 1.28)	0.28		
R1000-R1999	0.99 (0.60 - 1.63)	0.95		
>=R2000	0.52 (0.28 - 0.98)	0.04*		
Alcohol use				
No	**1**	-		
Yes	2.07 (1.41 - 3.04)	<0.01*		
Alcohol days	**1.14 (0.96 – 1.37)**	**0.14**		
Smoking (cigarettes)				
No	**1**	-	-	-
Yes	2.84 (1.78 - 4.51)	<0.01*	2.08 (1.24 - 3.46)	0.01*
Smoking (other)				
No	**1**	-		
Yes	1.67 (1.03 - 2.79)	0.04*		
Previous medical history				
TB	**1**	-		
Other chest conditions	0.20 (0.10 - 0.41)	<0.01*		

Note. CI = confidence interval; OR = odds ratio; *Significant at p<0.05

Environmental related factors

The researcher conducted a univariate analysis to identify significant environmental related risk factors associated with TB incidence in order to inform the multivariate model. Table 3.4 presents the results (reference categories are in bold print).

Individuals who had been in prison were 3.02 times more likely to develop TB disease than those who had not been in prison (OR= 3.02; 95% CI= 1.84 - 4.95). There was no significant association between developing TB and living next door to pigeons/birds in a cage, previous occupational exposure to silica dust or other hazards, or cooking fuels used in household (Table 3.4).

Table 3-4 Logistic regression analysis for Environmental related factors of TB.

Variable and category	Univariate	p-value	Multivariate	p-value
	OR (95% CI)	(<0.05)*	OR (95% CI)	(<0.05)*
	Environmental related factors			
Exposure to silica dust				
Yes	**1**	**-**		
No	0.78 (0.41 - 1.38)	0.35		
Exposure to other hazards				
Yes	**1**	**-**		
No	0.76 (0.50 - 1.16)	0.21		
Exposure birds in a cage				
Yes	**1**	**-**		
No	1.82 (0.88 - 3.77)	0.11		
Cooking Fuel				
Electricity	**1**	**-**		
Other fuels	1.78 (0.76 - 4.14)	0.18		
Prison				
No	**1**	**-**	**-**	**-**
Yes	3.02 (1.84 - 4.95)	<0.01*	1.88 (1.09 - 3.23)	0.02*

Note. CI = confidence interval; OR = odds ratio, *Significant at p<0.05

3.4.2 Multivariate logistic regression model for risk of tuberculosis host and environmental related factors

In multivariate logistic regression models, an analysis with host and environmental variables was assessed and effect modification was also investigated. In the final multivariate model, host and environmental related factors were assessed together. Reference categories used compare the odds of developing to TB (for example,

females compared with males) are underlined in bold. Only factors found to be significantly associated with development of TB ($p<0.05$) are presented in the final model.

Among host related factors, cohabiting was significantly associated with the odds of developing TB ($p=0.03$) in an adjusted model (OR= 2.09; 95% CI= 1.05 – 4.17). Smoking remained strongly associated with TB disease (OR= 2.19; 95% CI= 1.48 - 4.14). Gender, age, monthly income, alcohol use and a previous history of TB were not significantly associated with TB disease in multiple models (Table 3.3).

Among the environmental related factors, living in a household which used other fuels for cooking was not significantly associated with the odds of developing TB disease. A history of imprisonment was significantly associated with increased odds of TB disease ($p=0.02$) in the adjusted model (OR= 1.88; 95% CI= 1.09 – 3.23) (Table 3.4).

Several variables were evaluated for possible effect modification. The researcher tested the possible effect of age on marital status, alcohol use, smoking and being in prison, the possible effect of sex on alcohol use, smoking and being in prison, and also investigated the possible interaction effect between cigarette smoking and alcohol use as well as use of other drugs. The researcher investigated the interaction effect of

household income had on the type of household fuel used for cooking. No interaction between these variables was found to be statistically significant.

3.5 Population Attributable Fraction (PAF) estimates

The population attributable fraction (PAF) estimates and 95% confidence intervals for risk factors for TB are shown in Appendix 2. Cohabitation had population attributable fraction of 12.4%. The PAF for smoking was the highest (42.9%), reflecting the high prevalence of the risk factor (57.6%). Imprisonment had PAF of 9.9%. The combined PAF for these three factors accounted for 53.2% of the TB cases.

CHAPTER 4. DISCUSSION

4.1 Introduction

The main objective of this study was to determine factors associated with TB incidence in Ravensmead and Uitsig; two community areas within the Cape Metropolis in the Western Cape Province in South Africa. Data for predetermined potential risk factors were recorded at baseline from 3 493 participants recruited at the beginning of 2003. The results showed that the average annual incidence rate in Ravensmead and Uitsig was 632 per 100 000. Cohabiting, smoking and history of imprisonment were found to be significantly associated with TB incidence even after adjusting for other factors. However, gender, age and alcohol use were found not to be significantly associated with TB incidence.

4.2 Marital status/cohabiting

Marital status has long been associated with the risk of developing TB in Africa (Lienhardt *et al*., 2005). The plausible mechanism of the association is that the family

structure determines the risk of exposure and reflects the socioeconomic status of individuals (Gustafson *et al*., 2004; Lienhardt *et al*., 2005).

A multi-centre study conducted in three Western African countries found that people living without children, alone, or with adults of their own sex only, had a higher risk of developing TB than people living in households with children or/and adults of the opposite sex (Lienhardt *et al*., 2005), while in a Guinea-Bissau study found that being single and living alone was an independent risk factor for TB (Gustafson *et al*., 2004).

A Malawian study reported previous marriage (divorce, separation or widowhood) as a strong risk factor for TB (Crampin *et al*., 2004). According to the 2001 census there were more individuals living together like married partners (cohabiting) than those who were divorced, widowed or separated among coloured population in the Western Cape (Stats SA, 2003). In this study, cohabiting was associated with the risk of developing TB after adjusting for other factors. Cohabiting may be a proxy indicator of the low socioeconomic status since cohabitation is associated with less education, lower earnings, and more uncertain economic prospects (Kerr *et al*., 2006). This finding suggests that cohabiting may be increasingly prevalent in this population. The study estimated that 12.4% of incident TB cases were attributable to cohabiting.

4.3 Smoking

The most important risk factor influencing the incidence of TB identified in this study is smoking, which showed an estimated PAF of 42.9%. The specific mechanisms by which cigarette smoking increases the risk of TB are multi-factorial and probably interactive in their effects; they include structural and immunologic mechanisms (Arcavi & Benowitz, 2004). An alternative explanation is the site-specific effect of an airborne insult (Bates *et al*., 2007).

These findings were consistent with those reported in two studies carried out in West Africa and in South Africa. A study in West Africa showed the risk of TB was two times higher in current smokers compared with non-smokers (Lienhardt *et al*., 2005). A study carried out in South Africa found that cigarette smoking as an independent risk factor for TB (Harling *et al*., 2008). Smoking has also been previously reported as a strong risk factor for TB infection in this population (Den Boon *et al*., 2005). A recent study in Taiwan found that tobacco smoking was associated with a two-fold increased risk of active TB. Authors reported that 17% of incident TB cases in this population were attributable to smoking (Lin *et al*., 2009). Western Cape province has the highest rates of smoking especially among the Coloured population (SADHS, 2007; SADHS, 2003). Therefore smoking is not only important as a risk factor for TB but its prevalence was also very high in this population.

4.4 Imprisonment

Evidence has shown that a history of imprisonment is associated with a risk of developing TB (Tekkel *et al*., 2002; Lobacheva *et al*., 2007). The plausibility for this association is that imprisonment increases the risk of exposure to tubercle bacilli since prisons are usually overcrowded and living in the poor ventilated rooms, thus facilitating the transmission of tubercle bacilli.

This study found that being in prison was strongly associated with increased odds of developing TB. A history of imprisonment accounted for 9.9% of incident TB cases in this population. Similar findings have been reported elsewhere; a study carried out in Russia has shown that a prison or detention history was an independent risk for TB. Authors reported a population attributable risks of 0.8% and 2% for having been in prison or a pre-trial detention centre, respectively (Coker *et al*., 2006). A study in Estonia had previously reported that TB risk was higher for those who had been in prison (Tekkel *et al*., 2002).

In South Africa, prisons are known to be overcrowded, hence an increased likelihood of coming into contact with infected persons. The total capacity of South Africa's prisons stood at 114 821 prisoners, while the actual number of inmates stood at 184 806, with the occupation rate of 161% in 2004 (Steinberg, 2005). .

4.5 Gender

The male gender has been reported as an independent risk factor in other studies in sub-Saharan Africa (Gustafson *et al*., 2004). According to literature, more men than women are diagnosed with TB worldwide (Rieder, 1999; Uplekar *et al*., 1999; Uplekar *et al*., 2001).

This gender discrepancy in TB rates has been attributed to differential exposure to risk behaviours associated with TB. While it is widely acknowledged that there has been an increase in women engaging in risk behaviours such as alcohol, substance abuse and incarceration, such behaviours are still predominantly seen in men (Watkins & Plant, 2006; EUROWHO, 2007). Other contributing factors include differential access to care, health-seeking behaviour and stigmatisation (Uplekar *et al*., 2001).

This study, gender was not important risk factor for active TB disease after adjusting for others factors including smoking. The lack of the association between being a male and TB in this study may be partly explained by the following; the descriptive data analysis showed no difference in smoking between males and females in this population, according to the South African Demographic and Health Survey (SADHS), the health service utilisation by adults is higher in females compared to males and it has not changed much between the 1998 and 2003 surveys (SADHS, 2003). This suggests

that the lack of association may be due to the absence of factors contributing to gender differentials in this population.

These findings are further supported by previous studies conducted in South Africa that found no association of TB with the male gender. Harling *et al*. reported that being female was associated with a 31% reduced odds of recent TB after adjusting for individual and household level variables; however this association was not statistically significant (Harling *et al*., 2008).

4.6 Age and HIV

The risk of developing TB is age dependent (Vynnycky and Fine, 2000). This is partially attributed to ccumulative prevalence of TB infection (Rieder, 1999). Other plausible hypotheses include that the estimated lifetime risks of developing TB were higher for the elderly and adults (Vynnycky & Fine, 1997, 2000).

Chaimowicz suggested that the contributing factor was the high frequency of reactivation of TB in older people, due to an interaction between age-associated immune dysregulation and the high proportion of individuals with latent infections (Chaimowicz, 2001). There is a reported shift to younger adults in African and Asians

countries; this shift has been attributed to the increase in HIV prevalence in these countries (WHO, 2007).

This study has shown no association between age and TB incidence. An increasing age has been reported as an independent risk factor for TB incidence. A Malawian study reported the lower risk of TB in age groups under the age of 30 years compared with adults and the elderly (Glynn *et al*., 2000). An increasing age was reported as a strong risk factor for TB incidence in Guinea-Bissau study (Gustafson *et al*., 2004).

A study in Ottawa Canada found the highest age-specific incidence in the elderly population (Kim *et al*., 2008). This suggests that age is not a predictor for the development of TB in this study population and this may also partially suggest that the HIV prevalence is low in this population. HIV infection may be the most important predetermining factor, thus the trends in younger age.

4.7 Alcohol

Alcohol use is a recognised risk factor for TB. Possible causal pathways include specific social mixing patterns among people with alcohol use disorders, leading to a higher risk of infection (Lönnroth *et al*., 2008) or a weakened immune system leading to

a higher risk of break down from infection to TB disease (Mason *et al*., 2004; Lönnroth *et al*., 2008).

Previous studies have reported alcohol use as a strong risk factor for TB in South Africa. An earlier study carried out on the Mamre population in South Africa showed that alcohol use was a strongly associated with TB (Coetzee *et al*., 1988). Recently, Harling and colleagues (2008) reported alcohol use as an independent risk factor for TB in South Africa.

This study's results show that alcohol use was not statistically associated with TB incidence after adjusting for others factors including smoking. These results are supported by similar findings shown elsewhere. In West Africa, Lienhardt *et al*. (2005) reported similar findings where they showed that alcohol intake was not associated with TB after adjusting for other factors. A Gambian study showed evidence that alcohol use was not a strong predictor of TB disease (Hill *et al*., 2006). A study in India showed no effect of alcohol consumption on TB (Shetty *et al*., 2006).

The weak association may be attributed to the fact that alcohol use is associated with smoking. This hypothesis has been supported by the recent evidence from a study conducted in India. The authors have shown that the effects of smoking, after

adjustment for drinking, were stronger than those of drinking after adjustment for smoking (Gajalakshmi & Peto, 2009).

Cooking smoke has been shown to increase the risk of TB (Mishra *et al*., 1999). Cooking smoke might increase the risk of tuberculosis by reducing resistance to the initial infection, by promoting the development of active tuberculosis in people who are already infected, or both (Mishra *et al*., 1999). A recent case control study in India found an association between biomass smoke and pulmonary tuberculosis. The authors reported that 36% of cases were attributable to biomass fuel usage (Kolappan & Subramani, 2009). A study in Mexico showed an association between cooking with traditional wood stoves and tuberculosis (Pérez-Padilla *et al*., 2001).

In this study household fuel for cooking was not independently associated with TB. These findings are consistent with evidence from previous studies; a Malawian study showed no effect of cooking smoke on TB (Crampin *et al*., 2004). In India, Shetty and colleagues (2006) reported that the type of cooking fuel was not an independent risk factor for TB. The lack of association with cooking fuel in this study may also partly be due to few households using biomass fuels.

4.8 HIV

HIV infection is the most potent risk factor for TB risk factors given that infection with tubercle bacilli has already occurred (Corbett *et al*., 2003). This is because co-infection with HIV and tubercle bacilli increases the risk of rapid progression from latent to active TB (Bacaër *et al*., 2008). The spatial and temporal variation in TB incidence is strongly associated with the prevalence of HIV infection (Corbett *et al*., 2003).

While TB remains one of the most common manifestations of HIV infection in South Africa, its impact is surprisingly unapparent on TB cases (SADHS, 2003). For example, KwaZulu-Natal with the highest HIV seroprevalence rate nationally, has the lowest TB prevalence (SADHS, 2003). Western Cape province has the highest TB incidence rate in the country while it also has the lowest antenatal HIV prevalence rate in South Africa (SADHS, 2003; National Department of Health, 2008; WHO, 2009). In the Western Cape, the antenatal HIV prevalence rate slightly decreased during the study period from 13.1% in 2003 to 12.6% in 2007 (National Department of Health, 2004; National Department of Health, 2008).

In this study, HIV infection was not measured among the study participants, therefore its impact on TB incidence could not be assessed, especially age-specific incidence rates.

In the absence of this explanatory variable, the study could not assess the effect HIV infection on other factors which were investigated.

However, the study area has been reported to have a relatively low proportion of the individuals of HIV-infected (Verver *et al*., 2004). A very low HIV prevalence of 6% among new TB cases has been reported in Ravensmead and Uitsig (Den Boon, 2007). This supports the argument that increasing TB incidence rates observed in the Ravensmead and Uitsig population may be strongly associated with other well established and more prevalent TB risk factors other than HIV infection.

4.9 Limitations of the study

There are several limitations of our study. One limitation of this study is that the 2002 Lung Health Survey was a cross-sectional study and therefore the information on the explanatory variables was collected once.

Another limitation is that the cohort was passively followed-up and it was assumed that change in explanatory variables over time was minimal. Therefore, various information biases were also likely. Considering that exposure levels were self-reported, the reporting of some variables may be inaccurate. Only variables present in the dataset were analysed.

The important information on HIV status of participants and other known risk factors such as crowding was not captured by the 2002 LHS, therefore such variables could not be included in the analysis. This raises issues of potential uncontrolled confounding which may affect the results of this study. TB cases were extracted from paper-based TB Treatment Register, the ascertaining or diagnosis may be missing and in some cases might no have been categorised as new cases.

Although migrant workers make up a small proportion of the Ravensmead and Uitsig population, there is a high level of mobility both within the community and to and from neighbouring areas. It is therefore possible that some of the cases may be missed. There is no active case finding in the communities. The cases are registered when they present themselves in the clinics. Therefore there is a possibility of an underestimation of the incidence rate. The quality of datasets depends on the completeness of data. Since the paper-based TB treatment register is not properly filled in by nurses and doctors, some of the variables in the TB dataset were not completed.

CHAPTER 5. CONCLUSION AND RECOMMENDATIONS

5.1 CONCLUSION

Examining both host and environmental related factors is important in understanding the epidemiology of TB. This study investigated both host and environmental factors associated with TB disease in a population with a high TB incidence.

Cohabiting, cigarette smoking and a history of imprisonment were strongly associated with an increased risk of developing TB in this population. The combined population attributable fraction for these three factors accounted for more than half of the TB cases.

This variation in factors associated with the risk of TB may be partly explained by the prevalence of the different risk factors in the population. Therefore it has been suggested that a better understanding of TB risk factors may help unearth why TB risk varies across countries, within countries, and within communities (Lönnroth & Raviglione, 2008). Interventions focusing on reducing the prevalence of the TB risk factors will help reduce TB incidence (Lönnroth *et al*., 2009).

This study presents evidence on the association between host and environmental related factors and the risk of tuberculosis disease. These findings highlight the importance of including environmental related factors in a study, particularly emerging characteristics such as history of imprisonment.

Despite the limitations, this study suggests that both host and environmental related factors may play an important role in determining an individual's risk of developing TB.

5.2 RECOMMENDATIONS

The evidence presented in this study suggests that a greater emphasis on social and economic policies focusing on assisting the poor and marginalised population is needed in the discourse of tuberculosis control.

Cigarette smoking was the single most important factor that increases the likelihood of developing TB in this population, and the prevalence of smoking is high in this population. TB control programmes in this community should incorporate the recommendations contained in the WHO's Practical Approach to Lung Health (PAL), issued in 2008 (WHO, 2008b; IUATLD & WHO, 2007).

This study confirms that a history of imprisonment is associated with a significant increase in the risk of developing TB. There is a need to strengthen the implementation of two very important general measures for the TB control in prisons. These include decreasing over-crowding and also improving nutrition and hygiene as well as improving access to health services. Active case finding among prisoners and periodically among symptomatic and close contact of the index cases is also recommended.

Further research on risk factors for TB is needed to address the limitations of this study. TB prevention strategies need to focus on interventions which reduce or limit the impact of TB risk.

REFERENCES

Alland, D., Kalkut, G.E., Moss, A.R., McAdam, R.A., Hahn, J.A., Bosworth, W. 1994. *Transmission of tuberculosis in New York City: an analysis by DNA fingerprinting and conventional epidemiologic methods*. N Engl J Med; 330:1710–1716.

Anderson, B.A., Phillips, H.E. 2006. *Adult mortality (age 15-64) based on death notification data in South Africa: 1997-2004.* Report No. 03-09-05. Pretoria: Statistics South Africa.

Arcavi, L., Benowitz, N.L. 2004. *Cigarette smoking and infection.* Arch Intern Med. Nov 8;164 (20):2206-16.

Bacaër, N., Ouifki R., Pretorius C, Wood R, Williams B. 2008. *Modeling the joint epidemics of TB and HIV in a South African township.* J. Math. Biol. 57:557–593.

Barnes, .PF., Yang, Z., Preston-Martin, S., Pogoda, J.M., Jones, B.E., Otaya, M.. 1997. *Patterns of tuberculosis transmission in central Los Angeles.* JAMA 1997; 278: 1159–1163.

Bates, M.N., Khalakdina, A.; Pai, M., Chang, L., Lessa, F., Smith, K.R. 2007. *Risk of Tuberculosis from exposure to tobacco smoke: A systematic review and meta-analysis.* Arch Intern Med. 167:335-342.

Buskin, S.E., Gale, J.L., Weiss, N.S., Nolan C.M. 1994. *Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990.* Am J Public Health. Nov. 84(11):1750-6.

Cain, K.P., Benoit, S.R., Winston, C.A., MacKenzie, W.R. 2008. *Tuberculosis among foreign-born persons in the United States*. JAMA, 300(4):405-412.

CDC. 1992. *Tuberculosis morbidity – United States 1992.* MMWR1993;42:6967. Center for Disease Control and Prevention. [Online] Available at: http://www.cdc.gov/MMWR/preview/mmwrhtml/00021813.html.

Chaimowicz, F. 2001. *Age transition of tuberculosis incidence and mortality in Brazil*. Rev Saúde Pública, 35(1):81-7 81.

Chaisson, R.E., Martinson, N.A. 2008. *Tuberculosis in Africa – Combating an HIV-Driven Crisis*. N Engl J Med. 358(11):1089-1092.

Churchill, D., Hannan, M., Miller, R., Williams, I., Nelson, M., Kupek, E. 2000. *HIV associated culture proved tuberculosis has increased in north central* London from 1990 to 1996. Sex Transm Inf. 76:43–45.

Coetzee, N., Yach, D., Joubert, G. 1998. *Crowding and alcohol abuse as risk factors for tuberculosis in the Mamre population. Results of a case-control study*. S Afr Med. 74:352–54.

Coker, R., McKeem M., Atunm R., Dimitrovam B,, Dodonovam E,, Kuznetsov, S. 2006. *Risk factors for pulmonary tuberculosis in Russia: a case-control study*. BMJ. 322:85-87.

Corbett, E.L., Churchyard, G.J., Clayton, T., Herselman, P., Williams, B., Hayes, R. 1999. *Risk factors for pulmonary mycobacterial disease in South African gold miners: a case-control study.* Am J Respir Crit Care Med. 159:94–99.

Corbett, E.L., Churchyard, G.J., Clayton, T.C., Williams, B.G., Mulder, D., Hayes, R.J. 2000. *HIV infection and silicosis: the impact of two potent risk factors on the incidence of mycobacterial disease in South African miners*. AIDS; 14:2759-2768.

Corbett, E.L., Watt, C.J., Walker, N., Maher, D., Williams B.G., Raviglione, M.C. 2003. *The growing burden of tuberculosis: global trends and interactions with HIV epidemic*. Arch Int Med. 163: 1009–1021.

Crampin, A.C., Floyd, S., Ngwira, B.M.M., Mwinuka, V.K.J.N., Mwaungulu, K., Branson, P.E.M. 2008. *Assessment and evaluation of contact as a risk factor for tuberculosis in rural Africa*. Int J Tuberc Lung Dis. 12(6): 612–618.

Crampin, A.C., Glynn, J.R., Floyd, S., Malema, S.S., Mwinuka, V.K., Ngwira, B.M.M. 2004. *Tuberculosis and gender: gender: exploring the patterns in a case control study in Malawi.* Int J Tuberc Lung Dis. 8(2):194–203.

Crimi, P., Macrina, G., Saettone, F., Turello, W., Ramorino, P., Gasparini, R. 2005. *Epidemiological trend in tuberculosis in the Italian region of Liguria: Impact of immigration and AIDS.* Eur J Public Health, 15(4):339–342.

Den Boon, S., van Lill, S.W.P., Borgdorff, M.W., Enarson, D.A., Verver, S., Bateman, E.D. 2007. *High prevalence of tuberculosis in previously treated patients, Cape Town, South Africa*. *Emer Infect Dis*, 13: 1189–1194.

Den Boon, S., Van Lill, S.W.P., Borgdorff M.W., Verver, S., Bateman, E.D., Lombard, C.J. 2005. *Association between smoking and tuberculosis infection: a population survey in a high tuberculosis incidence area*. Thorax; 60: 555-557.

Den Boon, S. 2007. *Tuberculosis epidemiology in Cape Town*, South Africa. PhD Thesis, University of Amsterdam.

DeRiemer, K., Kawamura, L.M., Hopewell, P.C., Daley, C.L. 2007. *Quantitative Impact of Human Immunodeficiency Virus Infection on Tuberculosis Dynamics.* Am J Respir Crit Care Med., 176:936–944.

De Vries, G., Van Hest, R.A. 2005. *From contact investigation to tuberculosis screening of drug addicts and homeless persons in Rotterdam*. Eur J Public Health, 17:1101–262.

Dye, C., Watt, C.J., Bleed, D.M,. Hosseini, S.M., Raviglione, M.C. 2005. *Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally*. JAMA; 293: 2767–75.

El Sahly, H.M., Adams, G.J., Soini, H., Teeter, L., Musser, J.M., Graviss, E.A. 2001. *Epidemiologic differences between United States- and foreign born tuberculosis patients in Houston, Texas.* J Infect Dis. 183:461–468.

EUROWHO. 2007. *Tuberculosis and gender.* EUR/TB/FS05. 3 September 2007.

Frieden, T.R., Sterling, T.R., Munsiff, S.S., Watt, C.J., Dye, C. 2003. *Tuberculosis*. Lancet; 362: 887–99.

Gajalakshmi, V., Peto, R. 2009. *Smoking, drinking and incident tuberculosis in rural India: population-based case-control study*. Int J of Epidem. 2009;1–8.

Glynn, J.R., Crampin, A.C., Ngwira, B.M., Mwaungulu, F.D., Mwafulirwa, D.T., Floyd, S. 2004. *Trends in tuberculosis and the influence of HIV infection in northern Malawi, 1988-2001.* AIDS. 18(10):1459-63.

Glynn,, J.R., Warndorff D.K., Malema, S.S., Mwinuka, V., Pőnnighaus, J.M., Crampin, A.C. 2000. *Tuberculosis: associations with HIV and socioeconomic status in rural Malawi.* Trans Royal Soc Trop Med Hyg. 94:500-503.

Gustafson, P., Gomes, V.F., Vieira, C.S., Rabna, P., Seng, R., Johansson, P. 2004. *Tuberculosis in Bissau: incidence and risk factors in an urban community in sub-Saharan Africa*. Int J of Epidem. 33:163–172.

Harling, G., Ehrlich, R., Myer. L. 2008. *The social epidemiology of tuberculosis in South Africa: A multilevel analysis*. Social Science & Medicine, 66: 492–505.

Hill, P.C., Jackson-Sillah, D., Donkor, S.A., Out, J., Adegbola, R.A., Lienhardt, C. 2006. *Risk factors for pulmonary tuberculosis: a clinic-based case control study in The Gambia*. BMC Public Health, 6:156-73.

Hill P.C., Sillah, J.S., Donkor, S., Out, J., Adegbola, R.A., Lienhardt, C. 2003. *Risk factors for tuberculosis infection in sub-Saharan Africa: a contact study in The Gambia.* Am J Respir Crit Care Med; 168:448–55.

Houston, S., Ray, S., Mahari, M., Neill, P., Legg, W., Latif, A.S. 1994. *The association of tuberculosis and HIV infection in Harare, Zimbabwe*. Tuber Lung Dis., 75(3):220-6.

Inigo, J., Arce, A., Rodrı´guez, E., Garcıa de Viedma, D., Palenque, E., Ruiz Serrano, M.J. 2006. *Tuberculosis trends in Madrid (1994–2003): impact of immigration and HIV infection*. Int. J. Tuberc. Lung Dis, 10:550–553.

IUATLD, & WHO. 2007. *A WHO/The Union monograph on TB and tobacco control – Joining efforts to control two related global epidemics*. WHO/HTM/TB/2007.390. Geneva: World Health Organization.

Jeon, C.Y., Murray, M.B. 2008. *Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies*. PLoS Med ;5(7): e152.

Kleinschmidt, I., Churchyard, G.J. 1997. *Variation in tuberculosis incidence rates in subgroups of South African gold miners*. Occup. Environ. Med; 54:636–641.

Kerr, D., Moyser, M., Beaujot, R. 2006. *Marriage and Cohabitation: Demographic and Socioeconomic Differences in Quebec and Canada.* Canadian Studies in Population, Vol. 33.1, pp. 83-117 83.

Kim, J., Langevin, M., Wylie, E.L., McCarthy, A.E. 2008. *The epidemiology of tuberculosis in Ottawa, Canada, 1995–2004.* Int J Tuberc Lung Dis, 12(10):1128–1133.

Kolappan, C., Subramani, R. 2009. *Association between biomass fuel and pulmonary tuberculosis: a nested case-control study*. Thorax. Aug; 64(8): 705-8.

Kolappan, C., Gopi, P.G., Subramani, R., Narayanan, P.R. 2007. *Selected biological and behavioral risk factors associated with pulmonary tuberculosis.* Int J Tuberc Lung Dis; 11(9):999–1003.

Lienhardt, C., Fielding, K., Sillah, J.S., Bah, B., Gustafson, P., Warndorff, D. 2005. *Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa.* Int J of Epidemiol; 34:914–923.

Lienhardt, C. 2001. *From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis*. Epidemiol Rev, 23:288–301.

Lienhardt, C.. Ogden, J.A. 2004. *Tuberculosis control in resource-poor countries: have we reached the limits of the universal paradigm?* Trop Med Int Health, 9(7):833–841.

Lin, H., Ezzati, M., Murray, M. 2007. *Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis*. PLoS Med, 4(1):e20.

Lin, H., Ezzati, M., Chang, H., Murray, M. 2009. *Association between Tobacco Smoking and Active Tuberculosis in Taiwan: Prospective Cohort Study*. Am J Respir Crit Care Med, 180: 475–480.

Long, R., Sutherland, K., Kunimoto, D., Cowie, R., Manfreda, J. 2002. *The epidemiology of tuberculosis among foreign-born persons in Alberta, Canada, 1989–1998: identification of high risk groups*. Int J Tuberc Lung Dis, 6(7):615–621.

Lobacheva, T., Asikainen, T., Giesecke, J. 2007. *Risk factors for developing tuberculosis in remand prisons in St. Petersburg, Russia - a case-control study*. Eur J Epidemiol, 22(2):121-7. Epub 2007 Mar 3.

Lönnroth, K., Raviglione, M.C. 2008. *Global Epidemiology of Tuberculosis: Prospects for Control*. Semin Respir Crit Care Med, 29:481–491.

Lönnroth, K., Jaramillo, E., Williams, B.G., Dye, C., Raviglione, M. 2009. *Drivers of tuberculosis epidemics: The role of risk factors and social determinants*. Social Science & Medicine 68, 2240–2246.

Lönnroth, K., Williams, B.G., Stadlin, S., Jaramillo, E., Dye, C. 2008. *Alcohol use as a risk factor for tuberculosis – a systematic review*. BMC Public Health, 8:289.

Mason, C.M., Dobard, E., Zhang, P., Nelson, S. 2004. *Alcohol Exacerbates Murine Pulmonary Tuberculosis.* Infect Immun, 72, (5): 2556–2563.

McKenna, M.T., McCray, E., Onorato, I. 1995. *The epidemiology of tuberculosis among foreign-born persons in the United States,* 1986 to 1993. N Engl J Med; 332:1071-6.

Mishra, V.K., Retherford, R.D., Smith, KR. 1999. *Biomass cooking fuels and prevalence of tuberculosis in India*. Int J Infect Dis, 3: 119–129.

National Department of Health. 2004. *The National HIV and Syphilis Sero-prevalence Survey 2003.* Pretoria: Department of Health.

National Department of Health. 2008. *The National HIV and Syphilis Sero-prevalence Survey 2007.* Pretoria: Department of Health.

Oeltmann, J.E., Kammerer, J.S.; Pevzner, E.S., Moonan, P.K. 2009. *Tuberculosis and Substance Abuse in the United States, 1997-2006.* Arch Intern Med, 169(2):189-197.

Orege, P.A., Fine, P.E., Lucas. S.B., Obura, M., Okelo, C., Okuku, P. 1993. *A case control study on human immunodeficiency virus-1 (HIV-1) infection as a risk factor for tuberculosis and leprosy in western Kenya.* Tuber Lung Dis.;74(6):377-81.

Passannante M, Ahamed N. 2005. *Basic Epidemiology for Tuberculosis Programme Staff*. New Jersey Medical School National Tuberculosis Center. 2005.

Pérez-Padilla, R., Pérez-Guzmán, C., Báez-Saldaña, R., Torres-Cruz, A. 2001 *Cooking with biomass stoves and tuberculosis: a case control study.* Int J Tuberc Lung Dis, 5(5):441–447.

Raviglione, M.C. 2003. *The TB epidemic from 1992 to 2002.* Tuberculosis, 83:4-14.

Rieder, H.L. 1999. *Epidemiologic Basis of Tuberculosis Control.* 1st Ed. Paris: International Union Against Tuberculosis and Lung Disease.

Romaszko, J., Bucinski, A., Wasinski, R., Roslan, A., Bednarski, K. 2008. *Incidence and risk factors for pulmonary tuberculosis among the poor in the northern region of Poland*. Int J Tuberc Lung Dis, 12(4):430–435.

Rose, A.M.C., Watson, J.M., Graham, C., Nunn, A.J., Drobniewski, F., Ormerod, L.P. 2001. *Tuberculosis at the end of the 20th century in England and Wales: results of a national survey in 1998*. Thorax; 56;173-179.

SADHS. 2003. Department of Health, South African Medical Research Council, Measure DHS+. *South Africa Demographic and Health Survey 1998*, Full Report. Pretoria: Department of Health.

SADHS. 2007. Department of Health, Medical Research Council, OrcMacro. *South Africa Demographic and Health Survey 2003.* Pretoria: Department of Health.

Schoeman, J.H., Westaway, M.S., Neethling, A. 1991. *The relationship between socioeconomic factors and pulmonary tuberculosis.* Int J Epidemiol, 20(2):435-40.

Shaikh, N., Abdullah, F., Lombard, C.J., Smit, L., Bradshaw, D., Makubalo, L. 2006. *Masking through averages – intra-provincial heterogeneity in HIV prevalence within the Western Cape*. S Afr Med J, 96: 539-543.

Shetty, N., Shemko, M., Vaz, M., D'Souza, G. 2006. *An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study*. Int J Tuberc Lung Dis, 10(1):80–86.

Small, P.M., Hopewell, P.C., Singh, S.P., Paz, A., Parsonnet, J., Ruston, D.C. 1994. *The epidemiology of tuberculosis in San Francisco: a population-based study using conventional and molecular methods*. N Engl J Med, 330:1703–9.

Stats SA. 2003. *Census 2001.* Pretoria: Statistics South Africa.

Stats SA. 2006. *Mortality and causes of death in South Africa, 2003 and 2004: Findings from death notification*. Report No. 03-09-03. Pretoria: Statistics South Africa.

Steinberg. J. 2005. *Prison Overcrowding and the Constitutional Right to Adequate Accommodation in South Africa.* Centre for the Study of Violence and Reconciliation, January 2005. [Online] Available at; http://www.csvr.org.za/docs/correctional/prisoncovercrowding.pdf.

Stevenson, C.R., Forouh,i N.G., Roglic, G., Williams, B.G., Lauer, J.A., Dye, C. 2007. *Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence.* BMC Public Health, 7:234.

Stop TB. 2002. *An expanded framework for effective tuberculosis control*. Int J Tuberc Lung Dis, 6:378-88.

Story, A. 2004. *Tuberculosis – A general introduction*. The Pharmaceutical Journal, 273: 289-291. [Online] Available at: www.pjonline.com.

Tekkel, M., Rahu, M., Lioit, H-M., Baburin, A. 2002. *Risk factors for pulmonary tuberculosis in Estonia.* Int J Tuberc Lung Dis, 6:887-94.

Uplekar, M., Rangan, S., Ogden, J. 1999. *Gender and tuberculosis control: towards a strategy for research and action,* WHO/TB/2000.280. Geneva: World Health Organization.

Uplekar, M.W., Rangan, S., Weiss, M.G., Ogden, J., Borgdorff, M.W,, Hudelson, P. 2001. *Attention to gender issues in tuberculosis control.* Int J Tuberc Lung Dis, 5: 220–224.

Van Cleeff, M.R., Chum, H.J. 1995. *The proportion of tuberculosis cases in Tanzania attributable to human immunodeficiency virus.* Int J Epidemiol, 24(3):637-42.

Van den Broek, J., Borgdorff, M.W., Pakker, N.G., Chum, H.J., Klokke, A.H., Senkoro, K.P. 1993.. *HIV-1 infection as a risk factor for the development of tuberculosis: a case-control study in Tanzania.* Int J Epidemiol., 22(6):1159-65.

Vendramini, S.H.F., Santos, M.L.S.G., Gazetta, C.E., Chiaravalloti-Neto, F., Ruffino-Netto, A., Villa, T.C.S. 2006. *Tuberculosis risks and socioeconomic level: a case study*

of a city in the Brazilian south-east, 1998–2004. Int J Tuberc Lung Dis, 10(11):1231–1235.

Verver, S., Warren, R.M., Munch, Z., Vynnycky, E., van Helden, P.D., Richardson, M. 2004. *Transmission of tuberculosis in a high incidence urban community in South Africa*. Int J Epidemiol; 33:351–357.

Volmink, J., Garner, P. 2007. *Directly observed therapy for treating tuberculosis.* Cochrane Database Syst Rev (4):CD003343.

Vynnycky, E., Fine, P.E. 2000. *Lifetime Risks, Incubation Period, and Serial Interval of Tuberculosis*. Am J Epidemiol, 152:247–63.

Vynnycky, E., Fine, P.E. 1997. *The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of re-infection*. Epidemiol Infect., Oct; 119(2):183-201.

Ward, H.A. 2004. *Risk Factors in the Progression from Tuberculosis Infection to Disease*, MSc Thesis, University of Saskatchewan.

Watkins, R.E., Plant, A.J. 2006. *Does smoking explain sex differences in the global tuberculosis epidemic?* Epidemiol Infect, 134: 333–339.

Weis, S.E., Pogoda, J.M., Yang, Z.M., Cave, D., Wallace, C., Kelley, M. 2002. *Transmission Dynamics of Tuberculosis in Tarrant County, Texas.* Am J Respir Crit Care Med, 166:36–42.

WHO. 2008a. *Global tuberculosis control: surveillance, planning, financing*. WHO report. Geneva, World Health Organization (WHO/HTM/TB/2008.393).

WHO. 2007. *Global tuberculosis control: surveillance, planning, financing*. WHO report. Geneva, World Health Organization (WHO/HTM/TB/2007.376).

WHO. 2009. *Global tuberculosis control: surveillance, planning, financing*. WHO report. Geneva, World Health Organization (WHO/HTM/TB/2009.393).

WHO. 2001. *Health Research Methodology: A guide for training in research methods*. Second Edition. Geneva: World Health Organization.

WHO. 2005. *TB EMERGENCY DECLARATION.* issued by WHO Regional Office for Africa. [Online] Available at: http://www.who.int/tb/features_archive/tb_emergency_declaration/en/.

WHO. 2008b. *Practical Approach to Lung Health: Manual on initiating PAL implementation.* Geneva: WHO. http://whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.410_eng.pdf

WHO. 2003. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. (WHO/CDS/TB/2003.313).Geneva: World Health Organization.

APPENDICES

APPENDIX 1. Variables of interest and their definitions

Variable	Categories	Definition
Host related factors		
Sex	1=Female, 2=Male	Sex
Age groups	1="15-24",2="25-34",3="35-44",4="45-54",5=">=55"	Age groups
Marital status	1=Married, 2=Single, 3=Widowed, 4=Divorced, 5=Cohabiting	Marital status
Employment	1=Yes, 2=No	Employment status
Education status	1=None, 2=Primary, 3=Secondary, 4=Started tertiary	Level of education
Monthly income	1=<R500,2=R500-R999, 3=R1000-R1999,4=R2000-R4999,5=>=R5000	Usual monthly income
Previous medical history	1=TB 2=Other chest conditions	Previous history of chest condition
Smoking (cigarettes)	1=Yes, 2=No	Smoked cigarettes for a year or longer
Smoking (Other)	1=Yes, 2=No	Smoked anything other than tobacco
Alcohol use	1=Yes, 2=No	Drink alcohol
Alcohol days		Number of alcohol drinking days (Monday to Sunday)?
Environmental related factors		
Exposure to silica dust	1=Yes, 2=No	Previous occupational exposure to silica dust
Exposure to other hazards	1=Yes, 2=No	Previous occupational exposure to other dusts, gases, strong smells, chemicals, fumes
Exposure to birds in a cage	1=Yes, 2=No	Live next to pigeons/birds in a cage (not chickens)?
Cooking fuel	1= Electricity, 2=Other fuels	Fuels mostly used for cooking in the dwelling
Prison	1=Yes, 2=No	Spent time in prison

APPENDIX 2. Population Attributable Fraction (PAF) Estimates

Variable	Multivariate logistic OR (95% CI)	Population attributable fractions (95% CI)*
Cohabiting	2.19 (1.09 - 4.38)	0.124 (-0.02 - 0.25)
Smoking	2.08 (1.24 - 3.46)	0.429 (0.15 - 0.60)
Prison	1.88 (1.09 - 3.23)	0.099 (0.01 - 0.18)
Total	-	0.532 (0.30 - 0.69)

Note. CI = confidence interval; OR = odds ratio.

* CI calculated on log (1-AF) scale

APPENDIX 3. Ethics Clearance certificates

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ncayiyana

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080971**
PROJECT	Risk Factors Associated with TB Incidence in an Adult Population from Poorly Resourced South African Urban Communities with High TB Prevalence
INVESTIGATORS	Mr JR Ncayiyana
DEPARTMENT	School of Public Health
DATE CONSIDERED	08.09.26
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.09.29 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Mr E Marinda

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 4 Data User Agreement Form

Data Transfer Agreement Page 1:

Date…08/09/2008….

Agreement between:

The Desmond Tutu TB Centre, Faculty of Health Science, University of Stellenbosch, Tygerberg, South Africa

and

School of Public Health, Faculty of Health Science, University of Witwatersrand, Parktown, South Africa

Mr J.R. Ncayiyana

CELL: 083 516 4337

FAX2EMAIL: 086 620 9616

EMAIL: jrncayiyana@hotmail.com

Conditions of data transfer.

1) Reason for data transfer:

The data will be used only for the secondary data analysis study. The aim of this study is to investigate the host related (age, gender, marital status) and environmental related factors (household cooking and heating fuel, being in prison,) associated with TB incidence. Data from Lung Health Survey in 2002 linked to TB cases documented in the National TB Register in Ravensmead and Uitsig from January 1, 2003 to December 31, 2007 will be analyzed. Exclusion criteria include TB prevalent cases during Lung Health Survey in 2002, or cases with missing data. Host and environmental factors data will be obtained from the Lung Health Survey database. TB cases will be obtained by matching individual names with National TB Register.

Data Transfer Agreement Page 2:

2). Data transferred between the above institutions will be kept confidential and will not be copied, sent or made available to other institutions.

3) Any additional analysis of the data (not listed above) must be pre-approved by the submission of an additional protocol describing the proposed study.

4) It must be accepted that the data will change from time to time and therefore the recipient institution must enquire about updates before final analysis and publication.

5) All data transfers must be viewed as collaborative research.

6) All manuscripts arising from the analysis of the data must be reviewed by a collaborative researcher in the institution where the data originated.

7) Queries used to select the data must accompany the data to inform the collaborator of what data has been sent.

8) Stellenbosch University cannot be held responsible for errors occurring in the data.

9) On completion of the study all the transferred data must be destroyed. Similarly, when a new version of the data is issued the old version should be destroyed.

10) First and Senior authorship must be agreed upon, prior to the initiation of the study.

Agreed by:

Director (Clinical Studies)

Professor N. Beyers

Date: 08/09/08

The above signatory does not necessarily entitle the right to co-authorship

Data manager or co-investigator

K. A. Lawrence

Date: 08/09/2008

The above signatory does not necessarily entitle the right to co-authorship

Agreed by Collaborative institution:

Name: Prof Sharon Fonn

Signature:

Date: 8 September 2008

Entity: Head of School

This above signatory does not necessarily entitle the right to co-authorship

Research Investigator

Mr J.R. Ncaylyana

Date: 07/09/2008