Trends in the presenting clinical profile of patients with pulmonary tuberculosis in the Western Cape, 1991 - 2009

Veronique Rejean de Jager

A mini-thesis submitted in partial fulfilment of the requirements for the degree of Master in Public Health at the School of Public Health,

University of the Western Cape

Supervisor: Prof. Helen Schneider

17 July 2017

Keywords

Pulmonary tuberculosis (TB); TB clinical profile; TB transmission; TB case detection; National

Tuberculosis Programme (NTP); TB/HIV co-infection; Sputum smear positivity.

Abbreviations

AFB – Acid fast bacilli

BMI – Body mass index [weight (kg) / height (m^2)]

LTBI – Latent tuberculosis infection

TB - Tuberculosis

WHO – World Health Organization

Definition of key terms

Case detection rate   - the ratio of notified TB cases to incident TB cases per year.

TB contact   - generally indicative of household contacts, i.e. those sharing a household with the index TB case, but may be extended to other persons with which an index case spends a considerable part of the day over an extended period of time.

Index case   - the first patient within a household diagnosed with tuberculosis.

Sputum smear microscopy   - the examination of a sputum sample under a microscope, after appropriate preparation, for determining the presence or absence of acid fast bacilli as an indicator of *Mycobacterium tuberculosis* infection.

Treatment cure   - TB treatment completed successfully with evidence of a sputum smear or culture negative for TB in the last month of treatment and on at least one previous occasion during the treatment period.

Treatment completion   - TB treatment completed successfully, but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion during the treatment period were negative.

iii
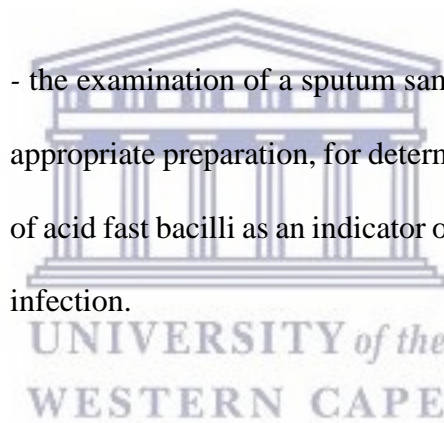
Abstract

Background

Over the past two decades, despite a growing tuberculosis (TB) epidemic, the South African health system and National TB Programme (NTP) have taken significant steps to ensure improved clinical awareness, early diagnosis, prompt treatment initiation and follow-up of treatment outcomes in cases of TB. The effects of these programmatic measures over time on changes in the severity of disease and presenting clinical profile of patients with pulmonary TB have not been studied. Doing so may provide another window on the impact of TB control initiatives in South Africa.

Aim

Drawing on the clinical and laboratory data of patients with pulmonary TB in a clinical trial setting, this study aimed to describe trends in the clinical presentation, at diagnosis, of adults with pulmonary TB over the past two decades. It also aimed to examine associations between clinical parameters (BMI, sputum microscopy and chest X-ray).

Methodology

A retrospective review of adult TB patient data collected between 1991 and 2009 at a TB clinical research centre in Cape Town, South Africa was conducted. Demographic and clinical parameters were analysed and plotted over time to illustrate trends. Associations between disease severity variables were also determined. All clinical trials included in this review received approval from either the Pharma-Ethics or Stellenbosch University Ethics Committee and the South African Medicines Control Council (MCC). Database entries were anonymized using patient initials and a unique numerical identifier.

Results

Overall, 1178 patient entries were available in the database between 1991 and 2009, representing the clinical profile at diagnosis of adults with pulmonary TB. Mean age (33 years)

iv

and gender (56% male) remained constant over the period. HIV status was unavailable for 42% of patients. In those where HIV status was recorded, a relatively small percentage (11%) were positive. Overall, mean BMI ranged in the lower end of normal (interquartile range: 17-20 kg/m^2), increasing significantly over the study period (p<0.001). On sputum microscopy, 39% and 23% of patients were "3+" & "2+" smear positive, respectively, with a decline in the "3+" grade from 2005 onwards. Mean colony forming units (CFU) also showed a declining trend from 2005 onwards. Just over half the patients had moderate (28%) or extensive (24%) disease on chest X-ray. Toward the later years, more patients showed minimal or mild disease on chest X-ray, not present in earlier years. Regression modeling showed a significant relationship between increasing disease severity on smear microscopy and grade of disease on chest X-ray (p value=0.0041). BMI was significantly higher in females (p value<0.001), those with minimal disease on chest X-ray (p value<0.001), and smear negative TB patients (p value=0.0028).

Conclusion

Across all clinical parameters, patients appeared to present with less severe TB disease at diagnosis during the later study years (2005-2009). This may be due to a number of interacting factors, such as increased self-recognition of TB symptoms within the community, as well as improved access to and effectiveness of the health system and NTP over this period. Evaluating trends in disease severity at diagnosis may highlight both successes and shortcomings in TB case-detection and help direct resources appropriately. Earlier diagnosis of infectious pulmonary TB cases will ultimately lead to decreased community transmission and support eventual TB elimination goals. Increased support for active TB case-finding is essential for reaching these goals.

Declaration

I declare that *Trends in the presenting clinical profile of patients with pulmonary tuberculosis in the Western Cape, 1991 - 2009* is my own work, that it has not been submitted for any degree or examination at any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

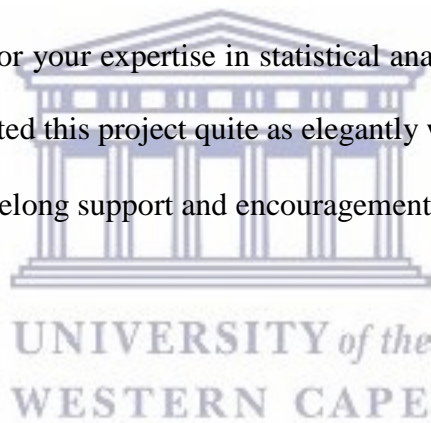**Veronique de Jager**   17 July 2017

Signature

UNIVERSITY *of the*
WESTERN CAPE

Acknowledgements

I would like to thank the following individuals and institutions for their support and assistance during the conceptualization, performance and completion of this project:

Contents

ix

Figures

In-text Tables

Appendix Tables

Introduction

Background

Tuberculosis (TB) today remains one of the most formidable foes of mankind, with an estimated 9.6 million people having fallen ill with TB as recently as 2014 (WHO, 2015). From the mid-1990s, with increasing prevalence of Human Immunodeficiency Virus (HIV) infection, the incidence of new TB infections soared (Churchyard *et al*, 2014). South Africa is one of the 22 World Health Organization (WHO) high TB-burden countries and currently has an estimated TB incidence of over 800 per 100 000 population, highest both in the WHO African region and globally (WHO, 2015). South Africa also has the highest HIV/TB co-infection rate globally (61%).

Health system interventions addressing the South African TB burden

Significant advances in diagnostic and health system capacity to address TB have been made in South Africa over the past 20 years. There has also been increased health promotion and health literacy regarding the features of TB in communities and amongst health care professionals.

Post-1994, the newly-elected South African government established the National Tuberculosis Programme (NTP) to allow for a more organised and systematic approach to the country's growing burden of TB. The South African NTP adopted the WHO-recommended TB control strategy, Directly Observed Therapy Short-course (DOTS) in 1997 (Churchyard *et al,* 2014). Although uptake of the DOTS strategy throughout the country was initially slow and fragmented (Schneider *et al*, 2006), by 2003 coverage was 100% across all 9 provinces (Weyer, 2007).

Based on five key components, DOTS is a set of measures to detect, treat, and monitor not only the progression of therapy in individual TB patients but also the performance of the system at local, regional and national levels. The five components of DOTS include government commitment to sustained TB control activities; TB case detection by approved microbiological methods; use of a standardised treatment regimen, with directly observed therapy (DOT); an uninterrupted supply of essential anti-TB drugs; and use of a standardised recording and reporting system (Maher & Mikulencak, 1999).

Despite the troubled history of the HIV/AIDS response and delayed government provision of antiretroviral therapy (ART) in earlier years, South Africa currently has the largest ART programme in the world, with over 3 million HIV infected persons currently receiving treatment (WHO, 2014). Health worker "provider-initiated" HIV testing has been implemented as standard practice for all patients presenting to public health facilities with symptoms suggestive of TB, with up to 93% of TB patients having a "known HIV status" and 79% of HIV positive TB patients on ART as of 2014 (WHO, 2015). TB symptom screening has also been integrated into the routine procedures performed at each visit for HIV positive patients, whether on ART, wellness follow-up of those not yet on ART or basic antenatal care for pregnant women.

Use of the Xpert® MTB/RIF assay (Cepheid, CA, USA) was introduced into the South African NTP diagnostic algorithm in 2011. This nucleic acid amplification test can detect a significantly higher proportion of TB infections in both HIV infected and uninfected persons than conventional sputum smear microscopy. It is also able to provide evidence of TB drug resistance (to rifampicin) within a turnaround time of approximately 24 hours, allowing health

care professionals to immediately classify a patient with TB as drug-susceptible or drug-resistant and initiate appropriate anti-TB therapy. South Africa has now adopted use of the Xpert® MTB/RIF assay as the primary diagnostic test for all persons presenting to public health care facilities with symptoms suggestive of pulmonary TB (DoH, 2014).

Prior to the introduction of the Xpert® MTB/RIF (GeneXpert) assay, a diagnosis of pulmonary TB was primarily made on sputum smear microscopy, a technique that remains the mainstay of TB diagnosis in many high-burden low-income countries around the world. In South Africa, sputum smear microscopy is now performed once a diagnosis of pulmonary TB has been made based on a positive GeneXpert result. Sputum smear grading, determined by the number of acid fast bacilli (AFB) detected on microscopy, is then used to determine a patient's level of infectiousness and prioritise contact tracing for TB screening, as well as to assess a patient's response to TB therapy during and before completion of the treatment period.

Sputum smear microscopy uses a technique of visual enumeration of the number of *Mycobacterium tuberculosis (M.tb)* bacilli present in a prepared sample of expectorated sputum. The result is reported as either negative or positive for the presence of *M.tb*, as acid fast bacilli (AFB). Positive samples are further graded according to a standardised classification system, reflecting an increasing bacterial load from "scanty" to "3+", (see Appendix A, Table A.1).

Due to its suppressive effect on the immune system the presence of HIV infection has resulted in changes in TB sputum smear microscopy profiles, with a higher rate of paucibacillary and smear negative cases of TB disease observed in co-infected patients (Elliot *et al*, 1993).

However, changes in sputum smear positivity are difficult to interpret in isolation due to the impact of HIV infection in this population.

Study rationale

Recent observations at a TB clinical research facility in Cape Town, where the researcher is based, have shown a trend toward a lower bacterial load of *M.tb* in the sputum of patients with pulmonary TB (de Jager *et al*, 2017). Although HIV infection is known to be associated with an increased rate of smear negative pulmonary TB, the population enrolled in studies undertaken at this facility over the past two decades has either excluded those with HIV infection in earlier years or has only included HIV infected persons with relatively intact immune function (CD 4 > 350 cells/mm^3) in later years, with an average HIV/TB co-infection rate well below 20%. It thus appears that patients included in these studies have presented with less severe TB disease in later years compared to earlier years, with HIV infection presenting less of a confounding influence than in the general population.

TB incidence, case detection rate and treatment outcome remain key performance indicators for assessing the efficacy of national TB programmes. However, these do not assist in determining progress made toward diagnosis of pulmonary TB earlier during the disease process and the associated decreased transmission risk of a shortened symptomatic period (Dye *et al*, 2009). As TB prevalence in high-incidence areas, such as South Africa, is driven through transmission of the bacilli from infectious pulmonary TB cases, early recognition of symptoms, diagnosis and treatment initiation are critical in achieving TB elimination goals. A description of the changing profile of the bacterial load and clinical features of patients with pulmonary TB at diagnosis may provide a window into these key factors. Estimation of the severity of

TB disease at the time of diagnosis could serve as a proxy indicator for the duration of the symptomatic period, and be used as an adjunct in assessing TB control initiatives.

Setting

The study was conducted in Cape Town, South Africa, using both clinical and laboratory data of adult pulmonary TB patients taking part in various TB-related clinical trials at TASK Applied Science, Tuberculosis Clinical Research Centre (TASK). TASK was founded in 2005 to accelerate the development and evaluation of novel anti-TB drugs, collaborating mainly with international NGOs, government-funded consortia, academic centres and pharmaceutical companies. The company has compiled an electronic database capturing an array of data from over 1000 trial participants over the years. This database also includes data from trials performed by the principal investigator and his associates prior to the founding of TASK. The patient populations (age and gender) and geographic recruitment areas have remained constant for the period under review.
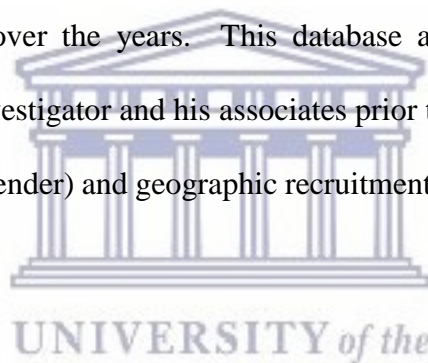
The Western Cape Province is home to 5.8 million inhabitants, approximately two-thirds residing in the City of Cape Town. It reported the fourth highest number of pulmonary TB cases in the country in 2014, over 38 000 (Day & Gray, 2016). Cape Town is divided into 8 health sub-districts, 3 of which are the principal areas from which patients included in this study were recruited. These include the Tygerberg, Eastern and Northern sub-districts, hosting many of the high TB-burden suburbs in the city.

Literature review

Introduction

This section provides a historical overview of the TB burden in South Africa, as well as trends in other key TB programme performance indicators, such as treatment outcomes and case detection rate over the past two decades. The trends were compiled from data published in multiple South African Health Review (SAHR) publications, available on the Health Systems Trust website, www.hst.org.za. This is followed by a summary description of some of the key TB control programme interventions that have been implemented over the same period.

An overview of the changes in the clinical profile of TB patients and the influence of HIV co-infection since the late 1980's is also presented. Factors influencing TB transmission risk are then briefly outlined. Finally, evidence on the benefits of active TB screening as opposed to passive case-finding is presented.
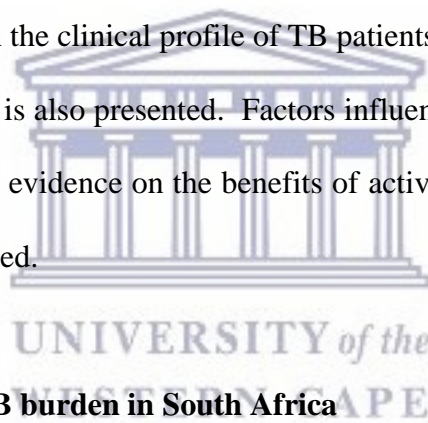
Historical overview of the TB burden in South Africa

Although effective anti-TB drug therapy has been available since the early 1950s, little progress in the fight against tuberculosis was made in South Africa in these early years. This has been attributed largely to the lack of a nationally co-ordinated health system and TB control programme, segregation of health services along racial lines in both colonial and Apartheid-era South Africa, as well as the poor socio-economic circumstances these systems created for a large majority of the population (Packard, 1989).

Due to this fragmentation in the health system in earlier years, data on the prevalence and incidence of tuberculosis during this period is scarce. Where data is available, it is largely

unreliable due to exclusion of data from what was then considered "independent homelands", territories to which large proportions of black Africans were forcefully relocated during this era (Packard, 1989).

Figure 1 below shows overall TB incidence per 100 000 population, along with ante-natal HIV sero-prevalence and HIV/TB co-infection rates (secondary y-axis) between 1990 and 2014. From the mid-1990's, when the prevalence of HIV infection increased, the incidence of tuberculosis saw an almost exponential rise, from approximately 300 per 100 000 population in 1994 to a peak of just under 1000 per 100 000 in 2011. Relatively small gains in decreasing overall TB incidence have only recently been made.
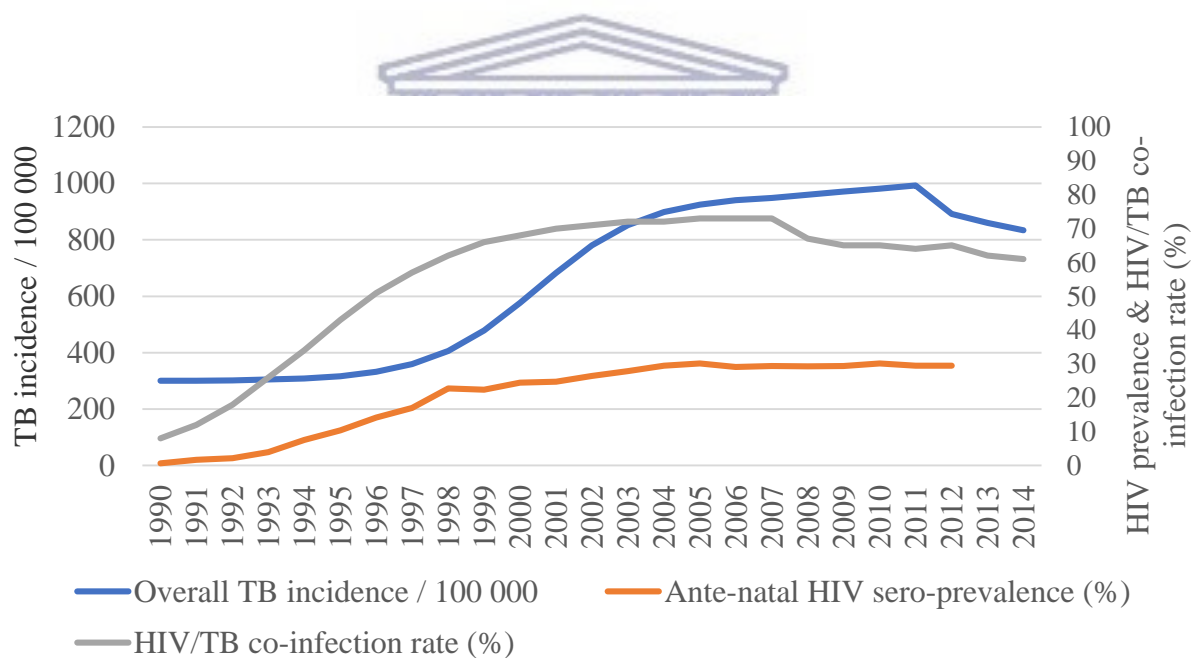
Figure 1. TB incidence, HIV prevalence & HIV/TB co-infection, 1990 – 2014 (Source: South African Health Reviews 1995-2016)

Other indicators used to assess the performance of the NTP include treatment outcomes and case detection rate. Measures of TB treatment outcome, i.e. treatment cure and success rates, for smear positive pulmonary TB, are shown in Figure 2. Prior to 1995, when a unified NTP was established, no comprehensive data regarding treatment outcomes are available.

Treatment cure and success rates hovered around 50% and 70%, respectively, for almost 10 years, between 1995 and 2004. It is only since 2005 that there has been a trend toward improved treatment outcomes, although still falling short of the >85% South African National Strategic Plan target (SANAC, 2011).

Case detection rate (CDR) has also increased steadily, from approximately 40% in 2000 to meeting the WHO-recommended target of 70% by 2008, and hovering just below since then (WHO, 1991) (Figure 2). CDR reflects the ratio of TB cases reported by the NTP to the estimated total TB incident cases for a given period. Meeting a target of 70% would mean that 30% of patients with infectious TB remain undiagnosed and untreated within their communities.
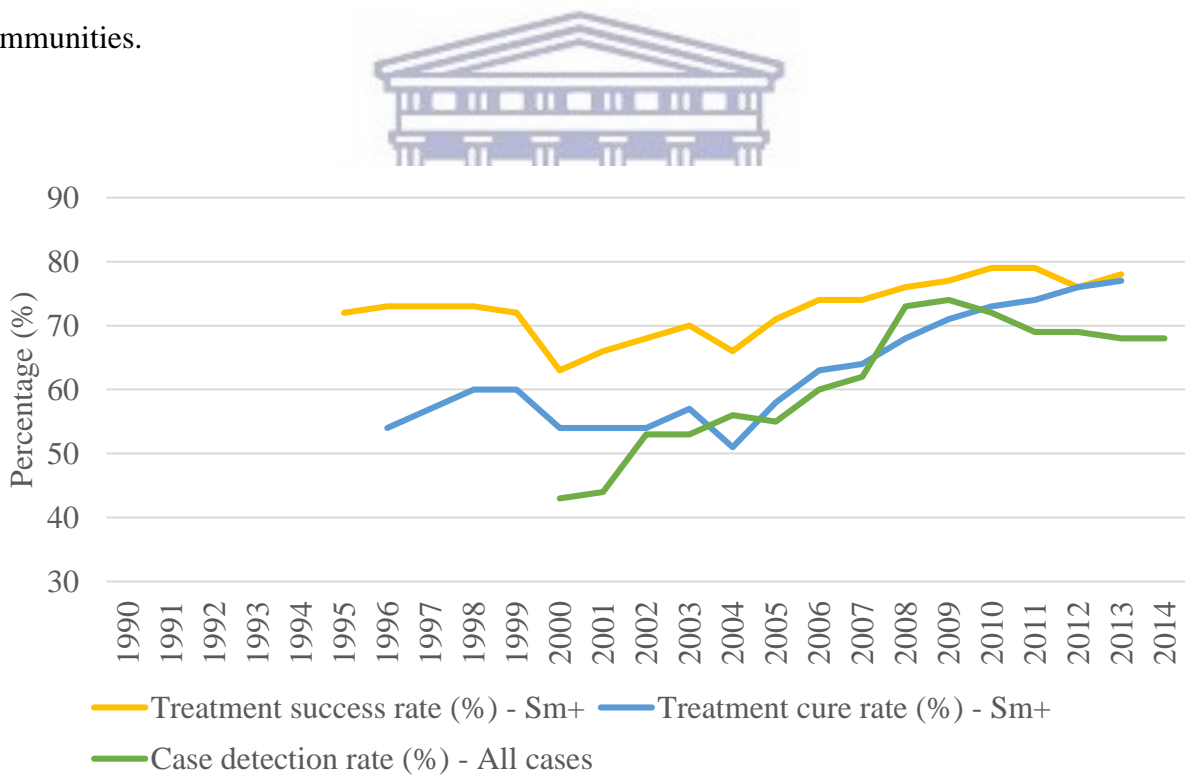
Figure 2. TB case detection, treatment cure and success rates, 1995 – 2014 (Source: South African Health Reviews 1995-2016)

Key interventions in the history of the South African TB-control response

Establishing a unified National TB Programme

The NTP was established in 1994, at the dawn of democracy in South Africa, creating the first unified, all-inclusive national programme for tuberculosis control in the country. Shortly thereafter, during 1995/1996, the DOTS strategy, widely endorsed by the World Health Organization, was adopted. Full implementation of DOTS throughout all 9 provinces was achieved by 2003 (Weyer, 2007).

Post-1994, the South African Ministry of Health also committed itself to the development of the District Health System for implementation of health services to the public, with the aim of providing increased access to quality comprehensive health care in an equitable manner (Naidoo, 1997). This provided the context for the implementation of the NTP, where access to health care was for the first time becoming a reality for many South Africans.

Implementation of DOTS-associated strategies

A national TB register was introduced in 1995, before which time aggregate data on the success of TB treatment was largely unknown (Weyer, 1997). The introduction of such a data capturing platform formed one of the tenets of the DOTS strategy, namely, the recording of patient treatment outcomes and evaluation of the efficacy of the programme at both district and national level. Establishment of the first Demonstration and Training Districts (DTDs) followed in 1998. These were established to serve as template models for the successful implementation of the DOTS strategy throughout the rest of the country (Weyer, 1997).

The first fixed-dose combination-drug anti-TB treatment regimen was introduced in 1999. By 2001, the NTP had introduced a fixed-dose combination regimen containing all four drugs used

during the intensive phase of drug-sensitive TB therapy. Fixed-dose combination regimens were introduced with the aim of enabling increased treatment adherence, with a decreased pill burden for patients, as well as improved treatment management in terms of prescribing the correct drugs and drug dosages.

Introduction of the Electronic TB Register

The Electronic TB Register, ETR.Net, is a software programme designed for TB/HIV surveillance, program monitoring and evaluation. It was adopted in South Africa in 2004 and is currently implemented nationwide throughout all 9 provinces. The system is designed to "capture patient-based information at the district level directly from paper TB registers, [is able to] generate data quality checks, as well as standardized cohort reports for case finding, sputum smear conversion, treatment outcomes and HIV testing" (www.etrnet.info).

Antiretroviral therapy and integrated TB/HIV care

In 2004, highly active antiretroviral therapy (HAART) for the treatment of HIV infection was made freely available in the South African public health system for the first time. This three-drug combination regimen was for a long time known to reduce the risk and incidence of new TB infections in HIV-infected persons. The availability of antiretroviral therapy (ART) in the public sector was, however, long opposed by the state and became available only after continued civil pressure and legal action by civil society organisations (Heywood, 2009). Currently, South African TB and HIV guidelines provide that all TB co-infected HIV positive patients are eligible for ART regardless of CD4 cell count (DoH, 2014).

Realising the importance of an integrated approach to TB and HIV care, the first pilot integrated TB/HIV management sites were established in 1999. By this time, the TB/HIV co-infection

rate in South Africa was already just under 50%, from less than 10% only 9 years earlier (Kironde, 2000).

Adoption of new diagnostics for TB and drug-resistance detection

In 2011, the South African NTP adopted use of the Xpert® MTB/RIF assay as the first line diagnostic for pulmonary TB with concurrent detection of rifampicin resistance. This nucleic acid assay is significantly more sensitive for diagnosing TB disease than the previous standard diagnostic test, sputum smear microscopy, dramatically increasing the likelihood of a positive TB test, particularly in the presence of HIV co-infection.

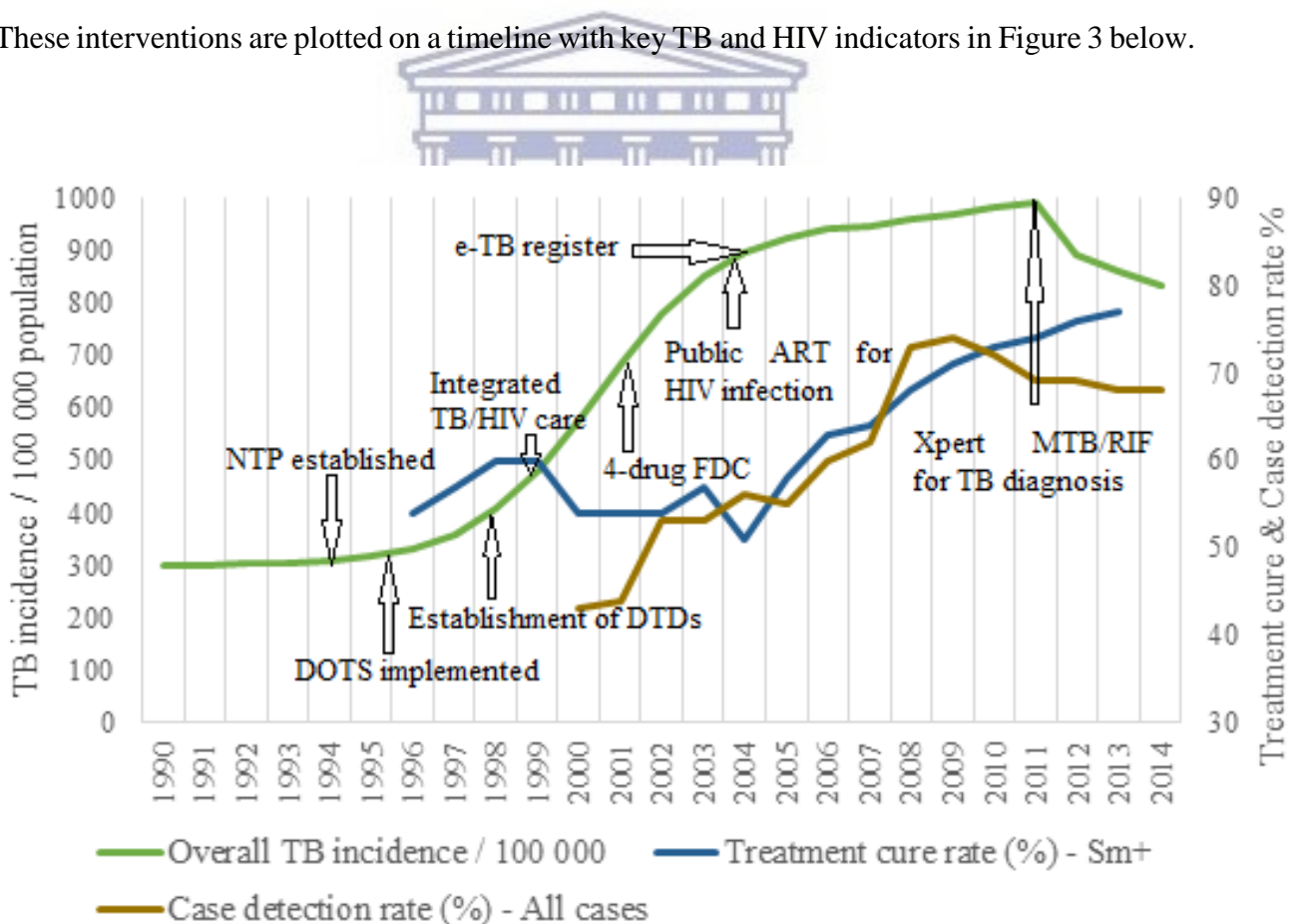These interventions are plotted on a timeline with key TB and HIV indicators in Figure 3 below.

Figure 3. Key interventions in the South African tuberculosis control response, 1990-2014

Trends in the clinical profile of TB patients

The sputum smear positivity rate represents the percentage of pulmonary TB patients with a positive sputum smear microscopy result at diagnosis. These patients make up the largest reservoir of those actively transmitting TB to contacts within their social and workplace environments. The smear positivity rate has shown a steady decline from 54% in 2003, to 28% in 2014 (Day & Gray, 2005, 2016). This decline is thought to be largely associated with increasing HIV/TB co-infection.

In the pre-HIV era, there were approximately 1.2 cases of smear negative and/or extra-pulmonary TB for every smear positive case. This ratio has changed significantly in countries worst affected by the HIV/TB syndemic, with disproportionately higher rates of smear negative (and extra-pulmonary) disease now seen in HIV positive compared to HIV negative patients (Colebunders & Bastian, 2000). Immune suppression due to HIV infection has been shown to result in decreased pulmonary cavity formation and an increased likelihood of paucibacillary or smear negative TB disease (De Kock *et al*, 1992; Perkins & Cunningham, 2007). Little is known about the smear-positive to smear-negative ratio, or any changes in smear positivity in non-HIV infected populations of similar TB disease-burden.

Between 2003 & 2010, Virenfeldt and colleagues (2014) performed a longitudinal prospective cohort study in the west-African country of Guinea Bissau to determine the effect of treatment delay on the severity of TB at diagnosis. Disease severity was determined using the Bandim TB score, a tool which uses a variety of TB symptoms, signs and Body Mass Index (BMI), amongst others, to calculate a numerical score or mortality risk index. Although the study found the delay between the onset of symptoms and initiation of TB treatment to be unacceptably high (12 weeks), they also found treatment delay to have decreased over the

duration of the study period, by 10.3% annually (interquartile range: 7.9 – 12.6%) (Virenfeldt *et al*, 2014). The authors suggest that improved socioeconomic factors, as well as increased community awareness of TB symptoms, influenced the changes observed.

Not surprisingly, the study also found a prolonged treatment delay to be significantly associated with TB disease-severity at diagnosis. The proportion of severely ill TB patients increased by 15% as treatment delay increased from up to 8 weeks to between 12 & 21 weeks (Virenfeldt *et al*, 2014).

Factors influencing TB transmission risk

Numerous factors influence the likelihood of pulmonary TB transmission, with a higher grade of positivity on sputum smear microscopy, the presence of cavities on chest X-ray and longer duration of symptoms prior to diagnosis significantly increasing transmission risk (Lohmann *et al*, 2012). In a retrospective study of TB contact investigations performed in the Netherlands over a 5-year period, between 2000-2001 and 2005-2007, Lohmann and colleagues (2012) demonstrate a significant risk of TB transmission from patients with pulmonary TB to close contacts (overall relative risk [RR] 9.9; 95% confidence interval [CI] 1.4 - 71.2), with the risk increasing as sputum smear grade and bacterial load in index TB cases increases (AFB grade 5+; RR 18.8; 95% CI 2.6 - 139).

Golub *et al* (2006) also found both sputum smear positivity and long duration of symptoms ("total treatment delay") to be associated with increased transmission of TB to close contacts. This prospective cohort study performed in Maryland, USA, between 2000 and 2001, found pulmonary TB patients with a symptomatic period of 90 days or more to be twice as likely to have contacts with a positive tuberculin skin test (TST), indicating latent TB infection (LTBI),

than those with a shorter duration of TB symptoms prior to treatment initiation. Significantly, this association was independent of sputum smear grade and chest X-ray findings, demonstrating the importance of early symptom recognition, diagnosis and treatment initiation in decreasing TB transmission and eventual prevalence. Both Lohmann (2012) and Golub (2006) also found evidence of increased TB transmission risk among pulmonary TB cases with cavities on chest X-ray.

Active TB screening versus passive case-finding

Passive case finding describes a process whereby an ill, symptomatic patient presents him- or herself to a health facility for assessment, followed either by the exclusion or diagnosis of TB disease. This is the approach routinely adopted by health systems or TB programmes world-wide. Alternatively, active TB screening requires a community-oriented approach whereby disease is sought or excluded in people who may not feel ill, are unable to access health care for various reasons, or are unable to do so within a timely manner.

Persons with TB detected through active screening and contact-tracing are less likely to present with a cough, the most common TB symptom, or to be smear-positive on sputum microscopy, compared to those diagnosed through passive detection (Ward *et al*, 2004). Other researchers have also found those screened actively for TB to have a significantly shorter duration of symptoms (4.2 weeks), and thus a shorter infectious period, than those detected passively upon self-presentation to a health facility (10.5 weeks), (p<0.001) (Verver *et al*, 2001).

Conclusion

Despite South Africa's ongoing high TB incidence, significant improvements in both the health system and NTP have occurred over the past two decades. TB incidence has shown a declining trend over the past few years. NTP indicators, such as CDR and treatment outcomes have improved significantly.

The presenting clinical profile of patients with TB have also changed over time. This can be seen in the declining rate of sputum smear positive cases of pulmonary TB diagnosed in recent years. Interpretation of the changes in smear positivity is difficult because of increasing HIV prevalence, influencing the sensitivity and diagnostic yield of sputum microscopy in the diagnosis of TB. In other African countries, there is evidence that TB disease is being diagnosed earlier than in previous years.

A lower burden of *M.tb* bacilli at diagnosis, particularly in HIV-negative patients, may be an indicator of TB diagnosis earlier in the disease process and a shortened infectious period before treatment is initiated. Such findings may also imply a strengthening and more effective national TB control programme.

Study aim

Drawing on the clinical and laboratory data of patients with pulmonary TB in a clinical trial setting, this study aimed to describe trends in the clinical presentation, at diagnosis, of adults with pulmonary TB over the past two decades.

Primary objectives

- To describe the trend in sputum microscopy smear positivity of adult patients with pulmonary TB, at diagnosis, between 1991 and 2009

- To describe the trend in mean Body Mass Index (BMI) of adults with pulmonary TB, at diagnosis, between 1991 and 2009

- To describe the trend in chest X-ray findings of adults with pulmonary TB, at diagnosis, between 1991 and 2009

Secondary objectives

- To determine the association between sputum smear grade and chest X-ray findings of adults with pulmonary TB

- To determine the association between BMI and sputum smear grade of adults with pulmonary TB

- To determine the association between BMI and chest X-ray findings of adults with pulmonary TB

Methodology

Study design

This was a retrospective observational study, using a time-series analysis to describe trends in the clinical presentation of adults with pulmonary TB, at diagnosis, over an 18-year period, between 1991 and 2009.

Population and sampling

The study population consisted of adults with confirmed pulmonary TB living in Cape Town, South Africa, recruited as participants in trials conducted by a TB clinical research centre between 1991 and 2009. Patients for the trials were enrolled consecutively until the required number of participants were recruited per study.

Data extraction

Data were extracted from an electronic database containing over 1000 patient entries and included individual demographic variables (age in years & male or female gender), as well as sputum microscopy grade, BMI, chest X-ray findings and HIV status. Sputum microscopy grade was determined using the WHO/IUATLD (International Union Against Tuberculosis and Lung Disease) classification system for TB fluorescence microscopy, (see Appendix A. Table A.1). Sputum microscopy grade was recorded as either "negative", "scanty", "1+", "2+", or "3+". BMI was calculated from weight (kg) and height (m) using the standard formula **BMI = weight (kg) / height (m^2)**. Chest X-ray findings were recorded as "extent of disease" graded according to an increasing order of disease severity based on the extent of tuberculous lung involvement, as well as "grade of cavities" based on the presence and size of lung cavities, (see Appendix A. Table A.2). HIV status was recorded as positive or negative, reflecting the presence or absence of HIV infection, respectively.

Standard operating procedures (SOPs) were in place for all clinical measurements, such as height and weight, HIV testing (either performed on-site or at an accredited laboratory), as well as sputum sample preparation and microscopy techniques and grading. The same mycobacterial laboratory and internationally-accepted sputum microscopy grading classification system has been used for the duration of the study period. Chest X-ray evaluations were performed using a standardised scoring and classification system. All measurements and evaluations were performed by appropriately trained medical and laboratory personnel.

Data analysis

Statistical support was provided by a qualified statistician. Analyses were performed using two statistical software packages, R packages (R core team, 2016) and Minitab® Statistical Software (Minitab Inc., Coventry, United Kingdom).

Descriptive statistics, using measures of central tendency (mean/median), variability (standard deviation/interquartile range), and relative frequency were used to analyse the demographic (age, gender and HIV status) and the disease-severity variables (sputum microscopy grade, chest X-ray findings, BMI). Time-trend analyses were performed for all key variables and displayed visually. Analysis of variance (ANOVA), together with the F-test, was used to determine significant differences in mean BMI over the study period. Age and gender remained relatively constant over the study period, thus age-sex standardisation was not required.

In addition, the analysis examined the associations between the disease severity variables, BMI, sputum microscopy grade and chest X-ray findings, using linear mixed-effects models. The t-test was used to determine the significance of the difference in means between two variables.

Ethical considerations

All clinical trials included in this review received approval from either Pharma-Ethics or the Stellenbosch University Ethics Committee and the South African Medicines Control Council (MCC). All study participants previously provided written informed consent. All trials ensured patient confidentiality using participant initials and a unique numerical identifier for all study records. Due to the retrospective nature of this review, renewed individual consent was not sought. This current study was approved by the Biomedical Science Research Ethics Committee of the University of the Western Cape (Reference number: BM/17/1/6).
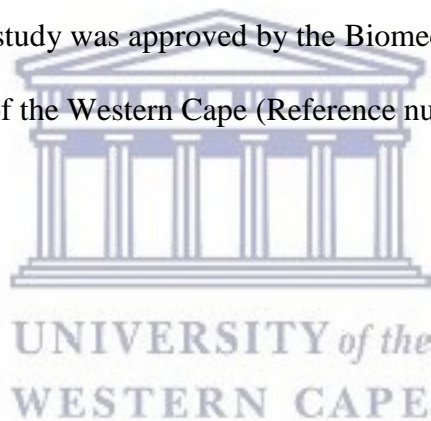
Study results

A total of 1178 patients were included in this review, from 1991 to 2009. Seventeen TB clinical drug trials undertaken in Cape Town, South Africa, were included. The number of studies performed per year and number of patients recruited per study are not equally distributed over the study period (Figure 4). There are years where no study data is available: 1993, 1998, 2002 – 2004, and 2007.
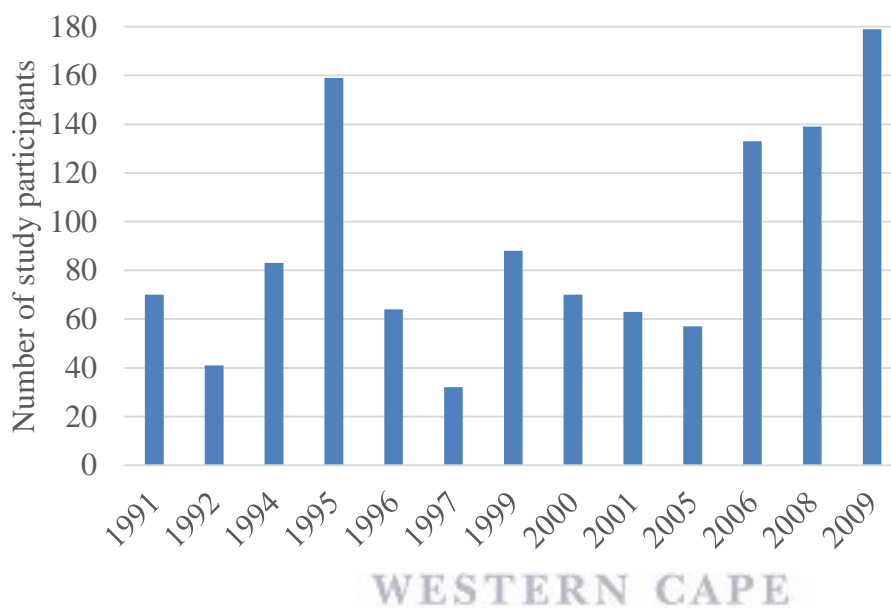
Figure 4. Number of study participants per year (n=1178)

Demographic profile

Descriptive statistics were calculated using the entire dataset, including patients with missing data points for certain variables. Both mean age and gender remained relatively constant over the study period, at 32.7 years and 56% for males, respectively, removing the need for age-sex standardisation. Most patients (67%) were classified as "Coloured" race (as opposed to African or White) (Table 1).

Table 1. Demographic variables (n=1178)

Variable	N	Summary measure
Age (years)		
mean (SD)	1027	32.7 (10.4)
median (IQR)	1027	31 (24-40)
missing data	151	12.8%
Gender		
male	662	56.2%
female	384	32.6%
missing data	132	11.2%
Race		
African	184	15.6%
Coloured	787	66.8%
White	3	0.3%
missing data	204	17.3%
HIV status		
negative	602	51.1%
positive	72	6.1%
missing data	504	42.8%

HIV status

Nearly half the patients (43%) had a missing HIV status (Table 1). When considering only those with a known HIV status, 89% were HIV negative. Where HIV status was recorded, the co-infection rate ranged from 1% to 23% per study year. Due to the large proportion of missing HIV data, particularly in the later study years (Figure 5), it is difficult to classify with certainty this population as a low HIV-burden compared to the general population of TB patients in South Africa.
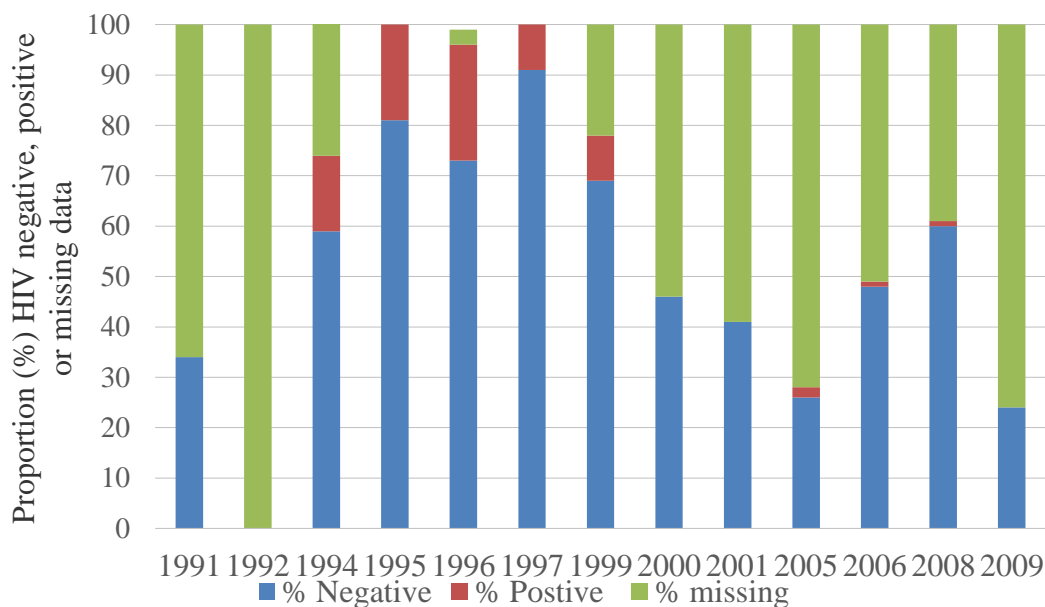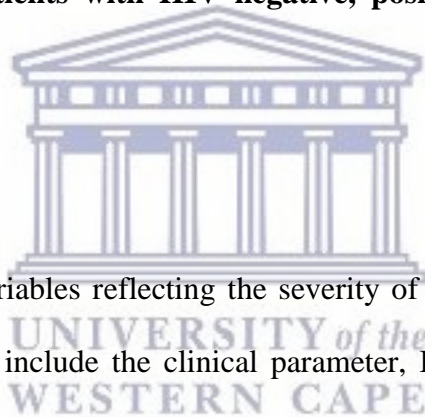
Figure 5. Proportion of patients with HIV negative, positive or missing HIV status (n=1178)

Disease-severity variables

Summary statistics for the variables reflecting the severity of TB disease, at diagnosis, are

displayed in Table 2. These include the clinical parameter, Body Mass Index (BMI), the

bacteriological parameters, sputum microscopy grade & colony forming unit (CFU) count, and

the radiological parameters, extent of disease- & presence of cavities on chest X-ray.

Table 2. Disease severity variables (n=1178)

Variable	N	Summary measure
BMI (kg/m^2)		
mean (SD)	917	18.9 (2.75)
median (IQR)	917	18.5 (17.1-20.3)
missing data	261	22.2%
Sputum smear microscopy grade		
negative "0"	35	2.9%
scanty "0.5"	66	5.6%
positive "1+"	218	18.5%
very positive "2+"	268	22.8%
extremely positive "3+"	457	38.8%
missing data	134	11.4%
log$_{10}$(CFU) count (per ml sputum)		
mean (SD)	714	6.75 (0.76)
median (IQR)	714	6.89 (6.34-7.26)
missing data	464	39.4%
Chest X-ray: extent of disease		
I	8	0.7%
II	13	1.1%
III	130	11.0%
IV	329	27.9%
V	283	24.0%
VI	109	9.3%
missing data	306	26.0%
Chest X-ray: cavitation		
I	29	2.5%
iia	8	0.7%
iib	27	2.3%
iic	29	2.5%
iiia	143	12.0%
iiib	303	25.7%
iiic	333	28.3%
missing data	306	26.0%

Body Mass Index

Mean and median BMI were 18.9 (standard deviation [SD]=2.8) and 18.5, respectively. Mean BMI in this cohort of TB patients was at the bottom end of the normal range (18.5 - 25), with 39% (455) of patients underweight (BMI < 18.5) (Figure 6). Thirty-seven percent (435) of patients were within the normal range, while 2% (26) were overweight (BMI > 25).
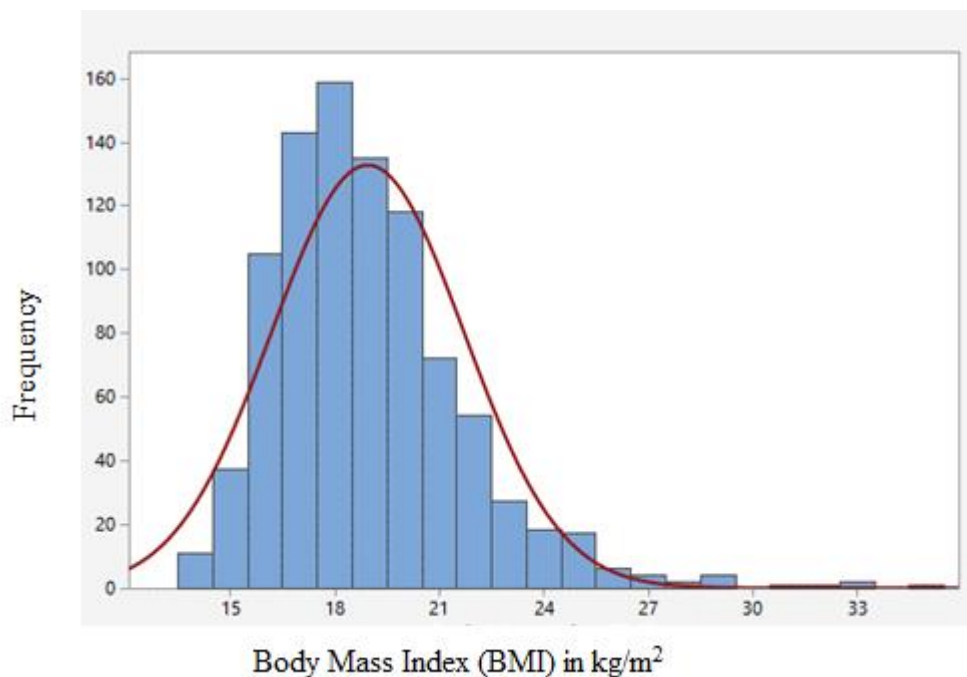

Figure 6. Histogram of Body Mass Index (n=917)

Mean BMI per year, with 95% confidence intervals (CI) was plotted over the study period (Figure 7). One way analysis of variance (ANOVA) showed a significant difference in mean BMI over the study period, ($p < 0.001$). Tukey pairwise comparisons were used to identify differences in mean BMI between the study years and showed significant differences for 1997, 2000 and 2008.
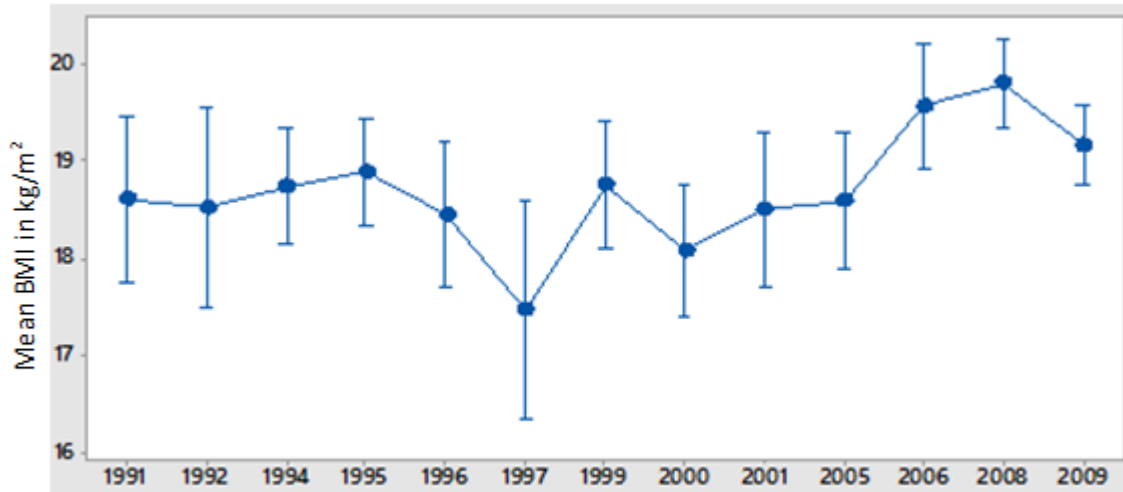
Figure 7. Mean Body Mass Index with 95% confidence intervals (n=917)

Sputum smear microscopy

Over the entire study period, sputum smear microscopy showed a predominance of extremely positive (3+) and very positive (2+) grades, 39% and 23%, respectively (Table 2). Figure 8 shows changes in the proportions of the disease-severity grades on sputum microscopy per year, with higher grades indicating a greater bacterial load and disease burden. Between 1996 and 2001 the majority of sputum samples were extremely positive ("3+") for *M.tb* on smear microscopy.   This period correlates roughly with the initial exponential increase in TB incidence and HIV prevalence (Figure 1). From 2005 onwards, a greater spectrum of disease severity appears to be present, with a smaller proportion of samples being "3+" or extremely positive.
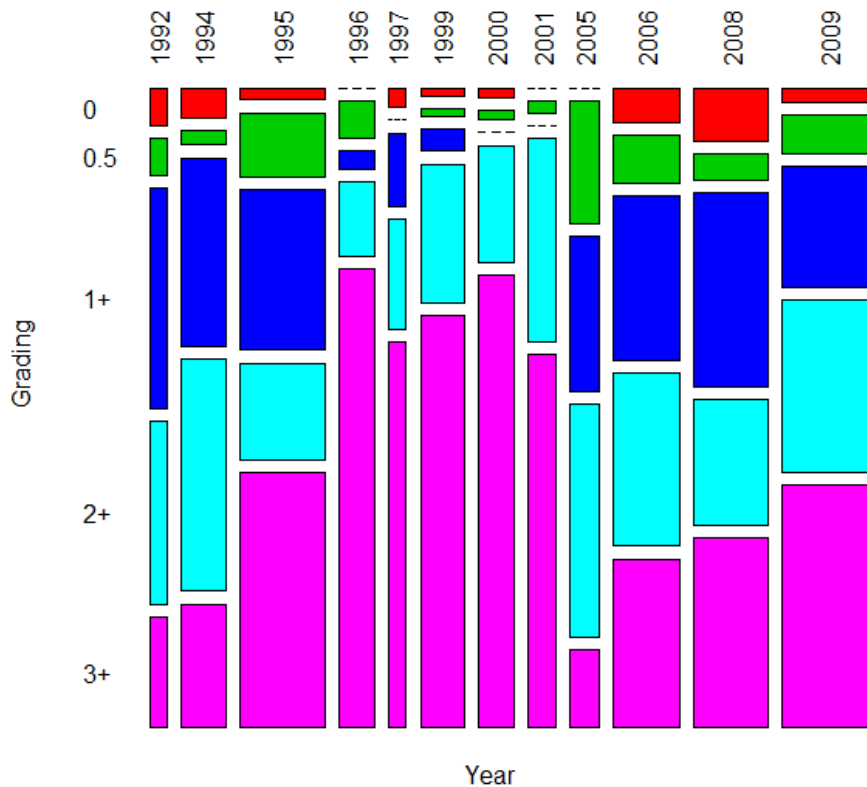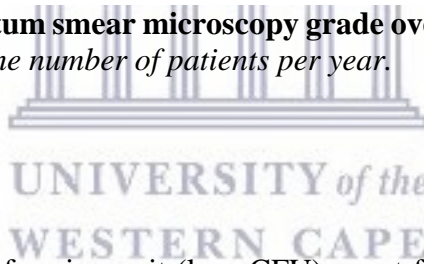
Figure 8. Distribution of sputum smear microscopy grade over the study period (n= 1044)
Width of the bar represents the number of patients per year.

Colony forming unit count

Mean log-transformed colony forming unit (log_{10}CFU) count for the entire study period was 6.75 per millilitre (ml) sputum (SD = 0.76). The colony forming unit (CFU) count enumerates live colonies of *M.tb* bacilli on solid culture medium, with a larger number reflecting a greater load of bacilli per ml sputum. Mean log_{10}(CFU) showed an initial increase to a peak in 2001 followed by a sharp decline towards the later part of the study period, from 2005 to 2009, as depicted in figure 9 below. No study data is available for 2002 to 2004.
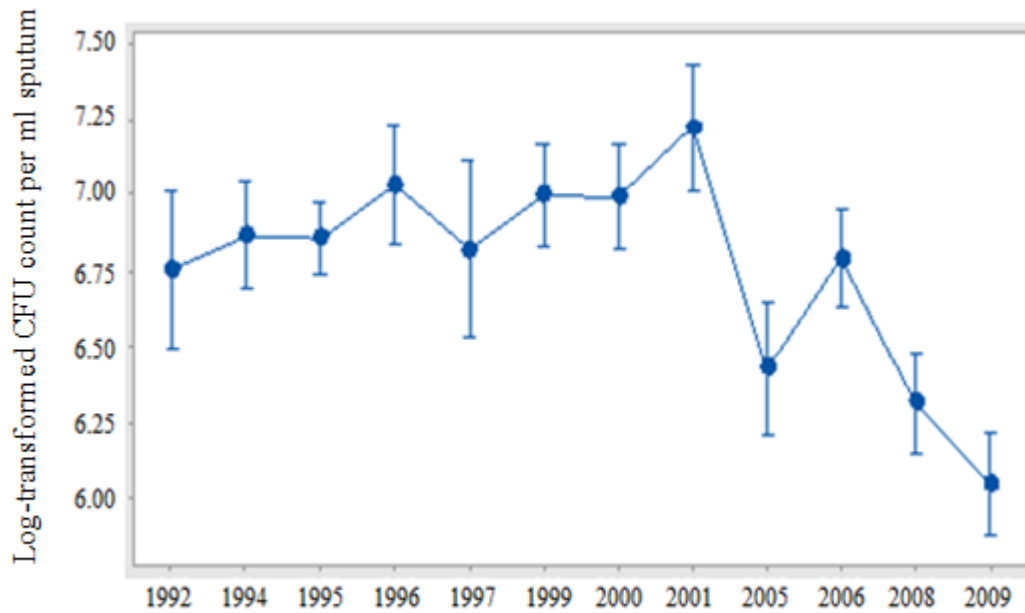
Figure 9. Log-transformed colony forming unit (CFU) count with 95% confidence intervals (n=719)

Chest X-ray extent of disease

Overall, most patients had moderate (grade IV) or extensive (grade V) lung disease on chest X-ray, 28% and 24%, respectively. Figure 10 shows a box-plot with extent of disease on chest X-ray (X-axis) over the study period (Y-axis). Minimal disease/lung involvement (grade I) became more frequent during the later study years, while extensive bilateral disease (grade VI) was more frequent in earlier years.
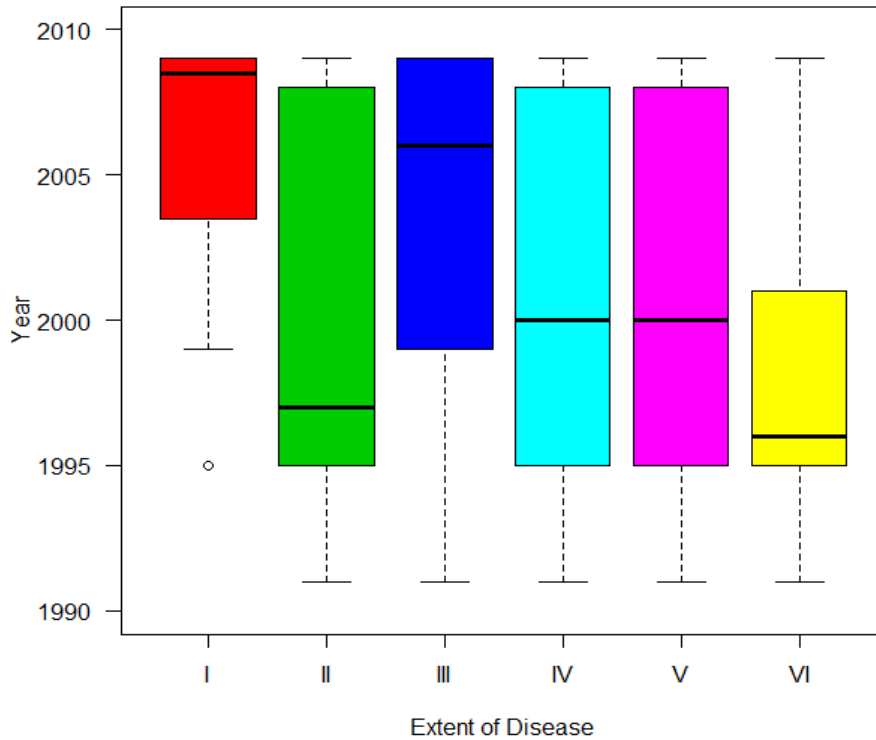
Figure 10. Box-plot of extent of disease on chest X-ray over the study period (n=827)

Cavities on chest X-ray

For presence and size of lung cavities on chest X-ray, grade iii (multiple cavities) account for the largest proportion of observations (66%) throughout the study period (Figure 11). Later years, 2006 – 2009, show an increased proportion of patients with absent or single lung cavities (grades I and ii, respectively), than earlier years. This trend is highly significant, (p-value < 0.0001).

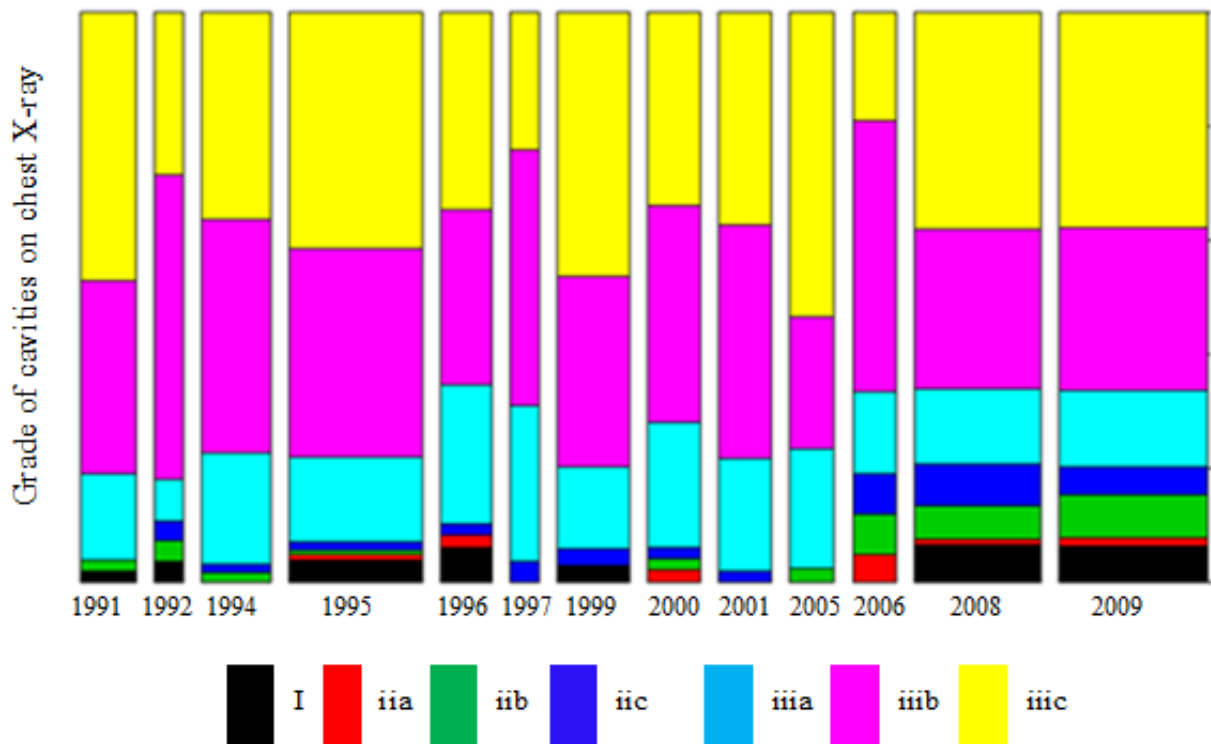**Figure 11. Grade of cavities on chest X-ray over the study period (n=827)**

Width of the bar represents the number of patients per year.
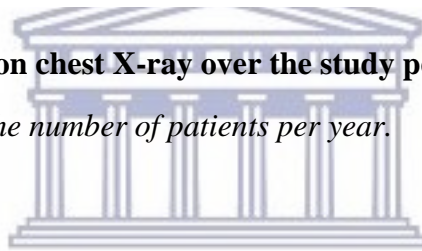
Association between microbiological and radiological variables

The association between disease severity on smear microscopy and chest X-ray cavities is displayed in Figure 12 below. Ordinal logistic regression modelling for grade of lung cavities predicting smear microscopy grade and vice versa both showed highly significant effects, p-values = 0.002 and 0.0041, respectively. These remained significant after adjusting for age and gender, p-values = 0.0030 and 0015, respectively.
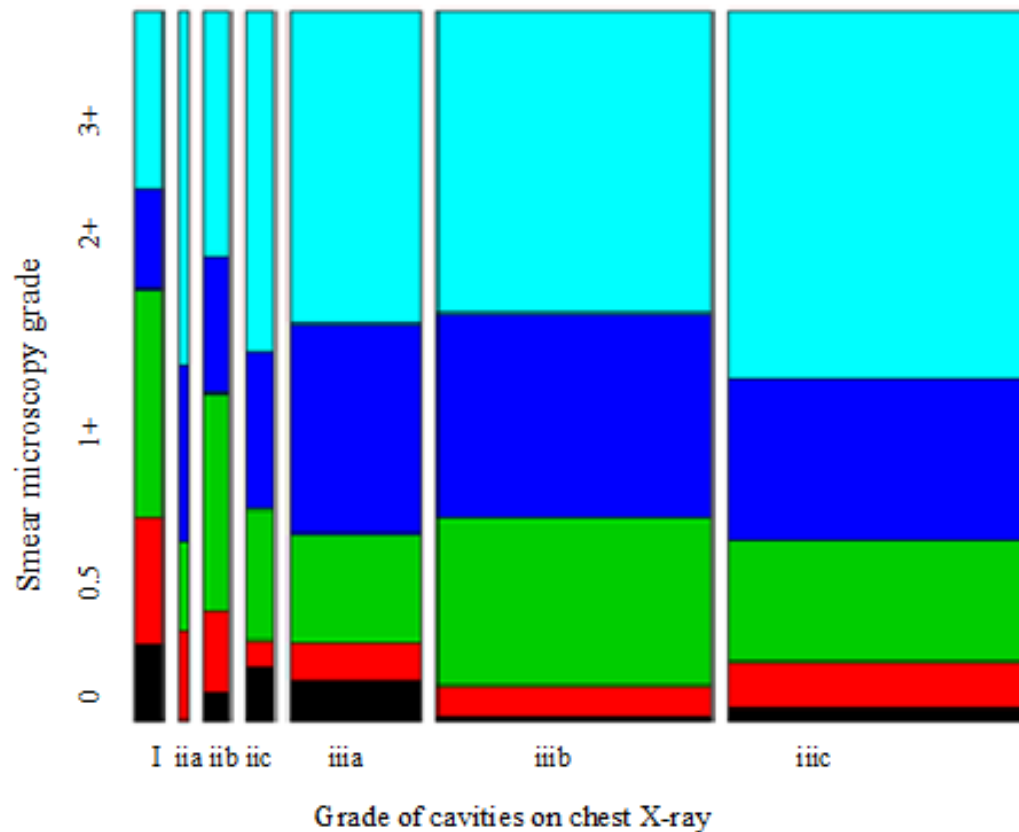
Figure 12. Mosaic plot for grade of sputum smear microscopy versus chest X-ray cavities (n = 781)

Size of the blocks represent the number of patients.
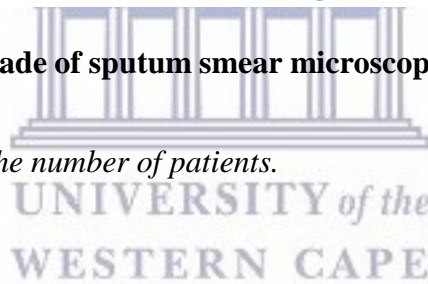
Association between BMI and demographic variables

Mean BMI was significantly lower in male than female patients, (p-value <0.001) (Figure 13), while being significantly higher in black and white than coloured patients, (p-value = 0.0116) (Figure 14). No associations were detected between BMI and age (p-value = 0.5463), or HIV status (p-value = 0.2739). BMI was not normally distributed when applying the Anderson-Darling test for normality, (p-value = 0.0050) (Figure 6). Log-transformed data were therefore used in these analyses.

Figure 13. Box-plot of log(BMI) for gender*
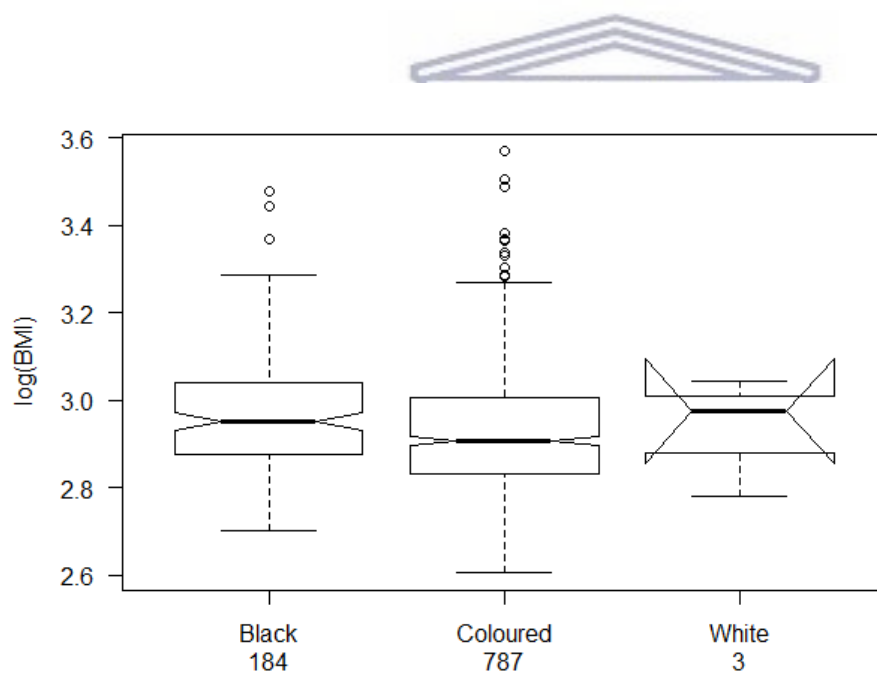
Figure 14. Box-plot of log(BMI) for race*

The central bands in each box represent mean log(BMI) with 95% confidence intervals represented by the wedges on each side. The horizontal lines represent the interquartile ranges, while the dots represent outliers.

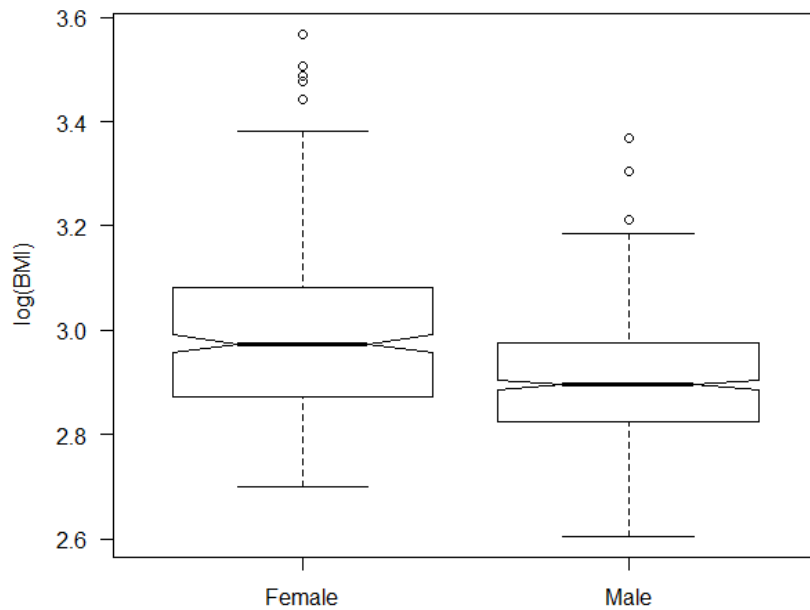**Association between BMI and disease severity variables**

The association between BMI and sputum smear microscopy grade was not significant, except for the difference between a negative (0) and any positive smear grade (p-value = 0.0028). BMI was 7.9% lower (95% CI: 2.8% to 12.7%) in sputum smear positive than smear negative patients. The association between BMI and CFU was significant (p-value = 0.0152), with a higher bacterial load associated with a lower BMI (Figure 15).
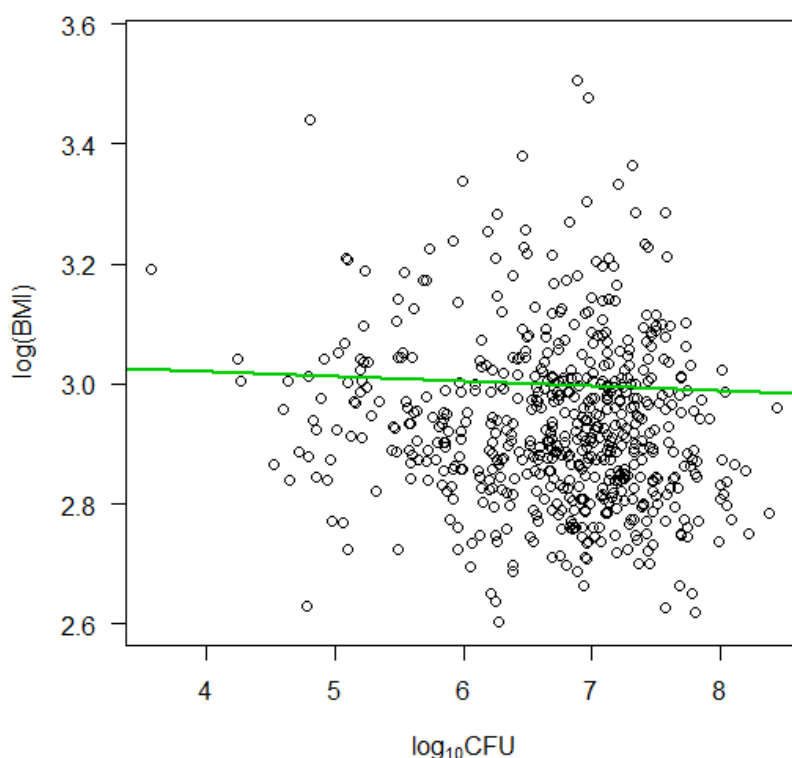
Figure 15. Scatterplot of log(BMI) versus $\log_{10}$(CFU) per ml sputum (n=592)

Slope of the line: -0.0079 (95% CI: -0.0150 to -0.0034).

Both radiological parameters, extent of disease and grade of cavities on chest X-ray were significantly associated with BMI, (p-value <0.001), with more extensive lung disease associated with a lower BMI (Figures 16 & 17).
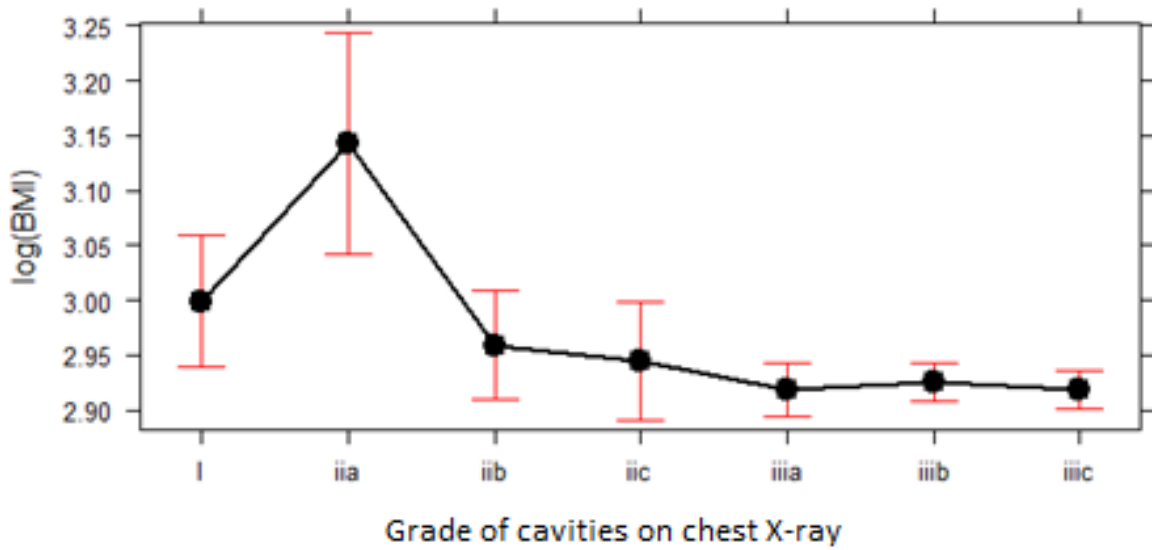
Figure 16. Effect plot of grade of cavities on chest X-ray versus log(BMI) (n=689)
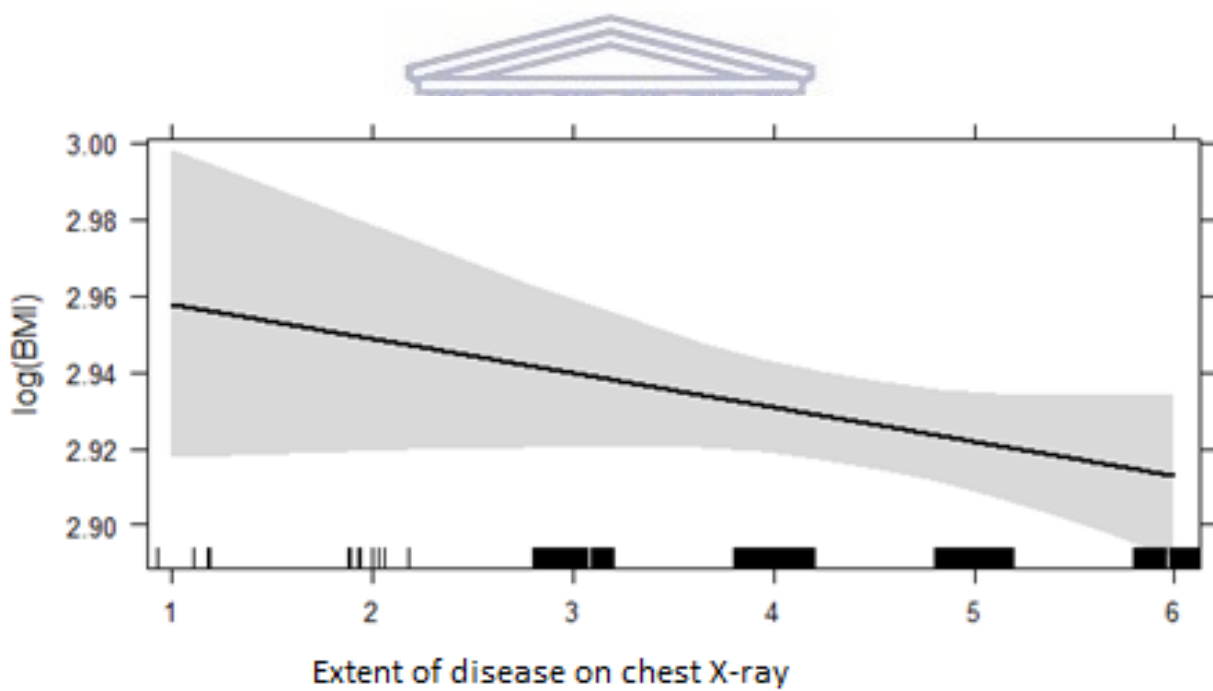
Figure 17. Effect plot of extent of disease on chest X-ray versus log(BMI) (n=689)

Discussion

Decreasing TB incidence

Despite the ongoing high incidence of TB in South Africa, small wins in key programme indicators have been observed recently. Since 2012, TB incidence has shown a steady, although small, downward trend. This may be linked to the plateauing HIV-prevalence rate, as well as various interventions implemented in the health system and national TB programme over the past few years.

The South African NTP has implemented a series of interventions aimed at improving both access to and effectiveness of the TB programme since its establishment in 1994. These include the implementation of the WHO-recommended DOTS strategy for improved programme monitoring and effective management, development of the District Health System to decentralise and increase access to primary health care, and integration of TB & HIV health services, with the provision of life-saving antiretroviral therapy (ART) for all TB/HIV co-infected patients.

Decreasing TB disease-severity at diagnosis

This study reviewed the clinical records of adults with pulmonary TB in a clinical research setting over an 18-year period, from 1991 to 2009. The results thus present a longitudinal overview of changes in objective measures of disease severity in adults with pulmonary TB from a largely unchanged geographic location. Although a sizeable proportion of patients had an unrecorded HIV status, HIV prevalence was relatively low where it was recorded.

Data from the study suggest an initial worsening of the infectious burden in pulmonary TB patients, based on microbiological parameters, over the first part of the study period, until 2001. This correlates roughly with the period of exponential rise in new TB infections (1996 - 2004) and ongoing steady increase in HIV prevalence. No study data is available between 2002 & 2004.

Over the later study years, 2005 - 2009, TB disease severity appears to have decreased, with mean BMI increasing, bacterial load on solid culture medium decreasing, and more patients having minimal or moderate disease on chest X-ray compared to earlier years. This period correlates roughly with changes seen in key NTP performance indicators, such as TB incidence, case detection rate (CDR) and treatment outcomes. From 2005 to 2009, although TB incidence continued to increase, the rate of this increase was much lower. Over the same period, CDR reached a peak and first met the 70% World Health Organization-recommended target required for meaningful impact on the TB epidemic. TB treatment outcomes also improved from 2005 onward, although these haven't yet reached recommended targets.

A complex interplay of the various health system and NTP interventions over the years have likely led to a change in the presenting clinical profile of patients with TB, as observed in this study. If patients with pulmonary TB are indeed less severely ill by the time they are diagnosed, earlier detection of disease with a shorter symptomatic period is certainly an underlying reason. This, in turn, could be due to factors in the remit of the NTP: increased community awareness of the common features of TB; training of health professionals with implementation of diagnostic aids and algorithms for TB diagnosis and management; integrated TB/HIV management with consistent screening of HIV infected patients for TB at every health visit; increased efforts toward tracing and screening household contacts of those diagnosed with TB.

Public health implications

Decreased TB disease-severity at diagnosis is associated with both improved treatment outcomes for the individual, as well as a decreased risk of transmission of TB to contacts within households and other social environments. It is this latter benefit that requires further exploration in the quest toward TB elimination within the foreseeable future. One way to achieve this is through active screening for TB in high-prevalence, high-risk communities and settings.

Limitations

Data available for analysis in this study was from patients voluntarily taking part in TB clinical drug trials, with enrolment occurring consecutively until recruitment targets were reached. TB patients enrolled into clinical trials may represent a less severely ill population of patients and may not accurately reflect the general population of pulmonary TB patients. A second limitation was that the database had many missing data points, for different variables between patients, i.e. not all patient entries contained all key variables. The large proportion of missing HIV status data limited the ability of the study to evaluate the clinical features of TB patients with reference to HIV status. Although the trials included in this review enrolled only HIV negative patients in the earlier years and included only HIV positive patients with relatively intact immune function in later years, the database is composed of all recruited patients and not only those enrolled onto these trials. This may imply that the HIV/TB co-infection rate of this study population more closely mirrored the general adult TB population than the eventual trial participants. HIV could thus be a confounder in the secular changes observed in sputum and X-ray findings. However, concomitant improvements in BMI suggest that the trends are independent of HIV status.

Conclusion

Patients appeared to present with less severe TB disease at diagnosis during the later study years (2005-2009). This could be due to a number of interacting factors, such as increased self-recognition of TB symptoms in the community, as well as improved access to & effectiveness of the health system and NPT over this period. Earlier diagnosis of patients with infectious pulmonary TB is imperative to decrease the risk of ongoing transmission within communities and to achieving TB elimination goals.

The importance of activities geared toward the detection and treatment of TB early within the disease process cannot be overstated. The symptomatic period, from the first appearance of TB symptoms to treatment initiation, presents one of the greatest opportunities for health systems, TB control programmes and communities alike to make a meaningful impact on the TB epidemic. Analysing the presenting clinical profile of patients with pulmonary TB at initial diagnosis may add to our understanding of TB control efforts over time. Where aggregate findings show patients to be less ill at diagnosis, this may point toward a shorter symptomatic period and a well-functioning TB programme, whereas findings of more significant illness at diagnosis may be an indication that increased efforts toward early diagnosis and active case-finding are required.

Recommendations

Documentation of the clinical profile of patients when first diagnosed with pulmonary TB may serve as a proxy measure to determine progress made toward diagnosing TB early during the symptomatic period. Clinical measures that could be incorporated either individually or as part of a clinical scoring system include the following: BMI, duration and total number of TB-related symptoms, sputum smear grade or level of *M.tb* positivity on Xpert MTB/RIF, and chest X-ray findings where possible.

The South African National Strategic Plan for HIV, STIs & TB (2012-2016) included the objective of annual TB screening for *all persons* to identify infectious disease early and decrease transmission within communities. Policy for this goal is thus already present. What is required are the resources for implementation. Greater use of lay persons and community health workers to conduct and assist with active TB case-finding within their communities is one possible strategy. Increased importance should be placed on active case-finding activities, with the required resources made available to health facilities in order to reach the required targets.

References

Churchyard, G., Mametja, L., Mvusi, L., Ndjeka, N., Hesseling, A., Reid, A., Babatunde, S. and Pillay, Y. (2014). Tuberculosis control in South Africa: Successes, challenges and recommendations. *South African Medical Journal,* 104(3 Suppl 1), pp.244-248.

Colebunders, R. and Bastian, I. (2000). A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease,* 4, pp.97-107.

Day, C. and Gray, A. Health and related indicators. In: Fonn, S. and Padarath, A., editors. (2010). *South African Health Review 2010*. Durban: Health Systems Trust. Available online: http://www.hst.org.za/publications/876

Day, C. and Gray, A. Health and related indicators. In: Padarath, A. and English, R., editors. (2013). *South African Health Review 2012/2013*. Durban: Health Systems Trust. Available online: http://www.hst.org.za/publications/south-african-health-review-2012/13

Day, C. and Gray, A. Health and related indicators. In: Padarath, A., King, J., Mackie, E. and Casciola, J., editors. (2016). *South African Health Review 2016*. Durban: Health Systems Trust. Available online: http://www.hst.org.za/publications/south-african-health-review-2016

De Cock, K., Soro, B., Coulibaly, I., Lucas, S. (1992). Tuberculosis and HIV Infection in Sub-Saharan Africa. *Journal of the American Medical Association*, 268, pp.1581-1587.

Department of Health (DOH). (2014). *National Tuberculosis Management Guidelines 2014*. Pretoria: Department of Health, South Africa.

De Jager, V., Van Der Merwe, L., Venter, A., Donald, P. and Diacon, A. (2017). Time trends in sputum mycobacterial load and 2-day bactericidal activity of INH-containing anti-tuberculosis therapies. *Antimicrobial Agents and Chemotherapy,* 61(4), pp.e02088-16.

Dye, C., Lönnroth, K., Jaramillo, E., Williams, B. and Raviglione, M. (2009). Trends in tuberculosis incidence and their determinants in 134 countries. *Bulletin of the World Health Organisation*, 87, pp.683–691.

Elliott, A, Hayes, R., Halwiindi, B., Luo, N., Tembo, G., Pobee, J., Nunn, P. and Mcadam, K. (1993). The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. *Aids*, 7, pp.981-7.
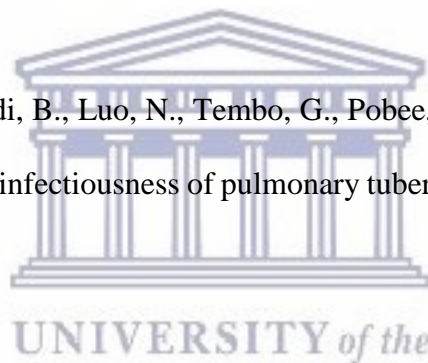
Golub, J., Bur, S., Cronin, W., Gange, S., Baruch, N., Comstock, G. and Chaisson, R. (2006). Delayed tuberculosis diagnosis and tuberculosis transmission. *International Journal of Tuberculosis and Lung Disease*, 10, pp.24-30.

Heywood, M. (2009). South Africa's Treatment Action Campaign: combining law and social mobilization to realize the right to health. *Journal of Human Rights Practice,* 1(1), pp.14–36.

Kironde, S. Tuberculosis. In: Ntuli, A, Crisp, N., Clarke, E. and Barron, P., editors. (2000). *South African Health Review 2000*. Durban: Health Systems Trust. Available online: http://www.hst.org.za/sahr

Lohmann, E., Koster, B., Le Cessie, S., Kamst-van Agterveld, M., Van Soolingen, D. and Arend, S. (2012). Grading of a positive sputum smear and the risk of Mycobacterium tuberculosis transmission. *International Journal of Tuberculosis and Lung Disease*, 16, pp.1477-84.

Maher, D. and Mikulencak, M. (1999). What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS. Geneva: *World Health Organization*.

Mahtab, S. and Coetzee, D. (2017). Influence of HIV and other risk factors on tuberculosis. *South African Medical Journal*, 107(5), pp.428-434.

Naidoo, S. Local government in a move to a district health system. In: Barron, P., editor. (1997). *South African Health Review 1997*. Durban: Health Systems Trust.

Ntuli, A., Crisp, N., Clarke, E. and Barron, P., editors. 2000. *South African Health Review 2000*. Durban: Health Systems Trust. Available online: http://www.hst.org.za/sahr

Packard, R. (1989). Introduction: industrialization and the political economy of tuberculosis. In: White Plague, Black Labor: tuberculosis and the political economy of health and disease in South Africa. Los Angeles: *University of California Press*, pp.xxvii-xlvii.

Perkins, M. and Cunningham, J. (2007). Facing the Crisis: Improving the diagnosis of tuberculosis in the HIV era. *Journal of Infectious Diseases*, 196, pp.S15-S27.

R Core Team. (2016). R: A language and environment for statistical computing. Vienna: *R Foundation for Statistical Computing*.

South African National Aids Counsel (SANAC). (2011). National Strategic Plan on HIV, STIs and TB 2012 – 2016. Republic of South Africa: *SANAC*.

Schneider, H., Gilson, L., Ogden, J., Lush, L. and Walt, G. (2006). Health systems and the implementation of disease programmes: case studies from South Africa. *Global Public Health*, 1 (1), pp.49-64.

Stinson, K., Eisenach, K., Kayes, S., Matsumoto, M., Siddiqi, S., Nakashima, S., Hashizume, H., Timm, J., Morrissey, A., Mendoza, M. and Mathai, P, editors. (2014). Mycobacteriology laboratory manual. *World Health Organization / Global laboratory initiative*.

Verver, S., Bwire, R. and Borgdorff, M. (2001). Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. *International Journal of Tuberculosis and Lung Disease,* 5(5), pp.419–425.

Virenfeldt, J., Rudolf, F., Camara, C., Furtado, A., Gomes, V., Aaby, P., Petersen, E. and Wejse, C. (2014). Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study. *BMJ Open*, 4, pp.e004818.

Ward, H., Marciniuk, D., Pahwa, P. and Hoeppner, V. (2004). Extent of pulmonary tuberculosis in patients diagnosed by active compared to passive case finding. *International Journal of Tuberculosis and Lung Disease*, 8(5), pp.593 - 597.

Weyer, K. Tuberculosis. In: Barron, P., editor. (1997). South African Health Review 1997. Durban: *Health Systems Trust*.

Weyer, K. (2007). Case study: South Africa. *Bulletin of the World Health Organisation*, 85(5), pp.391–392.

World Health Organization (WHO). (1991). First programme report (1898-1990) and future plan (1991-1995). Geneva: *World Health Organization*.

World Health Organization (WHO). (2010). The global plan to stop TB 2011-2015: transforming the fight toward elimination of tuberculosis. Geneva: *World Health Organization*.

World Health Organization (WHO). (2014). Global tuberculosis report 2014. Geneva: *World Health Organization*.

World Health Organization (WHO). (2015). Global tuberculosis report 2015. Geneva: *World Health Organization*.
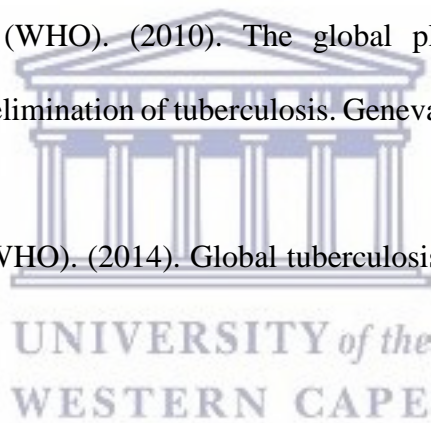
Appendix A.

Table A.1. Acid fast bacilli (AFB) grading scale for fluorescent stain (Stinson et al, 2014)

What you see (200x)	What you see (400x)	What to report*
No AFB in one length	No AFB in one length	No AFB observed
1-4 AFB in one length	1-2 AFB in one length	Confirmation required**
5-49 AFB in one length	3-24 AFB in one length	Scanty
3-24 AFB in one field	1-6 AFB in one field	1+
25-250 AFB in one field	7-60 AFB in one field	2+
> 250 AFB in one field	> 60 AFB in one field	3+

*The number of AFB indicates how infectious the patient is. It is important to record exactly what you see.

**Confirmation required by another technician or prepare another smear, stain and read.

Table A.2. Chest X-ray classification system

Cavity: a lucency completely surrounded by parenchymal opacification of ≥ 1cm in diameter in its maximum dimension (measured at point of maximum dimension). It can be scored as:	
I	Absent / None
ii	Single cavity - a. ≤ 2cm b. 2 – 4cm c. > 4cm
iii	Multiple cavities - a. largest ≤ 2cm b. largest 2 – 4cm c. largest > 4cm
Extent of disease can be scored as:	
I	Minimal disease (no active disease on radiological grounds)
II	Minimal disease, slightly more extensive than I (active on radiological grounds)
III	Limited disease, more than II, involving an area ≤ the upper lobe of the lung
IV	Moderate disease, more than III, involving an area ≤ to one lung
V	Extensive disease, involving a total or > one lung (but with health lung tissue still visible)
VI	Massive, extensive bilateral disease (no healthy lung visible)