UNIVERSITY OF CALGARY

Assessing the Impact of the Directly Observed Treatment Short-Course (DOTS) for the Control of Tuberculosis in DOTS-Recipient Countries: Cross-National Evidence for 1996-2006

by

Halima Mohamed

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCES

DEPARTMENT OF COMMUNITY HEALTH SCIENCES

CALGARY, ALBERTA

MAY 31, 2011

UNIVERSITY OF
CALGARY

Abstract

Objective: To assess the impact of the World Health Organization (WHO) Directly Observed Treatment Short-Course (DOTS) TB control strategy for reducing the burden (i.e., incidence, prevalence and mortality rates) of TB infections in the last decade.

Research question: To what extent has the WHO's DOTS strategy for TB control influenced the growth and levels of TB in DOTS recipient countries in the last decade?

Method: Descriptive study using country-level aggregate data from the WHO global TB and the Human Development Index (HDI) United Nations Human Development Program (UNDP) databases for the period of 1985-2006.

Results: DOTS has influenced the growth and levels of TB burden in countries it was applied except in Africa. Differences in both disease burden levels and DOTS impact on TB control outcomes between DOTS and Non-DOTS recipient countries were significantly influenced by socio-economic conditions of individual countries. There is evidence that, to make the DOTS impact on TB control outcomes comparable in Africa to that of the rest of the world, health system strengthening is a key challenge to improving the delivery of effective, accessible and affordable TB care.

Conclusion: Overall, global TB prevalence fell, but incidence rose and mortality remained unchanged in the last decade. Although it was difficult to link the observed differences with DOTS, and TB burden levels, more TB cases were reported in DOTS-recipient than non-DOTS-recipient countries. While the DOTS strategy seemed effective in reducing TB burden levels in all other regions, significant differences were observed between Africa and the rest of the world.

Preface

The goal of this thesis was to determine the impact of the WHO DOTS policy on TB control outcomes and ascertain whether the DOTS strategy influenced TB burden levels in DOTS-recipient countries, particularly in Africa where TB burden levels have risen at alarming rates over the last decade. TB control in resource-poor settings is complex, costly and requires enormous resources (financial and human). Though mostly successful in slowing down the growing TB epidemic, it is not yet clear whether the WHO DOTS strategy has had any added effect in reducing TB burden levels in high prevalence countries. Not only does it need to be effective, affordable, accessible and equitable to all populations, it needs sustained resources. Recognising the roles, responsibilities, financial and knowledge capacities of those receiving and providing TB care is essential in the battle against an ever-growing global TB epidemic.

The WHO's DOTS strategy has been the framework for TB control for nearly two decades. However, DOTS's impact on TB control outcomes in high prevalence settings like the African region has been overlooked in the current TB literature. Why has the TB burden declined globally but risen in Africa? What are the factors contributing to rising TB burden levels in the African region? Is it that DOTS has simply failed in halting the rising TB epidemic in the African region, or are there other factors undermining its effectiveness? Finding answers for such questions demands pragmatic and rigorous analysis to determine whether the negative effects of complex and expensive TB control interventions outweigh the benefits. The current TB literature has not demonstrated the extent to which the introduction of expensive policies or complex strategies can produce tangible results in all settings.

Acknowledgements

My deep-felt gratitude goes to my supervisor Dr. Herb Emery for his outstanding guidance, professionalism, and encouragement throughout the course of this work. Dr. Emery, thank you very much for your patience, understanding and unconditional support without which I could not have done it. I would like to thank Dr. Misha Eliasziw who provided useful statistical input and made a valuable contribution to my thesis writing.

Many thanks to the Department of Community Health Sciences for all the support I received during my study at the school. Special thanks to Dr. Mingshan Lu for her critical comments and constructive feedback on the structure, content and the quality of thesis writing which I needed the most.

My thanks to the Department of Community Health Sciences Graduate Program Coordinator, Dr. Marilynne Hebert for her inspiration, outstanding support and most importantly for believing in me and the importance of my work and making sure that I finished my degree. My thanks to the Library Resource Centre people Dr. Atak Fung, Giesla Angels and Sharon Neary for their help with data cleaning. Folks! It worked!

Table of Contents

List of Tables

List of Figures and Illustrations

List Abbreviations

DOTS	Directly Observed Treatment Short-Course
WHO	World Health Organization
TB	Tuberculosis
NTPs	National Tuberculosis Programs
BCG	Bacillus Calmette-Guérin
USA	United States of America
CDR	Case Detection Rate
TSR	Treatment Success Rates
HBCs	High Burden Countries
PCH	Primary Health Care
HIV	Human Immuno-Deficiency Virus
AFR	The World Health Organization, the African Region
AMR	The World Health Organization, the Americas Region
EUR	The World Health Organization, the European Region
EMR	The World Health Organization, Eastern Mediterranean Region
WPR	The World Health Organization, the Western Pacific Region
UNDP	United Nations Development Program
UNHDI	United Nation's Human Development Index
HDI	Human Development Index
AC	All Countries
DR	DOTS-Recipient
NDR	Non-DOTS-Recipient
RR	Resource-Rich
RP	Resource-Poor
RRDR	Resource-Rich DOTS Recipient
RPDR	Resource-Poor DOTS Recipient
RRNDR	Resource-Rich Non-DOTS Recipient
RPNDR	Resource-Poor Non-DOTS Recipient
Ho	The Null Hypothesis
Ha	The Alternative Hypothesis
SES	Socio-Economic Status
SD	Standard Deviation
SDΔ	The Standard Deviation of the Differences
MeanΔ	Mean Differences
Δ	Difference
μ	Population Mean Values
SE	The Standard Error
SED	Standard Error of the Differences
t	The Test Statistics
P	P-Values

Chapter One: **Introduction**

1.1 **Background**

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium* (1). TB is a preventable and curable disease but if it is not properly controlled, one person with TB can indirectly infect 10-15 of people each year (1). A person can have active or inactive tuberculosis and people with active TB in their lungs can pass the bacteria on to anyone they come into close contact with (48). Active TB disease means the bacteria are active in the body and the immune system is unable to stop them from causing illness (48). When a person with active tuberculosis coughs, sneezes or spits, people nearby may breathe in the tuberculosis bacteria and become infected (48). Left untreated, each person with active tuberculosis will infect on average between 10 and 15 people every year and the time from infection to death is two to five years (48).

According to the World Health Organization's (WHO) annual report in 2008, one third of the world's population is now infected with TB infections (2;3). The rise of TB burden levels is a public health concern not only because TB kills millions of people around the world, particularly among the reproductive age group, but also because it threatens the livelihoods of families and communities worldwide (4-8).

Developing countries, where 95% of all new TB cases and 99% of deaths occur, are the hardest hit (2;9). The rising global TB burden is attributed to, among other things, high transmission rates, inadequate sanitation, poor control of TB infections, widespread malnutrition exacerbated by poverty and a high incidence of HIV/TB co-infection rates in high prevalence settings (2;3;9;10). Arguably a lack of adequate education and knowledge in the community is also a key

factor in the rising global TB burden (1). The most effective way to control the spread of TB infections is to identify new TB cases and treat them successfully as early as possible (11-14). To deal with the growing global TB problem, the WHO declared TB as a global emergency and introduced the Directly Observed Treatment Short-Course (DOTS) strategy in 1994 (1). This study investigated the impact of the DOTS on TB control outcomes in countries that have adopted DOTS into their national TB programs (NTPs) between 1996 and 2006 (2;3). This chapter presents a brief overview of the history of TB infections together with the role of DOTS in global TB control in the last decade.

1.2 **The History, Control and Treatment of TB infections**

The history of global TB control began with René Theophile Hyacinthe Laennec who in 1819 published the "De l'auscultation médiate" – the first book that provided a clear understanding about the pathological and descriptive nature of TB infections (15;16). The first global TB vaccine was developed in 1906 in Germany, and the only treatment available besides sanatoria at the time was a surgical intervention which consisted of collapsing an infected lung to "rest" it and allow lesions to heal (16;17). This technique was of little benefit and was largely discontinued by the 1950s (16;17).

The first genuine success of modern TB control began with the discovery of vaccines against TB bacilli (16;17). In 1908 Albert Calmette and Camille Guérin developed a TB vaccine from attenuated bovine-strain tuberculosis using culture media in order to control virulence of bovine TB (16;17).

This is a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus that has lost its virulence in humans by being specially cultured in an artificial medium for years. The bacilli have retained enough strong antigenicity to become a somewhat effective vaccine for the prevention of human tuberculosis. At best, the BCG vaccine is 80% effective in preventing tuberculosis for a duration of 15 years; however, its protective effect appears to vary according to geography (16;18;19). This new vaccine was later named Bacillus Calmette-Guérin or Bacille Calmette-Guérin (BCG), and was first used on humans in 1921 in France (16;17). However, this new vaccine did not receive widespread acceptance in other countries (i.e., USA, Great Britain, and Germany) until after World War II (16;17).

Between the 1940s and the 1960s, the standard treatment for TB infections was a combination of four to five drugs (Table-1, in Appendix A) given for nine months, depending on the bacterial load and the disease progression of individual TB patients (17;20;21). With the drugs being given daily or bi-weekly for six to nine months, this type of multi-drug treatment combination proved to be highly effective and well-tolerated in all patients (17;20;21).

In the 1960s, empirical evidence that supported the efficacy and the use of vaccines as well as multi-drug treatment became available (17;18;20;22). This new approach established two basic principles of treatment: (i) effective treatment should combine two or more drugs capable of killing TB bacteria; (ii) the cure of TB infections needed prolonged treatment after the sputum conversion and amelioration of symptoms, to prevent disease re-occurrence (21).

In terms of efficacy and effectiveness, the highest anti-bacterial activity was found in Isoniazid, Rifampicin and Streptomycin (26;28;30). Ethambutol was the least toxic drug and prevented drug-resistance, while Streptomycin and Pyrasinamide were known to be the most potent drugs but highly toxic (32-34;36-38). Streptomycin is the least effective and requires constant and direct supervision which makes it difficult for both patients and health care workers to commit to the long duration of treatment (18-24 months) (17-19;21;23;24). Pyrasinamide is assumed to be a good supplement to other two drugs (Rifampicin and Isoniazid) but little or limited information is available about its effectiveness (17;23).

The combination of multi-drugs resulted in rapid clinical improvement and significant drops in bacterial count within the first two to three months of treatment (also known as the intensive phase) (8;17-19;21;25). This treatment also improved the quality of life for TB patients, produced long-term cure rates and was widely used in many parts of the world (15-17;20-22).

Due to the long duration of TB treatment, and the high cost of drugs, low patient compliance was widely reported, mainly in developing countries (32;33). In some areas, failure and relapse rates among TB patients ranged from 10-60% resulting in the wide spread of multi-drug-resistance (32;33). In addition to the increased difficulty in treating the disease, the patient remained infectious for longer, increasing the risk to the public and to healthcare workers. Multi-drug resistant (MDR) TB also appears in association with HIV infection and AIDS, further compromising the health and the immune system of these patients (4;9). HIV itself does not increase the chance of drug resistance, but it does accelerate the progression of TB infection into active TB disease (26;27). Tuberculosis can become resistant if a patient is not treated long

enough, does not take prescribed medications properly or does not receive the right drugs (26;27). As drug-resistant TB became widely reported throughout the world, more robust treatment and delivery strategies were urgently needed to increase the efficacy of modern drug therapy (15;16;22).

In 1995, more TB cases than previously expected were reported throughout the world (26). The rising global TB epidemic was believed to have been attributed to increased transmission rates exacerbated by poverty, drug-resistance and inadequate TB control interventions in countries with high TB prevalence (32;33).

1.3 **The History and Role of DOTS in Global TB Control for the Last Decade**

DOTS strategy is the internationally recommended, most effective and cost-effective TB control strategy, particularly in low income countries (1). Although the origin of DOTS is disputed, it is often noted in the TB literature that DOTS was first introduced in the Indian sub-continent in the 1950s where sub-optimal diagnosis and treatment among TB patients had become widely prevalent (68). The DOTS strategy was re-invented by the World Bank and was presented as the most effective and cost-effective TB control strategy, particularly for developing countries where approximately 90% of the world's population resides (68). The World Bank had been criticised for increased ill-health in many developing countries, mainly in Africa and Latin America, due to severe cutbacks in health care spending (1;18;68).

The WHO endorsed, introduced and recommended DOTS to all countries of the world that they adopt, implement and integrate the DOTS into their NTPs through primary health care (PHC) (1). *"We have a Cure and we need to mobilize the world to use it"* (1). The aim was to detect

70% of new TB cases and successfully treat 85% of detected TB cases (1). What differentiates DOTS from other conventional strategies is that, under DOTS (i) TB cases are diagnosed, (ii) cases are treated for six to eight months with high quality TB drugs, and (iii) the strategy promotes adherence to the relatively difficult treatment regimen (1). DOTS is considered to be the most cost-effective TB control strategy at a estimated cost of as little as $150-$750 per death averted, depending on existing health system capacities at the country level (1).

DOTS as a TB control strategy combines a treatment protocol (short-course drug therapy) and a delivery policy (direct observation) (1). As a treatment protocol, six to nine months of standardised treatment (short-course therapy) is given to TB patients under direct observation by a health care or community worker or a family member (1). The aim is to ensure that TB medications are taken in the right combination (the first five essential drugs are a combination of Streptomycin, Izoizid, Rifampicin, Ethamabutol, Pryzynimide at the right time and using the correct dosage (2).

As a delivery strategy, DOTS ensures appropriate diagnosis of TB infections and a good registration system for all cases detected, followed by standardised treatment regimens with a secure supply of high quality anti-TB drugs (2). For delivery, DOTS is used as an administrative protocol performed by a designated observer to increase treatment compliance among TB patients (1).

However, the successes and failures of DOTS depend on the successful implementation of its five essential elements: (i) government commitment to sustained TB control; (ii) sputum-smear

microscopy to detect the infectious cases among those people attending health care facilities with pulmonary symptoms (most notably, a cough of three weeks' duration or more); (iii) standardised short-course anti-TB treatment for at least all sputum smear-positive (SS+) pulmonary TB cases, with direct observation of treatment for at least the initial two months; (iv) a regular, uninterrupted supply of anti-TB drugs and diagnostics and (v) a monitoring and accountability system for program supervision, and evaluation of the treatment outcome for each patient diagnosed with TB (1).

The WHO declared TB as a global emergency in 1993 and introduced DOTS strategy in 1994 as a response (1). It was universally implemented in all countries (1). The aim of introducing DOTS was to achieve the set targets (to detect 70% new TB cases and cure 85% of those detected successfully) and to halve global TB prevalence and deaths by 2015, relative to the 1990s levels (1). If these targets were reached, the total global TB incidence would be reduced to less than 1 case per million population per year by 2050 (2;9;28). Such global TB control initiatives have been pushing for extended DOTS coverage in all countries of the world in order to eradicate TB by 2015 (2;9;28).

Chapter Two: **Literature Review**

2.1 **Introduction**

This chapter presents a critical review of the relevant literature on the impact of DOTS on global TB burden levels for the period of 1996-2006. The objectives of the literature review were (i) to examine relevant literature on DOTS' impact on TB control outcomes and determine whether this strategy has succeeded in producing the expected and predicted outcomes in the areas it was applied; (ii) to determine whether TB burden levels varied across national settings in DOTS areas and (iii) to investigate factors contributing to differences in the observed outcomes in DOTS effect and difference in TB burden levels in DOTS-recipient countries.

With the introduction of DOTS, the WHO's global TB control policy changed from passive to active case finding through extended DOTS coverage in all countries of the world by 2005 (2;29). Passive case finding was used to examine the number of self-referred symptomatic TB cases to health care facilities in a given population (1). This type of approach is often used to find the number of smear-positive pulmonary tuberculosis cases through household contacts (1). Active case finding was used to find, diagnose, treat and follow up tuberculosis patients in a given population (1). This type of active approach is expected to reduce TB transmission as well as morbidity and mortality among individual patients (1).

To track progress in TB control under DOTS worldwide, the WHO established the global surveillance and monitoring system (2;3;10). The aim was determine whether their successful TB control outcomes i.e., good reporting, recording systems and the ability to administer TB control activities under DOTS were or could be influenced by existing health system capacity at

the national and global levels. In other words the ability of the national tuberculosis programs (NTPs) to detect new TB cases under DOTS provides an indication of how effective NTPs was in finding people with active TB and diagnosing them appropriately (2;9;28). The reported TB estimates were based on data collected from countries thought to have reliable and good reporting systems (2). Through this approach all countries would submit data on TB control progress to the WHO global TB database annually (1).

Progress in control and achievement towards the set targets in a given country were determined by levels of case notification rates (CNR), annual risk of infection (ARI) reported from tuberculin surveys and the number of smear-positive pulmonary disease (new TB cases) from prevalence surveys and levels of DOTS coverage (30). The levels, burden and trends of TB were determined by the percentage of people newly infected (incidence), living with (prevalence) and dying of (mortality) TB infections in any given country (47-48;59).

In 2003, the WHO reported dramatic successes in most of the countries where DOTS was applied (19-23). TB morbidity and mortality around the world is enormous, as 2 billion of the world's population is now infected with TB (1;18). Between 9 and 13 million develop TB each year in the world (2;9). Although the introduction of the DOTS strategy might have slowed the growth and levels of TB burden in DOTS-recipient countries, strong evidence linking DOTS with the observed outcomes is unclear or lacking in the current TB literature (14;31-33).

In 2006, the proportion of detected TB cases under DOTS was less than one third of the world's TB cases, which continued to undermine success in TB control efforts (34). Empirical evidence

supporting DOTS efficacy over conventional treatment from cross-national settings is lacking. Randomised control trials (RCTs) that assessed the long-term effects of DOTS on TB control outcomes concluded that the DOTS strategy had no inherent effects over non-DOTS strategies (13;35;36). However, whether there is a direct correlation between DOTS and decline in TB burden levels in the last decade is unclear in the current TB literature.

The notion that DOTS is more efficacious than conventional treatment has been widely contested in the current TB literature (4;11;12;26;37;38). DOTS critics argue that countries reporting good outcomes were settings that were optimal for DOTS and were already producing good results without DOTS (12;13;35;36;39-41). DOTS projected effects were based almost entirely on historical comparisons and clinical impressions supported by uncontrolled data and common sense, not on scientific grounds (12;13;35;36;39-41). Therefore, the introduction of complex and expensive programmes such as DOTS in places that had already produced good results under non-DOTS strategies was simply unjustified (13).

Critics argue that the enormous public health burden inflicted by HIV/TB legitimises the use of cross-national data to gain insights into their transmission dynamics and to determine the effectiveness of current control strategies (14;15;16). In the Sub-Saharan Africa (SSA) region the burden of HIV/TB co-infections is particularly high, and the dual epidemics of these two diseases are of growing concern worldwide (1). Critics argue that the current challenge is to find ways of preventing both TB and HIV, and to improve diagnosis and management of co-infections (1).

The WHO's reported annual figures (incidence, prevalence and mortality rates) were used to assess progress in TB control and changing TB trends in DOTS-recipient countries only (42). Conflicting conclusions have been drawn as to whether DOTS is an effective TB control strategy in high prevalence settings like the SSA (1;34;39;41;43). Critics argue that DOTS's impact on TB control outcomes was influenced by several factors.

First, increased TB control outcomes depended on DOTS through patient-friendly treatment approach only (45;47). Secondly, WHO and its global control partners assumed that poor TB control outcomes were attributed to inadequate health service delivery and needed to be corrected with health sector reform (34;44). Thirdly, DOTS was assumed to be the best and most suitable approach to reduce the growing global TB problem, without addressing the root causes of the problem such as health delivery policies/practices and most importantly poverty (34;44). It was applied as a prevention-based strategy which solely relied on case notification data (acquired through passive rather than active surveillance) (1). Such strategies have never eradicated diseases, and have often ignored the potential effects of other determinant factors, such as health systems' capacity influenced by the income levels of individual countries (45).

Others argue not only that TB control interventions delivered through DOTS were complex, expensive and ineffective in halting the spread and growth of TB infection but they created more harm than good (34;44). They were ultimately harmful because such interventions were funded through foreign dollars, and when the cash stopped, programs also stopped (34;44). Thus, the adverse effects of frequently interrupted TB care on population health outcomes were often unprecedented (34;44).

DOTS critics argue that the observed outcomes in TB control were only reported in settings that were optimal for DOTS and already producing good results without DOTS, and that the net effect of the DOTS strategy in high prevalence areas is unclear (4;11;12;26;37;38). Consequently, current estimates of global TB burden seem to be based on patients' numbers (case notification rate rather than case detection rate and treatment outcomes), and not merely on understanding the magnitude and levels of TB burden (i.e., new cases detected, treatment/cure rates or deaths) in a given setting (13;35;41). This is partly because the successful implementation of DOTS required much more than the basic improvement of health services in regions like the SSA and other heavily affected areas (1;34;39;41;43).

The provision of effective and reliable TB care under DOTS required an uninterrupted drug supply, good and reliable health care system infrastructure (i.e., good laboratory services) and skilled and knowledgeable health care personnel capable of providing appropriate diagnosis and management of TB infections (34;44). Due to political, social, economic and environmental conditions on the ground in these settings, DOTS strategy was deemed ineffective in reducing TB burden levels in regions like the SSA (45). Therefore, if the current approach with no clear strategy continues to dominate the debate, the globally set targets will be missed and the situation is likely to worsen (35;45).

To determine changes in trends and levels as well as the impact of the DOTS strategy on the global TB disease, the epidemiological nature and relationship of applied measures of effects

(incidence, prevalence and mortality rates) together with operational definitions are discussed in the following paragraphs.

2.2 **Operational Definitions**

2.2.1 ***The Burden of TB***

The burden of TB disease in any given population is the cumulative number of people who are newly infected (incidence), living (prevalence) and have died (mortality) of TB disease per 100,000 population per year (28;46). Therefore, the burden of TB disease is defined as "the total number of healthy lives lost to all TB related illnesses" (28;46). The number of reported TB cases arising in one year per 100,000 population is reported as the ″rate″ (1). The reported estimates of TB burden are based on expert opinion and an analytical process for each country derived from one or more of four approaches, given available data:

(i) Reported incidence = case notifications /estimated proportion of cases detected (in most countries under DOTS)

(ii) Incidence = prevalence/duration of condition including the annual risk of TB infection in a year per 100,000 population Stýblo Rule (see Chapter Five for details)

(iii) Mortality= deaths/proportion of incident cases that die.

2.2.2 ***TB Incidence Rates***

The estimated TB incidence is expressed as the number of new TB cases per 100,000 population per year (10). Periodic incidence includes three important elements; the number of new TB cases (numerator), the population at risk (denominator) and the period during which TB cases accrue (57). The denominator for incidence rates is the population at risk, thus individuals who have already developed the disease are excluded (1-5). The incidence rate uses the

frequency of new TB cases in the numerator, which means that individuals who have a history of TB disease are not included.

2.2.3 *TB Prevalence Rates*

TB prevalence is expressed as the total number of existing (all forms) TB cases per 100,000 population per year at a specified period of time (21). It measures the proportion of the population with the disease at a specified period of time (2;9;47). In other words, prevalence provides information about occurrence of status types - illness, risk of getting infected with TB infections, risk of remaining in prevalence pool (i.e., cured or diseased) and the cumulative incidence and duration of being in the prevalence pool (7;8;44).

2.2.4 *Mortality Rates*

TB mortality is expressed as the estimated number of TB deaths (all forms) per 100,000 per population per year (11;12;48;49). Mortality estimate includes all TB deaths during a specified time (21).

2.2.5 *Case Detection Rate*

The term "case detection rate" (CDR) refers to the number of TB patients reported per 100,000 population per year within the national surveillance system in a given country (2;9;28). The CDR is the number of reported TB cases per 100,000 persons per year divided by the estimated incidence rate per 100,000 per year (12;48;50). It is important not to confuse TB CDR with TB incidence. TB incidence is the estimated number of new tuberculosis (all forms) cases arising in one year per 100,000 population, while TB CDR is the ratio of newly notified tuberculosis cases (including relapses) to estimated incident cases (case detection, all forms) (1).

The proportion of estimated new TB cases detected under DOTS provides an indication of how effective national tuberculosis programmes (NTPs) were in finding people with active TB and diagnosing them appropriately (2;9;28). Although the type of treatment, diagnosis and delivery strategies used play a significant role in the final TB control outcomes, an increased case detection rate is expected to foster higher and better treatment outcomes (6;7).

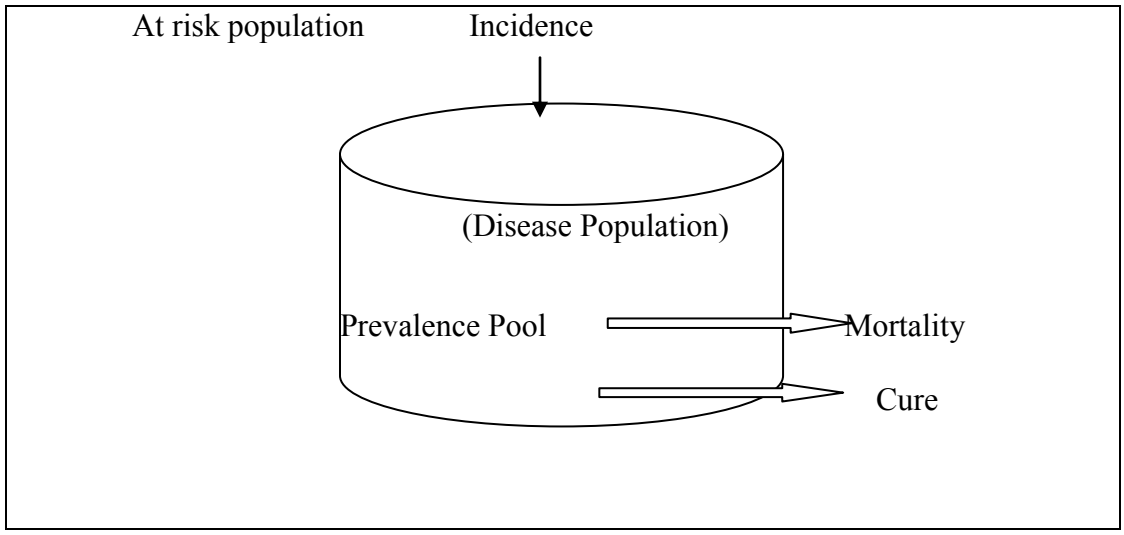
2.2.6 ***Treatment Outcomes under DOTS***

The treatment outcomes are determined by the percentage of TB patients (new smear-positive cases) who are cured (free of TB infections based on sputum smear test), plus the percentage of TB patients who have completed the full course of their treatment, but are not cured of TB (11;12;48).

2.3 **The Epidemiological Relationships Among Outcome Measures**

To examine the impact of DOTS on TB burden levels over the last decade, the relationships among incidence, prevalence and mortality rates were used as outcome measures as illustrated in the *Soup Can Model* (Figure 1) (2). The epidemiological relationships among measures of effects is determined by the number of people newly infected, living with or dying from TB in specified period of time in a given population (7-8). Such relationships are influenced by the number of people entering (incidence) or exiting (mortality/cure) the at-risk population (the prevalence pool) in a given population (47-48;59).

Figure 1 - The Epidemiological Relationships Among the Three Measures of Effects



Therefore, the number of people entering and exiting from the prevalence pool equals the number of people at risk for TB disease in a specified period of time (11;12;48).

The *Soup Can Model* was used to illustrate two things: (i) the relationships among incidence, prevalence and mortality rates as measures of effect and (ii) how these measures of effect influence each other in epidemiological terms. *The Soup Can Model* illustrates that if there is no change in the number of people entering and exiting the prevalence pool (mortality, recovery and cure) the disease burden level in a given population is considered to be in a steady state (11;12;47;48).

In the context of this study, the number of people entering (incidence) and exiting (deaths/cure) in the global TB prevalence pool was expected to change during the DOTS period given the application of improved TB control interventions (1). This is to say if the DOTS had an impact on global TB control outcomes the number of TB cases entering the prevalence pool was

expected to decline (1). Similarly, the number of people exiting the prevalence pool was expected to increase as access to diagnosis and treatment increased in the DOTS period (1).

2.4 **Research Study**

2.4.1 ***Problem Description***

The DOTS strategy was predominantly applied as the most effective and cost-effective approach (1). It is, however, unclear whether it is the only strategy that has influenced the observed differences in its effectiveness across national settings (12;13;22;29;36;39;51). Limited empirical evidence is available on DOTS's impact on both the expected and observed outcomes in the African region (52). Studies that have examined the effects of the DOTS effects in reduced TB burden have provided mixed results and often did not control factors contributing to the differences in TB burden levels in and across national settings (52). While the escalation of the TB epidemic in Africa demands urgent attention, the WHO has been subject to criticism that the working conditions under which DOTS operates are inadequate, particularly in the SSA (43;53;54).

The assumption that successful TB control depends essentially on DOTS impact is based on an understanding of the aetiology and epidemiological nature of TB infections in DOTS-recipient countries (2;36;55). However, this must be carefully examined under three conditions. Firstly, the direct correlation between TB burden decline and the DOTS strategy is virtually unknown. Secondly, the observed differences in TB burden levels across national settings might be attributed to factors other than DOTS. Third, there may be multiple factors contributing to the difference in DOTS influence, some which may be unknown and hence difficult to assess (11-14).

2.4.2 *Study Rationale*

The rationale for this study was to explore factors contributing not only to the observed differences in TB burden levels but also differences in DOTS' effectiveness in reducing the TB burden in DOTS-recipient countries. This evaluation study may have significant implications for TB control in high prevalence settings such as Africa in identifying factors contributing to the rising TB burden levels, as well as the ineffectiveness of the DOTS strategy in such settings.

To achieve the expected outcome (70% case detection and 85% treatment success rates), a minimum of 60-65% case detection rate and 85% TB care coverage were needed (1). These targets were chosen to significantly reduce TB incidence and decrease TB prevalence by approximately 10% per year without any major changes in global TB epidemiology (1). What is promising about the DOTS TB control is that it can easily be integrated into local health services and readily made available and accessible to all populations (1). However, DOTS is a complex and expensive strategy to implement, and many countries were faced with enormous challenges due to their SES conditions, making it impossible therefore to sustain TB control (14;53;56). Nearly two decades later, the extent to which the DOTS strategy influenced the growth and levels of TB burden is not clear in the current TB literature, particularly in DOTS-recipient countries.

2.4.3 *Study Significance*

Differences in health systems capacity, influenced by the SES conditions of individual countries, became a limiting factor to successful implementation of DOTS in different settings. Available evidence suggests that the differences in TB care service in many cross-national settings can be attributed to inequalities in access to affordable TB care, which tend to produce disparate TB

control outcomes among different sub-groups (1). However, a clear conclusion cannot be drawn about the impact of DOTS on TB control outcomes from the current TB literature, as little or no evidence is available from cross-national studies to support DOTS effectiveness over usual care.

Because clinical and epidemiological evidence linking DOTS with current TB outcomes is still inconclusive, the need to research the subject further was justified. The purpose of this study was to explore further whether the DOTS strategy has the potential effect for producing the expected and predicted outcomes in areas where it has been applied, particularly in high prevalence settings (2;3). The need is most urgent in Africa where TB burden levels are increasing in alarming rates (2;3;9;10;47).

2.4.4 ***Study Objectives***

1. To determine whether the WHO DOTS strategy has influenced the growth and levels of the global TB burden in the last decade
2. Investigate whether the observed TB control outcomes varied in and across national settings in DOTS-recipient countries
3. To assess whether the observed differences in TB burden levels between and within settings were attributed to DOTS (treatment-effect), influenced by growth and development levels (SES-effect) or other naturally occurring events (period-effect).

2.4.5 ***Study Questions***

1. To what extent has the WHO's DOTS strategy for TB control influenced the growth and levels of TB in DOTS recipient countries?
2. If it has, under what circumstances has DOTS impact on TB control outcomes varied in and across national settings, and why?

3. What factors have contributed to the observed differences in both TB burden levels and DOTS impact on TB control outcomes in and across national settings.

2.4.6 ***Expected Outcomes***

The expected outcomes were:

1. The working conditions in which DOTS operated were inadequate, and therefore DOTS failed to halt the growing TB burden in Africa, particularly in the SSA region.
2. Because DOTS impact on TB control outcomes is unknown, the observed differences in TB burden levels between Africa and the rest of the world might be attributed to factors other than DOTS impact (i.e., HIV and socio-economic conditions of individual countries).

Chapter Three: **Methods**

3.1 **Study Design**

This study adopted a descriptive comparative analysis approach with country-level aggregate data from two large institutional databases: the WHO global TB and the United Nations Development (UNDP) Human Development Index (HDI) databases. This comparative approach was adopted to determine if the differences in TB burden levels across countries and time periods were suggestive that DOTS has been effective. Descriptive comparative analysis was adopted to describe and also explain the differences between the comparison groups. However, it did not aim at generating changes in the comparison groups. Instead, it examined whether the observed findings (if any) were generalizable to all groups in the study population (70). The purpose of these types of comparisons was to explain whether the observed differences in TB burden levels were truly reflective of the differences in and/or outside the study population.

3.2 **Study Population**

The study population comprised 212 countries that have submitted data on TB trends to the WHO as well as on growth and development levels to the HDI between 1985 and 2006 (1;5). Countries were classified in two ways: whether they received DOTS or not, and SES where a country was considered to be resource-poor (RP; n=95) if 70% of its population lived on less than 2 dollar a day (52) (Table 1). A country was classified as resource-rich (RR; n=117) if more than 70% of its population lived on more than 2 dollar a day (52). A comparison of the differences in TB burden levels between RR-DOTS-recipient (RRDR) and RP DOTS-recipient (RPDR) countries was performed.

Table 1 - SES and DOTS-Status for All Countries

	SES		
DOTS	RR	RP	Total
Recipient	117	85	196
Non- Recipient	10	6	16
Total	127	95	212

Source: WHO and HDI Reports 1985-2006.

The inclusion and exclusion criteria for the number of participating countries in the HDI and the WHO TB burden annual rankings were those that provided information on growth and development each year between 1985 and 2006 (Table 2) (42). In the HDI database, the growth and development levels of individual countries were determined by three dimensions:

1. life expectancy at birth (an index of population health and longevity);
2. knowledge and education measured by the adult literacy rate of two thirds weighting combined with primary, secondary and tertiary gross enrolment ratio with one-third weighting; and
3. the standard of living (measured by a natural logarithm of gross-domestic products (GDP) per capita at purchasing power parity) (57;58).

GDP is a basic measure of a country's overall economic output: it is the market value of all final goods and services made within the borders of a country in a year, and it is often positively correlated with the standard of living (52). The aim of classifying countries into such categories was to assess whether countries with higher SES conditions had better treatment (DOTS) outcomes than those with lower SES conditions.

Table 2 - Inclusion and Exclusion Criteria Relating to Study

Inclusion	Exclusion
All countries that submitted data on TB incidence, prevalence and mortality rates to the WHO global TB database between 1985-2006	Countries that did not report data on TB incidence, prevalence and mortality rates to the WHO global TB database between 1985 and 2006
All countries that submitted data to HDI using growth and development data from the period 1985-2006	All countries that did not submit data to HDI on country-specific growth and development data from period 1985-2006 as composite measures
All countries that adopted DOTS into NTP between 1996 and 2006	All countries with no clear treatment or intervention (DOTS) and income status in each of the chosen databases
All countries that did not adopt DOTS into their NTP between 1996 and 2006	

3.3 **Data and Sources of Data**

The data used in this analysis were extracted from two databases: The WHO global TB database and the United Nations Human Development Index (UNHDI) that compiled data from country-specific TB trends (i.e., mortality, incidence and prevalence rates) during pre (1985-95) and DOTS (1996-2006) periods, representing 99.6% of the world's population (1).

The first set of data were extracted from the quarterly reports of the number of TB cases registered that were compiled and sent (either directly or via intermediate levels) to the central office of the national TB control program in participating countries (1). Annual case notifications (and other data on program performance) were collected by WHO via an annual data collection form, distributed to national TB control programs through the WHO regional and country offices (1). The country-specific data were compiled through forms submitted to the WHO country offices, designated TB experts and to the regional offices by WHO head office in Geneva (1).

Using the complete set of data for each country, a profile was constructed to tabulate all key indicators on epidemiological trends and burden of TB which was then returned to individual countries to be verified and reviewed by the NTP (1). The reported TB burden estimates were accumulated using country-specific data and consultation with national and international experts (1). Thus, as a result of this, data (case notifications, treatment outcomes, etc) presented for a given year may differ from those published previously (1).

A second of set of data was compiled to measure the growth and development levels of individual countries (1;52). Such data were compiled to rank and assess TB burden levels in countries with different SES profiles of 212 that have reported on TB trends to the WHO for the 2006 report and (2;9).

3.4 **Data Analysis**

3.4.1 ***Introduction***

For the purpose of this study data were analyzed in three ways: 1) to determine changes in global TB burden levels, differences in mean values in incidence, prevalence and mortality between pre and pre-DOTS period (the comparison of two samples) were compared at the global, regional and national levels without controlling for any treatment or SES conditions of individual distributions using paired t-test (42); 2) to assess whether the DOTS had influenced TB control outcomes, differences in mean scores in TB incidence, prevalence and mortality between the DOTS and Non-DOTS countries (between-groups) were compared using un-paired t-test (59); 3) to assess variability in DOTS effects in reduced TB burden, differences in mean scores in TB incidence, prevalence and mortality across-sub-sets within the DOTS group (within-groups) were compared using un-paired t-test.

3.4.2 *The Comparison of Means of Two Samples*

A comparison of two sample means compares the across-period mean differences in TB incidence, prevalence and mortality rates among the same group of countries (N=212) that reported on TB trends between 1985 and 2006. At this level of the analysis, TB burden levels were assessed by comparing the absolute mean values of the pre (1985-1995) and DOTS (1996-2006) period for 212 countries that have reported on TB trends to the WHO during that period.

The baseline characteristics of all participating countries were first grouped into nine clusters: all countries (AC); DOTS-recipient (DR); non-DOTS-recipient (DNR); resource-rich (RR); resource-poor (RP); resource-rich-recipient (RRDR); resource-poor-recipient (RPDR); resource-rich-non-recipient (RRDNR); and resource-poor-non-recipient (RPDNR). Second, countries of the world were grouped into six geographical regions: Africa (AFR), the Americas (PAHO), the Eastern Mediterranean (EMRO), Europe (EURO), South East Asia (SEAR) and the Western Pacific (WP) regions.

The aim was to assess whether TB burden levels were lower in the DOTS (1996-2006) period than the pre-DOTS (1985-1995) levels without controlling for the applied TB control inventions (DOTS) in a specified country or region. TB incidence, prevalence and mortality rates were used as measures of DOTS effect in changed TB burden levels. Two independent data sets (paired data) but equal samples sizes (from the pre and DOTS period were used. The dependent variable was the observed change in TB burden levels (incidence, prevalence and mortality rates) and the independent variable was the DOTS strategy.

Because the standard error (SE) is reliable and an unbiased estimate, it was used to determine the difference between the two group means, where each sample has range of probable value for its population mean (58;59). Thus, the SE of the *difference* was computed as**:**

where s_1 and s_2 denote the standard deviation (SD) for the two samples of the pre (= 212) and DOTS (=212) period. The statistical significance for the difference in means determined by paired t-distribution was computed as:

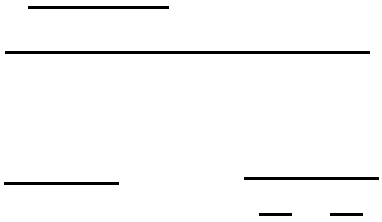
The ratio of the statistic divided by its SE estimates whether difference in means is equal to zero, and compared this ratio to a t-distribution. Such a ratio is a product of two group means (unexposed; =1985-1995, and the exposed; =1996-2006). The probability that the *difference* in TB burden levels between the unexposed and the exposed group was attributed to events other than DOTS was determined. The null hypothesis (**Ho)** was that the DOTS strategy has not influenced the growth and levels of TB burden ($\mu_1=\mu_2$ or $\mu_1-\mu_2=0$, or $\Delta=0$) at the national, regional and global levels using paired t-test. The alternative hypothesis (**H_1)** was that the DOTS strategy has influenced the growth and levels of TB burden in the DOTS period ($\mu_1\neq\mu_2$) or $\mu_1-\mu_2 \neq 0$ or $\Delta\neq 0$) at alpha ($\alpha=0.05$) level.

3.4.3 ***Between-Group Mean Difference Comparison***

For between-group differences, a comparison involved comparing the differences in population means between DOTS-recipient (DR; $n_1=196$) and non-DOTS-recipient (NDR; $n_2=16$) countries for the period 1996-2006. It compares the absolute differences in DOTS impact on TB control outcomes (*treatment-effect)* and TB burden levels between DOTS-recipient (DR) and Non-

DOTS-recipient (NDR) countries. *Treatment-effect* is defined as the average difference-in-differences between the DR and NDR group (21).

The t-test for independent samples was used to evaluate the effects the DOTS strategy might have had on TB control outcomes in the treatment (n_1=196) group compared to control group (n_2=16) for the period of 1996-2006. The test for significance was computed used $\mathbf{sd_1}$ and $\mathbf{sd_2}$ which are the standard deviations in samples 1 ($\mathbf{n_1}$) and 2 ($\mathbf{n_2}$) for between-groups comparison. Similar to two sample mean comparison, the statistical significance for the difference in the sample mean for between-group comparison is determined by t-distribution (un-paired t-test) computed as follows:



It was assumed that the two population means were normally distributed and that each value was sampled independently from the other values (where each observation provides only one value) were met under the null hypothesis (**Ho:** $\mu_{1\text{-}1985\text{-}1995}=\mu_{2\text{-}1996\text{-}2006}$) using unpaired t-test.

3.4.4 *Within-Group Mean Difference Comparison*

A comparison of within-group mean differences in TB burden levels across sub-sets among the DR group was performed. The aim was to examine whether TB burden levels across sub-sets varied, whether the observed differences (if any) were influenced by the SES conditions of individual countries. Countries were stratified into two groups: resource-rich

(RR) and resource-poor (RP), where RR =1 and RP=0. RRDR and RPDR were then matched with the number of countries reporting on TB trends for the period of 1985-2006. It was assumed that the across-period differences in TB burden between the RPDR and RRDR was attributed to the SES conditions of individual countries under the hypothesis: **Ho:** $\mu_{RR}\Delta=\mu_{PR}\Delta$, $\mathbf{H_1}$: $\mu_{RR}\Delta \neq \mu_{RR}\Delta$.

3.4.5 ***Statistical Analysis***

This study used paired and unpaired t-tests to compare before and after DOTS, between-group and within-group mean differences using statistical software (STATA version 9, Houston TX, 2006) (60;61). The test for statistical significance relied on the mean (SD) for the differences and p-values (if p=.002 strong superiority is shown, P= 0.05 superiority is shown, and if P= 0.20 superiority is not shown) determined by t-test ratios to generate estimates for the differences (70). All tests were two tailed at significance level of alpha = 0.05.

The probability estimate (p-value) illustrates that, if the null hypothesis is true, the observed difference between the group means might be due chance alone, based on how extreme the size of the departure is from the null hypothesis, and its direction. Figures and tables were used: (i) to provide clear depictions of how TB trends changed or did not change in the pre and DOTS periods; (ii) to visualize the distribution of mean differences of the two periods around the centre and (iii) to show the extent of the differences before and after, between and within groups. In figures, the vertical axis (1996-2006) depicted the average changes in TB burden levels across groups, whereas the horizontal axis (1985-1995) depicted the extent of the changes in TB trends.

To detect changes, TB burden levels in the DOTS period were compared to that of the pre-DOTS period. The reported mean values of the pre-DOTS period were subtracted from the DOTS. If the

difference between the two periods is negative, it indicates an increase in TB burden levels. If the difference is positive, it indicates a decline in TB burden.

3.5 **Summary**

This study relied on secondary data analysis and used a quantitative comparative methodological approach to create a platform for conclusive, informative and rigorous analyses. It determined whether the DOTS strategy had influenced the growth and levels of TB over the last decade.

Chapter Four: **Results**

4.1 **Introduction**

This chapter presents a comprehensive analysis of the study results with respect to the study objectives and questions. This study examined the extent to which the WHO's DOTS strategy for TB control has influenced the growth and levels of TB burden in DOTS recipient countries. If it has, under what circumstances has DOTS impact on TB control outcomes varied in and across national settings, and why?

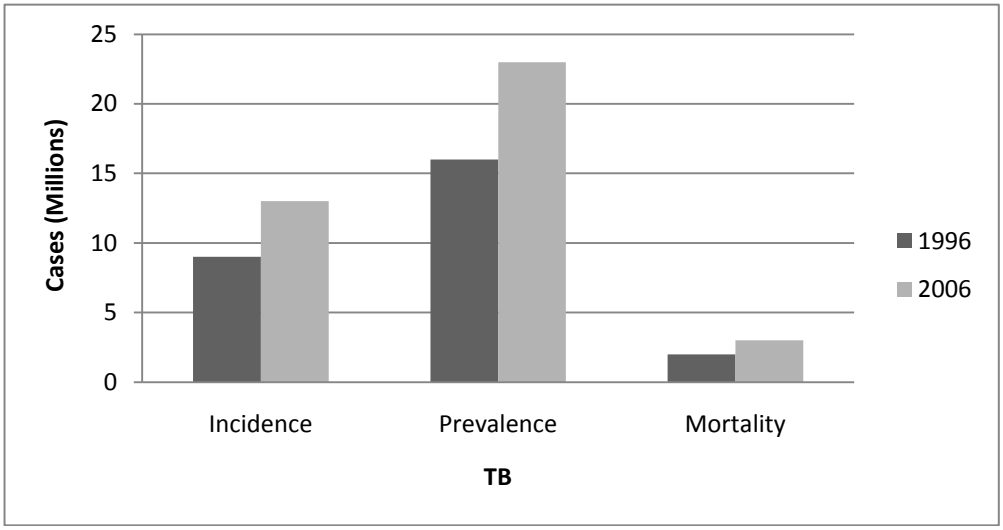
Overall, this study revealed that the WHO DOTS strategy has influenced the growth and levels of TB burden in areas it was applied except in Africa. The observed differences in both disease burden levels and DOTS impact on TB control outcomes between DOTS and Non-DOTS recipient countries were significantly influenced by socio-economic conditions of individual countries. There is evidence that to make the DOTS impact on TB control outcomes comparable in Africa to that of the rest of the world, health system strengthening is a key challenge to improving the delivery of effective, accessible and affordable TB care.

4.2 **DOTS Impact on Global TB Control Outcomes -1996-2006 (Question 1)**

To determine whether DOTS had influenced the global TB burden levels in the last decade, this study examined changes in TB trends at the global, regional and national levels. From the global perspective, since 1996 a decline in TB trends was reported in some areas (50-52; 56), however the overall general trend was on the rise. Between 1996 and 2006, 196 countries have adopted, implemented and integrated DOTS into their national primary health care services (1). In the DOTS period, the total cumulative number of people with TB (period prevalence) reached 1.9 billion (383 per 100,000 population per year) (18; 22; 32; 36). The estimated number of people

newly infected (incidence) increased from 9 to 13 million; living with the disease (prevalence) was 16-24 million and dying (mortality) from TB was 2-3 million each year (Figure 2) (18;22;32;36).

Figure 2-Estimated TB Burden Levels for 212 Countries by 1985 and 2006



Source: WHO TB Report; 1996-2009

If the DOTS strategy has influenced the growth and levels of TB, under what circumstances such influence varied in and across national settings, and why? To determine DOTS impact on TB burden levels the mean values of TB incidence, prevalence and mortality were compared between the 10 years prior to DOTS (1985-1995) and 10 years following DOTS introduction (1996-2006). The presented values were means of the determined outcome measures (i.e., incidence, prevalence and mortality rates) per 100,000 population per year that were reported as mean rates by individual countries to the WHO annually (1).

To assess whether TB burden levels were higher or lower, the mean values of TB incidence, prevalence and mortality rates in the DOTS period (1996-2006) were compared to the pre-DOTS period (1985-1995) for the same set of 212 countries at the national, regional global levels. If the difference between the two periods was negative, it indicates an increase in TB burden levels. If the difference was positive, it indicates a decline in TB burden. This was to determine whether there is an observable difference in TB incidence, prevalence and mortality before and after DOTS was applied, and whether such difference varied across national settings for the1996-2006 period.

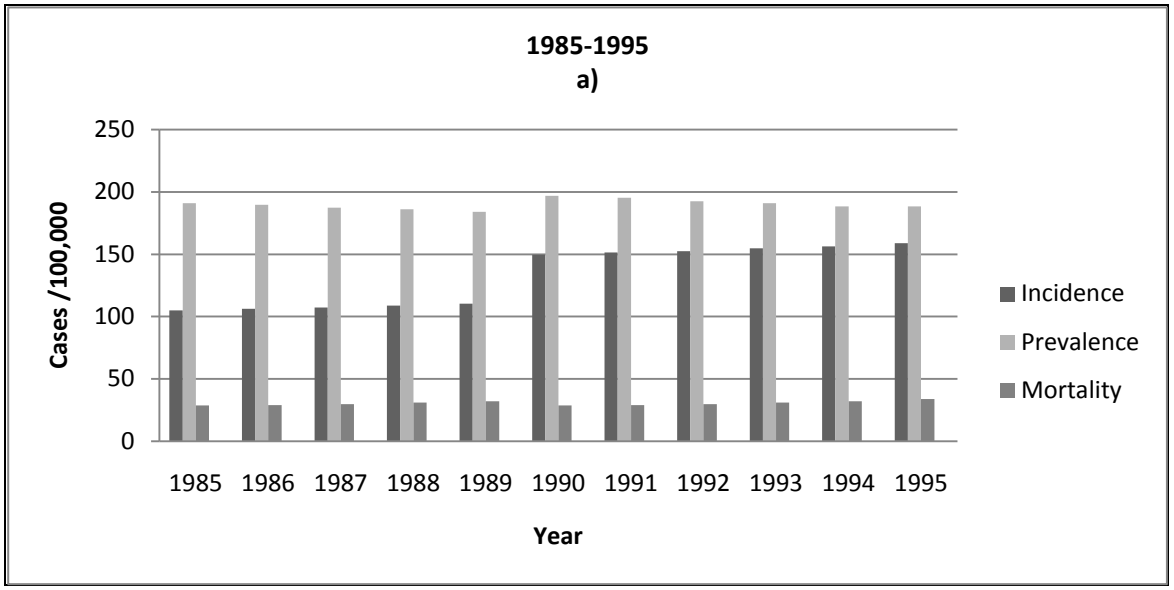
At the global level, TB incidence increased significantly with -20.3 [t (62) = -2.7; *p*=.004], but prevalence fell significantly in the second period reporting [t (63)=2.5; *p*=0.007] per 100,000 populations per year. Mortality remained unchanged with 1.7
[t (63)= -0.09; *p*=.0.183] per 100,000 populations per year in the second period (Table 3).

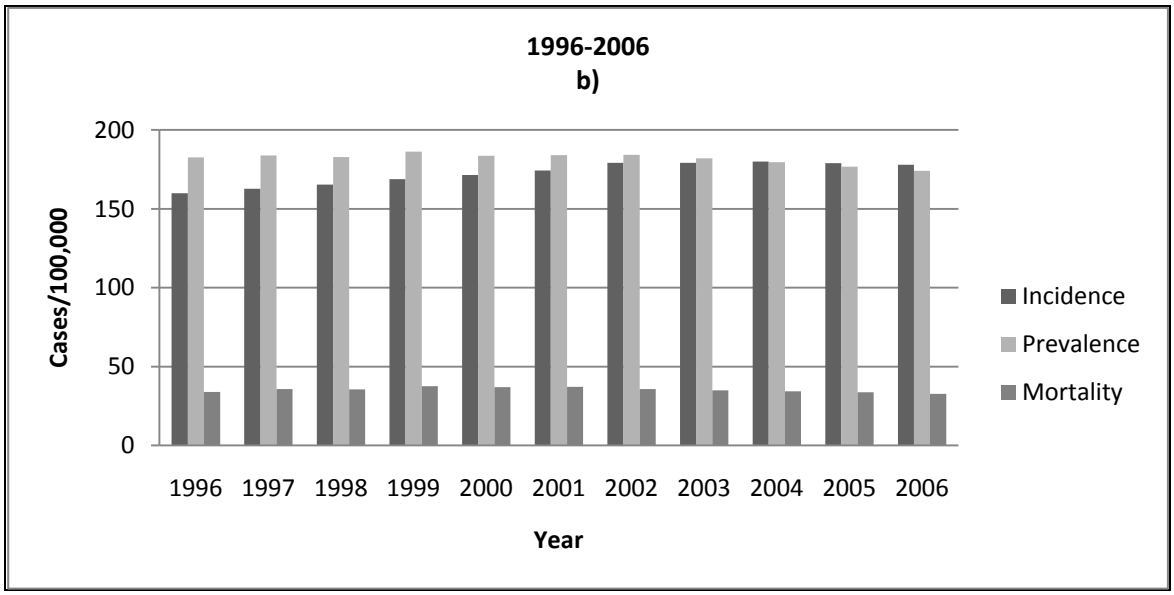
Table 3-Sumary Statistics of Mean TB Burden Measures for all Comparison Groups for Pre (1985-1995) and Post-DOTS (1996-2006) period

Countries	OBS	Outcome	Periodic Changes								
			1985-1995 (Mean)		1996-2006 (Mean)		Difference				
			Mean	sd	Mean	sd	d.f	Mean	sd	t	*p*
All countries (AC)	211	Incidence	128.3	162.8	107.9	112.9	210	-20.3	109	-2.7	0.004
	212	Prevalence	182.1	236.6	210.8	252.9	211	28.7	167	2.5	0.001*
	212	Mortality	24.9	38.6	23.2	28.2	211	-1.7	27.5	-0.9	0.183
DOTS recipient (DR)	195	Incidence	132	166.4	111.9	115.5	194	-20	112	-2.5	0.004
	196	Prevalence	185.4	240.1	218.4	259.3	195	32.9	170.3	2.7	0.001*
	196	Mortality	25.6	39.6	24.1	28.9	195	-1.4	28.2	-0.7	0.235
Non-DOTS(NDR)	16	Incidence	81.9	101.9	59.3	58.6	15	-22.7	64.2	-1.4	0.894
	16	Prevalence	141.5	188.1	117.6	123.8	15	-23.9	111.6	-0.9	0.202
	16	Mortality	17.3	23.9	12.6	14.1	15	-4.8	15.9	-1.2	0.125
Resource-Rich (RR)	116	Incidence	65.6	75.7	81.9	92.2	115	16.3	49.7	3.5	0.001*
	117	Prevalence	92.1	140.8	150.6	199.9	116	58.5	129.8	4.9	0.001*
	117	Mortality	11.9	28.3	15.5	21.6	116	3.6	23	1.6	0.001*
RR-Yes-DOTS(RRDR)	110	Incidence	67.2	76.9	84.9	93.7	109	17.6	50.3	3.7	0.001*
	111	Prevalence	94.5	143.8	156	203	110	61.5	132.5	4.9	0.001*
	111	Mortality	12.3	28.9	16	21.9	110	3.8	23.6	1.6	0.001*
RR-No-DOTS(RRNDR)	6	Incidence	35	39.1	26.9	18.2	5	-8.2	28	-0.7	0.1253
	6	Prevalence	48.9	49.9	50	42.1	5	1.2	23.8	0.2	0.908
	6	Mortality	5.7	6.1	4.4	2.9	5	-1.4	4.1	-08	0.234
Resource-Poor (RP)	95	Incidence	204.7	203.5	139.8	127.5	94	-64.9	141	-4.5	0.001*
	95	Prevalence	292.9	280.6	284.9	290.1	94	-8	198.5	0.4	0.347
	95	Mortality	40.9	43.5	32.8	32.4	94	-8.1	30.9	-2.6	0.006
RP-Yes-DOTS(RPDR)	85	Incidence	215.9	208.9	146.9	131.2	84	-68.9	37.4	-4.4	0.001*
	85	Prevalence	304.2	285.8	299.8	299.8	84	-4.4	204.6	-0.2	0.423
	85	Mortality	42.9	44.7	34.6	33.3	84	-8.3	32	-2.4	0.009
RP-No-DOTS(RPNDR)	10	Incidence	110.1	118.9	78.8	66.4	9	-31.3	78.9	-1.2	0.120
	10	Prevalence	197.1	220.1	158.1	140.3	9	-39	140.6	-0.9	0.201
	10	Mortality	24.3	28.1	17.5	159	9	-6.8	19.9	-1.1	0.154

Note* significant at 0.05 level

Figure 3- Mean TB Burden Measures for 212 Countries





Source: WHO Annual Reports 1985-2006

Among the DOTS-recipient group, the differences in TB incidence, prevalence and mortality levels were similar in all countries yielding -20[t(194)=-2.5;p=0.004], 32.9[t(195)=2.7;p<0.001], -1.4[(t(195)=-0.7;p=0.235] respectively (Figures 3: a & b). Of all groups, although mortality remained unchanged yielding mean differences 3.6[t(37)-1.6;p< 0.001], the highest difference in incidence was reported among the RR group reporting 49.7[t(37)=3.5;p<0.001] and RR-DOTS50.3 [t(14)=3.7;
p<0.001], whereas differences in prevalence were similar in both groups yielding 58.[t(64)=4.9 p<;0.001] and 61.5[t(64)=4.9;p<0.001].

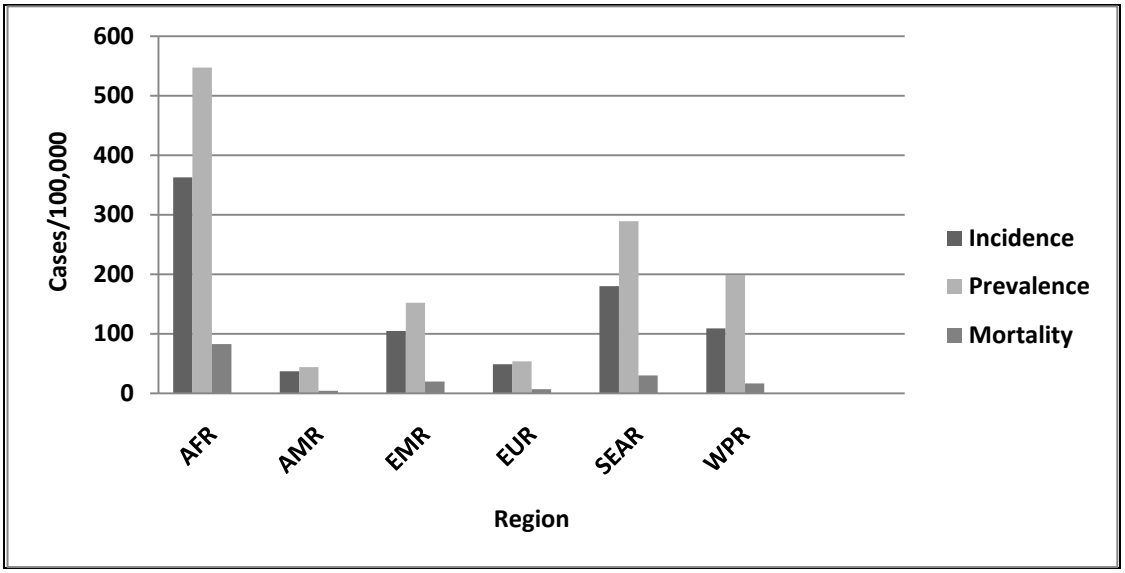
The highest increase in TB incidence, prevalence and mortality were reported among the RP and the RP-DOTS group with mean differences -64.9[t (94) = -4.5; p<0.001],
-8[t (94) = 0.4; p=0.347],-8[t (94) = -2.6; p=0.006], and -68.9[t (84) = -4.4; p<0.001],
-4.4[t (84) = -0.2; p=0.423], -8.3[t (84) = -2.4; p=0.009] respectively (Table 3).

The WHO divides the world into six geographical regions: African (AFR), the Americas (AMR), Eastern Mediterranean (EMR), South East Asia (SEAR), European (EUR) and Western Pacific (WPR) regions. Across these regions changes in TB burden levels varied from region to region (2;9;47). While a steady decline in TB incidence in five of the six WHO regions was reported, the African region experienced the highest increase in TB burden levels (Figure 4) (2).

The highest number of reported TB cases were seen in AFR; however, TB burden levels were already higher in AFR in the pre-DOTS period (1985-1995) (2;9;47). TB incidence rates in AFR were nearly twice those of the SEAR region, with over 350 new TB cases per 100,000 populations per year reported each year (Figures 4) (5; 17; 56).

While global TB prevalence rates fell sharply from 240 to 180 per 100,000 population per year in 1996 and 2006 respectively, they almost doubled in the AFR region (3;9;10;55). Between 1985 and 2006, TB prevalence rates fell sharply in five of the six geographical regions, but rose in AFR and were two or three times higher than those of the AMR, EUR and WPR regions in the DOTS period (1996-2006) (Table 4 & Figure 4) (3;9;10;55).

Figure 4- Mean TB Burden Measures for all Regions by 1985-2006.



Source WHO Reports 1985-2006

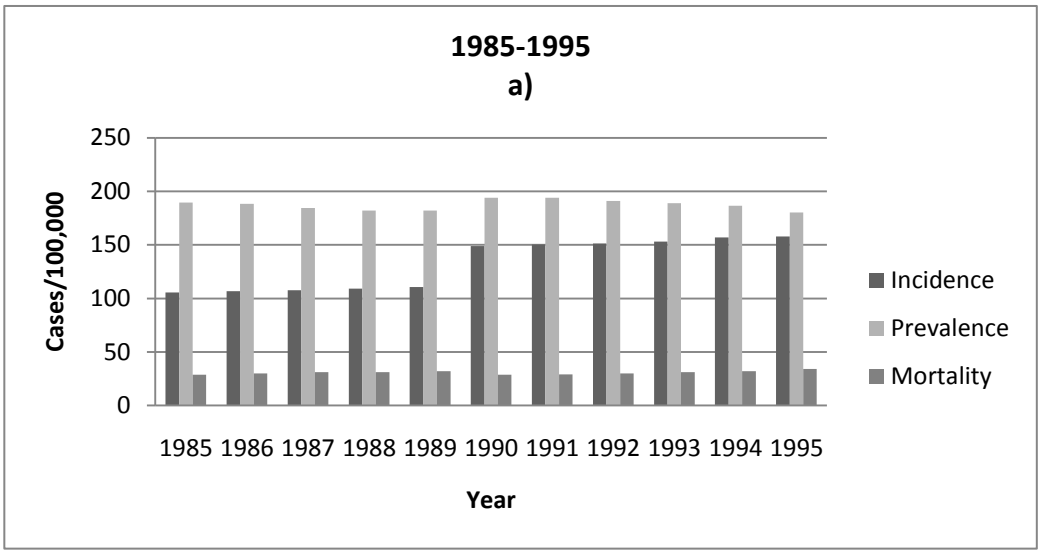
While TB death rates remained unchanged for the rest of the world, significant differences were found in the AFR region (1). Approximately 50% of the global TB deaths occurred in the AFR (SSA region) and were still rising (2;9;47). While TB death rates also declined rapidly and were no longer considered a problem in the EUR and AMR regions, they were two or three times higher in AFR compared to all other regions (2;3;10). It also shows that although TB death rates were high in SEAR, these rates have been steadily declining since 1996 (Table 4) (3;9;10;55).

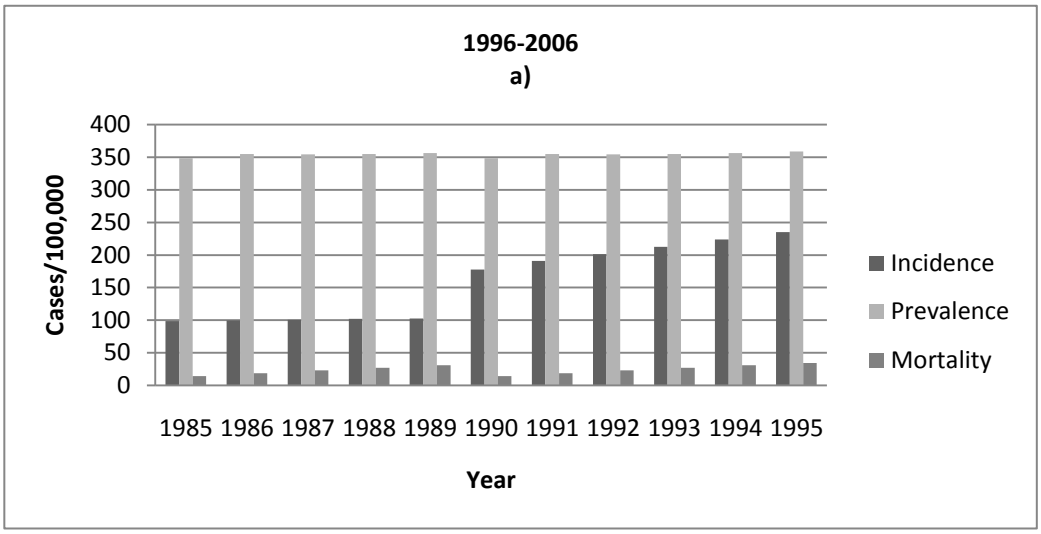
Table 4- Mean TB Burden Measures by Region for 1985-2006

Region	Outcome	N	1985-1995	1996-2006
AFR	Incidence	(47)	163.9	314.5
	Prevalence	(47)	341.4	472
	Mortality	(47)	42.4	72.4
AMR	Incidence	(43)	76.9	49.8
	Prevalence	(44)	122.4	64.9
	Mortality	(44)	13.4	7.9
EMR	Incidence	(22)	97.5	93.3
	Prevalence	(22)	201.5	137.6
	Mortality	(22)	20.6	16
EUR	Incidence	(54)	43.3	46.3
	Prevalence	(54)	65.6	54.2
	Mortality	(54)	6.7	6.7
SEAR	Incidence	(14)	146.4	137.9
	Prevalence	(14)	341.	178.1
	Mortality	(14)	36.5	19.3
WPR	Incidence	(31)	161.6	117.9
	Prevalence	(31)	338.6	165
	Mortality	(31)	33	17.6

To assess whether the rising global burden of TB disease was attributed to the rising TB burden levels in Africa or other unknown factors, a trend (to show how TB burden levels changed over time) analysis excluding Africa from the rest of the world was performed. It showed a significant decline in the rest of the world excluding Africa's DOTS recipient countries (Figures 5: a & b).

Figure 5- Mean TB Burden Measures for DR and NDR Countries except Africa for Pre (1985-1995) and Post-DOTS (1996-2006) period





Source: WHO Annual Reports 1985-2006

There is a clear indication from the observed differences in TB burden levels that the AFR region is not benefiting from any applied TB control interventions under DOTS, and that

these interventions have only been effective in all other regions but Africa (10; 16). What is not clear in the study findings, however, is whether the DOTS strategy has simply been ineffective in Africa, or there are other factors contributing to the ineffectiveness of DOTS and the rising TB burden levels in the region (1-11).

4.3 **The Impact of DOTS on TB Control Outcomes in Africa (Question 2)**

Since 1996 41 out of 47 African countries have adopted and introduced DOTS for TB control, and 6 did not. To detremine whether the WHO DOTS strategy had an effect in reducing the burden of TB in Africa, TB burden levels in the pre (1985-1995) and post (1996-2006) DOTS period among the DOTS group were compared.

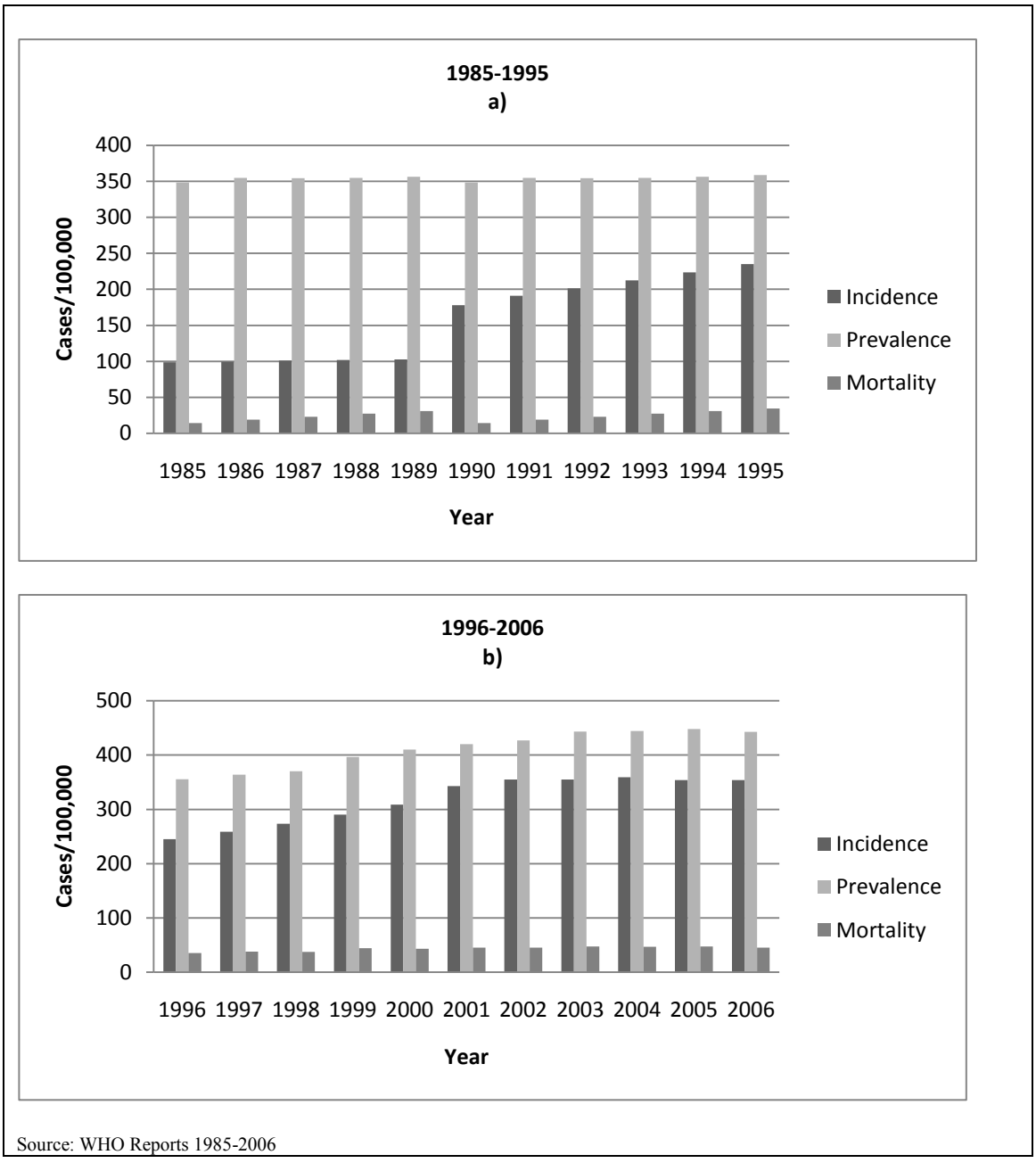
4.3.1 ***Africa's TB Burden Levels in the Pre-DOTS period (1985-1995)***

In the pre-DOTS period, the highest number of TB cases was seen in the Africa region (1). However, TB burden levels were already higher in AFR in the pre-DOTS period (1985-1995) (2;9;47). TB incidence rates in AFR were nearly twice those of the SEAR region with over 350 new TB cases per 100,000 population per year reported each year (5; 17; 56). In Africa, TB incidence, prevalence and mortality rates were significantly lower in the pre-DOTS period with mean values 163.9, 341.4 and 42.4 respectively (Table 4).

4.3.2 ***Africa's TB Burden Levels in the DOTS period (1996-2006)***

While the DOTS strategy seemed effective in reducing TB burden levels in all other regions, significant differences were observed between Africa and the rest of the world. TB burden levels were significantly higher in the DOTS period than the pre-DOTS period with mean differences of -150.6 [$t(46)=-6.8; p<.001$], -130.6[$t(46)= -4.9; p<.001$] and -30[$t(46)= -5; p<.001$] respectively (Figure 7; a & b).

Figure 6 – Mean TB Burden Measures for Pre and Post-DOTS period for DOTS Recipient Countries (AFR)

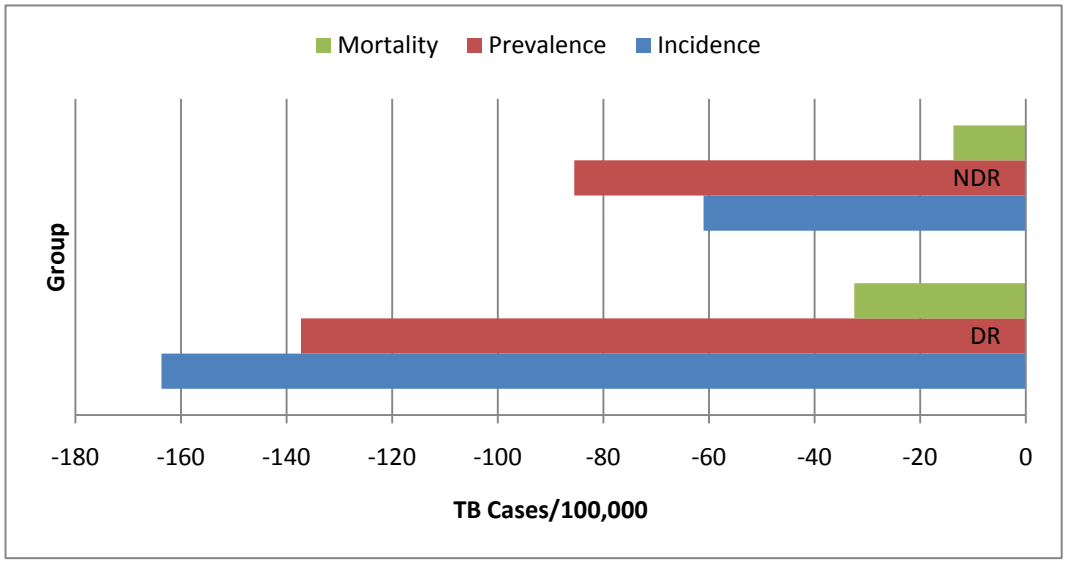


Source: WHO Reports 1985-2006

Despite renewed efforts in the last decade, differences in TB incidence, prevalence and mortality were significantly higher for the DR group in the second than the first period with

mean differences -163.7 [t(40) = -6.7; *p*=.001],-137.2 [t(40)= -4.8; *p*=.001] and -32.5[t(40)=-4.9;*p*<.001] compared to -61[t(1)=-1.6; *p*=.080],-85.5[t(1)= -1.3; *p*=.129] and -13.6[t(1)= -1.5;*p*=.105] of the NDR group respectively (Figures 6; a & b).

Figure 7- Differences in Mean TB Burden Measures for DR and NDR Countries (AFR) by 1996-2006



Sources: WHO Reports 1996-2006

4.4 **Factors Contributing to the Rising TB Burden Levels Africa (Question 3)**

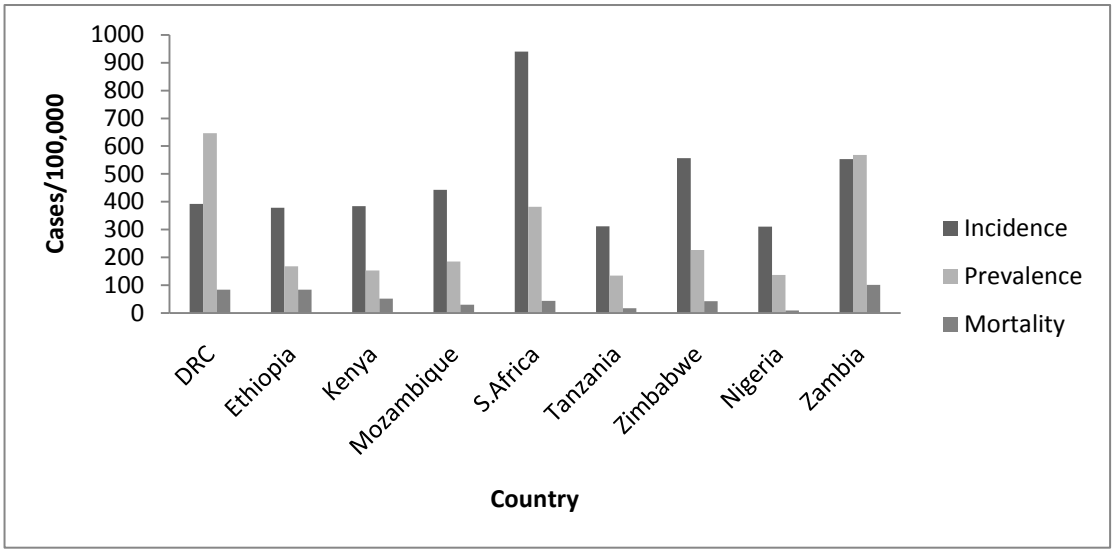
The African region has experienced the highest increase in TB burden levels for the last decade (1). Among other things, the observed differences in DOTS's impact on both the expected and observed outcomes in the African region are believed to have attributed to higher TB burden levels in the pre-DOTS period, high prevalence of HIV, HIV/TB co-infections and low TB case detection rates in Africa, particularly in the SSA region (52).

While eighty percent of the total global TB death rates were reported in countries with the highest number of TB cases per capita, also known as high burden countries, (HBCs)

(11;12;48;49). Nine of the HBCs were in the African region and had shown a disproportionate increase in TB burden levels in the last decade (Figure 8) (1).

In African HBCs, TB incidence peaked at alarming rates, ranging from 350 (Tanzania) to 1000 (South Africa) per 100,000 population per year (Figure 8) (1). TB prevalence rates also peaked from 280 (Zambia) to 600 (Democratic Republic of the Congo (DRC) per 100,000 population per year (1). TB mortality rates remained unchanged for all countries in the region (Figure 8) (1). Such a difference in the TB burden decline could reflect the results of the differences in existing TB burden across national settings, particularly between Africa and rest of the world (2;3;10).

Figure 8– Mean TB Burden Measures for Africa's HBCs (1996-2006)



Source: WHO Report 1996-2006.

Although cure and treatment completion rates reached 83% and 98.7% respectively in some African HBCs, death and relapse rates exceeding 100% were reported in almost all African HBCs due to high HIV infection rates in the SSA region (3;9;12;47;52). Countries (S. Africa, Zambia, Zimbabwe and Mozambique) with the highest incidence, prevalence and mortality rates

per capita also reported the highest relapse rates (Table 5) (1). In such settings, death and relapse rates ranged from 158% to 450% (3;9;12;47;52). It is undoubtedly clear in the study findings that the African region has experienced the highest increase in TB burden levels in the DOTS period (1).

Table 5 –Mean TB Burden and Treatment Outcome Measures for HBCs by 1985-2006 (AFR)

Country	Incid/ (100K)	Preval/ (100K)	Mort/ (100K)	CDR (DOTS)	CDR (all Cases)	DOTS Cover (%)	Relap (%)	Cured/ complet DOTS (%)	HIV-cases (%)
DRC	392	647	84	61	39	100	158	85	4.2
Ethiopia	379	168	84	27	39	100	151	29	2.10
Kenya	384	153	52	70	75	100	296	82	6.7
Mozambique	43	186	30	47	36	100	168	79	12.5
S. Africa	940	382	44	71	60	100	628	58	18.1
Tanzania	312	135	18	45	47	100	150	77	6.2
Zimbabwe	557	227	43	42	42	100	335	60	15.3
Nigeria	311	137	9.6	20	15	49	75	75	3.1
Zambia	553	568	102	41	58	100	450	85	15.2

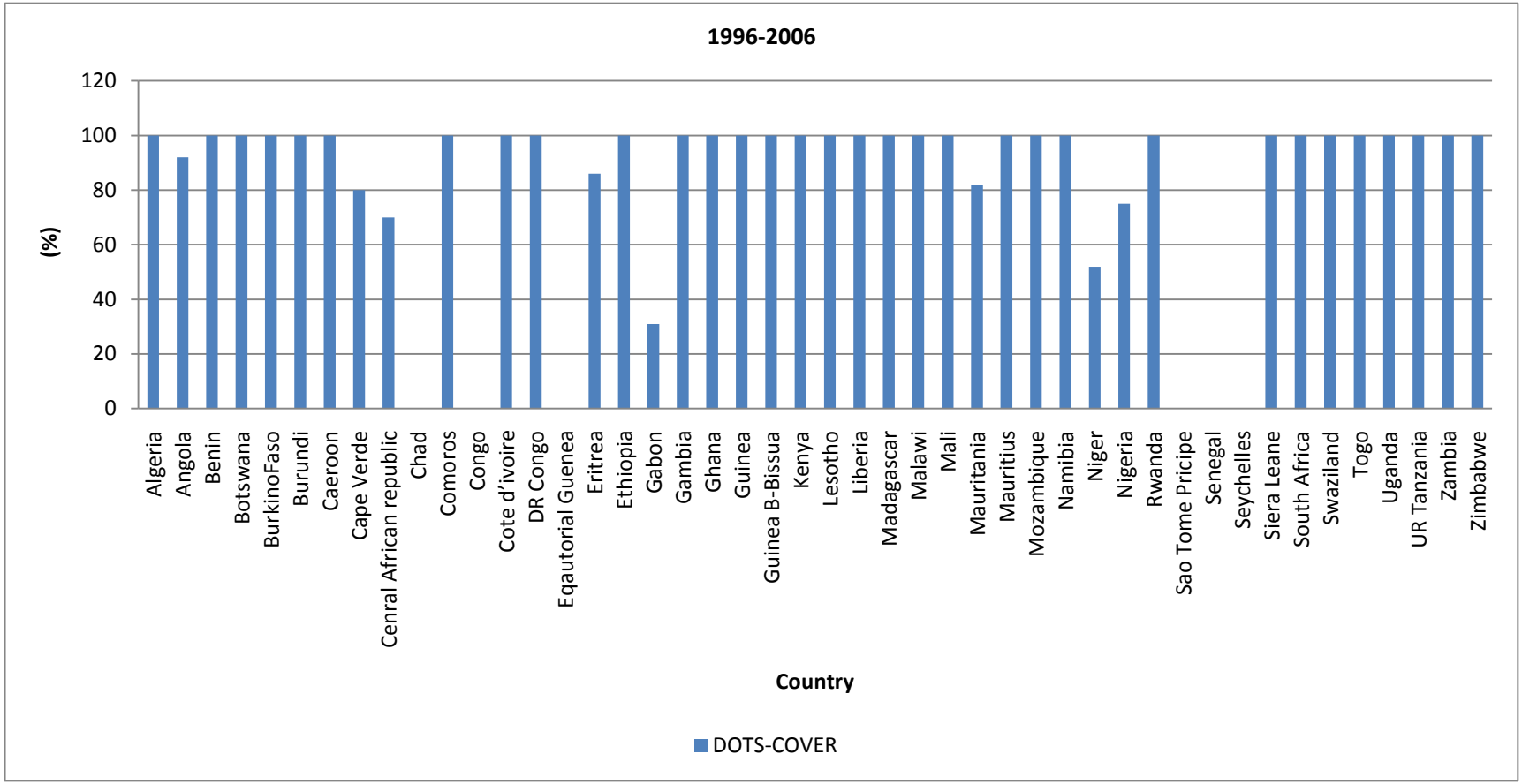
Source: WHO Reports 1985-2006

4.4.1 *DOTS Coverage in Africa*

On the assumption that the expansion and coverage of the DOTS strategy was widely implemented, more targeted and specific in scope in settings where it was applied, the burden of TB was expected to change by 2005 (2;9;28). To determine coverage, reported TB case detection rates (CDRs) were used as verifiable indicators for reduced TB burden in DOTS areas (9). It determined the percentage of the population covered and who benefited from DOTS as well as the outcomes attributable to improved TB care under DOTS in a given setting (34;36;39;53;65).

According to the WHO annual TB reports, 41 countries had implemented DOTS by the end of 2003, and 96% of the Africa's population was living in DOTS-recipient countries (Figure 9) (1). Although close to 92% of DOTS coverage was realised, the net effect of the DOTS in reduced TB burden in the African region is unclear (13;14;31-34;66).

Figure 9 –Reported DOTS Coverage for all African Countries by 1996-2006



Source: WHO TB Database; 2009

4.4.2 ***Case Detection Rate in Africa***

While global TB CDR increased from 49% in 1996 to 58% in 2006 (only a 9% increase from 1996) only 45% of the 58% reported TB cases were detected under DOTS (2;3;10). Although the type of treatment, diagnosis and delivery strategies used play a significant role in the final TB control outcomes, an increased case detection rate is critical and expected to foster higher and better treatment outcomes (6; 7). In the DOTS period, in Africa, TB CDR did not exceed 70%, despite the fact that 99% of Africa's countries were recipients of DOTS and had reported 100% DOTS coverage (Table 5 & Figure 9) (12;52).

4.4.3 ***Treatment Outcomes under DOTS in Africa***

The treatment outcomes are determined by the percentage of TB patients (new smear-positive cases) who are cured (free of TB infections based on a sputum-smear test), plus the percentage of TB patients who have completed the full course of their treatment, but are not cured of TB (11;12;48). Between 1996 and 2003, approximately 17.1 million patients were treated under DOTS worldwide (1). Comparatively, TB burden levels increased at alarming rates in Africa, particularly in HBCs (1).

4.5 **Differences in TB Burden Levels Due to Socio-Economic Effect**

TB burden levels in the second period were compared to the first period and showed variation for the same set of countries given their SES. This part of the analysis assessed whether TB burden levels in the second period from that of the first period varied for the same set of countries given their SES. The across period differences in TB incidence, prevalence and mortality were significantly higher for the RR group in the second period with -30[t (38) =1.2; p=0.124], -342 [t (38) =-2.6; p<0.001],-115 [t (38) = -3.3; p< 0.001] in the second period than the first period (Tables 6 and 7).

Table 6-Between-Group Differences in Treatment Effects Given SES-Effects (1985-1995)

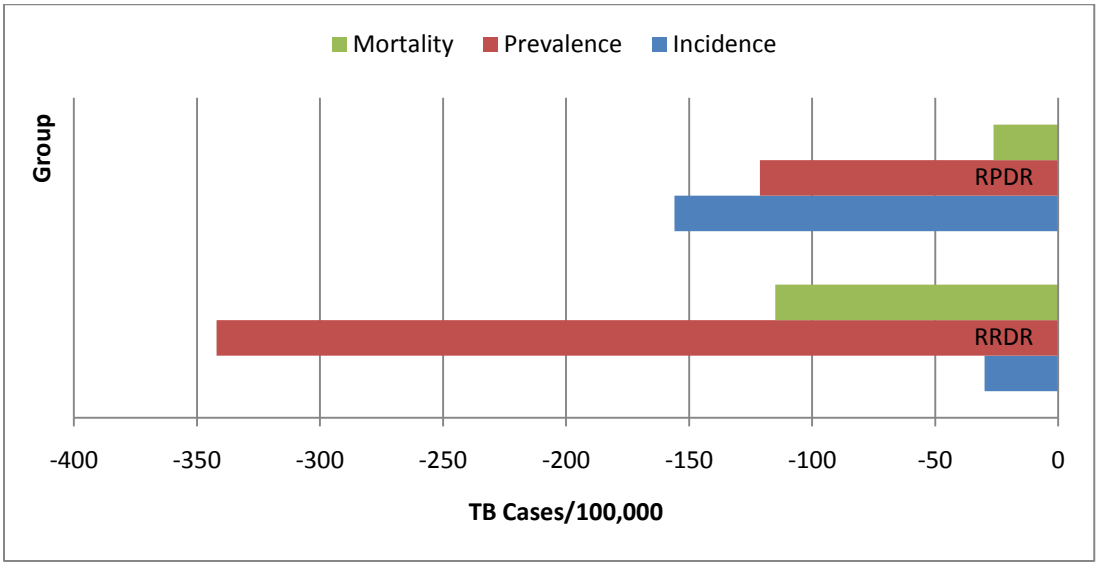
	1985-1995	
Outcome	RR-DOTS (Mean)	RP-DOTS (Mean)
Incidence	67.2	215.9
Prevalence	94.5	304.2
Mortality	12.3	42.9

Table 7-Between-Group Differences in Treatment Effects Given SES-Effects (1996-2006)

	1996-2006	
Outcome	RR-DOTS (Mean)	RP-DOTS (Mean)
Incidence	84.9	146.9
Prevalence	156	299.9
Mortality	16	34.6

TB burden levels were significantly higher for the RP group in the second than the first period, reporting differences in TB incidence, prevalence and mortality of -115.9[t (38) = -7.0; p<0.00], -121.3[t (38) = -4.5; p<0.001], -26.3[t (38) = -5.3; p<0.001] (Tables 6 and 7). Although TB prevalence rates increased significantly for both groups, such increases were three times higher for the RRDR group than for RPDR (Figure10).

Figure 10- Differences in Mean TB Burden Measures for RRDR and RPDR Countries (AFR) by 1996-2006



Source: WHO and HDI Reports 1985-2006

However, in the second period, TB incidence levels declined significantly among the RRDR group with a mean difference of -342 [t(1) =-4.5; *p*=.07] and -115 [t(1) =-1.4; *p*.2]. These levels increased significantly for the RPDR group reporting -121.3[t (38) =-4.5; *p*<.001], -26.3[t (38) =-5.3; *p*<.001]. Similarly, TB death rates were five times higher for the RPDR group than the RRDR group (Figure 10).

4.5.1 ***The Impact of HIV on TB Control Outcomes in Africa***

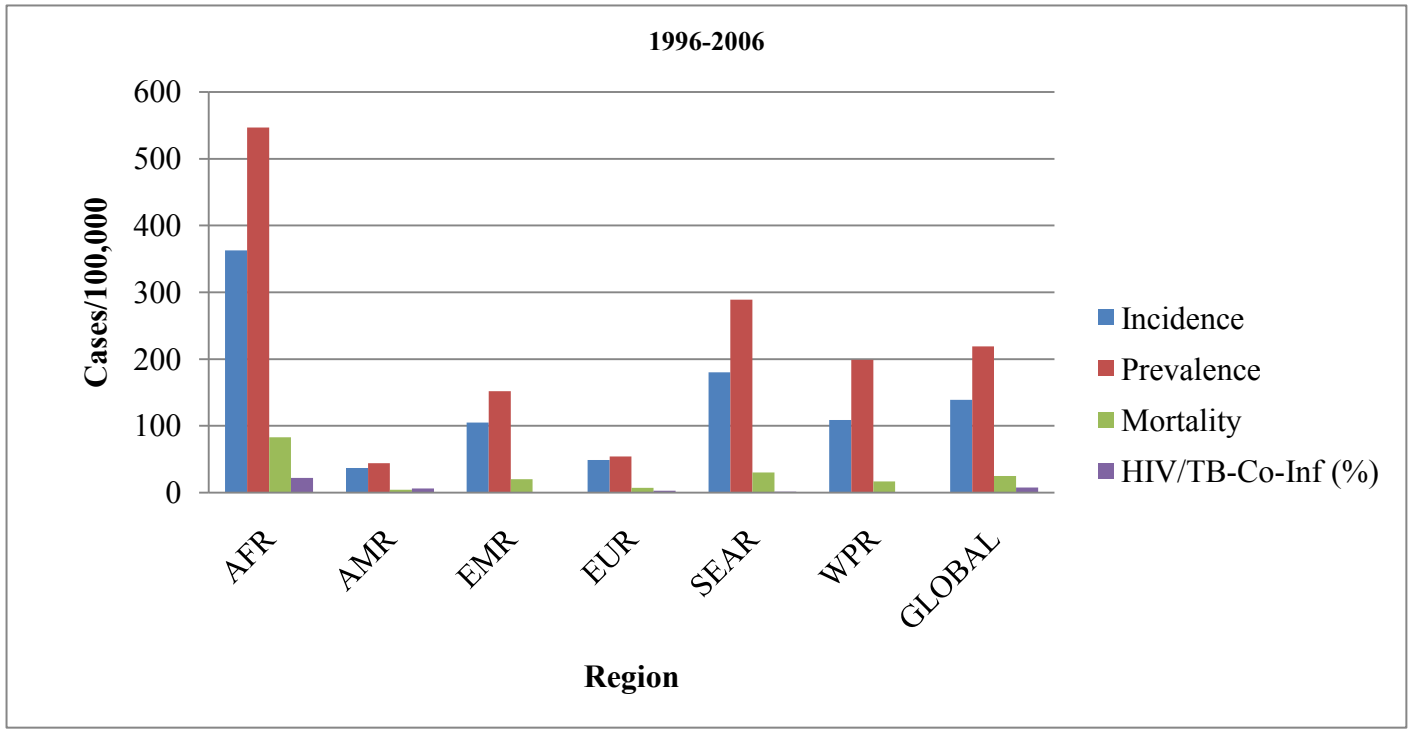
TB is a major cause of death among people living with HIV/AIDS, whose impaired immune systems make them particularly vulnerable to the devastating effects of TB (1). The pathogenesis and epidemiology of TB and HIV are not only inextricably linked, they also share a synergistic relationship as each influences and accelerates the other's progression (1).

4.5.2 *The Impact of HIV/TB Co-Infection on TB Control Outcomes in Africa*

Currently, 12 to 14 million people have co-infections and approximately 8% of global TB cases are attributable to HIV infection, and is expected to increase in the future (1). The largest number of TB cases occurs in the SSA region, which accounts for an estimated 3 million new cases (one-third of the global total) (1). These increases were relatively higher in areas with higher HIV/TB co-infection rates (1). However, the estimated incidence of HIV per capita in SSA is nearly twice that of Southeast Asia, at 383 cases per 100,000 population (Figures 11 & 12) (1).

In Africa, the highest TB deaths were reported to be in the countries below the Sahara; also known as Sub-Sahara Africa (SSA), which also reported the highest HIV/TB co-infections (Figure 12) (1). Effective treatment exists for each of these deadly diseases (1). For HIV, the use of anti-retroviral drugs (ARVs), the highly active antiretroviral therapy (HAART) has proven to be effective in controlling the spread of AIDS-related mortality and morbidity (1). However, these life-saving drugs are still not widely available in most resource-poor settings with high burden of HIV levels, particularly in the SSA (1).

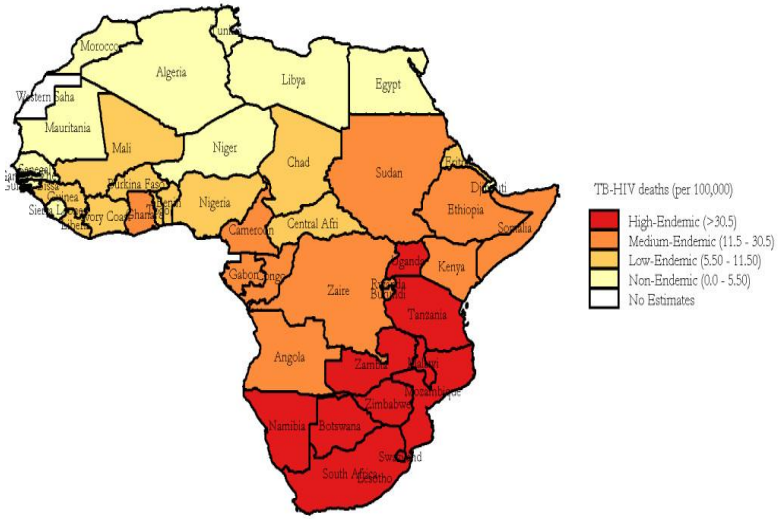
Figure 11- Mean TB-HIV Co-infection Measures for all Regions



Source: WHO Reports 1985-2006

Figure 12- The Distribution of TB-HIV Burden in Africa

Source: WHO TB/HIV Reports 1996-2006



Chapter Five: **Discussion**

5.1 **Introduction**

This study investigated the extent to which WHO's DOTS strategy for TB control influenced the growth and levels of TB in DOTS recipient countries. Over all, global TB prevalence fell in settings the DOTS strategy was applied, while incidence and mortality remained unchanged. Studies that have assessed DOTS impact on control outcomes did not test for differences in the rising TB burden across national settings, particularly in the African region. Available literature suggests that commonly-used terms such as effectiveness and cost-effectiveness to evaluate DOTS impact on TB control outcomes were often based on anecdotal estimates, while failing to recognise the widening gaps in TB burden levels across national settings (2;3;9).

5.2 **Discussion of Findings**

Overall globally, it appears that the DOTS had influenced the growth and levels of TB burden in all other regions, but not in Africa. Similarly, TB burden levels did not differ between DOTS and Non-DOTS-recipient countries for the last decade for all groups studied. Differences in both disease burden levels and DOTS impact on TB control outcomes between DOTS and Non-DOTS recipient countries were significantly influenced by socio-economic conditions of individual countries. There is evidence that to make the DOTS impact on TB control outcomes comparable in Africa to that of the rest of the world, health system strengthening is a key challenge to improving the delivery of effective, accessible and affordable TB care.

In Africa, despite renewed efforts, the TB burden levels have risen at alarming rates, and doubled in the DOTS period relative to 1985-1995 levels (1). The Sub-Saharan African (SSA) countries

were the hardest hit (1). In the SSA region, the number of people newly infected, living and dying of TB infections increased more significantly in the second than in the first period.

The number of reported TB cases in the DOTS period was three or four times higher than that of the pre-DOTS period (Figures 9-10). Africa's HBCs accounted for 70% of the total population in the region (1). These increases were relatively higher in areas with higher HIV/TB co-infection rates (Figure 1: Appendix B). While TB mortality rates remained unchanged in the SSA region, both incidence and prevalence rates doubled in South Africa, Namibia, Lesotho, Botswana, Sierra Leone, Zambia, Zimbabwe and Swaziland. The highest increases in TB incidence and prevalence were reported in South Africa and Swaziland (1000 and 1200 per 100,000 populations per year respectively) (Figures 9-10). These countries were also reported to have the highest HIV incidence levels in all Africa (Swaziland has the highest HIV cases in the world) (1).

The observed differences in TB incidence, prevalence and mortality mean rates were two or three times higher for the DR compared to the NDR group. Similarly, differences in TB incidence rates were significantly lower for the RRDR group compared to RPDR group. However, both prevalence and mortality differences were two or three times higher for the RRDR compared to the RPDR group.

The factors contributing to the observed differences between and within groups in TB burden levels may be (i) increased case detection rate and DOTS coverage with insufficient treatment success outcomes; (ii) unknown levels of TB burden in the pre-DOTS period; (iii) higher HIV/TB co-infection rates fuelled by weak health care systems and inadequate laboratories; (iv)

types of case-finding strategies influenced by the degree of classification and confirmation of TB cases and diagnostic strategies applied at the local level (13;36;45;51;53;65). These conditions have promoted and contributed significantly to the transmission of TB infection in the region.

Therefore, the observed differences in TB prevalence in RRDR countries were mainly attributed to increased TB care coverage, through DOTS or otherwise, which resulted in increased case detection and treatment success/cure rates among confirmed TB cases (12;52). Comparatively, partial or incomplete reporting of existing TB burden levels, over- or under-reported case detection rates and the use of unreliable disease classification methods were widely reported in RPDR countries (12;52). These factors are believed to have contributed significantly to over- or under-estimation of the differences in TB burden levels and DOTS-effect in and across national settings (1).

5.3 **Study Strengths**

This study used secondary data as this is low-cost, accessible and less time- consuming to compile. They are also readily available from databases often regarded as high quality, accurate and able to provide data suitable for comparative research analysis. The use of secondary data is considerably less expensive, faster and more flexible than conducting an original study and provides an opportunity to study trends and disease frequency from probability samples available from large populations. While the benefits of secondary analysis are substantial and growing, the use of aggregate data also provides an opportunity for rigorous analysis (61;67).

Despite evidence of under- and over-reporting, the use of incidence, prevalence and mortality rates as measures of effects is sufficiently reliable and permits comparative analysis (68). For

example, the use of mean differences for between and within-groups enables one to understand the changes in TB burden trends over time, which are also determined by between and within-group mean variations. Another advantage is the use of the same subjects for variability, since this study intended to observe the average change or difference in TB burden levels before and after the application of treatment intervention (DOTS).

5.4 **Study Weaknesses**

A critical concern about use of secondary data to estimate the burden of disease in a given population is that data from population-based surveys or vital registration systems is known to be imprecise due to measurement errors and misclassifications (12). In this study, the use of the case notification rate as a proxy measure for incidence is often considered as problematic and invalid for measuring the burden of TB disease in a given population (11;12;47;48). For example, data from case notification is relied on as a proxy measure for TB incidence only if the quality and completeness are assured and verified from reliable surveillance systems (i.e., National TB Programs) (11;48).

Where TB control efforts change over time, it is difficult to differentiate between changes in incidence and changes in the proportion of cases notified (21). An analysis of the reliability, validity and representativeness of such routine data (how, where, what types and for what purposes the collected data was checked) identified the following limitations. Such data is expected to reflect: (i) the extent of TB burden not only at the global level but also at the regional and national level; (ii) the extent of DOTS impact on population health outcomes; (iii) the effectiveness of current surveillance systems or strategies (through DOTS) in generating and improving the quality and quantity of available data in recipient countries.

Selection bias may be an issue for assessing the effects of DOTS on TB burden outcome patterns. Selection bias is a distortion of evidence or data that arises from the way data is collected (60;61). Therefore, the relationship between omitted variables bias, causality and treatment-effects can be seen most clearly using the potential-outcome variables (i.e., incidence, prevalence and mortality**).** Selection bias is the most serious analytical concern which is likely to arise in the estimation of treatment effects. Because the use of one sample or two sample t-tests might result in estimated effect of treatment from single-equation, these estimations will generally be biased away from the null (towards zero).

5.5 **Internal Validity**

Internal validity is defined as the extent to which the chosen independent variable (DOTS) has produced the observed outcome or effect (70). The validity of study findings might be affected by three factors related to systematic error: countries selected, methods used to compile data and sample size. Thus, a principle threat to internal validity involves the reliability and accuracy of measurements or methods (i.e., the consistency of instruments or techniques) used to compile and collect data by individual countries, which could ultimately distort the study findings. Sample size is an influential factor here. For example, with between-group comparison, the sample size of the control group is small and might not be large enough to detect the subtle difference in treatment-effect in disease burden or being insufficient to detect real effects (60;61). Therefore, the sampling error is likely to be large, and this might lead to a non-significance test even when the observed difference is caused by a real effect. Finally, the possibility of omitted variables bias arising from unobserved and uncontrolled differences in the

compiled data sets between and within groups could provide misleading estimates for group variability and the true effects of treatment.

5.6 **External Validity**

External validity refers to the extent the observed findings can be generalised to the defined population or settings (70). A threat to external validity involved sample sizes (i.e., the number of reporting countries and territories providing data) which varied from year to year. Among the treatment group, the countries selected for the between-group comparison might not be representative of the population to which the study findings were applied. Another critical treat to external validity is the selection and comparability of the comparison groups before DOTS was applied (a selection bias). In other words, there might be a good chance that the comparison groups were not comparable in the first place.

5.7 **Study Reliability**

Reliability refers to the consistency of study measurement, or the degree to which an instrument measures the same outcome each time it is used under the same condition with the same subjects (70). Therefore, it is the repeatability of the study measurement. It is important to remember that reliability is not measured, but estimated, and this is where a measure is considered reliable if the observed scores on the same test given twice were similar (70).

In this study it would be difficult to determine how much of the observed differences between and within groups were attributable to treatment, SES and period effects or simply other unknown factors. Such variable effects in the study findings might not be reflective of all population health outcomes. Thus, the representativeness of the study findings might be spurious since the main sources of data-sets were TB registry systems and non-random assignment of the

comparison groups. Therefore, it was impossible to adjust for confounding factors for within-group comparisons investigating the relationship between treatment-effects and the TB burden levels influenced by SES-effects.

In the HDI reports data were often incomplete or insufficient because non UN-member states had all the necessary data to calculate the HDI for their individual indices (42). The data used for HDI composite measures came from different sources, including so-called data agencies that often provided incomplete data with many gaps in basic areas of human development (i.e., growth and development levels). Similarly, a large number of countries did not submit their development reports annually, and data was often recycled from the previous year or from years before (42). Therefore, outdated and unrepresentative data may limit the generalizability of the study findings to all study populations, and might not yield realistic estimates for the true measured outcomes.

Chapter Six: **Conclusion**

6.1 **Introduction**

Directly observed treatment short-course (DOTS) was introduced and recommended by the WHO for all countries as the most effective and efficient strategy for global TB control (1). The WHO projected that the global TB burden would be halved and death rates would be reduced by 85% by 2000 and 2005 respectively, relative to 1990s levels (1). Since 1996, 196 countries have adopted and integrated DOTS into their national TB programmes (NTPs), and of these, 41 were in the African region (1). The question this study posed was: has the DOTS strategy influenced the growth and levels of TB burden in the last decade?

Though it is impossible to causally link decline in TB burden with DOTS, TB burden levels have declined in DR countries (1). While the reported declines were not generalizable to all areas, significant differences were observed between Africa and the rest of the world. According to the findings of this study, TB burden levels declined in all other WHO geographical regions, but increased in Africa over the last decade, and more people are now infected, living and dying from TB than ever in the African region (1).

Factors contributing to the observed differences in TB burden between Africa and rest of the world were believed to be: (i) lack of access to better TB diagnosis and treatment; (ii) inadequate or weak health care systems or TB care delivery policies; (iii) higher HIV/TB co-infection and transmission rates fuelled by poverty, population density, overcrowding and insufficient or unreliable surveillance systems at the local level in Africa; (iv) the fact that all Africa's HBCs

were also DR countries, which accounted for 80% of the world's TB burden levels - this in turn contributed significantly to the rising cumulative number of TB cases in the region (13;36;45;51;53;65).

Two of the factors that contributed to the observed differences in DOTS's impact on TB control outcomes between Africa and the rest of the world were: (i) the lack of resources (human and financial) and strong, well-established health system structures required for a successful implementation of DOTS; and (ii) the absence of political commitment from many central states, as well as shortages of skilled and effectively trained health care workers, good laboratories and surveillance systems (69). Most challenging of all was setting up a consistent and sustainable delivery system to implement DOTS strategy successfully in the African SSA region (2;3). Because 39 out of the 47 African countries were classified as RP, and relied heavily on international technical and financial support to sustain their national control programs, the DOTS strategy became too costly to implement in RP settings (63). Even in areas with 100% DOTS coverage and highly functional NTPs in Africa, case detection and cure rates under DOTS did not exceed 50% and 29% respectively (54).

While TB burden levels varied between Africa and the rest of the world, significant differences were also observed in and across national settings within Africa. Differences in both existing TB burden levels and reported cases were significantly higher for DR and RRDR than the NDR and RPDR countries (1). Countries that reported the highest TB incidence, prevalence and mortality rates per capita, namely South Africa, Zambia and Zimbabwe, also reported some of the lowest case detection and treatment success rates in the region. Furthermore, Kenya and South Africa

were the only two countries to have achieved the required case detection rate (1). But these countries also reported the lowest treatment success rates and the highest relapse rates under DOTS (Table 3).

While a clear conclusion cannot be drawn regarding the extent of the observed differences in both TB control outcomes and TB burden levels, it appears that more TB cases were reported in DR than NDR countries in Africa (Table 3). Another possible explanation of the rising TB burden levels might be the use of case notification rates by the WHO as a measurable indicator of disease burden, which could over- or under- estimate the cumulative number of TB cases in NDR and RPDR countries. The use of case notification rate as a key measurable indicator for TB burden levels is problematic as it uses data on reported (passive surveillance) rather than detected (active surveillance) TB cases (1;48).

The relationship between TB incidence, prevalence and mortality is an epidemiological one and depends on the number of primary TB infections (incidence) and the existing cases (prevalence) in a given population (1:6). Incidence and prevalence provide important highlights for TB estimates, including the following factors that determine the risk of becoming infectious: (i) the number of TB cases infected; (ii) the duration and length of infection; (iii) the level of interaction between cases in a given population (9;11).

The quantification of TB burden levels in a given country or population is often determined by the number of TB cases entering (the number of people entering the prevalence pool) and exiting (cure and mortality rates) the prevalence pool illustrated in the *Soup Can Model* (Figure 8). When the TB incidence rate increases, the prevalence is also expected to increase, which in turn

influences TB mortality rates, depending on the existing TB burden levels in a given country (11;12;31;45;51;70). For incidence to decline, the transmission of TB infections, particularly primary infections, must be stopped (47-48; 59). Although an increased case detection rate is key to stopping the growth and spread of TB, higher TB case detection rates do not always translate into higher cure rates (47-48; 59). Similarly, increased treatment success rate (cure rate), is expected to result in higher survivability among TB patients, which also contributes to declining prevalence rates (11;12).

According to the Styblo Rule, an annual risk of infection (ARI) of 50 smear-positive TB cases per 100,000 population is expected to generate an incidence rate of 1% (9;11). The Styblo Rule illustrates a way to estimate, albeit indirectly, an important but elusive quantity (disease incidence) from a comparatively simple measurement procedure (risk of infection via tuberculin surveys). The ARI is the proportion of persons in a community who become infected with TB within one year based on estimated large-scale tuberculin skin test (TST) surveys in the general population (9;11).

The TB-caused mortality is expected to be half of the existing TB incidence, and the number of prevalent cases at given point in time is twice the number of incidence cases in a year, while the duration of the disease is two years (9;11;68). Therefore, the number of detected TB cases treated in a given year is an important indicator for TB burden in a given country (11;12). To stop the spread of primary infections, which are also influenced by the levels of TB care coverage, particularly in high burden areas, case detection and cure rates must increase (1; 6). However, an increase in TB care coverage in regions like Africa relies heavily on the capacity of

existing health care system infrastructures, including available and accessible laboratory services and TB care delivery systems/practices at the country level (1; 6).

Among other factors, health system strengthening was a key challenge to improving the delivery of effective and affordable TB care in Africa's DOTS areas (1). A lack of effective TB care delivery strategies within the health system limited the successful implementation of DOTS in Africa countries, particularly in the SSA region (12;71-73). Consequently, implementing DOTS successfully required enormous resources (human and financial), and strong and well established health system infrastructures that could facilitate effective TB care delivery (18). In addition, most African countries became heavily dependent on international technical and financial support to sustain their NTPs, and the DOTS strategy became too costly to implement in resource-poor settings (63).

The disproportionate distribution of available resources for TB control programs has resulted in disproportionate differences in disease distribution across national settings (1). Three factors seemed to have contributed to the disproportionate distribution in disease burden between and within groups in Africa: (i) 39 out of the 47 African countries were classified as least developed countries (LDCs) and these countries often struggled to find the much-needed resources necessary for successful TB control in these settings; (ii) 9 of the 22 high burden countries were in the SSA region, which also reported the highest TB burden levels and lowest budget figures for their TB control programs ($25 million) compared to that of Russia ($722 million), South Africa ($352 million) and China ($225 million); (iii) most of the countries that reported the

highest TB burden levels were countries or settings that relied heavily on foreign aid dollars for their TB control programs (1).

In summary, TB is a disease of poverty, overcrowding and poor nutrition, and as such its prevalence is socio-economically determined. As these conditions have improved in developed countries, TB prevalence has been in long-term decline even before modern chemotherapy became available (6; 7). It is, therefore, possible to suggest that the observed differences in disease burden within and between settings are explained mainly by the differences in the growth and development levels of individual countries. The introduction and implementation of policies and strategies alone will not be sufficient; the world must address all the factors contributing to the observed differences in the distribution of disease burden, such as poverty and income polarisation between and within countries. To derive effective and appropriate strategies and policies, the current global TB control agenda needs normative principles that consider the wider SES canvas, rather than confining policy designs to the conventional status quo.

More importantly, the WHO and its global TB control partners need to understand what is behind the numbers that explain differences in the distribution of disease burden between and within national settings. The issues raised in this analysis apply not only to understanding the disproportionate differences in DOTS impact on TB control outcomes but also in disease burden levels in and across settings.

6.2 **Study Implications**

This empirical analysis is the first of its kind to assess the differences in the impact of DOTS on TB control outcomes from a cross-national context. This type of analysis is a step forward in the direction of research which examines the effectiveness of current strategies and policies for

global TB control. Similar studies providing comprehensive and country-specific empirical analyses were lacking. It adds to the existing body of knowledge related to the effectiveness of the DOTS as a TB control strategy to reduce the rising burden of TB in the African region. It also provides illustrations of factors that have contributed to both the differences in TB burden levels and DOTS's ineffectiveness in reducing the TB burden across national settings, in Africa and the rest of the world. Such factors ultimately undermine the effectiveness of suitable policies and strategies.

To make the DOTS strategy work for TB control, three important and critical issues must be addressed head on. Firstly, the WHO and its global TB control partners must obtain accurate empirical evidence on the disease burden at global and national levels, so that we can effectively direct TB control interventions and formulate policies to evaluate program performance. Secondly, the WHO and its global TB partners must come up with TB control strategies and policies that are technologically sound, financially feasible, appropriate to local conditions and capable of producing tangible results, not only in the short term but also in the long term. Most importantly, international TB control entities, including the WHO and its partners, must be willing to learn from and adapt to local conditions and change preconceptions, if preferred strategies are to work in target areas. In such an approach, TB control efforts are most likely to be supported and facilitated through local capacities. Thirdly, the availability of sufficient resources is critical to successful TB control programs, whether delivered under DOTS or otherwise through sustainable funding and partnerships between institutions at national and global levels.

6.3 **Topics for Future Research**

Limited research has been conducted to examine the impact of DOTS on TB control outcomes, particularly in countries experiencing high prevalence in HIV/TB-co-infections (SSA). The capacity of existing health systems to facilitate the delivery of effective TB care, whether through delivery through DOTS or otherwise, plays a significant role finding (case finding) the source of TB infections in a given population. Effective case finding, however, depends heavily on the access to effective diagnostic services, which is also influenced by the capacity and networks of existing laboratory services in a given country.

Future research would investigate this deficiency by exploring the health impact of complex and expensive TB control interventions such as DOTS in crisis settings from a health system capacity perspective. It will address (i) To what degree assessing TB control outcomes accurate and meaningful based on the current TB control principles and practices in resource-poor settings? (ii) What are the verifiable indicators used to monitor and evaluate the impact of applied TB control interventions (DOTS) on population health outcomes in resource-poor settings, particularly in the SSA Africa? (iii) What does decline or change in TB burden really means in pragmatic and statistical terms when assessing success in TB control outcomes? Although finding answers for these important questions legitimises and demands further rigorous analysis, this enquiry ends by stressing the importance of revisiting all the necessary attributes for successful TB control programs in and across national settings.

Reference List

(1) Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Archives of Internal Medicine 2003;163(9):1009-21.

(2) TB: WHO report on the tuberculosis epidemic 1997. Geneva Switzerland: WHO; 1997.

(3) Anti-tuberculosis drug resistance in the world. Report No. 3: The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance, 1999-2002. Anti-tuberculosis drug resistance in the world 1999;Report.

(4) Harries T. TB control programmes: the challenges for Africa. Africa Health 1996;19(9):19-20.

(5) Jakubowiak WM, Bogorodskaya EM, Borisov ES, Danilova DI, Kourbatova EK. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. International Journal of Tuberculosis and Lung Disease 2007;International(IUATLD):2007-53.

(6) Kamolratanakul P, Sawert H, Kongsin S, Lertmaharit S, Sriwongsa J, Na-Songkhla S, et al. Economic impact of tuberculosis at the household level. International Journal of Tuberculosis & Lung Disease 1999 Jul;3(7):596-602.

(7) Lienhardt C, Ogden JA. Tuberculosis control in resource-poor countries: have we reached the limits of the universal paradigm? Tropical Medicine & International Health 2004 Jul;9(7):833-41.

(8) MILDNER T. One can cure tuberculosis in this way, too. A contribution to medical history. Praxis der Pneumologie Vereinigt Mit der Tuberkulosearzt 1964 Jan;18(1):37-43.

(9) Global tuberculosis control: surveillance, planning, financing - WHO report 2008. Global tuberculosis control: surveillance, planning, financing 2008;World:Health.

(10) Addressing poverty in TB control: options for national TB control programmes. World Health Organization 2005.

(11) Dye C, Watt CJ, Bleed D. Low access to a highly effective therapy: a challenge for international tuberculosis control. Bulletin of the World Health Organization 2002;80(6):437-44.

(12) Dye C, Watt CJ, Bleed DM, Williams BG. What is the limit to case detection under the DOTS strategy for tuberculosis control? Tuberculosis 2003;83(1-3):35-43.

(13) Hill AR, Manikal VM, Riska PF. Effectiveness of directly observed therapy (DOT) for tuberculosis: a review of multinational experience reported in 1990-2000. Medicine (Baltimore) 2002;9(3):183-93.

(14) Thiam S, LeFevre AM, Hane F, Ndiaye A, Ba F, Fielding KL, et al. Effectiveness of a strategy to improve adherence to tuberculosis treatment in a resource-poor setting: a cluster randomized controlled trial. JAMA, Journal of the American Medical Association 2007;297(4):280-386.

(15) Bjune G, Heldal E. The global tuberculosis problem. An apparition from history. Tidsskrift for Den Norske Laegeforening 1994 Feb 20;114(5):578-81.

(16) Daniel TM. The history of tuberculosis. Respiratory Medicine 2006 Nov;100(11):1862-70.

(17) Lordi GM, Reichman LB. Treatment of tuberculosis. American Family Physician 1991 Jul;44(1):219-24.

(18) Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. American Journal of Respiratory & Critical Care Medicine 2005 Apr 1;171(7):699-706.

(19) Potter B, Rindfleisch K, Kraus CK. Management of active tuberculosis. American Family Physician 2005 Dec 1;72(11):2225-32.

(20) Daniel TM. Robert Koch, tuberculosis, and the subsequent history of medicine. American Review of Respiratory Disease 1982 Mar;125(3):1-3.

(21) Snider DE, Jr., Cohn DL, Davidson PT, Hershfield ES, Smith MH, Sutton FD, Jr. Standard therapy for tuberculosis 1985. Chest 1985 Feb;87(2):117-24.

(22) Bates JH, Stead WW. The history of tuberculosis as a global epidemic. Medical Clinics of North America 1993 Nov;77(6):1205-17.

(23) Strull GE, Dym H. Tuberculosis: diagnosis and treatment of resurgent disease. Journal of Oral & Maxillofacial Surgery 1995 Nov;53(11):1334-40.

(24) Tattevin P. Tuberculosis treatment in 2007. Medecine et Maladies Infectieuses 2007 Oct;37(10):617-28.

(25) Gao XF, Wang L, Liu GJ, Wen J, Sun X, Xie Y, et al. Rifampicin plus pyrazinamide versus isoniazid for treating latent tuberculosis infection: a meta-analysis. International Journal of Tuberculosis & Lung Disease 2006 Oct;10(10):1080-90.

(26) Gopi PG, Vasantha M, Muniyandi M, Chandrasekaran V, Balasubramanian R, Narayanan PR. Risk factors for non-adherence to directly observed treatment (DOT) in a rural tuberculosis unit, South India. Indian Journal of Tuberculosis 2007;54(2):66-70.

(27) Ormerod LP. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. British Medical Bulletin 2005;73-74(1):17-24.

(28) Tuberculosis-the WHO/IUATLD global project on antituberculosis drug-resistance surveillance. Weekly Epidemiological Record 1996;71(38):281-5.

(29) Macq JC, Theobald S, Dick J, Dembele M. An exploration of the concept of directly observed treatment (DOT) for tuberculosis patients: from a uniform to a customised approach. International Journal of Tuberculosis and Lung Disease 2003;7(2):103-9.

(30) Espinal MA. The global situation of MDR-TB. Tuberculosis 2003;83(1-3):44-51.

(31) Erhabor GE, Adewole O, Adisa AO, Olajolo OA. Directly observed short course therapy for tuberculosis - a preliminary report of a three-year experience in a teaching hospital. Journal of the National Medical Association 2003;95(11):1082-8.

(32) Okanurak K, Kitayaporn D, Wanarangsikul W, Koompong C. Effectiveness of DOT for tuberculosis treatment outcomes: a prospective cohort study in Bangkok, Thailand. International Journal of Tuberculosis and Lung Disease 2007;International(IUATLD):2007-768.

(33) Wandwalo E, Kapalata N, Egwaga S, Morkve O. Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. International Journal of Tuberculosis and Lung Disease 2004;8(10):1248-54.

(34) Cock KM, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. International Journal of Tuberculosis and Lung Disease 1999;3(6):457-65.

(35) Walley JD, Khan MA, Newell JN, Khan MH. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. Lancet 2001;357(9257):664-9.

(36) Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. BMJ 2008;366(7642):484-7.

(37) Doveren RF. Why tuberculosis control in an unstable country is essential: desperate TB patients embrace DOTS in Angola. International Journal of Tuberculosis and Lung Disease 2001;5(5):486-8.

(38) Khan MA, Walley JD, Witter SN, Shah SK, Javeed S. Tuberculosis patient adherence to direct observation: results of a social study in Pakistan. Health Policy and Planning 2005;20(6):354-65.

(39) Caminero JA. Is the DOTS strategy sufficient to achieve tuberculosis control in low- and middle-income countries? 2. Need for interventions among private physicians, medical

specialists and scientific societies. International Journal of Tuberculosis and Lung Disease 2003;7(8):623-2630.

(40) Smith I. Stop TB: is DOTS the answer? Indian Journal of Tuberculosis 1999;46(2):81-90.

(41) Whalen CC. Failure of directly observed treatment for tuberculosis in Africa: a call for new approaches. Clinical Infectious Diseases 2006 Apr 1;42(7):1048-50.

(42) United Nations Development Programme. Overcoming human poverty. New York: UNDP; 2000.

(43) Carroll K, Malefoasi G. Comparison of outcomes from a district tuberculosis control programme in the Pacific: before and after the implementation of DOTS. Tropical Doctor 2004;34(1):11-4.

(44) Frieden TR, Driver CR. Tuberculosis control: past 10 years and future progress. Tuberculosis 2003;83(1/3):82-5.

(45) Enarson DA, Billo NE. Critical evaluation of the Global DOTS Expansion Plan. (Special issue: Tuberculosis control.). Bulletin of the World Health Organization 2007;85(5):395-8.

(46) Tuberculosis epidemic poses international threat. World Health Organization. AIDS Weekly Plus 1995 Nov 20;20(27):24-5.

(47) Global tuberculosis control: key findings from the December 2009 WHO report. Weekly Epidemiological Record 2010;2010.:85-79.

(48) Dye C, Scheele S, Dolin P, Vikram P, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. JAMA, Journal of the American Medical Association 1999;1999.:282-686.

(49) Rieder HL. Methodological issues in the estimation of the tuberculosis problem from tuberculin surveys. Tubercle and Lung Disease 1995 Apr;76(2):114-21.

(50) Dye C, Lonnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. Bulletin of the World Health Organization 2009;2009.:87-691.

(51) Gonzales RI, Monroe AA, de Assis EG, Palha PF, Villa TC, Netto AR. The performance of health services in providing DOTs in households to control tuberculosis. Revista Da Escola de Enfermagem Da Usp 2008 Dec;42(4):628-34.

(52) Obermeyer Z, bbott-Klafter J, Murray CJL. Has the DOTS Strategy Improved Case Finding or Treatment Success? An Empirical Assessment. PLoS ONE 2008 Mar 5;3(3):e1721.

(53) Bam TS, Gunneberg C, Chamroonsawasdi K, Bam DS, Aalberg O, Kasland O, et al. Factors affecting patient adherence to DOTS in urban Kathmandu, Nepal. International Journal of Tuberculosis and Lung Disease 2006;International(10):3-270.

(54) Pope DS, Chaisson RE. TB treatment: as simple as DOT? International Journal of Tuberculosis and Lung Disease 2003;7(7):611-2615.

(55) Adatu F, Odeke R, Mugenyi M, Gargioni G, McCray E, Schneider E, et al. Implementation of the DOTS strategy for tuberculosis control in rural Kiboga District, Uganda, offering patients the option of treatment supervision in the community, 1998-1999. International Journal of Tuberculosis and Lung Disease 2003;International(IUATLD):2003-S71.

(56) Kumaresan JA, Ali AKM, Parkkali LM. Tuberculosis control in Bangladesh: success of the DOTS strategy. International Journal of Tuberculosis and Lung Disease 1998;1998.:2-998.

(57) Eslava-Schmalbach J, Alfonso H, Oliveros H, Gaitan H, Agudelo C. A new Inequity-in-Health Index based on Millennium Development Goals: methodology and validation. Journal of Clinical Epidemiology 2008;61(2):142-50.

(58) Zellner A. Statistics, econometrics, and forecasting. 1-1-2004.
Ref Type: Generic

(59) Espinal MA, Laserson K, Camacho M, Fusheng Z, Kim SJ, Tlali E, et al. Determinants of drug-resistant tuberculosis: analysis of 11 countries. International Journal of Tuberculosis and Lung Disease 2001;5(10):887-93.

(60) Norman GR. PDQ statistics. 1-1-2003.
Ref Type: Generic

(61) Streiner DL. PDQ epidemiology. 1-1-1989.
Ref Type: Generic

(62) Mahadev B, Kumar P. History of tuberculosis control in India. Journal of the Indian Medical Association 2003 Mar;101(3):142-3.

(63) Vuorinen HS. Some aspects of the history of tuberculosis with special reference to Finland. Dansk Medicinhistorisk Arbog 2001;213(2):154-62.

(64) Veron LJ, Blanc LJ, Suchi M, Raviglione MC. DOTS expansion: will we reach the 2005 targets? (Special section: Stop TB partnership). International Journal of Tuberculosis and Lung Disease 2004;8(1):139-46.

(65) Cambanis A, Yassin MA, Ramsay A, Squire SB, Arbide I, Cuevas LE. Rural poverty and delayed presentation to tuberculosis services in Ethiopia. Tropical Medicine and International Health 2005;Blackwell:ublishing-335.

(66) Tigani B, Kurhasani X, Adams LV, Zhuri G, Mehmeti R, Cirillo D, et al. DOTS implementation in a post-war, United Nations-administered territory: lessons from Kosovo. Respiratory Medicine 2008;102(1):121-7.

(67) Lai D. Temporal analysis of human development indicators: principal component approach. Social Indicators Research 2000;2000.:51-366.

(68) Pearce N. Traditional epidemiology, modern epidemiology, and public health. American Journal of Public Health 1996 May;86(5):678-83.

(69) Chakraborty AK, Krishnamurthy MS, Shashidhara AN, Sanjay J. Missed opportunities for diagnosis of pulmonary tuberculosis: a study among rural patients seeking relief on their own under the tuberculosis programme in India. Indian Journal of Tuberculosis 2001;48(4):181-92.

(70) Geyndt Wd. Managing the quality of health care in developing countries. World Bank Technical Paper 1995;1995.

(71) Collins CD, Green AT, Newell JN. The relationship between disease control strategies and health system development: the case of TB. Health Policy 2002;62(2):141-60.

(72) De Cock KM, Wilkinson D. Tuberculosis control in resource-poor countries: alternative approaches in the era of HIV.[see comment]. Lancet 1995 Sep 9;346(8976):675-7.

(73) Delfino D, Simmons PJ. Dynamics of tuberculosis and economic growth. Environment and Development Economics 2005;10(06):719-43.

(74) Coninx R. Tuberculosis in complex emergencies. Bulletin of the World Health Organization 2007;85(8):637-40.

APPENDICES

APPENDIX A

Table 1 - Essential Drug Combination for Tuberculosis

Drug	C_{max} (mg/L	T_{max} (h)	AUC_0 (mgXhr/L)	$\beta t_{1/2}$ (h)
Isoniazid	4	1-2	17	2-3
Rifampicin	14	1-3	71	2-4
Pyrazinamide (1,500 mg)	25-30	1.2	420	10
Streptomycin (1mg)	25-50	1-2		2-3
Ethambutol(25 mg/kg)	5	3	30	12
Thioacetazone (150 mg)	1.8	4	34	13

Source: Snider et al, 1985 (Ref list # 21).

Table 2 – Mean TB Burden Measures for HBCs (1985-2006)

Year	Obs	Incidence (Mean)	Prevalence (Mean)	Mortality (Mean)
1985	22	123.0952	394.1364	2.95454
1986	22	122.7619	395.6818	40.10909
1987	22	122.2857	393.5909	43.91818
1988	22	123.0000	392.6818	47.10000
1989	22	123.9524	391.9545	51.85909
1990	22	205.5714	395.9545	55.23636
1991	22	214.1429	397.4091	40.10909
1992	22	219.5238	395.2273	43.91818
1993	22	225.6667	394.1818	47.10000
1994	22	231.8095	393.3636	51.85909
1995	22	239.0952	394.7273	55.23636
1996	22	245.2857	391.3182	59.21818
1997	22	254.2857	390.7727	62.28636
1998	22	264.1429	388.1818	64.28636
1999	22	275.8095	393.6364	56.75670
2000	22	289.9524	402.9545	57.94680
2001	22	303.0952	406.5455	62.93636
2002	22	315.6667	407.1818	64.19546
2003	22	323.6190	409.3636	63.98182
2004	22	325.3333	402.6818	66.90455
2005	22	321.3810	392.8636	65.39545
2006	22	315.0476	379.0455	64.42273

*Source WHO Reports; 1985-2006.

Table 3- Mean TB Burden Measures by Region (Cases/100,000) (1985-2006)

	Incidence						Prevalence						Mortality					
Year	AFR	AMR	EMR	EUR	SEAR	WPR	AFR	AMR	EMR	EUR	SEAR	WPR	AFR	AMR	EMR	EUR	SEAR	WPR
1985	25.8	106.1	102.9	111.5	255.3	8.9	37.8	5.14	58.2	15	524.3	263.7	12.6	12.1	1.3	51	58.9	33
1986	29.5	107.6	102.8	114.1	265.7	56	43.8	3.39	54.7	8.9	506.9	261.2	17	11.9	1.9	48.9	57.8	32.5
1987	31.6	109.2	103.7	115.7	255	54	343.7	1.31	52.7	8.5	490.4	256	21.3	11.6	2.5	48.5	56.5	31.7
1988	40.7	111.2	105	118.7	253	55	344.3	0.03	50	8.8	474.8	256.5	26.5	11.5	3.2	48.8	55.5	31.4
1989	59.5	113.9	108.1	120.5	252.9	50	345.4	8.58	48.5	0.1	459.6	245.5	30.7	11.2	4	50.1	54.5	29.4
1990	71.5	100.1	106.4	85.6	247.8	57	337.8	6.69	58.2	1	524.3	263.7	25.5	12.1	1.3	51	58.9	33
1991	83.8	82.8	105.6	79.5	243.5	55	343.8	2.61	54.7	8.9	506.9	261.2	30	11.9	1.9	48.9	57.8	32.5
1992	93.4	81.1	105.7	65.4	239.3	52	343.7	8.11	52.7	8.5	490.4	256	26.7	11.6	2.5	48.5	56.5	31.7
1993	203.8	79.2	105.4	53	235.4	53	344.3	5.03	50	8.8	474.8	256.5	26.5	11.5	3.2	48.8	55.5	31.4
1994	214.1	71.5	106	49.6	231.5	49	345.4	1.81	48.5	0.1	459.6	245.5	30.7	11.2	4	50.1	54.5	29.4
1995	224.9	57.61	106	38.88	227.8	49	347.9	9.39	46.2	2	445.9	249.3	34.8	11.1	4.9	52	53.4	30.9
1996	234.3	56.64	105.6	41.1	224.3	39	345.3	6.22	41.5	4.2	431.5	219.8	36.9	10.8	3.9	54.2	51.7	26.5
1997	246.8	55.61	104.5	43.45	220.9	37	354	4.56	36.8	7.7	424.2	216.2	40.2	10.9	4.2	57.7	51.1	26
1998	260.7	54.69	104	45.39	217.6	32	360.8	2.97	30.9	7.7	410.5	208.2	41.1	10.6	5.1	57.7	49.8	24.4
1999	276.4	53.69	103.9	45.9	214.4	33	384.4	0.75	24.4	8.1	393.6	207.3	48.9	10.3	4.8	58.1	48.1	25.1
2000	293.8	52.56	103.8	46	211.5	24	397	7.14	18.6	7.4	376.9	183.1	50.1	9.8	5.5	57.4	46.5	21.4
2001	310.3	51.72	103.7	46	208.5	21	410.2	5.75	15.4	6	358.3	178.5	53.6	9.69	5.4	56	44.3	21.6
2002	326	51.11	103.5	45.71	205.6	32	17.8	3.92	9.2	4.2	310.3	196.1	49.4	9.34	7.3	54.2	38.7	24.1
2003	337.1	50.53	103.1	44.78	202.9	17	35	2.83	6.5	2	293.9	164.8	52.1	9.4	7.6	52	36.9	19.1
2004	341.1	49.78	103.4	44.12	200.4	19	32.6	0.75	1.9	0	282.9	166.5	52.6	9.23	8	50	35.2	19.1
2005	339.9	49.14	103.9	43.71	197.8	16	35.2	9.58	.3	7.5	272.4	154.3	54.1	9	8.1	47.5	33.6	17.7
2006	336.3	48.39	105	43.49	195.5	16	29.8	8.11	.35	6.2	269.9	152	52.3	8.83	8.5	46.2	32.9	17.5

*Source WHO Reports; 1985-2006. Table 2 shows the mean rates for TB incidence, prevalence and mortality rates from 1996 to 2006. The TB burden levels were standardised to correspond to rates per 100,000 population for the last decade (11;12;28;46;48). Standardisation is critical to provide illustrative estimates for changes in global TB burden levels

Table 4 - TB Case Detection (Cases/100,000) by Region by 1996-2006

Year	GLOBAL	AFR	AMR	EMR	SEAR	EUR	WPR
1996	49	41	69	27	55	44	69
1997	46	38	70	25	48	44	76
1998	46	40	74	41	46	42	76
1999	47	40	69	30	52	42	77
2000	45	38	70	25	49	40	76
2001	45	38	69	28	49	41	77
2002	46	40	72	32	50	41	78
2003	59	40	72	34	52	50	77
2004	53	43	75	39	55	59	78
2005	55	42	75	46	58	65	79
2006	58	44	76	51	61	68	80

*Source WHO Report; 1996-2006.

Table 5- TB Treatment Rates/100,000 by Region by 1996-2006

Year	Global	AFR	AMR	EMR	SEAR	EUR	WPR
1996	54	56	51	66	31	58	72
1997	60	64	58	73	29	72	91
1998	64	70	67	57	40	63	92
1999	64	68	79	79	34	75	91
2000	69	71	76	81	50	75	90
2001	73	70	69	82	63	72	91
2002	76	73	81	84	68	74	90
2003	80	73	80	82	79	75	91
2004	83	74	79	83	84	69	92
2005	85	76	78	83	87	71	92
2006	84	75	75	86	87	69	92

*Source WHO Report; 1996-2006.

Table 6 - TB Burden and Case Detection by Region in 1995

Region	Incidence	Prevalence	Mortality	CDR (Cases/100,000
AFR	1,400,000.00	171,000,000.00	660,000,000.00	26
AMR	560,000,000.00	117,000,000.00	220,000,000.00	36
EMR	594,000,000.00	52,000,000.00	160,000,000.00	21
SEAR	2,480,000.00	426,000,000.00	940,000,000.00	48
WPR	2,560,000.00	576,000,000.00	890,000,000.00	25
EUR	410,000,000.00	382,000,000.00	40,000,000.00	98
GLOB	8,004,000.00	1,722,000.00	2,910,000.00	35

Source: WHO TB Report; 1995

Table 7 –Mean TB Burden Measures for HBCs by 1985-2006

Year	Incidence Cases/100,000	Prevalence Cases/100,000	Mortality Cases/100,000
1985	140.9	398.5	41.6
1986	139.9	400.0	44.4
1987	139.0	397.1	46.5
1988	139.0	395.2	50.3
1989	139.4	393.4	52.7
1990	207.9	400.4	41.6
1991	215.5	401.7	44.4
1992	220.2	398.7	46.5
1993	225.6	396.7	50.3
1994	230.9	394.8	52.7
1995	237.4	394.8	55.6
1996	242.8	390.6	57.7
1997	250.7	387.0	58.7
1998	259.4	381.8	55.4
1999	269.7	384.4	55.6
2000	282.2	392.6	59.2
2001	293.8	396.2	59.5
2002	304.9	397.3	58.0
2003	311.9	397.9	59.2
2004	313.4	392.5	57.6
2005	309.9	383.9	56.1
2006	304.3	373.2	53.4

*Source WHO Reports; 1985-2006.

Table 8 -Mean TB Burden Measures for Pre (1985-1995) and Post-DOTS (1996-2006) Period

	Period	1985-1995			1996-2006	Difference				
OBS	Outcome	Mean	SD	Mean	SD	MeanΔ	SD	d.f	t	*p*
211	Incidence	107.9	112.9	128.2	162.8	-20.3	109	210	-2.7	.001
212	Prevalence	210.8	252.9	182.1	236.6	28.7	167	211	2.5	.007
212	Mortality	23.3	28.2	24.9	38.6	-1.7	27.5	211	-.09	.183

*Source WHO Reports; 1985-2006. *(Table 2 Summarises the Cross-Period Mean Differences in TB Incidence, Prevalence and Mortality Cases. Overall, significant change is observed at α=0.05 Level.

Table 9 - Mean Change in TB Burden in AFR (1996-2006)

Outcome	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Incidence	238	252	267	285	305	324	341	353	358	357	354
Prevalence	345	354	361	384	397	410	418	435	433	435	430
Mortality	36.9	40.2	41.1	48.9	50.1	53.6	49.4	52.1	52.6	54.1	52.3

*Source WHO Reports; 1996-2006.

Table 10 -Mean Difference in TB Burden Levels for AFR Region (1985-1995 between 1996 2006)

Period			**1985-1995**	**1996-2006**	**Difference**			
Group	Outcome	Obs	Mean (SD)	Mean (SD)	Mean (SD)	d.f	*t*	*p*
AC	Incidence	47	163.9 (75.3)	314.6 (188.9)	-150.6 (151.5)	46	-6.8	.001*
	Prevalence	47	341.5(182.9)	472.1(241.1)	-130.6 (181.6)	46	-4.9	.001*
	Mortality	47	42.5 (22.9)	72.5 (51.5)	-30.1 (41.2)	46	-5	.001*
DR	Incidence	41	172.8 (73.7)	336.5 (187.7)	-163.7 (154.9)	40	-6.8	.001*
	Prevalence	41	359.4(183.8)	496.6(235.9)	-137.3(184.9)	40	-4.8	.001*
	Mortality	41	45.2(22.8)	77.7(52.2)	-32.5(42.9)	40	-4.9	.001
NDR	Incidence	6	103.5 (60.3)	164.5(124.8)	-61(90.6)	5	-1.7	.001*
	Prevalence	6	218.4(130.5)	304.4(225.7)	-85.5(-1.3)	5	-1.3	.001*
	Mortality	6	23.7(15.2)	37.4(29.8)	-13.7(23.4)	5	-1.5	.001*
RR	Incidence	2	225 (87.7)	255(141.5)	-30 (229.2)	1	-0.185	.001*
	Prevalence	2	480.5(260.9)	822.5 (369.8)	-342 (108.9)	1	-4.5	.001*
	Mortality	2	66 (14.2)	181(137.2)	-115 (74)	1	-1.328	.001*
RP	Incidence	5	161.2 (74.6)	317.2(191.6)	-155.9(148.7)	44	-7.1	.001*
	Prevalence	45	335.3(180.4)	456.5(227.7)	-121.3(179.3)	44	-4.6	.001*
	Mortality	45	41.4 (22.9)	67.7(42.2)	-26.3 (32.9)	44	-5.4	.001*
RPDR	Incidence	39	170.1(73.2)	340.7(190.3)	-170.6(151.3)	38	-7.1	.001*
	Prevalence	39	353.2(181.6)	479.9(221.6)	-126.8(182.8)	38	-4.4	.001*
	Mortality	39	44.1(22.8)	72.4(42.2)	-28.3(34.1)	38	-5.2	.001*

Source: WHO Reports 1985-2006

APPENDIX B:

Table 1 - The Comparison of Sample Means (1985-1995)

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_inc~5	47	163.9149	10.97119	75.21472	141.831	185.9988
tb_inc~6	47	314.5106	27.55734	188.9236	259.0406	369.9807
diff	47	-150.5957	22.09383	151.4677	-195.0683	-106.1232

mean(diff) = mean(tb_incid_19~1995 - tb_incid_19~2006) t = -6.8162
Ho: mean(diff) = 0 degrees of freedom = 46

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0000 Pr(T > t) = 0.0000 Pr(T > t) = 1.0000

. ttest tb_prev_1985_1995 == tb_prev_1996_2006 if region==1

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_pre~5	47	341.4255	26.68485	182.9421	287.7117	395.1393
tb_pre~6	47	472.0426	35.16182	241.0573	401.2655	542.8196
diff	47	-130.617	26.50264	181.693	-183.9641	-77.26997

mean(diff) = mean(tb_prev_198~1995 - tb_prev_199~2006) t = -4.9285
Ho: mean(diff) = 0 degrees of freedom = 46

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0000 Pr(T > t) = 0.0000 Pr(T > t) = 1.0000

. ttest tb_mort_1985_1995 == tb_mort_1996_2006 if region==1

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_mor~5	47	42.40426	3.352503	22.9836	35.65602	49.15249
tb_mor~6	47	72.46809	7.503367	51.44049	57.36459	87.57158
diff	47	-30.06383	6.009429	41.19857	-42.16018	-17.96748

mean(diff) = mean(tb_mort_198~1995 - tb_mort_199~2006) t = -5.0028
Ho: mean(diff) = 0 degrees of freedom = 46

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0000 Pr(T > t) = 0.0000 Pr(T > t) = 1.0000

ttest tb_incid_1985_1995 == tb_incid_1996_2006 for Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_inc~5	211	107.9431	7.776512	112.9604	92.6131	123.2732
tb_inc~6	211	128.2275	11.20369	162.7429	106.1414	150.3136
diff	211	-20.28436	7.508465	109.0668	-35.08598	-5.482737

mean(diff) = mean(tb_incid_19~1995 - tb_incid_19~2006) t = -2.7015
Ho: mean(diff) = 0 degrees of freedom = 210

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0037 Pr(T > t) = 0.0075 Pr(T > t) = 0.9963

ttest tb_prev_1985_1995 == tb_prev_1996_2006 for Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_pre~5	212	210.7642	17.36938	252.9021	176.5244	245.0039
tb_pre~6	212	182.1038	16.24689	236.5583	150.0768	214.1308
diff	212	28.66038	11.47247	167.0417	6.045025	51.27573

mean(diff) = mean(tb_prev_198~1995 - tb_prev_199~2006) t = 2.4982
Ho: mean(diff) = 0 degrees of freedom = 211

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.9934 Pr(T > t) = 0.0132 Pr(T > t) = 0.0066

ttest tb_mort_1985_1995 == tb_mort_1996_2006 for Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_mor~5	212	23.24057	1.937067	28.20412	19.42208	27.05905
tb_mor~6	212	24.9434	2.650282	38.58869	19.71897	30.16782
diff	212	-1.70283	1.885874	27.45874	-5.420398	2.014738

mean(diff) = mean(tb_mort_198~1995 - tb_mort_199~2006) t = -0.9029
Ho: mean(diff) = 0 degrees of freedom = 211

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.1838 Pr(T > t) = 0.3676 Pr(T > t) = 0.8162

ttest tb_incid_1985_1995 == tb_incid_1996_2006 FOR Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_inc~5	211	107.9431	7.776512	112.9604	92.6131	123.2732
tb_inc~6	211	128.2275	11.20369	162.7429	106.1414	150.3136
diff	211	**-20.28436**	7.508465	109.0668	-35.08598	-5.482737

mean(diff) = mean(tb_incid_19~1995 - tb_incid_19~2006) **t = -2.7015**
Ho: mean(diff) = 0 degrees of freedom = 210

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = **0.0037** Pr(|T| > |t|) = 0.0075 Pr(T > t) = 0.9963

ttest tb_prev_1985_1995 == tb_prev_1996_2006 FOR Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_pre~5	212	210.7642	17.36938	252.9021	176.5244	245.0039
tb_pre~6	212	182.1038	16.24689	236.5583	150.0768	214.1308
diff	212	**28.66038**	11.47247	167.0417	6.045025	51.27573

mean(diff) = mean(tb_prev_198~1995 - tb_prev_199~2006) **t = 2.4982**
Ho: mean(diff) = 0 degrees of freedom = 211

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.9934 Pr(|T| > |t|) = 0.0132 Pr(T > t) = **0.0066**

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==1 for paired t-test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_inc~6 |      47    314.5106    27.55734    188.9236    259.0406    369.9807
tb_inc~5 |      47    163.9149    10.97119    75.21472     141.831    185.9988
---------+--------------------------------------------------------------------
    diff |      47    150.5957    22.09383    151.4677    106.1232    195.0683
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =   6.8162
    Ho: mean(diff) = 0                           degrees of freedom =       46

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000


ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==1 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_pre~6 |      47    472.0426    35.16182    241.0573    401.2655    542.8196
tb_pre~5 |      47    341.4255    26.68485    182.9421    287.7117    395.1393
---------+--------------------------------------------------------------------
    diff |      47     130.617    26.50264     181.693    77.26997    183.9641
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =   4.9285
    Ho: mean(diff) = 0                           degrees of freedom =       46
 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000

ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==1 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_mor~6 |      47    72.46809    7.503367    51.44049    57.36459    87.57158
tb_mor~5 |      47    42.40426    3.352503     22.9836    35.65602    49.15249
---------+--------------------------------------------------------------------
    diff |      47    30.06383    6.009429    41.19857    17.96748    42.16018
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =   5.0028
    Ho: mean(diff) = 0                           degrees of freedom =       46

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 1.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 0.0000
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==2 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_inc~6 |      43     49.7907    9.663128    63.36536    30.28972    69.29168
tb_inc~5 |      43     76.97674    15.60069    102.3006    45.49328    108.4602
---------+--------------------------------------------------------------------
    diff |      43    -27.18605    8.048115    52.77502    -43.4278   -10.94429
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =  -3.3779
    Ho: mean(diff) = 0                           degrees of freedom =       42

 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0008         Pr(|T| > |t|) = 0.0016          Pr(T > t) = 0.9992


ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==2 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_pre~6 |      44     64.95455    12.74187    84.51997    39.25813    90.65097
tb_pre~5 |      44     122.3864    25.68724    170.3899    70.58311    174.1896
---------+--------------------------------------------------------------------
    diff |      44    -57.43182    14.83476    98.40268   -87.34897   -27.51467
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -3.8714
    Ho: mean(diff) = 0                           degrees of freedom =       43

 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0002         Pr(|T| > |t|) = 0.0004          Pr(T > t) = 0.9998

ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==2 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_mor~6 |      44     7.954545    1.716403    11.38533    4.493088      11.416
tb_mor~5 |      44     13.34091    3.063966    20.32405    7.161832    19.51999
---------+--------------------------------------------------------------------
    diff |      44    -5.386364    1.590211    10.54826   -8.593329   -2.179399
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =  -3.3872
    Ho: mean(diff) = 0                           degrees of freedom =       43

 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0008         Pr(|T| > |t|) = 0.0015          Pr(T > t) = 0.9992
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==3 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_inc~6 |      22    93.22727    36.99034    173.5001    16.30164    170.1529
 tb_inc~5 |      22        97.5    27.70076    129.9281    39.89311    155.1069
-------------+----------------------------------------------------------------
        diff |      22   -4.272727    13.08682    61.38263   -31.48826     22.9428
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =  -0.3265
    Ho: mean(diff) = 0                     degrees of freedom =       21

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.3736         Pr(|T| > |t|) = 0.7473          Pr(T > t) = 0.6264
ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==3 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_pre~6 |      22    137.5909     59.8104    280.5357    13.20837    261.9735
tb_pre~5 |      22    201.5455    72.59172    340.4853    50.58272    352.5082
-------------+----------------------------------------------------------------
        diff |      22   -63.95455    23.47832    110.1231   -112.7804   -15.12871
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -2.7240
    Ho: mean(diff) = 0                     degrees of freedom =       21
 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0064         Pr(|T| > |t|) = 0.0127          Pr(T > t) = 0.9936

ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==3 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_mor~6 |      22    16.09091    6.827151    32.02218    1.893071    30.28875
tb_mor~5 |      22    20.54545    7.411156     34.7614    5.133113     35.9578
-------------+----------------------------------------------------------------
        diff |      22   -4.454545    3.490077    16.36991   -11.71256    2.803467
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =  -1.2763
    Ho: mean(diff) = 0                     degrees of freedom =       21
 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.1079         Pr(|T| > |t|) = 0.2158          Pr(T > t) = 0.8921
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==4 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_inc~6 |      54    46.22222    7.035582    51.70076    32.11063    60.33381
tb_inc~5 |      54    43.31481    6.139186    45.11362    31.00117    55.62846
-------------+----------------------------------------------------------------
        diff |      54    2.907407    5.020661    36.89417   -7.162763    12.97758
------------------------------------------------------------------------------
    mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =   0.5791
        Ho: mean(diff) = 0                     degrees of freedom =       53

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.7175         Pr(|T| > |t|) = 0.5650          Pr(T > t) = 0.2825
ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==4 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_pre~6 |      54    54.18519    9.981257    73.34696    34.16532    74.20505
tb_pre~5 |      54    65.61111    12.54338    92.17465    40.45227    90.76995
-------------+----------------------------------------------------------------
        diff |      54   -11.42593     6.85385    50.36531   -25.17301    2.321157
------------------------------------------------------------------------------
    mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -1.6671
        Ho: mean(diff) = 0                     degrees of freedom =       53

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.0507         Pr(|T| > |t|) = 0.1014          Pr(T > t) = 0.9493
ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==4 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_mor~6 |      54    6.703704    1.201452    8.828833    4.293896    9.113511
tb_mor~5 |      54    6.685185    1.411202    10.37018    3.854672    9.515698
-------------+----------------------------------------------------------------
        diff |      54    .0185185    .9227654    6.780913   -1.832314    1.869352
------------------------------------------------------------------------------
    mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =   0.0201
        Ho: mean(diff) = 0                     degrees of freedom =       53

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.5080         Pr(|T| > |t|) = 0.9841          Pr(T > t) = 0.4920
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==5 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_inc~6 |      14    137.9286    38.44512    143.8485    54.87294    220.9842
tb_inc~5 |      14    161.9286    39.11163    146.3423    77.43304    246.4241
-------------+----------------------------------------------------------------
        diff |      14         -24    10.31962    38.61247   -46.29418   -1.705822
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =  -2.3257
    Ho: mean(diff) = 0                           degrees of freedom =       13

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0184         Pr(|T| > |t|) = 0.0369          Pr(T > t) = 0.9816
ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==5 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_pre~6 |      14    178.1429    53.53646    200.3151    62.48437    293.8013
tb_pre~5 |      14         341    86.43005    323.3916    154.2792    527.7208
-------------+----------------------------------------------------------------
        diff |      14   -162.8571    36.90779    138.0963   -242.5916    -83.1227
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -4.4125
    Ho: mean(diff) = 0                           degrees of freedom =       13

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0004         Pr(|T| > |t|) = 0.0007          Pr(T > t) = 0.9996
ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==5 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
tb_mor~6 |      14    19.28571    6.733081    25.19288    4.739777    33.83165
tb_mor~5 |      14        36.5    9.813508    36.71879     15.2992     57.7008
-------------+----------------------------------------------------------------
        diff |      14   -17.21429    4.733768    17.71214   -27.44097   -6.987603
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =  -3.6365
    Ho: mean(diff) = 0                           degrees of freedom =       13

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0015         Pr(|T| > |t|) = 0.0030          Pr(T > t) = 0.9985
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_inc~6 |      31    117.9032    21.21023    118.0936    74.58616    161.2203
tb_inc~5 |      31    161.6452    27.28616    151.9229    105.9194    217.3709
---------+--------------------------------------------------------------------
    diff |      31   -43.74194    9.038147    50.32227   -62.20029   -25.28358
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =  -4.8397
    Ho: mean(diff) = 0                       degrees of freedom =       30
 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_pre~6 |      31         165     30.6998    170.9292    102.3027    227.6973
tb_pre~5 |      31    338.6774     60.7547    338.2679    214.5998    462.7551
---------+--------------------------------------------------------------------
    diff |      31   -173.6774    35.00041     194.874   -245.1578    -102.197
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -4.9622
    Ho: mean(diff) = 0                       degrees of freedom =       30

 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_mor~6 |      31     17.6129    3.641067     20.2726    10.17685    25.04895
tb_mor~5 |      31          33    6.155162    34.27049    20.42948    45.57052
---------+--------------------------------------------------------------------
    diff |      31    -15.3871    3.114198    17.33912   -21.74714   -9.027055
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =  -4.9409
    Ho: mean(diff) = 0                       degrees of freedom =       30

 Ha: mean(diff) < 0          Ha: mean(diff) != 0          Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_inc~6 |      31    117.9032    21.21023    118.0936    74.58616    161.2203
tb_inc~5 |      31    161.6452    27.28616    151.9229    105.9194    217.3709
---------+--------------------------------------------------------------------
    diff |      31   -43.74194    9.038147    50.32227   -62.20029   -25.28358
------------------------------------------------------------------------------
mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =  -4.8397
    Ho: mean(diff) = 0                       degrees of freedom =       30

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000

ttest tb_prev_1996_2006 == tb_prev_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_pre~6 |      31         165     30.6998    170.9292    102.3027    227.6973
tb_pre~5 |      31    338.6774     60.7547    338.2679    214.5998    462.7551
---------+--------------------------------------------------------------------
    diff |      31   -173.6774    35.00041     194.874   -245.1578    -102.197
------------------------------------------------------------------------------
mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -4.9622
    Ho: mean(diff) = 0                       degrees of freedom =       30

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
ttest tb_mort_1996_2006 == tb_mort_1985_1995 if region==6 for Paired t test
------------------------------------------------------------------------------
Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
tb_mor~6 |      31     17.6129    3.641067     20.2726    10.17685    25.04895
tb_mor~5 |      31          33    6.155162    34.27049    20.42948    45.57052
---------+--------------------------------------------------------------------
    diff |      31    -15.3871    3.114198    17.33912   -21.74714   -9.027055
------------------------------------------------------------------------------
mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =  -4.9409
    Ho: mean(diff) = 0                       degrees of freedom =       30

 Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
 Pr(T < t) = 0.0000         Pr(|T| > |t|) = 0.0000          Pr(T > t) = 1.0000
```

ttesti 16 81.94 101.9 196 131.56 166 –for Two-sample t test with unequal variances-incidence

	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	16	81.94	25.475	101.9	27.64132 136.2387
y	196	131.56	11.85714	166	108.1753 154.9447
combined	212	127.8151	11.15441	162.4107	105.8267 149.8035
diff		**-49.62**	42.18911		-132.7884 33.54844

diff = mean(x) - mean(y) **t = -1.1761**
Ho: diff = 0 degrees of freedom = 210
Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = **0.1204** Pr(|T| > |t|) = 0.2409 Pr(T > t) = 0.8796

ttesti 16 141.50 188.2 196 185.42 240.1-for Two-sample t test with unequal variances-prevalence

	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	16	141.5	47.05	188.2	41.2153 241.7847
y	196	185.42	17.15	240.1	151.5967 219.2433
combined	212	182.1053	16.24253	236.4948	150.0869 214.1237
diff		**-43.92**	61.56124		-165.2772 77.43721

diff = mean(x) - mean(y) **t = -0.7134**
Ho: diff = 0 degrees of freedom = 210
Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = **0.2382** Pr(|T| > |t|) = 0.4764 Pr(T > t) = 0.7618

ttesti 16 17.31 23.9 196 25.57 39.5-for Two-sample t test with unequal variances-mortality

	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	16	17.31	5.975	23.9	4.574589 30.04541
y	196	25.57	2.821429	39.5	20.00557 31.13443
combined	212	24.9466	2.648716	38.56589	19.72527 30.16794
diff		-8.26	6.607653		-21.95102 5.431015

diff = mean(x) - mean(y) **t = -1.2501**
Ho: diff = 0 Satterthwaite's degrees of freedom = 22.3497
Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = **0.1121** Pr(|T| > |t|) = 0.2242 Pr(T > t) = 0.8879

ttesti 85 -68.9 146.4 110 17.6 50.3 for Two-sample t test with unequal variances-incidence

Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	85	-68.9	15.87931	146.4	-100.4777	-37.32225
y	110	17.6	4.795917	50.3	8.094649	27.10535
combined	195	-20.10513	8.022755	112.0317	-35.92815	-4.282109
diff		-86.5	14.97828		-116.0421	-56.95786

diff = mean(x) - mean(y) t = -5.7750
Ho: diff = 0 degrees of freedom = 193

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.0000 Pr(|T| > |t|) = 0.0000 Pr(T > t) = 1.0000

ttesti 85 -4.3 204.5 111 61.5 132.4 for Two-sample t test with unequal variances-prevalence

Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	85	-4.3	22.18114	204.5	-48.40963	39.80963
y	111	61.5	12.56685	132.4	36.59545	86.40455
combined	196	32.96429	12.15803	170.2124	8.986166	56.9424
diff		-65.8	24.13807		-113.4067	-18.19327

diff = mean(x) - mean(y) t = -2.7260
Ho: diff = 0 degrees of freedom = 194

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.0035 Pr(|T| > |t|) = 0.0070 Pr(T > t) = 0.9965

ttesti-For Two-sample t test with unequal variances-Mortality

Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]
x	85	-8.3	3.470887	32	-15.20224	-1.39776
y	111	3.8	2.240013	23.6	-.6391797	8.23918
combined	196	-1.447449	2.009459	28.13242	-5.410511	2.515613
diff		-12.1	3.97128		-19.93243	-4.267574

diff = mean(x) - mean(y) t = -3.0469
Ho: diff = 0 degrees of freedom = 194

Ha: diff < 0 Ha: diff != 0 Ha: diff > 0
Pr(T < t) = 0.0013 Pr(|T| > |t|) = 0.0026 Pr(T > t) = 0.9987

```
ttest tb_incid_1996_2006 == tb_incid_1985_1995 if DOTS==1 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
  tb_inc~6 |     195    132.0256      11.913     166.356      108.53    155.5213
  tb_inc~5 |     195    111.9333    8.269889    115.4827     95.6229    128.2438
-------------+----------------------------------------------------------------
        diff |     195    20.09231    8.024626    112.0578    4.265599    35.91902
------------------------------------------------------------------------------
    mean(diff) = mean(tb_incid_19~2006 - tb_incid_19~1995)       t =   2.5038
        Ho: mean(diff) = 0                     degrees of freedom =      194

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.9934         Pr(|T| > |t|) = 0.0131          Pr(T > t) = 0.0066
ttest tb_prev_1996_2006 == tb_prev_1985_1995 if DOTS==1 for Paired t test

------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
  tb_pre~6 |     196    185.4184    17.15507     240.171    151.5851    219.2517
  tb_pre~5 |     196    218.3724    18.52435    259.3409    181.8387    254.9062
-------------+----------------------------------------------------------------
        diff |     196   -32.95408    12.16172    170.2641   -56.93948   -8.968687
------------------------------------------------------------------------------
    mean(diff) = mean(tb_prev_199~2006 - tb_prev_198~1995)       t =  -2.7097
        Ho: mean(diff) = 0                     degrees of freedom =      195

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.0037         Pr(|T| > |t|) = 0.0073          Pr(T > t) = 0.9963
ttest tb_mort_1996_2006 == tb_mort_1985_1995 if DOTS==1 for Paired t test
------------------------------------------------------------------------------
    Variable |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
-------------+----------------------------------------------------------------
  tb_mor~6 |     196    25.56633    2.823011    39.52215    19.99877    31.13388
  tb_mor~5 |     196    24.11224    2.064372     28.9012    20.04088    28.18361
-------------+----------------------------------------------------------------
        diff |     196    1.454082    2.014758    28.20662   -2.519433    5.427596
------------------------------------------------------------------------------
    mean(diff) = mean(tb_mort_199~2006 - tb_mort_198~1995)       t =   0.7217
        Ho: mean(diff) = 0                     degrees of freedom =      195

    Ha: mean(diff) < 0           Ha: mean(diff) != 0           Ha: mean(diff) > 0
     Pr(T < t) = 0.7643         Pr(|T| > |t|) = 0.4713          Pr(T > t) = 0.2357
```

one-way tb_incid_1996_2006 region for Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	2297728.61	5	459545.722	28.93	0.0000
Within groups	3271749.22	206	15882.2777		
Total	5569477.83	211	26395.6295		

Bartlett's test for equal variances: chi2(30) = 102.8684 Prob>chi2 = 0.000

one-way tb_prev_1996_2006 region for Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	5491374.71	5	1098274.94	35.82	0.0000
Within groups	6316149	206	30660.9175		
Total	11807523.7	211	55959.828		

Bartlett's test for equal variances: chi2(30) = 102.1473 Prob>chi2 = 0.000

one-way tb_mort_1996_2006 region for Analysis of Variance

Source	SS	df	MS	F	Prob > F
Between groups	140656.42	5	28131.284	33.39	0.0000
Within groups	173540.901	206	842.431557		
Total	314197.321	211	1489.08683		

Bartlett's test for equal variances: chi2(30) = 172.5746 Prob>chi2 = 0.000

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf.	Interval]
tb_mo~95	8	38.5	3.099539	8.766821	31.17075	45.82925
tb_mo~06	8	89.75	7.918671	22.39739	71.02532	108.4747
diff	8	-51.25	7.386643	20.89258	-68.71664	-33.78336

mean(diff) = mean(tb_mort_95 - tb_mort_06) t = -6.9382

Ho: mean(diff) = 0 degrees of freedom = 7

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0

Pr(T < t) = 0.0001 Pr(|T| > |t|) = 0.0002 Pr(T > t) = 0.9999

Paired t test

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
tb_pr~95	8	261.75	19.68933	55.68983	215.1921	308.3079
tb_pr~06	8	559.5	38.62642	109.252	468.163	650.837
diff	8	-297.75	25.12451	71.06285	-357.16	-238.34

mean(diff) = mean(tb_prev_95 - tb_prev_06) t = -11.8510
Ho: mean(diff) = 0 degrees of freedom = 7

Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0000 Pr(T > t) = 0.0000 Pr(T > t) = 1.0000

AFRICA HBBCs
Paired

Variable	Obs	Mean	Std. Err.	Std. Dev.	[95% Conf. Interval]	
tb_in~95	8	150.125	8.179761	23.13586	130.7829	169.4671
tb_in~06	8	391.5	28.16216	79.65461	324.9071	458.0929
diff	8	-241.375	30.10098	85.13844	-312.5525	-170.1975

mean(diff) = mean(tb_incid_85_95 - tb_incid_06) t = -8.0188
Ho: mean(diff) = 0 degrees of freedom =
Ha: mean(diff) < 0 Ha: mean(diff) != 0 Ha: mean(diff) > 0
Pr(T < t) = 0.0000 Pr(|T| > |t|) = 0.0001 Pr(T > t) = 1.0000