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# **Gender-specific epidemiology of tuberculosis in a population with high HIV prevalence**

**A mini-dissertation submitted to the Faculty of Health Sciences,  
University of Cape Town, in partial fulfillment of the requirements  
for the Master of Public Health degree (Epidemiology)**

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Submitted: May 2013

## DECLARATION

I, Kimberly Racow, Student Number, RCWKIM001, declare that the work I have submitted is my own and where the work of others has been used (whether quoted verbatim, paraphrased or referred to) it has been attributed and acknowledged.

Signature: \_\_\_\_\_

Date: 20 May 2013

Signed by candidate

University of Cape Town

## **DEDICATION**

I would like to dedicate my dissertation to Tyrone Bloch, for his endless support and inspiration, which has given me the confidence and strength to persevere through this journey and *own* every step of the way.

## DISSERTATION ABSTRACT

South Africa is faced with one of the worst dual epidemics of tuberculosis (TB) and HIV worldwide. Gender is intrinsically linked to the way individuals experience health outcomes. Globally, there are significant gender differences in the clinical characteristics of TB cases as well as in the occurrence of TB disease. Studies have identified a range of factors potentially contributing to these differences. However, despite the strong association between HIV and TB as well as the well-established fact that females are more susceptible to HIV infection than males, few studies in HIV-burdened settings such as South Africa have explored gender differences in TB, let alone investigated the effect of HIV on gender differences. We hypothesized that the increased burden of TB disease among young females in Cape Town is primarily due to HIV infection in this age group.

During 2009, City of Cape Town TB clinics prospectively collected routine notification data on 29,478 new TB cases. The objectives of this analysis were to describe the 2009 Cape Town TB case population by gender, age, and HIV; explore associations between gender, clinical characteristics, and HIV in TB cases; and estimate age-specific TB notification rates by gender and HIV.

The protocol (Part A) describes the research methodology and statistical analysis used in this study. The literature summary (Part B) describes the burden of HIV and TB; differences in the burden of TB by age and gender; differences in the clinical characteristics of male and female TB cases; and factors potentially affecting these gender differences. Lastly, this summary identifies gaps in the literature, which the following study aims to address.

The journal ready article (Part C) presents the results of this study and discussion on key findings. To our knowledge this is the first study to investigate the effect of HIV on gender differences in TB in South Africa. The crude female:male ratio among cases was 0.83. Among 15-54 year old adult cases, females were significantly younger than males and less likely than males to have pulmonary TB, have smear results recorded, be smear-positive, or have advanced smear-positivity grading. Females were more likely than males to be HIV-positive. HIV co-infection widened pre-existing clinical differences between male and female cases. Among HIV-negative adults, age-specific male notification rates exceeded female rates at all ages to a 2.5-fold difference among 45-49 year olds. The rate in 15-19 year old HIV-positive females was 12.4% higher than in males of that age, after which male rates increasingly exceeded female rates to a 2-fold difference among 45-49 year olds. The disparity between male and female rates was smaller among HIV-positive than HIV-negative individuals.

This is the first study to conduct an in-depth analysis of the effect of HIV on TB-related gender differences in South Africa. The age and gender pattern of TB disease in the HIV-positive population has only been reported in Malawi, Uganda, and mid-20<sup>th</sup> century countries. The HIV-negative pattern mirrors gender differences in all other countries reporting disaggregated data. HIV co-infection is associated with an increased risk of TB disease, particularly among young females, and has led to decreased gender differences. Controlling for HIV did not nullify gender differences, which indicates that there are additional contributing factors. This study warrants improved HIV and TB testing and treatment practices as well as educational programmes targeted at younger females and older males.

## **ACKNOWLEDGEMENT**

I would like to thank the City of Cape Town for providing me with these data to do my analysis as well as the TB clinic staff and management who maintain the TB register. I would also like to thank Francesca Little for her statistical guidance.

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University of Cape Town

## PART A: PROTOCOL

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## 1.0 INTRODUCTION

### 1.1 Background

#### 1.1.1 TB and HIV in South Africa

South Africa, a country of approximately 50.6 million people [1], reported nearly 400,000 total tuberculosis (TB) cases in 2011 [2]. This estimate accounts for one-quarter of the burden of TB disease in sub-Saharan Africa [3, 4]. In addition, South Africa carries the largest burden of Human Immunodeficiency Virus (HIV) in the world, contributing 5.6 million HIV positive individuals to the global burden of 34 million [5]. South Africa's efforts to reduce the burden of TB has been hindered by insufficient TB cure rates and TB case detection rates, a generalised HIV epidemic, and deep-rooted social issues such as poverty and poor living conditions [2, 3, 6–10].

Dubbed the “cursed duet”, HIV and TB have a synergistic relationship whereby people living with HIV experience a significantly increased risk of developing TB disease compared to those not living with HIV [11]. Wood et al. [6] reported 29,478 incident TB cases in 2009, of which 51.4% of those who tested were HIV positive. In this population, there was a 17-fold increased risk of developing TB disease among HIV positive individuals compared to HIV negative individuals [6]. In the HIV negative population, the highest number of TB cases was among 20-24 year olds, and in the HIV positive population, the highest number of TB cases was among 30-34 year olds [6].

#### 1.1.2 Gender differences in TB disease

Differences in male and female TB notification rates have been observed throughout history. During the 1930s to 1950s in industrialised countries such as England and Wales, there was a very high burden of TB disease which varied by age and gender. TB notification rates in children were similar among males and females, after which the notification rates in young adults were higher among females than males and the notification rates in older adults were higher among males than in females [12]. As a result of effective TB control programs, TB notification rates decreased substantially by 1970 and the distribution of TB disease among males and females changed. While TB notification rates among male and female children still remained equal, male notification rates increasingly exceeded female notification rates from adolescence through adulthood, and the excess rates previously seen among young females diminished [12]. Figure 1, taken directly from Holmes et al.'s [12] paper, illustrates the shift in age-specific male and female tuberculosis notification rates in England and Wales in 1952 and 1970.

The burden of TB disease (absolute TB case numbers and TB notification rates) in low- and middle-income countries today is similar in magnitude to what was experienced in industrialised countries during the mid-20<sup>th</sup> century [12, 13]. However, two different age and gender patterns of TB cases and notification rates have been identified in current literature. The majority of literature published in low- and middle-income countries today report an age and gender pattern of TB disease similar to that of 1970 in industrialized countries [12, 14–16]. However, Malawi, Uganda, and South Africa reported a TB disease burden similar to the age and gender pattern observed earlier in the century [12, 15, 17, 18].



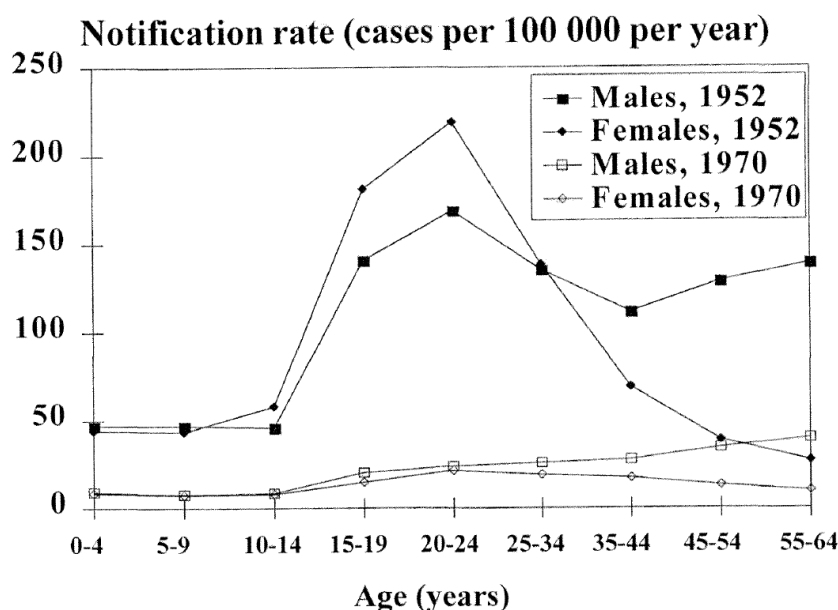


Figure 1 - Shift in tuberculosis notification rates in England and Wales, 1952 and 1970 [12]

Under notification, sex-specific mechanisms, and epidemiological differences are frequently cited as factors associated with the disproportionate burden of TB disease among males after childhood in many low- and middle-income countries. Under notification of females is commonly associated with barriers that decrease access to care for females such as lack of access to finances, legal rights, and education [12], lower social status [12], lower prioritization of health [19], feelings of embarrassment or shame [20], and TB clinics being inaccessible by foot [21]. In addition, findings show that certain genetic polymorphisms increase males' susceptibility to TB [22]. Mice studies also found that testosterone treatment increased susceptibility to *M.marinum* and *M.intracellulare* [23, 24] while oestrogen treatment reduced susceptibility to *M.avium* [25]. Lastly, males engage in higher levels of social interactions than females in some settings, thereby increasing their risk of TB exposure and subsequent development of TB disease [26, 27]. All of these factors may explain why adolescent and adult males have a higher burden of TB disease than females in the majority of low- and middle-income countries who reported gender differences related to TB disease.

However, in Malawi, Uganda, and South Africa, there were high prevalences of HIV during the time these data were collected [18, 28, 29], which may largely explain why females had an increased susceptibility to TB in these settings. This supposition is substantiated by findings of increased numbers of TB cases in populations with high prevalences of HIV infection; increased prevalences of HIV among TB cases; and a higher risk of developing TB disease in immune suppressed individuals [18]. Furthermore, Lawn et al. [18] and Crampin et al. [17] identified HIV as a major factor shifting the age and gender distribution of TB disease in their populations, particularly among young females. Therefore, it is likely that HIV and its underlying immunological and socio-behavioural pathways is a major contributor to the unique age and gender pattern of TB disease observed in these three settings. In addition, contrary to other studies, one study conducted in South Africa found that females

rather than males engage in higher levels of social mixing, which may also be influencing females' risk of TB in South Africa [30].

Further to gender differences in the risk of TB disease, there are also differences in the clinical characteristics of male and female TB cases. Research shows that females are less likely than males to be asked by healthcare providers to submit sputum for analysis [31–33]. Authors suggested that this is a result of provider bias, whereby providers are less likely to suspect females of having TB and therefore less likely to acquire sputum samples from them [33]. In addition, another study suggested that females are less able to produce sputum than males [34], which may be biological or a socio-cultural barrier related to social norms and not feeling comfortable expectorating sputum in public [35].

Of the females that submit sputum for analysis, studies mainly found that females were less likely than males to be smear positive [31–33]. This could again be due to females producing poor quality sputum that is in fact saliva rather than sputum, which could lead to false negative results [31]. In addition, it is well established that HIV-related immune suppression leads to disseminated TB and fewer bacilli present in sputum [36, 37], which reduces the likelihood of smear positivity. This is particularly relevant in HIV-burdened Malawi, Uganda, and South Africa.

## **1.2 Dissertation rationale**

Although gender is intrinsically linked to health outcomes, the most recent review on gender and TB epidemiology was published by Holmes et al. [12] in 1998. Since then, a number of studies have been published but many have discussed the need for further research on this topic to fill the gaps and draw clearer conclusions. Furthermore, despite the strong association between TB and HIV, few studies conducted in HIV-burdened countries have explored the effect that HIV may be having on gender differences related to TB disease. My hypothesis is that the increased burden of TB disease among young females in Cape Town is primarily due to HIV infection among this age group.

The need for further research is particularly relevant for South Africa, which is struggling to curb the dual epidemic of HIV and TB. Yet, in this setting, only one study by Austin et al. [33] has been published and it did not analyze the impact of HIV on observed gender differences. In addition, 2009 was the first year that TB clinics in Cape Town began recording HIV-related information in the electronic TB register. High HIV testing rates and the availability of these data will enable a rigorous analysis of gender differences in TB disease as well as HIV's affect on these differences in Cape Town. This analysis aims to enhance knowledge about gender, TB disease, and HIV in Cape Town as well as provide evidence to support a multi-pronged approach to TB control that considers age, gender, and HIV.

## **1.3 Research questions**

1. What are the demographic and clinical differences between male and female Cape Town TB cases?
2. What is the age distribution of TB notification rates by gender and HIV in Cape Town?

3. How does HIV affect differences in the clinical characteristics and TB notification rates between males and females in Cape Town (Figure 2)?

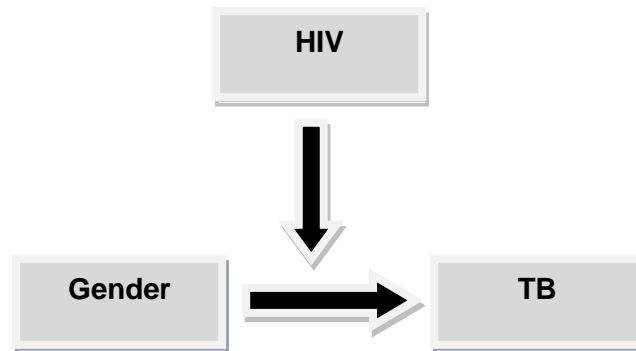


Figure 2 - Effect modification

#### 1.4 Dissertation objectives

1. To describe the 2009 Cape Town TB case population by gender, age, and HIV and determine corresponding standardized female:male ratios;
2. to explore associations between gender and clinical characteristics of TB cases and the impact of HIV on these associations;
3. to estimate age-specific TB notification rates by gender and HIV and determine corresponding notification rate ratios; and
4. to draw conclusions regarding the impact of HIV on observed gender differences.

## 2.0 METHODS

### 2.1 Study design

These routine data were prospectively collected from City of Cape Town public TB clinics from 1 January to 31 December, 2009. TB clinics are governed by City of Cape Town local authorities and provide free TB services to residents. All patient information is consecutively recorded in standardised paper TB registers at each health facility and then collated into a centralised electronic TB database as per the guidelines of the South African National TB Control Program [40].

The primary analysis of these data was published in 2011 by Wood et al. [6] entitled "Burden of New and Recurrent TB in a Major South African City Stratified by Age and HIV-Status". This dissertation will be a secondary analysis of these data.

## 2.2 Population

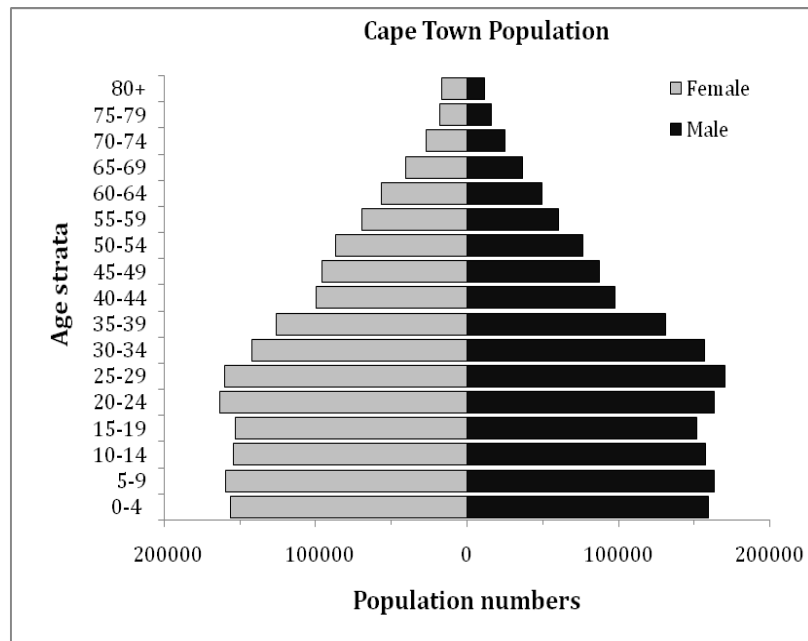


Figure 3 - 2009 mid-year Cape Town population structure [6]

Cape Town, South Africa is an urban city located in the Western Cape province and has a population of approximately 3,443,010 people [6, 41]. The population pyramid in Figure 3 describes this population by age and gender [6]. Males and females appear to have similar age distributions with the largest proportion of the population being 20-29 years old. The infectious diseases burden in this population has been described above.

## 2.3 Sampling

### 2.3.1 Inclusion criteria

- All new TB cases commencing TB treatment at City of Cape Town TB clinics from 1 January to 31 December, 2009.

### 2.3.2 Exclusion criteria

- Cases who were not enrolled at City of Cape Town TB clinics for TB treatment.
- Cases who commenced TB treatment before 1 January, 2009 or after 31 December, 2009.
- Cases who were receiving TB treatment at a clinic outside of the metropolitan area and subsequently transferred to a City of Cape Town TB clinic during treatment.
- Cases who were receiving TB treatment at a clinic inside of the metropolitan area and subsequently transferred to another City of Cape Town TB clinic during treatment.

### 2.3.3 Sample size

The original dataset included the entire Cape Town TB case population, which consisted of 31,093 cases. However, as a result of the exclusions specified above, the primary analysis included 29,478 cases. Therefore, the proposed analysis will also use the same exclusion criteria and include 29,478 cases.

## 2.4 Measurement

### 2.4.1 Instruments

These data were acquired from the Cape Town electronic TB register.

### 2.4.2 Variables

Variable	Type	Options
Gender	Binary	Male, female
Case number	Nominal	1-29,478
Age	Continuous	0-105 years
Age	Ordinal	0-75 years across 5-year age strata
Disease classification	Nominal	Pulmonary, extra-pulmonary, both
HIV status	Nominal	Positive, negative, unknown
Baseline sputum submitted	Nominal	Yes, no, no data
Baseline smear microscopy results	Nominal	Negative, positive, not done
Baseline smear positivity grading	Ordinal	Scanty, +, ++, +++, (no data)

### 2.4.3 Definitions

- *Sputum smear-positive*: Individuals who have had a positive sputum smear result on one or more occasions.
- *HIV positive*: Individuals were considered HIV positive if they were recorded as HIV positive in the TB register OR met any of the following criteria based on their TB register data: had a CD4 count recorded, were on antiretroviral therapy, or had taken cotrimoxazole prophylaxis.
- *HIV negative*: Individuals were considered HIV negative if they were recorded as HIV negative in the TB register and did not meet any of the criteria for being HIV positive.
- *HIV Unknown*: Individuals were considered HIV unknown if their HIV-related information was inconclusive.

#### *2.4.4 Validity and reliability of instruments*

Data collection for the TB register is ongoing and the clinic staff receive in-depth training on how to correctly capture information. In addition, organisations such as Desmond Tutu HIV Centre work closely with the TB register and run consistency checks to minimize data errors. Completed pages of the TB register are also regularly sent to the City of Cape Town offices for review and data entry.

### **3.0 ANALYSIS PLAN**

#### **3.1 Data management**

All data will be managed, carefully cleaned, systematically coded and password protected in Microsoft Excel and STATA 11.0 (StataCorp, College Station, Texas).

#### **3.2 Data analysis**

- Descriptive statistics will be employed to summarize demographics and clinical characteristics of TB cases.
- A bivariate analysis will be employed to explore differences in clinical characteristics between male and female TB cases.
- Standardized female:male ratios for each age stratum among TB cases will be calculated by dividing age-specific female:male ratios among TB cases by the overall crude female:male ratio among TB cases.
- Logistic and multinomial regression modelling will be used to explore associations between gender and clinical characteristics of TB cases, while adjusting for potential confounders.
- A sensitivity analysis will be conducted to best approximate the probable HIV status of TB cases with indeterminate HIV information. HIV unknown TB cases will be apportioned as (A) HIV positive, (B) HIV negative, and (C) as HIV positive or negative according to existing HIV rates among TB cases.
- Cape Town population denominators stratified by age, gender, and HIV will be estimated using Western Cape province data acquired from the Actuarial Society of South Africa. Using these data, Cape Town TB notification rates per 100,000 by age, gender, and HIV as well as corresponding notification rate ratios will be estimated using Poisson regression modelling.

### **4.0 ETHICAL CONSIDERATIONS**

#### **4.1 Ethics approval**

Wood et al. [6] did not receive ethics approval prior to conducting their analysis, as these data were routine notification data and analysed at the population level without identifying information. However, for the purposes of this dissertation, ethics approval from University of Cape Town's Health Research Ethics Committee was obtained on 20 April 2012 (REF# 187/2012). In addition, approval from City of Cape Town, City Health to use these data for a secondary analysis was also obtained on 26 July 2012 (ID# 10318).

#### **4.2 Risks and benefits**

These data have not been collected specifically for research study purposes but rather through routine TB surveillance. There are no risks involved in the analysis of these data. However, these findings may provide beneficial gender-specific information for improving TB control strategies in the future.

#### **4.3 Informed consent process**

These data are routinely collected for all TB cases and will be analysed without identifiers, so no informed consent was obtained.

#### **4.4 Privacy and confidentiality**

All patient information will be kept strictly confidential and the analysis will be conducted without any personal identifying information.

#### **4.5 Reimbursement for participants**

These data were not collected as part of a research study and thus no reimbursements were given to TB cases.

#### **4.6 Stakeholders**

- TB/HIV organisations such as Desmond Tutu HIV Centre
- University of Cape Town
- Residents of Cape Town
- Public health officials
- City of Cape Town clinics
- Gender-based organisations

### **5.0 REPORTING AND IMPLEMENTATION**

Using these data, I will write my Master of Public Health degree dissertation. I will aim to publish one journal article in a peer-reviewed journal and present my findings at a Desmond Tutu HIV Foundation research meeting and any conferences upon request. Furthermore, all data will be available upon request.

## 6.0 LOGISTICS

### 6.1 *Timetable*

**Table 1 - Timetable for dissertation completion**

Milestone	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan
Write/edit protocol	■										
Submit protocol to ethics		■									
Conduct analysis			■	■	■	■	■	■			
Write/edit journal article			■	■	■	■	■	■	■	■	■
Write/edit literature review					■	■	■	■	■	■	■
Format dissertation											■
Submit dissertation											■

### 6.2 *Budget*

This dataset is pre-existing and thus no funding to analyse these data is required.



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## PART B: LITERATURE REVIEW

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## 1.0 INTRODUCTION AND OBJECTIVES

Males and females are differentially affected by tuberculosis (TB). Studies have identified a range of socio-cultural, economic, epidemiological, and biological factors potentially contributing to these differences. Despite the strong association between Human Immunodeficiency Virus (HIV) and TB as well as the fact that females are more susceptible to HIV infection than males, few studies have been conducted in HIV-burdened settings such as South Africa to investigate the effect of HIV on observed gender differences.

This dissertation investigates gender differences in the clinical characteristics of TB cases as well as in the age-specific occurrence of TB disease in Cape Town. In addition, the effect of HIV on these gender differences will also be explored. The hypothesis is that the increased burden of TB disease among young females in Cape Town is primarily due to HIV infection among this age group.

This literature review was conducted to provide background information to inform the dissertation. The objectives were:

- to identify the burden of TB and HIV in the global and South African context;
- to describe gender differences in the occurrence of TB disease historically and currently;
- to describe gender differences in the clinical characteristics of TB cases; and
- to ascertain factors, such as HIV, potentially contributing to these gender differences.

## 2.0 SEARCH STRATEGY

The following search strategies were used for this literature review:

### 1.1 *Search engines*

PubMed and Google Scholar were used to search for relevant articles using various combinations of the search terms below. Article abstracts were screened for relevance, quality, and whether they met the inclusion criteria below. In addition, related references in the obtained articles were identified and followed up on.

### 1.2 *Exclusion criteria*

- Studies investigating gender differences in TB infection
- Non-English journal articles
- Non-published or non-peer reviewed articles

### 1.3 *Inclusion criteria*

- Global and South African studies
- Qualitative and quantitative studies of all study designs
- Studies exploring gender differences in the clinical characteristics of TB cases
- Studies exploring gender differences in the number of absolute TB cases

- Studies exploring gender differences in crude and age-specific TB notification rates
- Studies investigating epidemiological, socio-cultural, economic, and biological factors associated with gender differences in TB disease

#### **1.4 Search terms**

The search terms listed below were used in varying logical combinations to identify relevant literature.

- Gender; sex; male; female
- Gender differences; sex differences; gender inequality
- Tuberculosis; TB; HIV; HIV/TB co-infection
- South Africa
- Biological; socio-cultural; economic
- Epidemiology; burden; incidence; transmission; seroconversion
- Social mixing; social interactions
- Health seeking behaviors

### **3.0 REVIEW OF LITERATURE**

#### **1.5 TB transmission**

TB is an airborne infectious disease caused by the bacterium *Mycobacterium Tuberculosis* (*M.tuberculosis*), that has plagued humans from all walks of life since 1000 B.C. [1, 2]. It primarily affects the lungs but also disseminates to other organ systems as well, particularly among immune suppressed individuals [1, 3]. Through the act of sneezing, coughing, or even talking, infectious individuals release *M.tuberculosis* particles from their lungs, which form stable droplet nuclei that remain suspended in the air for long periods of time [4]. Even in a single sneeze, there are more than one million *M.tuberculosis* particles [4]. Susceptible individuals acquire TB infection through the inhalation of infected respiratory droplet nuclei [4]. Overcrowding, poor living conditions and poor ventilation are conducive environments associated with an increased risk of developing TB disease [5, 6].

#### **1.6 The global burden of TB**

Approximately 1/3 of the world's population is infected with latent TB[1]. HIV negative individuals with latent TB have a 10% lifetime risk of developing TB disease and individuals co-infected with HIV and latent TB have as high as a 30-40% lifetime risk of developing TB disease [1, 7]. Although annual global TB incidence rates declined by approximately 2.2% from 2010 to 2011, there are still an estimated 8.7 million annual incident TB cases worldwide [8]. The male:female ratio among new smear-positive TB notifications was 1.9 [8]. More than half (59%) of new cases occurred in Asia, 26% in Africa, and the remaining 15% in the Eastern Mediterranean region, the European region, and the Americas [8]. The five countries contributing the largest numbers of incident TB cases during 2011 were India, China, South Africa, Indonesia, and Pakistan [8].

TB is the second leading cause of infectious disease death worldwide after HIV and Acquired Immune Deficiency Syndrome (AIDS) [1]. According to research on the natural history of TB, approximately 70% of HIV-negative cases with smear-positive pulmonary TB and 20% of HIV-negative culture-positive, smear-negative cases would die within ten years without treatment [8]. Although the mortality rate of TB has decreased by 41% since 1990, there were an estimated 1.4 million TB-related deaths in 2011 worldwide, which indicates the need for improved TB control programs; however, this estimate excludes deaths among HIV positive individuals [8].

### **1.7 The global burden of HIV**

HIV is primarily a sexually transmitted virus that impairs the immune system and leads to AIDS and death if not treated with antiretroviral therapy (ART). Although the global incidence of HIV infection has stabilized and even begun to decline in many countries, there were approximately 2.7 million incident cases in 2010, contributing to the 34.0 million people living with HIV globally [10]. Sub-Saharan Africa continues to be the region with the highest incidence of HIV infection, with an estimated 1.9 million individuals newly infected in 2010 [10]. Women accounted for approximately 50% and 59% of adults living with HIV worldwide and within sub-Saharan Africa respectively [10]. Fortunately, access to ART in low- and middle-income countries has increased substantially. Such treatment decreases the risk of sexual HIV transmission between sero-discordant couples and may therefore reduce the number of new HIV infections [11, 12].

HIV-related mortality is also steadily decreasing worldwide as a result of increased access to ART and improved care and support [10]. However, HIV continues to be the leading cause of infectious disease deaths, with approximately 1.8 million AIDS-related deaths in 2010 [10]. Despite efforts to reduce global HIV-related mortality rates, specific regions such as the Middle East, North Africa, Eastern Europe, and Central Asia still continue to experience high rates [10].

### **1.8 HIV/TB co-infection**

HIV is the single most significant predisposing risk factor for developing TB disease [13, 14]. HIV/TB co-infection has been denounced the “cursed duet”, whereby HIV infected individuals have a significantly increased risk of developing TB disease compared to HIV uninfected individuals [13, 14]. In 2011, 13% of all incident TB cases were co-infected with HIV and 79% of those co-infected were from the African Region [8]. In addition, approximately 30% of TB-related deaths were among HIV-positive individuals [8]. This interaction has been substantiated by findings of increased TB case loads in populations with high burdens of HIV infection, an increased prevalence of HIV infection among TB cases, and an increasing risk of TB disease in people with advancing immunosuppression [15].

### **1.9 HIV and TB in South Africa**

South Africa, located at the southern-most tip of Africa, is a country with nine provinces and approximately 50.6 million residents [15]. It is currently faced with one of the worst HIV and TB epidemics in the world [17]. In 2011, South Africa reported approximately 390,000 total

TB cases, which accounted for one-quarter of the total burden of TB in sub-Saharan Africa [8, 18]. Furthermore, as previously mentioned, South Africa carries the third largest burden of TB disease after India and China [8].

While South Africa contains only 0.7% of the world's population, the prevalence of HIV continues to be the highest in the world, with approximately 5.6 million people living with HIV [10, 17]. The national prevalence of HIV among adults is approximately 16.9%, which varies by provinces from 5.3% in the Western Cape province to a dramatically high prevalence of 25.8% in KwaZulu-Natal province [20].

The interaction between TB and HIV is highly evident in South Africa. South Africa's maturing HIV epidemic contributed to a four-fold increase in TB notification rates from 163 per 100,000 in 1986 to 628 per 100,000 in 2006 [21]. Prior to the onset of the HIV epidemic, the Western Cape province had the highest TB rates [17]. Currently, KwaZulu-Natal province not only has the highest HIV rates but also some of the highest TB notification rates [17]. South Africa's efforts to control TB have failed given the insufficient TB cure rates and TB case detection rates, a generalized HIV epidemic, and deep-rooted social issues such as poverty, overcrowding and poor living conditions [17, 22, 23].

Cape Town, located in the Western Cape province, is a socio-economically and ethnically diverse city with approximately 3.4 million residents [24]. In 2009 in Cape Town alone, there were 29,478 incident TB cases notified; more than half were co-infected with HIV [25]. TB notification rates per person in each age group were calculated using absolute TB case numbers acquired from routine data and estimated denominators according to National Department of Health age- and sex-disaggregated population data and Provincial age- and sex-disaggregated HIV prevalence rates. Among HIV negative individuals, there were three peak TB notification rates of 511, 553, and 628 per 100,000 among 0-4, 20-24, and 45-49 year olds, respectively [25]. TB notification rates among HIV positive individuals were dramatically higher than rates among HIV negative individuals in each age group. These rates gradually increased from 5,253 per 100,000 among 20-24 year olds to a peak of 8,598 per 100,000 among 40-45 year olds, which then gradually decreased to 7,215 per 100,000 among 50-54 year olds [25]. Wood et al. [25] reported a 17-fold increased risk of developing TB disease if HIV co-infected as opposed to HIV uninfected in this population. The age distribution of TB disease parallels the age distribution of HIV disease in this population [25]. The burden in people whose HIV status is unknown was not ascertained.

### ***1.10 Gender-based approach to public health***

Gender is intrinsically linked to the way individuals experience health outcomes. Differences in the susceptibility to disease among males and females can be explained as biologically prescribed characteristics or as a socially constructed phenomenon that determines gender norms in society and is often associated with stigma, power, barriers, and disparity. According to the World Health Organization (WHO),

A gender-based approach to public health begins from the recognition of the differences between women and men. It helps us to identify the ways in which the



health risks, experiences, and outcomes are different for women and men...and to act accordingly... [26]

With this framework, public health professionals should examine biological, socio-cultural, economic and epidemiological mechanisms driving the differential burden of TB among males and females globally and in South Africa.

### **1.11 Historical TB-related differences between males and females**

Historically, males and females have been differentially affected by TB disease. Holmes et al.'s [31] 1998 review of sex differences in the epidemiology of TB compared the age-specific burden of TB disease among males and females in industrialized countries during the 1930s to the mid-1950s as well as during the 1970s. Industrialized countries such as Denmark (1939-1941), Norway (1937), and England and Wales (1952-1954) reported consistent gender differences across age-specific TB notification rates, which showed similar rates among male and female children but higher rates among adolescent and young adult females followed by higher rates in older adult males [27].

However, as a result of concerted efforts to reduce the burden of TB during the 1970s, TB notification rates in these countries fell from a high TB incidence of 100 per 100,000 to a low TB incidence of less than 30 per 100,000 [27]. The age and gender pattern of TB disease also changed; males of all ages had higher TB notification rates than females [27]. The shift in the age-distribution of male and female TB notification rates was also observed in Greenland during a period of mobilization by the government to improve public health, a lower income country compared to Denmark, Norway, England and Wales [28].

### **1.12 Differences between the number of male and female TB cases**

Some studies analyzed only absolute TB case numbers and therefore relied primarily on ratios. However, these studies showed similar age and gender patterns of TB disease as compared to studies which reported age- and gender-specific TB notification rates (which will be described in the following section of this review).

Some studies found that the number of male TB cases outnumbered the number of female TB cases across all ages. Begum et al. [33] found that females in Bangladesh were less likely than males to attend out-patient clinics with respiratory complaints at any age - a gap which widened with increasing age, from a female:male ratio of 0.73 among <15 year olds to 0.18 among ≥65 year olds. A South African study by Austin et al. [34] reported similar findings - a male:female ratio of 1.45 among all TB cases and 2.08 among smear-positive cases. Among smear-positive TB cases, male:female ratios steadily increased from 1.18 among 15-24 year olds to 3.64 among 55-64 year olds and then decreased thereafter [30].

Conversely, other studies observed more female than male TB cases at certain ages. Crampin et al.'s [35] study conducted in Malawi reported a female:male ratio of 2.6 among cases ≤25 years old, which decreased with increasing age. Among HIV positive TB cases, age-specific female:male ratios were pushed farther away from unity, which exacerbated the

younger female and older male pattern of TB disease in this population more than in HIV negative cases [31]. Another South African study by Lawn et al. [14] also described more female than male TB notifications among  $\leq 30$  year olds, after which age there were more male than female TB notifications. Salim et al. [36] reported a female:male ratio of 1.19 among 0-14 year old TB cases which decreased to 0.54 among  $\geq 65$  year olds in Bangladesh. This is the only study to find a higher proportion of female to male children cases; in all other studies, male and female children had similar burdens of disease.

### **1.13 Differences between male and female TB notification rates**

Today, the age and gender distribution of TB notification rates in the majority of low- and middle-income countries which reported disaggregated data mirrors the pattern observed in industrialized countries in the 1970s. Jiménez-Corona et al. [37] reported a crude incidence rate ratio in males versus females of 1.41, 1.64 and 1.58 among clustered TB cases, reactivated TB cases, and total TB cases in Southern Mexico. Borgdorff et al. [38] found that crude female:male smear-positive notification rate ratios never exceeded 1.0 and decreased with increasing age in nearly all 14 countries analyzed. Holmes et al. [31] reported that age-specific smear-positive notification rates among males and females in Nicaragua, Kenya, Tanzania and China were similar until the age of 14 years, after which males had higher TB rates than females. Martinez et al. [39] cited an overall male:female incidence rate ratio of 2.1 (95% confidence interval (CI) 1.9-2.3) from 1991-1996 in America. There were similar notification rates among males and females  $\leq 24$  years old, after which age rates in males  $\geq 25$  years old were approximately 2-3-fold higher than in females [35]. However, stratifying by HIV revealed crude male:female incidence rate ratios of 1.8 (95% CI 1.6-1.9) and 0.5 (95% CI 0.3-0.8) in HIV negative and HIV positive TB cases respectively, which indicates that HIV co-infection significantly increased TB rates among females in this population [35].

In contrast to the majority of low- and middle-income countries, this literature search identified Malawi and Uganda as the only two countries which mirror age-specific TB notification rates observed in males and females during the mid-20th century. Borgdorff et al. [38] reported female:male notification rate ratios of 1.3 and 1.6 among 15-24 year old Malawian females in 1990 and 1996 respectively, which decreased with increasing age. Similarly, in 1996, 15-24 year old Ugandan females had a female:male notification rate ratio of 1.2, which also decreased with increasing age [34]. While Borgdorff et al.'s [34] study is the only one to report this pattern of gender differences in age-specific TB notification rates, as previously mentioned, Crampin et al. [31] and Lawn et al. [15] confirmed similar age and gender patterns in TB count data.

### **1.14 Factors causing gender differences in the occurrence of TB disease**

#### **1.14.1 Under notification**

In countries with low prevalences of HIV, differences in the incidence of TB disease among males and females are attributable to under notification of TB cases, sex specific mechanisms and epidemiological differences. Research suggests that lower TB notification rates reported among young females in many lower- and middle-income countries today,

compared to young females in industrialized countries historically, may be a result of under notification. However, these findings are counterintuitive to the expectation of increased TB case finding given the advancements in modern technology and public health as well as improvements in social and gender inequalities. Despite that, one must remember that these findings compare industrialized, wealthier countries to developing, lower income countries, which are comprised of different social, economic, and health structures.

The Gender Inequality Index (GII), developed by the United Nations Development Programme, provides an index of females' disadvantage over males based on reproductive health, empowerment, and labour market indicators [36]. This index ranges from 0 (females and males fare equally) to 1 (females fare poorly in all three areas) [36]. The Gini-coefficient of inequality is also a commonly used indicator of relative inequality when comparing one population to another. This index also ranges from 0 (complete equality) to 1 (complete inequality) [37]. According to Dorius and Firebaugh [42], who used the Gini-coefficient, gender inequality in education, mortality, political representation, and economic activity has been largely declining across the world. However, lower- and middle-income developing countries had worse Gender Inequality scores compared to higher-income developed countries from 1995-2011. For example, developing countries such as Bangladesh, South Africa, Mexico, Nicaragua, Kenya, and Tanzania had scores that ranged from 0.69 in Kenya (1995) to 0.49 in South Africa (2011) [36]. In contrast, developed countries such as the United Kingdom, Norway, and Denmark had significantly better scores that ranged from 0.24 (United Kingdom 1995) to 0.06 (Denmark 2011) [36]. Although this index represents modern gender inequalities, these scores provide an indication of why under notification of females may be worse in lower- and middle-income countries today compared to industrialized countries in the mid-20th century.

Researchers largely attributed under notification to lack of access, TB- and HIV-related stigma, and health facility characteristics. Holmes et al. [27] described gender inequalities towards females such as lack of access to income, legal rights, education, and lower social status as potential factors associated with under notification. Onifade et al. [43] found that the females' health was not as important as males' health in shantytowns in Peru, which led to females accessing healthcare services less than males and potentially living with undetected TB. Salim et al. [36] attributed their findings to the strict Muslim beliefs in Bangladesh and the tendency for females to have restrictive lifestyles and be dependent on their male partners, making it difficult for females to seek health services and be diagnosed with TB.

Somma et al.'s [44] study found that various aspects of stigma affected females more than males in Bangladesh, Malawi, Colombia, and India. For example, females were more likely than males in at least 3 of the 4 countries to desire to keep their TB diagnosis secret, think less of themselves, feel ashamed or embarrassed, be concerned that others will think less of them, be concerned that others will refuse to visit them, and be concerned that they will have problems getting married. In addition, in Malawi, there was HIV-related stigma associated with TB disease, whereby symptoms of TB were associated with HIV infection, which exacerbated the above perceived and actual stigmatization [40].

Khan et al. [45] assessed the influence of diagnostic centre characteristics on the number of male and female TB suspects. The authors found that more females than males sought services at facilities that catered to the local catchment area and were accessible on foot, whereas facilities that were larger, more centralized, and had evening hours catered more to males than females. These findings suggest that facilities that do not cater to the local catchment area and are not accessible by foot may deter females from accessing care and lead to under notification. According to Begum et al., [33] females tend to utilize private healthcare more than public healthcare, which may also explain why fewer females than males are notified as TB cases in the public sector. Begum et al. [33] also postulated that the high female:male ratio of 0.73 among young TB cases may be a result of increased utilization of healthcare services for children's healthcare needs, which enhances the likelihood of TB case detection. The authors also proposed that the declining attendance among older female TB cases (female:male ratio 0.18) may be because of an increased preference for non-Western medicine [29].

However, research done by Balasubramanian et al. [46] in south India refuted the argument that lower TB notification rates in young females are a result of under notification. This study found that despite greater TB-related stigma and barriers to accessing services, females were more likely than males to access services and be notified, while still showing a lower prevalence of TB than males. This indicates that other factors besides socially-driven under notification may be contributing to lower notification rates among females in some populations.

#### 1.14.2 *Sex-specific mechanisms*

The literature also attributes the higher burden of TB disease in males than in females to sex-specific mechanisms that affect susceptibility. Neyrolles et al. [47] described a variety of studies that have identified male sex as an independent risk factor for TB disease after adjusting for various confounders, which is suggestive of underlying biological mechanisms. Davila et al. identified polymorphisms in the X-chromosome associated paradoxically with male-restricted susceptibility to TB disease [44]. Mice models also showed that treatment of testosterone increased susceptibility to *M.marinum* and *M.intracellulare* [45, 46], while estrogen decreased susceptibility to *M.avium* [47]. Neyrolles et al. [43] postulated that nutrition and metabolism may also affect susceptibility to TB disease but these factors remain largely inconclusive. For example, some studies suggest that high levels of iron may increase the risk of TB [48, 49]. Therefore, the lower levels of iron commonly in females may provide a protective effect against TB infection in females [43]. Thus, these findings may partially explain why males post-puberty have higher rates of TB disease compared to females.

#### 1.14.3 *Epidemiological factors*

Some studies identified epidemiological factors contributing to an increased risk of TB among males. Hudelson et al. [54] suggested that the sexual division of labor, cultural practices, and socialization patterns in certain countries may affect the risk of exposure to TB and the subsequent development of TB disease. For example, Hudelson et al. [54] cited

a study conducted in India, which found that males engaged in higher levels of socializing while females tended to stay at home or work outside in the fields. As a result, males were more susceptible to developing TB disease in this population [50]. Salim et al. [36] also observed that Bangladeshi females were more likely to be confined to their homes and therefore less likely to engage in social mixing and be exposed to TB infection. In both of these settings, restrictive social mixing among females may have led to lower TB rates than in males.

In contrast, other studies identified epidemiological factors contributing to an increased risk of TB among females. Holmes et al. [31] reported multiple studies which found that females of reproductive age have a higher rate of progression from TB infection to TB disease, which may partially explain increased TB rates among young females of reproductive age. In addition, a South African study found that females rather than males engage in higher levels of social mixing, which may reflect a less constrained lifestyle for South African females compared to Bangladeshi or Indian females [51]. Crampin et al. [31] reported that having a TB case in the family or household increased the risk of both male and female participants developing TB themselves, although the risk was higher among females [adjusted Odds Ratio (OR) 1.9 (95% CI 1.2-3.1) versus adjusted OR 2.6 (95% CI 1.8-4.0)]. This may be a result of females interacting more closely and more frequently with individuals in the household compared to males who work longer hours and are away from home more often. Therefore, these factors may be increasing the risk of TB exposure and subsequent disease among young females in certain populations.

#### 1.14.4 *HIV*

While the aforementioned factors may play contributing roles, both Malawi and Uganda had high prevalences of HIV during the 1990s [52, 53], and South Africa in recent years [10, 15]. Gender differences affect the prevalence of HIV in males and females differently, which in turn lead to further differences between males and females in regards to TB disease. This is corroborated by Crampin et al. [35] who found that HIV infection exacerbated the younger female and older male pattern of TB disease more than HIV negative individuals. In addition, Lawn et al. [14] reported that the annual TB notification rates among South African adolescents increased from 1996-2004, particularly among females, which they also attributed to the maturing HIV epidemic in the study population. HIV's effect on gender differences related to TB disease can be explained by HIV-related immunological and health systems pathways.

It is well-established that HIV suppresses immune functioning and significantly increases susceptibility to developing TB disease. Young people 15-24 years old living in countries such as South Africa are at greatest risk of contracting HIV and consequently accounted for nearly half of all HIV infections in 2010, of which 80% occurred in sub-Saharan Africa [10, 54–56]. However, young females in particular have an approximate 2-4-fold increased risk of HIV infection than males in HIV-burdened populations [54, 56].

There have been concerted efforts to scale-up HIV services in HIV-burdened countries. For example, in South Africa, about 10 million individuals were tested for HIV in 2010 [10, 17] and 1.79 million HIV positive individuals received ART in 2011, of which there were more

females than males [57]. These statistics indicate that thousands of HIV positive individuals, especially disproportionately affected young females, are in the healthcare system, returning for follow-up visits, and being monitored. Therefore, they are more likely to be suspected, tested, and diagnosed with TB. These factors increase case finding and may also be contributing to higher notification rates of TB among young HIV positive females than males in this population. Boeree et al. [61] reported that proportionally more females 15-24 years old in Malawi submitted sputum for analysis than males of the same age, which they attributed to high HIV rates in this population and the strong association between HIV and TB. Perhaps the authors were also alluding to the increased level of case finding as a result of HIV positive young females being identified by the health system.

The higher burden of TB disease among young females in Malawi, Uganda, and South Africa suggest that females may not be experiencing socio-cultural barriers accessing services more than males. This contrasts with research from other low- and middle-income countries such as Bangladesh where the consistently higher burden of TB disease among males is commonly attributed to females' lack of access and under notification of TB [27, 39, 40, 59]. If females in these populations experienced barriers accessing TB care and were therefore under notified, it is likely that we would not observe the excess burden of TB disease seen in young females. Thus, it appears as if immunological as well as health systems factors outweigh any socio-cultural barriers preventing females from accessing services in these populations. Furthermore, HIV positive individuals are more likely to be smear-negative and are therefore difficult to diagnose [60], which provides evidence for speculation of an even larger burden of TB disease among HIV positive young females with undetected TB in these countries.

### **1.15 Differences between the clinical characteristics of male and female TB cases**

#### **1.15.1 Sputum submission**

Sputum submission in this context refers to requests from health professionals for TB suspects to provide sputum samples for analysis. There were differing findings related to the ratio of female to male TB suspects who submitted sputum for analysis. Begum et al. [33] cited an overall female:male ratio of 0.51 for sputum submission, which decreased from 0.73 among <15 year olds to 0.18 among ≥65 year olds. Similarly, Boeree et al. [61] reported an OR in males versus females of 1.15 (95% CI 1.12-1.19) among participants in Malawi. Austin et al. [34] found that males submitted proportionally more sputum tests than females across all ages. There was a minor difference in the number of sputum tests requested between male and female adolescents and young adults, an increasing difference between middle-aged males and females, and receding differences between older adults [30].

The literature describes individual- and provider-level factors associated with decreased sputum submission among females. Some authors have suggested that provider bias leading to a higher index of suspicion of TB disease among males may explain why females are less likely than males to be asked to submit sputum [29, 30, 61]. Another author found that the primary reason for not submitting sputum for analysis was the inability to produce sputum, which affected females more than males [62]. This may result from physical inability

or socially constructed standards for females and how they should conduct themselves in public, which may lead to females' reluctance to expectorate sputum out of fear of embarrassment [63].

In contrast, although Boeree et al.'s [61] crude association indicated that males had a higher likelihood of submitting sputum, an age stratified analysis revealed that there were significantly more female than male TB suspects 15-24 years who submitted sputum. Furthermore, Begum et al. [33] reported that the number of sputum samples taken were similar between males and females, although the data were not shown in the article.

As mentioned above, Boeree et al. [61] linked the increase in sputum submissions among young females to the disproportionate effect of HIV on young females in Malawi, which may have resulted in an increased usage of healthcare services and therefore increased opportunities to identify female suspects and request sputum samples for analysis. Begum et al.'s [59] findings, also from Malawi, may also be associated with HIV, which may have increased the number of females submitting sputum and shifted female:male ratio closer to unity.

#### 1.15.2 *Sputum smear-positivity*

Studies consistently found that females were less likely than males to be sputum smear-positive at any age, except for one study that identified a higher smear positivity rate among young females. Begum et al. [33] reported an overall female:male ratio of 0.36 among smear-positive cases, which ranged from 0.89 among <15 year olds to 0.03 among ≥65 year olds . Boeree et al. [58] and Austin et al. [30] found that males had a higher odds of being smear-positive than females [OR=1.31 (95% CI 1.19-1.44) and OR=1.54 respectively] [30, 58]. In addition, as previously mentioned, the male:female ratio among Austin et al.'s [34] smear-positive cases increased from 1.18 among <25 year olds to 3.64 among 55-64 year olds . However, while Salim et al. [36] reported a smear positivity female:male rate ratio of 0.35 overall, an age and gender stratification revealed a higher smear positivity rate among females 15-24 years than males (female:male rate ratio 1.39) but a lower smear positivity rate in all other ages.

In addition, Austin et al. [34] also showed that among the 10% of confirmed cases with smear positivity grading recorded, males had increasingly severe positivity than females, which ranged from a male:female ratio of 1.8 among those who had an acid-fast bacilli (AFB) count of + (10 to 99 AFB per 100 fields) to 2.5 among those who had an AFB count of +++ (>10 AFB per field in at least 20 fields) . However, this was the only study to conduct this analysis.

The literature suggests that individual-level factors may reduce the likelihood of females being smear positive. Begum et al. [33] reported anecdotal evidence which suggests that females are less likely to produce "good quality" sputum , which may lead to increased false negative smear results. As previously mentioned, "Poor quality" sputum may be a result of physical or social barriers to expectorating sputum, which may result in fewer bacilli. Begum et al. [33] also proposed that the lower smear positivity rates in females may be a true

indication that females have a lower prevalence of TB compared to males, rather than a result of the aforementioned barriers .

In addition, it is also well-established that HIV-related immunosuppression often leads to widespread dissemination of TB and reduced cavitation [13, 64]. As a result, expectorating sputum becomes more difficult and sputum tends to contain a low bacillary load, which leads to diagnostic obstacles [13]. Given that HIV disproportionately affects females, females are therefore more likely to be immune suppressed and have extra pulmonary TB, which may also explain why fewer Malawian, Ugandan, and South African females than males are smear-positive.

#### **4.0 GAPS IN THE LITERATURE**

In 1996, Hudelson [54] highlighted the gaps in knowledge and understanding about gender differences in TB disease, which was addressed in 1998 by Holmes et al.'s [31] review. However, subsequent research has been scarce as well as inconclusive, which led WHO in both 2011 and 2012 to emphasize the need for improved reporting of TB data disaggregated by age and gender [8, 70].

Among countries which published disaggregated TB disease data, there were two age and gender distributions of TB disease identified - one that is ubiquitous and another that is reported by only three countries. However, very few studies have confirmed the age and gender distributions described or the risk factors associated with these two patterns of TB disease worldwide.

Despite the inherent differences in susceptibility to TB and HIV among males and females as well as the strong association between the two diseases, few studies conducted in HIV-burdened settings such as South Africa have explored gender differences related to TB disease, nor how HIV infection effects these gender differences. In South Africa, there has only been one in-depth study published on TB-related gender differences by Austin et al. but it did not explore HIV.

#### **5.0 CONCLUSIONS**

In conclusion, the dual epidemic of HIV and TB is plaguing low- and middle-income countries around the world. Yet despite that gender is intrinsically linked to both diseases, few studies have been published in high-burdened countries and no study has investigated the effect of HIV on TB-related gender differences. The scarce literature on epidemiological differences in TB disease between males and females has identified differences in the occurrence of TB disease and differences in clinical characteristics. The majority of countries which have published papers on this subject have reported that rates in children are similar among males and females, after which age male rates significantly exceed female rates throughout adolescence and adulthood. However, Malawi, Uganda and South Africa have identified a different pattern of TB disease whereby younger females are more affected by TB disease than younger males. In addition, females are less likely than males to present to clinic, submit sputum samples for diagnosis and be diagnosed as smear positive. These gender



differences have largely been attributed to biology, epidemiology, and health seeking behaviors. However, our hypothesis is that HIV is largely responsible for females' increased risk of developing TB or being notified as TB cases in high-HIV burdened countries including South Africa, which this thesis sought to further investigate.

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## PART C: JOURNAL READY ARTICLE

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## **1.0 TITLE PAGE**

**Journal name:** BMC Infectious Diseases

**Article type:** Research article

**Gender-specific epidemiology of tuberculosis in a population with high HIV prevalence**

**Running title:** Gender and tuberculosis

**Word count:** Abstract=350; Manuscript=5,189

University of Cape Town



**Footnote:** Variations from the BMC Infectious Diseases format include: embedded figures, titles above figures, embedded figure legends and embedded tables.

## 2.0 ARTICLE ABSTRACT

### *Background*

Males and females are differentially affected by tuberculosis (TB) disease. Despite South Africa's dual epidemic, no study has investigated the effect of HIV on TB-related gender differences. We hypothesized that the increased burden of TB disease among young females in Cape Town is primarily due to HIV infection in this age group. Our objectives were to describe Cape Town TB cases; explore associations between gender and clinical characteristics of cases; estimate TB notification rates; and ascertain the effect of HIV.

### *Methods*

From 1 January to 31 December, 2009, City of Cape Town TB clinics prospectively collected routine notification data on 29,478 new cases. These data were analysed using descriptive statistics, bivariate analyses, standardized female:male ratios, regression modelling and TB notification rate estimations.

### *Results*

The crude female:male ratio among cases was 0.83. Among 15-54 year old adult cases, females were significantly younger than males and less likely than males to have pulmonary TB, have smear results recorded, be smear-positive, or have advanced smear-positivity grading. Females were more likely than males to be HIV-positive. HIV co-infection widened pre-existing clinical differences between male and female cases. Among HIV-negative adults, age-specific male notification rates exceeded female rates at all ages to a 2.5-fold difference among 45-49 year olds. The rate in 15-19 year old HIV-positive females was 12.4% higher than in males of that age, after which male rates increasingly exceeded female rates to a 2-fold difference among 45-49 year olds. The disparity between male and female rates was smaller among HIV-positive than HIV-negative individuals.

### *Conclusions*

The age and gender pattern of TB disease in the HIV-positive population has only been reported in Malawi, Uganda, and mid-20<sup>th</sup> century countries. The HIV-negative pattern mirrors gender differences in all other countries reporting disaggregated data. HIV co-infection is associated with an increased risk of TB disease, particularly among young females, and has led to decreased gender differences. Controlling for HIV did not nullify gender differences, which indicates that there are additional contributing factors. This study warrants improved HIV and TB testing and treatment practices as well as educational programmes targeted at younger females and older males.

### *Keywords*

Tuberculosis, gender, notification rates, HIV, age, standardized female:male ratio

### 3.0 BACKGROUND

HIV is considered the single most important predisposing risk factor for tuberculosis (TB) [1–3]. This is particularly relevant for South Africa, which, despite concerted efforts, continues to have one of the worst dual epidemics of TB and HIV globally [4]. In 2012, South Africa reported approximately 400,000 incident TB cases, which accounts for one-quarter of all incident cases in sub-Saharan Africa [5, 6]. In addition, South Africa has the highest number of individuals living with HIV in the world at 5.6 million [7]. In Cape Town, South Africa, a city of about 3.4 million residents [8], there were nearly 30,000 incident TB cases notified in 2009, of whom 51% were HIV positive [9]. Wood et al. [9] found that HIV positive individuals living in Cape Town had a 17-fold increased risk of developing TB disease compared to HIV negative residents.

Gender, and the biological, social, and cultural factors associated with it, is intrinsically linked to TB. According to international literature, male and female children typically have similar TB notification rates while adolescent and adult males and females have different TB notification rates [10]. Data from industrialized countries from the 1930s to 1950s consistently showed that young females 15-34 years old had higher TB notification rates than young males and older males  $\geq 35$  years old had higher TB notification rates than older females [10]. As a result of effective TB control during the 1970s, TB notification rates in both males and females in industrialized countries significantly decreased [10]. In addition, the age and gender pattern of TB disease shifted; after childhood, TB notification rates in males significantly exceeded TB notification rates in females and the higher rates previously seen among young females diminished [10].

TB notification rates and the absolute number of TB cases in the majority of low- and middle-income countries today which report disaggregated data are similar in magnitude to what was reported in industrialised settings during the 1930s-1950s; however, the age and gender distribution is more similar to distributions reported during the 1970s [10–15]. The consistently higher TB notification rates among adolescent and adult males has been partially attributed to under notification of female TB cases resulting from lack of access to TB services [10, 11, 16]; insufficient funds [10]; poor education [10]; a lower priority placed on women's health [17]; and fear of social isolation or rejection [18]. In addition, biological factors such as higher levels of testosterone from the onset of puberty may be contributing to males' increased susceptibility to TB disease and the subsequently higher TB notification rates in adolescent and adult males [12]. Lastly, in some populations males engage in more frequent social interactions than females and are therefore at higher risk of TB exposure and transmission, which may also be contributing to the higher notification rates seen among males [19].

In contrast, studies show that the magnitude of TB disease in Malawi, Uganda, and South Africa, as well as the corresponding age-specific gender differences, are comparable to the burden seen in mid-20<sup>th</sup> century industrialized societies [15, 20, 21]. At the time these data were collected, Malawi, Uganda, and South Africa had high prevalences of HIV [7, 21–23]. Given that HIV disproportionately affects young females and is strongly associated with TB, it is most likely a major contributing factor associated with the age and gender pattern of TB disease in these three populations. In addition, one South Africa study found that females

rather than males engage in higher levels of social mixing, which may also partially explain why young females have higher TB notification rates than males in this population [24].

Apart from risk, male and female TB cases also differ by clinical characteristics. Females are typically less likely than males to be asked by health professionals to submit sputum samples for investigation [11, 14, 25]. This may be a result of health professionals having a higher index of suspicion towards males due to the belief that males are at higher risk of developing TB disease than females [11, 14]. Females who submit sputum are less likely than males to be smear-positive [11, 14, 25], which may be partially attributable to females being less able, or less likely as a result of socio-cultural barriers, to expectorate sputum [11]. In HIV-burdened countries, HIV-related immune suppression often leading to the development of extra-pulmonary TB, a lack of cavitation and lower bacillary loads may also contribute to females being less smear-positive than males [2, 26, 27].

Despite the ever growing pool of knowledge that gender is a major determinant of health outcomes, gender has been a neglected aspect of TB research; the most recent review on gender and TB disease was published by Holmes et al. [10] in 1998. Furthermore, although HIV is a major risk factor for TB disease, few studies conducted in HIV-burdened countries including South Africa have addressed the effect of HIV on gender differences in regards to TB disease. Significantly improved HIV testing rates [9, 28] and new guidelines to record HIV information for TB cases has enabled us to effectively explore these aspects of TB disease in Cape Town, South Africa for the first time. We hypothesize that the increased burden of TB disease among young females in Cape Town is primarily due to HIV infection in this age group.

Therefore, this study aims to: (a) describe the 2009 Cape Town TB case population by age, gender, and HIV and determine corresponding standardized female:male ratios; (b) explore associations between gender and clinical characteristics of TB cases and the impact of HIV on these associations; (c) estimate age-specific TB notification rates by gender and HIV and determine corresponding notification rate ratios (NRRs); and (d) draw conclusions regarding the impact of HIV on observed gender differences. Through this research, we hope to gain a better understanding of how HIV positive as well as HIV negative males and females experience TB disease, which may provide insights for a multi-pronged approach to TB control in South Africa that considers the effects of age, gender, and HIV.

## **4.0 METHODS**

### **4.1 Study population**

TB clinics, located throughout the eight City of Cape Town districts, offer free TB screening, diagnosis, and Directly Observed Therapy, Short-course (DOTS) treatment as per the South African national TB guidelines [29]. In all City of Cape Town TB clinics, a standardized paper TB register is used to collect demographic information, disease classification, treatment regimen, monitoring, and outcomes for all TB cases. This information is then collated into a centralized electronic TB register database for monitoring and evaluation [29].

From January 1, 2009 to December 31, 2009 there were 31,093 TB cases prospectively recorded in the electronic TB register. Of those, 1,615 cases had transferred in or moved in to City of Cape Town clinics during their course of treatment and were excluded from this analysis. Thus, this analysis included 29,478 newly registered TB cases who commenced on TB treatment at City of Cape Town TB clinics during the study period. Cases were categorized into 16 five-year age strata ranging from 0 to  $\geq 75$  years.

#### **4.2 Ethics approval**

This study was approved by the Faculty of Health Sciences Health Research Ethics Committee, University of Cape Town, and the City of Cape Town City Health directorate. No informed consent was obtained from patients, as this study used routinely collected TB data per South African national TB guidelines and all personal identifiers were removed prior to analysis.

#### **4.3 Statistical analysis**

These data were analyzed using Microsoft Excel and STATA 11.0 (StataCorp, College Station, Texas). Descriptive statistics were employed to summarize demographic and clinical characteristics of TB cases. Bivariate analysis using appropriate hypothesis testing was employed to interpret differences between proportions of male and female TB cases. Logistic and multinomial regression modelling was employed to explore associations between gender and clinical characteristics of TB cases, while adjusting for potential confounders such as age and HIV.

Age-specific female:male ratios of TB cases were divided by the overall crude female:male ratio of TB cases to determine a *standardized female:male ratio* for each age stratum. A standardized female:male ratio  $>1.0$  indicates a larger proportion of female cases than expected in a particular age group, whereas a standardized female:male ratio  $<1.0$  indicates a smaller proportion of female cases than expected for a particular age group, using the overall crude ratio as the expected value.

Cases were considered HIV positive if they were recorded in the TB register as being HIV positive or met any of the following criteria: had a CD4 count recorded, were on antiretroviral therapy or had been given cotrimoxazole prophylaxis. Cases were considered HIV negative if they were recorded as HIV negative and did not meet any of the criteria for being HIV positive. Lastly, cases were considered HIV unknown if they had inconclusive HIV-related information.

TB cases with indeterminate HIV information were apportioned as: (A) HIV positive, (B) HIV negative, and (C) HIV positive or HIV negative according to existing HIV rates among TB cases with known HIV statuses. Under scenario C, for each age stratum, the true number of HIV unknown TB cases was multiplied by the HIV rate in TB cases with known HIV results and the product was added to the true number of HIV positive TB cases to yield the estimated number of HIV positive cases.

To estimate age- and gender-specific Cape Town population denominators stratified by HIV, the age- and gender-specific Cape Town population was multiplied by the 2009 age- and

gender-specific HIV prevalence in the Western Cape acquired from the Actuarial Society of South Africa (ASSA) model [30, 31]. A sensitivity analysis to compare TB notification rates given scenarios A, B and C showed little variation between scenarios (analysis not shown, but available in Table 3 in the Appendices). Therefore, scenario C was selected as the most probable distribution of HIV infection among cases 15-54 years old. Poisson regression modelling was conducted to estimate 2009 TB notification rates per 100,000 by age, gender and HIV as well as TB notification rate ratios (NRRs) comparing genders, while adjusting for age and HIV.

## **5.0 RESULTS**

### **5.1 TB case population**

#### **5.1.1 All cases**

In 2009, there were 29,478 newly registered TB cases treated at 99 clinics throughout the eight Cape Town districts. Less than half (45.4%) of all cases were female (13,379/29,478), which yielded a crude female:male ratio of 0.83 ( $p < 0.001$ ). Male cases were a median age of 34 years old with an interquartile range (IQR) of 24-44 years old. Female cases were significantly younger than male cases, with a median age of 29 years old and an IQR of 21-38 years old ( $p < 0.001$ ). There were significantly different numbers of male and female cases across 5-year age strata ( $p < 0.001$ ), which is shown in the age distribution of male and female cases in Figure 1. There were two peak age-specific notifications; the first peak occurred in male and female cases 0-4 years old ( $n=1,456$  vs.  $n=1,397$ ), and the second peak occurred among females 25-29 years old ( $n=2,341$ ) and males 35-39 years old ( $n=2,321$ ). (A table of TB cases stratified by age, gender and HIV is available in the Appendices, Table 1).

**Figure 1 - Male and female tuberculosis cases by five-year age strata (0 - ≥75 years old)**

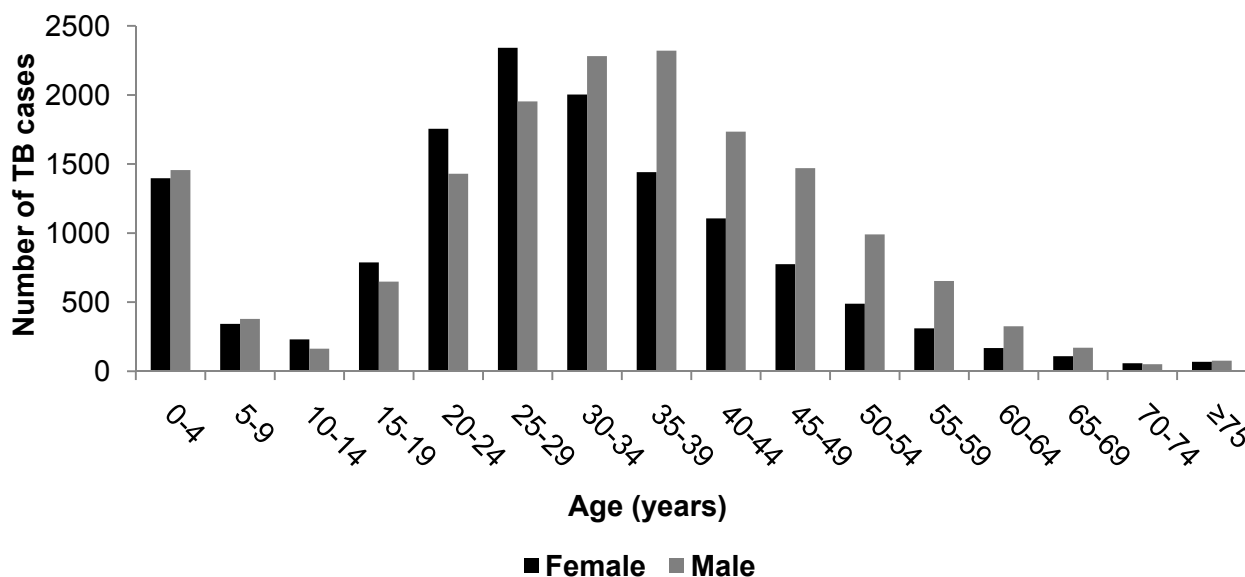


Figure 1 shows two peak caseloads among males and females. The first peak occurred among 0-4 year old males and females, and the second peak occurred among 25-29 year old females and 35-39 year old males. There were more female than male cases 15-29 years old.

#### 5.1.2 Child cases (0-14 years old)

The differences in demographic and clinical characteristics between male and female child cases (0-14 years old), adult cases (15-54 years old), and older adult cases (≥55 years old) are shown in Table 1. Of the total TB cases, 13.5% (3,968/29,478) were children 0-14 years old. Between male and female children, there was no significant difference in the number of cases ( $p=0.71$ ), age ( $p=0.21$ ), disease classification ( $p=0.26$ ), smear positivity grading ( $p=0.64$ ), and HIV status ( $p=0.06$ ). Although there was a significant difference in smear results, the majority of data on smear results were missing.

#### 5.1.3 Older adult cases (≥55 years old)

Older adults ≥55 years old accounted for 6.7% (1,986/29,478) of total TB cases. Female older adults were a median age of 61 years old (IQR=57-68 years old) and significantly older than males who were a median age of 59 years old (IQR=57-64 years old) ( $p<0.001$ ). Between male and female older adults, there was no significant difference in the number of cases ( $p=0.05$ ), disease classification ( $p=0.68$ ), sputum smear results ( $p=0.96$ ), and HIV status ( $p=0.08$ ). However, standardized female:male ratios decreased significantly with increasing sputum smear positivity (the number of acid-fast bacilli present in sputum) from 1.51 among cases who were scanty positive, to 1.43 among those who were P+, 1.07 among those who were P++, and 0.81 among those who were P+++ ( $p=0.002$ , test for trend).

**Table 1 – Demographic and clinical differences between male and female tuberculosis cases - children (0-14 years old), adults (15-54 years old), and older adults (≥55 years old)**

	Children (0-14 years old)			Adults (15-54 years old)			Older adults (≥55 years old)		
	Male	Female	P-value	Male	Female	P-value	Male	Female	P-value
<b>N</b>	1,998	1,970	0.71†	12,827	10,697	<0.001†	1,274	712	0.05†
<b>Age (years), med (IQR)</b>	2 (1-5)	3 (1-5)	0.21†	35 (28-42)	31 (25-38)	<0.001†	59 (57-64)	61 (57-68)	<0.001†
<b>Disease classification</b>			0.26‡			<0.001‡			0.68‡
Pulmonary TB	1,849 (92.5)	1,848 (93.8)		10,919 (85.1)	8,427 (78.8)		1,075 (84.4)	603 (84.7)	
Extra-pulmonary TB	137 (6.9)	114 (5.8)		1,679 (13.1)	2,020 (18.9)		183 (14.4)	97 (13.6)	
Both	12 (0.6)	8 (0.4)		229 (1.8)	250 (2.3)		16 (1.3)	12 (1.7)	
<b>Smear results*</b>			<0.001‡			<0.001‡			0.96‡
Smear-negative	134 (7.2)	139 (7.5)		3,970 (35.6)	3,802 (43.8)		476 (43.6)	273 (44.4)	
Smear-positive	57 (3.1)	134 (7.2)		6,727 (60.3)	4,414 (50.9)		547 (50.1)	304 (49.4)	
No data	1,670 (89.7)	1,583 (85.3)		451 (4.1)	461 (5.3)		68 (6.2)	38 (6.2)	
<b>N</b>	1,861	1,856		11,148	8,677		1,091	615	
<b>Smear grading**</b>			0.64‡‡			<0.001¥			0.002¥
Scanty	2 (3.5)	10 (7.6)		209 (3.1)	193 (4.4)		20 (3.7)	17 (5.6)	
P+	14 (24.6)	38 (28.4)		1,229 (18.3)	1,043 (23.6)		92 (16.8)	73 (24.0)	
P++	9 (15.8)	24 (17.9)		1,043 (15.5)	718 (16.3)		86 (15.7)	51 (16.8)	
P+++	26 (45.6)	54 (40.3)		3,737 (55.6)	2,070 (49.6)		290 (53.0)	130 (42.8)	
No data	6 (10.5)	8 (6.0)		509 (7.6)	390 (8.8)		59 (10.8)	33 (10.9)	
<b>N</b>	57	134		6,727	4,414		547	304	
<b>HIV status</b>			0.06‡			<0.001‡			0.08‡
HIV negative	1,085 (54.3)	1,096 (55.6)		5,819 (45.4)	3,257 (30.5)		803 (63.0)	447 (62.8)	
HIV positive	245 (12.3)	276 (14.0)		5,643 (44.0)	6,647 (62.1)		258 (20.3)	168 (23.6)	
HIV unknown	668 (33.4)	598 (30.4)		1,365 (10.6)	793 (7.4)		213 (16.7)	97 (13.6)	

\*Of cases with pulmonary TB and both. \*\* Of cases with smear-positive pulmonary TB. † Rank sum for not normally distributed data. ‡ Chi-squared test ‡‡ Fisher's exact test. ¥ Chi-squared test for trend, excluding "no data" category.



#### 5.1.4 Adult cases (15-54 years old)

More than three-quarters (23,524/29,478) of total TB cases were adults 15-54 years old. Male and female cases were significantly different across all demographic and clinical characteristics presented in Table 1 ( $p < 0.001$ ).

In this group, there was a larger proportion of male than female cases overall (standardized female:male ratio=0.83). In addition, males were older than females [median age 35 years old (IQR=28-42 years old) versus median age 31 years old (IQR=25-38 years old)].

In terms of clinical characteristics, a larger proportion of male than female cases had pulmonary TB (standardized female:male ratio=0.93), while a larger proportion of female than male cases had extra-pulmonary TB (standardized female:male ratio=1.44) and both pulmonary and extra-pulmonary TB (standardized female:male ratio=1.28). Of the cases with pulmonary TB, a larger proportion of female than male cases had no smear results recorded (standardized female:male ratio=1.29). Among those with results recorded, a larger proportion of female than male cases were smear-negative (standardized female:male ratio=1.23). Of the cases with smear-positive pulmonary TB, standardized female:male ratios decreased with increasing smear positivity from 1.42 among those who were scanty positive, to 1.29 among those who were P+, 1.05 among those who were P++, and 0.89 among those who were P+++ ( $p < 0.001$ , test for trend).

#### 5.1.5 HIV-stratified analysis

Since HIV predominantly affects younger and middle aged adults (15-54 years old) via sexual transmission, children (0-14 years old) and older adult ( $\geq 55$  years old) cases were excluded from this analysis.

Among adult cases, a significantly greater proportion of males than females were HIV negative (standardized female:male ratio=0.67) and HIV unknown (standardized female:male ratio=0.70), while a greater proportion of females than males were HIV positive (standardized female:male ratio=1.41) ( $p < 0.001$ ). Age distributions for HIV positive and HIV negative male and female adult cases 15-54 years old are presented in Figures 2a and 2b respectively. Figure 2a shows that among HIV positive TB cases, the peak number of female cases occurred among 25-29 year olds ( $n=1,697$ ) while the peak number of male cases occurred among 35-39 year olds ( $n=1,398$ ). The age distribution of HIV negative TB cases (Figure 2b) shows a very different pattern with much smaller peaks. The first peak among 20-24 year olds consisted of 711 female cases and 982 male cases, followed by a slight second peak in female cases 40-44 years old ( $n=351$ ) and in older male cases 45-49 years old ( $n=733$ ).

A graphical representation of standardized female:male ratios among HIV positive, HIV negative, and HIV unknown TB cases 15-54 years old is shown in Figure 3. While standardized female:male ratios among HIV negative and HIV unknown cases peaked at similar ratios of 1.55 and 1.62 respectively, HIV positive cases had a dramatically higher peak of 5.96. All standardized female:male ratios decreased with age to similar ratios of

0.60, 0.65, and 0.66 among 54 year old HIV positive, HIV negative, and HIV unknown TB cases respectively.

**Figure 2a - HIV positive male and female tuberculosis cases by five-year age strata (15-54 years old)**

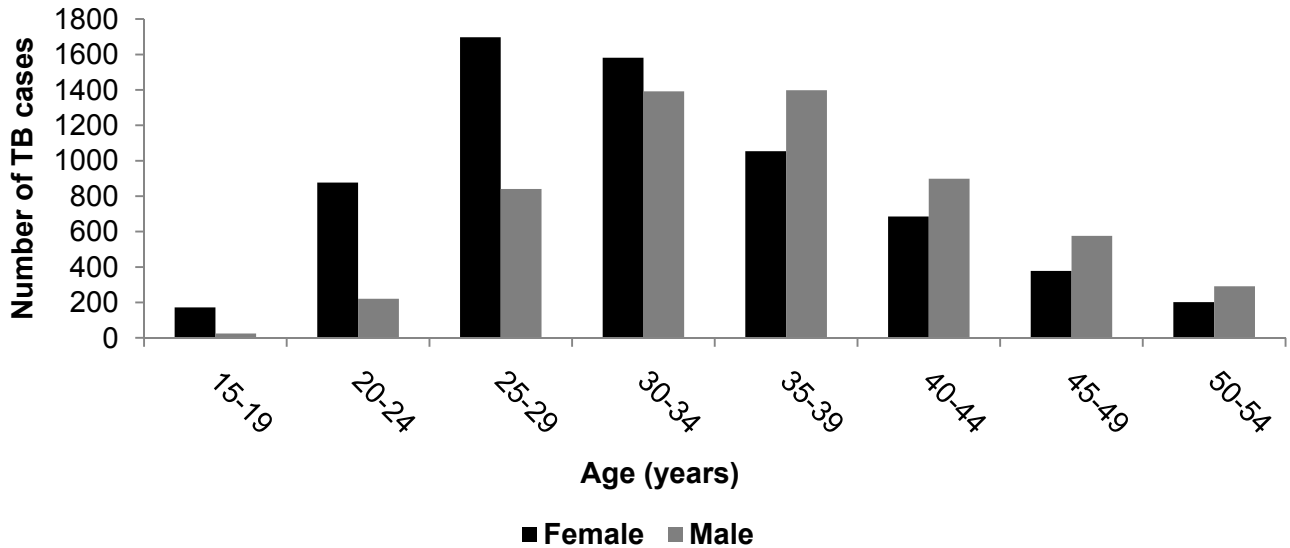


Figure 2a shows that the highest number of HIV positive female cases was among 25-29 year olds and the highest number of HIV positive male cases was among 35-39 year olds.

**Figure 2b - HIV negative male and female tuberculosis cases by five-year age strata (15-54 years old)**

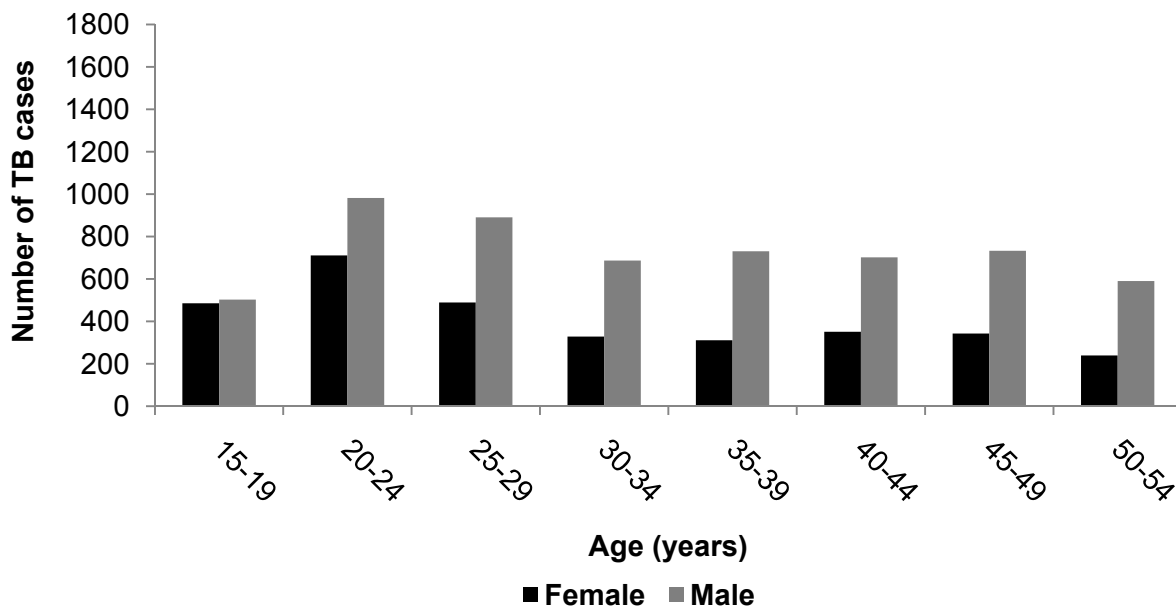


Figure 2b shows that HIV negative males and females had a peak number of cases among 20-24 year olds followed by a slight peak among 40-44 year old females and 45-49 year old males. The number of male cases exceeded the number of female cases across all age strata.

**Figure 3 - Standardized female:male ratios\* among HIV positive, HIV negative and HIV unknown tuberculosis cases (15-54 years old)**

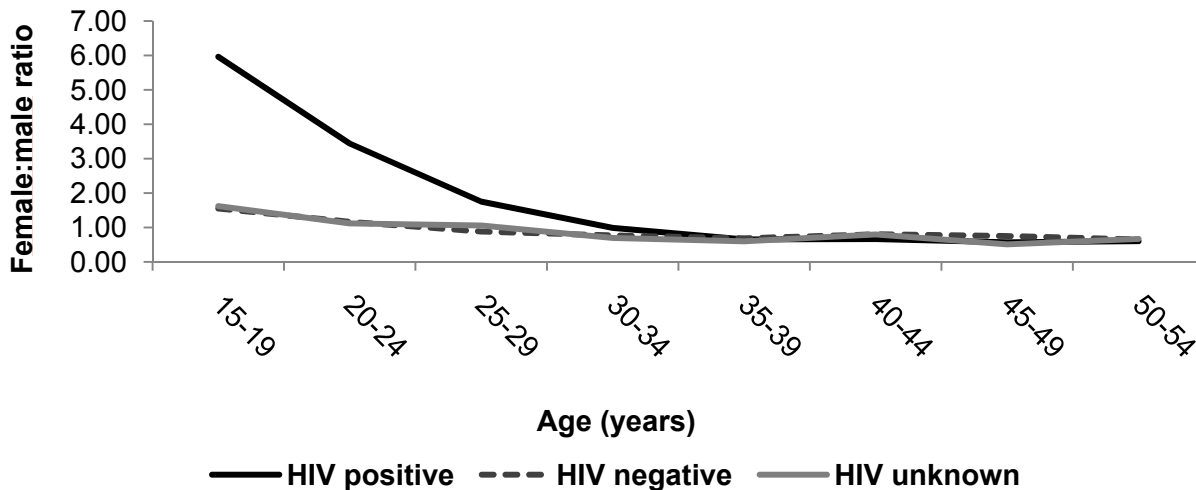


Figure 3 shows that HIV negative, HIV unknown, and HIV positive TB cases had peak standardized female:male ratios of 1.55, 1.62 and 5.96 among 15-19 year olds respectively, which decreased with age. \*Standardized female:male ratios were determined by dividing age-specific female:male ratios by the overall crude female:male ratio of 1.15, 0.62 and 0.66 among HIV positive, HIV negative and HIV unknown TB cases respectively.

#### 5.1.6 Associations between female cases and clinical characteristics

Section 5.1.4 describes crude clinical differences between males and females whereas this section describes associations between female cases and clinical characteristics adjusted for HIV. Table 2 shows unadjusted and adjusted associations between gender and clinical characteristics in five regression models. Unadjusted associations were stronger than adjusted associations across all characteristics investigated except HIV status.

Females were more likely than males to have extra-pulmonary TB rather than pulmonary TB (adjusted odds ratio (OR)=1.22; 95% Confidence Interval (CI)=1.13–1.32). Females were less likely than males to have a smear microscopy result recorded in the electronic TB register (adjusted OR=0.80; 95% CI=0.72–0.89). Of those with smear microscopy results recorded, females were less likely than males to be smear-positive (adjusted OR=0.77; 95% CI=0.73–0.83). The odds of having severe smear positivity grading decreased in females. When comparing females to males, females had a higher odds of being P+ versus scanty positive (adjusted OR=1.03; 95%CI=0.82–1.28), which shifted to a lower odds of being P++ versus scanty positive (adjusted OR=0.84; 95%CI= 0.67-1.06) and P+++ versus scanty positive (adjusted OR=0.72; 95%CI=0.58–0.89). In addition, females had a 2.48-fold increase in the odds of being HIV positive compared to males (adjusted OR=2.48; 95%CI=2.34-2.64).

**Table 2 – Associations between female cases and clinical characteristics (15-54 years old)**

Model	Outcome	Unadjusted OR* (95%CI)	P-value	Adjusted OR* (95%CI)	P-value
	<b>Disease classification</b>				
1	Pulmonary TB	1.00	NA	1.00 <sup>†</sup>	NA
	Extra-pulmonary TB	1.42 (1.33-1.52)	<0.001	1.22 <sup>†</sup> (1.13-1.32)	<0.001
	Both	1.34 (1.12-1.59)	0.001	1.13 <sup>†</sup> (0.93-1.37)	0.22
	<b>Smear microscopy results</b>				
2	Test not done	1.00	NA	1.00 <sup>‡</sup>	NA
	Test done	0.75 (0.71-0.80)	<0.001	0.80 <sup>‡</sup> (0.72-0.89)	<0.001
3	Smear negative	1.00	NA	1.00 <sup>‡</sup>	NA
	Smear positive	0.71 (0.67-0.74)	<0.001	0.77 <sup>‡</sup> (0.73-0.83)	<0.001
4	Scanty positive	1.00	NA	1.00 <sup>‡</sup>	NA
	P+	0.93 (0.77-1.13)	0.49	1.03 <sup>‡</sup> (0.82-1.28)	0.83
	P++	0.75 (0.61-0.91)	0.005	0.84 <sup>‡</sup> (0.67-1.06)	0.14
	P+++	0.60 (0.50-0.72)	<0.001	0.72 <sup>‡</sup> (0.58-0.89)	0.002
	<b>HIV status</b>				
5	Negative	1.00	NA	1.00 <sup>¥</sup>	NA
	positive	2.24 (2.12 - 2.37)	<0.001	2.48 <sup>¥</sup> (2.34 - 2.64)	<0.001

\*OR=Odds ratio for females compared to males derived from logistic and multinomial regression models.  
<sup>†</sup>Adjusted for age and HIV status; <sup>‡</sup>Adjusted for age, HIV status and disease classification; <sup>¥</sup>Adjusted for age.

## 5.2 Cape Town population denominators

In 2009, there were approximately 3,044,010 Cape Town residents, of which 50.2% (1,728,714/3,044,010) were female (crude female:male ratio=1.01). Among residents, 5.85% were HIV positive, of which 61.1% (123,094/201,502) were female (p<0.001). The Cape Town population by age and HIV status has been previously described by Wood et al. [9] and a table of the Cape Town population stratified by age, gender and HIV is shown in the Appendices, Table 2.

## 5.3 Estimated TB notification rates

Less than one-tenth of TB cases were HIV unknown, of which 63.25% (1,365/2,158) were male. The age-specific distribution of 15-54 year old HIV unknown male and female TB cases was similar to the HIV negative age distribution for male and female TB cases shown in Figure 2b, but consisted of fewer cases overall.

The Poisson regression model estimated an overall unadjusted NRR for TB in females compared to males of 0.84 (95% CI=0.82-0.86). However, an HIV-stratified analysis revealed that HIV modified the association between gender and TB notification rates. In the HIV positive sub-population, TB notification rates in females were 12.4% higher than males, although this did not reach statistical significance (adjusted NRR=1.12; 95%CI=0.99-1.28). In contrast, in the HIV negative sub-population, TB notification rates in females were 12.9% lower than in males (adjusted NRR=0.87; 95%CI=0.78-0.97).

Estimated age-specific TB notification rates per 100,000 for HIV positive and HIV negative males and females are shown in Figures 4a and 4b respectively. In addition, Table 4 in the Appendices provides an age-specific breakdown of TB notification rates per 100,000 by age, gender, and HIV. Figure 4a shows a small peak in TB notifications among HIV positive males and females 15-19 years, which was 12.4% higher in females (7,380 per 100,000 vs. 6,568 per 100,000). Thereafter, TB notification rates in females 20-54 years old decreased and remained relatively stable, with the exception of a second peak notification of 7,827 per 100,000 among 40-44 year olds, which was slightly higher than the first peak notification. In contrast, notification rates among males  $\geq 20$  years old increasingly exceeded female notification rates and peaked at 13,397 per 100,000 among 40-44 year olds, which was 71.2% higher than the notification rate in females of the same age. The most disparate notification occurred among 45-49 year olds, where the notification rate in males nearly doubled the notification rate in females of the same age.

Figure 4b indicates that HIV negative individuals have lower TB notification rates overall as well as a different age and gender pattern compared to HIV positive individuals. Unlike the HIV positive population, HIV negative TB notification rates in females did not exceed male rates at any age. In addition, HIV negative peak TB notification rates occurred five years later than HIV positive peak TB notification rates. In addition, the disparity between HIV negative TB rates in males and females was larger than observed among HIV positive individuals.

In contrast to 15-19 year old HIV positive females, 15-19 year old HIV negative females had a TB notification rate 12.9% lower than the rate among males of the same age. TB notification rates peaked among 20-24 year olds at 757 per 100,000 in males and 515 per 100,000 in females. Thereafter, rates in females remained relatively stable, with the exception of a slight peak of 410 per 100,000 among 45-49 year olds. Males in their mid-30s, on the other hand, had rates that substantially increased to a peak of 1,018 per 100,000 among 45-49 year olds. The disparity between HIV negative male and female TB notification rates increased with age to a nearly 2.5-fold higher rate among 45-49 year old males than females.

**Figure 4a - Estimated age-specific tuberculosis notification rates in HIV positive males and females (15-54 years old)**

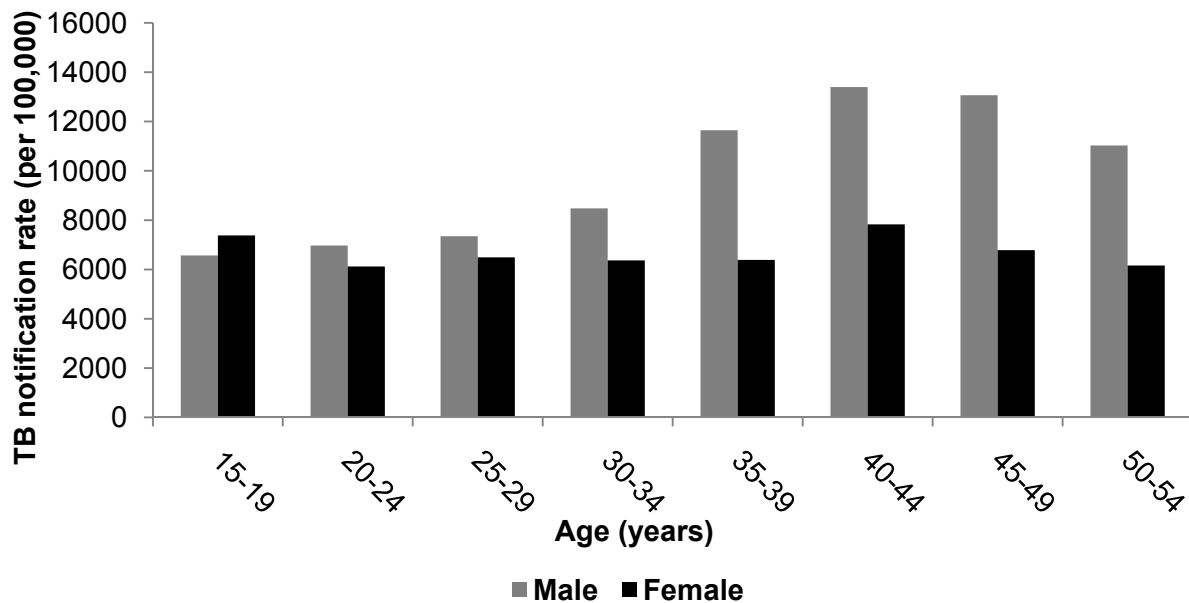


Figure 4a shows that the TB notification rate among 15-19 year old females was 12.4% higher than the rate in males of the same age. Thereafter, rates in males increasingly exceeded rates in females, which peaked among 40-44 year olds. Rates in males 45-49 years old was 2-fold higher than rates in females of the same age.

**Figure 4b - Estimated age-specific tuberculosis notification rates in HIV negative males and females (15-54 years old)**

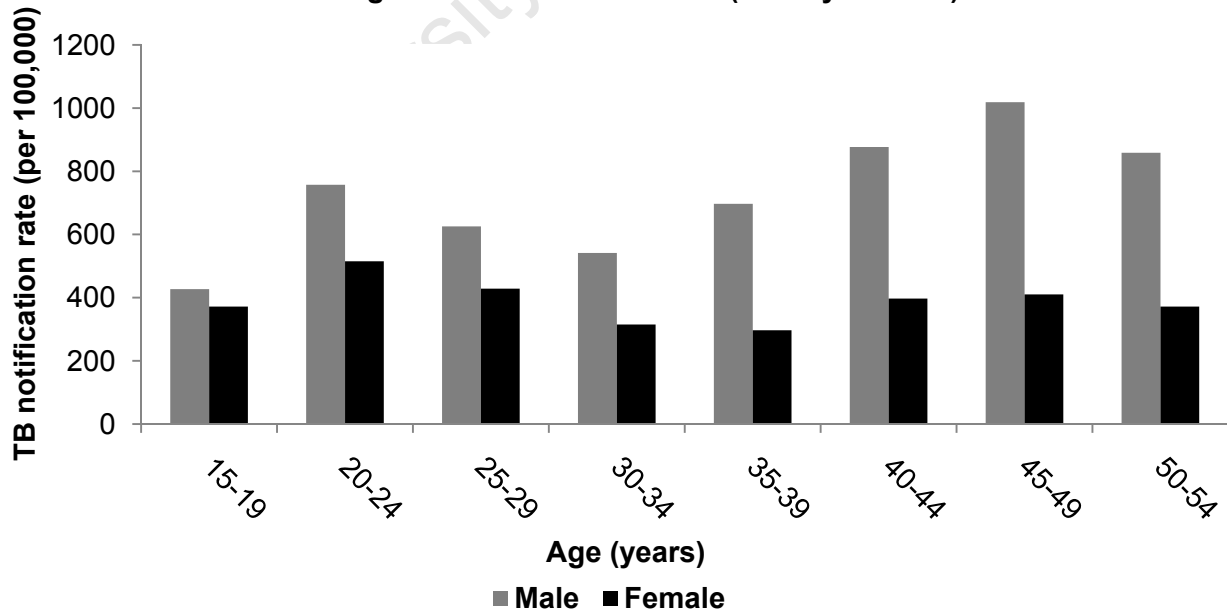


Figure 4b shows that the TB notification rates among HIV negative females did not exceed male rates at any age. Males and females had peak rates among 20-24 year olds and 45-49 year olds. The rate in 45-49 year old males was 2.5-fold higher than the rate in females of the same age.

## 6.0 DISCUSSION

This study analysed nearly 30,000 newly notified TB cases and estimated corresponding TB notification rates in Cape Town during 2009. Our findings confirm that there are significant differences in the age-specific absolute number of male and female TB cases and in the TB notification rates among males and females, which are significantly affected by HIV co-infection. In contrast to the majority of low- and middle-income countries which reported disaggregated data, the age and gender pattern TB disease in this population is similar to that observed in Malawi, Uganda and mid-20<sup>th</sup> century industrialized countries such as England and Wales [10, 15, 20]. In addition, our findings substantiate the age and gender pattern of TB notifications in South Africa reported by Lawn et al. [21] using a more accurate measure of TB notification *rates*.

Stratifying by HIV revealed that HIV is having a significant heterogeneous effect on the age-specific distribution of TB notification rates in males and females in this population. In the HIV *positive* sub-population, young females 15-19 years old have a higher TB notification rate than young 15-19 year old males, after which age male rates increasingly exceed female rates throughout adulthood. This pattern of TB disease is similar to what has been reported in Malawi, Uganda and industrialized countries during the 1930s-1950s [10, 15, 20, 21]. In contrast, in the HIV *negative* sub-population, female TB notification rates never exceed male rates at any age; instead, male rates increasingly exceed female rates after childhood. This pattern of TB disease is similar to what has been reported in the majority of low- and middle-income countries [10, 13, 15, 32]. This is the first study to ascertain that HIV co-infection narrows the overall disparity between male and female TB notification rates and moves notification rate ratios closer to parity compared to rate ratios for HIV negative individuals. HIV co-infection even *reverses* the TB notification rates among young people: young HIV positive females have higher TB rates than young HIV positive males, whereas young HIV negative females have lower TB rates than young HIV negative males. Thus, the high TB burden among young females in this population is largely attributable to the high prevalence of HIV in these individuals.

In addition, we also identified clinical differences between male and female TB cases, which were consistent with findings elsewhere. In this population, fewer females than males have smear results recorded, which we considered an indicator of sputum submission [11, 25]. Among the females who had smear results recorded, they were less likely than males to be diagnosed as smear-positive or have severe smear positivity grading [11, 14, 25]. This is the first study to report that HIV co-infection consistently widens pre-existing clinical differences between males and females.

HIV's effect on TB-related gender differences can be explained by HIV-related immunological and health systems pathways. It is well-established that HIV suppresses immune functioning and significantly increases susceptibility to developing TB disease. Young South Africans 15-24 years old comprise the age group most at risk of HIV infection [33, 34]. Young females in particular have an approximate 4-fold increased risk of HIV infection compared to males in this population [34]. These factors may explain why young HIV positive females in this population have higher TB notification rates than their male counterparts. In addition, immunosuppression often leads to widespread dissemination of TB and reduced cavitation [2, 26, 27]. As a result, expectorating sputum becomes more difficult

and sputum tends to contain a low bacillary load, which leads to diagnostic obstacles [2]. This may explain why fewer females than males in this population have smear microscopy results recorded and are smear-positive.

As a result of massive efforts to scale-up HIV services in South Africa, about 10 million individuals were tested for HIV in 2010 [4, 7] and 1.79 million HIV positive individuals received ART in 2011, of which there were more females than males [35]. These statistics indicate that thousands of HIV positive individuals, especially disproportionately affected young females, are in the healthcare system, returning for follow-up visits and being monitored. Therefore, they are more likely to be suspected, tested, and diagnosed with TB. These factors increase case finding and may also be contributing to the higher TB notification rates observed in young HIV positive females compared to HIV positive males in this population. This also suggests that young females in this population are not experiencing socio-cultural barriers accessing services relative to males. This contrasts with other countries such as Bangladesh where consistently higher TB notification rates among males is commonly attributed to females' lack of access and under notification of TB [10, 11, 17, 18]. Furthermore, as previously mentioned, HIV positive individuals are more likely to have extra-pulmonary TB and less TB bacilli present [27], which is difficult to diagnose and may lead to under diagnosis. Therefore, these notification rates may only be the tip of the iceberg of an even higher incidence of TB among young females that remains undetected.

While HIV has a significant effect on TB-related gender differences, controlling for HIV does not nullify epidemiological differences of TB disease in males and females in this population. This indicates that there are additional underlying biological and lifestyle risk factors differentially affecting males and females. For example, males are more likely than females to smoke cigarettes and drink alcohol [37] as well as have genetic polymorphisms [12], which may increase their risk of developing TB disease. Females, on the other hand, are more likely than males to be obese, have diabetes, or be exposed to domestic fuels [37], which may also explain their increased risk of developing TB disease. These risk factors may also contribute to the observed TB-related gender differences in this population.

There were some limitations to this study. We were confined to the data recorded in the electronic TB register, which had some missing data and inconsistencies, although rigorous data cleaning was employed to avoid introducing information bias. In addition, we were unable to investigate un-notified TB cases or explore associations between gender and other known risk factors for TB such as socio-economic status, living conditions, and substance abuse. The apportioning of HIV unknown TB cases as probable HIV positive and HIV negative was an estimate; however, the sensitivity analysis concluded that all three scenarios yielded similar results, which indicates that these estimates are robust. In addition, while the Cape Town population denominators were also estimates, they were derived from the ASSA model, which is accepted as the most valid source of population estimates for South Africa. The caveat, though, is that the ASSA model lacks reliable HIV positive denominators for adolescents. However, this was addressed with the Poisson regression model, which estimated more accurate rates for adolescents that were consistent with the age- and gender-specific notification rates of TB in other HIV-burdened populations [10, 15, 20, 21].



## **6.1 Recommendations**

It is important to improve HIV and TB testing and treatment rates for females, particularly young females who are most vulnerable to both infections. Females who test smear-negative should be highly encouraged to test for HIV. Those who test HIV positive and are eligible for ART should start ART immediately to reduce the risk of developing TB or suffering TB-related complications. Conversely, HIV positive females require early diagnosis and treatment to decrease the likelihood of serious TB-related complications. Clinicians need to have a higher index of suspicion of TB in young females and pay closer attention to signs and symptoms of extra-pulmonary TB. Although diagnosing extra-pulmonary TB is difficult, initial TB symptom screening as well as non-invasive clinical exams to detect extra-pulmonary TB through palpating lymph nodes or utilizing the point-of-care Lipoarabinomannan (LAM) urine dipstick could be done at schools, followed by further investigation. However, given the high prevalence of HIV among young females in this population, which often leads to smear-negative TB, it is likely that they are less infectious and therefore not the primary transmitters of TB infection in this population.

In this population, older males are more likely than females to be HIV negative and have smear-positive, pulmonary TB, rendering them more infectious. They are therefore more likely to be the primary drivers of the TB epidemic in this population. While the HIV epidemic has significantly affected females' susceptibility to TB, it most likely has not had such an effect in HIV negative individuals, particularly males. To curb TB disease in males, more aggressive symptom screening and rapid diagnosis for smear-positive TB using technologies such as GeneXpert should be considered in the workplace and communities to target older, HIV negative males.

In addition to clinical interventions, upstream educational programmes are a necessary component of TB prevention and control strategies. Particularly for young females, it is important to strengthen HIV prevention strategies such as improved sexual and reproductive health services, TB/HIV integration and life skills courses to enhance decision-making, power, and communication skills. These programmes should also focus on reducing transactional or cross-generational sexual relationships, a common occurrence in this population, which may also be putting young females at risk of developing not only HIV but also TB [40, 41]. For older males, it is also important to strengthen education about TB symptoms, transmission, and risk factors for transmission.

Further research should consider investigating additional underlying risk factors for gender differences in TB such as lifestyle, epidemiological, socio-cultural, and biological pathways. In addition, further epidemiological research to identify risk factors for TB transmission in younger females and older males, including transactional sex and "hotspot" locations for TB transmission, such as transportation and schools, should be undertaken. In order to strengthen research methodology, researchers along with public health officials should also acquire more accurate population denominators to measure TB incidence rates, particularly in adolescents, as part of routine surveillance and TB control strategies.

## 7.0 CONCLUSIONS

In conclusion, there are significant gender differences related to TB in this population and HIV is a major contributing factor affecting these differences, especially among young females. HIV/TB co-infection increases pre-existing clinical differences between male and female TB cases. In the presence of HIV infection, even fewer females than males have smear results recorded and among those with recorded results, they are less likely than males to be diagnosed as smear-positive or have severe smear positivity grading. In addition, similar age and gender distributions of TB notification rates have been reported only in Uganda, Malawi and during the mid-20th century. Among HIV co-infected individuals, young females had a higher TB notification rate than young males and there were decreased differences between male and female rates overall as compared to HIV negative individuals. However, even when HIV is controlled for, gender differences persist, which indicates that there are additional underlying biological and lifestyle risk factors for gender differences in TB that require further investigation. These findings warrant the need to implement a multi-pronged approach to TB control which focuses on young females and older males and includes integrated, rapid HIV testing and TB screening, educational programmes, and behaviour-change interventions.

## 8.0 LIST OF ABBREVIATIONS

ASSA	Actuarial Society of South Africa
CI	Confidence Interval
DOTS	Directly Observed Therapy, Short-course
HIV	Human Immunodeficiency Virus
IQR	Interquartile range
NRR	Notification rate ratio
OR	Odds ratio
TB	Tuberculosis

## 9.0 COMPETING INTERESTS

The authors have no competing interests to declare.

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## PART D: APPENDICES

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University of Cape Town

## 1.0 LETTERS OF APPROVAL

### 1.1 Health Research Ethics Committee, University of Cape Town



UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences  
Human Research Ethics Committee  
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20 April 2012

HREC REF: 187/2012

Prof R Wood,  
Dermond Tulu, HIV Foundation  
ICMBA  
Medical School

Dear Prof Wood,

**PROJECT TITLE: GENDER DIFFERENCES IN TUBERCULOSIS WITHIN AN HIV CONTEXT IN CAPE TOWN, SOUTH AFRICA**

Thank you for submitting your new study to the Faculty of Health Sciences Human Research Ethics Committee

It is a pleasure to inform you that the Ethics Committee has formally approved the above-mentioned study.

Approval is granted until 20 April 2013

Please submit an annual progress report (FHS010) if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file (FHS013).

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

**PROFESSOR MARC BLOCKMAN**  
**CHAIRPERSON: FHS HUMAN RESEARCH ETHICS**

Human Write Assistance Number: FHS0001057  
National Review Board (REF) number: R90001944

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies with the Ethics Standards for Clinical Research (a) a new set of regulations, based on the Medical Research Council (MRC) (SA), Food and Drug Administration (FDA) USA, International Convention on Harmonisation Good Clinical Practice (ICH) GCP, and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (ICH E6(R2) GCP) and HCA Code of Federal Regulations Part 312.20 and 312.

## 1.2 City Health, City of Cape Town



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CITY HEALTH — Specialised Health

2012-07-26

re: Research Request: "Gender Differences in Tuberculosis within an HIV Context in Cape Town, South Africa". (ID No: 10318)

Dear Ms Racow

Permission has been granted for you to do your research as per your protocol

Please note the following:

1. A copy of the final report must be sent to the City Health Head Office, P O Box 2815 Cape Town 8001, within 3 months of its completion and feedback must also be given to the clinics involved.
2. Your project has been given an ID Number (ID10318). Please use this in any future correspondence with us.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Yours sincerely

DR G H VISSER  
MANAGER: SPECIALISED HEALTH

cc. Dr K Jennings  
Ms Caldwell



## 2.0 APPENDICES OF JOURNAL READY ARTICLE

**2.1 Table 1 - 2009 Cape Town tuberculosis cases by age, gender and HIV (0 - ≥75 years old)**

Age (years)	HIV positive TB cases				HIV negative TB cases				HIV unknown TB cases			
	Total	Female	Male	Standardized F:M ratio*	Total	Female	Male	Standardized F:M ratio*	Total	Females	Males	Standardized F:M ratio*
0-4	313	170	143	1.03	1,582	777	805	1.55	958	450	508	1.34
5-9	133	62	71	0.76	372	184	188	1.57	217	97	120	1.22
10-14	75	44	31	1.23	227	135	92	2.36	91	51	40	1.92
15-19	197	172	25	5.96	988	485	503	1.55	251	130	121	1.62
20-24	1,098	877	221	3.44	1,693	711	982	1.16	393	167	226	1.12
25-29	2,538	1,697	841	1.75	1,380	489	891	0.88	376	155	221	1.06
30-34	2,974	1,582	1,392	0.99	1,015	328	687	0.77	295	93	202	0.69
35-39	2,452	1,054	1,398	0.65	1,042	311	731	0.68	268	76	192	0.60
40-44	1,584	685	899	0.66	1,053	351	702	0.80	203	70	133	0.79
45-49	954	378	576	0.57	1,076	343	733	0.75	215	54	161	0.51
50-54	493	202	291	0.60	829	239	590	0.65	157	48	109	0.66
55-59	269	107	162	0.57	571	173	398	0.70	123	30	93	0.49
60-64	105	39	66	0.51	315	108	207	0.84	73	21	52	0.61
65-69	34	16	18	0.77	195	79	116	1.09	50	14	36	0.59
70-74	11	3	8	0.33	72	42	30	2.25	24	12	12	1.51
≥75	7	3	4	0.65	97	45	52	1.39	40	20	20	1.51
<b>Total</b>	<b>13,237</b>	<b>7,091</b>	<b>6,146</b>	<b>1.00</b>	<b>12,507</b>	<b>4,800</b>	<b>7,707</b>	<b>1.00</b>	<b>3,734</b>	<b>1,488</b>	<b>2,246</b>	<b>1.00</b>

\*Standardized female:male ratios were determined by dividing age-specific female:male ratios by the overall crude female:male ratio of 1.15, 0.62 and 0.66 among HIV positive, HIV negative and HIV unknown tuberculosis cases respectively.

**2.2 Table 2 - Estimated 2009 mid-year Cape Town population by age, gender and HIV (0-75 years old)**

Age (years)	Total population				HIV positive sub-population				HIV negative sub-population			
	Total	Female	Male	Standardized F:M ratio*	Total	Female	Male	Standardized F:M ratio*	Total	Female	Male	Standardized F:M ratio*
0-4	316,078	156,309	159,769	0.97	6,630	3,286	3,344	0.63	309,448	153,023	156,425	1.00
5-9	322,819	159,618	163,201	0.97	3,493	1,731	1,762	0.63	319,326	157,887	161,439	1.00
10-14	312,137	154,837	157,300	0.98	430	215	216	0.63	311,707	154,622	157,084	1.00
15-19	304,903	153,305	151,598	1.00	3,456	3,348	109	19.64	301,447	149,957	151,489	1.01
20-24	327,113	163,577	163,536	0.99	20,903	17,397	3,506	3.16	306,210	146,180	160,030	0.93
25-29	330,742	160,541	170,201	0.94	43,582	29,232	14,350	1.30	287,160	131,309	155,851	0.86
30-34	298,919	142,233	156,686	0.90	47,194	27,455	19,739	0.89	251,725	114,778	136,947	0.85
35-39	257,267	126,089	131,178	0.95	33,229	18,704	14,525	0.82	224,038	107,385	116,653	0.94
40-44	197,947	100,073	97,874	1.01	18,423	10,331	8,093	0.81	179,524	89,742	89,781	1.02
45-49	183,414	95,804	87,610	1.08	12,019	6,452	5,568	0.74	171,395	89,352	82,042	1.11
50-54	163,071	86,690	76,381	1.13	6,833	3,135	3,698	0.54	156,238	83,555	72,683	1.17
55-59	130,157	69,752	60,405	1.15	3,419	1,250	2,169	0.37	126,738	68,502	58,236	1.20
60-64	106,269	56,599	49,670	1.13	1,551	479	1,072	0.28	104,718	56,120	48,598	1.18
65-69	77,547	40,919	36,628	1.11	316	77	240	0.20	77,231	40,842	36,388	1.14
70-74	52,142	27,233	24,909	1.08	22	4	19	0.13	52,120	27,229	24,890	1.11
≥75	62,485	35,135	27,350	1.27	0.23	0.03	0.19	0.11	62,485	35,135	27,350	1.31
<b>Total</b>	<b>3,443,010</b>	<b>1,728,714</b>	<b>1,714,296</b>	<b>1.00</b>	<b>201,502</b>	<b>123,094</b>	<b>78,408</b>	<b>1.00</b>	<b>3,241,508</b>	<b>1,605,620</b>	<b>1,635,888</b>	<b>1.00</b>

\*Standardized female:male ratios were determined by dividing age-specific female:male ratios by the overall crude female:male ratio of 1.01, 1.57 and 0.98 among the total, HIV positive and HIV negative populations respectively.

**2.3 Table 3 - Sensitivity analysis of notification rate ratios for apportioning HIV unknown tuberculosis cases as probable HIV positive and HIV negative (15-54 years old)**

Age (years)	Scenario A*		Scenario B <sup>†</sup>		Scenario C <sup>‡</sup>	
	HIV positive	HIV negative	HIV positive	HIV negative	HIV positive	HIV negative
	TB NRR**	TB NRR	TB NRR	TB NRR	TB NRR	TB NRR
15-19	0.22	1.00	0.22	1.00	0.16	0.95
20-24	0.80	0.80	0.80	0.80	0.73	0.74
25-29	0.99	0.69	0.99	0.69	0.94	0.62
30-34	0.82	0.57	0.82	0.57	0.77	0.54
35-39	0.59	0.46	0.59	0.46	0.54	0.45
40-44	0.60	0.50	0.60	0.50	0.56	0.49
45-49	0.57	0.41	0.57	0.41	0.51	0.41
50-54	0.82	0.36	0.82	0.36	0.79	0.35

\*HIV unknown tuberculosis cases apportioned as HIV positive cases; <sup>†</sup>HIV unknown cases apportioned as HIV negative cases; <sup>‡</sup>HIV unknown cases apportioned as HIV positive according to existing HIV rates among cases with known HIV results. \*\*NRR=notification rate ratio.

**2.4 Table 4 - Estimated\* 2009 Cape Town tuberculosis notification rates (per 100,000) by age, gender, and HIV (15-54 years old)**

Age (years)	HIV positive TB notification rate (per 100,000)			HIV negative TB notification rate (per 100,000)		
	Female	Male	Crude female:male ratio	Female	Male	Crude female:male ratio
<b>15-19</b>	7,380	6,568	1.12	372	427	0.87
<b>20-24</b>	6,123	6,972	0.88	515	757	0.68
<b>25-29</b>	6,495	7,346	0.88	429	625	0.69
<b>30-34</b>	6,367	8,476	0.75	315	541	0.58
<b>35-39</b>	6,387	11,640	0.55	296	697	0.43
<b>40-44</b>	7,827	13,397	0.58	397	877	0.45
<b>45-49</b>	6,785	13,063	0.52	410	1,018	0.40
<b>50-54</b>	6,161	11,025	0.56	372	859	0.43

\*TB notification rates were estimated according to the Poisson regression model which included gender, age, and HIV as variables.

### 3.0 BMC INFECTIOUS DISEASES INSTRUCTION FOR AUTHORS

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- Endnotes
- References
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