PREVALENCE OF HIV/AIDS IN TUBERCULOSIS PATIENTS LIVING IN THE LOWLANDS OF MAFETENG DISTRICT IN LESOTHO

by

Rethabile Ramosoeu

A dissertation submitted in partial fulfilment of the requirements for the degree of

Master of Health: Environmental Health

in the Faculty of Health and Environmental Sciences

Central University of Technology, Free State

Bloemfontein

2021

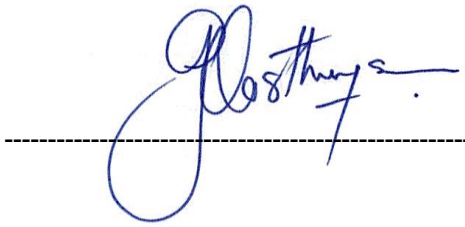
Declaration

The work described in this dissertation was carried out in the Faculty of Health and Environmental Sciences; Central University of Technology, Free State, under the supervision of Doctor Jeanné Oosthuysen and the co-supervision of Professor Annabel Fossey.

We hereby certify that this statement is correct, and as the candidate's supervisors agree to the submission of this dissertation.

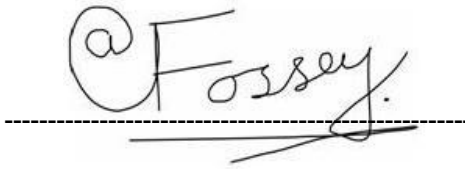
Doctor Jeanné Oosthuysen

Supervisor



Professor Annabel Fossey

Co-supervisor



Acknowledgements

I, the undersigned, hereby declare that the work contained in this dissertation is my own independent work and that all sources consulted or cited have been indicated in full. This dissertation, or any part thereof, has not been submitted before to any other institution by myself or any other person in order to obtain a degree.

Rethabile Ramosoeu

Date: November 2020

Table of Contents

List of Tables

List of Figures

Abbreviations

AIDS:	Acquired Immune Deficiency Syndrome
ART:	Anti-Retroviral Therapy
BCG:	Bacillus Calmette-Guérin
CDC:	Centre for Disease Control and Prevention
DOT:	Directly Observed Treatment
DR-TB:	Drug-Resistant Tuberculosis
EP-TB:	Extra-pulmonary Tuberculosis
HCCs:	Health Care Centres
HIV:	Human Immunodeficiency Virus
HIV/AIDS:	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
IPT:	Isoniazid Preventive Therapy
LTBI:	Latent Tuberculosis Infection
MDR-TB:	Multidrug-resistant Tuberculosis
M.TB	*Mycobacterium tuberculosis*
PTB:	Pulmonary Tuberculosis
RNA:	Ribonucleic Acid
SDGs:	Sustainable Development Goals
TB:	Tuberculosis
TDR-TB:	Totally Drug-resistant Tuberculosis

WHO:	World Health Organization
XDR-TB:	Extensively Drug-resistant Tuberculosis

Abstract

Background: Tuberculosis (TB) is one of the oldest known diseases that kills humans, yet still remains among the top infectious disease killers worldwide today. The World Health Organization (WHO) states that up to 10 million people continue to fall ill with TB every year. Almost three-quarters of the TB infections are reported from the African region and almost a quarter of these are mentioned to be co-infected with human immunodeficiency virus (HIV) (WHO, 2018). WHO classified Lesotho as one of the countries carrying a large burden of TB/HIV co-infection in the Africa region (MOH, 2016). Therefore, this study was conducted in order to determine the prevalence of HIV among TB patients living in the lowlands of the Mafeteng district in Lesotho from 2014–2016.

Methodology: A quantitative research approach was conducted by means of a convenience purposeful method of sampling. The method followed was to collect TB/HIV data from the five participating Health Care Centres (HCCs) for the years 2014 – 2016. These data were sourced from handwritten TB registries of the five identified HCCs and the sampling size of 1,109 study participants was selected from all age groups located in the lowlands of the Mafeteng district in Lesotho.

Results: Out of the 1,109 TB patients studied, 780 (70.3%) were also co-infected with HIV. Among the HIV patients, the most prevalent site of TB infection was pulmonary including a total of 665 patients (85.3%), while 115 (14.7%) had extra-pulmonary TB (ET-TB). The number of new TB patients with HIV was 638 (81.2%) and retreated patients numbered 142 (18.2%). A total of 457 (41.2%) fell in the mean age group of 15 to 35 years. 99% of these co-infected patients were receiving anti-retroviral therapy (ART).

Most of these HIV/AIDS patients were from the Mafeteng HCC with 501 (64.2%) of the 1,109 patients. The most affected age group among the patients were the young adult age group (>15 to 35 years) and the adult age group (>35 to 55 years) with 45.8% and 40.6% of the total 780 HIV/AIDS patients, respectively. The distribution of male HIV/AIDS patients among the participating HCCs was 470 (60.3%), while the distribution of female HIV/AIDS patients among the participating HCCs was 310 (39.7%) of the total 780 HIV/AIDS co-infected patients. Most of these HIV/AIDS patients were reported from the Mafeteng main HCC.

Discussion: In this study, TB notification cases declined substantially when comparing reporting Year 1 and 2 with reporting Year 3. It was also interesting to take note that the number of HIV/AIDS cases in the most affected young adult age group interval (>15 to 35) dropped in reporting Year 3. Ultimately, the number of HIV/AIDS cases in the age group interval of adults (>35 to 55) was more in reporting Year 3 compared with the number of cases in the young adult group in the same reporting year.

Conclusion: The findings of the study concluded that there is a high prevalence of HIV/AIDS among TB patients living in the lowlands of the Mafeteng district in Lesotho. Therefore, National and district level administrative bodies and health care centres should collaborate to strengthen the efforts and place TB and HIV/AIDS services among their priority interventions. These include identifying the possible routes of TB transmission because of limited infection control measures, drug resistance, poor TB prognosis and adherence to treatment. Future researchers could consider assessing the main reasons behind the high prevalence of HIV/AIDS among male TB patients in the Mafeteng district of Lesotho.

Key words: Acquired Immune Deficiency Syndrome, Anti-Retroviral Therapy, Bacillus Calmette-Guérin, Drug-Resistant Tuberculosis, Extra-pulmonary Tuberculosis, Health Care Centres

Chapter 1

Introduction to the Study

1.1 Introduction

Tuberculosis has existed since the earliest record of human history. It is estimated that humans have been infected with *Mycobacterium tuberculosis* (MTB) from as early as three million years ago (Cheon et al., 2016). Global statistics released by the World Health Organization (WHO) in 2014, indicated that the infectious disease, Tuberculosis, remains one of the world's deadliest communicable diseases (Mugomeri et al., 2018). The WHO further mentioned that an estimated 10.0 million people developed the Tuberculosis disease (TB) in 2017 of which 5.8 million were men, 3.2 million women and 1.0 million children (WHO, 2018). The report also mentioned that between 2000 and 2017, close to 54 million deaths caused by TB were reported worldwide (WHO, 2018).

Every year, the WHO declares 24th March as World Tuberculosis Day. This marks the anniversary of the announcement by Dr Robert Koch in 1882 that he had identified *M. tuberculosis* (MTB) as the cause of the disease (Floyd et al., 2018). This German doctor was the first microbiologist to report the successful isolation of the causative agent MTB (Cambau & Drancourt, 2014). Although MTB is the major causative agent of TB, other pathogens, such as *Mycobacterium bovis* and *Mycobacterium africanum,* can also cause TB (Ibrahim et al., 2017).

Bacterial infection by the pathogens typically targets the lungs and is referred to as pulmonary TB. However, these organisms can also affect other areas of the body, including the bones, brain, kidneys as well as regional lymph nodes, which is then referred to as extra-pulmonary TB (Demile et al., 2018). In 2017, the WHO reported that pulmonary infection is the most common site for TB with about 5.5 million new and relapsed patients of which 56% were confirmed bacteriological (WHO, 2018). In addition, WHO also confirmed that extra-pulmonary TB represented only 14% of the total

6.4 million incident cases of TB in 2017 (WHO, 2018). However, it is now more than a century after Robert Koch discovered MTB, yet still TB remains the number one global public health concern because of the increasing number of deaths due to TB (Padhi et al., 2014).

Most TB infections do not present symptoms initially and this is referred to as latent TB infection (LTBI). Approximately 10% of LTBI progress to active disease that, if left untreated, kills about half of those infected (Kwok et al., 2015). In 2014, it was estimated that approximately 1.7 billion individuals were latently infected, totalling just less than a quarter of the global population (Houben & Dodd, 2016). What is even more worrying is the fact that the African regions had the highest prevalence and accounted for around 80% of those with LTBI (Houben & Dodd, 2016).

Due to LTBI in particular, the cascade of care in diagnosis and treatment of TB is identified as challenging. Currently there is no gold-standard testing tool for the identification of LTBI (Alsdurf et al., 2016). However, based on currently available immune-based tests, a third of the world's population has probable LTBI (Alsdurf et al., 2016). It is estimated that of those with LTBI, 100 million people will develop active, contagious TB during their lifetimes (WHO, 2015).

The classic symptoms of active TB are a chronic cough with blood stained sputum, fever, night sweats and weight loss (Barberis et al., 2017). Historically, these classical symptoms have been described from the time of Hippocrates through to the 18th Century and, at that time, people showing these symptoms were referred to as suffering from white plague as well as other names that conjure the despair or horror of this disorder, such as suffering from King's Evil, the Graveyard Cough and the Captain of all these Men of Death (Frith & Villemin, 2014). As these symptoms were mostly seen in young active industrial mineworkers who lived in low socio-economic crowded living conditions, the symptoms were also called Robber of Youth because of the ability of these opportunistic symptoms to weaken the immune systems of young industrial mineworkers (Rosner & Markowitz, 1992).

TB is an opportunistic infection. Opportunistic infections are infections that occur more often or are more severe in people with weakened immune systems than in people with normal healthy immune systems (Scott et al., 2017). So, the emergence of the human immunodeficiency virus (HIV) around 1981 has driven the TB epidemic at an shocking rate (Gakkhar & Chavda, 2012). The common infection routes for HIV are through sexual contact, syringes, blood products and vertical transmission from infected persons or products to another person (Beyrer et al., 2000). HIV attacks the immune system of the infected person and thus severely weakens the immune system (Marais et al., 2013). Therefore, HIV infected people are highly vulnerable to the opportunistic TB infections (Sabin & Lundgren, 2013). TB and the acquired immune deficiency syndrome (AIDS) caused by HIV remain the most common causes of death from an infectious disease worldwide (Zumla et al., 2015; Marx et al., 2018). Therefore, the extraordinary growth of the TB epidemic, especially on the African continent, is due to several factors including HIV/AIDS.

The environmental risk factors associated with the transmission and spread of TB is dependent on the socio-economic status of the area or country (Duarte et al., 2018). Also environmental factors, such as the exposure to inhalable silica, dust or cigarette smoke, increase the probability of developing active TB (Adhikari et al., 2018). In addition, overcrowding further increases the risk of transmitting TB (Berube et al., 2019). Furthermore, a lack of or poor infection prevention and control precautions also contribute to an increased risk of contracting TB (Aldridge et al., 2016). Although all these factors play a role in furthering the TB epidemic, the most significant factor contributing to the growth of the TB epidemic is HIV/AIDS (Chatterjee & Pramanik, 2015).

Finally in 2019, the WHO report introduced new infection and prevention guidelines to address this need (WHO, 2019). The infectious agent *M. tuberculosis* is classified as a dangerous microbial pathogen as it is responsible for infecting more people than any other microbial species (Luba et al.,

2019). Because *M. tuberculosis* is an air-borne disease, the mode of transmission occurs effortlessly (Gunda et al., 2017).

1.2 Aim and objectives

Lesotho is one of the smallest inland countries on the African continent. The country has an estimated population of 2.29 million and is among the 22 highest TB burdened countries in the world (WHO, 2018). Lesotho is also among the leading countries where all forms of TB have been diagnosed (MOH, 2016). In Lesotho, TB is associated with HIV co-infections with an estimated 62 new HIV infections and 50 AIDS associated deaths each day (MOH, 2016).

Little is known about the extent of the prevalence of HIV/AIDS among TB patients living in Lesotho. Therefore, this study was undertaken to obtain an understanding of the prevalence of HIV among TB patients living in the lowlands of the Mafeteng district in Lesotho. In the Mafeteng district, there are 19 Health Care Centres (HCCs) with five of these HCCs located in the lowlands of the Mafeteng district. These five HCCs, namely Mafeteng Hospital, Teba, Motsekuoa, Samaria and LeCoop HCCs, were integral to this study.

The following objectives were devised to meet the aim of this study:

1. To undertake a review of the literature to obtain an understanding of the prevalence of HIV/AIDS among TB patients;
2. To source data of TB patients living in the lowlands of the Mafeteng district;
3. To identify TB patients who are HIV-positive or who are living with AIDS;
4. To analyse and interpret the results to establish trends amongst the TB patients; and
5. To reach conclusions about the prevalence of HIV/AIDS among TB patients living in the lowlands of the Mafeteng district in Lesotho.

1.3 Ethical considerations and limitations

Ethical approval was obtained from the Ministry of Health of Lesotho, National Health Research Ethics Committee (NH-REC) for this study (Reference: ID161-2018). The Ethics Committee provided the necessary consent for the relevant handwritten TB registries of the participating HCCs to be accessed. In addition, the Faculty and Institutional Research Committees of the Central University of Technology, Free State approved the study. To safeguard patient information privacy, the researcher observed standard professional and ethical principles. All information collected from the medical records was treated as confidential and only unique patient numbers were used to identify patients, instead of their birth names. Thereafter, the data of the different variables were captured in an electronic spreadsheet. The ethical approval certificate is included as Appendix A.

1.4 Layout of the dissertation

This dissertation is arranged into seven chapters:

Chapter 1: Introduction

Chapter 1 provides a brief introduction to the study, aim, objectives, ethical clearance, limitations and the layout of the study.

Chapter 2: Prevalence of Tuberculosis: Review of the literature from 2010 to 2019

Chapter 2 provides a review of the literature addressing the prevalence of HIV/AIDS among TB patients from 2010 to 2019.

Chapter 3: Materials and Methods

Chapter 3 provides detail on the methodology used in this study.

Chapter 4: Biographical Information of the Study Population

Chapter 4 provides information about the biographical data of the TB patients living in the lowlands of the Mafeteng district as captured from the handwritten registries of the five participating HCCs.

Chapter 5: **The distribution of Tuberculosis types and treatment outcomes in the lowlands of the Mafeteng district in Lesotho**

Chapter 5 provides information about the prevalence of TB patients in the lowlands of the Mafeteng district in Lesotho.

Chapter 6: **Tuberculosis Patients co-infected with Human Immunodeficiency Virus**

Chapter 6 provides information on the co-infection of the TB patients with HIV as obtained from the participating centres in the lowlands of the Mafeteng district in Lesotho.

Chapter 7: **Discussion and Conclusion**

Chapter 7 provides an overall discussion and conclusion of the study as well as recommendations.

Appendix A: Copy of the ethical approval certificate awarded by Lesotho's Ministry of Health for the study.

Appendix B: A copy of the letter requesting access to the handwritten Tuberculosis (TB) registry books containing patient data as sourced from the five Health Care Centres (HCCs) located in the lowlands of the Mafeteng district in Lesotho.

Appendix C: Certificate of language editing.

.

Chapter 2

Prevalence of Tuberculosis: Review of the literature from 2010 to 2019

2.1 Introduction

The history of Tuberculosis is full of countless human catastrophes and still today, tuberculosis (TB) is an infectious disease that claims most human lives worldwide. TB was well known in Ancient Greece and was called “phthisis”, whereas it was called “tabes” in Ancient Rome. A deadly disease, especially for young adults, with symptoms of a characteristic night sweat accompanied with continuous coughing (Barbier & Wirth, 2016). During the 18th and 19th centuries, it came to be known as “consumption” because of its ability to cause weight loss in humans (Cheon et al., 2016). During the industrialisation era, the disease was associated with concentration of labourers and poor socio-economic surroundings that ultimately favoured its spread (Barberis et al., 2017). Moreover and still true today, transmission through the easy mode of air-borne inhalation, which is considered as the common transference method, has positioned TB as one of the top ten human killer diseases (Mhimbira et al., 2019).

2.2 Mycobacterium Tuberculosis Pathogenesis

To date, *Mycobacterium tuberculosis* (M.TB) is one of the oldest and most successful infectious agents specific to humans on earth. This infectious agent is characterised by a slow growing, non-spore forming bacterium that belongs to the genus *Mycobacterium Tuberculosis* (Floyd et al., 2018). M.TB infections are difficult to clear primarily because of the infectious agent’s complex composition and unique secretion system. Also, it has multiple mechanisms of escaping host immune responses (Li et al., 2019). Furthermore, M.TB has the ability of developing the most sophisticated ways to evade distinctive and adaptive immune defences against the host immune responses (Orgeur &

Brosch, 2018). Hence, this is the most important reason why M.TB has succeeded and continues to infect a quarter of the global human population (Berube et al., 2019).

Other *M. tuberculosis* complex bacteria include *M. leprae* which causes leprosy; *M. africanum* which causes less severe forms of TB; and *M. bovis* which is another human TB bacteria contracted mainly from infected cattle (Kaufmann et al., 2014). Another type is *M. Macroti* which causes tuberculosis in small rodents, such as voles, wood mice and shrews, that in some instances can affect mammals, including humans (Orgeur & Brosch, 2018).

M.TB, classified as a highly infectious pathogen, is the most common and of interest in this study. Under optimal conditions of oxygen and nutrients at 37°C, M.TB has a mean generation time of 18 to 24 hours, which implies the organism can form visible colonies much longer than other bacteria (Friedrich et al., 2019). The growth of these colonies causes infected persons to generate and release tiny droplets containing live M.TB from the respiratory tract (Marzouk et al., 2013). When this pathogen is inhaled from the environment, it is primarily transmitted through the respiratory route of susceptible persons (Fogel, 2015). The lungs, as part of the respiratory system, are the most commonly affected organs of the body and this is referred to as pulmonary infection (Lange et al., 2014). In the lung alveoli, the M.TB grow and multiply and then may spread via the bloodstream to other organs and tissues throughout the body. When the infection spreads to other organs, it is called extra-pulmonary TB (Chatterjee & Pramanik, 2015).

However, the majority of healthy people over the age of five years who become infected with M.TB, will develop latent TB infection. Latent TB infection is when a person has the M.TB in the body but does not show any signs of illness because the M.TB agents are inactive (Bamrah et al., 2014). The likelihood of latent TB infection progressing and developing into active TB is extremely possible because the immunity starts to depreciate (Centis et al., 2017). Immune-supressed individuals, such

as children younger than five years, elderly people and people who are immune-compromised by other conditions, such as diabetes or pregnancy, are highly likely to develop TB soon after exposure (Lange et al., 2014).

2.3 Clinical symptoms of Tuberculosis

TB has had a profound impact on humans throughout history, not only on an individual and social level but also on human physiology as it presents itself with several symptoms, including chronic coughing. Coughing is a predominant symptom in pulmonary TB infection, both as a symptom and also as a means of disease transmission (Pan et al., 2015). Coughing is an early symptom of TB and physiologically serves to clear and expel infections from the respiratory system to protect the respiratory tract (Turner, 2019). However, coughing is also a means of transport as it has the ability to carry and expel tiny droplets from the respiratory tract, which contain live M.TB, to other systems of the body, such as the lymphatic and nervous systems (Caulfield & Wengenack, 2016). Furthermore, other symptoms, such as a loss of appetite, shortness of breath, chest pain and lung alleviation, occur as a result of prolonged coughing in TB patients (Turner et al., 2017). Coughing also has the ability to facilitate the successful aerial transmission of M.TB droplets into the environment and, if such tiny droplets are inhaled deep into the lungs, they are able to infect a new host (Butov et al., 2016). Other respiratory symptoms that accompany coughing are fever, night sweat, pleuritic pain, general discomfort and exudative pleural effusion with lymphocytic predominance (Raj et al., 2016).

However, in the clinical presentations of extra-pulmonary infection, the most common sites are the bone and joints, followed by the genital-urinary system, abdomen and lymph nodes (Farajnia et al., 2019). Prompt and accurate diagnosis of extra-pulmonary TB is important but adequate diagnosis is often delayed because symptoms vary depending on the affected sites (Whitehorn & Ayles, 2010). Therefore, with extra-pulmonary infection, patients may have few or almost none of the common

known signs and symptoms of coughing, fever, night sweats, weight loss, anorexia or fatigue (Whitehorn & Ayles, 2010).

2.4 Diagnosis and treatment of Tuberculosis patients

There is a wide range of diagnostic applications in TB detection in a suspected person, which involves clinical presentation as well as laboratory tests. The majority of TB cases are pulmonary, which is considered a respiratory infection. Therefore, most TB cases are diagnosed through a smear of M.TB from sputum samples and smear of acid-fast bacilli (Tamez-Torres et al., 2018). The tuberculin skin test (TST) is one of the diagnostic methods used. This is only considered to be suitable for children who have not been given the Bacillus Calmette-Guérin (BCG) vaccine before, who are continually exposed to TB infected patients, and who cannot be separated from infected adults (CDC, 2011). Culture examination of urine samples can improve the detection rate of M.TB in pulmonary infections among suspected HIV-positive patients, as it was reported that M.TB can be cultured in urine of HIV-positive patients (Chemeda et al., 2019). Therefore, early detection and prompt diagnosis is important in TB control, especially in the highly affected regions, such as developing countries.

However, the definitive diagnostic methods, including the culture of M.TB bacteria from sputum samples and smear of acid-fast bacilli, demonstrate some limitations in identifying all TB cases (Centis et al., 2017). Other adjunctive diagnostic methods, such as radiography and nucleic acid amplification tests, also exhibit poor performances in the diagnosis of active TB (Schito et al., 2017). Xpert M.TB/RIF (Cepheid) is another advanced rapid laboratory application direct molecular test in the diagnosis of pulmonary TB and the detection of Rifampicin resistance among TB patients (Parcell et al., 2017). Moreover, the non-specific clinical presentations of extra-pulmonary TB and its pauci-bacillary load in poorly accessible sites of affected organs results in a lower chance of establishing a definitive diagnosis (Heller et al., 2018). As it is less common and less familiar to most

physicians to establish appropriate confirmatory evidence, invasive procedures are therefore needed to assist in the confirmation of extra-pulmonary TB. As physicians often confirm extra-pulmonary infection on clinical suspicion alone, this has resulted in a number of TB suspects being on the wrong treatment (Heller et al., 2018).

In most nations, the treatment of active TB depends on the following drugs; Isoniazid; Rifampicin; Pyrazinamide and Ethambutol (McBryde et al., 2017). However, these drugs have been exposed to a challenge from resistant M.TB. In 2015, there were 10.4 million new cases of TB, 490,000 of them were multidrug-resistant TB (MDR-TB). The WHO further estimated that there were also 8,000 extensively drug-resistant TB (XDR-TB) cases worldwide (Faksri et al., 2019). Globally in 2016, there was an estimated increase of 600,000 new cases with resistance to MDR-TB, especially to the most powerful first-line drug for TB treatment, Rifampicin (Floyd et al., 2018). In 2017, the WHO reported a slight drop from 600,000 new cases to an estimated 558,000 cases that were resistant to the Rifampicin TB drug (Honeyborne et al., 2019). In the same year, WHO further reported that 3.5% of the new TB cases and 18% of the retreated TB cases were resistant to the first-line multidrug (WHO, 2018). The findings in the WHO report indicated that the development of MDR-TB occurs as a result of the mismanagement of patients and inadequate administration of anti-microbial therapy, which contributes to the drug-resistant TB (DR-TB) (WHO, 2018).

Two modes exist by which patients' contract DR-TB. Primary resistance results from infection with a drug-resistant strain, whereas resistance that develops during the period of therapy administration is referred to as secondary or acquired resistance (Juarez-Eusebio et al., 2017). The increase of resistance might occur when additional drugs are administered during the course of treatment, often in association with inadequate therapy (Chia & Crum-Cianflone, 2018). The most common resistance experienced among TB patients is MDR-TB. MDR-TB is a form of drug-resistant TB in which M.TB can no longer be killed by the two best antibiotics most commonly used to cure TB, i.e.

Isoniazid and Rifampicin (Mulisa et al., 2015). These two drugs are classified as the most powerful first-line drugs used for TB treatment (Ferlazzo et al., 2018). The treatment of MDR-TB is expensive as it is prolonged for almost 18 to 24 months and this is associated with a higher incidence of adverse reactions among TB patients due to the extended process of administration of cure (Lemos & Matos, 2013). The treatment is also complex because it involves a TB clinical history and the administration of at least five drugs, three of which should not have been used previously as well as the use of a Fluoroquinolone and the use of an injectable anti-TB drug (Lange et al., 2014). The standardised drugs used for the management of MDR-TB, as approved by WHO, are Terizidone, Levofloxacin, Pyrazinamide, Ethambutol and Streptomycin or Amikacin (McBryde et al., 2017).

MDR-TB development is often associated with patients who default in their TB treatment. Some reports suggested that running out of stock of the first-line drugs, especially in poor under developing nations, is the main reason driving MDR-TB (Abubakar et al., 2019). In addition, extremely poor prognosis of TB patients, low adherence to TB treatment and inadequacy of a drug regimen are also persuading causes of MDR-TB (Fonseca et al., 2015). Furthermore, HIV infection has also been implicated among the causes of MDR-TB and indicated as the strongest predictor of death among MDR-TB patients (Rendon et al., 2018). The impact of MDR-TB is predominately in low-income countries, such as the sub-Saharan African region, rather than in the high income countries, such as the United Kingdom (Vella et al., 2018).

Low-income countries experience a shortage of health resources, finances and skilled personnel required for the diagnosis and management of TB. This causes additional challenges, which complicates the containment and control of TB (Mulisa et al., 2015). Further, MDR-TB requires prolonged therapy with a combination of second-line anti-TB drugs, many of which are less effective, more toxic and more expensive than first-line drugs (Brynildsrud et al., 2018). It was found that poor quality directly observed treatment (DOT) has resulted in poor adherence, thus causing previously

treated cases to develop a resistance to TB drugs (Mugomeri et al, 2018). Moreover, South Africa, a neighbour of Lesotho, was ranked as a high burden MDR-TB country with an estimated 13,000 cases being diagnosed with MDR-TB in 2008 (Streicher et al., 2012). According to the World Bank global report of 2018, the prevalence of TB and HIV/AIDS among migrant mineworkers and ex-mineworkers across neighbouring nations, including Lesotho, has hugely contributed to the spread of MDR-TB. The report further said that the South African mining sector reported about 2,500 to 3,000 cases of MDR-TB per 100,000 workers (The World Bank, 2019). In Lesotho, people living with HIV are particularly susceptible to TB infection and are often exposed to DR-TB while seeking care at hospitals and outpatient clinics (Kose et al., 2015).

On top of all these challenges, there is also a more ominous strain of TB, which is highly drug-resistant. This strain is known as extensively drug-resistant tuberculosis (XDR-TB). XDR-TB is described when M.TB is resistant to Isoniazid, Rifampicin, Fluoroquinolone and at least one of the three injectable second-line anti-TB drugs, namely Capreomycin, Kanamycin or Amikacin (Maitra et al., 2015). The primary index cases of XDR-TB were detected in two Italian women who died after 422 and 625 days spent in hospital and 94 and 60 months of treatment, respectively (Dheda et al., 2014). In South Africa, an index case of XDR-TB was described for the first time in KwaZulu-Natal in a population of HIV/AIDS patients, where the mean survival time between diagnosis by sputum smear microscopy and death was 16 days (Lemos & Matos, 2013). Historically, this strain that is responsible for the spread of XDR-TB, was dispersed by Europeans to South Africa about 130 years ago (Brynildsrud et al., 2018). Furthermore, in poor nations with poor healthcare infrastructures and limited resources, this strain can be difficult to detect and managed, which adds an additional challenge.

In addition to new TB patients being infected specifically by the XDR-TB strain, there are also reports indicating that the majority of MDR-TB patients progress to XDR-TB (Mellado Peña et al.,

2017). This progression is often linked to the delaying of a specific treatment regime and also less knowledgeable and skilled healthcare providers not able to confirm the diagnosis of MDR-TB in time (Sharma et al., 2018). Furthermore, the Linezolid drug was found effective at achieving culture conversion in the treatment of XDR-TB patients, however, 82% of patients treated with Linezolid developed significant adverse side effects, namely peripheral neuropathy and myelo-suppression (Akkerman et al., 2019). Moreover, the other two drugs, Pretomanid and Tedizolid, while commercially available for the treatment of XDR-TB are not licensed for commercial use because they are currently still being used in pilot studies. However, it is anticipated that they will bring new hope for the control and management of MDR/XDR-TB (Tiberi et al., 2019).

Another devastating strain of multidrug-resistant TB is called totally drug-resistant Tuberculosis (TDR-TB), which is resistant to all first-line and second-line drugs and is untreatable. Often people infected by this strain end up dying, thus complicating TB management further (McBryde et al., 2017). The TDR-TB was noted in China, India, Africa and Eastern Europe (Hoagland et al., 2016). TDR-TB has also been discovered in Iran and South Africa (Streicher et al., 2012). The major reason for the development of TDR-TB is the fact that M.TB is capable of exploiting different enzymatic strategies to change the arrangement of drug synthesis intended to treat XDR-TB patients (Demile et al., 2018). Moreover, there are also new reports that mentioned that the M. TB has the ability to directly modify the anti-TB drugs into another form. This ability leads to the inactivation of the target drug compound action normally used for the explicit function of treating M.TB (Akkerman et al., 2019). Additionally, in many countries, there is an accumulated number of patients who receive a delayed specific treatment regime due to a lack of experts to diagnose XDR-TB (Juarez-Eusebio et al., 2017). Finally, when treatment can be initiated for these patients, the treatment regimen is toxic, slower to reduce the bacterial burden and less successful, which often leads to treatment failures and withdrawals, thus giving further opportunity for TDR-TB to develop and these patients never being cured and eventually dying (McBryde et al., 2017).

2.5 Prevalence of Tuberculosis

Tuberculosis is one of the oldest diseases affecting humans and yet it remains the number one killer disease worldwide, despite centuries of advanced health care. TB has caused millions of deaths worldwide (Tornheim & Dooley, 2019). In a study conducted in 2015, it was found that approximately one-third of the world's population was infected with M.TB (Dodd et al., 2017). In 2016, WHO estimated that there were 10.4 million new cases of TB with 1.3 million deaths of non-HIV infected people being recorded (Hanna et al., 2017). Thus was substantially greater than 2014 where there was an estimated 9.6 million new TB infections and it was reported that 1.5 million deaths were caused by TB (Chetty et al., 2017). Amongst the estimated 1.5 million TB deaths recorded in 2014, 90% of these deaths originated from the sub-Saharan African region (Brynildsrud et al., 2018). Nevertheless, in 2017 there were 10.0 million people who were infected with M.TB and among these 5.8 million were men, 3.2 million were women and 1.0 million were children (WHO, 2018).

Therefore, the latest report results indicate that there was a decrease in new infections of TB because of improved disease prevention and management of TB and co-infections in most high burden countries (WHO, 2018). These 10.0 million TB infections in 2017 were recorded from all the regions of the world. However, two-thirds were in eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa (WHO, 2018). Apart from these eight countries, Lesotho was number 22 on the WHO's list of the 30 high TB burden countries in the world (WHO, 2018). The prevalence of TB in South-East Asia was estimated to be 244 per 100,000 of the population while, in Africa alone, it was estimated that about 300 per 100,000 of the population is suffering from TB (Nagu et al., 2017). For this increase in infections, Africa was identified to have the highest global TB burden (Tiberi et al., 2017).

Lesotho is experiencing extraordinary challenges due to its high TB burden. TB is a major cause of illness and death in this small African country (Mugomeri et al., 2018). With a population of 2.29

million people, Lesotho has the world's second highest TB incidence with an estimated 788 per 100,000 people suffering from TB in 2014 (Hayes-Larson et al., 2017). In 2017, the WHO reported a substantial increase in the number of TB infections in Lesotho with 2,000 per 100,000 (WHO, 2018). Therefore, appropriate prevention and control efforts are needed to fight the TB disease.

2.6 Relationship between TB and HIV epidemics

The human immunodeficiency virus (HIV) is the epidemic that assists in creating a large pool of persons at high risk of developing TB. This increases the number of people who will ultimately develop and transmit TB to other HIV infected and HIV uninfected persons. HIV, as a ribonucleic acid (RNA) retrovirus, targets host immune defences by infecting and eventually destroying the person's immune response (Chandra et al., 2013). Furthermore, TB/HIV have a synergistic relationship. This relationship works where TB causes cell activation and excessive cytokine and chemokine production in the infected person (Lee et al., 2019). This later helps HIV production and speeds up the progression to acquired immune deficiency syndrome (AIDS) (Pinto & Carvalho, 2017). It does this by attacking the immune system of the infected person and thus, severely weakens the immune system (Marais et al., 2011). This weakened immune system is then also favourable for TB as the infected person is highly vulnerable to opportunistic M.TB infection (GBC, 2018).

This said, HIV infection itself does not kill the infected person. People die from the development of AIDS that is helped by opportunistic infections and other health conditions, which are aggravated by the weakened immune system of the infected person (Sah et al., 2016). Moreover, it is estimated that people living with TB are 26 to 31 times more likely to be co-infected with HIV, mainly within the South African region where co-infection rates are predominately high (Chanda-Kapata et al., 2017). Therefore, the risk of TB doubles and progressively increases with advancing immunodeficiency (Mahtab & Coetzee, 2017). TB has always been there, occurring in a sporadic or in cluster form and

killing a minority of the world population in smaller clusters (Locatelli et al., 2016; Ramírez et al., 2018). But after 1981, with the emergence of HIV, TB cases started to increase at an alarming rate (Wingfield et al., 2018). The two epidemics depleted many human lives because of new infections as well as deaths caused by the development of AIDS (Sabbagh et al., 2019).

TB in patients with HIV infection can be presented in many forms; one of these forms can be anaemic condition. This condition is an independent predictor of early incidences of TB among HIV infected patients, mostly in sub-Saharan Africa (Mntonintshi et al., 2017). Furthermore, anaemia is one of the most common blood vessel conditions, often diagnosed among patients with TB (Barzegari et al., 2019). The results from a recent study indicated that more than 43% of the TB co-infected patients suffered from moderate to severe anaemia and about half of them had chronic anaemia disease (Barzegari et al., 2019). Another condition associated with TB/HIV is pleural effusion, which is a manifestation of excess fluid between the layers outside the lungs and inside the chest cavity, making the isolation of M.TB more difficult than in other human organs (Michot et al., 2016). This condition often occurs in extra-pulmonary TB patients as a result of the migration of infection to other organs, such as the lymph nodes and the brain (Krauss et al., 2015).

2.7 Prevalence of TB patients co-infected with HIV/AIDS

TB remains one of the major causes of death for millions of people living with HIV/AIDS. In 2016, there was an estimated 10.6 million new TB patients of which 4.2 million were HIV-positive people and who also died from TB (Adhikari et al., 2018). However in 2017, TB caused an estimated 1.3 million deaths among HIV-negative people with an additional 300,000 deaths among TB/HIV-positive people (WHO, 2018). TB and HIV are found to be common among pregnant mothers and it is estimated that among 300,000 pregnant women are infected with TB/HIV. If left untreated, it can increase the chance of premature death by up to 40% (Suresh et al., 2016).

The number of TB/HIV infections and deaths of patients has increased in the African region. The African region bears the highest global TB/HIV disease burden with over 50% of TB patients being co-infected. Globally in 2014, an estimated 1.2 million of the 9.6 million new cases were HIV-positive. Among these 1.2 million HIV co-infected cases, 74% were recorded from patients living in the sub-Saharan Africa region (Ntoumi et al., 2016). While in 2015, there were 10.4 million cases of TB recorded all over the world, with the Africa region carrying the highest global TB/HIV burden (Rendon et al., 2018). There were 1.4 million new cases of TB reported among HIV-positive patients and approximately 1.3 million TB deaths recorded among HIV-negative people as well as an additional 374,000 deaths recorded among HIV-positive people (Fiore-Gartland et al., 2018).

In Lesotho, TB is often associated with the HIV/AIDS pandemic. The country has the highest TB co-infected HIV rate that is estimated to be 238 per 100,000 of the population, followed by Mozambique with 114 per 100,000, Zambia 74 per 100,000 and Namibia at 35 per 100,000 (Musuka et al., 2018). In 2015, approximately 270,000 of the people in Lesotho were diagnosed as HIV-positive and out of this number, 11,801 were infected children and the remaining 258,472 were infected adults (WHO, 2016). Furthermore in this country, HIV/AIDS alone is also a major health concern with HIV co-infection estimated to occur among 62 people and 50 associated deaths believed to be caused by AIDS each day (Malangu & Adebanjo, 2015). In 2017, WHO classified Lesotho as one of the top 22 countries globally carrying a huge burden of TB and TB/HIV infection (WHO, 2018). The WHO report further indicated that the incidence of TB/HIV patients was 788 patients per 100,000 of the population in Lesotho (Luba et al., 2019).

2.8 Risk factors associated with Tuberculosis

One of the targets of the Sustainable Development Goals (SDGs) for the period 2015 to 2030 is to end the global TB epidemic by emphasising the need for prevention across all sectors with the approach being infection prevention and control (IPC) in healthcare services and other places where

the risk of *Mycobacterium Tuberculosis* transmission may be high. There are a number of risk factors associated with the transmission and spread of M.TB (Cui et al., 2017). The spread of M.TB is dependent on the socio-economic status of the area or a country (Carter et al., 2018). This means that the poorer the country, the higher the instances of TB possibilities (Granich & Gupta, 2018). Unfortunately, this is the case in most countries on the African continent (Parsons et al., 2011).

In most African communities, living arrangements are less than adequate with poor ventilation in households that adds additional challenges (Magadi, 2011). A South African study conducted to determine the link between TB transmission and ventilation in traditional homes, indicated that natural ventilation contributed to TB prevention (Lygizos et al., 2013). Environmental factors, such as working in silica industries, poor infection control and overcrowding, increases the risk of transmitting TB (Berube et al., 2019). Exposure to inhalable silica, dust or cigarette smoke also increases the chances of developing active TB (Adhikari et al., 2018). This was confirmed in a previous study, which estimated that the global prevalence of infection among prisoners living in overcrowded conditions was only 2.8% for active TB (Adhikari et al., 2018).

Other risk factors in the spread of TB include migrants from high TB endemic countries and homeless populations. More than 50% of TB cases in low incidence countries occur amongst people born outside of those countries and in some cases, this figure increases to 90% (Craig et al., 2017). They also comprise 38% of non-treatment adherent cases, 44% of cases lost to follow-up and 30% of cases deemed as highly infectious to transmit TB (Craig & Zumla, 2015). The economy of neighbouring countries, including Lesotho, is dependent mostly on migrant labourers and domestic servants working in neighbouring South Africa, which has a population highly infected with TB (Harries et al., 2010). South Africa completely surrounds Lesotho and ranks among the top ten countries in the world with a high burden of TB disease (WHO, 2018). This completely exposes the

poor countries, like Lesotho as well as Botswana, Swaziland and even Namibia, further to TB infection through migrants (Kwok et al., 2015).

Furthermore, prevalence of TB and HIV/AIDS among migrant mineworkers and ex-mineworkers across national borders has ultimately resulted in a larger disease burden, and the loss of being able to follow-up on patients who migrate across the health systems further contributes to the spread of TB (The World Bank, 2019). A cross-border response to TB involves a number of policies and service delivery considerations and the success of these efforts largely depend on improved combination strategy among the border nations (Osewe & Nkrumah, 2018). From 2003 to 2011, the South African TB patients default rates had increased from 6% to 11%, which was above the South African national target of maintaining less than 5% each year. Failure of the treatment success was mainly because of the weak follow-up possibilities and poor delivery of health management systems at grassroots level (Kigozi et al., 2017).

The relationship between unemployment, stigma, risk factors and disease is well known. Direct correlation between these factors cause young people in custodial centres to be distinguished by a high prevalence of complex health-related needs (Verma et al., 2019). Additional challenges present are substance use and risky sexual behaviour (Craig et al., 2017). Consequently, the combination of complex health-related needs and additional challenges is the result of low education, unemployment, poverty and stigma, which exposes the young people to a higher increased chance of developing active TB (Kinner et al., 2018).

In sub-Saharan Africa, stigma and adverse perceptions about the link between TB and HIV, at both community and individual levels, have delayed diagnosis, poor treatment outcomes and increased transmission of TB infection (Musasa, 2011). Stigma and discrimination in some communities has contributed to women contracting the TB infection and this skewed perception about TB infections

often causes these women to be outcast by their families and communities (Barnabishvili et al., 2016). Cultural and financial barriers can act as major obstacles for women seeking health care and this results in delayed diagnoses that causes them to end up with more severe illnesses. TB mainly affects women when they are economically and reproductively active, thus the impact of the disease also has a detrimental effect on their children and families (WHO, 2018).

In Lesotho, it has also been reported with extensive evidence that TB/HIV patients with mental health conditions have poor treatment outcomes and thus they continue to spread TB/HIV even further to their close contacts (Hayes-Larson et al., 2017). The ripple effect of these circumstances among women within families and communities indicates a serious need for further investigation and intervention.

Living and working in overcrowded conditions has fuelled the spread of TB. However, with the help of good urban planning, environmental protection and a strong, well-co-ordinated urban health system, the TB epidemic can be managed. Lesotho has developed its own TB infection control (IC) guidelines (Hirsch-Moverman et al., 2017). These guidelines aid healthcare providers in reducing the spread of TB. But a lack of equipment, knowledge and work overload remain major constraints to TB infection control in Lesotho (Mugomeri et al., 2015). Development and implementation of IC guidelines in resource-limited centres should be a priority in the high TB/HIV prevalence areas as these preventative measures can reduce multiple infections caused by M.TB droplets (Mugomeri et al., 2017). In 2019, the WHO introduced new infection and prevention guidelines to bridge the gap in previous guidelines so the current challenges can be address accordingly (WHO, 2019).

2.9 Prevalence of Tuberculosis among gender and age groups

In 2014, Tuberculosis prevalence was significantly higher among males compared with females in low- and middle-income countries (Shimeles et al., 2019). There is strong evidence that males are

more reluctant in seeking and/or accessing TB care in many health care centres (Shimeles et al., 2019). Over the past 20 years, TB case notifications among males have exceeded those among females in most of the health care centres (Horton et al., 2016). There was also a confirmatory report from an earlier study conducted at a Hospital DOTS clinic between September 2009 and August 2012. Among a total of 2,096 patients, 1,246 patients (59.4%) were male and 850 (40.6%) were female with the most participated age group being between 25 to 34 years. Of these females, 471 (22.5%) were positive with pulmonary TB and 299 (14.3%) with extra-pulmonary TB (Tarekegne et al., 2016). The study further indicated that 89.5% (1,876) of all the patients were new TB cases, while 5.6% (118) and 4.9% (102) were retreatment and transferred TB cases, respectively (Tarekegne et al., 2016).

In an earlier eastern India study, out of 406 participating TB patients, the most affected gender was male with 267 while 139 were female. Furthermore, the affected age group interval was the adult group of 31 to 45 years (Manjareeka & Nanda, 2013). In a similar study conducted in Nepal, among the total 995 TB patients tested for HIV, 716 were males of which 2.8% were HIV-positive and 279 female of which 1.4% were HIV-positive (Sah et al., 2016). In this Nepal study, the most significant proportion of their TB study population was HIV affected and also among the more mature adults of 35 to 39 years of age. However, one conflicting report came from a retrospective cohort study conducted in Cameroon where the results indicated significantly more HIV-positive TB female patients. A possible reason behind this was that significantly more of the male TB patients, that is one out of eight, failed to undergo HIV testing and ultimately were infecting their partners (Yone et al., 2012).

The WHO Tuberculosis Report of 2014 stated that in 2013 there were an estimated 3.3 million TB cases and 510,000 deaths among females worldwide as well as a third co-infected with HIV (Bates et al., 2015). While in an audit of maternal mortality in Johannesburg in South Africa, the study

revealed that 70% of the deaths in females infected with HIV were HIV-related rather than maternal causes and these deaths were caused mainly due to TB (Suresh et al., 2016). In a study conducted in Lesotho, it was revealed that among 371 participants, 56% were TB co-infected with HIV/AIDS male patients aged between 30 and 44 years (Hayes-Larson et al., 2017). These alarmingly high mortality rates among female TB patients and male TB patients failing to undergo HIV testing should be investigated in much more detail. The true causes behind losing so many male and female TB patients in the sub-Saharan African countries may be due to other causes not initially identified.

In a study investigating HIV associated TB deaths at the Matema Hospital in northwest Ethiopia, the findings of the age groups indicated that the median age of the 1,246 study participants was 28 years. More than a third of the patients (633) were in the age group of >25 to 34 years (Tarekegne et al., 2016). Similarly, a cross-sectional retrospective record review in a high-burdened province of South Africa between 2009 to 2012 revealed that of the total 66,940 new TB cases among patients categorised into the age group interval of 15 years and above, almost less than two-thirds of those patients were co-infected with HIV (Engelbrecht et al., 2017). In the study conducted at the Central Hospital of South Eastern India, of the 406 TB patients included in this study, the most commonly affected age group was 31 to 45 years (Manjareeka & Nanda, 2013). In the same year, it was estimated that at least two-thirds of all age group cases in sub-Saharan Africa go undiagnosed or unreported.

Often extra-pulmonary paediatric TB is especially difficult to diagnose with standard sputum-based tests (Kendall, 2017). The WHO estimated that one million children contracted TB in 2015 resulting in 210,000 deaths (Marais, 2017). Reports indicated that at least 5,000 children were likely to have died from MDR-TB and around 40,000 were co-infected with HIV (Marais, 2017). TB among the young age group interval was estimated at 1 million, which represented 10% of the global TB burden (Caminero & Scardigli, 2016). Some of the cases go undiagnosed or unreported in TB programmes

because of difficulties examining children with TB (Caulfield & Wengenack, 2016). These findings are reason for concern and are indicative of the need for further investigation and intervention.

2.10 Major challenges facing prevention and treatment of TB

The WHO End TB Strategy sets ambitious goals for the post 2015 agenda. One goal is to ensure that no TB affected household experiences catastrophic costs due to TB by 2030. The increasing numbers of TB cases in developing countries is one of the main concerns of this goal (Padayatchi et al., 2017). This unique strategy goal is faced with numerous challenges, especially because the true burden of TB remains difficult to quantify and is dreadful (Schito et al., 2017). The burden of TB disease accounts for more than 10 million new cases per year of which less than two-thirds were reported cases (Granich & Gupta, 2018). Unreported cases of nearly 3 million TB patients were considered to be unaccounted for in 2009; they were either not diagnosed or not reported to TB control programmes (Pai & Temesgen, 2017). Furthermore, from the period 2009 to 2015, the number of undiagnosed TB cases was reported to have increased to 4.3 million, a difference of 1.3 million from 2009 to 2015 (Kendall, 2017). This figure was expected to increase further to 4.8 million in 2016. Sadly, nations have neglected TB for far too long (Tanday, 2017) although the global number of TB deaths decreased by 42% between 2000 and 2017 and the annual decline in the worldwide new TB infections was reported to be only 1.5% (WHO, 2018).

Furthermore, TB in the young age group of less than five years is a hidden epidemic, particularly because a large proportion of these cases remain undetected or not reported. It was stated that what is seen about TB is only the tip of the iceberg (Uplekar et al., 2015) because often when children are diagnosed with TB, treatment outcomes are poor (Dodd et al., 2014). Most children dying from TB are often misdiagnosed or incorrectly classified as having pneumonia, meningitis, some drug-resistant disease, HIV/AIDS or malnutrition (Marais, 2017).

In addition, HIV-positive patients are often associated with a high rate of extra-pulmonary TB, which offers daunting diagnostic challenges on its own (Chanda-Kapata et al., 2017). Gaps in the understanding of the pathophysiologic networks between the human body and M.TB are one of the reasons for the low effectiveness of treatment (Butov et al., 2016). Consequently, combined therapeutic approaches are required to obstruct M.TB and block systemic infection migrating to other body tissues (Butov et al., 2016). To address these challenges and misdiagnoses, it is important to strengthen all the links right through from diagnosis to successful treatment completion (Mwangwa et al., 2017).

The only preventative vaccine licensed by WHO to prevent TB of all types is not effectively adequate. Therefore, TB continues to be a global epidemic despite the availability of Bacillus Calmette-Guérin (BCG) vaccine for more than sixty years (Husain et al., 2016). Even to date, there is still no replacement for the BCG vaccine, which is the only TB vaccine developed and licensed for human use (Méndez-Samperio, 2019). BCG vaccine was developed as early as 1921 and remains the only WHO-prequalified vaccine to prevent TB. Thus, the discovery and development of new TB vaccines currently remains a priority (Vekemans et al., 2019). The BCG, which is extensively used as part of the Expanded Program on Immunisation globally, prevents against only severe forms of childhood TB (Darrah et al., 2019). BCG vaccine is given by intradermal administration at birth and is effective at protecting infants from the systemic appearances of TB (Darrah et al., 2019). However, the current vaccine does not protect against the most prevalent form of this disease, namely pulmonary TB, in all age groups (Gröschel et al., 2014). Thus, an improved vaccine against TB is desperately needed (Zumla et al., 2015).

The current goal of the End TB Strategy will be difficult to achieve unless the scientific community pools its resources in all areas to develop an alternative protective vaccine (Sathkumara et al., 2019). In an effort to eradicate TB, vaccinologists around the world have made substantial efforts to

develop improved vaccine candidates. These efforts are based on the understanding of BCG developing a favourable immune response reaction against TB (Husain et al., 2016). The current vaccine that gives protection against pulmonary TB is incomplete, variable and not durable (Centis et al., 2017). Moreover, there are a number of critical barriers retarding the development of new TB vaccines (Graham et al., 2015). These barriers include TB vaccine administered intradermal but these have resulted in low vaccine protection efficacy (Petersen et al., 2017). Furthermore, the best route of delivery of the TB vaccine still needs to be debated (Da Costa et al., 2015).

Elimination of TB is not an easy goal. A realistic approach to TB elimination has to rely on the development of innovative diagnoses, treatment and preventive tools. However, one more emphasis is that it will be impossible without a strong political commitment towards TB elimination around the world (Carvalho et al., 2018). At present, the development of new drugs for the treatment of TB does not keep pace with the development of M.TB drug-resistance (Honeyborne et al., 2019). Evidently, innovative interventions are needed to combat the emerging pandemics of MDR-TB and XDR-TB (Tiberi et al., 2019).

In Africa, where limited resources exist, it is largely under reported as many of the MDR-TB patients are remaining undiagnosed due to the low socio-economic status of the population, lack of awareness and inaccessibility to health services (Castro et al., 2019). In some sub-Saharan regions, more than half of the patients prefer to seek private medical care. However, the private sector has often failed to provide high-quality TB case detection, which is the case with National Tuberculosis Programmes (NTPs) that are well positioned to deliver such care services (Lei et al., 2015). Available data show that in the Republic of Congo, the HIV prevalence rate was 3.5% nationally but peaked at 5% in urban areas. However, HIV testing was not systematically performed among TB patients and the actual prevalence of TB/HIV co-infection remains unknown (Linguissi et al., 2017).

WHO estimated that there were among one million incident cases of children affected by TB and at least 210,000 TB deaths recorded among these children in 2015 (WHO, 2016). Despite the high burden of TB in children, it was estimated that at least two-thirds of cases in sub-Saharan Africa go undiagnosed or unreported (Mwangwa et al., 2017). Investigation of children suspected of having TB is difficult (Caminero & Scardigli, 2016). In clinical practice, the diagnosis requires a systematic approach that is comprised of obtaining clinical history, detailed physical examination and identification of the pathogen (Carvalho et al., 2018). The disease has variable clinical presentations and symptoms are often non-specific (Duarte et al., 2018). For most children, TB cannot be confirmed bacteriologically because sputum specimens are usually not accessible, thus making bacteriologic confirmation difficult. Therefore, the diagnosis is often presumed rather than confirmed (Duarte et al., 2018).

An HIV-positive patient, who may be infected with M. TB, also presents challenges for proper TB detection. Clinical evidence has shown that the likelihood of misdiagnosing M.TB is higher in patients infected with HIV (Parcell et al., 2017). The diagnostic difficulty arises from non-specific symptoms, absence of typical radiological presentations and sputum smears that are negative for acid fast bacilli (Parcell et al., 2017). The diagnosis of TB is further complicated in HIV infected children who have advanced immune-suppression because of the presence of pneumonia, disseminated bacterial, fungal and viral infections or other mycobacterial agents, which often inhibit TB bacilli disease (Krauss et al., 2015). Furthermore, in HIV-positive patients who present signs and symptoms of active TB, such as chronic cough, fever, night sweats and weight loss over extended periods, the normal chest radiographs are often non-indicative to the effects of TB bacilli (Tamez-Torres et al., 2018). These challenges are associated because of the viral load suppression of the bacilli in the body of patients affected with HIV/AIDS (Mwangwa et al., 2017).

Treatment of TB in children is challenging, particularly due to the lack of paediatric formulations, drug toxicity and difficult adherence to current treatment strategies (Carvalho et al., 2018). There are also interactions between some anti-TB drugs and anti-retroviral therapy (ART) for people living with HIV (Lienhardt et al., 2016). New drugs are required to shorten treatment duration, affordability, efficacy and tolerability of treatment for MDR-TB. The two drugs, Bedaquiline and Delamanid, recently received conditional regulatory approval to treat MDR-TB (Lessem et al., 2015). However, the two drugs still face financial and scientific access challenges from the perspective of patients, providers and programmes in poor countries (Lessem et al., 2015).

The importance of aligning and integrating TB and HIV treatment services is vital and should include follow-up and adherence to support services through co-ordinated and collaborative efforts between individual TB and HIV programmes (Hirsch-Moverman et al., 2017). Also, it is important that co-infection is addressed within the broader WHO DOTS framework (Hirsch-Moverman et al., 2017). If a HIV-positive person has a latent TB infection (LTBI), the WHO recommends the provision of Isoniazid preventive therapy (IPT), which prevents the progression to active TB and thus, has no interactions with anti-retroviral medication (Linguissi et al., 2017).

In Lesotho, TB is associated with HIV/AIDS co-infection, social problems, difficulties in patient treatment adherence and the threat of resistance against anti-TB drugs (Lessells et al., 2015). Lesotho, with a population of 2.29 million, has the world's second highest TB incidence. In 2015, this was estimated at 788 per 100,000 with approximately 72% of patients with TB also co-infected with HIV (Hayes-Larson et al., 2017). Other problems manifest and complicate matters, including the social movement interaction between Lesotho and the South African Province of the Free State, which had an estimated 709 per 100,000 TB incidence cases in 2012 (Heunis et al., 2017). The Mountain Kingdom has the highest adult HIV prevalence in the world at a staggering 23% (Howard et al., 2016). There are an estimated 52 new HIV infections and 26 deaths because of AIDS each

day. Mafeteng district, in particular, was among five districts that account for 75% of all the people living with HIV/AIDS in Lesotho in 2013 (MOH, 2017).

The Government of Lesotho has made admirable strides in addressing the dual epidemics. The introduction of highly active anti-retroviral therapy (HAART) seems to be working and there is remarkable evidence of reduced morbidity and mortality among HIV infected patients (Hayes-Larson et al., 2017). At the time of a study conducted on TB and HIV patients in Lesotho in 2012, 88% of TB patients had a known HIV status and 97% of those diagnosed with HIV were placed on ART prophylaxis (Howard et al., 2016). Therefore, through the help of the Centre for Disease Control (CDC), all TB activities are integrated into all HIV clinical services funded by the CDC. Recently, CDC support for TB control efforts included an evaluation of the national TB/HIV programme, a research project involving TB services for miners and a survey on drug resistance (CDC, 2018).

The Government also developed a five-year strategic plan for DOTS and strategies to combat the spread of TB (MOH, 2016). Lesotho has adapted the WHO TB infection control guidelines. These guidelines aid healthcare providers in reducing the spread of TB. However, lack of equipment, knowledge and work overload remain major constraints in preventing or reducing TB infection in Lesotho (Howard et al., 2016).

2.11 Tuberculosis and HIV co-infection burden reduction

“We face an uphill battle to reach the global targets for tuberculosis”, concluded Margaret Chan, Director General of WHO, during the launching of her report (WHO, 2018). Recent statistics have indicated that the proportion of people with TB, who died from the disease in 2000, declined from 23% to 16% (WHO, 2018). Indicators predicted that worldwide the TB incidence rate would be able to decline at about 2 to 3% per year by 2020 (Shimeles et al., 2019). These figures need to improve to 4 to 5% and 10% per year, respectively, so that incidences can decline faster in order that the first

milestone of the 2020 End TB Strategy can be reached (Sharma, 2019). The fastest regional decline of 5% per year was observed in the WHO European Region from 2013 to 2017 and the WHO African Region was at 4% per year (WHO, 2018). In the same five year period, particularly impressive reductions of 4% to 8% per year were reported in Southern Africa among the high burden countries, such as Eswatini, Lesotho, Namibia, South Africa, Zambia and Zimbabwe (WHO, 2018).

Investment in preclinical research and development has yielded almost 20 vaccine candidates for TB prevention (Kaufmann et al., 2014). Most of these still remain at different stages of the clinical trial with a few dropouts. Moreover, several new candidates are ready to enter into the market thus bringing hope to a reduction in TB (Kaufmann et al., 2014). WHO has endorsed the use of supervised pill-taking as the standard of care to promote adherence (Craig & Zumla, 2015). The two new drugs, Bedaquiline and Delamanid, recently received conditional regulatory approval to treat MDR-TB. These drugs offer renewed hope for curing those with MDR-TB and achieving a world free of TB (Lessem et al., 2015).

HIV incidence has dropped from a peak of 3.5 million in 1996 to 2.1 million new infections in 2015 (Mahtab & Coetzee, 2017). After years of denial most nations now own responsibility for the HIV epidemic due to a change in political will and pressure from civil society and this has resulted in the largest worldwide ART roll-out programme with over 3.5 million individuals on ART (Daftary & Padayatchi, 2016). Today, the global response to HIV has reached a defining moment by uniting efforts, promptly integrating major scientific findings for both treatment and prevention and scaling up services (Daftary & Padayatchi, 2016). Collaboration between TB and HIV programmes at national level in some African countries, such as Malawi, Kenya, South Africa, Lesotho, Cameroon and Ethiopia, was taken forward to varying degrees of success in the control of TB and HIV/AIDS (Linguissi et al., 2017). For the majority of sub-Saharan African countries, strict adherence to WHO

guidelines for collaborative TB/HIV activities will maintain the hope of TB reduction, which is the aim of the End TB Strategy (Linguissi et al., 2017).

2.12 Conclusion

The WHO End TB Strategy, endorsed by the World Health Assembly in May 2014, has the ambitious goal of ending the global TB epidemic by 2035 (Mellado Peña et al., 2017). It has targets of a 95% decline in deaths due to TB when compared with 2015 figures; a 90% reduction in incidences of TB to ten cases per 100,000 or less; and no TB-affected household experiencing catastrophic costs due to TB (Lienhardt et al., 2016). To achieve these targets, a steep acceleration of the annual decline in global TB incidence from an average of 2% per year in 2015 to 10% per year by 2025 will be required (Marx et al., 2018). Therefore, understanding transmission dynamics will contribute to the knowledge of factors that enhance the spread of TB disease, which is useful for developing preventive interventions (Asare et al., 2018). The BCG vaccine, which is extensively used as part of the Expanded Program on Immunisation, prevents against only severe forms of childhood TB and does not protect against the most prevalent form of this disease, namely pulmonary TB, in all age groups (Fiore-Gartland et al., 2018). This acceleration will only be possible through the development and rapid uptake of new tools, including an effective TB vaccine, safe and shorter treatment of latent TB infection and disease and rapid point-of-care diagnostics, combined with efficient health systems and care provision (Lienhardt et al., 2016). The four main objectives driving TB prevention activities include improving case detection and treatment adherence, combating stigma and discrimination, empowering people affected by TB and mobilising political commitment and resources.

The literature consulted showed that many studies have been conducted on the prevalence of TB co-infection with HIV/AIDS. In addition, the literature was reviewed to get more insight and understanding of the prevalence of TB patients co-infected with HIV and to identify the gaps in

current literature to support the research topic. Different sources were accessed to find the literature and the literature reviewed assisted in formulating the understanding of concepts, such as co-infection of TB and HIV and the prevalence of HIV/AIDS among TB patients. The current understanding of these concepts is highlighted in this literature review and the findings from the strengths and weaknesses of the previous studies are identified to justify the choice of the topic of this study. The studies were of a high scientific value and were drawn from a wide range of regions, such as South America, Europe, Asia and both Central and North Africa, which have social conditions, different levels of education and other cultures compared with the sub-Saharan region where Lesotho is situated. Some of the studies were excellent using Surveillance study design, such as cohort studies and cross-sectional studies. However, none of the studies reviewed or consulted were done on the prevalence of HIV/AIDS among TB patients living in the lowlands of the Mafeteng district in Lesotho, which justifies the choice of the topic of this study.

Chapter 3

Materials and Methods

3.1 Study setting

Lesotho is a mountainous country and one of the smallest inland countries in the Southern African region. It is completely landlocked within the South African borders. The total length of the country's borders is 909 kilometres. It is the 141st largest country in the world. The country has an estimated population of 2.29 million. It has an estimated gross domestic product (GDP) per capita of US$1,318 and is thus classified as a low-income country (PEPFAR Lesotho, 2017).

Lesotho is divided into ten administrative districts. Each district has its own capital, which is called a camp town. The ten districts are Berea, Butha-Bothe, Leribe, Mafeteng, Maseru Mohales'hoek, Mokhotlong, Qacha's Nek, Quthing and Thaba-Tseka. These districts are further subdivided into 80 constituencies consisting of 129 local community councils of Lesotho (PEPFAR Lesotho, 2017).

The Mafeteng district is situated alongside the Free State border. On the north-east of Mafeteng district is the capital city of Lesotho called Maseru. On the southern side is Mohales'hoek. These three districts of Mafeteng, Maseru and Mohales'hoek are the most populated and where most economic activities take place. As a result, high numbers of Tuberculosis (TB) and human immunodeficiency virus (HIV) infections have been reported in these districts (PEPFAR Lesotho, 2017). Furthermore, these three districts are alongside the border of South Africa's Free State Province and there is an interrelationship between the citizens of the Free State and the three districts, such as business connections and family members. This interrelationship keeps these citizens together and ensures that the possibility of cross border TB infections is highly possible. In 2012, the TB incidence in the Free State was reported to be 708.5 cases per 100,000 population (Engelbrecht et al., 2017).

Lesotho is among 22 global countries that carry a large burden of TB disease. The WHO reported 2,000 TB cases per 100,000 of the population (WHO, 2018). Because of this large burden of disease, Lesotho has put in place several projects to control the spread of TB and HIV infections. The healthcare system of Lesotho consists of 22 general hospitals, one TB and HIV/AIDS referral hospital located in Maseru and 192 health care centres (HCCs) distributed throughout the country (MOH, 2016). These HCCs offer management of diseases and conditions, including TB and HIV/AIDS services.

3.2 Study location

The Mafeteng district has 19 distributed health care centres (HCCs). The five participating HCCs in this study are located in the lowlands of the district with three of these located within the camp town called Mafeteng. These HCCs are Teba, Mafeteng and LeCoop and the other two, namely Samaria and Motsekuoa, are located 7 and 25 kilometres (km), respectively, from the camp town (Figure 3.1).

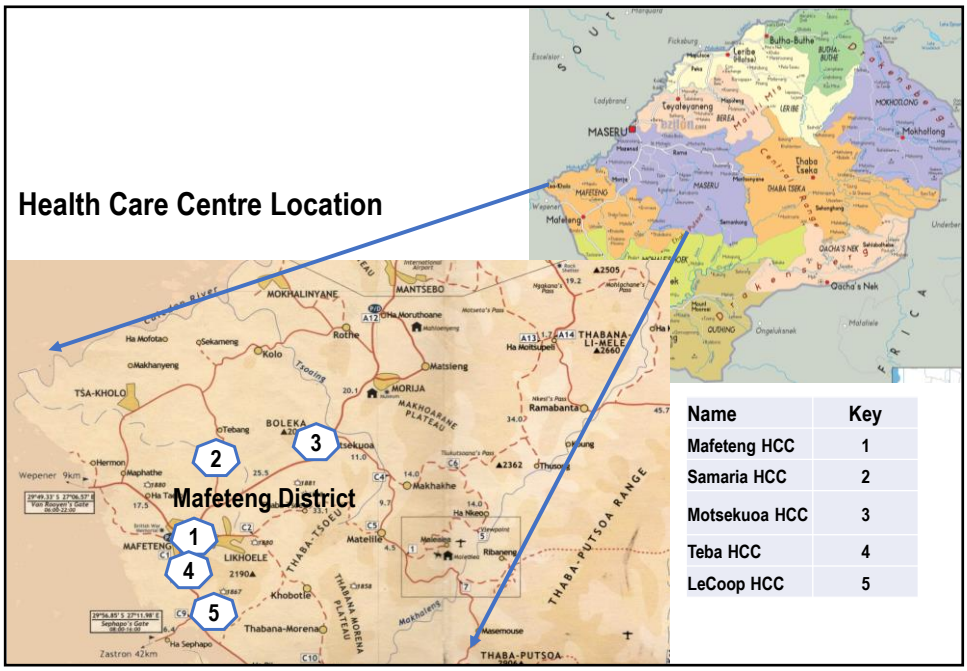


Figure 3.1 Map showing the distribution of participating health care centres in the lowlands of the Mafeteng district, Lesotho

The population size of the lowlands of the Mafeteng district is approximately 60,000 of the general population. This population is served by the five participating HCCs in the lowlands of the Mafeteng district for general healthcare services, including management of TB and HIV/AIDS (Table 3.1).

Table 3.1 Population size of the lowlands of the Mafeteng District 2017 (Adapted from BOS, 2019)

Health Care Centre	Total population	Male population	Female population	Live births populations	Surviving infants	Under-five population	Child bearing women
Mafeteng HCC	14,756	7,260	7,496	390	379	1,901	3,760
Samaria HCC	18,695	9,198	9,497	494	480	2,409	6,758
Motsekuoa HCC	9,990	4,915	5,075	264	257	1,287	2,545
Lecoop HCC	17,262	8,493	8,769	456	443	2,224	4,398
Teba HCC	Lesotho Miners working in Africa and their families. No specific data available here.						

3.3 Study design

The study followed a quantitative research approach under which a cross sectional retrospective record review of the registry books of TB patients seen between 2014 and 2016 was conducted in five participating HCCs in Mafeteng district (Whittemore & Melkus, 2018). The method was used to collect TB and HIV/AIDS data from the five participating HCCs located in the lowlands of the Mafeteng district in Lesotho. Data were collected from the five TB registry books of the participating HCCs for the years 2014 – 2016. The data was selected using non-probability or non-random sampling of readily available patients' data in the registry books (Suen et al., 2014). The study sampling size of 1,109 participants was drawn from all age groups.

Handwritten TB registries of the five participating HCCs were used for the data sourcing. These registries contained both TB and HIV/AIDS information that stretch over multiple years. It was

preferable to collect data for a three-year period so that the prevalence in the years could be analysed. The handwritten TB registries of the HCCs were used to compile electronic spreadsheets and patient data variables relevant to this study were captured. These included biographical data, such as age, gender and their geographic location. In addition, medical data from the patients' records, such as the type of TB and their HIV results, were also included.

The sample size of 1109 represents all the patients that were seen in the five participating HCCs during the period 2014 to 2016. Therefore, all the records of these patients were included in the study, and no sample size estimation was required

In Chapter 6, the data is analysed to get an understanding of the prevalence of HIV/AIDS in TB patients in the study area. In the final chapter, results are discussed and concluded. Figure 3.2 provides a flow diagram of the study design.

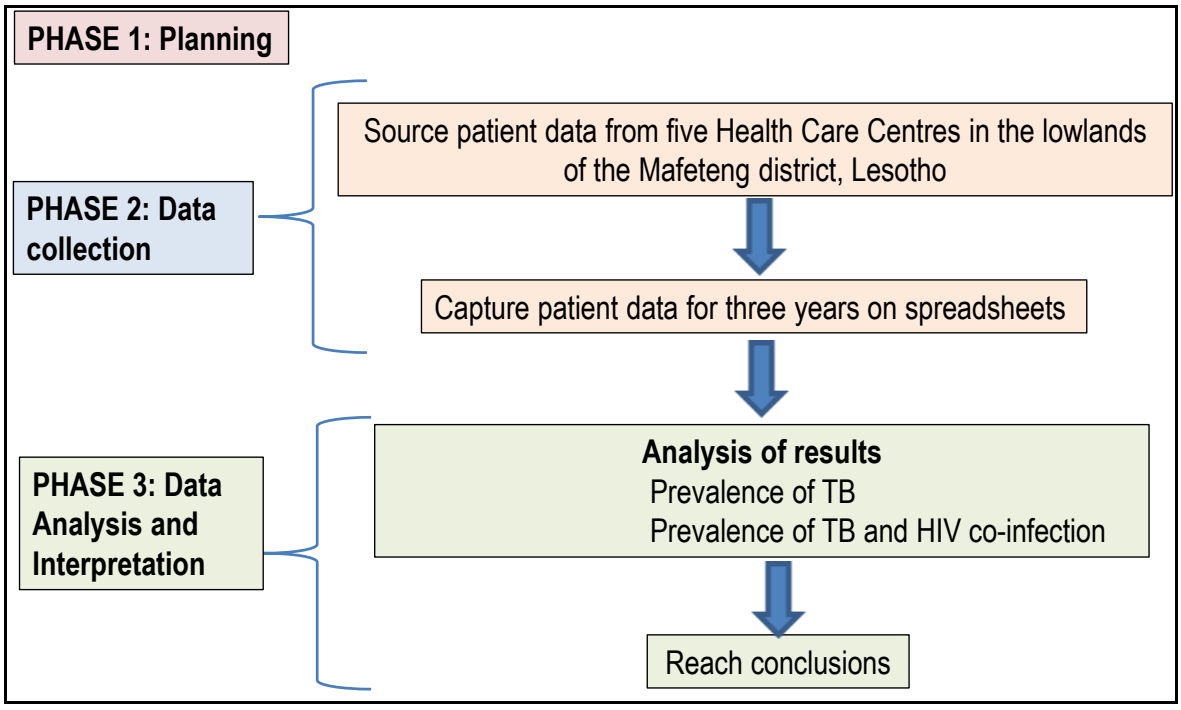


Figure 3.2 Study design of the research project

3.3.1 Study population

The population for this study was defined as all the records of the TB patients that were seen at Mafeteng HCC, Samaria HCC, Motsekuoa HCC, Lecoop HCC and Teba HCC from January 2014 to December 2016. The patients' data for this study was obtained from five HCCs located in the lowlands of the Mafeteng district in Lesotho. These HCCs make provision for the management of healthcare services as well as treatment of diseases, including patients suffering from TB, in the lowlands of the Mafeteng district. Before data entry analysis, duplicate case entries were deleted from the spreadsheet and patients' names were ignored. Only their unique patient numbers were used in this study. However, the uniqueness of these numbers may only apply for a year because, if a registered patient is re-infected with TB over a year after the completion of treatment, the patient is given a new number, this time as a retreatment patient. This means some TB patients may be recorded twice, as a new patient and then as a retreatment patient. The information from the TB registry books was extracted to the spreadsheet. Cases transferred in, previously treated and the occupation of the patient were also excluded as a recorded outcome from the analysis.

3.3.2 Study population treatment outcome definitions

The following case and treatment outcome definitions, according to the standard definitions of National TB guidelines of Lesotho (MOH, 2016), were applied to identify the study population:

- **New case:** If a patient has never been treated for TB or has previously been on anti-TB treatment for less than four weeks in the past;

- **Relapse:** If a patient was declared cured or whose treatment was completed for any form of TB in the past, but who reports back to the HCC and is then found to be microscopic smear positive or culture positive;

- **Treatment failure:** If a patient is smear positive at the end of the fifth month or later after commencing treatment. It also includes a patient who was initially sputum smear negative but becomes smear positive during treatment; and

- **Treatment after default:** If a patient, previously recorded as defaulting from treatment, returns with a positive sputum smear to the health care centre.

3.3.3 Methods

Phase 1: Planning

A comprehensive review of the literature pertaining to TB and HIV/AIDS was undertaken to obtain an understating of their prevalence in Lesotho, sub-Saharan Africa and the world. Prior to the execution of the project, ethical approval was obtained from the Ethics Committee of the Ministry of Health in Lesotho (NH-REC) Reference: ID161-2018. Participating HCCs in the lowlands of the district of Mafeteng in Lesotho were identified.

Phase 2: Data collection

Ethical approval for the execution of this study was obtained from the Ministry of Health in Lesotho prior to collection of data (see Appendix A). The Ethics Committee provided the necessary consent for the relevant handwritten TB registries of the participating HCCs to be accessed. In addition, the Faculty and Institutional Research Committees of the Central University of Technology, Free State approved the study. To safeguard patient information privacy, the researcher observed standard professional and ethical principles. All information collected from the medical records was treated as confidential and only unique patient numbers were used to identify patients, instead of their birth names. Thereafter, the data of the different variables were captured in an electronic spreadsheet.

Measurements in patient identification areas included the following variables:

- Age
- Gender
- Area of origin
- Treatment category
- Type of patient
- TB classification, whether pulmonary or extra-pulmonary
- HIV Status
- CD4 Count
- ART

Phase 3: Data analysis and interpretation

Prior to data analysis, the data were edited to identify errors and questionable values and also compared with the original handwritten TB registries for correctness. The data analysis of this study was partitioned into three different data sections. These sections were:

- Biographical information of the study population;
- Prevalence of TB in the lowlands of the Mafeteng district in Lesotho; and
- HIV/AIDS prevalence amongst TB patients in the lowlands of the Mafeteng district in Lesotho

3.3.4 Biographical information of the study population

Several variable combinations were examined and compared. These included patient distribution (area, gender and age) amongst the HCCs; age distribution of participating TB patients; gender distribution of participating TB patients; and gender distribution by age group of participating TB patients.

The overall prevalence of TB in the lowlands of the Mafeteng district in Lesotho was determined, as well as the prevalence during the individual years. An attempt was made to establish any trends over the years. Distribution of the following variables was analysed: the distribution of treatment categories, either new cases or retreated cases as well as the infection site; pulmonary or extra-pulmonary TB and the type of patient; and default from treatment, relapsed or treatment failed cases. Also, HIV/AIDS prevalence amongst TB patients of the lowlands of the Mafeteng district in Lesotho, the prevalence of HIV/AIDS amongst the TB patients of the participating HCCs as well as the prevalence of patients processed for anti-retroviral therapy (ART) were calculated.

Finally, the results were interpreted to establish if any overall trends existed amongst the TB patients from the lowlands of the Mafeteng district in Lesotho. Statistical analysis of the data was performed to establish an understanding of the prevalence of HIV/AIDS in TB patients in the study area. Conclusions were reached and recommendations given where possible.

3.4 Conclusion

This chapter of Materials and Methods discusses the methodology used to assess the prevalence of TB and HIV/AIDS co-infection among tuberculosis patients in the lowlands of the Mafeteng district. A quantitative method and a convenience purposeful method were used to select data from the five selected HCCs, including data of 1,109 cases. In addition, the chapter discusses the data collection method as well as data capturing in the electronic spreadsheet.

Chapter 4

Biographical Information of the Study Population

4.1 Introduction

Handwritten Tuberculosis (TB) registry books were sourced from the five participating health care centres (HCCs) in the lowlands of the Mafeteng district in Lesotho. The information contained in the registry books included biographical information, TB treatment information and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) information. The biographical information provided by these handwritten TB registries included the name, age and gender of each participating TB patient (Figure 4.1). The age varied from very young children under one year old to elderly people.

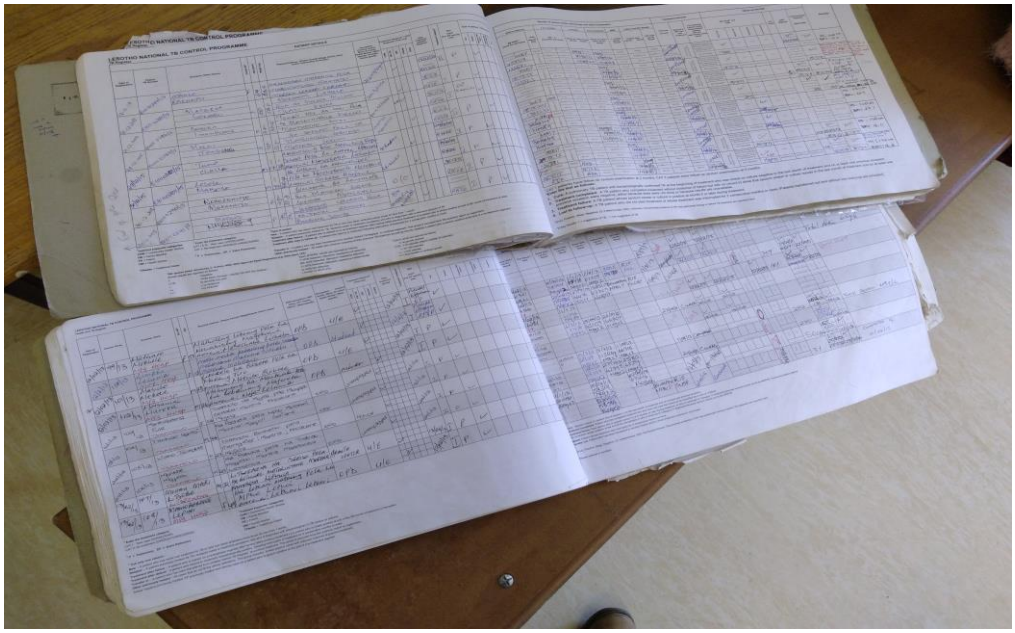


Figure 4.1 Examples of pages from TB patient registry books

4.2 Patient distribution by Health Care Centre

The biographical information provided by the handwritten registries of the five participating HCCs contained TB and HIV/AIDS data about children, adults and the elderly. Information was obtained for

more than 1,000 patients for the three reporting years of this study. The vast majority, approximately two-thirds (62.3%) of the patients, were from the Mafeteng HCC, which is the main HCC in the lowlands of the Mafeteng district (Table 4.1). Motsekuoa HCC contributed less than 15% of the total number of TB patients, while Samaria and LeCoop each contributed approximately one-tenth of the total number of participating TB patients for the three years. The Teba HCC was the smallest participating HCC in the study, representing an estimated 1% of the total number of TB patients.

Table 4.1 Number of patients per participating HCC

Health Care Centre	Total number of patients	Percentage of patients per HCC	Type of patient
Mafeteng	691	62.3	Children and adults of all ages
Samaria	113	10.2	Children and adults of all ages
Motsekuoa	164	14.8	Children and adults of all ages
LeCoop	126	11.4	Children and adults of all ages
Teba	15	1.3	Mineworkers
Total	**1,109**	**100**	

4.3 Patient distribution by age and reporting years

The ages of the participating TB patients for the three reporting years covered a wide spectrum, ranging from patients that were less than one year old to elderly patients. The young adult group of TB patients represented the largest group in the study, closely followed by the adult group. Together the young adult and adult groups represented more than 75% of all the TB patients (Table 4.2). As expected, the elderly group was the smallest group of the study TB patients. When viewing the number of TB patients for the three reporting years, it was found that the numbers in reporting Year 1 and Year 2 were mostly similar. In contrast, however, the percentages of the different age interval

groups in reporting Years 1 and 2 were substantially different. In particular, the young age group was much less in reporting Year 2 compared with Year 1.

Table 4.2 Distribution of age groups for the three reporting years

Age group	Age interval name	Total number of patients (%)	Number of patients in Year 1 (%)	Number of patients in Year 2 (%)	Number of patients in Year 3 (%)
0 - 15	Young	62 (5.5)	35 (56.4)	22 (35.5)	5 (8.1)
>15 - 35	Young adult	457 (41.2)	191 (41.7)	183 (40.1)	83 (18.2)
>35 - 55	Adult	390 (35.2)	156 (40.0)	140 (35.9)	94 (24.1)
>55 - 75	Mature adult	180 (16.2)	55 (30.6)	80 (44.4)	45 (25.0)
>75	Elderly	20 (1.8)	10 (50.0)	6 (30.0)	4 (20.0)
Total		**1,109**	**447**	**431**	**231**

4.4 Patient distribution by gender

In this study, males were the highest in terms of gender distribution, accounting for 62.4% of the total participants from the HCCs in the lowlands of the Mafeteng district. Female participants accounted for more than one-third of the total gender participants (Table 4.3). The majority of the males were from the Mafeteng and Motsekuoa HCCs being more than one-third and one-tenth, respectively. Samaria and LeCoop HCCs combined contributed to less than one-fifth of the male participants, while Teba, as expected, had the lowest contribution with just below 1% of the male patients participating in this study.

Table 4.3 Gender distribution of the patients by participating HCC

Health Care Centre	Total number of patients	Number of females (%)	Number of males (%)
Mafeteng HCC	691	269 (24.3%)	422 (38.1%)
Samaria HCC	113	37 (3.3%)	76 (6.9%)
Motsekuoa HCC	164	58 (5.2%)	106 (9.6%)
LeCoop HCC	126	47 (4.2%)	79 (7.1%)
Teba HCC	15	6 (0.1%)	9 (0.8%)
Total	**1,109**	**417 (37.6%)**	**692 (62.4%)**

4.5 Patient distribution by gender and age group intervals

The percentage representation of females and males amongst the different age group intervals differed substantially. In the elderly age group interval (>75 years), the number of females and males were equal, whereas in the mature adult age group interval (>55 to 75 years) and the adult age group interval (>35 to 55 years), males represented more than two-thirds of the respective age group interval (Figure 4.2). Furthermore, the young children age group interval (0 to 15 years) and young age group interval (>15 to 35), the males represented more than half of the participants in each of the respective age groups.

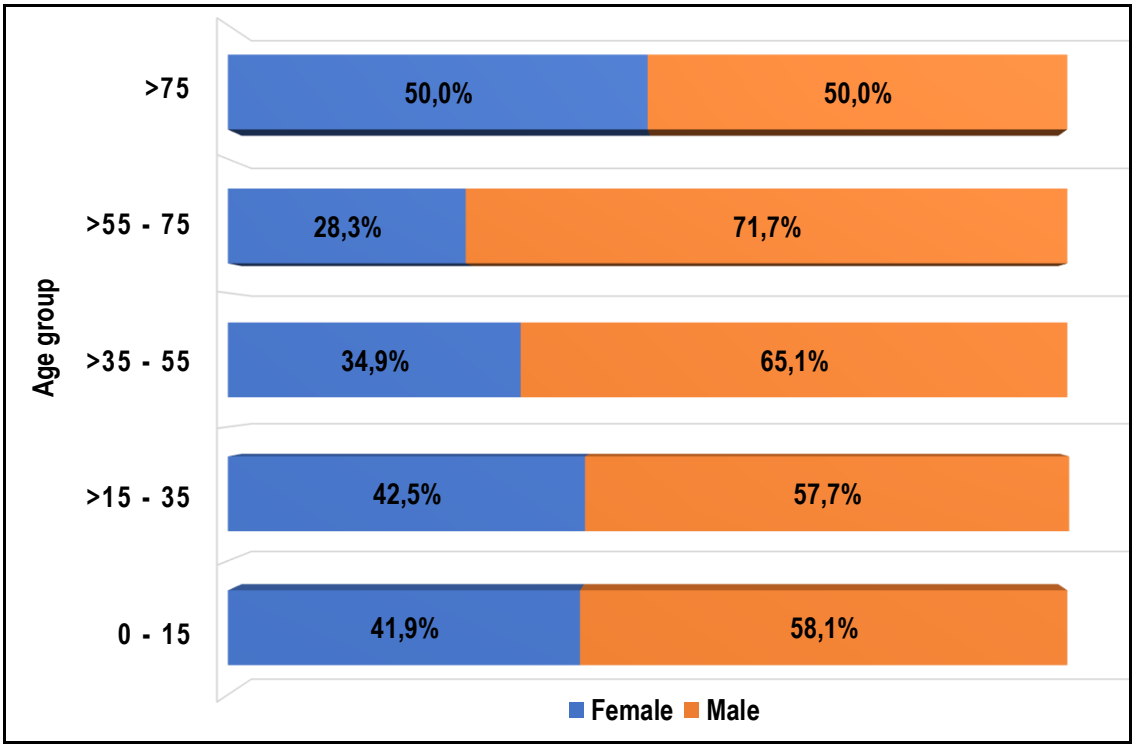


Figure 4.2 Distribution of participating TB patients by gender and age group

4.6 Patient distribution by gender and reporting years

For the three reporting years of the study, the majority of the participants were male. In reporting Year 1 and Year 2, the males represented less than two-thirds of the total gender participants. It was interesting to note that in reporting Year 3, the number of males slightly increased to two-thirds of the participants (Figure 4.3). The female numbers were constant in both reporting Year 1 and Year 2 with more than one-third of the total gender participants. However, a slight decrease to less than one-third was recorded for female participants in reporting Year 3.

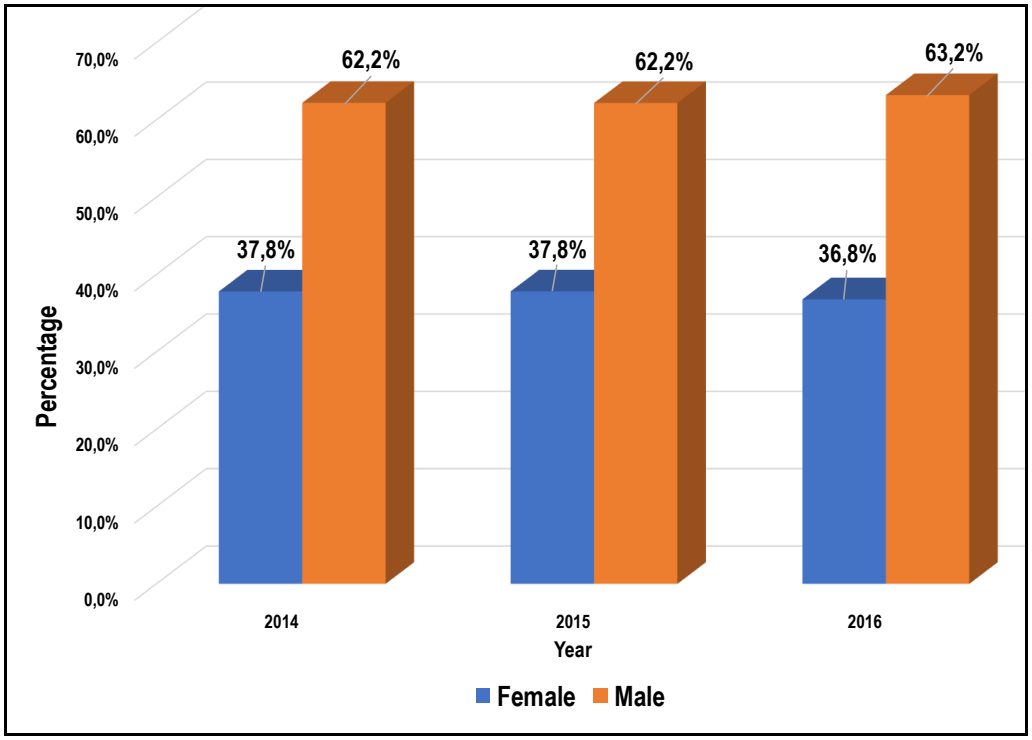


Figure 4.3 Distribution by gender for the three reporting years

4.7 Discussion

The biographical information of the participating study population was extracted from five handwritten Tuberculosis (TB) registry books. As expected, the main HCC, which is Mafeteng, was the major contributor of TB patient data accounting for 62.3% of the total study population. The biographical results further indicated that the predominant participated age group interval was the young adult age group (>15 to 35 years) with 41.2% of the study population, followed by the adult age group interval (>35 to 55) with 35.2% of the participants. From findings in a previous study, the young adult age group of 15 to 29 years was identified as the most sexually active group of Tuberculosis patients (Horton et al., 2016). The most participated gender was males with 62.4% of the total participants in this study from the lowlands of the Mafeteng district. The findings from this study correlates with a similar study conducted at Metema hospital in Ethopia in 2012 where a total of 2,096 TB patients were registered and out of this number 1,246 (59.4%) were male and 850 (40.6%) were female (Tarekegne et al., 2016).

Chapter 5

Distribution of Tuberculosis types and treatment outcomes in the lowlands of the Mafeteng district in Lesotho

5.1 Introduction

In this study, Tuberculosis (TB) cases were extracted from five TB registry books. These registry books contained TB information, such as treatment category, infection site and type of patient. Firstly, the treatment category was classified as either new TB cases or retreatment TB cases; secondly, the infection site was classified as pulmonary or extra-pulmonary TB; and thirdly, the type of patient was categorised as either new TB patient, relapsed treatment patient, treatment failed patient or default after treatment patient.

5.2 Distribution of new TB patients by HCC for the three reporting years

In the study population, the overall number of new Tuberculosis (TB) patients who received TB treatment for the first time, was 912 (82.2%) of the total of 1,109 study participants for the three reporting years. Out of these 912 new TB patients, Mafeteng main Health Care Centre reported the highest number of new TB patients with less than two-thirds for the three reporting years. The HCC to report the second most new TB patients for the three reporting years was Motsekuoa with less than one-sixth of the new TB patients. The two HCCs Samaria and LeCoop each reported more than one-fifth of the new TB patients. Meanwhile, Teba HCC contributed the lowest number of new TB patients with 1.6% of the total new TB patients participating in this study for the three reporting years (Table 5.1). When reviewed, it is interesting to notice the decline to almost half the number of new TB infections in reporting Year 3 when compared with reporting Year 1 and Year 2, respectively.

Table 5.1 Number and percentage of new TB patients per HCC for the three reporting years

Health Care Centre	Total number of patients	Total number of New patients	Number New TB patients Year 1			Number New TB patients Year 2			Number New TB patients Year 3			New TB patients per HCC (%)
			Nr. of patients	Pulmonary	Extra-pulmonary	Nr. of patients	Pulmonary	Extra-pulmonary	Nr. of patients	Pulmonary	Extra-pulmonary	
Mafeteng HCC	691	**557**	268	222	46	218	184	34	71	59	12	61.1
Samaria HCC	113	**99**	41	35	6	31	26	5	27	27	0	10.9
Motsekuoa HCC	164	**138**	49	40	9	52	46	6	37	35	2	15.1
Leccop HCC	126	**103**	14	11	3	46	39	7	43	38	5	11.3
Teba HCC	15	**15**	7	7	0	8	8	0	0	0	0	1.6
Total number of New patients	**1,109**	**912**	379	315	64	355	303	52	178	159	19	100.0
% of New patients out of total			34.1			32.0			16.1			82.2

5.2.1 Distribution of new TB patients per HCC in reporting Year 1

In reporting Year 1, the total number of reported new TB patients was 379 patients from the participating HCCs. Mafeteng HCC reported more than two-thirds of these patients, while, Motsekuoa and Samaria HCCs each reported more than one-tenth of the new TB patients. LeCoop and Teba HCCs reported the lowest numbers with less than one-tenth of new TB patients in reporting Year 1 (Figure 5.1).

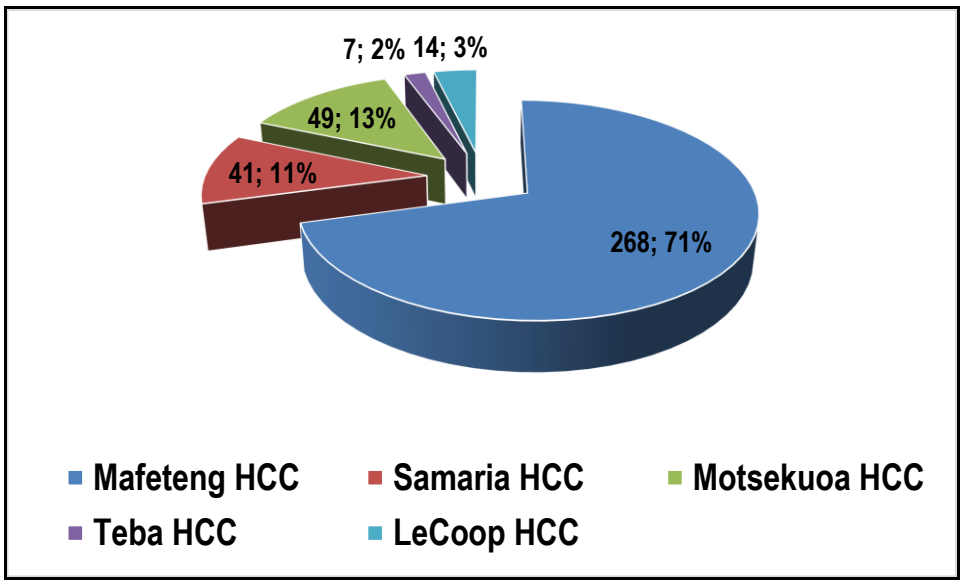


Figure 5.1 Distribution of new TB infections per HCC in reporting Year 1

5.2.2 Distribution of new TB patients per HCC in reporting Year 2

The total number of new TB patients was 355 in reporting Year 2. Less than two-thirds of these patients were reported by Mafeteng HCC. Combined Motsekuoa and LeCoop HCCs were second with more than one-quarter of the new TB patients. Samaria reported below one-tenth of the new TB patients, while Teba reported just 2% of the new TB patients in reporting Year 2 (Figure 5.2).

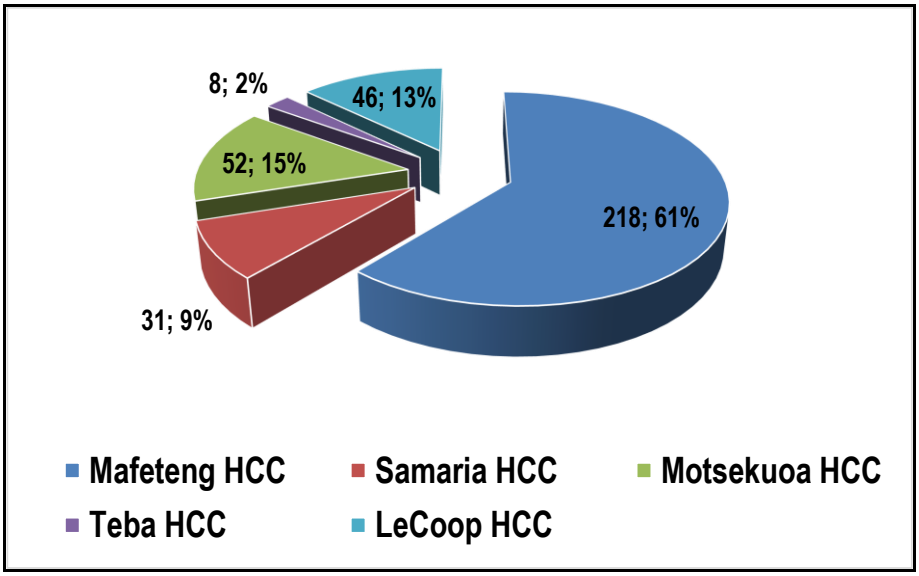


Figure 5.2 Distribution of new TB infections per HCC in reporting Year 2

5.2.3 Distribution of new TB patients per HCC in reporting Year 3

The total number of new TB patients in reporting Year 3 was 178 patients. As expected, Mafeteng HCC reported approximately two-fifths of new TB patients. Meanwhile, LeCoop and Motsekuoa HCCs each reported less than one-quarter of the new TB patients in reporting Year 3 (Figure 5.3). Samaria HCC reported less than one-fifth of new TB patients, while Teba HCC did not report any new TB patients in reporting Year 3.

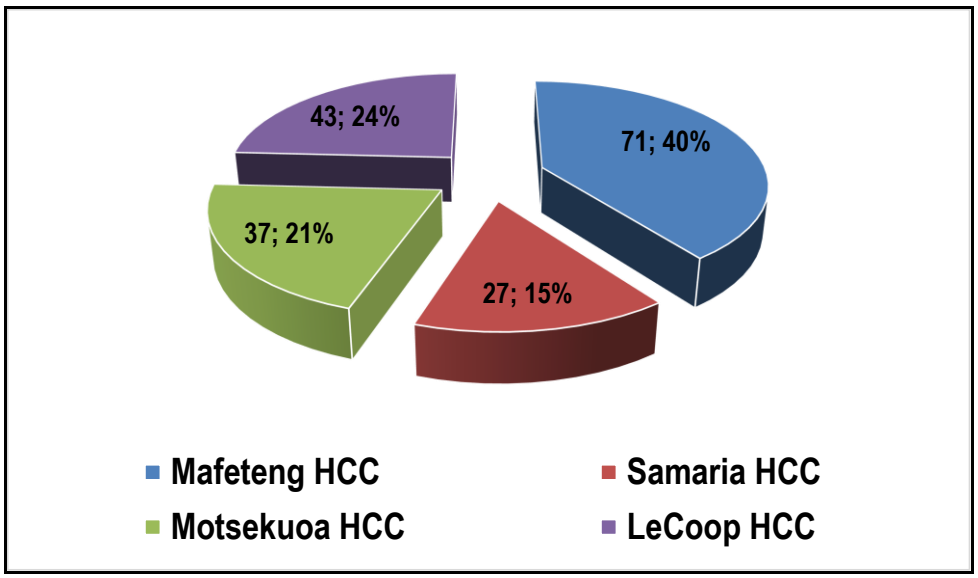


Figure 5.3 Distribution of new TB infections per HCC in reporting Year 3

5.3 Distribution of retreatment TB patients per HCC for the three reporting years

Distribution of retreatment TB patients per HHC differs substantially for the three reporting years. Out of the total of 1,109 TB patients, retreatment TB patients were only 197 (17.8%) for all three reporting years. Reporting Year 2 reported the most retreatment TB patients with approximately 6.9% of the total TB patients. In reporting Year 1, the retreatment TB patients were approximately 6.1% of the total (Table 5.2). Meanwhile, reporting Year 3 contributed only 4.8% retreatment TB patients. It is also important to note that the majority of retreatment patients were reported by

Mafeteng main HCC with more than two-thirds of the total retreatment patients for the three reporting years.

Table 5.2 Number and percentage of retreatment TB patients per HCC for the three reporting years

Health Care Centre	Total Nr of patients	Total Nr of Retreatment patients	Nr Retreatment TB patients Year 1			Nr Retreatment TB patients Year 2			Nr Retreatment TB patients Year 3			Retreatment TB patients per HCC (%)
			Nr. of patients	Pulmonary	Extra-pulmonary	Nr. of patients	Pulmonary	Extra-pulmonary	Nr. of patients	Pulmonary	Extra-pulmonary	
Mafeteng HCC	691	**134**	53	44	9	46	41	5	35	32	3	68.0
Samaria HCC	113	**14**	4	1	3	6	5	1	4	3	1	7.1
Motsekuoa HCC	164	**26**	11	10	1	8	8	0	7	7	0	13.2
Leccop HCC	126	**23**	0	0	0	16	16	0	7	5	2	11.7
Teba HCC	15	**0**	0	0	0	0	0	0	0	0	0	0.0
Total nr of Retreatment patients	**1109**	**197**	68	55	13	76	70	6	53	47	6	100.0

The number of retreatment TB patients in reporting Year 1 was 68 out of a total of 197 patients. Mafeteng HHC reported more than three-quarters of the retreatment TB patients in reporting Year 1. Motsekuoa was the second highest with more than one-tenth of the retreatment TB patients. Meanwhile, Samaria HCC reported less than one-tenth of the retreatment TB patients (Table 5.3). The remaining two HCCs, namely Teba and LeCoop, did not report any retreatment TB patients. It is also important to note that the number of retreatment TB patients in reporting Year 3 declined significantly, compared with reporting Year 1 and Year 2.

Table 5.3 Number of retreatment TB patients per HCC in reporting Year 1

Health Care Centre	Retreatment TB patients in Year 1							
			Pulmonary TB			Extra-pulmonary TB		
	Total Retreatment patients	Nr and % of Retreatment in Year 1	Treatment default	Relapsed	Treatment failed	Treatment default	Relapsed	Treatment failed
Mafeteng	134	53 (77.9)	17	25	2	6	3	0
Samaria	14	4 (5.9)	0	1	0	2	1	0
Motsekuoa	26	11 (16.2)	7	2	1	0	1	0
Teba	0	0 (0)	0	0	0	0	0	0
Lecoop	23	0 (0)	0	0	0	0	0	0
Total	197	68	24	28	3	8	5	0

The number of retreatment TB patients in reporting Year 2 was 76 out of the total of 197. Mafeteng HCC reported less than two-thirds of the retreatment TB patients in reporting Year 2. LeCoop HCC reported the second highest with almost one-fifth of the retreatment TB patients. Meanwhile, combined Motsekuoa and Samaria HCCs reported less than one-fifth of the retreatment TB patients in the same year (Table 5.4). It is very important to note that Teba HCC did not report any retreatment TB patients in reporting Year 2.

Table 5.4 Number of retreatment TB patients per HCC in reporting Year 2

Health Care Centre	Retreatment TB patients in Year 2							
	Total Retreatment patients	Nr and % of Retreatment in Year 2	Pulmonary TB			Extra-pulmonary TB		
			Treatment default	Relapsed	Treatment failed	Treatment default	Relapsed	Treatment failed
Mafeteng	134	46 (60.5)	3	36	2	0	4	1
Samaria	14	6 (7.9)	2	3	0	1	0	0
Motsekuoa	26	8 (10.5)	2	6	0	0	0	0
Teba	0	0 (0)	0	0	0	0	0	0
Lecoop	23	16 (21.1)	3	13	0	0	0	0
Total	197	76	10	58	2	1	4	1

The number of retreatment TB patients in reporting Year 3 was 53 out of total of 197 retreatment TB patients. Mafeteng HCC reported approximately two-thirds of the retreatment TB patients in reporting Year 3. Motsekuoa, and LeCoop HCCs each reported more than one-tenth of the retreatment TB patients. On the other hand, Samaria HCC reported the lowest number with less than one-tenth of the retreatment TB patients in reporting Year 3 (Table 5.5). It is important to mention that Teba HCC did not report any retreatment patients in reporting Year 3.

Table 5.5 Number of retreatment TB patients per HCC in reporting Year 3

Health Care Centre	Retreatment TB patients in Year 3							
	Total Retreatment patients	Nr and % of Retreatment in Year 3	Pulmonary TB			Extra-pulmonary TB		
			Treatment default	Relapsed	Treatment failed	Treatment default	Relapsed	Treatment failed
Mafeteng	134	35 (66.0)	5	26	1	0	3	0
Samaria	14	4 (7.5)	0	3	0	0	1	0
Motsekuoa	26	7 (13.2)	1	6	0	0	0	0
Teba	0	0 (0)	0	0	0	0	0	0
Lecoop	23	7 (13.2)	0	5	0	1	1	0
Total	197	53	6	40	1	1	5	1

5.4 Distribution of TB infection site for the three reporting years

The most recorded TB infection site was pulmonary TB with 949 (85.6%) cases, while extra-pulmonary TB accounted for 160 (14.4%) of the total 1,109 TB patients for the three reporting years. The highest number of pulmonary TB cases was reported in both reporting Year 1 and 2, which added up to 743 TB cases. While on the other hand, in reporting Year 3, the numbers declined substantially to 206 pulmonary TB cases (Figure 5.4). However, it is interesting to note that a substantial decline in extra-pulmonary TB was observed from reporting Year 1 to Year 3, at a roughly 20% decline each year.

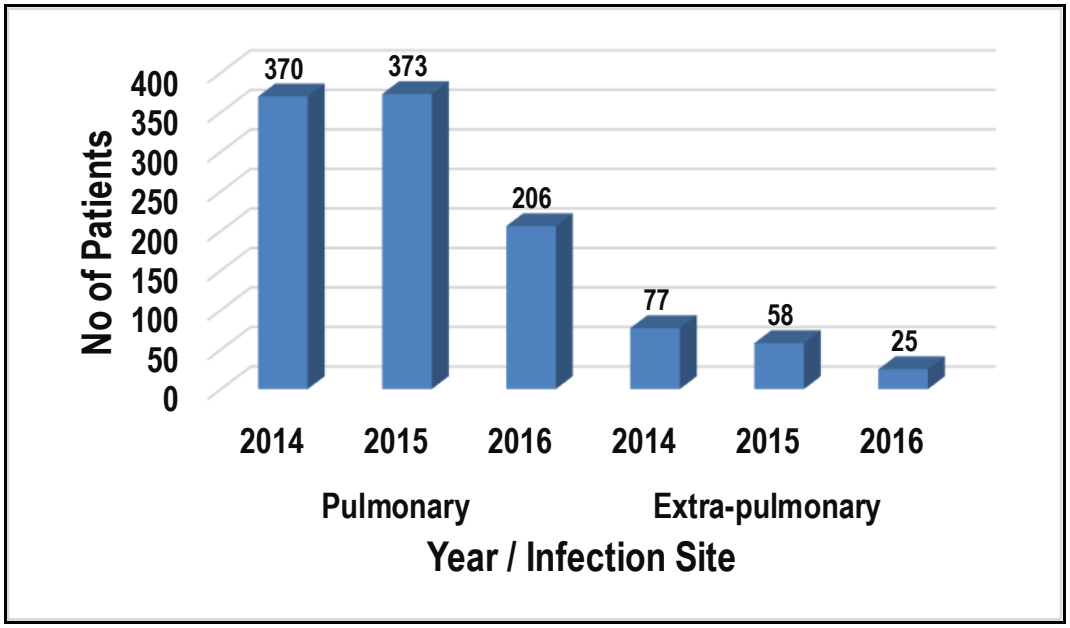


Figure 5.4 Comparison of TB infection site for the three reporting years

5.5 Distribution of pulmonary TB patients per HCC for the three reporting years

The number of pulmonary TB cases was 949 out of the total of 1,109 TB patients. Mafeteng HCC contributed the highest number of pulmonary TB infected patients with 582 (61.3%) out of the total 949 pulmonary TB patients. The three HCCs, namely Motsekuoa, LeCoop and Samaria, contributed 146 (15.4%), 109 (11.5%) and 97 (10.2%), respectively (Figure 5.5). Teba HCC contributed the lowest number of pulmonary TB infected patients with 15 (1.6%) cases for the three reporting years.

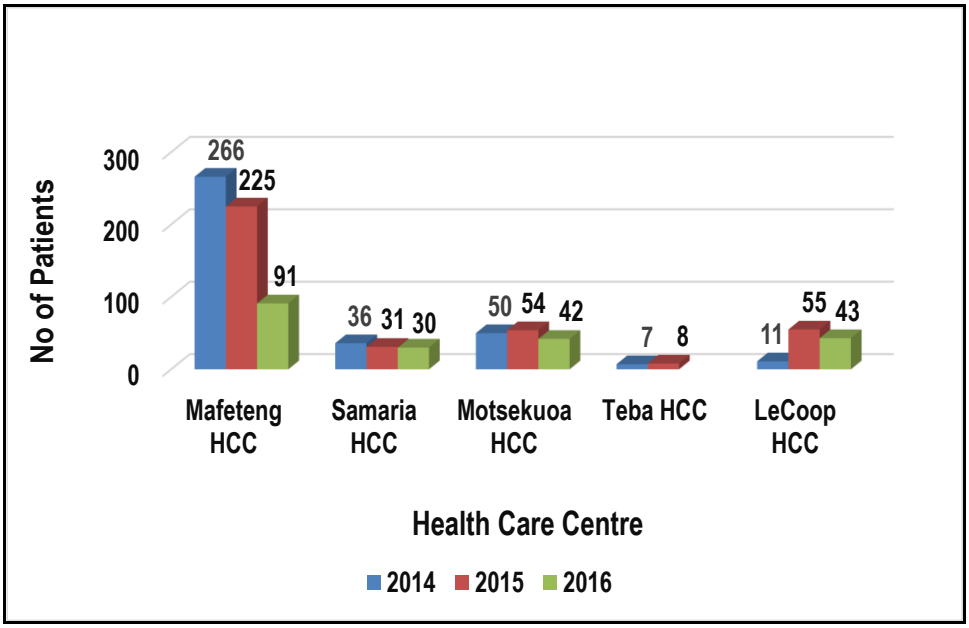


Figure 5.5 Comparison of pulmonary TB by HCC for the three reporting years

5.6 Distribution of extra-pulmonary TB per HCC for the reporting years

The total number of extra-pulmonary TB cases was 160 out of the total of 1,109 participating TB patients for the three reporting years. Mafeteng HCC contributed the highest number of extra-pulmonary infected patients with 109 (68.1%). Motsekuoa, LeCoop and Samaria HCCs contributed 18 (11.3%), 17 (10.6%) and 16 (10.0%), respectively (Figure 5.6). However, the majority of patients affected by extra-pulmonary TB were in reporting Year 1 and 2. In reporting Year 3, the numbers declined substantially with approximately 15.7% of the extra-pulmonary TB patients being recorded.

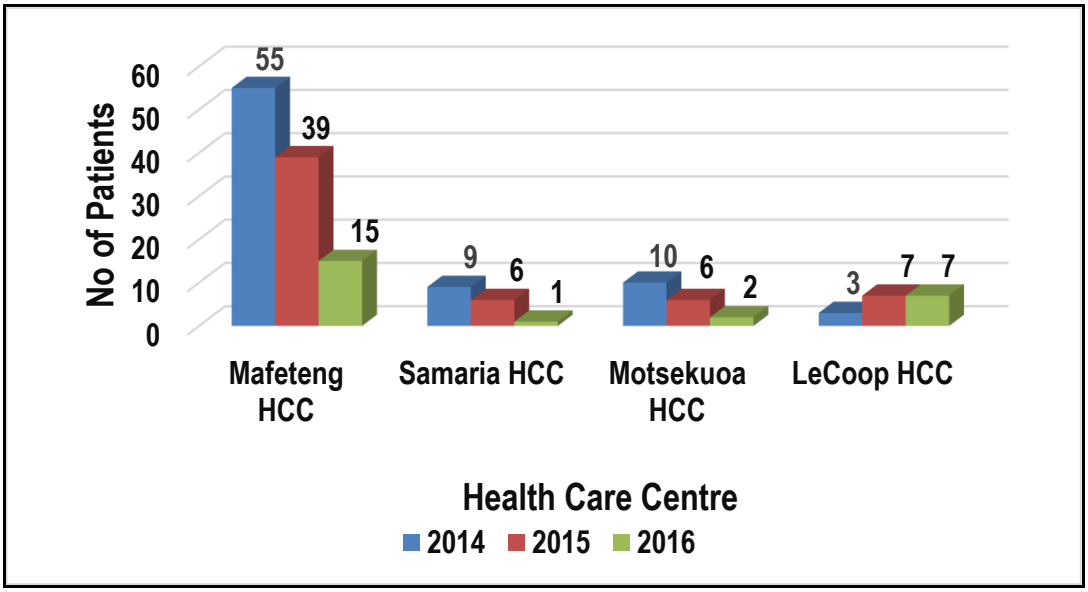


Figure 5.6 Distribution of extra-pulmonary TB infection by HCC

5.7 Distribution of TB site infection by gender and reporting years

The representation of females and males for the TB infection sites differs hugely throughout the reporting years. More than half of the total number of participants for the three reporting years was represented by males affected by pulmonary TB infection. While on the other hand, more than one-third of the pulmonary TB infections in each of the reporting years was comprised of female TB patients affected by pulmonary TB infection (Figure 5.7). For all three reporting years, extra-pulmonary TB infection in both genders was limited to less than one-tenth of the gender participants.

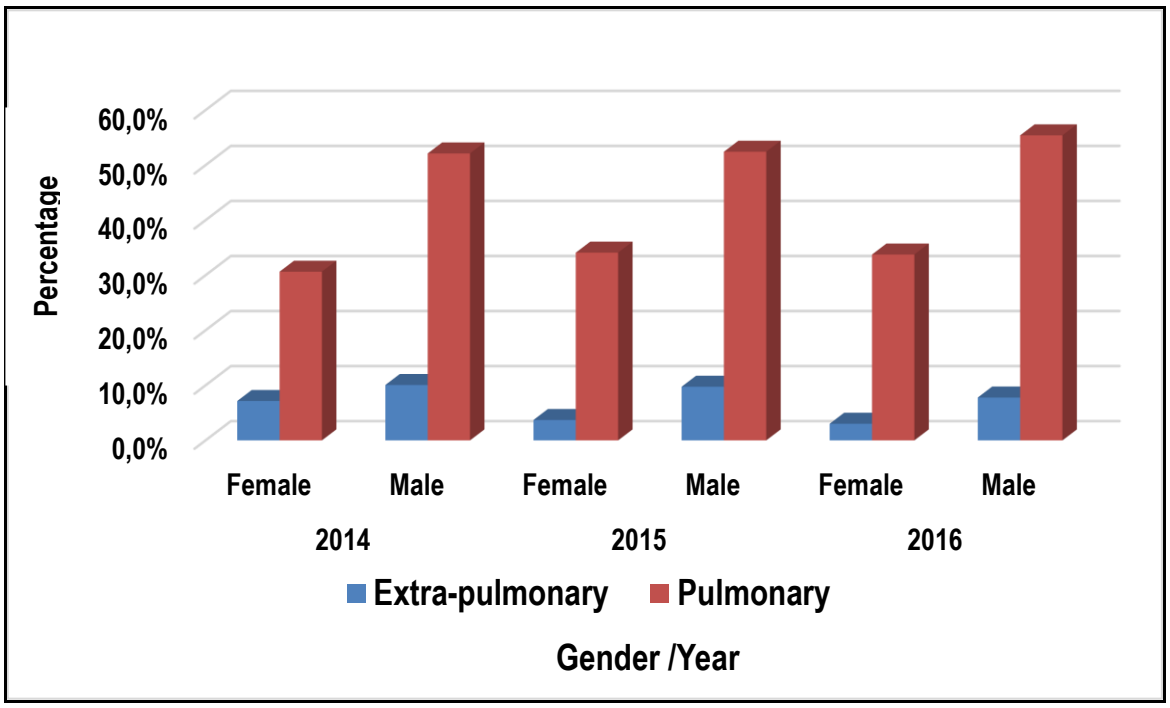


Figure 5.7 Distribution of type of TB infections by gender group

5.8 Discussion

The results of the prevalence of Tuberculosis among the 1,109 participating patients for the three reporting years were included in this study. The study was conducted in the lowlands of the Mafeteng district in Lesotho and the treatment category observed the most was new TB patients at 82.2%. These findings correlate with another study on the African continent (Matena hospital in Ethopia) where approximately 89.5% of the 1,876 patients were classified in the treatment category of new TB cases. Only 9.5% of these 1,876 patients (118) were retreatment TB cases (Tarekegne et al., 2016). This is confirmation of what was found in the lowlands of the Mafeteng district in Lesotho. The most noted infectious site of TB was pulmonary with approximately 85.6% of cases for all the reporting years. A similar study among patients with TB in Nepal revealed comparable findings where 80.9% of the total TB patients were pulmonary positive and the remainder (19.1%) were extra-pulmonary (Sah et al., 2016).

Chapter 6

Tuberculosis Patients co-infected with Human Immunodeficiency Virus

6.1 Introduction

Tuberculosis patients co-infected with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) from the participating health care centres in the lowlands of the Mafeteng district in Lesotho were studied. The HIV/AIDS and anti-retroviral therapy information for the three reporting years was recorded from the five Tuberculosis (TB) handwritten registry books.

6.2 HIV co-infected patient distribution per HCC for the three reporting years

The overall prevalence of HIV/AIDS co-infection among TB patients for the three reporting years was 780 (70.3%) out of the total of 1,109 TB patients included in the study. More than two-thirds of the HIV co-infected patients were reported from the Mafeteng HCC for the three reporting years. Most of these HIV/AIDS co-infection cases among the TB patients were recorded in reporting Year 1 and 2. It is alarming to note that in both of these reporting years, these patients accounted for more than one-quarter of the patient population. Meanwhile, in reporting Year 3, the lowest number of HIV/AIDS co-infections among the TB patients was recorded, which was less than a fifth of the participants (Table 6.1). It was interesting to note that patients from four participating HCCs were on anti-retroviral therapy (ART). Motsekuoa was the only HCC with 1% of the patients not on ART. The reason for the lack of ART initiation at this HCC is debatable and should be investigated further.

Table 6.1 The prevalence of HIV co-infection among TB patients for the three reporting years

Health Care Centre	Total nr of TB patients	Year 1		Year 2		Year 3		Total nr (%) TB patients with HIV	Total % HIV patients on treatment
		TB patients with HIV	HIV+ patients on ARV	TB patients with HIV	HIV+ patients on ARV	TB patients with HIV	HIV+ patients on ARV		
Mafeteng HCC	691	230	230	195	195	76	76	501 (64.2%)	100%
Samaria HCC	113	28	28	25	25	20	20	73 (9.4%)	100%
Motsekuoa HCC	164	38	37	31	31	33	33	102 (13.1%)	99%
LeCoop HCC	126	10	10	45	45	45	45	100 (12.8%)	100%
Teba HCC	15	2	2	2	2	0	0	4 (0.5%)	100%
Nr of HIV patients out of total	1,109	308	307	298	298	174	174	780	70.3%
% of HIV patients out of total		27.8	27.7	26.9	26.8	15.7	15.7	70.3	70.3%

6.3 Distribution of HIV/AIDS co-infected TB patients by gender and age group intervals

The distribution of HIV/AIDS among the gender groups by age intervals in the lowlands of the Mafeteng district revealed interesting results. The most affected age group was within the age interval of the young adult group (>15 – 35) with slightly less than half of the study participants co-infected with HIV/AIDS. The second most affected age group interval was the adult group (>35 – 55) with approximately two-fifths of the total HIV/AIDS participants (Table 6.2). The young children age group interval (0 – 15) and very old people age group interval (>75) recorded only a few affected patients, with a combined total of less than one-tenth of the total HIV/AIDS participating patients in the lowlands of the Mafeteng district.

Table 6.2 HIV prevalence by gender and age group intervals in three reporting years

Age group	HIV infections in Year 1			HIV infections Year 2			HIV infections Year 3			Total nr of HIV infections (%)
	Nr of patients	Females	Males	Nr of patients	Females	Males	Nr of patients	Females	Males	
0-15	12	5	7	8	3	5	3	1	2	(2.9%)
>15-35	148	63	85	146	68	78	63	23	40	45.8%
>35-55	120	47	73	117	41	76	80	33	47	40.6%
>55-75	27	8	19	27	8	19	27	9	18	10.4%
>75	1	0	1	0	0	0	1	1	0	0.3%
Total all ages	**308**	**123**	**185**	**298**	**120**	**178**	**174**	**66**	**107**	**100.0%**

6.4 Prevalence of HIV/AIDS co-infected TB patients by gender and HCC

The prevalence of HIV/AIDS according to gender was obtained from the TB registries of all participating HCCs. This information was derived from the five participating centres in the lowland area of the Mafeteng district in Lesotho for the study period of three years.

6.4.1 Distribution of female HIV/AIDS patients by HCC for the three reporting years

The distribution of female HIV/AIDS patients among the participating HCCs was 310 (39.7%) of the total 780 HIV/AIDS co-infected patients. Most of the female HIV/AIDS patients were reported from the Mafeteng HCC with 207 (66.7%) out of a total of 310 (Figure 6.1). For the three reporting years, Motsekuoa, LeCoop and Samaria each reported 42 (13.5%), 36 (11.6%) and 24 (7.7%) co-infected female patients, respectively. However, Teba HCC only noted one TB female patient (0.3%) to be HIV/AIDS co-infected.

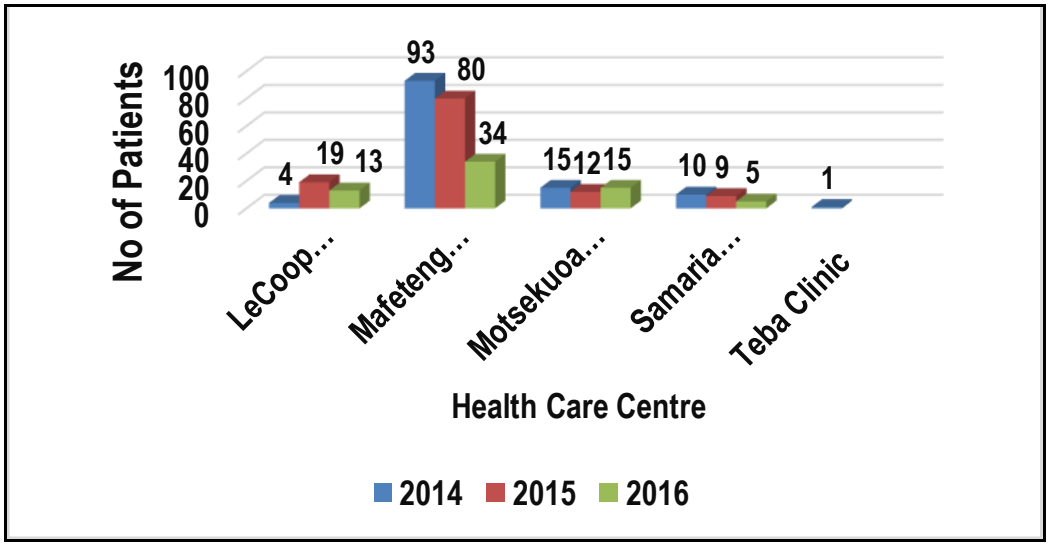


Figure 6.1 Distribution of female HIV/AIDS patients by HCC for the three reporting years

6.4.2 Distribution of male HIV/AIDS patients by HCC for the three reporting years

The distribution of male HIV/AIDS patients among the participating HCCs was 470 (60.3%) of the total 780 HIV/AIDS co-infected patients. As expected, Mafeteng, as the main HCC, reported the most male patients affected with HIV/AIDS with 294 (62.5%) of the total 470. LeCoop HCC was the second highest with 64 male patients (13.6%) of the total number of 470 (Figure 6.2). The remaining two centres, Motsekuoa and Samaria, each reported 60 (12.7%) and 49 (10.4%), respectively, male HIV/AIDS patients affected over the three reporting years. The smallest HCC, namely Teba, reported only 3 (0.6%) male HIV/AIDS patients.

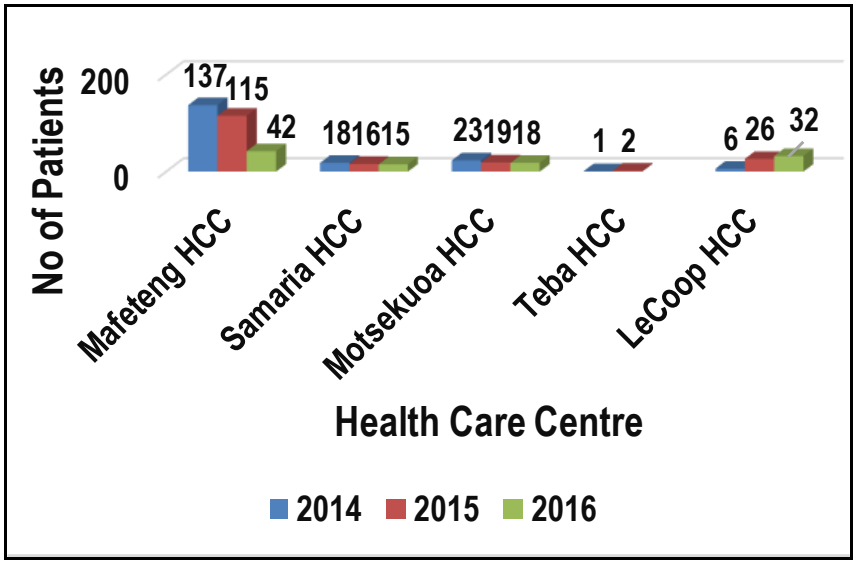


Figure 6.2 Distribution of male HIV/AIDS patients by HCC for the three reporting years

6.5 Percentage of HIV/AIDS co-infected TB patients on ART

The information of patients on anti-retroviral therapy (ART) was obtained from the five participating HCCs in the lowlands of the Mafeteng district in Lesotho. The ART patients' data were extracted from the five TB registry books of the participating centres. The information contained in these books included the ART and HIV/AIDS status. The results, as illustrated on the pie chart, show that almost all the 780 HIV-positive patients from the five HCCs of the lowlands of the Mafeteng district were 100% compliant in taking ART medication (Figure 6.3). Motsekuoa HCC was the only HCC where one percent of the patients was non-compliant.

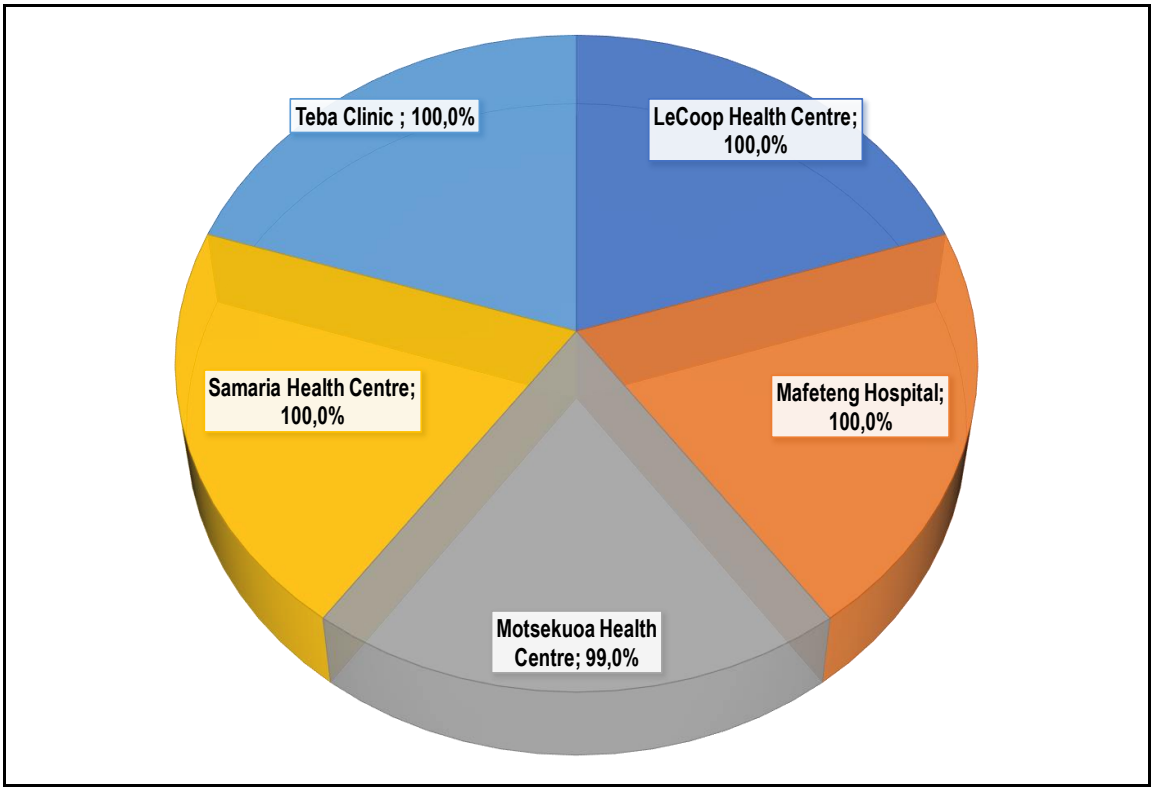


Figure 6.3 Percentage of HIV/AIDS co-infected TB patients on ART

6.6 Distribution of site of TB infection among HIV/AIDS patients by HCC

The most reported TB infection site was pulmonary with 665 (85.3%) out of the total of 780 HIV/AIDS affected patients, while extra-pulmonary infection site accounted for only 115 (14.7%) of the total for the three reporting years. Most of these patients were recorded in reporting Year 1 with pulmonary and extra-pulmonary infection numbers among the HIV/AIDS patients being 257 and 51, respectively. The second highest was reporting Year 2 with pulmonary and extra-pulmonary infections of 254 and 44, respectively. While reporting Year 3 showed declined numbers of TB infections with pulmonary and extra-pulmonary numbers of the HIV/AIDS affected patients being 154 and 20, respectively. It was interesting to note that most of these TB infections were from the Mafeteng HCC for all three reporting years.

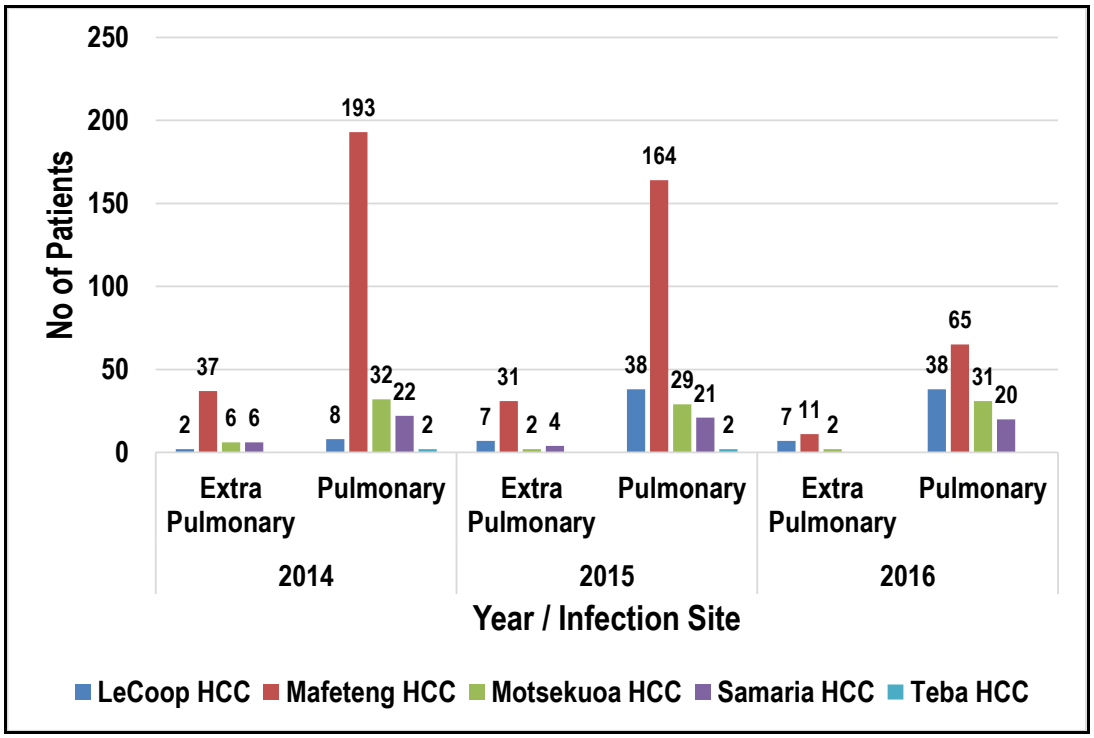


Figure 6.4 Distribution site of TB infection among patients co-infected with HIV/AIDS by HCC

6.7 Distribution of TB treatment category among patients co-infected with HIV/AIDS by HCC

The most reported treatment category recorded was the new TB patient category with 638 (81.8%) of the total of 780 HIV/AIDS patients, whereas, the remaining 142 (18.2%) TB cases were reported as retreatment cases. Most of these new TB cases co-infected with HIV/AIDS were reported in reporting Year 1 and 2 with 257 (32.9%) and 248 (31.8%), respectively (Figure 6.5). It is interesting to note that retreatment TB cases remained constant in reporting Year 1 and 2, however, in reporting Year 3, a slight decline was observed.

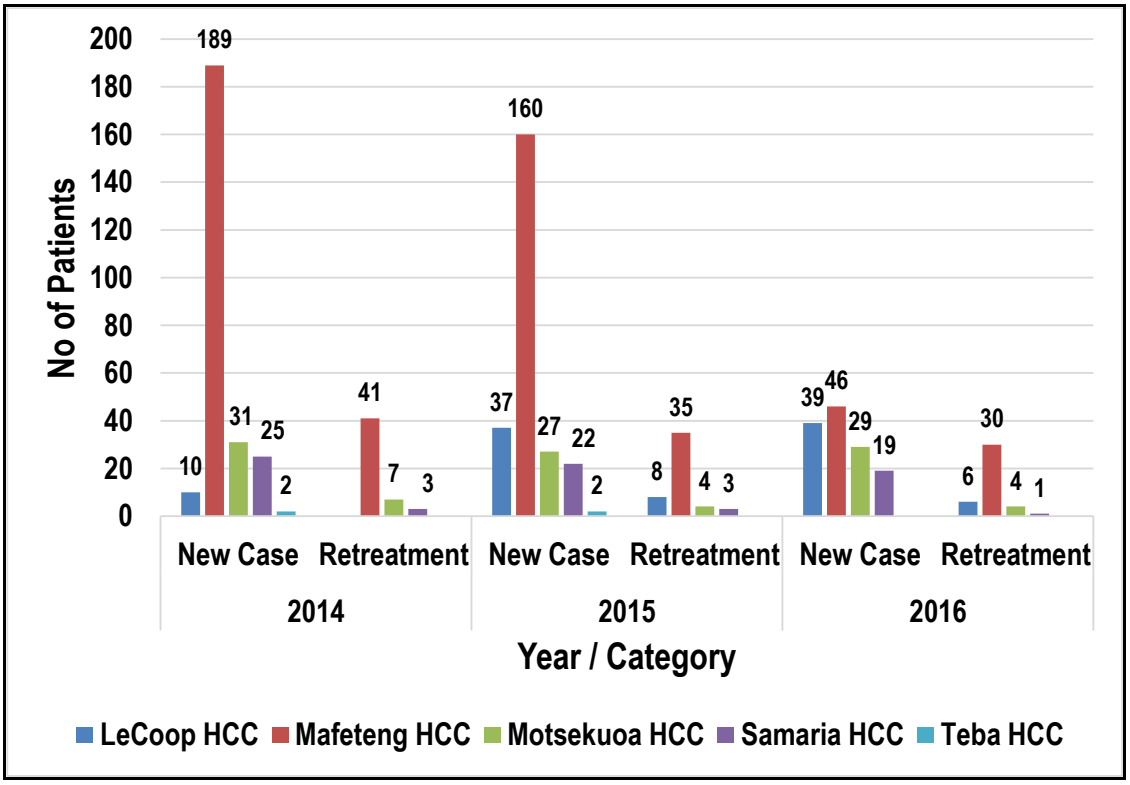


Figure 6.5 Distribution of TB treatment category among patients co-infected with HIV/AIDS by HCC

6.8 Discussion

The prevalence of TB patients co-infected with HIV/AIDS was 70.3% of the study participants in the lowlands of the Mafeteng district, Lesotho. The results further indicated that the most co-infected age group was the young adult's interval group (>15 to 35) with 45.8% of the total participants. This correlates with the results from a cross-sectional retrospective record review of high-burden TB patients from South Africa where, from 66,940 co-infected new TB cases, 40.4% were of a similar age group (Engelbrecht et al., 2017). A similar Zambian study also correlates with these findings, where the HIV prevalence was indicated among the adult age group interval of 15 to 34 years. In this Zambian study, young adults were found to have the highest prevalence of TB/HIV co-infection, namely 38.9% (Chanda-Kapata et al., 2017).

In this current study conducted among TB patients co-infected with HIV/AIDS, few of the patients from the participating centres were found to be children or old people. It is evident that males were the most affected gender amongst the HIV/AIDS TB patients and only 1% were not on ART. In Lesotho in 2016, it was reported that 88% of the TB patients had a known HIV status and 97% of those found to be HIV-positive were put on ART (Howard et al., 2016). This is clear indication that ART is highly practiced among HCCs.

.

Chapter 7

Discussion and Conclusion

7.1 Introduction

The End Tuberculosis Strategy, recommended by the World Health Assembly in May 2014, has set a target for ending the tuberculosis epidemic by 2035. In this strategy, WHO states that it aims to reduce the number of global deaths caused by TB by 95% from 2015 to 2035. This will be achieved by implementing appropriate preventative measures, early TB detection, prompt treatment, improved adherence to medication and political commitment. This will help to reduce 90% of the new TB cases, i.e. ten cases per 100,000 population or less. The strategy further says that if infection control procedures are followed conscientiously, there will be no affected family members suffering catastrophic costs because of TB by 2035. To meet these aims, countries should be aiming at reducing TB at a rate of 10% per year. Meanwhile before 2020, there were positive milestones with the End TB Strategy where WHO reported declines per year from 2013 to 2017. The WHO European Region reported a 5% decline per year and the WHO African Region reported a 4% decline per year (Sharma, 2019). Most interesting was that a 4 to 8% reduction per year occurred in the Southern African countries, such as Eswatini, Lesotho, Namibia, South Africa, Zambia and Zimbabwe, where the largest burden of TB disease exists (WHO, 2018).

Tuberculosis (TB) is a major public health problem severely affecting lower and middle-income countries. Furthermore, the introduction of the human immunodeficiency virus (HIV) has fuelled TB at a frightening rate and thus was classified as the number one highly infectious disease ranking above HIV/acquired immune deficiency syndrome (AIDS). Together TB and HIV/AIDS have complicated public health efforts to manage the two pandemics worldwide because both of them

need skilled health workers to provide the necessary care and they also come with large financial costs due to the expensive equipment and tools required.

In Lesotho, the Mafeteng district alone has 19 Health Care Centres (HCCs), which are distributed throughout the district. Of the 19 HCCs in Mafeteng, five (5) of them are in the lowlands, which is considered to be the urban location of the district and where HIV and TB are most prevalent. The five participating HCCs in the lowlands of the Mafeteng district were Mafeteng, Teba, Motsekuoa Samaria and LeCoop HCCs. These HCCs have recorded the highest infection rates of HIV and TB mainly due to the fact that they are located in the most populated region of the district. Therefore, the extent of the disease burden that TB has placed on the public health system of the Mafeteng district is known.

A convenient purposeful method of sampling was selected for this study so that an understanding and knowledge of the co-prevalence of HIV/AIDS and TB in the lowlands of the Mafeteng district could be obtained. The aim of this study was to obtain an understanding of the prevalence of HIV/AIDS in TB patients living in the lowlands of the Mafeteng district in Lesotho.

7.2 Results

Biographical information of the Study Population Results included data of more than 1,000 participating TB patients. The age group interval representing the majority of the patients in this study was from the young adult age interval (>15 – 35 years) with 457 (41.2%) out of the total of 1,109 TB patients. Furthermore, the majority of the participating patients were male with 692 (62.4%) for the three reporting years. Most of the patients came from the Mafeteng HCC with 691 (62.3%) of the 1,109 participating patients.

An attempt was made to establish the prevalence trends of HIV/AIDS in TB patients living in the lowlands of the Mafeteng district over the period of the three reporting years. The most infectious site of TB noted was pulmonary TB with 85.6% of the patients. In addition, most of them were new patients on TB treatment with 912 (82.2%) out of the total of 1,109 participating patients.

The prevalence of HIV/AIDS amongst the TB patients of the participating HCCs as well as the number of patients initiated for anti-retroviral therapy (ART) were analysed in this study. The results showed that the HIV/AIDS infection rate among TB patients was 780 (70.3%) of the study population of 1,109 TB patients. Most of these HIV/AIDS patients were from the Mafeteng HCC with 501 (64.2%) of the 1,109 patients. The most affected age group intervals among the patients were the young adult age group (>15 to 35 years) and the adult age group (>35 to 55 years) with 45.8% and 40.6% of the total 780 HIV/AIDS patients, respectively. Furthermore, with the exception of 1% of patients from the Motsekuoa HCC, all other HIV/AIDS positive patients were on ART.

7.3 Discussion

The cases of extra-pulmonary TB declined at a constant rate from reporting Year 1 to Year 3. In fact, in this study, TB notification cases declined substantially when comparing reporting Year 1 and 2 with reporting Year 3. It was also interesting to take note that the number of HIV/AIDS cases in the most affected young adult age group interval (>15 to 35) dropped in reporting Year 3. Ultimately, the number of HIV/AIDS cases in the age group interval of adults (>35 to 55) was more in reporting Year 3 compared with the number of cases in the young adult group in the same reporting year.

7.4 Study limitation

Only purposeful data readily available to analyse were included in this study. A few human errors in the handwritten registry books identified during the data capturing could not be corrected or included in the study. This included some patient information, such as CD4 counts that were not filled in for

some HIV/AIDS patients. This made it impossible to determine and analyse them. The occupation of the patients was not recorded, thus making it impossible to relate prevalence of TB influence by occupation. It would have been interesting to draw conclusions from information relating to the occupations, such as mining, industrial factories or domestic services, of the tuberculosis patients co-infected with HIV/AIDS living in the lowlands of the Mafeteng district in Lesotho.

7.5 Prospective recommendations

In order to improve financial resources, a big portion of the community and family members in Lesotho take on employment in neighbouring South Africa. Suggestions to improve the data capturing and information recorded for the patients in the study may be well worth investigating for future research.

Most of the patients who were HIV-positive were put on ART treatment. The exception was at Motsekuoa HCC where 1% of the patients were not on ART treatment. The reason for this lack of ART treatment is debatable and should be investigated further.

In the reporting years, Teba HCC never had any TB cases requiring retreatment. This successful treatment story indicates a very interesting trend. The alarmingly high mortality rates among female and male TB patients who fail to undergo HIV testing should also be investigated in much more detail. The true cause behind losing so many male and female TB patients in the sub-Saharan African countries may have other reasons than initially identified.

7.6 Conclusion

Possible routes of TB transmission because of limited infection control, drug resistance, poor TB prognosis and inefficiency of BCG vaccine remains challenging. Tuberculosis infection control measures at health facilities need to be assessed and strengthened continuously. This includes

administrative, managerial, environmental and personal protective measures to minimise the risk of TB transmission as well as proper treatment adherence. National and district level administrative bodies and health care centres should collaborate to strengthen the efforts and place TB and HIV/AIDS services among their priority interventions. Future researchers could consider assessing the main reasons behind the high prevalence of HIV/AIDS among male TB patients in the Mafeteng district of Lesotho.

LIST OF APPENDIXES

Appendix A: Ethical clearance certificate from Minister of Health Lesotho

LESOTHO

Ministry of Health
PO Box 514
Maseru 100

Category of Review:
[x] Initial Review
[ ] Continuing Annual Review
[ ] Amendment/Modification
[ ] Reactivation
[ ] Serious Adverse Event
[ ] Other _____

REF: ID161-2018

Date: January 22, 2019

To
Rethabile Ramosoeu
Central University of Technology,
Free State
Student Number 212002449

Dear Mr. Ramosoeu

RE PREVELANCE OF HIV/AIDS IN TUBERCULOSIS PATIENTS LIVING IN THE LOWLANDS OF MAFETENG DISTRICT IN LESOTHO.

This is to inform you that the Ministry of Health Research and Ethics Committee reviewed and **APPROVED** the above named protocol and hereby authorizes you to conduct the study according to the activities and population specified in the protocol. Departure from the approved protocol will constitute a breach of this permission.

This approval includes review of the following attachments:
[x] Protocol dated November 02, 2018
[ ] English informed consent form
[ ] Data collection tools in English and Sesotho
[ ] Participant materials *[insert types, versions)*
[x] Other materials: Letter of request for approval, CV, Enrollment Letter, Proof of registration

This approval is **VALID** until January 22, 2020.
Please note that an annual report and request for renewal, if applicable, must be submitted at least 6 weeks before the expiry date.

All serious adverse events associated with this study must be reported promptly to the MOH Research and Ethics Committee. Any modifications to the approved protocol or consent forms must be submitted to the committee prior to implementation of any changes.

We look forward to receiving your progress reports and a final report at the end of the study. If you have any questions, please contact the Research and Ethics Committee at rcumoh@gmail.com (or) 22226317.

Sincerely

DR. LUCY MAPOTA
Director General Health Services (a.i)

DR. Llang Bridget Maama-Maime
Member, National Health Research Ethics Committee
(NH-REC)

Appendix B: Letter of consent

Central University of Technology, Free State

FACULTY OF HEALTH AND ENVIRONMENTAL SCIENCES

Dear TB Coordinator or Public Health Nurse

District Health Management Team Masfeteng, LESOTHO

RE: PERMISSION TO GRANT ACCESS TO INFORMATION RELATING TO TUBERCULOSIS (TB) CASES IN YOUR DISTRICT.

With this letter I hereby request permission to access data from tuberculosis registries from health care centres in the lowlands area of the Mafeteng district.

I would like to pursue my M-Tech in Environmental Health at the Central University of Technology under the supervision of Dr. Jeanne Oosthuysen. The focus of this research is to gain an understanding on the prevalence of HIV/AIDS in tuberculosis patients living in the lowlands area of Mafeteng. To achieve this aim, the following objectives were formulated, to:

- Review the literature on TB and HIV;
- Source data of TB patients living in the foothills of the Mafeteng district;
- Identify TB patients that are HIV positive or are living with AIDS; and
- Record and analyse data;
- Reach conclusions

I would like to inform you that only patient data will be used and such data will not be linked to any specific individual or facility. Results obtained from this research shall remain confidential and only the results obtained shall form part of the report submitted. I also promise to conform to all the rules and regulations you may require of me.

For any queries or questions, please contact me on:

- +266 57888235 or email to rramosoeu75@gmail.com

DISTRICT PUBLIC HEALTH NURSE
MAFETENG DHMT
2018 -03- 07
TEL: 22 700 300
P.O. BOX 16
MAFETENG, 900, LESOTHO

Permission granted. Sign
Paulina Mokosoane Public Health Nurse

Appendix C: Certificate of language editing

20 October 2020

Att: Mr R Ramosoeu
Faculty of Health & Environmental Sciences
Central University of Technology
Private Bag X20539
Bloemfontein 9300

Per email to rramosoeu75@gmail.com

CERTIFICATION OF PROOFREADING & EDITING

Thesis Title: Prevalence of HIV/AIDS in Tuberculosis Patients Living in the Lowlands of Mafeteng District in Lesotho

Author: Rethabile Ramosoeu

Length: 123 pages, 26340 words

This confirms that the above thesis to be submitted in partial fulfilment for the degree of Master of Health: Environmental Health to the Central University of Technology, Free State, South Africa was proofread and edited for proper English language, grammar, punctuation and spelling.

This was executed by an experienced academic proficient in the English language. Neither the research content nor the author's intended meaning was altered in any way during the review. All references and citations were checked online.

All amendments were tracked with the Microsoft Word *Track Changes* feature. Therefore, the author had the option to reject or accept each change individually. For this reason, the edited work described here may not be identical to that submitted.

Yours faithfully

Bev Hourquebie
B.Sc (Hons) HED

Critters design studio cc
30 World's View Road • PIETERMARITZBURG • 3201
Fax: 086 678 5989 • Cell: 083 455 1324 • email: hawksonhillside@mweb.co.za

References

Abubakar, I., Chakaya, J., Maeurer, M. and Zumla, A. (2019). Towards optimal treatment for latent Mycobacterium tuberculosis infection. *The Lancet Respiratory Medicine*, 7(3): 195–197. DOI: https://doi.org/10.1016/S2213–2600(19)30036-0

Adhikari, N., Bhattarai, R., Basnet, R. and Joshi, L.R. (2018). Tuberculosis Infection Control Measures at Health Facilities providing Tuberculosis Services in Nepal. *SAARC Journal of Tuberculosis Lung Diseases and HIV/AIDS*, XVI(2): 20–26. DOI: 10.3126/saarctb.v16i2.23338

Akkerman, O., Aleksa, A., Alffenaar, J., Al-Marzouqi, N.H., Arias-Guillén, M., Belilovski, E., Bernal, E., Boeree, M., Borisov, S., Bruchfeld, J., Loidi, J.C., Cai, Q., Caminero, J., Gallardo, J.J., Centis, R., Codecasa, L., D'Ambrosio, L., Dalcolmo, M., Danila, E., Dara, M., Davidavičienė, E., Forsman, L.D., Jefe, J.D., Denholm, J., Duarte, R., Elamin, S.E., Ferrarese, M., Filippov, A., Ganatra, S.R., Garcia, A., García-García, J., Gayoso, R., Montoya, Á.M., Rosso, R.G., Gualano, G., Hoefsloot, W., Ilievska-Poposka, B., Jonsson, J., Khimova, E., Kuksa, L., Kunst, H., Laniado-Laborín, R., Li, Y., Magis-Escurra, C., Manfrin, V., Manga, S., Marchese, V., Robles, E.M., Maryandyshev, A., Matteelli, A., Migliori, G., Mullerpattan, J., Muñoz-Torrico, M., Hamdan, H.M., Marcos, M.N., Noordin, N.M., Palmero, D., Palmieri, F., Payen, M., Piubello, A., Pontali, E., Pontarelli, A., Quirós, S., Rendon, A., Skrahina, A., Šmite, A., Solovic, I., Sotgiu, G., Souleymane, M.B., Spanevello, A., Stošić, M., Tadolini, M., Tiberi, S., Udwadia, Z., Boom, M.V., Vescovo, M., Viggiani, P., Visca, D., Zhurkin, D. and Zignol, M. (2019). Surveillance of adverse events in the treatment of drug-resistant tuberculosis: A global feasibility study. *International Journal of Infectious Diseases,* 83: 72–76. DOI: https://doi.org/10.1016/j.ijid.2019.03.036

Aldridge, R.W., Zenner, D., White, P.J., Muzyamba, M.C., Loutet, M., Dhavan, P., Mosca, D., Hayward, A.C. and Abubakar, I. (2016). Prevalence of and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study. *The Lancet Infectious Diseases*, 16(8): 962–970. DOI: https://doi.org/10.1016/S1473–3099(16)00072–4

Alsdurf, H., Hill, P.C., Matteelli, A., Getahun, H. and Menzies, D. (2016). The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *The Lancet Infectious Diseases*, 16(11): 1269–1278. DOI: https://doi.org/10.1016/S1473–3099(16)30216–X

Asare, P., Asante-Poku, A., Prah, D.A., Borrell, S., Osei-Wusu, S., Otchere, I.D., Forson, A., Adjapong, G., Koram, K.A., Gagneux, S. and Yeboah-Manu, D. (2018). Reduced transmission of *Mycobacterium africanum* compared to *Mycobacterium tuberculosis* in urban West Africa. *International Journal of Infectious Diseases*, 73: 30–42. DOI: https://doi.org/ 10.1016/j.ijid.2018.05.014

Bamrah, S., Brostrom, R., Dorina, F., Setik, L., Song, R., Kawamura, L.M., Heetderks, A. and Mase, S. (2014). Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. *International Journal of Tuberculosis and Lung Disease*, 18(8): 912–918. DOI: https://doi.org/10.5588/ijtld.13.0028

Barberis, I., Bragazzi, N.L., Galluzzo, L. and Martini, M. (2017). The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. *Journal of Preventive Medicine and Hygiene*, 58(1): E9–E12. Available at URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC5432783>

Barbier, M. and Wirth, T. (2016). The Evolutionary History, Demography, and Spread of the Mycobacterium tuberculosis Complex. *Mircrobiology Spectrum*, 4(4): 1–21. DOI: https://doi.org/0.1128/microbiolspec.TBTB2-0008-2016

Barnabishvili, M., Ulrichs, T. and Waldherr, R. (2016). Role of acceptability barriers in delayed diagnosis of Tuberculosis: Literature review from high burden countries. *Acta Tropica*, 161: 106–113. DOI: https://doi.org/10.1016/j.actatropica.2016.06.014

Barzegari, S., Afshari, M., Movahednia, M. and Moosazadeh, M. (2019). Prevalence of anemia among patients with tuberculosis: A systematic review and meta-analysis. *The Indian Journal of Tuberculosis*, 66(2): 299–307. DOI: https://doi.org/10.1016/j.ijtb.2019.04.002

Bates, M., Ahmed, Y., Kapata, N., Maeurer, M., Mwaba, P. and Zumla, A. (2015). Perspectives on tuberculosis in pregnancy. *International Journal of Infectious Diseases*, 32: 124–127. DOI: https://doi.org/10.1016/j.ijid.2014.12.014

Berube, B.J., Russell, D., Castro, L., Choi, S., Narayanasamy, P. and Parish, T. (2019). Novel MenA inhibitors are bactericidal against *Mycobacterium tuberculosis* and synergize with electron transport chain inhibitors. *Antimicrobial Agents and Chemotherapy*, 63(6): 1–21. DOI: https://doi.org/10.1128/AAC.02661–18

Beyrer, C., Razak, M.H., Lisam, K., Chen, J., Lui, W. and Yu, X. (2000). Overland heroin trafficking routes and HIV-1 spread in south and south-east Asia. *AIDS*, 14(1): 75–83. DOI: https://doi.org/10.1097/00002030–200001070–00009

Brynildsrud, O.B, Pepperell, C.S., Suffys, P., Grandjean, L., Monteserin, J., Debech, N., Bohlin, J., Alfsnes, K., Pettersson, J.O., Kirkeleite, I., Fandinho, F., da Silva, M.A., Perdigao, J., Portugal,

I., Viveiros, M., Clark, T., Caws, M., Dunstan, S., Thai, P.V.K., Lopez, B., Ritacco, V., Kitchen, A., Brown, T.S., van Soolingen, D., O'Neill, M.B., Holt, K.E., Feil, E.J., Mathema, B., Balloux, F. and Eldholm, V. (2018). Global expansion of *Mycobacterium tuberculosis* lineage 4 shaped by colonial migration and local adaptation. *Science Advances*, 4(10): 1–12. DOI: https://doi.org/10.1126/sciadv. aat5869

Butov, D., Zaitseva, S., Butova, T., Stepanenko, G., Pogorelova, O. and Zhelezniakova, N. (2016). Efficacy and safety of quercetin and polyvinylpyrrolidone in treatment of patients with newly diagnosed destructive pulmonary tuberculosis in comparison with standard antimycobacterial therapy. *International Journal of Mycobacteriology*, 5(4): 446–453. DOI: https://doi.org/10.1016/j.ijmyco.2016.06.012

Cambau, E. and Drancourt, M. (2014). Steps towards the discovery of Mycobacterium tuberculosis by Robert Koch, 1882. *Clinical Microbiology and Infection*, 20(3): 196–201. DOI: https://doi.org/10.1111/1469–0691.12555

Caminero, J.A. and Scardigli, A. (2016). Tuberculosis in children. Challenges and opportunities. *Anales de Pediatría (English Edition)*, 85(6): 281–283. DOI: https://doi.org/10.1016/j.anpede.2016.10.002

Carter, D.J., Glaziou, P., Lönnroth, K., Siroka, A., Floyd, K., Weil, D., Raviglione, M., Houben, R.M.G.J. and Boccia, D. (2018). The impact of social protection and poverty elimination on global tuberculosis incidence: a statistical modelling analysis of Sustainable Development Goal 1. *The Lancet Global Health*, 6(5): E514–E522. DOI: https://doi.org/10.1016/S2214–109X(18)30195–5

Carvalho, A.C.C., Cardoso, C.A.A., Martire, T.M., Migliori, G.B. and Sant'Anna, C.C. (2018).

Epidemiological aspects, clinical manifestations, and prevention of pediatric tuberculosis from the perspective of the End TB Strategy. *Jornal Brasileiro de Pneumologia: publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia*, 44(2): 134–144. DOI: https://doi.org/10.1590/S1806-37562017000000461

Castro, S. de S., Scatena, L.M., Miranzi, A., Miranzi Neto, A. and Nunes, A.A. (2019). Characteristics of cases of tuberculosis coinfected with HIV in Minas Gerais State in 2016. *Revista do Instituto de Medicina Tropical de São Paulo*, 61: e21. DOI: https://doi.org/10.1590/S1678–9946201961021

Caulfield, A.J. and Wengenack, N.L. (2016). Diagnosis of active tuberculosis disease: From microscopy to molecular techniques. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 4: 33–43. DOI: https://doi.org/10.1016/j.jctube.2016.05.005

Centers for Disease Control and Prevention (CDC). (2011). *TB elimination – BCG vaccine*. Atlanta, Georgia: US Department of Health and Human Services. Available at URL: <https://www.cdc.gov/tb/publications/factsheets/ prevention/BCG.pdf>

Centers for Disease Control and Prevention (CDC). (2018). *Global HIV & TB – Country Profile: Lesotho*. Atlanta, Georgia: US Department of Health and Human Services. Available at URL: <https://www.cdc.gov/globalhivtb/where-we-work/Lesotho.pdf>

Centis, R., D'Ambrosio, L., Zumla, A. and Migliori, G.B. (2017). Shifting from tuberculosis control to elimination: Where are we? What are the variables and limitations? Is it achievable? *International Journal of Infectious Diseases*, 56: 30–33. DOI: https://doi.org/10.1016/j.ijid.2016.11.416

Chanda-Kapata, P., Kapata, N., Klinkenberg, E., Grobusch, M.P. and Cobelens, F. (2017). The prevalence of HIV among adults with pulmonary TB at a population level in Zambia. *BMC Infectious Diseases*, 17(1): 4–9. DOI: https://doi.org/10.1186/s12879–017–2345–5

Chandra, A., Firth, J., Sheikh, A. and Patel, P. (2013). Emergencies related to HIV infection and treatment (part 1). *African Journal of Emergency Medicine*, 3(3): 142–149. DOI: https://doi.org/10.1016/j.afjem.2013.03.005

Chatterjee, D. and Pramanik, A.K. (2015). Tuberculosis in the African continent: A comprehensive review. *Pathophysiology*, 22(1): 73–83. DOI: https://doi.org/10.1016/j.pathophys.2014.12.005

Chemeda, A., Abebe, T., Ameni, G., Worku, A. and Mihret, A. (2019). Utility of urine as a clinical specimen for the diagnosis of pulmonary tuberculosis in people living with HIV in Addis Ababa, Ethiopia. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 17: DOI: https://doi.org/10.1016/j.jctube.2019.100125

Cheon, S.A., Cho, H.H., Kim, J., Lee, J., Kim, H.J. and Park, T.J. (2016). Recent tuberculosis diagnosis toward the end TB strategy. *Journal of Microbiological Methods*, 123: 51–61. DOI: https://doi.org/10.1016/j.mimet.2016.02.007

Chetty, S., Ramesh, M., Singh-Pillay, A. and Soliman, M.E.S. (2017). Recent advancements in the development of anti-tuberculosis drugs. *Bioorganic and Medicinal Chemistry Letters*, 27(3): 370–386. DOI: https://doi.org/10.1016/j.bmcl.2016.11.084

Chia, L. and Crum-Cianflone, N.F. (2018). Emergence of multi-drug resistant organisms (MDROs) causing Fournier's gangrene. *The Journal of Infection*, 76(1): 38–43. DOI: https://doi.org/10.1016/j.jinf.2017.09.015

Craig, G.M. and Zumla, A. (2015). The social context of tuberculosis treatment in urban risk groups in the United Kingdom: A qualitative interview study. *International Journal of Infectious Diseases*, 32: 105–110. DOI: https://doi.org/10.1016/j.ijid.2015.01.007

Craig, G.M., Daftary, A., Engel, N., O'Driscoll, S. and Ioannaki, A. (2017). Tuberculosis stigma as a social determinant of health: a systematic mapping review of research in low incidence countries. *International Journal of Infectious Diseases,* 56: 90–100. DOI: https://doi.org/ 10.1016//j.ijid.2016.10.011

Cui, Z., Lin, M., Nie, S. and Lan, R. (2017). Risk factors associated with Tuberculosis (TB) among people living with HIV/AIDS: A pair-matched case-control study in Guangxi, China. *PLoS ONE*, 12(3): 1–12. DOI: https://doi.org/10.1371/journal.pone.0173976

Da Costa, C., Walker, B. and Bonavia, A. (2015). Tuberculosis vaccines – state of the art, and novel approaches to vaccine development. *International Journal of Infectious Diseases*, 32: 5–12. DOI: https://doi.org/10.1016/j.ijid.2014.11.026

Daftary, A. and Padayatchi, N. (2016). Provider perspectives on drug-resistant tuberculosis and human immunodeficiency virus care in South Africa: a qualitative case study. *International Journal of Tuberculosis and Lung Disease*, 20(11): 1483–1488. DOI: https://doi.org/ 10.5588/ijtld.16.0111

Darrah, P.A., DiFazio, R.M., Maiello, P., Gideon, H.P., Myers, A.J., Rodgers, M.A., Hackney, J.A., Lindenstrøm, T., Evans, T., Scanga, C., Prikhodko, V., Andersen, P., Lin, P.L., Laddy, D., Roederer, M., Seder, R.A. and Flynn, J.L. (2019). Boosting BCG with proteins or rAd5 does not enhance protection against tuberculosis in rhesus macaques. *NPJ Vaccines*, 4: 21. DOI: https://doi.org/10.1038/s41541–019–0113–9

Demile, B., Zenebu, A., Shewaye, H., Xia, S. and Alemu, A.G. (2018). Risk factors associated with multidrug-resistant tuberculosis (MDR-TB) in a tertiary armed force referral and teaching hospital, Ethiopia. *BMC Infectious Diseases*, 18(1): 1–10. DOI: https://doi.org/10.1186/s12879–018–3167–9

Dheda, K., Gumbo, T., Gandhi, N.R., Murray, M., Theron, G., Udwadia, Z., Migliori, G.B. and Warren, R. (2014). Global control of tuberculosis: from extensively drug-resistant to untreatable tuberculosis. *The Lancet Respiratory Medicine*, 2(4): 321–338. DOI: https://doi.org/ 10.1016/S2213–2600(14)70031–1

Dodd, P.J., Gardiner, E., Coghlan, R. and Seddon, J.A. (2014). Burden of childhood tuberculosis in 22 high-burden countries: A mathematical modelling study. *The Lancet Global Health*, 2(8): E453–E459. DOI: https://doi.org/10.1016/S2214–109X(14)70245–1

Dodd, P.J., Yuen, C.M., Sismanidis, C., Seddon, J.A. and Jenkins, H.E. (2017). The global burden of tuberculosis mortality in children: a mathematical modelling study. *The Lancet Global Health*, 5(9): E898–E906. DOI: https://doi.org/10.1016/S2214–109X(17)30289–9

Duarte, R., Lönnroth, K., Carvalho, C., Lima, F., Carvalho, A.C.C., Muñoz-Torrico, M. and Centis, R. (2018). Tuberculosis, social determinants and co-morbidities (including HIV). *Pulmonology*, 24(2): 115–119. DOI: https://doi.org/10.1016/j.rppnen.2017.11.003

Duarte, R., Migliori, G.B., Zumla, A. and Cordeiro, C.R. (2018). Strengthening tuberculosis control to advance towards elimination: The 2018 Rev. Port. Pneumol. (RPP) TB Series. *Pulmonology*, 24(2): 67–68. DOI: https://doi.org/10.1016/j.pulmoe.2018.01.002

Engelbrecht, M.C., Kigozi, N.G., Chikobvu, P., Botha, S. and van Rensburg, H.C.J. (2017).

Unsuccessful TB treatment outcomes with a focus on HIV co-infected cases: a cross- sectional retrospective record review in a high-burdened province of South Africa. *BMC Health Services Research*, 17(1): 1–10. DOI: https://doi.org/10.1186/s12913–017–2406–x

Faksri, K., Kaewprasert, O., Ong, R.T., Suriyaphol, P., Prammananan, T., Teo, Y., Srilohasin, P. and Chaiprasert, A. (2019). Comparisons of whole-genome sequencing and phenotypic drug susceptibility testing for Mycobacterium tuberculosis causing MDR-TB and XDR-TB in Thailand. *International Journal of Antimicrobial Agents*, 54(2): 109–116. DOI: https://doi.org/10.1016/j.ijantimicag.2019.04.004

Farajnia, S., Ansarin, K., Khalili, M., Shariat, M. and Sahebi, L. (2019). Effectiveness of Bacillus Calmette-Guerin vaccine on Drug Resistance in Mycobacterium tuberculosis Patients. *Research & Reviews: Journal of Microbiology and Biotechnology*, 17: 100126. Available at URL: <https://www.rroij.com/open-access/effectiveness-of-bacillus-calmetteguerin-vaccine-on-drug-resistance-in-mycobacterium-tuberculosis-patients.php?aid=87653>

Ferlazzo, G., Mohr, E., Laxmeshwar, C., Hewison, C., Hughes, J., Jonckheere, S., Khachatryan, N., de Avezedo, V., Egazaryan, L., Shroufi, A., Kalon, S., Cox, H., Furin, J. and Isaakidis, P. (2018). Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. *The Lancet Infectious Diseases*, 18(5): 536–544. DOI: https://doi.org/10.1016/S1473–3099(18)30100–2

Fiore-Gartland, A., Carpp, L.N., Naidoo, K., Thompson, E., Zak, D.E., Self, S., Churchyard, G., Walzl, G., Penn-Nicolson, A., Scriba, T.J. and Hatherill, M. (2018). Considerations for biomarker-targeted intervention strategies for tuberculosis disease prevention. *Tuberculosis*, 109: 61–68. DOI: https://doi.org/10.1016/j.tube.2017.11.009

Floyd, K., Glaziou, P., Zumla, A. and Raviglione, M. (2018). The global tuberculosis epidemic and progress in care, prevention, and research: an overview in year 3 of the End TB era. *The Lancet Respiratory Medicine*, 6(4): 299–314. DOI: https://doi.org/10.1016/S2213–2600(18)30057–2

Fogel, N. (2015). Tuberculosis: A disease without boundaries. *Tuberculosis*, 95(5): 527–531. DOI: https://doi.org/10.1016/j.tube.2015.05.017

Fonseca, J.D., Knight, G.M. and McHugh, T.D. (2015). The complex evolution of antibiotic resistance in *Mycobacterium tuberculosis*. *International Journal of Infectious Diseases*, 32: 94–100. DOI: https://doi.org/10.1016/j.ijid.2015.01.014

Friedrich, S.O., Kolwijck, E., Karinja, M.N., van der Merwe, L. and Diacon, A.H. (2019). Quantification of viable bacterial load in artificial sputum spiked with *Mycobacterium tuberculosis*. *Tuberculosis*, 115: 140–145. DOI: https://doi.org/10.1016/j.tube.2019.03.001

Frith, J. (2014). History of Tuberculosis. Part 1 – Phthisis, consumption and the White Plague. *Journal of Military and Veterans' Health*, 22(2): 29–35. Available at URL: <https://jmvh.org/article/history-of-tuberculosis-part-1-phthisis-consumption-and-the-white-plague>

Gakkhar, S. and Chavda, N. (2012). A dynamical model for HIV-TB co-infection. *Applied Mathematics and Computation*, 218(18): 9261–9270. DOI: https://doi.org/10.1016/j.amc.2012.03.004

Global Burden of Disease (GBD) Tuberculosis Collaborators. (2018). The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *The Lancet Infectious Diseases*, 18(3): 261–284. DOI: https://doi.org/10.1016/S1473–3099(17)30703–X

Graham, S.M., Grzemska, M., Brands, A., Nguyen, H., Amini, J., Triasih, R., Talukder, K., Ahmed, S., Amanullah, F., Kumar, B., Tufail, P., Detjen, A., Marais, B., Hennig, C. and Islam, T. (2015). Regional initiatives to address the challenges of tuberculosis in children: Perspectives from the Asia-Pacific region. *International Journal of Infectious Diseases*, 32: 166–169. DOI: https://doi.org/10.1016/j.ijid.2014.12.013

Granich, R. and Gupta, S. (2018). 90-90-90 HIV targets: implications for HIV-associated tuberculosis. *Current Opinion in HIV and AIDS*, 13(6): 528–537. DOI: https://doi.org/10.1097/coh.0000000000000498

Gröschel, M.I., Prabowo, S.A., Cardona, P., Stanford, J.L., and van der Werf, T.S. (2014). Therapeutic vaccines for tuberculosis – A systematic review. *Vaccine*, 32(26): 3162–3168. DOI: https://doi.org/10.1016/j.vaccine.2014.03.047

Gunda, D.W., Kalluvya, S.E., Kasang, C., Kidenya, B.R., Mpondo, B.C. and Klinker, H. (2017). Sub therapeutic drug levels among HIV/TB co-infected patients receiving Rifampicin in northwestern Tanzania: A cross sectional clinic based study. *Alexandria Journal of Medicine*, 53(3): 271–279. DOI: https://doi.org/10.1016/j.ajme.2016.10.001

Hanna, D., Romero, K. and Schito, M. (2017). Advancing tuberculosis drug regimen development through innovative quantitative translational pharmacology methods and approaches. *International Journal of Infectious Diseases*, 56: 208–211. DOI: https://doi.org/10.1016/j.ijid.2016.10.008

Harries, A.D., Zachariah, R., Corbett, E.L., Lawn, S.D., Santos-Filho, E.T., Chimzizi, R., Harrington, M., Maher, D., Williams, B.G. and de Cock, K.M. (2010). The HIV-associated tuberculosis epidemic—when will we act? *The Lancet*, 375(9729): 1906–1919. DOI: https://doi.org/

10.1016/S0140–6736(10)60409–6

Hayes-Larson, E., Hirsch-Moverman, Y., Saito, S., Frederix, K., Pitt, B., Maama, B.L. and Howard, A.A. (2017). Prevalence, patterns, and correlates of HIV disclosure among TB-HIV patients initiating antiretroviral therapy in Lesotho. *AIDS Care*, 29(8): 978–984. DOI: https://doi.org/10.1080/09540121.2017.1280124

Heller, T., Bélard, S., Weber, S.F. and Joekes, E. (2018). Response to the review article "Imaging in extrapulmonary tuberculosis" from the International Atomic Energy Agency Extra-pulmonary TB Consortium; March 2017, volume 56, pages 237–247. *International Journal of Infectious Diseases*, 66: 143. DOI: https://doi.org/10.1016/j.ijid.2017.11.004

Heunis, J.C., Kigozi, N.G., Chikobvu, P., Botha, S. and van Rensburg, H.C.J.D. (2017). Risk factors for mortality in TB patients: a 10-year electronic record review in a South African province. *BMC Public Health*, 17(38): 1–7. DOI: https://doi.org/10.1186/s12889–016–3972–2

Hirsch-Moverman, Y., Howard, A.A., Frederix, K., Lebelo, L., Hesseling, A., Nachman, S., Mantell, J.E., Lekhela, T., Maama, L.B. and El-Sadr, W.M. (2017). The PREVENT study to evaluate the effectiveness and acceptability of a community-based intervention to prevent childhood tuberculosis in Lesotho: study protocol for a cluster randomized controlled trial. *Trials*, 18(1): 1–11. DOI: https://doi.org/10.1186/s13063–017–2184–0

Hoagland, D.T., Liu, J., Lee, R.B. and Lee, R.E. (2016). New agents for the treatment of drug-resistant Mycobacterium tuberculosis. *Advanced Drug Delivery Reviews*, 102: 55–72. DOI: https://doi.org/10.1016/j.addr.2016.04.026

Honeyborne, I., Lipman, M., Zumla, A. and McHugh, T.D. (2019). The changing treatment landscape

for MDR/XDR-TB — Can current clinical trials revolutionise and inform a brave new world? *International Journal of Infectious Diseases*, 80: S23–S28. DOI: https://doi.org/10.1016/j.ijid.2019.02.006

Horton, K.C., MacPherson, P., Houben, R.M.G.J., White, R.G. and Corbett, E.L. (2016). Sex Differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *PLoS Medicine*, 13(9): 1–23. DOI: https://doi.org/10.1371/journal.pmed.1002119

Houben, R.M.G.J. and Dodd, P.J. (2016). The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Medicine*, 13(10): 1–8. DOI: https://doi.org/10.1371/journal.pmed.1002152

Howard, A.A., Hirsch-Moverman, Y., Frederix, K., Daftary, A., Saito, S., Gross, T., Wu, Y. and Maama, L.B. (2016). The START Study to evaluate the effectiveness of a combination intervention package to enhance antiretroviral therapy uptake and retention during TB treatment among TB/HIV patients in Lesotho: rationale and design of a mixed-methods, cluster-randomized trial. *Global Health Action*, 9(1): 31543. DOI: https://doi.org/10.3402/gha.v9.31543

Husain, A.A., Daginawala, H.F., Singh, L. and Kashyap, R.S. (2016). Current perspective in tuberculosis vaccine development for high TB endemic regions. *Tuberculosis*, 98: 149–158. DOI: https://doi.org/10.1016/j.tube.2016.03.006

Ibrahim, E., Baess, A.I. and Al Messery, M.A. (2017). Pattern of prevalence, risk factors and treatment outcomes among Egyptian patients with multidrug resistant tuberculosis. *Egyptian Journal of Chest Diseases and Tuberculosis*, 66(3): 405–411. DOI: https://doi.org/

10.1016/j.ejcdt.2016.11.002

Juarez-Eusebio, D.M., Munro-Rojas, D., Muñiz-Salazar, R., Laniado-Laborín, R., Martinez-Guarneros, J.A., Flores-López, C.A. and Zenteno-Cuevas, R. (2017). Molecular characterization of multidrug-resistant Mycobacterium tuberculosis isolates from high prevalence tuberculosis states in Mexico. *Infection, Genetics and Evolution*, 55: 384–391. DOI: https://doi.org/10.1016/j.meegid.2016.09.012

Kaufmann, S.H.E., Lange, C., Rao, M., Balaji, K.N., Lotze, M., Schito, M., Zumla, A.I. and Maeurer, M. (2014). Progress in tuberculosis vaccine development and host-directed therapies–a state of the art review. *The Lancet Respiratory Medicine*, 2(4): 301–320. DOI: https://doi.org/ 10.1016/S2213–2600(14)70033–5

Kendall, E.A. (2017). Tuberculosis in children: under-counted and under-treated. *The Lancet Global Health*, 5(9): E845–E846. DOI: https://doi.org/10.1016/S2214–109X(17)30305–4

Kigozi, G., Heunis, C., Chikobvu, P., Botha, S. and van Rensburg, D. (2017). Factors influencing treatment default among tuberculosis patients in a high burden province of South Africa. *International Journal of Infectious Diseases*, 54: 95–102. DOI: https://doi.org/ 10.1016/j.ijid.2016.11.407

Kinner, S.A., Snow, K., Wirtz, A.L., Altice, F.L., Beyrer, C. and Dolan, K. (2018). Age-Specific Global Prevalence of Hepatitis B, Hepatitis C, HIV, and Tuberculosis Among Incarcerated People: A Systematic Review. *Journal of Adolescent Health*, 62(3): S18–S26. DOI: https://doi.org/ 10.1016/j.jadohealth.2017.09.030

Kose, L.S., Moteetee, A. and van Vuuren, S. (2015). Ethnobotanical survey of medicinal plants used

in the Maseru district of Lesotho. *Journal of Ethnopharmacology*, 170: 184–200. DOI: https://doi.org/10.1016/j.jep.2015.04.047

Krauss, M.R., Harris, D.R., Abreu, T., Ferreira, F.G., Ruz, N.P., Worrell, C. and Hazra, R. (2015). Tuberculosis in HIV-infected infants, children, and adolescents in Latin America. *Brazilian Journal of Infectious Diseases*, 19(1): 23–29. DOI: https://doi.org/10.1016/j.bjid.2014.08.007

Kwok, P.C.L., Grabarek, A., Chow, M.Y.T., Lan, Y., Li, J.C.W., Casettari, L., Mason, A.J. and Lam, J.K.W. (2015). Inhalable spray-dried formulation of D-LAK antimicrobial peptides targeting tuberculosis. *International Journal of Pharmaceutics*, 491(1–2): 367–374. DOI: https://doi.org/10.1016/j.ijpharm.2015.07.001

Lange, C., Abubakar, I., Alffenaar, J.C., Bothamley, G., Caminero, J.A., Carvalho, A.C.C., Chang, K.C., Codecasa, L., Correia, A., Crudu, V., Davies, P., Dedicoat, M., Drobniewski, F., Duarte, R., Ehlers, C., Erkens, C., Goletti, D., Günther, G., Ibraim, E., Kampmann, B., Kuksa, L., de Lange, W., van Leth, F., van Lunzen, J., Matteelli, A., Menzies, D., Monedero, I., Richter, E., Rüsch-Gerdes, S., Sandgren, A., Scardigli, A., Skrahina, A., Tortoli, E., Volchenkov, G., Wagner, D., van der Werf, M.J., Williams, B., Yew, W., Zellweger, J. and Cirillo, D.M. (2014). Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: A TBNET consensus statement. *European Respiratory Journal*, 44(1): 23–63. DOI: https://doi.org/10.1183/09031936.00188313

Lee, S., Lee, Y., Lee, S., Islam, S.M.S. and Kim, S.Y. (2019). Toward Developing a Standardized Core Set of Outcome Measures in Mobile Health Interventions for Tuberculosis Management: Systematic Review. *JMIR mHealth and uHealth*, 7(2): DOI: https://doi.org/10.2196/12385

Lei, X., Liu, Q., Escobar, E., Philogene, J., Zhu, H., Wang, Y. and Tang, S. (2015). Public-private mix

for tuberculosis care and control: A systematic review. *International Journal of Infectious Diseases*, 34: 20–32. DOI: https://doi.org/10.1016/j.ijid.2015.02.015

Lemos, A.C.M. and Matos, E.D. (2013). Multidrug-resistant tuberculosis. *Brazilian Journal of Infectious Diseases*, 17(2): 239–246. DOI: https://doi.org/10.1016/j.bjid.2013.01.007

Lessells, R.J., Swaminathan, S. and Godfrey-Faussett, P. (2015). HIV treatment cascade in tuberculosis patients. *Current Opinion in HIV and AIDS*, 10(6): 439–446. DOI: https://doi.org/10.1097/COH.0000000000000197

Lessem, E., Cox, H., Daniels, C., Furin, J., McKenna, L., Mitnick, C.D., Mosidi, T., Reed, C., Seaworth, B., Stillo, J., Tisile, P. and von Delft, D. (2015). Access to new medications for the treatment of drug-resistant tuberculosis: Patient, provider and community perspectives. *International Journal of Infectious Diseases*, 32: 56–60. DOI: https://doi.org/10.1016/j.ijid.2014.12.012

Li, Z., Liu, H., Li, H., Dang, G., Cui, Z., Song, N., Wang, Q., Liu, S. and Chen, L. (2019). PE17 protein from Mycobacterium tuberculosis enhances Mycobacterium smegmatis survival in macrophages and pathogenicity in mice. *Microbial Pthogenesis*, 126: 63–73. DOI: https://doi.org/10.1016/j.micpath.2018.10.030

Lienhardt, C., Lönnroth, K., Menzies, D., Balasegaram, M., Chakaya, J., Cobelens, F., Cohn, J., Denkinger, C.M., Evans, T.G., Källenius, G., Kaplan, G., Kumar, A.M.V., Matthiessen, L., Mgone, C.S., Mizrahi, V., Mukadi, Y.D., Nguyen, V.N., Nordström, A., Sizemore, C.F., Spigelman, M., Squire, S.B., Swaminathan, S., van Helden, P.D., Zumla, A., Weyer, K., Weil, D. and Raviglione, M. (2016). Translational Research for Tuberculosis Elimination: Priorities, Challenges, and Actions. *PLoS Medicine*, 13(3): 1–11. DOI: https://doi.org/

10.1371/journal.pmed.1001965

Linguissi, L.S.G., Gwom, L.C., Nkenfou, C.N., Bates, M., Petersen, E., Zumla, A. and Ntoumi, F. (2017). Health systems in the Republic of Congo: challenges and opportunities for implementing tuberculosis and HIV collaborative service, research and training activities. *International Journal of Infectious Diseases*, 56: 62–67. DOI: https://doi.org/10.1016/j.ijid.2016.10.012

Locatelli, L., Cadamuro, M., Spirli, C., Fiorotto, R., Lecchi, S., Morell, C.M., Popov, Y., Scirpo, R., de Matteis, M., Amenduni, M., Pietrobattista, A., Torre, G., Schuppan, D., Fabris, L. and Strazzabosco, M. (2016). Macrophage recruitment by fibrocynstin-defective biliary epithelial cells promotes portal fibrosis in congenital hepatic fibrosis. *Hepatology*, 63(3): 965–982. DOI: https://doi.org/10.1002/hep.28382.

Luba, T.R., Tang, S., Liu, Q., Gebremedhin, S.A., Kisasi, M.D. and Feng, Z. (2019). Knowledge, attitude and associated factors towards tuberculosis in Lesotho: a population based study. *BMC Infectious Diseases*, 19(1): 1–10. DOI: https://doi.org/10.1186/s12879–019–3688–x

Lygizos, M., Shenoi, S.V., Brooks, R.P., Bhushan, A., Brust, J.C.M., Zelterman, D., Deng, Y., Northrup, V., Moll, A.P. and Friedland, G.H. (2013). Natural ventilation reduces high TB transmission risk in traditional homes in rural KwaZulu-Natal, South Africa. *BMC Infectious Diseases*, 13(1): 300. DOI: https://doi.org/10.1186/1471–2334–13–300

Magadi, M.A. (2011). Household and community HIV/AIDS status and child malnutrition in sub-Saharan Africa: Evidence from the demographic and health surveys. *Social Science and Medicine*, 73(3): 436–446. DOI: https://doi.org/10.1016/j.socscimed.2011.05.042

Mahtab, S. and Coetzee, D. (2017). Influence of HIV and other risk factors on tuberculosis. *South African Medical Journal*, 107(5): 428–434. DOI: https://doi.org/10.7196/SAMJ.2017.v107i5.11271

Maitra, A., Bates, S., Kolvekar, T., Devarajan, P.V., Guzman, J.D. and Bhakta, S. (2015). Repurposing-a ray of hope in tackling extensively drug resistance in tuberculosis. *International Journal of Infectious Diseases*, 32: 50–55. DOI: https://doi.org/10.1016/j.ijid.2014.12.031

Malangu, N. and Adebanjo, O.D. (2015). Knowledge and practices about multidrug-resistant tuberculosis amongst healthcare workers in Maseru. *African Journal of Primary Health Care and Family Medicine*, 7(1): 1–5. DOI: https://doi.org/10.4102/phcfm.v7i1.774

Manjareeka, M. and Nanda, S. (2013). Prevalence of HIV infection among tuberculosis patients in Eastern India. *Journal of Infection and Public Health*, 6(5): 358–362. DOI: https://doi.org/10.1016/j.jiph.2013.04.004

Marais, B.J. (2017). Improving access to tuberculosis preventive therapy and treatment for children. *International Journal of Infectious Diseases*, 56: 122–125. DOI: https://doi.org/10.1016/j.ijid.2016.12.015

Marais, B.J., Lönnroth, K., Lawn, S.D., Migliori, G.B., Mwaba, P., Glaziou, P., Bates, M., Colagiuri, R., Zijenah, L.S., Swaminathan, S., Memish, Z., Pletschette, M., Hoelscher, M., Abubakar, I., Hasan, R., Zafar, A., Pantaleo, G., Craig, G.M., Kim, P., Maeurer, M., Schito, M.L. and Zumla, A. (2013). Tuberculosis comorbidity with communicable and non-communicable diseases: Integrating health services and control efforts. *The Lancet Infectious Diseases*, 13(5): 436–448. DOI: https://doi.org/10.1016/S1473–3099(13)70015–X

Marais, B.J., Rabie, H. and Cotton, M.F. (2011). TB and HIV in children – advances in prevention and management. *Paediatric Respiratory Reviews*, 12(1): 39–45. DOI: https://doi.org/ 10.1016/j.prrv.2010.09.002

Marx, F.M., Yaesoubi, R., Menzies, N.A., Salomon, J.A., Bilinski, A., Beyers, N. and Cohen, T. (2018). Tuberculosis control interventions targeted to previously treated people in a high-incidence setting: a modelling study. *The Lancet Global Health*, 6(4): E426–E435. DOI: https://doi.org/ 10.1016/S2214–109X(18)30022–6

Marzouk, M., Ferjani, A., Dhaou, M., Ali, M.H., Hannachi, N. and Boukadida, J. (2013). Comparison of LED and conventional fluorescence microscopy for detection of acid-fast bacilli in an area with high tuberculosis incidence. *Diagnostic Microbiology and Infectious Disease*, 76(3): 306–308. DOI: https://doi.org/10.1016/j.diagmicrobio.2013.03.023

McBryde, E.S., Meehan, M.T., Doan, T.N., Ragonnet, R., Marais, B.J., Guernier, V. and Trauer, J.M. (2017). The risk of global epidemic replacement with drug-resistant Mycobacterium tuberculosis strains. *International Journal of Infectious Diseases*, 56: 14–20. DOI: https://doi.org/10.1016/j.ijid.2017.01.031

Mellado-Peña, M.J., Santiago-García, B., Baquero-Artigao, F., Moreno-Pérez, D., Piñeiro Pérez, R., Méndez Echevarría, A., Amador, J.T.R., Durán, D.G. and Julián, A.N. (2017). Tuberculosis treatment for children: An update. *Anales de Pediatría (English Edition)*, 88(1): 52.e1–52.e12. DOI: https://doi.org/10.1016/j.anpede.2017.05.001

Méndez-Samperio, P. (2019). Novel vaccination strategies and approaches against human tuberculosis. *Scandinavian Journal of Immunology*, 90(2): e12774 DOI: https://doi.org/ 10.1111/sji.12774

Mhimbira, F., Hiza, H., Mbuba, E., Hella, J., Kamwela, L., Sasamalo, M., Ticlia, M., Said, K., Mhalu, G., Chiryamkubi, M., Schindler, C., Reither, K., Gagneux, S. and Fenner, L. (2019). Prevalence and clinical significance of respiratory viruses and bacteria detected in tuberculosis patients compared to household contact controls in Tanzania: a cohort study. *Clinical Microbiology and Infection*, 25(1): 107.e1–107.e7. DOI: https://doi.org/10.1016/j.cmi.2018.03.019

Michot, J.M., Madec, Y., Bulifon, S., Thorette-Tcherniak, C., Fortineau, N., Noël, N., Lambotte, O., El Jahiri, Y., Delacour, H., Delfraissy, J.F. and Blanc, F.X. (2016). Adenosine deaminase is a useful biomarker to diagnose pleural tuberculosis in low to medium prevalence settings. *Diagnostic Microbiology and Infectious Disease*, 84(3): 215–220. DOI: https://doi.org/10.1016/j.diagmicrobio.2015.11.007

Ministry of Health (MOH), Government of Lesotho. (2016). *National Tuberculosis Programme: Policy and Manual*. Maseru, Lesotho: Ministry of Health. Available at URL: <http://158.232.12.119/hiv/pub/guidelines/lesotho_tb.pdf>

Ministry of Health (MOH) Lesotho and ICF International. (2016). *Lesotho Demographic and Health Survey 2014*. Maseru, Lesotho: Ministry of Health and ICF International. Available at URL: <https://www.dhsprogram.com/pubs/pdf/FR309/FR309.pdf>

Ministry of Health (MOH), Government of Lesotho. (2017). *Final report for a Joint Review of HIV/Tuberculosis and Hepatitis Programmes*. Maseru, Lesotho: Ministry of Health. Available at URL: <https://www.unaids.org/sites/default/files/country/documents/LSO_2018_countryreport.pdf>

Mntonintshi, M., O'Mahony, D., Mabunda, S. and Namugenyi, K.A.F. (2017). Undiagnosed tuberculosis in patients with HIV infection who present with severe anaemia at a district

hospital. *African Journal of Primary Health Care & Family Medicine*, 9(1): 1–6. DOI: https://doi.org/10.4102/phcfm.v9i1.1406

Mugomeri, E., Bekele, B.S., Mafaesa, M., Maibvise, C., Tarirai, C. and Aiyuk, S.E. (2017). A 30-year bibliometric analysis of research coverage on HIV and AIDS in Lesotho. *Health Research Policy and Systems*, 15(1): 1–9. DOI: https://doi.org/10.1186/s12961-017-0183-y

Mugomeri, E., Chatanga, P., Lefunyane, M., Ruhanya, V., Nyandoro, G. and Chin'ombe, N. (2015). Adherence to tuberculosis infection control guidelines by nurses in Lesotho. *American Journal of Infection Control*, 43(7): 735–738. DOI: https://doi.org/10.1016/j.ajic.2015.03.016

Mugomeri, E., Olivier, D. and van den Heever, W.M.J. (2018). Health system challenges affecting the implementation of isoniazid preventive therapy in people living with HIV in Lesotho. *HIV & AIDS Review*, 17(4): 299–307. DOI: https://doi.org/10.5114/hivar.2018.80263

Mulisa, G., Workneh, T., Hordofa, N., Suaudi, M., Abebe, G. and Jarso, G. (2015). Multidrug-resistant *Mycobacterium tuberculosis* and associated risk factors in Oromia Region of Ethiopia. *International Journal of Infectious Diseases*, 39: 57–61. DOI: https://doi.org/ 10.1016/j.ijid.2015.08.013

Musasa, J.I. (2011). Knowledge, attitude and practice with regard to tuberculosis and human immunodeficiency virus co-infection among patients with tuberculosis in Walvis Bay District, Namibia. MPH (Public Health). University of the Western Cape, Cape Town. Available at URL: <http://etd.uwc.ac.za/ xmlui/handle/11394/2583>

Musuka, G., Teveredzi, V., Mutenherwa, F., Chingombe, I. and Mapingure, M.P. (2018). Tuberculosis knowledge, misconceptions/myths in adults: findings from Lesotho, Malawi,

Namibia and Zambia Demographic Health Surveys (2013–2016). *BMC Research Notes*, 11(1): 1–6. DOI: https://doi.org/10.1186/s13104–018–3884–6

Mwangwa, F., Chamie, G., Kwarisiima, D., Ayieko, J., Owaraganise, A., Ruel, T.D., Plenty, A., Tram, K.H., Clark, T.D., Cohen, C., Bukusi, E.A., Petersen, M.L., Kamya, M.R., Charlebois, E., Havlir, D.V. and Marquez, C. (2017). Gaps in the child tuberculosis care cascade in 32 rural communities in Uganda and Kenya. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 9: 24–29. DOI: https://doi.org/10.1016/j.jctube.2017.10.003

Nagu, T.J., Aboud, S., Mwiru, R., Matee, M.I., Rao, M., Fawzi, W.W., Zumla, A., Maeurer, M.J. and Mugusi, F. (2017). Tuberculosis associated mortality in a prospective cohort in Sub Saharan Africa: Association with HIV and antiretroviral therapy. *International Journal of Infectious Diseases*, 56: 39–44. DOI: https://doi.org/10.1016/j.ijid.2017.01.023

Ntoumi, F., Kaleebu, P., Macete, E., Mfinanga, S., Chakaya, J., Yeboah-Manu, D., Bates, M., Mwaba, P., Maeurer, M.J., Petersen, E. and Zumla, A. (2016). Taking forward the World TB Day 2016 theme "Unite to End Tuberculosis" for the WHO Africa Region. *International Journal of Infectious Diseases*, 46: 34–37. DOI: https://doi.org/10.1016/j.ijid.2016.03.003

Orgeur, M. and Brosch, R. (2018). Evolution of virulence in the Mycobacterium tuberculosis complex. *Current Opinion in Microbiology*, 41: 68–75. DOI: https://doi.org/ 10.1016/j.mib.2017.11.021

Osewe, P.L. and Nkrumah, Y. (2018). *Managing Tuberculosis and Occupational Health in the Mining Sector in Southern Africa*. Health, Nutrition and Population Discussion Papers. Washington, DC: World Bank. DOI: https://doi.org/10.1596/30161

Padayatchi, N., Naidu, N., Friedland, G., Naidoo, K., Conradie, F., Naidoo, K. and O'Donnell, M.R. (2017). Turning the tide against tuberculosis. *International Journal of Infectious Diseases*, 56: 6–9. DOI: https://doi.org/10.1016/j.ijid.2017.01.012

Padhi, A., Sengupta, M., Sengupta, S., Roehm, K.H. and Sonawane, A. (2014). Antimicrobial peptides and proteins in mycobacterial therapy: Current status and future prospects. *Tuberculosis*, 94(4): 363–373. DOI: https://doi.org/10.1016/j.tube.2014.03.011

Pai, M. and Temesgen, Z. (2017). Mind the gap: Time to address implementation gaps in tuberculosis diagnosis and treatment. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 6: 14–15. DOI: https://doi.org/10.1016/j.jctube.2016.02.001

Pan, L., Jia, H., Liu, F., Sun, H., Gao, M., Du, F., Xing, A., Du, B., Sun, Q., Wei, R., Gu, S. and Zhang, Z. (2015). Risk factors for false-negative T-SPOT.TB assay results in patients with pulmonary and extra-pulmonary TB. *Journal of Infection*, 70(4): 367–380. DOI: https://doi.org/10.1016/j.jinf.2014.12.018

Parcell, B.J., Jarchow-MacDonald, A.A., Seagar, A.L., Laurenson, I.F., Prescott, G.J. and Lockhart, M. (2017). Three year evaluation of Xpert MTB/RIF in a low prevalence tuberculosis setting: A Scottish perspective. *Journal of Infection*, 74(5): 466–472. DOI: https://doi.org/10.1016/j.jinf.2017.02.005

Parsons, L.M., Somoskövi, Á., Gutiérrez, C., Lee, E., Paramasivan, C.N., Abimiku, A., Spector, S., Roscigno, G. and Nkengasong, J. (2011). Laboratory diagnosis of tuberculosis in resource-poor Countries: Challenges and opportunities. *Clinical Microbiology Reviews*, 24(2): 314–350. DOI: https://doi.org/10.1128/CMR.00059–10

Petersen, E., Maeurer, M., Marais, B., Migliori, G.B., Mwaba, P., Ntoumi, F., Vilaplana, C., Kim, K., Schito, M. and Zumla, A. (2017). World TB Day 2017: Advances, Challenges and Opportunities in the "End-TB" Era. *International Journal of Infectious Diseases*, 56: 1–5. DOI: https://doi.org/10.1016/j.ijid.2017.02.012

Pinto, C.M.A. and Carvalho, A.R.M. (2017). The HIV/TB coinfection severity in the presence of TB multi-drug resistant strains. *Ecological Complexity*, 32: 1–20. DOI: https://doi.org/10.1016/j.ecocom.2017.08.001

President's Emergency Plan for AIDS Relief (PEPFAR) (2017). *Lesotho Country Operational Plan FY 2016*. United States of America: US Department of State. Available at URL: <https://copsdata.amfar.org/ COPS/2016/Lesotho.pdf>

Raj, A., Singh, N., Gupta, K.B., Chaudhary, D., Yadav, A., Chaudhary, A., Agarwai, K., Basil, M.V., Prasad, R., Khuller, G. and Mehta, P.K. (2016). Comparative evaluation of several gene targets for designing a Multiplex-PCR for an early diagnosis of extrapulmonary tuberculosis. *Yonsei Medical Journal*, 57(1): 88–96. DOI: https://doi.org/10.3349/ymj.2016.57.1.88

Ramírez, S., Mejía, F., Rojas, M., Seas, C., van der Stuyft, P., Gotuzzo, E. and Otero, L. (2018). HIV screening among newly diagnosed TB patients: a cross sectional study in Lima, Peru. *BMC Infectious Diseases*, 18(1): 1–12. DOI: https://doi.org/10.1186/s12879–018–3037–5

Rendon, A., Centis, R., Zellweger, J.P., Solovic, I., Torres-Duque, C.A., Robalo Cordeiro, C., de Queiroz Mello, F.C., Manissero, D. and Sotgiu, G. (2018). Migration, TB control and elimination: Whom to screen and treat. *Pulmonology*, 24(2): 99–105. DOI: https://doi.org/10.1016/j.rppnen.2017.11.007

Rosner, D. and Markowitz, G. (1992). Consumption, Silicosis, and the Social Construction of Industrial Disease. *Yale Journal of Biology and Medicine*. 64(5): 481–498. PMCID: PMC2589494, PMID:

Sabbagh, P., Riahi, S.M., Gamble, H.R. and Rostami, A. (2019). The global and regional prevalence, burden, and risk factors for methicillin-resistant *Staphylococcus aureus* colonization in HIV-infected people: A systematic review and meta-analysis. *American Journal of Infection Control*, 47(3): 323–333. DOI: https://doi.org/10.1016/j.ajic.2018.06.023

Sabin, C.A. and Lundgren, J.D. (2013). The natural history of HIV infection. *Current Opinion in HIV and AIDS*, 8(4): 311–317. DOI: https://doi.org/10.1097/COH.0b013e328361fa66

Sah, S.K., Verma, S.C., Bhattarai, R., Bhandari, K. and Bhatta, G.K. (2016). Surveillance of HIV Infection among Patients with Tuberculosis in Nepal. *SAARC Journal of Tuberculosis, Lung Diseases and HIV/AIDS*, 12(1): 25–30. DOI: https://doi.org/10.3126/saarctb.v12i1.15939

Sathkumara, H.D., Pai, S., Aceves-Sánchez, M. de J., Ketheesan, N., Flores-Valdez, M.A. and Kupz, A. (2019). BCG Vaccination Prevents Reactivation of Latent Lymphatic Murine Tuberculosis Independently of $CD4^+$ T Cells. *Frontiers in Immunology*, 10: 532. DOI: https://doi.org/10.3389/fimmu.2019.00532

Schito, M., Hanna, D. and Zumla, A. (2017). Tuberculosis eradication versus control. *International Journal of Infectious Diseases*, 56: 10–13. DOI: https://doi.org/10.1016/j.ijid.2016.11.007

Scott, L., da Silva, P., Boehme, C.C., Stevens, W. and Gilpin, C.M. (2017). Diagnosis of opportunistic infections: HIV co-infections: tuberculosis. *Current Opinion in HIV and AIDS*, 12(2): 129–138. DOI: https://doi.org/10.1097/COH.0000000000000345

Sharma, S. (2019). Emerging treatment trends in pediatric TB. *Indian Journal of Tuberculosis*, 66(1): 214–217. DOI: https://doi.org/10.1016/j.ijtb.2019.02.010

Sharma, S.K., Mohan, A., Singh, A.D., Mishra, H., Jhanjee, S., Pandey, R.M., Singh, B.K., Sharma, R., Pallipamu, P.B., Pai, M. and Dheda, K. (2018). Impact of nicotine replacement therapy as an adjunct to anti-tuberculosis treatment and behaviour change counselling in newly diagnosed pulmonary tuberculosis patients: An open-label, randomised controlled trial. *Scientific Reports*, 8(1): 1–9. DOI: https://doi.org/10.1038/s41598–018–26990–5

Shimeles, E., Enquselassie, F., Aseffa, A., Tilahun, M., Mekonen, A., Wondimagegn, G. and Hailu, T. (2019). Risk factors for tuberculosis: A case–control study in Addis Ababa, Ethiopia. *PLoS ONE*, 14(4): 1–18. DOI: https://doi.org/10.1371/journal.pone.0214235

Streicher, E.M., Müller, B., Chihota, V., Mlambo, C., Tait, M., Pillay, M., Trollip, A., Hoek, K.G.P., Sirgel, F.A., Gey van Pittius, N.C., van Helden, P.D., Victor, T.C. and Warren, R.M. (2012). Emergence and treatment of multidrug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in South Africa. *Infection, Genetics and Evolution*, 12(4): 686–694. DOI: https://doi.org/10.1016/j.meegid.2011.07.019

Suen, L.J.W, Huang, H.M. and Lee, H.H. (2014). [A comparison of convenience sampling and purposive sampling]. *Hu li za zhi Journal of Nursing*, 61(3): 105–111. DOI: https://doi.org/ 10.6224/JN.61.3.105

Suresh, S., Sharath, B.N., Anita, S., Lalitha, R., Prasad, T.J. and Rewari, B.B. (2016). TB-HIV co-infection among pregnant women in Karnataka, South India: A case series. *Journal of Infection and Public Health*, 9(4): 465–470. DOI: https://doi.org/10.1016/j.jiph.2015.11.016

Tamez-Torres, K.M., Torres-Gonzalez, P., Cervera-Hernandez, M.E., Chavez-Mazari, B., Barrientos-Flores, C. de J., Bobadilla-del-Valle, M., Ponce-de-Leon, A. and Sifuentes-Osornio, J. (2018). Mycobacterium tuberculosis complex bacteremia among HIV and non-HIV patients in a Mexican tertiary care center. *Brazilian Journal of Infectious Diseases*, 22(5): 387–391. DOI: https://doi.org/10.1016/j.bjid.2018.10.274

Tanday, S. (2017). Will we ever eliminate tuberculosis, the voiceless disease? *The Lancet Respiratory Medicine*, 5(4): 256–257. DOI: https://doi.org/10.1016/S2213-2600(17)30080–2

Tarekegne, D., Jemal, M., Atanaw, T., Ebabu, A., Endris, M., Moges, F., Tessema, B. and Deressa, T. (2016). Prevalence of human immunodeficiency virus infection in a cohort of tuberculosis patients at Metema Hospital, Northwest Ethiopia: A 3 years retrospective study. *BMC Research Notes*, 9(1): 1–6. DOI: https://doi.org/10.1186/s13104–016–2004–8

The World Bank, (2019). *Tuberculosis Must Fall: Reducing the Rapid Transmission of Tuberculosis in the Mining Sector in Southern Africa*. Washington, DC: World Bank. Available at: URL <https://www.worldbank.org/en/results/2019/04/18/tuberculosis-must-fall-reducing-the-rapid-transmission-of-tuberculosis-in-the-mining-sector-in-southern-africa

Tiberi, S., Carvalho, A.C.C., Sulis, G., Vaghela, D., Rendon, A., Mello, F.C. de Q., Rahman, A., Matin, N., Zumla, A. and Pontali, E. (2017). The cursed duet today: Tuberculosis and HIV-coinfection. *Presse Medicale*, 46(2): e23–e39. DOI: https://doi.org/10.1016/j.lpm.2017.01.017

Tiberi, S., Pontali, E., Tadolini, M., D'Ambrosio, L. and Migliori, G.B. (2019). Challenging MDR-TB clinical problems – The case for a new Global TB Consilium supporting the compassionate use of new anti-TB drugs. *International Journal of Infectious Diseases*, 80: S68–S72. DOI: https://doi.org/10.1016/j.ijid.2019.01.040

Tornheim, J.A. and Dooley, K.E. (2019). The Global Landscape of Tuberculosis Therapeutics. *Annual Review of Medicine*, 70: 105–120. DOI: https://doi.org/10.1146/annurev–med–040717–051150

Turner, R.D. (2019). Cough in pulmonary tuberculosis: Existing knowledge and general insights. *Pulmonary Pharmacology & Theraupticss*, 55: 89–94. DOI: https://doi.org/10.1016/j.pupt.2019.01.008

Turner, R.D., Chiu, C., Churchyard, G.J., Esmail, H., Lewinsohn, D.M., Gandhi, N.R. and Fennelly, K.P. (2017). Tuberculosis Infectiousness and Host Susceptibility. *Journal of Infectious Diseases*, 216(Suppl 6): S636–S643. DOI: https://doi.org/10.1093/infdis/jix361

Uplekar, M., Weil, D., Lonnroth, K., Jaramillo, E., Lienhardt, C., Dias, H.M., Falzon, D., Floyd, K., Gargioni, G., Getahun, H., Gilpin, C., Glaziou, P., Grzemska, M., Mirzayev, F., Nakatani, H. and Raviglione, M. (2015). WHO's new End TB Strategy. *The Lancet*, 385(9979): 1799–1801. DOI: https://doi.org/10.1016/S0140–6736(15)60570–0

Vekemans, J., Gebreselassie, N., Zignol, M., Friede, M., Kasaeva, T. and Swaminathan, S. (2019). A new tuberculosis vaccine: breakthrough, challenges, and a call for collaboration. *The Lancet Infectious Diseases*, 19(2): 123–125. DOI: https://doi.org/10.1016/S1473–3099(19)30003–9

Vella, V., Broda, A. and Drobniewski, F. (2018). Should all suspected tuberculosis cases in high income countries be tested with GeneXpert? *Tuberculosis*, 110: 112–120. DOI: https://doi.org/10.1016/j.tube.2017.10.006

Verma, M., Furin, J., Langer, R. and Traverso, G. (2019). Making the case: developing innovative adherence solutions for the treatment of tuberculosis. *BMJ Global Health*, 4(1): e001323. DOI:

https://doi.org/10.1136/bmjgh–2018–001323

Whitehorn, J., Ayles, H. and Godfrey-Faussett, P. (2010). Extra-pulmonary and smear-negative forms of tuberculosis are associated with treatment delay and hospitalisation. *International Journal of Tuberculosis and Lung Disease*, 14(6): 741–744. Available at URL: <https://www.ingentaconnect.com/contentone/iuatld/ijtld/2010/00000014/00000006/art00013>

Whittemore, R. and Melkus, G. (2018). *Design Decisions in Research – Behavioral and Social Sciences Research, OBSSR E-Source* [online]. Bethesda, Maryland: Office of Behavioral & Social Science Research. Available at URL: <https://obssr.od.nih.gov/wp-content/uploads/2016/05/Design-Decisions-in-Research.pdf>

Wingfield, T., Tovar, M.A., Datta, S., Saunders, M.J. and Evans, C.A. (2018). Addressing social determinants to end tuberculosis. *The Lancet*, 391(10126): 1129–1132. DOI: https://doi.org/10.1016/S0140–6736(18)30484–7

World Health Organization (WHO). (2015). *Guidelines on the management of latent tuberculosis infection*. Geneva: World Health Organization. Available at URL: <https://www.who.int/tb/publications/latent-tuberculosis-infection/en/>

World Health Organization (WHO). (2016). *Global Tuberculosis Report 2016*. Geneva: World Health Organization. Available at URL: <https://apps.who.int/iris/handle/10665/250441>

World Health Organization (WHO). (2018). Country profiles for 30 high tb burden countries; 20 high TB burden countries based on absolute number of incident cases; 10 high TB burden countries based on severity of disease burden (incidence per capita). *Global Tuberculosis Report 2018, Annex 2*: 171–231. Available at URL: <https://www.who.int/tb/publications/global_report/

gtbr2018_annex2.pdf>

World Health Organization (WHO). (2018). *Global Tuberculosis Report 2018*. Geneva: World Health Organization. Available at URL: <https://apps.who.int/iris/handle/10665/274453>

World Health Organization (WHO). (2019). *WHO Guidelines on tuberculosis infection prevention and control, 2019 update*. Geneva: World Health Organization. Available at URL: <https://www.who.int/tb/publications/2019/guidelines-tuberculosis-infection-prevention-2019/en/>

Yone, E.W.P., Kuaban, C. and Kengne, A.P. (2012). HIV testing, HIV status and outcomes of treatment for tuberculosis in a major diagnosis and treatment centre in Yaounde , Cameroon: a retrospective cohort study. *BMC Infectious Diseases*, 12(1): 190. DOI: https://doi.org/ 10.1186/1471–2334–12–190

Zumla, A., Petersen, E., Nyirenda, T. and Chakaya, J. (2015). Tackling the Tuberculosis Epidemic in sub-Saharan Africa – unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) programme 2015–2024. *International Journal of Infectious Diseases*, 32: 46–49. https://doi.org/10.1016/j.ijid.2014.12.039