



**NAMIBIA UNIVERSITY
OF SCIENCE AND TECHNOLOGY**

**IMPACT OF DIABETES ON THE TREATMENT OF TB PATIENTS IN KHOMAS REGION,
NAMIBIA**

By

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Thesis presented in fulfilment of the requirements for the degree of Master of Health Sciences, Faculty of Health and Applied Sciences, Namibia University of Science and Technology, Windhoek, Namibia

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October 2019

DECLARATION

I, Anita Beukes, hereby declare that the work contained in the thesis entitled “Impact of Diabetes on the treatment of TB patients in Khomas Region, Namibia” is my own original work and that I have not previously in its entirety or in part submitted it at any university or other higher education institution for the award of a degree.

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DEDICATIONS

To my husband, Jan Beukes and my children Jiaan and Jeandrè who supported me and often had to make sacrifices to allow me to complete my studies.

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ABSTRACT

Introduction

Tuberculosis and diabetes mellitus are public health challenges globally. The World Health Organization (WHO) Global report on diabetes reiterated that diabetes is a well-known risk factor for tuberculosis (TB) and that diabetes is associated with poor tuberculosis treatment outcomes, while tuberculosis is linked with deteriorating glycemic control. Namibia is among the top 30 high TB burden countries in the world (WHO, 2016) and added to that is the increasing prevalence of diabetes among women and men of about 6% and 7% respectively as reported by National Demographic Health Survey (MoHSS, 2013). The report further reiterated that the prevalence of diabetes differs among the geographical regions as well as according to gender. The same distribution is also noted on the prevalence of TB in Namibia. This may suggest a possible connection in the prevalence of diabetes among TB cases and vice versa, which will have implications on the management of both diseases. However, no current or past surveillance data is available on diabetes and TB comorbidities in Namibia to support policy and management strategies for comorbidities of these two diseases. This study therefore aimed to assess the prevalence of diabetes among TB patients in the Khomas region and established if diabetes and TB comorbidity influences the treatment outcomes of TB patients

Methodology

This was a cross sectional study to determine the burden of Diabetes among active Tuberculosis patients in the Khomas region of Namibia and looked at the treatment regime, smear conversion and treatment outcomes of study participants.

The participants included in the study were active TB patients selected from public health facilities. Convenience sampling was done of TB patients visiting the facility according to the treatment follow-up dates. Only patients with drug susceptible TB, who consented for taking part in the study were included in the study. Each patient was assigned a study identification number for easy tracing of records recorded in the facility TB records. The targeted population for this study was TB patients within the Khomas region. This study population was sampled from 12 public health facilities. Data which was collected from patient files included demographics, TB classification, smear conversion at 2 and 5 months and HIV status. Patients were tested for diabetes using the HbA1c method as recommended by Clover Infopia,

Anyang-si, Gyeonggi-do, Korea) and Cobas/Roche, Mannheim, Germany. The methods were correlated before they were used on patient samples and quality control was processed as recommended by manufacturers. The results were interpreted according to the WHO criteria for diagnosis of diabetes using HbA1c. Data was analysed using Epi Info™ 7 and results presented as cross tabulations.

Results

In this study, the prevalence of Diabetes among TB patients in the Khomas region was 42% based on HbA1c testing and the WHO guideline of 6.5% as the cut-off for diabetes. This is higher than the pooled prevalence of 9.0% revealed by a meta-analysis of 16 studies conducted among tuberculosis patients in SSA. The study also revealed more men (65%) participated in the study and the prevalence of diabetes were higher among men (46%) than women (36%). In this study the prevalence of diabetes was the highest among the 65+ age group, followed by the >55 to ≤64 age group with 46%.

There was no statistical significance of being smear positive (p value = 0, 95), HIV positive (p value=0, 47) or being a new or previously treated patients (p value=0, 79) and testing positive for diabetes. There is also no statistical significance of smear conversion after 2 or 5 months of treatment and testing positive for diabetes with p values of 0, 89 and 0, 17 respectively.

The study participant's results showed an association between being on first line or other treatment regimens and testing positive for diabetes (p value = 0,012).

Conclusion & Recommendations.

The results of this current study showed that diabetes among TB patients was high in the Khomas region and mostly men and older people were affected by this co-morbidity. There was an association between treatment regimens for TB patients and diabetes.

Based on the results of this study, it is recommended to expand this study nationally in order to get a true reflection of the national impact of diabetes on the TB burden in Namibia and adjust programs and policies accordingly to better TBDM co-morbidities outcomes.

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ABBREVIATIONS

TB	Tuberculosis
WHO	World Health Organization
DM	Diabetes Mellitus
MoHSS	Ministry of Health and Social Services
NUST	Namibia University of Science and Technology
NIP	Namibia Institute of Pathology
NTLP	National TB and Leprosy Program
CNR	Case notification rate
WRD	WHO-approved rapid diagnostics
SSA	Sub-Saharan Africa
PLHIV	People Living with HIV
PTB	Pulmonary Tuberculosis
MTB	<i>Mycobacterium tuberculosis</i>
EPTB	Extra-pulmonary TB
AIDS	Acquired immune deficiency syndrome
HIV	Human immunodeficiency virus
MDR	Multi drug resistance
CNR	Case notification rate
SADC	Southern African Development Community
NAAT	Nucleic Acid Amplification Test)

RF	Rifampin (RF)
DST	drug sensitivity testing
LPA	Line-probe assay
MOTT	Mycobacterium other than tuberculosis
LAM	lipo-arabinomannan
LF	Lateral flow
FDC	Fixed dose combination
PDR	Poly-drug resistance
RR	Rifampicin resistance
XDR	Extensively drug-resistance
Hr	Isoniazid resistance
FPG	fasting plasma glucose
2-h PG	2-h plasma glucose
OGTT	oral glucose tolerance test
HbA1c	Glycated hemoglobin
EDTA	Ethylene Diamine Tetra acetic Acid
psp	pulmonary smear positive
psn	pulmonary smear negative

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Tuberculosis and diabetes mellitus are substantial public health challenges globally. The World Health Organization (WHO) Global report on diabetes reiterated that diabetes is a well-known risk factor for tuberculosis (TB) and that diabetes is associated with poor tuberculosis treatment outcomes, while tuberculosis is linked with deteriorating glycemic control (WHO, 2016).

In the last two decades, the incidence of diabetes has shown an extensive upturn globally with an estimated 422 million adults living with Diabetes mellitus (DM); this number is predicted to virtually increase twofold by 2030 due to upsurge in type 2 DM risk factors, particularly overweight or obese (Asmelash, 2019). Another source estimated the prevalence of diabetes in adults aged 20–79 years to be 8.8% in 2015 and anticipated it to increase to 10.4% in 2040 (Ogurtsova, 2017).

Sub-Saharan Africa (SSA), like the international community, is facing a growing prevalence of diabetes together with other non-communicable diseases with an estimated 12.1 million people living with diabetes in Africa in 2010, anticipated to rise to 23.9 million by 2030 (Hall, 2011). In Sub-Saharan Africa this inclination is evolving in a region struggling with peak rates of communicable diseases - together with the highest global prevalence of HIV, Tuberculosis and Malaria (Hall, 2011).

A systematic review (Workneh, Bjune, & Yimer, 2017) showed that DM among TB patients causes big challenges on a global level. In countries like Asia, North America and Oceania, the highest prevalence of DM among TB patients were recorded and elements related with TBDM comorbidity encompassed gender, old age, city residence, illicit drug use, alcoholism, smoking, inactive lifestyle, obesity, People Living with HIV (PLHIV), hypertension, pre-existing DM, uncontrolled glycaemia, being a PTB patient, and family history of DM (Workneh, Bjune, & Yimer, 2017).

China accounts for nearly 1, 5 million new TB cases annually, 17% of the global TB burden and also have 100 million people affected by DM whilst in 2011, India had 61.3 million diabetics and 1.98 million TB

cases; additionally Indonesia have 450,000 new TB cases every year and ranked 6th place in terms of DM cases globally (Zheng, Hu, & Gao, 2017).

In SSA, study outcomes concerning the prevalence of DM among TB patients vary by geographical region and the contextual features of the participants of the study as reported that the prevalence of DM among TB patients in SSA ranged from 1.9% in Benin to 38% in Nigeria (Alebel, 2019).

Namibia is among the top 30 high TB burden countries in the world (WHO, 2016) and added to that is the increasing prevalence of diabetes among women and men of about 6% and 7% respectively as reported by National Demographic Health Survey (MoHSS, 2013). The report further reiterated that the prevalence of diabetes differs among the geographical regions as well as according to gender. The same distribution is also noted on the prevalence of TB in Namibia as shown in figure 1.1 below (MoHSS, 2019). This phenomena may suggest a possible connection in the prevalence of Diabetes among TB cases and vice versa, which will have implications on the management of both diseases. However, no current or past surveillance data is available on diabetes and TB comorbidities in Namibia to support policy and management strategies for comorbidities of these two diseases.

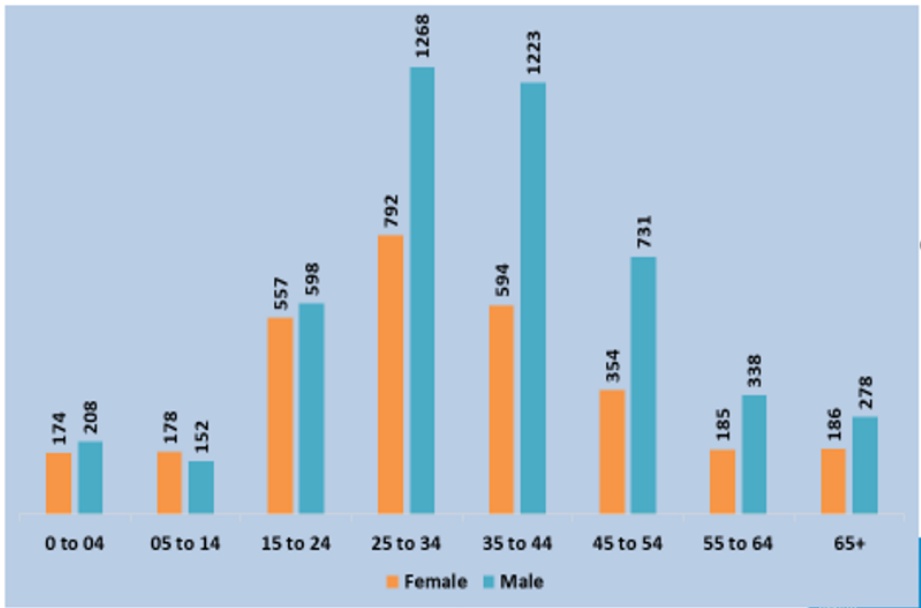


Figure 1. 1: Namibia age-sex distribution (MoHSS, 2019).

Pulmonary TB is the ninth most common problem in diabetes and due to an escalating prevalence of DM, the relative impact of DM on the TB epidemic is growing (Baghaei, 2013).

This study aims to assess the prevalence of diabetes among TB patients in the Khomas region and establish if diabetes and TB comorbidity influences the treatment outcomes of TB patients.

1.2 Literature Review

1.2.1 Tuberculosis disease

Tuberculosis (TB) is a communicable disease caused by *Mycobacterium tuberculosis* (MTB) that primarily affects the lungs causing pulmonary Tuberculosis (PTB). *Mycobacterium tuberculosis*, which is from the Mycobacteriaceae family is a rod shape, non-motile obligate aerobe bacterium; hence the bacilli are typically found in the well-aerated upper lobes of the lungs in classic MTB cases (Todar, 2019). Todar further explains that the virulence of MTB is extremely complex and multifaceted because the bacterium does not produce any toxins but it owns an enormous catalog of structural and physiological properties that impacts virulence and pathology of TB.

MTB has certain characteristics that add to its virulence. The TB bacillus gains entry into the cell by directly binding to mannose receptors on macrophages via the cell wall-associated mannosylated glycolipid, LAM. It can grow intracellularly which provides an effective way to escape the immune system (Todar, 2019). After MTB is phagocytosed, it can prevent phagosome-lysosome fusion by excretion of a protein that transforms the phagosome membrane. It may linger in the phagosome or leak from the phagosome, but in both cases it discovers a safe way to grow in the macrophage (Todar, 2019).

Todar, (2019) reported other characteristics like the slow generation time of MTB, causing the immune system not to easily distinguish the bacteria in order to trigger an elimination response. The high lipid concentration in cell wall causes impenetrability and resistance to antimicrobial agents, hampers killing by acidic and alkaline compounds in either the intracellular and extracellular locations, and confers resistance to osmotic lysis via complement deposition and attack by lysozyme (Todar, 2019).

Mycobacterium tuberculosis is an acid-fast bacilli and it causes PTB disease when the bacilli reach the pulmonary alveoli after inhalation. As a granulomatous inflammatory condition, TB triggers stages of tissue damage and necrosis followed by healing and fibrosis (Parvizi & Kim, 2010).

Tuberculous mycobacteria repel demolition by alveolar macrophages and reproduce, forming the major lesion or tubercle; they then move to regional lymph nodes, cross into the circulation, and re-enter the

lungs (McMurray, 1996). TB bacteria can also attack other parts of the body such as the spine, lymph nodes, brain and kidneys; this is known as extra-pulmonary TB (EPTB) (Ismael, 2019).

Figure 1.2 below extracted from the national TB guidelines (MoHSS, 2019) shows the model for TB epidemiology, displaying the impact of the main risks factors at various stages from infection to disease.

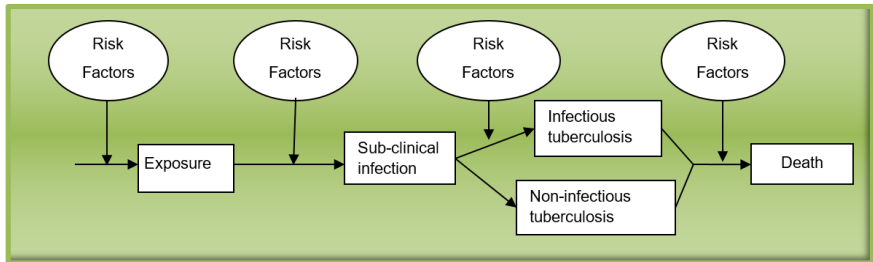


Figure 1. 2: Model for TB epidemiology (MoHSS, 2019).

The main drivers for TB disease are cited from the Namibia National TB guidelines, MoHSS in Table 1.1 below.

Table 1. 1: Main risk factors for the spread and burden of TB (MoHSS, 2019)

RISKS RELATED TO:	RISK FACTORS
1. Exposure	- Population density - Family size - Climatic conditions - Age of source of infection
2. Sub-clinical infection	- Airborne transmission through infectious droplet nuclei - Characteristics of the infectious patient - Air circulation and ventilation - Reducing expulsion of infectious material from source case - Host immune response - Other modes of transmission: <i>M. bovis</i>
3. TB disease	- HIV infection - Other medical conditions (e.g. diabetes mellitus) - Age - Genetic factors - Environmental factors - Pregnancy - Re-infection
4. Death	- Site of TB - Type of TB - Timeliness of diagnosis - HIV co-infection - Other comorbidities

The most commanding PTB symptoms according to the Namibia National TB guidelines are persistent cough for 2 weeks or more, hemoptysis (coughing up blood), chest pain, night sweats, dyspnea (shortness of breath), loss of appetite and loss of weight (MoHSS, 2019). However, when TB affects other body parts, signs and symptoms can vary based on the organ involved like TB of the spine can cause back pain (Fuentes Ferrer et al., 2012) while blood in urine can be a sign of kidney TB (Kapoor, 2008).

1.2.2 Transmission of TB

Transmission of TB takes place when individuals with infectious TB cough, sneeze, talk or spit propelling TB bacilli into the air. One cough can yield 3,000 infectious droplet nuclei and although direct sunlight destroys tubercle bacilli in minutes, they can stay alive in dark, stuffy locations for extended periods of time (Dye, 2006). The minute droplet nuclei sidestep the barricades of the bronchi and infiltrate into the terminal alveoli of the lungs, where duplication and infection starts (Dye, 2006). Transmission is more intense in crowded, poorly ventilated spaces with little ambient sunlight as it increases the likelihood of inhalation of infectious TB bacilli present in the air. If not treated, a person with active pulmonary TB disease will infect, on average, between 10 and 15 people every year (WHO, 2019). The possibility of becoming infected with TB is higher for people who have close contact with an individual with untreated TB (Association, 2018). American Lung Association, 2018 further states that those at risk people include people with infectious TB disease friends and family and people living in countries with a high TB burden like some African and Asian countries. Other vulnerable groups at risk for TB transmission are immune-compromised people like PLHIV and diabetics, homeless persons, injection drug users, smokers and people living or working in congregate settings like correctional facilities, nursing homes and hospitals.

TB transmission can also happen through other avenues. A study published in *Thorax* (Classen et al, 1999) twenty years ago, already suggested that while in low incidence areas transmission of TB often takes place in small areas like the household, in high incidence areas contact outside the house plays a major role in the transmission of TB. The study revealed that in a low income area with social drinking as the major recreational activity, 74% of all the patients drank regularly in social groups and therefore outdoor contact in social groups can be very close and intimate which could easily have contributed to the transmission of TB (Classen et al, 1999).

A study done in Brazil (Dowdy et al, 2012), concluded that geographic heterogeneity in TB transmission results in hotspots that may play an unequal role in spreading TB epidemics. The Brazil study further alluded that under conceivable situations, a hotspot with 6% of a city's inhabitants can attribute 35% or more of its ongoing TB transmission. It is therefore crucial to focus TB control efforts disproportionately on high transmission areas to have similar impact on long-term, community-wide TB incidence as achieving the same targets in the general community.

1.2.3 Types of TB

When people become infected with *M. tuberculosis* and the bacilli lies dormant in the body for many years without making one sick, it is called latent TB infection. In most cases, people inhale TB bacteria and they become infected; however, their immune system is capable of fighting the bacteria from growing into TB disease. People with latent TB infection do not feel sick, do not have any symptoms, and cannot spread TB bacteria to others (CDC, 2014).

In a person with a compromised immune system, the TB bacilli become active in the body and multiply. In such instances, the person will progress from having latent TB infection to being sick with TB disease. Factors that compromise the immune system and therefore stimulate the development of TB infection to TB disease are HIV infection, malnutrition, age, diabetes and cancer. WHO recommended that these high risk groups especially HIV infected persons receive isoniazid preventive therapy or similar treatment to prevent them from developing TB disease (WHO, 2011). The WHO guidelines further state that the chances of acquiring TB is between 20 and 37 times higher in people living with HIV than among those who do not have HIV infection. Figure 1.3 shows the differences between latent TB and TB disease.

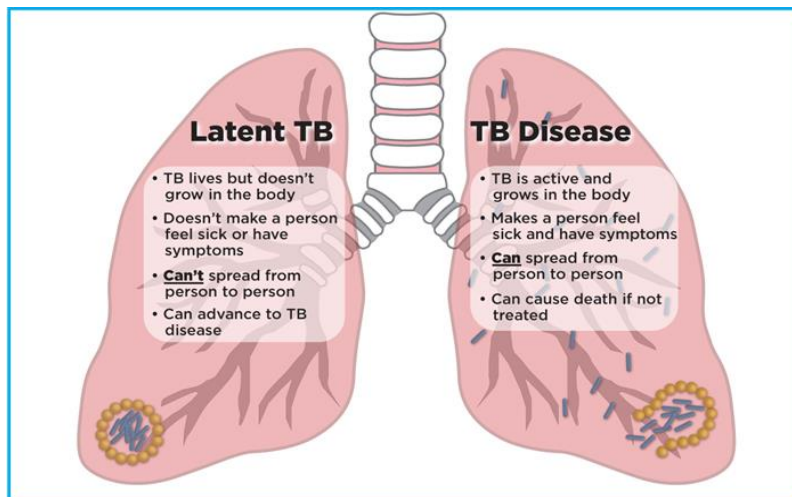


Figure 1. 3: Latent vs TB disease (TBFACTS.ORG, 2019)

1.2.4 Epidemiology of TB

1.2.4.1 Global epidemiology of TB

Notwithstanding centuries of scientific action and social struggle, tuberculosis continues to claim more than 1.6 million lives each year and continues to kill more people than any other infectious disease (Cox & Nicol, 2018). Tuberculosis is the number nine cause of death worldwide; resistance to antibiotics is on

an upward trend which creates a key hurdle to effective tuberculosis control globally (Dara & Zachariah, 2018).

Tuberculosis was the primary reason of 1.3 million deaths among human immunodeficiency virus (HIV)-negative people in 2016, surpassing the over-all number of HIV/acquired immune deficiency syndrome (AIDS) deaths and additionally was the causative agent of 374,000 HIV deaths (Glaziou, Floyd, & Riviglione, 2018). Even with the achievements gained with 90 years of vaccination (Bloom et al, 2017) and chemotherapy in the last seven decades, TB remains the top infectious killer worldwide (Glaziou, Floyd, & Riviglione, 2018).

Data from the Global TB Report indicated that in 2017, 6.4 million new cases of TB were notified, however it was only equivalent to 64% of the estimated 10.0 million new cases that occurred in 2017 (WHO, 2018). In 2017 WHO estimated that 90% of TB cases were adults (aged ≥ 15 years), 64% were male, and 9% were people living with HIV. The report further stated that 80% of the 3.6 million global shortfall comes from 10 countries, of which India (26%), Indonesia (11%) and Nigeria (9%) are on top of the list (WHO, 2018). Figure 1.4 below shows global estimated TB incidence rates of 2017.

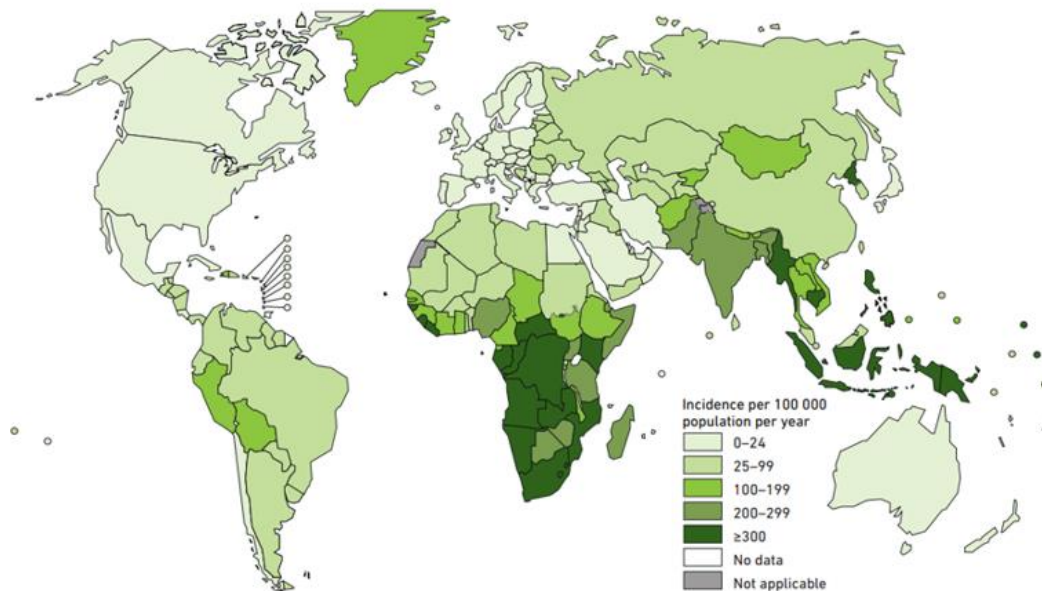


Figure 1. 4: Map of global estimated TB incident rates, 2017 (WHO, 2018)

TB ranks among the top 10 leading causes of death and was the top cause of death by a single infectious agent in the world in 2016 (WHO, 2018) as portrayed in Figure 1.5 below.

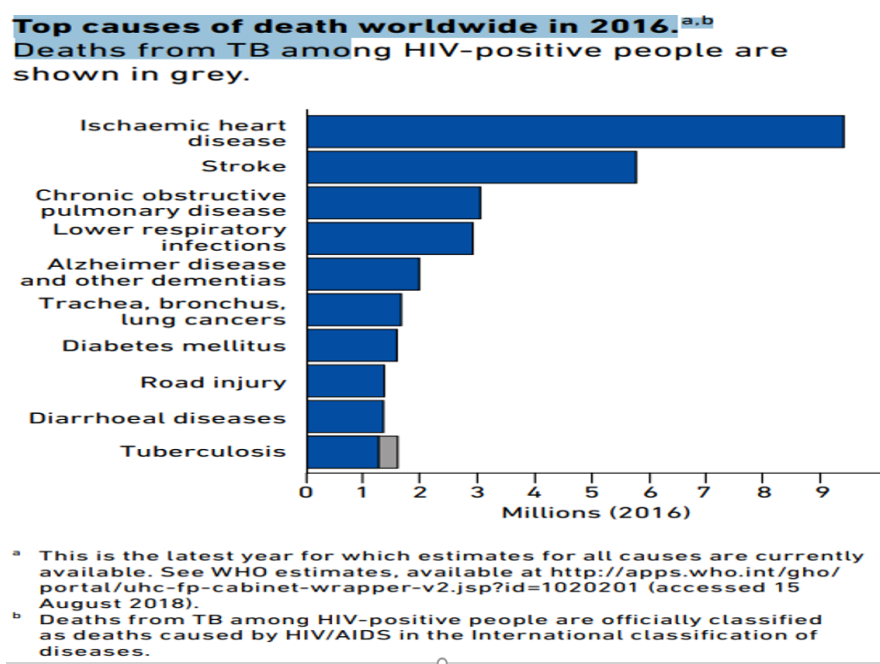


Figure 1. 5: Top causes of death worldwide in 2016 (WHO, 2018)

The report further states that an estimated 1.3 million people died of TB, in addition to 300 000 TB deaths among HIV-positive co-infected people (WHO, 2018).

The TB burden is fueled by the increased public health crisis of Multi drug resistance (MDR-TB) to the most effective first line anti TB drugs. MDR TB accounted for 82% of the estimated 558,000 people that developed drug resistant TB in 2017 (WHO, 2018). However, tuberculosis death rates have dropped by 22% worldwide and an expected 49 million lives were saved between 2000 and 2015 through effective diagnosis and treatment (Onyebujoh, Thirumala, & Piatek, 2017)

Tuberculosis is a key source of causing pulmonary and extra-pulmonary TB disease, and death in children in high burden areas but is also seen in low prevalence settings because of movement of people through global travel, population immigration, and refugee relocation (Marais & Schaaf, 2019).

1.2.4.2 Epidemiology of TB in the African Region

Twenty six percent of the projected incidence of all tuberculosis cases comes from Africa and is double the worldwide estimated incidence rates (239/100 000 people) of new tuberculosis cases (Onyebujoh, Thirumala, & Piatek, 2017). Death rates due to TB in Africa are triple the global average and even though TB incidence rates are decreasing since 2000 in sub-Saharan Africa, the tuberculosis/HIV dual epidemic

complicates efforts to correctly diagnose and effectively treat both diseases (Onyebujoh, Thirumala, & Piatek, 2017).

On August 26, 2005, the WHO Regional Committee for Africa declared TB as an emergency in response to an epidemic that quadrupled in number. In 2016, 2.5 million people fell ill with TB in the African region, accounting for a quarter of new TB cases worldwide. An estimated 417,000 people died from the disease in the African region accounting for about 25% of TB deaths globally (WHO, 2018).

In 2017, WHO estimated that Africa accounted for 25% of the 10 million TB incident cases (WHO, 2018). In the WHO, global report it is further estimated that the 30 high TB burden countries account for 87% of all global incident cases and 16 of these countries are located on the African continent. In 2017, 9% of the global number of new TB cases were from people living with HIV and 72% of those were from the African region (WHO, 2018).

The incidence rates of the African countries mostly affected by TB and listed among the 30 high burden countries are Angola(359), DR Congo(322), Ethiopia(164), Kenya(319), Mozambique(551), Nigeria(219), South Africa(567), UR Tanzania(269), Central African Republic(423), Congo(376), Lesotho(665), Liberia(308), Namibia(423), Sierra Leone(301), Zambia(361) and Zimbabwe(221) (Kanabus, 2018).

1.2.4.3 Epidemiology of TB in Namibia

In 2004, Namibia reported 16,156 cases of all forms of tuberculosis but the reported TB cases have since been declining steadily to 8855 cases reported in 2017 (MoHSS, 2017). Even though the case notification rate (CNR) decreased from 822 in 2004 to 374 in 2017, Namibia's CNR is still among the highest in the world.

The Deputy Health minister, Ms. Juliet Kavetuna disclosed in an interview held during the launch of the parliamentary TB caucus in Windhoek in 2018 that about 700 people died from tuberculosis-related infections in Namibia in 2017. She cited that "For our small population, 700 people is far too many deaths from one disease. This will have a devastating impact across the Southern African Development Community (SADC) region towards achieving the World Health Organization's End TB Strategy by 2035" (Kavetuna, 2018).

Namibia conducted its first TB Disease Prevalence Survey in 2017 to 2018 and the final prevalence rate of bacteriologically confirmed TB determined in this survey was 465/100,000(95%CI: 340-590) (MOHSS,

2019). This outcome confirms WHO’s estimate range of 250-799/100,000 population and Namibia’s position among the 30 TB high burden countries globally. Namibia is currently rated as having the 11th highest incidence rate of TB in the world and drug resistance is a key risk, with 7% of all TB patients in Namibia presenting resistance to the main first line medicine which necessitates multifaceted and costly second line treatment (US Embassy Namibia, 2019).

Figure 1.6 below shows the trend of TB case notification rates of ‘All Forms’ TB from 2007 to 2018 in Namibia.

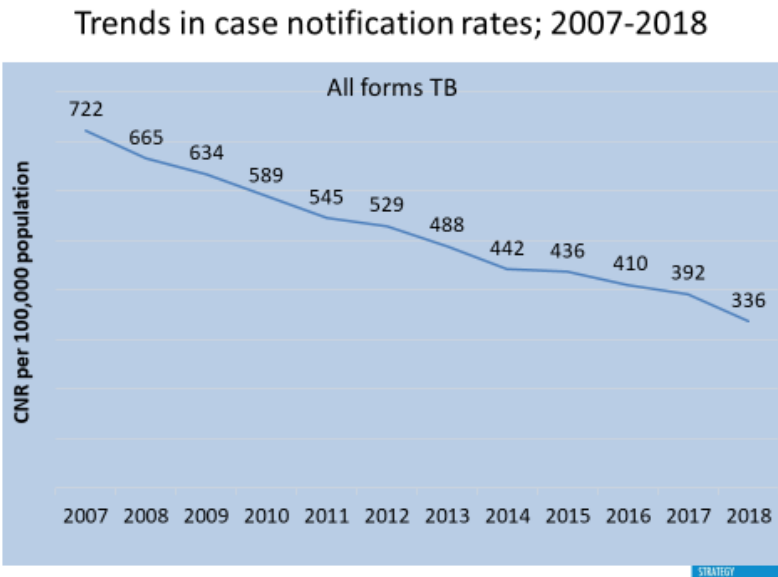


Figure 1. 6: Trends in CNR 2007-2018 in Namibia (MoHSS, 2019)

The burden of TB disease differs from region to region in Namibia, with Khomas, Ohangwena and Erongo regions reporting the highest number of cases as indicated in Figure 1.7 below (MoHSS, 2019).

Regional distribution of TB cases, 2017-2018

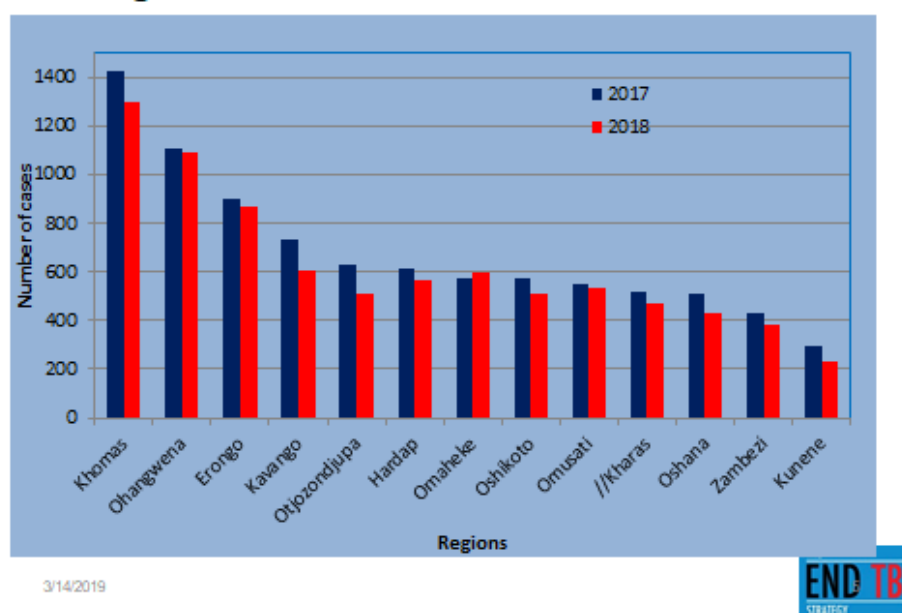


Figure 1. 7: All forms of TB cases by Namibian regions in 2017-2018 (MoHSS, 2019)

The burden of TB also differ from facility catchment population as indicated in table 1.2 of the Khomas facilities below.

Table 1. 2: TB patient's contribution per facility in the Khomas region (MoHSS, 2016)

Facility	forms of TB per facility (n)	Contribution per facility (%)	Expected Patients to be tested (n)
Katutura Hosp	251	16.1	62
Katutura HC	176	11.3	43
Khomasdal HC	95	6.1	23
Robert Mugabe	78	5.0	19
Donkerhoek clinic	94	6.0	23
Otjimuiise clinic	107	6.9	26
Okuryangava HC	299	19.2	73
Groot Aub clinic	23	1.5	6
<u>Dordabis clinic</u>	8	0.5	2
Hakahana clinic	212	13.6	52
Wanaheda clinic	214	13.8	53
Baumgartsbrum	1	0,0	0
Total	1558	100	382

1.2.5 Management of TB

1.2.5.1 Clinical Diagnosis of TB

Active TB case finding is defined as the systematic screening of people with signs and symptoms of active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly (WHO, 2019).

Routine screening of presumptive TB cases in Namibia is done as reflected in the flowchart (Figure 1.8) below as guided by the Namibia National TB guidelines (MoHSS, 2019).

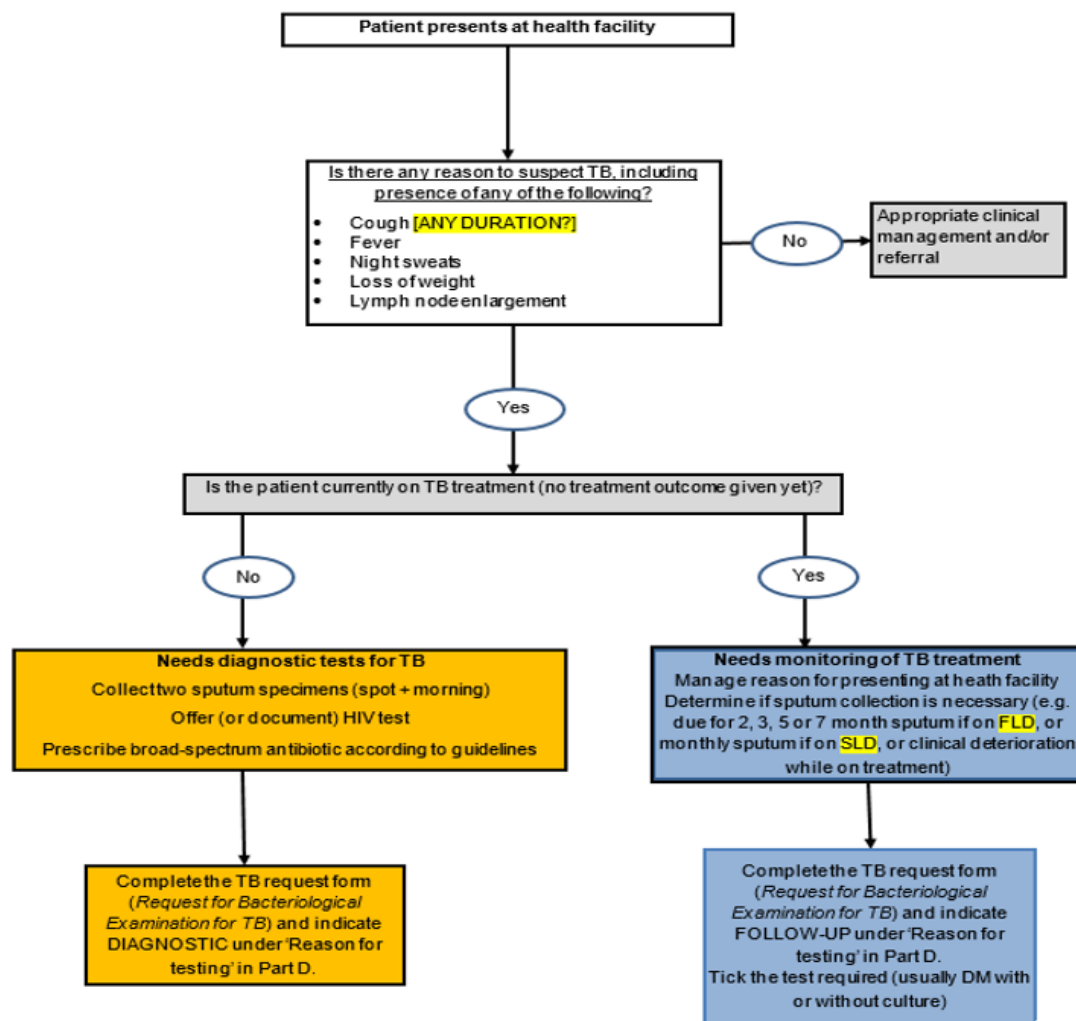


Figure 1.8: Diagnostic flow chart for TB (MoHSS, 2019)

1.2.5.2 Laboratory diagnosis of TB

Screening Tests

For more than 125 years smear microscopy was the most widely used test for TB diagnosis and efforts to improve techniques were non-existent, therefore TB tests were antiquated and inadequate (Small, 2010). TB diagnosis globally still depended on methods that are supposed to isolate the bacteria, which is a key drawback for low mycobacterial load. Hence, the reasons for delayed diagnosis of smear-negative TB or diagnosis made is centered on the clinical reaction to empiric anti-TB treatment without microbiological confirmation (Ryu, 2015).

A major milestone for TB diagnosis was reached on December 8, 2010 when WHO endorsed a new and novel rapid test for tuberculosis, especially in countries most affected by TB disease. Gene X-pert

MTB/RIF, a fully automated NAAT (nucleic acid amplification test) detects MTB and resistance to rifampin (RF) within 90 minutes, which is a revolution in TB care and control (WHO, 2019). Figure 1.9 outlines the step by step MTB/RIF test procedure on Gene X-pert.

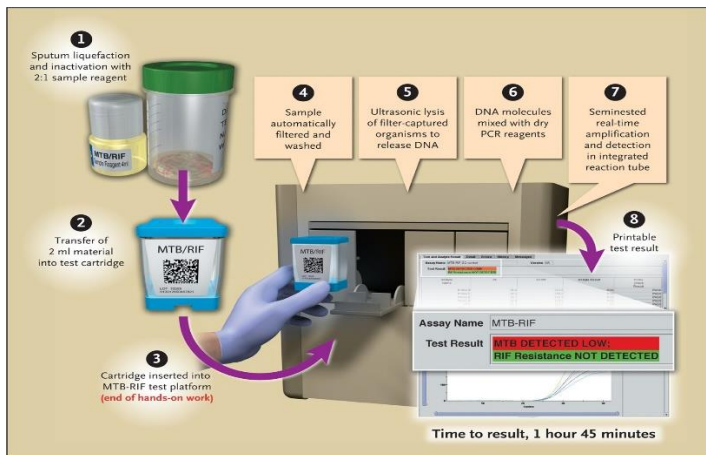


Figure 1. 9: Assay procedure for the MTB/RIF test (Boehme, 2010)

Line-probe assay (LPA)

Methods used for mycobacteriological culture, identification of and drug sensitivity testing (DST) take long and are cumbersome. Therefore, rapid DST of isoniazid and rifampicin or of rifampicin alone using molecular technologies is suggested over conservative testing in sputum smear-positive or culture confirmed cases at risk of multi-drug resistant (MDR)-TB, like in previously-treated patients (Ryu, 2015).

LPA is available as rapid DST and is a molecular test that permits explicit gene markers related with rifampicin resistance only or in combination with isoniazid to be detected (Ryu, 2015). Mutations in *katG*, followed by mutations at the *InhA* active sites are primarily responsible for Isoniazid resistance whilst *rpo B* region mutations is an indicator for about 96% of rifampicin -resistant *M. tuberculosis* isolates (Ryu, 2015).

LPA as a diagnostic tool is utilized in the following ways:

- Second line LPA is used as a follow-on test for rifampicin resistance. The tests use direct sputum for screening of resistance to fluoroquinolone (*gyrA* and *gyrB* mutations) and 2nd line injectables (*rrs* and *eis* mutations)
- First line LPA is used to confirm resistance to isoniazid and rifampicin

- LPA to detect *Mycobacterium* other than tuberculosis (MOTT) is useful when sputum smear tests positive but Xpert MTB/RIF tests negative, or to identify the species when culture grows MOTT (MoHSS, 2019)

Mycobacterial culture

Culture is the most sensitive diagnostic test for TB and continues to be the gold standard for the laboratory diagnosis of pulmonary tuberculosis (Asmar & Drancourt, 2015). Only 10 bacilli /ml are needed to get a growth (MoHSS, 2019). Culture of *M. tuberculosis* provides the advantage to microbiologists to differentiate between live versus dead organisms and define complex mixed infections when diagnosing TB in patients (Lagier, 2015).

Inoculation of decontaminated specimens is done on solid and liquid media with WHO promoting simultaneous inoculation on both media to enable the outcome as a combination result of the greater specificity of solid media with the greater sensitivity of liquid media (Asmar & Drancourt, 2015).

Customarily, solid culture media for mycobacteria are incubated at 37° Celsius for 8 weeks before a negative result is reported and although sound documentation is available that liquid media detects mycobacteria much sooner, most incubation procedures still need a maximum of 6 weeks before indicating a sample as negative (Pfyffer & Wittwer, 2012).

TB lateral flow (LF) urine lipo-arabinomannan (LAM) antigen test

The LF-LAM test is designed for use in urine samples as a point-of-care test. This test is only applicable in patients who have tested negative with a bacteriological method. TB LF-LAM can then be used to assist in the diagnosis of TB in HIV positive adult patients with signs and symptoms of TB (pulmonary and/or extra pulmonary) with a CD4 cell count of 100 cells/ μ l or less or seriously ill patients regardless of the CD4 count (MoHSS, 2019).

The test identifies lipo-arabinomannan (LAM), a lipopolysaccharide existing in mycobacterial cell walls, which is freed from metabolically live or deteriorating bacterial cells and seems to be available just in individuals with active TB disease (Shah, et al., 2016). The advantages of urine testing over sputum testing are that urine can be collected and stored easily and infection control threats are less compared with those related with sputum collection (Shah, et al., 2016).

LF-LAM has a collective sensitivity of 44%, but, this differs considerably depending on the health settings (54% in hospitalized patients and 21% in outpatients) and CD4 count (15%, 48% and 56% with >200, <200 and <100 cells/ μ L) (García-Basteiro et al., 2018). The article further suggests that WHO experts discouraged the use of LF-LAM as a screening tool (among HIV-positive patients irrespective of signs) due to a suboptimal specificity of 92%.

1.2.5.3 Radiological diagnosis of TB

Chest X-ray examination

Chest radiography in combination with clinical history of a patient is helpful in making a diagnosis of TB because many conditions can show TB-like changes on X-ray pictures. Radiological manifestations due to TB can be seen in lung parenchyma, interstitium, pleura, pericardium, lymph nodes and bones (Rabinovitch & Pai, 2018). HIV positive patients who have TB may have normal chest radiographs, thus a normal chest radiograph cannot reliably exclude TB in these patients (MoHSS, 2011).

The radiologic appearance of TB reflects the host response to infection. The most useful radiological marker of PTB is the manifestation of upper lobe opacities, cavities, a unilateral pleural effusion, and hilar or mediastinal lymphadenopathy. A typical radiographic appearance in TB patients is mostly seen in PLHIV due to their compromised immunity (Rabinovitch & Pai, 2018).

Figure 1.10 below is a classic picture of active PTB with multiple cavities in the right upper lobe.



Figure 1. 10: Classic active PTB case (Rabinovitch & Pai, 2018)

The competency of radiographers is of utmost importance because films need to be read cautiously to limit inter- and intra-reader variations (Frieden, 2004). Treatment of TB solely based on radiological

appearance can lead to wrong treatment with adverse consequences for patients and therefore X-ray pictures indicative of TB should have bacteriological confirmation (Rabinovitch & Pai, 2018).

1.2.5.4 Treatment of TB patients

TB is a treatable and curable disease and TB patients should be placed on effective treatment immediately after a positive diagnosis is made to ensure the disease is cured and transmission is stopped. Patients should be treated, irrespective of age, sex, gender or type of TB disease, bacteriological status, co-morbidities or legal status (WHO, 2019)

To enforce this global endeavor to eliminate TB, the World Health Assembly approved the post-2015 End TB Strategy with its ambitious targets in May 2014. The post-2015 End TB Strategy aims to end the global TB epidemic as part of the newly adopted Sustainable Development Goals (World Health Assembly, 2014).



Figure 1.11: The End TB strategy (World Health Assembly, 2014)

National governments are required to abide to 4 key principles in order to put the End TB strategy into operation:“(1) government stewardship and accountability with monitoring and evaluation; (2) strong coalition with civil society organizations and communities; (3) protection and promotion of human rights, ethics, and equity; and (4) adaptation of the strategy and targets at country level, with global collaboration” (Uplekar et al., 2015).

The WHO’s current strategic plan for TB control, the End TB Strategy is a multi-layered all-encompassing program compared to earlier iterations(Uplekar et al., 2015). Awareness of both the accomplishments of earlier programs in decreasing both mortality and prevalence and the gap of existing programs to

lessen incidence at a rate that will help countries to meet the SDG targets by 2035. It recommends a comprehensive and more aspiring program based on three pillars outlined below (Holmes et al, 2017).

a. Integrated, patient-centered care and prevention

- Early diagnosis of tuberculosis, including universal drug-susceptibility testing and systematic screening of contacts and high-risk groups;
- Treatment of all people with tuberculosis, including drug-resistant tuberculosis, and patient support;
- Collaborative tuberculosis and HIV/AIDS activities and management of comorbidities; and
- Preventive treatment of persons at high risk and vaccination against tuberculosis.

b. Bold policies and supportive systems

- Political commitment with adequate resources for tuberculosis care and prevention;
- Engagement of communities, civil society organizations, and public and private care providers;
- Universal health coverage policy and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control; and
- Social protection, poverty alleviation, and actions on other determinants of tuberculosis.

c. Intensified research and innovation

- Discovery, development, and rapid uptake of new tools, interventions, and strategies.
- Research to optimize implementation and impact and to promote innovations (World Health Assembly, 2014).

Pillars and Principles

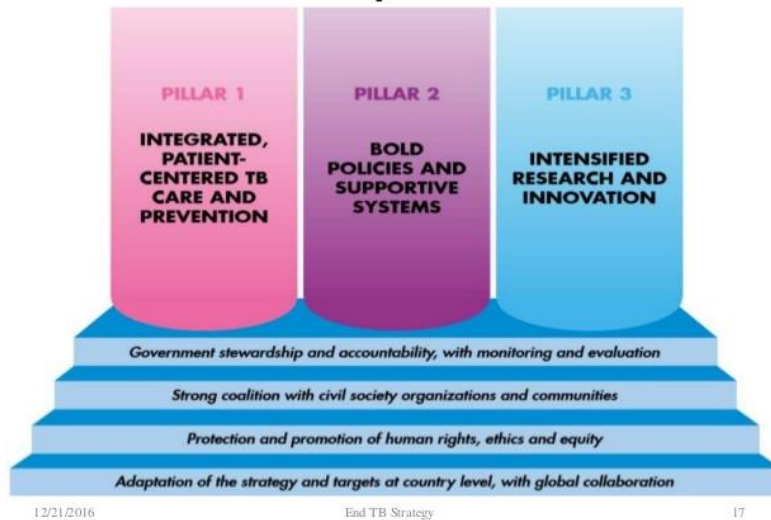


Figure 1. 1: Pillars and Principles of the End TB strategy (World Health Assembly, 2014).

The first pillar of the end TB strategy advocate for integrated, patient-centered care and prevention and the key actions is outlines in figure 1.13 below.

How pillar 1 works : Key actions

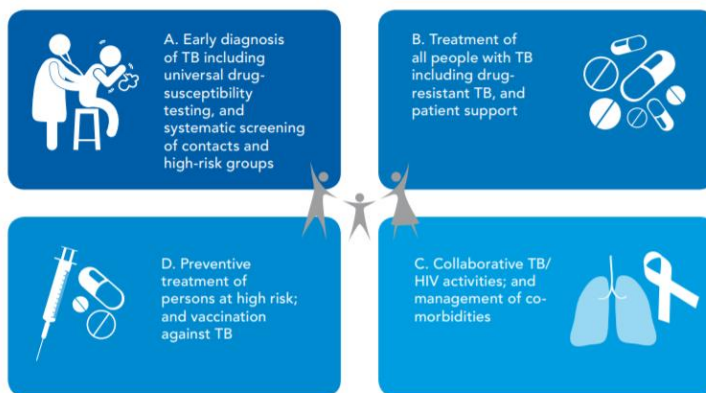


Figure 1. 2: How Pillar 1 works (World Health Assembly, 2014)

1.2.5.5 TB treatment regimes

Forty-three million individuals with TB were effectively cured by combination chemotherapy between 2000 and 2014 (Prasad, 2016).

Drug-sensitive TB disease is treated with a first line regime of 4 antimicrobial drugs over a period of 6 months. Effective treatment is only possible if patients are provided with information, supervision and support by health workers, otherwise treatment adherence leading to drug resistance can become a challenge. Most TB cases are curable with the completion of treatment regimes. The anti-TB medicines are provided as fixed-dose combinations (FDC's) as recommended by WHO as an abler for preventing acquisition of drug resistance; minimize prescription and dispensing errors and improve adherence by reducing pill burden. Table 1.3 below shows the current first line anti TB medicine used in Namibia.

Table 1. 3: First-line anti-TB medicines used in Namibia (MoHSS, 2019)

Generic name	Abbreviation	Mode of action
Rifampicin	R	Bactericidal
Isoniazid	H	Bactericidal
Pyrazinamide	Z	Bactericidal
Streptomycin	S	Bactericidal
Ethambutol	E	Bacteriostatic

Patients have drug resistant (DR) TB when they are infected with *M. tuberculosis* bacilli that are resistant to one or more anti-TB medicines. The categories of DR-TB that are of clinical significance as stated in the Namibia National TB guidelines are as follows:

- **Mono-resistance:** resistance to one first line anti-TB medicine.
- **Poly-drug resistance (PDR):** resistance to more than one first line anti-TB medicine, other than both isoniazid and rifampicin.
- **Multidrug resistance (MDR):** resistance to isoniazid and rifampicin with or without resistance to other medicines.
- **Rifampicin resistance (RR):** resistance to rifampicin, with or without resistance to other medicines. This category includes MDR, rifampicin non-resistance, rifampicin poly-resistance and those with rifampicin resistance detected by molecular methods such as X-pert MTB/RIF (where susceptibility to other medicines may be unknown).

- **Extensively drug-resistance (XDR):** resistance to any fluoroquinolone, and at least one of three injectable second-line medicines (capreomycin, kanamycin and amikacin), in addition to MDR.
- **Isoniazid resistance (Hr):** resistance to isoniazid but confirmed rifampicin susceptible (MoHSS, 2019). Drug resistant TB is treated with limited options of second line anti-TB medicine. It is crucial that second line medicines are used stringently according to the provided procedures to avoid further resistance. Table 1.4 is a list of 2nd line anti-TB medicines available in Namibia.

Table 1. 4: Second-line anti-TB medicines available in Namibia (MoHSS, 2019)

Group	Name	Abbreviation
A.	Levofloxacin OR Moxifloxacin	Lfx/Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
B.	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs/Trd
C.	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin OR Meropenem	Imp-cln/Mpm
	Amikacin OR Streptomycin	Am/S
	Ethionamide OR Prothionamide	Eto/Pto
	p-amino salicylic acid	PAS

1.2.5.6 TB/HIV management

HIV-1 infection changes the progression of *M. tuberculosis* infection and considerably upsurges the risk of active tuberculosis (TB) (Bell & Noursadeghi, 2018). According to Bell et al, 2018, it is evident that TB raises levels of HIV-1 duplication, propagation and genetic variety and consequently co-infection offers reciprocal gains to both pathogens. Signs of clinical disease manifestations are largely reliant on the severity of immunosuppression, hence the latter individuals have a higher possibility to develop extra-pulmonary or disseminated forms of TB (Trinh et al., 2015).

All HIV-infected TB patients should start Antiretroviral therapy (ART) regardless of their CD4 count as per 2010 WHO recommendation (World Health Organization, 2016). ART has the possibility to reduce mortality when initiated within 8 weeks of starting anti-tuberculosis treatment. Additional evidence from the CAMELIA, SAPIT and STRIDE trials shows that further reduction in mortality is possible if TB patients with a CD4 count of less than 50 cells/mm³ are started on ART within 2 weeks after the onset of anti-tuberculosis treatment (WHO, 2019).

The ideal time to start ART in TB/HIV co-infected patients is quite difficult because the risk of morbidity and mortality in progressive HIV disease must be controlled with the possible incidence of additive toxicities, drug–drug interactions, and TB-associated immune reconstitution inflammatory syndrome (IRIS) (Manosuthi, Wiboonchutikul, & Sungkanuparph, 2016).

IRIS, which can appear in the initial months of ART initiation, is a commonly known phenomenon that can complicate ART as it is the result of a quick recovery of pathogen-specific immune responses to opportunistic infections, which bring about the worsening of a treated infection or the new appearance of an earlier subclinical infection (Meintjes et al., 2010). The general estimated incidence range of TB-IRIS among co-infected patients varying between 7% and 36% (Trinh et al., 2015).

Treatment of co-infected patients is further complicated due to interaction of certain anti-TB drugs with specific ART's like the interaction of rifampin (RIF) with some protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NRTIs) (CDC, 2016). Experts recommend the use of Rifabutin, which have less challenging drug interactions as an alternative to RIF for HIV co-infected patients (Baciewicz et al., 2013).

The global treatment success rate for HIV-positive TB patients was 77% in 2017 (WHO, 2019), whilst Namibia had already treated 81% of the 2014 cohort of TB/HIV co-infected patients successfully (MoHSS, 2016).

1.2.6 Diabetes mellitus (DM)

Diabetes is a long-lasting, metabolic disease characterized by raised levels of blood glucose (or blood sugar), which leads over time to severe destruction of the heart, blood vessels, eyes, kidneys, and nerves (WHO, 2017). There are two common types of diabetes namely type 1 and type 2 diabetes. Type 2 diabetes, usually occurs in adults when the body becomes resistant to insulin or does not make enough insulin. In type 2 diabetes, the body continues to produce insulin, however the insulin does not trigger the body's regulatory system on the use and storage of glucose and fat (Nall, 2019). Type 2 diabetes is defined by the National Institute of Diabetes and Digestive and Kidney Diseases as the most common type of diabetes and is strongly linked with obesity.

The prevalence of type 2 diabetes has increased dramatically in countries of all income levels in the past three decades mainly due to overweight and physical inactivity (WHO, 2016). Type 1 diabetes, also known as juvenile onset diabetes or insulin-dependent diabetes, is a chronic disorder in which the

pancreas produces little or no insulin by itself and therefore patients must use artificial insulin daily to control glucose levels (Nall, 2019). The immune system attacks and breaks down the cells in the pancreas that produce insulin (NIH, 2019).

1.2.6.1 Global Diabetes

The prevalence of Diabetes is on the increase globally due to the impact of population ageing, urbanization, variations in diet and limited physical activity patterns resulting in growing obesity numbers (Restrepo, 2016). Restrepo further states that 80% of the 415 million projected DM cases worldwide are from low and middle income countries and the prevalence is anticipated to rise in regions with high TB incidence over the next 30 years.

According to The WHO Global report on Diabetes (WHO, 2016) it was expected that 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. This means that the global prevalence (age-standardized) of diabetes has increased two fold since 1980, from 4.7% to 8.5% in the adult population. This alarming rise in cases of diabetes poses a severe danger to global tuberculosis control. The number of people with Diabetes is expected to rise to at least 592 million by 2035 (Riza, 2014). This article further reported that 80% of the adults' diabetic burden resides in low-income or middle-income countries. However, diabetes already develops at a younger age in these countries.

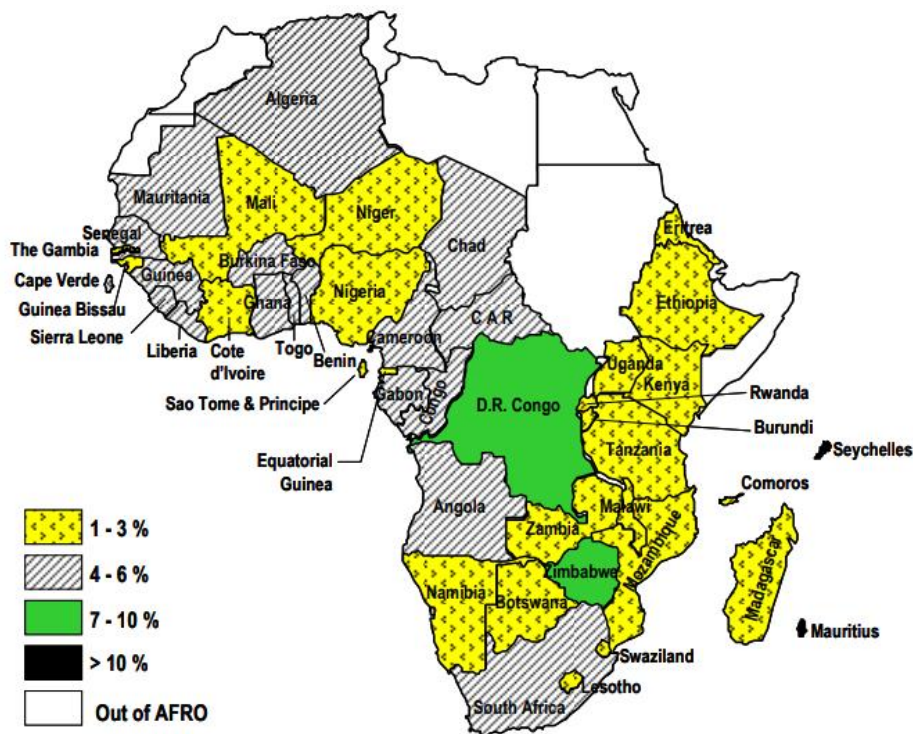
Worldwide, there has been a sharp upsurge in obesity among children and adolescence aged between 5-19 years old to 124 million in 2016 compared to 11 million in 1975 (Moeti, 2017). Current estimates shows that one in five children or adolescents are either overweight or obese. Overweight and obesity are risk factors for cardiovascular disease, diabetes and some cancers in later life (Moeti, 2017).

Diabetes increases the risk of developing tuberculosis 3 fold, and poor glycemic management undesirably impacts tuberculosis treatment results with effects such as extension of culture conversion, treatment failure, relapse, and death (Noubiap et al., 2019). Furthermore, diabetes was the cause of 10.6% of global tuberculosis deaths among HIV-negative persons in 2015 and with 425 million people distressed by diabetes globally in 2017, and an anticipated 48% rise to up to 629 million people diabetes cases expected in 2045, it is likely that this surge in the prevalence of diabetes will escalate the incidence of tuberculosis (Noubiap et al., 2019).

1.2.6.2 Diabetes Mellitus in Africa

In Africa, the number of children who are overweight or obese raised almost double from 5.4 million in 1990 to 10.3 million in 2016 (Moeti, 2017). Children who are overweight and obese are likely to become adults with the same challenges. The author (Moeti, 2017) iterated that estimations in 2014 showed that 22.9% of men and 38.6% of women above the age of 18 in the African Region were obese.

Sub-Saharan Africa is challenged by an increasing prevalence of diabetes together with other non-communicable diseases, like the rest of the global community (Hall *et al*, 2011). The article further stated that 90% of diabetes cases in Sub-Saharan Africa are type 2 Diabetes whilst type 1 diabetes and other variant forms constitute the remainder. Figure 1.14 below shows diabetetic prevalence rates in Africa.



Sources: 1. [Infobase.who.int](http://infobase.who.int);

2. Sobngwi E et al, Diabetes in Africans: Part 1: epidemiology and clinical specificities, *Diabetes and Metabolism* 27(6): 628–634, 2001.

Figure 1. 3: Diabetes prevalence rate in WHO African Region (WHO, 2017)

1.2.6.3 DM in Namibia

The prevalence of diabetes was estimated as 5.1% (95% confidence interval [CI]: 4.2–6.2), with no indication of gender variances ($P = 0.45$) in a recent study (Adekanmbi et al., 2018). The prediabetes

prevalence was 6.8% (95% CI 5.8–8.0) as per WHO criteria, ADA criteria estimate it as 20.1% (95% CI 18.4–21.9) whilst male sex, older age, higher body mass index (BMI), and occupation individually spiked the odds of diabetes in Namibia (Adekanmbi et al., 2018).

The 2013 Namibian Demographic Health survey (MoHSS, 2014) reported the prevalence of diabetes among people 35-65 years was 6% for women and 7% for men respectively. According to the WHO (WHO, 2016) the prevalence of diabetes in Namibia is on an increasing trajectory as seen in the Figure 1.15 below.

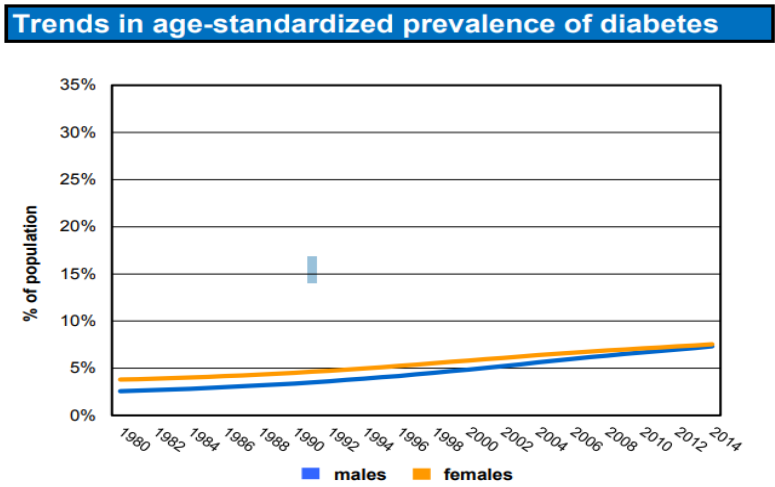


Figure 1. 4: Trends in age-standardized prevalence of diabetes (WHO, 2016)

This adds to the alarming prevalence of diabetic risk factors of 39.1 % for overweight and 29.7% for physical inactivity as shown in Table 1.5 below(WHO,2016).

Table 1. 5 Prevalence of diabetes and related risk factors (WHO, 2016)

Prevalence of diabetes and related risk factors			
	males	females	total
Diabetes	5.0%	5.8%	5.4%
Overweight	27.1%	50.4%	39.1%
Obesity	8.0%	25.2%	16.8%
Physical inactivity	23.9%	34.8%	29.7%

1.2.7 TB and DM Comorbidity

1.2.7.1 The burden of TB and DM

Documentation about the association between diabetes mellitus and tuberculosis is available for a long time (Dooley, 2009). In recent years, tuberculosis incidence has reduced in high-income countries, however there has been no change in incidence rates in countries with a high HIV burden, together with a high prevalence of malnutrition and overcrowded living conditions and poor tuberculosis control. In addition, obesity is driving the increase of diabetes mellitus prevalence globally (Hu, 2011).

There is growing confirmation that people with diabetes mellitus are at risk of developing tuberculosis and that might affect disease management and treatment response. The WHO report on TB comorbidities and risk factors (WHO, 2017) stated that diabetes increases the risk of TB by 3 fold. Subsequently the rates of TB are higher in people with diabetes than in the general population, and diabetes is a well –known comorbidity in people with TB. Diabetes can adversely affect the clinical course of TB, and TB can make glycemic control challenging in people with Diabetes (Siddiqui, Khayyam, & Sharma, 2016).

Over the last 10 years a fast growing epidemic of DM in low- and middle-income countries and a slower decline in global TB incidence rates have been reported which may lead to serious concerns about TB-DM comorbidity (Zheng, Hu, & Gao, 2017). According to Zheng et al,(2016), a systematic review done in 2015, identified 59 studies on DM and TB from 10 Middle East countries revealing that the prevalence of TB-DM comorbidity was varying among studies (from 4.2% in Iran to 60% in Yemen).

In 2012, an estimated of 371 million individuals had type 2 diabetes worldwide (Podell, 2014). The majority of these people (about 80%) lives in low and middle income countries where the possibility for *M. tuberculosis* transmission is much higher. A further threat to this population is that up to 50% of

diabetic patients stay undiagnosed in the most inaccessible areas, where the necessary health care and diagnostic services are limited (Podell, 2014). Therefore, a large percentage of the diabetic population is unwittingly affected by uncontrolled hyperglycemia and increase the bar of contracting TB. Added to patients with indicative criteria consistent with diabetes, 70% of people having prediabetes also live in TB high burden countries (Podell, 2014)

In Africa, DM prevalence among TB patients also varies greatly between studies (3.35–16.4%). A study by Zheng et al (2017) reported that HIV co-infection, age (older than 45), being overweight, and being male as risk factors for diabetes among TB patients.

A study done in Uganda indicated that the prevalence of DM among TB patients of 8.5% is considerably higher than the overall population estimated prevalence of DM in Uganda (2.2%) and the prevalence of DM on the medical units in the hospital during the study period (6.4%) (Kibirige, 2013).

A study in Nigeria reported a DM prevalence of 9.4% among newly diagnosed TB patients. However, these results were higher than the general population prevalence as well a city pilot study but lower than the 12.3% prevalence observed in some health facilities (Ekeke et al., 2017).

Studies done in Ethiopia revealed similar high DM prevalence rates (8.3%) among TB patients and these were comparable with a study done in Jammu-India (8.2%) but lower than studies done in Taiwan (29.5%), Southern-Mexico (29.3%) and Kerela-India (44%). Prevalence dissimilarities are attributed to differences in background between population and screening methods used in DM diagnosis (Workneh, Bjune, & Yimer, 2016).

The diabetes and tuberculosis burden of disease in southern Africa is significant (Reid, McFadden, & Tsimba, 2013). An incident rate of almost 400 000 cases was reported in South Africa in 2011 and 50% of the nearly two-million South Africans with diabetes are undiagnosed (Reid, McFadden, & Tsimba, 2013) .

In an interview on Health day in 2016, Ronacher from University of Stellenbosch stated that in South Africa about 12% of TB patients also have type 2 Diabetes and she elaborated that this number is anticipated to increase as the prevalence of Diabetes is alarmingly increasing due to the adoption a western lifestyle. An earlier South African study (Webb et al., 2009) reported an increased prevalence of TB in children and adolescents with DM1 in South Africa.

1.2.7.2 The pathogenesis of diabetes-tuberculosis comorbidity

Several studies have shown substantial biological evidence in backing of the causal relationship between DM and impaired host immunity to TB. Experimental study results done with human plasma cells showed that high levels of insulin promote a decrease in Th1 immunity, through a drop in the Th1 cell to Th2 cell ratio and IFN- γ to IL-4 ratio (Viardot, Grey, Mackay, & Chisholm, 2007). Furthermore, an in-vitro assessment of production of Th1 cytokines revealed that nonspecific IFN- γ levels were considerably reduced in people with diabetes compared to controls without diabetes (Stalenhoef, Alisjahbana, & Nelwan, 2008).

A dose–response relationship was evident in another study that showed IFN- γ levels correlate negatively with levels of HbA1c (Tsukaguchi et al, 1997). In addition, studies showed that neutrophils from diabetics had lower chemotaxis and oxidative killing power than those of nondiabetics (Delamaire et al, 1997), and leukocyte bactericidal action was reduced in people with diabetes, especially those with uncontrolled glucose (Rayfield et al, 1982). DM directly impairs the innate and adaptive immune responses necessary to counter the proliferation of TB (Jeon & Murray, 2008). Data from these human studies are in line with evolving evidence on the biological mechanisms by which hyperglycemia may influence the host immune response to TB (Jeon & Murray, 2008).

Jeon and Murray (2008) reported consistent evidence of a bigger threat for TB among people with diabetes notwithstanding heterogeneity in study design, environment, and underlying burden of TB, valuation of contact and effect, and regulation of possible confounders. Information from these studies are consistent with developing evidence on the biological mechanisms by which hyperglycemia may impact immunity of the host to TB

1.2.7.3 Diabetes and the risk of poor tuberculosis outcomes

Diabetes is a risk factor for active tuberculosis and increase the likelihood of poor treatment outcomes (Riza, 2014). A meta-analysis (Baker, 2011) point out that the mutual result of tuberculosis treatment failure and death was significantly higher in patients with diabetes than in those without diabetes (relative risk 1.69, 95% CI 1.36–2.12). Likewise, the mortality risk during tuberculosis treatment (1.89, 1.52–2.36) and relapse following treatment (3.89, 2.43–6.23) were greater in patients with diabetes in comparison with those without diabetes. Data from six of nine studies that assessed sputum conversion point out that there is a bigger likelihood of patients with tuberculosis and diabetes continuing to be sputum smear positive at 2–3 months after TB treatment initiation (Baker, 2011).

DM is often connected with prolonged mycobacterial clearance from sputum during treatment causing TB-DM having a bigger number of smear-positives after completion of the intensive phase of treatment, or than TB-no DM patients (Restrepo & Schlesinger, 2014). These outcomes show a possible treatment failure which is anticipated more in TB-DM than TB-no DM patients.

1.2.7.4 Clinical presentation

Data gathered through two systematic reviews done by (Tang et al, 2009) and (Ruslami et al, 2010), indicate there is no rock-hard evidence of differences in radiographic presentation of tuberculosis in patients with or without diabetes. On the other hand, in 2014, a large case series by (Chiang et al, 2014) revealed that TB patients with diabetes had more lung cavities and parenchymal lacerations than those without diabetes; amongst patients with diabetes, these radiographic deformities were more obvious in those with uncontrolled glycaemia. Indication of the clinical picture of TB in patients with diabetes is changing, however patients with tuberculosis and diabetes are classically older and heavier than the universal tuberculosis population and more likely to be male (Chiang et al, 2014). Figure 1.16 below shows the factors affecting glycemic control.

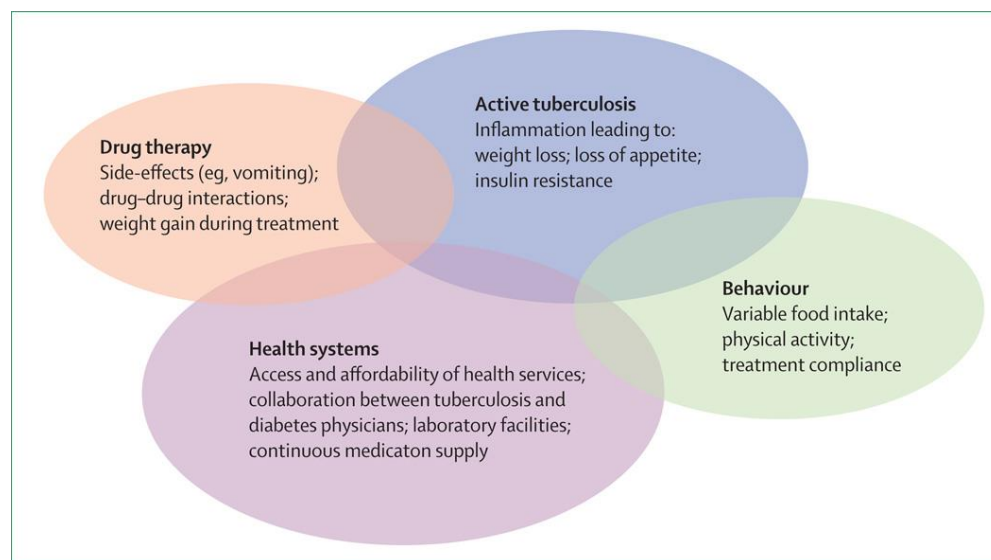


Figure 1. 5: Factors that affect glycaemic control for patients with diabetes during treatment for TB (Riza, 2014)

1.2.7.5 Methods for diagnosis of Diabetes

Diabetes is diagnosed using plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT), or HbA1c criteria (American Diabetes Association, 2019)

Glycated hemoglobin (HbA1c) was originally recognized as an uncommon hemoglobin in diabetic patients more than 40 years ago (Rahbar et al, 1969) as cited in (WHO, 2011). Several studies were conducted correlating HbA1c to glucose measurement, hence the decision to use HbA1c as a tool for glycemic control monitoring. HbA1c is a measure of the average plasma glucose over the past eight to twelve weeks and has become the cornerstone of assessing glycemic control in people with diabetes. It can be done at any given time and does not involve any patient preparations such as fasting. Lately, there is considerable attention in using HbA1c as a diagnostic test for diabetes and as a screening test for persons at high risk of diabetes (International Diabetes Experts, 2009).

1.2.7.6 Diabetes screening for patients with tuberculosis

WHO extensively promotes the screening of diabetes in TB mainly where the prevalence of diabetes is high (WHO, 2011).

The most appropriate time and methods to diagnose diabetes in patients with tuberculosis are unclear (Lin, 2012). The prevalence of diabetes rises sharply with age, but the actual cut-off age for screening is also undefined and varies between populations. Screening of blood glucose levels at a specific time might give a false diagnosis of diabetes in patients with tuberculosis as they could have intermittent hyperglycemia through commencement of insulin resistance, mediated by inflammation, due to tuberculosis infection (Riza, 2014).

Additional testing could identify temporary hyperglycemia. Testing of HbA1c concentration is the only diabetes test that indicates average glycaemia over a period of time (Kumpatla et al, 2013) . It was more reflective than fasting blood glucose when used as a screening test for newly diagnosed diabetes in patients with tuberculosis (Riza, 2014).

The point at which TB patients are tested for diabetes is important. In a systematic review Jeon et al, 2010 of four studies defined diabetes screening before tuberculosis treatment, seven studies after treatment introduction, four studies at numerous different follow-up times, and seven studies did not insist on the screening interims. If testing is done at treatment initiation then the next step would be to carry out a repeat test during tuberculosis treatment, or after completing treatment (Riza, 2014).

1.2.8 Case definitions

Active TB patient : The definition of a TB case in the study will be according to the WHO case definition (WHO, 2014) of bacteriologically confirmed or clinically diagnosed TB cases initiated or due be initiated on first line anti-TB drugs.

Diabetes case: Participants were classified as diabetic according to WHO classifications (WHO, 2011) of an HbA1c $\geq 6.5\%$ is recommended as the cut-off point for diagnosing Diabetes and self-reported diabetic.

Final patient outcome is defined as treatment completed or cured as outlined in the National guidelines for management of TB (MoHSS, 2019).

Interim patient outcome is defined as smear conversion after 2 months of anti-TB treatment initiation (MoHSS, 2019).

1.2.9 Statement of the problem

Namibia is among the top 30 high TB burden countries in the world (WHO, 2016) and added to that is the increasing prevalence of diabetes among women and men of about 6% and 7% respectively as reported by National Demographic Health Survey (MoHSS, 2013). The report further reiterated that the prevalence of diabetes differs among the geographical regions as well as according to gender. The same distribution is also noted on the prevalence of TB in Namibia (MoHSS, 2019). This phenomena may suggest a possible connection in the prevalence of Diabetes among TB cases and vice versa, which will have implications on the management of both diseases. However, no current or past surveillance data is available on diabetes and TB comorbidities in Namibia to support policy and management strategies for comorbidities of these two diseases. Pulmonary TB is the ninth most common problem in diabetes and due to an escalating prevalence of DM, the relative impact of DM on the TB epidemic is growing (Baghaei, 2013).

This study aims to assess the prevalence of diabetes among TB patients in the Khomas region and establish if diabetes and TB comorbidity influences the treatment outcomes of TB patients.

1.2.9.1 Research objectives

The main aim of this study is to establish the impact of Diabetes on TB treatment outcomes.

1.2.9.2 Specific objectives

- (i) To measure the prevalence of diabetes among patients currently on TB treatment in the Khomas region,
- (ii) To assess if the treatment duration and outcomes of TB patients with diabetes is any different than TB patients without diabetes,
- (iii) To clarify if the TB treatment regimens of TB patients with diabetes is different than TB patients without diabetes.

1.2.9.3 Research Questions

- What is the prevalence of Diabetes among current TB patients in the Khomas region of Namibia?
- Does Diabetes have any impact on the duration and treatment outcome and treatment regime of TB patients?

Chapter 2

Methodology

2.1 Study Design

This was a cross sectional study to determine the burden of Diabetes among active Tuberculosis patients in the Khomas region of Namibia and looked at the treatment regime, smear conversion and treatment outcomes of study participants.

The participants included in the study were active TB patients selected from public health facilities. Convenience sampling was done of TB patients visiting the facility according to the treatment follow-up dates. Only patients with susceptible TB, which consented for taking part in the study were included in the study. Each patient were assigned a study identification number for easy tracing of records recorded in the facility TB records.

2.2 Sampling frame

Namibia is divided into 14 administrative regions and the study was done in the Khomas Region. Khomas region was selected based for convenience. Khomas region have 12 health facilities that provide primary health care services to the public including TB services.

2.3 Study Population

The targeted population for this study was TB patients within the Khomas region. This study population was from 12 public health facilities.

2.4 Inclusion and exclusion criteria

2.4.1 Inclusion criteria

The following subjects were included in the study: All active TB patients as per study case definition, 15 years and older visiting the public health facility within the Khomas region were legible for inclusion in the study.

2.4.2 Exclusion criteria

The following subjects were excluded from the study: MDR TB patients were excluded from the study due to the duration of their treatment and individuals who were unable to consent for participating in the study were also excluded. Individuals who had a mental disability that made them unable to consent or comprehend the questions and/or procedures were excluded.

2.5 Sample size

The sample size calculation for the study was done based on the following assumptions:

Prevalence of diabetes among TB patients is estimated at 10.9% (Ronacher et al., 2016).

Precision = $\pm 5\%$, design effect = 2.0, Expected response rate = 85%

The calculation was done using a method adopted from Shiraishi, 2010.

The calculated sample size was 382.

2.6 Data collection

A survey team visited all Public Health-Care facilities in the Khomas region. TB patients visiting the public health facility were informed about the study and convenient sampling was done to select participants. When patients agreed to participate in the study, they gave written consent to participate in the study and permission for blood collection to do diabetes diagnosis.

A structured questionnaire was used to elicit demographic and clinical variables from patient records as well as interviews. (See Appendix I)

The assigned patient identification was used for tracking patient records in facility registers for smear conversion and final treatment outcomes records.

2.7 Testing

2.7.1 Blood collection

A trained Medical Laboratory scientist performed a finger prick on the first 121 participants that consented for measurement of HbA1c. Venous blood draw in an Ethylene Diamine Tetra acetic Acid (EDTA) tube for HbA1c testing was done for the rest of the study participants.

A study done by Keramati et.al, 2014 suggested that there is a high agreement between venous and capillary HbA1c levels and the use of capillary blood can be endorsed to be practical in diabetes clinical settings as a tool for diabetes control (Keramati, Razi, & Tootee, 2014).

Another study showed that Point-of-care capillary A1C did not do as good in the field as in the laboratory, however the bias can be corrected, and the error margin is ample that the test is clinically beneficial (Mackenzie-Feder & et.al, 2016).

2.7.2 Sample storage and transportation

No sample storage and transport was needed for finger prick blood collection which was done. Venous blood collected in EDTA tubes were transported to the Windhoek Central Reference laboratory in cooler boxes with ice and stored at 2-8°Celsius if testing could not be done immediately. Samples were tested within 7 days as indicated by manufacturers manual (Roche, 2018).

2.7.3 Testing Methodologies

2.7.3.1 HbA1c testing

The HbA1c testing of the first 121 samples was done using the CLOVER A1C point of care analyzer (Infopia, Anyang-si, Gyeonggi-do, Korea). The CLOVER A1C Self analyzer is an In Vitro Diagnostic Device (IVD) for measuring Hemoglobin A1c by the well-established method of boronate affinity (Clover Infopia, Anyang-si, Gyeonggi-do, Korea, 2011). It is able to analyze both capillary whole blood and venous blood. Anticoagulants such as EDTA or heparin may be used. This CLOVER A1C POCT system is designed to help controlling diabetes and it is intended to be used by patients and professionals at home, laboratories, clinics and hospitals (Clover Infopia Co., 2011).

A laboratory based correlation was done first, by comparing results from the CLOVER A1C point of care analyzer with those of the COBAS 6000 (Roche, Mannheim, Germany) analyzer used in the Windhoek Central Core laboratory according to NIP SOP QA 004 validation protocol. A correlation coefficient (R Squared) of 0, 95 or greater indicates acceptable correlation unless otherwise noted and the result of the correlation was R-square = 0.9504 indicating the correlation was acceptable.

The rest of the HbA1c testing was done using the COBAS 6000 analyzer due to challenges experienced with the availability of CLOVER A1C cartridges. It is good to give a breakdown of how many samples were tested by each method. The principle of HbA1c testing using COBAS 6000 is based on the turbidimetric

inhibition immunoassay (TINIA) for hemolyzed whole blood as outlined in the Cobas A1C package insert. HbA1c in the sample responds with anti-HbA1c antibody to form solvable antigen-antibody complexes. As the particular HbA1c antibody site is existing only once on the HbA1c molecule, formation of insoluble complexes does not take place. Adding buffer/polyhapten begins the reaction: The polyhaptens act in response with surplus anti-HbA1c antibodies to create an insoluble antibody-polyhapten complex which can be measured turbidimetrically (Roche, 2018). Results of both methods were reported in percentage (NGSP) and mmol/mol (IFCC)

Participants were classified as diabetic according to the WHO classification of an HbA1c $\geq 6.5\%$ which is recommended as the cut off point for diagnosing diabetes (WHO, 2011). Results were recorded manually according to patient's unique identifier and transferred to the electronic database.

2.7.3.2 HIV Testing

In Namibia HIV counselling and rapid testing (RT) services are available at most public health facilities and patients are offered these services routinely at the facility while being evaluated for TB. Namibia is using a serial testing algorithm and confirmations of all positive test is done using a second tests. A third tie-breaker test is used in cases of discordant results (MoHHS, 2018). The HIV status of the patients were retrieved from patient's records and recorded on the questionnaire.

2.7.3.3 TB Testing

Two sputum specimens are collected for examination, within 24 hours for all presumptive TB cases and clinical staff attending to the patient will indicate "diagnostic test" when completing the Request for Bacteriological Examination for TB form. The laboratory will automatically perform Xpert MTB/RIF as the first diagnostic test for all presumptive TB cases in Namibia (MoHSS, 2019). All samples with a positive MTB/RIF results and extra-pulmonary samples are analyzed further according to the national laboratory diagnostic algorithm (NTLP, 2016).

2.7.4 Quality Assurance

The CLOVER A1C[®] Check Cartridge is commercially available and was used to check that the optical and operating systems of the analyzer is intact. The checks were done daily before samples were tested as well as after the analyzer was moved to the next site and after an error message.

A laboratory based correlation was done first, by comparing results from the CLOVER A1C point of care analyzer with those of the COBAS 6000 (Roche, Mannheim, Germany) analyzer used in the Windhoek

Central Core laboratory according to NIP SOP QA 004 validation protocol. Quality control on the COBAS 6000 were done according to the NIP quality control procedures. Maintenance procedures for both instruments were done as per manufacturers procedures.

2.8 Data confidentiality

A unique identifier was allocated to each enrolled participant that facilitated tracking, reporting of results and data checking. No participant names were included in the analytic data set to protect confidentiality of patient data. Data was stored securely and access to electronic data was only possible through password protection that was limited to authorised study staff only.

2.9 Data validation

Data crosschecking was done through double data entry and comparing participant records from data collection tools with electronic TB registers to ensure data quality.

2.10 Data security

Questionnaires were kept in a secure place and electronic data was secured by a password. The existing NUST and MoHSS standard procedures are followed for archiving of electronic and paper data.

2.11 Confidentiality

Sensitive participant information collected, were delinked for data analysis. The unique identifiers system was used for all the data entries. However, names may still be used in the laboratory and NTLP for patient notification and linking patients to treatment. The study team signed a confidentiality declaration at the beginning of the study to ensure participant information confidentiality. (Annexure III)

2.12 Informed consent

All study participants or their guardians were informed about the study and were required to provide written informed consent prior to the screening. Each participant signed the informed consent form (Annexure II). Participants were allowed to opt-out of the process at any point during the process.

2.13 Ethical Clearance

The protocol was submitted for ethical approval to the Namibia University of Science and Technology (NUST) and Ministry of Health and Social Services (MoHSS). The protocol was further submitted to NIP

and Khomas Regional Health Directorate to gain permission for data collection and testing in these facilities. These documents is attached in Annexure IV- VII.

CHAPTER 3

RESULTS

3.1 Descriptive results of study participants

The participants in the study included patients with all forms of TB that was conveniently sampled at Khomas health facilities between April 1st and June 28th 2019. Study participants were selected from all patients coming for follow-up to the health facility, willing to participate and gave consent to be part of the study. In the study 171 participants had a known HIV status with 92 HIV positives and 79 HIV negative participants.

The total number of participants that took part take in the study was 181, about 47% of the initial estimated sample size. All 181 participants had an HbA1c tests done. The HbA1c tests were done as participants were recruited for participation, regardless of the treatment duration of the participants. The HbA1c testing of the first 121 participants was done using the CLOVER A1C point of care analyzer at the facility and 60 samples were done in the NIP Windhoek central laboratory using COBAS 6000 analyzer (Roche, Mannheim, Germany). Table 3.1 below depicts the distribution of the sample population by gender.

Table 3. 1: Distribution of sample population by gender

Gender	Frequency	Percent
Missing	1	0.55%
Male	118	65.19%
Female	62	34.25%
TOTAL	181	100.00%

Table 3.1 shows most participants were male (65.19%).

Table 3.2 below show the age range frequency of study participants.

Table 3. 2: Frequency distribution of participants according to age range

Age range	Frequency	Percent	Cumulative percent	Exact 95% LCL	Exact 95% UCL
15 to ≤24	22	12.43	12.43	7.96	18.21
>25 to ≤54	139	78.53	90.96	71.74	84.34
>55 to ≤64	13	7.34	98.31	3.97	12.23
>65	3	1.69	100.00	0.35	4.87
TOTAL	177	100.00	100.00		

Most of the participant (78, 5%) were between 25-54 years of age and 12, 4% of participants were between 15-24 years of age. Less than 2% of participants were 65 years and older.

The distribution of participants according to smear results is displayed in Table 3.3 below.

Table 3. 3: Frequency distribution of TB cases according to smear reactivity

Smear reactivity	Frequency	Percent	Cumulative percent	Exact 95% LCL	Exact 95% UCL
PSN	19	11.6	11.6	7.12	17.5
PSP	145	88.4	100	82.5	92.88

Key: PSN = Pulmonary smear negative

PSP = Pulmonary smear Positive

LCL = Lower control limit

UCL =Upper control limit

Most of the participants were pulmonary smear positive TB cases.

Participants were classified as diabetic according to the WHO classification of an HbA1c $\geq 6.5\%$ which is recommended as the cut off point for diagnosing diabetes (WHO, 2011). Table 3.4 below shows the frequency distribution of participants according to diabetes status.

Table 3. 4: Frequency distribution of participants according to WHO diabetes classification

Diabetes status	Frequency	%
Diabetic	76	42
Not diabetic	105	58
Total	181	100

The prevalence of diabetes among the participants in this study is 42%.

Table 3.5 below is a representation of the participant characteristics associated with the development of diabetes.

Table 3. 5: A representation of the participant characteristics associated with the development of diabetes.

Characteristic	DM tested positive(n)	%	DM tested negative(n)	Odds Ratio	p-value
Total	76	42	105		
Age(years)					
15 to ≤24	8	36	14		
>25 to ≤54	58	42	81		
>55 to ≤64	6	46	7		
>65	2	67	1		
Gender					
M	54	46	64	1,53	0,18
F	22	35	40		
Smear Reactivity					
PSN	8	42	11		
PSP	62	43	83	1.03	0,96
HIV status					
Positive	40	44	51	1,25	0,47
Negative	30	38	48		
TB Type					
New	62	42	84	1,11	0,79
Prev. treated	14	40	21		
Currently smoking					
Yes	4	36	7	0,74	0,64
No	72	44	93		

Characteristic	DM tested positive(n)	%	DM tested negative(n)	Odds Ratio	p-value
Alcohol consumption ever					
Yes	20	28	52	0,32	0,001
No	56	54	48		
Alcohol use in last year					
Yes	17	38	28	0,74	0,4
No	59	45	72		
TB Treatment Regime					
1 st line	74	45	91	5,6	0,012
other	2	12.5	14		
Sputum Conversion month 2					
Converted	28	35	52	1,08	0,95
Not converted	6	33	12		
Sputum Conversion month 5					
Converted	5	19	22	0,23	0,17
Not converted	4	50	2		

Based on the results displayed in Table above 4.5 there is no statistical significance of being smear positive (p value = 0, 96), HIV positive (p value = 0, 47) or being a new or previously treated patients (p value = 0, 79) and testing positive for diabetes.

There is also no statistical significance of smear conversion after 2 or 5 months of treatment and testing positive for diabetes with p values of 0, 89 and 0, 17 respectively.

The study participant's results showed an association between being on first line or other treatment regimens and testing positive for diabetes with a p value of 0,012. This study results also show a relationship between alcohol consumption ever and testing positive for diabetes with a p value of 0.001.

CHAPTER 4

DISCUSSION AND CONCLUSION

4.1 Discussion

This study findings shows that most participants were male (65.19%) as shown in Table 3.1, indicating that in this study there were more men with TB who were sampled. This finding is supported by Namibian routine programme data that the prevalence of TB is higher among men (MoHSS, 2019) and the phenomenon is reported by other studies that TB prevalence is considerably higher among men than women in low- and middle-income countries (Horton, 2016). Horton's study further claim that men are disadvantage in seeking or accessing TB care setting and therefore the higher TB prevalence among men in low- and middle-income countries. The worldwide detected dominance of tuberculosis among men has been ascribed to higher contact or modified susceptibility due to factors like greater lung volumes, sex hormones, and increase hepcidin levels (Saunders et al., 2019).

Most of the participant (78.5%) in this study were between 25-54 years of age, 12.4% were between 15-24 years of age and less than 2% of participants were 65 years and older as seen in Table 3.2. This finding indicates TB impacted the economically active people in the Khomas region. The same occurrence is evident in Namibian programme data (MoHSS, 2019). A study done in Zambia showed that the most affected by TB is between 18 to 47 years of age, the same age group with the highest HIV prevalence (Kapata, 2013). A study done in the Cape Town metropole, showed that the sexually active age group between 15-49 years had an increased incidence rates of TB disease and a higher co-infection with HIV (Nyabadza & Winkler, 2013). The conclusion derived from the above study findings indicate that HIV fuel the incidence of TB in the 25-54 age group

Table 3.3 shows that 88.4% of the participants were pulmonary smear positive TB cases. These results show concordance with other TB studies were pulmonary smear positive TB is more prevalent (Nugussie, 2017). The high prevalence of psp TB suggest that the population is highly exposed to the major risk factors for PTB namely HIV, immunosuppressive therapy, alcohol intake, cigarette smoking and staying in congregate setting Nwachukwu et al., 2016). Reduced glycemic control is related with a bigger risk of

progressive and more advance TB disease in the form of lung cavitations, positive sputum smear, and delayed smear conversion (Mahishale et al., 2017).

This study aimed to measure the prevalence of diabetes among patients currently on TB treatment in the Khomas region. In this study, the prevalence of Diabetes among TB patients in the Khomas region was 42% (as shown in Table 3.4) based on HbA1c testing and the WHO guideline of 6.5% as the cut-off for diabetes (WHO, 2011). This is significantly higher than the pooled prevalence of 9.0% revealed by a meta-analysis of 16 studies conducted among tuberculosis patients in SSA (Alebel, 2019). Another systematic review and meta-analysis on the worldwide prevalence of diabetes among patients with active tuberculosis used data from about 2.3 million patients with tuberculosis, and projected the diabetes prevalence to be 15.3% (95% prediction interval 2.5–36.1) (Noubiap et al., 2019). The latter review detected a wide-ranging inconsistency in the estimate prevalence of TBDM across countries, fluctuating from 0.1% in Latvia to 45.2% in Marshall Islands and the increase prevalence is driven by the diabetic epidemic in the general population (Noubiap et al., 2019). A study done in India also reported a 15.5% TBDM co-morbidity and that contribute to the existing knowledge about the relationship between DM and TB and identifying diabetes is an key risk element for developing TB (Agarwal, Agarwal, & Mahore, 2018).

The study also revealed more men (65%) participated in the study and the prevalence of diabetes was higher among men (46%) than women (36%). The findings from this study agree with a study done in Southern Nigeria by Ekeke et al (2017) who found that diabetes is higher in men with TB than women. However, the findings of this study do not agree with those of Gadallah et al (2018,) in Egypt who reported that diabetes was higher in women than men with TB. The development of diabetes can have a gender preponderance due to the impact of lethargy and obesity, inconsistencies in insulin tolerance and fat deposition (Gale & Gillespie, 2001).

In this study the prevalence of diabetes was highest among the 65+ age group. This is an age group which is prone to diabetes due to high glucose tolerance and the development of type 2 diabetes mellitus. A 2011 study done in India (Rawat, Biswas, & Sindhwani, 2011) showed patients in the PTB-DM group were much older (53.34 ± 14.06 years) than the PTB group (44.35 ± 18.14 years) ($P < 0.001$) with more severe lung lesions. Another study done in Egypt (Khalil & Ramadan, 2016) had similar findings with the mean

age of the DM-TB group was 52.90 ± 11.12 years. However, the results of this current study might not be a true reflection due to the small number (3) of participants in this group. The second highest prevalence of diabetes is among the >55 to ≤ 64 age group with 46%. This finding is in line with other studies that concluded that age >50 years was independently associated with an increase prevalence of diabetes in TB patients (Sharma, 2018).

The second objective of the study was to assess if the treatment duration and outcomes of TB patients with diabetes is any different than TB patients without diabetes. Treatment monitoring for TB patients is done by looking at smear conversion at 2 and 5 months after treatment initiation according to the Namibia TB Guidelines (MoHSS, 2019). In this current study there was no statistically significant difference between smear conversion after 2 or 5 months of treatment and testing positive for diabetes (p values of 0, 89 and 0, 17 respectively). The findings of this current study are in line with studies done Alisjahbana et al,(2007) in Indonesia and Singla et al., (2006)in Saudi Arabia who reported that diabetes was not a risk factor for sputum smear conversion (Chaisson, 2009). However another study by Nurwidya et al, (2018) in Indonesia reported that notwithstanding all proof that exists at present, the likely association of DM and prolonged sputum conversion remains conflicting (Nurwidya, Ratnawati, Wijaya, Nazaruddin, & Burhan, 2018).

This study showed that the association between being HIV positive and developing diabetes was not statistically significant as shown in Table 3.5 (p value=0, 47). A study done in Cape Town by Oni et al., (2017), that there was an association between TB, diabetes and only in participants with HIV-1 infection (Oni, 2017). Notwithstanding the contradicting study findings, another study identified the concept of multi-morbidity as an issue of public health significance where several studies report the increased prevalence of TB/HIV/DM concomitance resulting in complex disease patterns and health outcomes (Nwachukwu, 2016).

Further results from this study as displayed in table 3.5 show no association of being smear positive and testing positive for diabetes with a p value = 0,96. This outcome is contradicting with other studies that show diabetes is associated with a greater risk of severe TB disease manifested through lung cavitations, positive sputum smear, and slower smear conversion (Mahishale, 2017).

This current study revealed that there is an association between alcohol consumption and testing positive for diabetes (p value = 0,001). Alcohol use is a key contributor to the tuberculosis load of disease, with the most devastating impacts projected for the African Region (Imtiaz, 2017). Furthermore, studies have reported that increased alcohol use causes prolonged inflammation of the pancreas (pancreatitis), which can weaken its capability to produce insulin and possibly lead to diabetes (Zeratsky, 2019). Based on the impact of alcohol on both diseases, a conclusion can be derived that support the findings of this current study.

This study reported that there is no association between smoking tobacco and testing positive for diabetes (p value = 0.64) as shown in Table 3.5. Zeratsky an expert from a well-known clinic in the United states of America (USA) claims that tobacco consumption can raise blood sugar levels and cause insulin resistance and the more an individual smokes, the bigger the risk of developing diabetes (Zeratsky, 2019). Another source reported that smokers have a 30–40 percent more likelihood to acquire diabetes (Villines, 2019).

The third objective of the study was to clarify if the TB treatment regimens were associated with the development of diabetes. The results from this study showed treatment regimens were associated with the development of diabetes among TB patients (p -value = 0.012) as shown in Table 3.5. This means there is an association between being on first line treatment regimens of INH, PZA, Rif and E and testing positive for diabetes. The results of this study agree with the findings of a study done by Niazi et al.,(2012) in South Asia who found that anti-TB drugs (especially rifampicin and isoniazid) have interaction with oral anti-diabetic drugs causing suboptimal glycemic control (Niazi & Kalra, 2012). The latter study further claim that some of the latest oral anti-diabetic drugs react with anti-tuberculosis drugs and reduce their efficacy. This is because Rifampicin used for TB treatment is a compelling hepatic enzyme-inducer that fast-track the metabolism of several oral hypoglycemic agents and reduce their plasma levels causing hyperglycemia in diabetic patients. Isoniazid, in contrast, impedes the uptake of oral hypoglycaemic agents leading to poor glycemic control of diabetics on this medication (Niazi & Kalra, 2012).

4.2 Conclusion

This current study reported a high (42%) prevalence of diabetes among TB patients in the Khomas region implying that diabetes poses a threat to the TB burden in the region. The results of this study therefore

emphasis the need to screen TB patients routinely for diabetes. Males attributed 36% of the diabetes prevalence in the Khomas region and the older age groups of 65+ age in the study were more prone of testing positive for diabetes.

This study further revealed that there is no association of sputum conversion at 2 or 5 months of treatment and being diabetic. Lastly this study results indicate that the treatment regimen for TB is associated with the development of diabetes.

CHAPTER 5

LIMITATIONS OF THE STUDY

- The study was only conducted in Khomas region and therefore results may only apply to the specific region.
- A total number of 181 participants took part in the study. That is about 47% of the initial estimated sample size of 382.
- Drawing blood during sample collection was a challenge because we had to rely on nursing staff that already had a busy work schedule and therefore sample collection was slower than initially anticipated.
- Another challenge for sample collection was treatment supporters instead of TB patients visited clinics on scheduled follow-up dates to collect medicine which slowed down the pace of recruiting appropriate study participants.

CHAPTER 6

RESEARCH SIGNIFICANCE

This study provide baseline data on the prevalence of diabetics among TB patients in the Khomas region, which can serve as a yardstick of the magnitude of diabetes and TB comorbidity in the country.

This study results also provide guidance on the most suitable methods for creating a supportive policy and clinical environment for collaboration and integration of TB and diabetes comorbidity management

Results of this study also give insight into operative clinical methods for bidirectional screening and coordinated management of tuberculosis and diabetes

The research is important for capacity building in the area of TB and diabetes as one student will graduate with a Master of Health Science degree.

The research will be published in peer-reviewed Journals adding to the body of knowledge.

CHAPTER 7

RECOMMENDATIONS

Namibia is among the 30 high TB burden countries and the results of this study show that diabetes poses a threat to the TB burden in the Khomas region. The results of this study indicate the need to expand this study nationally to get a true reflection of the national impact of diabetes on the TB burden in Namibia and adjust programs and policies accordingly.

The national TB programme may benefit from a study that assess the impact and duration of diabetes on defaulter and mortality rates among DMTB patients.

References

- Adekanmbi, V. T., Uthman, O. A., Erqou, S., Echouffo-Tcheugui, J. B., Harhay, M. N., & Harhay, M. O. (2018). Epidemiology of prediabetes and diabetes in Namibia, Africa: A multilevel analysis. *Journal of Diabetes*, 11(2), 161-172.
- Agarwal, A., Agarwal, N., & Mahore, R. (2018). A comparative study of clinical variables in tuberculosis patients with coexisting diabetes. *Journal of Diabetology*, 9(3), 81.
- Alebel, A., Wondemagegn, A. T., Tesema, C., Kibret, G. D., Wagnew, F., Petrucka, P., ... Eshetie, S. (2019). Prevalence of diabetes mellitus among tuberculosis patients in Sub-Saharan Africa: a systematic review and meta-analysis of observational studies. *BMC Infectious Diseases*, 19(1).
- Alisjahbana, B., Sahiratmadja, E., Nelwan, E. J., Purwa, A. M., Ahmad, Y., Ottenhoff, T. H., ... Crevel, R. V. (2007). The Effect of Type 2 Diabetes Mellitus on the Presentation and Treatment Response of Pulmonary Tuberculosis. *Clinical Infectious Diseases*, 45(4), 428-435.
- Al-Rifai, R. H., Pearson, F., Critchley, J. A., & Abu-Raddad, L. J. (2017). Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLOS ONE*, 12(11).
- American Lung Association. (2018, December 13). ®Tuberculosis Symptoms, Causes & Risk Factors. Retrieved from <https://www.lung.org/>
- Asmar, S., & Drancourt, M. (2015). Rapid culture-based diagnosis of pulmonary tuberculosis in developed and developing countries. *Frontiers in Microbiology*, 6.
- Asmelash, D., Abdu, N., Tefera, S., Baynes, H. W., & Derbew, C. (2019). Knowledge, Attitude, and Practice towards Glycemic Control and Its Associated Factors among Diabetes Mellitus Patients. *Journal of Diabetes Research*, 2019, 1-9.
- Baciewicz, A. M., Chrisman, C. R., Finch, C. K., & Self, T. H. (2012). Update on rifampin, rifabutin, and rifapentine drug interactions. *Current Medical Research and Opinion*, 29(1), 1-12.
- Baghaei, P., Marjani, M., Javanmard, P., Tabarsi, P., & Masjedi, M. (2013). Diabetes mellitus and tuberculosis facts and controversies. *Journal of Diabetes & Metabolic Disorders*, 12(1), 58.
- Baker, M. A., Harries, A. D., Jeon, C. Y., Hart, J. E., Kapur, A., Lönnroth, K., ... Murray, M. B. (2011). The impact of diabetes on tuberculosis treatment outcomes: A systematic review. *BMC Medicine*, 9(1).

- Bell, L. C., & Noursadeghi, M. (2017). Pathogenesis of HIV-1 and Mycobacterium tuberculosis co-infection. *Nature Reviews Microbiology*, 16(2), 80-90.
- Berkowitz, N., Okorie, A., Goliath, R., Levitt, N., Wilkinson, R. J., & Oni, T. (2018). The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting. *Diabetes Research and Clinical Practice*, 138, 16-25.
- Boehme, C. C., Nabeta, P., Hillemann, D., Nicol, M. P., Shenai, S., Krapp, F., ... Perkins, M. D. (2010). Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. *New England Journal of Medicine*, 363(11), 1005-1015.
- CDC. (2018, December 11). The difference between latent TB infection and TB Disease: Fact Sheets. Retrieved from <https://www.cdc.gov/tb/publications/factsheets/general/lbtbiandactivetb.htm>
- CDC. (2018, December 12). Treatment of LTBI and TB for persons living with HIV. Retrieved 2018, from <https://www.cdc.gov/tb/topic/treatment/tbhiv.htm>
- Chiang, C., Lee, J., Chien, S., Enarson, D. A., Chang, Y., Chen, Y., ... Bai, K. (2014). Glycemic Control and Radiographic Manifestations of Tuberculosis in Diabetic Patients. *PLoS ONE*, 9(4),
- Classen, C. N., Warren, R., Richardson, M., Hauman, J. H., Gie, R. P., Ellis, J. H., ... Beyers, N. (1999). Impact of social interactions in the community on the transmission of tuberculosis in a high incidence area. *Thorax*, 54(2), 136-140.
- Clover Infopia Co. (2011, December 11). CLOVER A1C™ Self system user guide. Retrieved from <https://www.santeshop.eu/site/dl/INstruction-for-use-Clover-A1C-self.pdf>
- Cox, H., & Nicol, M. P. (2018). Tuberculosis eradication: renewed commitment and global investment required. *The Lancet Infectious Diseases*, 18(3), 228-229.
- Dara, M., & Zachariah, R. (2018). Ending tuberculosis calls for leaving no one behind. *The Lancet Infectious Diseases*, 18(4), 365-366.
- Delamaire, M., Maugeudre, D., Moreno, M., Le Goff, M., Allannic, H., & Genetet, B. (1997). Impaired Leucocyte Functions in Diabetic Patients. *Diabetic Medicine*, 14(1), 29-34.
- Dooley, K. E., & Chaisson, R. E. (2009). Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious Diseases*, 9(12), 737-746.

- Dooley, K. E., Golub, J. E., Cronin, W., Tang, T., & Dorman, S. E. (2009). Impact of Diabetes Mellitus on Treatment Outcomes of Patients with Active Tuberculosis. *The American Journal of Tropical Medicine and Hygiene*, 80(4), 634-639.
- Dowdy, D. W., Golub, J. E., Chaisson, R. E., & Saraceni, V. (2012). Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. *Proceedings of the National Academy of Sciences*, 109(24), 9557-9562.
- Ekeke, N., Ukwaja, K. N., Chukwu, J. N., Nwafor, C. C., Meka, A. O., Egbagbe, E. E., ... Oshi, D. C. (2017). Screening for diabetes mellitus among tuberculosis patients in Southern Nigeria: a multi-center implementation study under programme settings. *Scientific Reports*, 7(1).
- Ferrer, M. F., Torres, L. G., Ramírez, O. A., Zarzuelo, M. R., & Del Prado González, N. (2011). Tuberculosis of the spine. A systematic review of case series. *International Orthopaedics*, 36(2), 221-231.
- Floyd, K., Ravigliione, M., & Glaziou, P. (2018). Global Epidemiology of Tuberculosis. *Seminars in Respiratory and Critical Care Medicine*, 39(03), 271-285.
- Gadallah, M., Amin, W., Fawzy, M., Mokhtar, A., & Mohsen, A. (2018). Screening for diabetes among tuberculosis patients: a nationwide population-based study in Egypt. *African Health Science*, 18(4), 884-890.
- Gale, E. A., & Gillespie, K. M. (2001). Diabetes and gender. *Diabetologia*, 44(1), 3-15.
- García-Basteiro, A., DiNardo, A., Saavedra, B., Silva, D., Palmero, D., Gegia, M., ... Theron, G. (2018). Point of care diagnostics for tuberculosis. *Pulmonology*, 24(2), 73-85.
- Hall, V., Thomsen, R. W., Henriksen, O., & Lohse, N. (2011). Diabetes in Sub Saharan Africa 1999-2011: Epidemiology and public health implications. A systematic review. *BMC Public Health*, 11(1).
- Hoa, N. B., Phuc, P. D., Hien, N. T., Hoa, V. Q., Thuong, P. H., Anh, P. T., & Nhung, N. V. (2018). Prevalence and associated factors of diabetes mellitus among tuberculosis patients in Hanoi, Vietnam. *BMC Infectious Diseases*, 18(1).
- Holmes, K. K., Bertozzi, S., Bloom, B. R., & Jha, P. (2017). Tuberculosis. In *Disease Control Priorities, Third Edition (Volume 6): Major Infectious Diseases* (3rd Ed.). Washington, DC: World Bank Publications.

- Horton, K. C., MacPherson, P., Houben, R. M., White, R. G., & 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), e1002119.
- Hu, F.B., (2011). Globalization of Diabetes: The role of diet, lifestyle, and genes. *Diabetes Care*, 34(6): 1249-1257. Retrieved from <https://doi.org/10.2337/dc11-0442>.
- Imtiaz, S., Shield, K. D., Roerecke, M., Samokhvalov, A. V., Lönnroth, K., & Rehm, J. (2017). Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. *European Respiratory Journal*, 50(1), 1700216.
- Ismael, N. (2019, March 21). *TB doesn't only attack the lungs—other organs are also vulnerable*. Interview by I. Skosana. Retrieved from <https://theconversation.com/tb-doesnt-only-attack-the-lungs-other-organs-are-also-vulnerable-113791>
- Jamison, D. T. (2006). Tuberculosis. In *Disease and Mortality in Sub-Saharan Africa* (2nd Ed.). Washington, DC: World Bank Publications.
- Jeon, C. Y., Harries, A. D., Baker, M. A., Hart, J. E., Kapur, A., Lönnroth, K., ... Murray, M. B. (2010). Bi-directional screening for tuberculosis and diabetes: a systematic review. *Tropical Medicine & International Health*, 15(11), 1300-1314.
- Jeon, C. Y., & Murray, M. B. (2008). Correction: Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies. *PLoS Medicine*, 5(8), e181.
- Kanabus, A. (2018, June 20). Countries with TB - High & low burden TB countries. Retrieved from <https://www.tbfacts.org/countries-tb>
- Kapoor, R., Ansari, M., Mandhani, A., & Gulia, A. (2008). Clinical presentation and diagnostic approach in cases of genitourinary tuberculosis. *Indian Journal of Urology*, 24(3), 401.
- Kavetuna, J. (2018, September 13). *700 TB deaths in 2017*. Interview by S. Likela. Retrieved from <https://www.namibian.com.na/181338/archive-read/700-TB-deaths-in-2017>
- Keramati, T., Razi, F., Tootee, A., & Larijani, B. (2014). Comparability of hemoglobin A1C level measured in capillary versus venous blood sample applying two point-of-care instruments. *Journal of Diabetes & Metabolic Disorders*, 13(1).

- Khalil, N. H., & Ramadan, R. A. (2016). Study of risk factors for pulmonary tuberculosis among diabetes mellitus patients. *Egyptian Journal of Chest Diseases and Tuberculosis*, 65(4), 817-823.
- Kibirige, D., Ssekitoaleko, R., Mutebi, E., & Worodria, W. (2013). Overt diabetes mellitus among newly diagnosed Ugandan tuberculosis patients: a cross sectional study. *BMC Infectious Diseases*, 13(1).
- Kumpatla, S., Aravindalochanan, V., Rajan, R., Viswanathan, V., & Kapur, A. (2013). Evaluation of performance of A1C and FPG tests for screening newly diagnosed diabetes defined by an OGTT among tuberculosis patients—A study from India. *Diabetes Research and Clinical Practice*, 102(1), 60-64.
- Lagier, J., Hugon, P., Khelaifia, S., Fournier, P., La Scola, B., & Raoult, D. (2015). The Rebirth of Culture in Microbiology through the Example of Culturomics to Study Human Gut Microbiota. *Clinical Microbiology Reviews*, 28(1), 237-264.
- Lin, Y., Li, L., Mi, F., Du, J., Dong, Y., Li, Z., ... Harries, A. D. (2012). Screening patients with Diabetes Mellitus for Tuberculosis in China. *Tropical Medicine & International Health*, 17(10), 1302-1308.
- Lönnroth, K., Roglic, G., & Harries, A. D. (2014). Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. *The Lancet Diabetes & Endocrinology*, 2(9), 730-739.
- Mackenzie-Feder, J., Jin, A., Secombe, D. W., Sirrs, S., Neufeld, C., & Dawson, K. G. (2016). Agreement of Point-of-Care Capillary Glycated Hemoglobin Levels with Conventional Screening Tests for Diabetes Mellitus in a Canadian First Nations Population. *Canadian Journal of Diabetes*, 40(3), 242-246.
- Mahishale, V., Avuthu, S., Patil, B., Lolly, M., Eti, A., & Khan, S. (2017). Effect of Poor Glycemic Control in Newly Diagnosed Patients with Smear-Positive Pulmonary Tuberculosis and Type-2 Diabetes Mellitus. *Iran Journal Medical Science*, 42 (2), 144-151.
- Manosuthi, W., Wiboonchutikul, S., & Sungkanuparph, S. (2016). Integrated therapy for HIV and tuberculosis. *AIDS Research and Therapy*, 13(1).
- Marais, B. J., & Schaaf, H. S. (2014). Tuberculosis in Children. *Cold Spring Harbor Perspectives in Medicine*, 4(9), a017855-a017855.
- McMurray, D. (1996). Mycobacteria and Nocardia. In *Medical Microbiology. 4th Edition* (4th Ed.). Galveston, TX: University of Texas Medical.

Medical News Today. (2019, April 17). How does smoking affect the risk of diabetes? Retrieved from <https://www.medicalnewstoday.com/articles/317411.php>

Meintjes, G., Lawn, S. D., Scano, F., Maartens, G., French, M. A., Worodria, W., ... Colebunders, R. (2008). Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *The Lancet Infectious Diseases*, 8(8), 516-523.

MoHSS (NTLP) Namibia. (2016). National Tuberculosis and Leprosy Programme routine programme data.

MoHSS Namibia. (2014). Namibia DHS, 2013 - Final Report (English) (FR298). Retrieved from Namibia: MoHSS/Namibia and ICF International website: <https://dhsprogram.com/publications/publication-FR298-DHS-Final-Reports.cfm>

MoHSS Namibia. (2018). National Guidelines for HIV Counselling and Testing in Namibia.

MoHSS Namibia. (2019). National Guidelines for the Management of Tuberculosis.

MoHSS (NTLP) MoHSS. (2019). Presentation of 2018 TB and Leprosy Report. Windhoek, Namibia.

MoHSS (NTLP) Namibia. (2011). National Guidelines for the Management of Tuberculosis.

MoHSS (NTLP) Namibia. (2016). National TB Diagnostic Algorithm.

MoHSS (NTLP) Namibia. (2017). National Tuberculosis and Leprosy Programme routine programme data.

MoHSS(NTLP) Namibia. (2019). TB Disease Prevalence survey 2017-2018 summary report. Windhoek, Namibia.

Nall RN MSN, R. (2019, May 6). Diabetes: Symptoms, treatment, and early diagnosis. Retrieved from <https://www.medicalnewstoday.com/articles/323627.php>

Namibia Institute of Pathology. (2017). HbA1c test standard operating procedure. Windhoek, Namibia.

Nathan, D. M. (2009). International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes: Response to Kilpatrick, Bloomgarden, and Zimmet. *Diabetes Care*, 32(12), e160-e160.

The National Institute of Diabetes and Digestive and Kidney Diseases. (2016, November 30). What is Diabetes? Retrieved from <https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes>

- Niazi, A., & Kalra, S. (2012). Diabetes and tuberculosis: a review of the role of optimal glycemic control. *Journal of Diabetes & Metabolic Disorders*, 11(1), 28.
- Noubiap, J. J., Nansseu, J. R., Nyaga, U. F., Nkeck, J. R., Endomba, F. T., Kaze, A. D., ... Bigna, J. J. (2019). Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2·3 million patients with tuberculosis. *The Lancet Global Health*, 7(4), e448-e460.
- Nugussie, D. A., Mohammed, G. A., & Tefera, A. T. (2017). Prevalence of Smear-Positive Tuberculosis among Patients Who Visited Saint Paul's Specialized Hospital in Addis Ababa, Ethiopia. *BioMed Research International*, 2017, 1-5.
- Nurwidya, F., Ratnawati, Wijaya, D., Nazaruddin, A., & Burhan, E. (2018). The relationship between hemoglobin A1c levels and sputum conversion time in Indonesian patients with new cases of pulmonary tuberculosis. *Journal of Natural Science, Biology and Medicine*, 9(2), 217.
- Nwachukwu, N. O., Onyeagba, R. A., Nwaugo, V. O., Ugbogu, O. C., & Ulasi, A. E. (2016). Prevalence of pulmonary tuberculosis and its associated risk factors in Anambra state, Nigeria. *FUW Trends in Science & Technology Journal*, 1(2), pp 486 - 492.
- Nwachukwu, O. N., Onyeagba, R. A., Owanta, J. I., Okoronkwo, U. C., & Ononiwu, H. A. (2016). Prevalence and Patterns of Multimorbidity of Tuberculosis, Human Immunodeficiency Virus and Diabetes Mellitus in Anambra State, Nigeria. *Clinical Biotechnology and Microbiology*, 1(1), 1-8. Retrieved from <https://scientiaricerca.com/srcbmi/pdf/SRCBMI-01-00001.pdf>
- Nyabadza, F., & Winkler, D. (2013). A simulation age-specific tuberculosis model for the Cape Town metropole. *South African Journal of Science*, 109(9/10), 1-7.
- Ogurtsova, K., Da Rocha Fernandes, J., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N., ... Makaroff, L. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Research and Clinical Practice*, 128, 40-50.
- Oni, T., Berkowitz, N., Kubjane, M., Goliath, R., Levitt, N., & Wilkinson, R. J. (2017). Trilateral overlap of tuberculosis, diabetes and HIV-1 in a high-burden African setting: implications for TB control. *European Respiratory Journal*, 50(1), 1700004.
- Onyebujoh, P. C., Thirumala, A. K., & Piatek, A. (2017). Stronger tuberculosis laboratory networks and services in Africa essential to ending tuberculosis. *African Journal of Laboratory Medicine*, 6(2).

Parvizi, J. (2010). Tuberculosis 226. In *High Yield Orthopaedics* (pp. 473-474). St. Louis, MO: Elsevier Health Sciences.

Pfyffer, G. E., & Wittwer, F. (2012). Incubation Time of Mycobacterial Cultures: How long is long enough to issue a final negative report to the clinician? *Journal of Clinical Microbiology*, 50(12), 4188-4189.

Podell, B. K. (2014). *The Pathogenesis of Diabetes-Tuberculosis Comorbidity* (Doctoral dissertation, Colorado State University).

Prasad, A., Ross, A., Rosenberg, P., & Dye, C. (2016). A world of cities and the end of TB. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 110(3), 151-152.

Rabinovitch, B., & Pai, M. (2018). Interpretation of Chest X-rays in Tuberculosis. *Let's Talk TB*, 3.

Rahbar, S., Blumenfeld, O., & Ranney, H. M. (1969). Studies of an unusual hemoglobin in patients with diabetes mellitus. *Biochemical and Biophysical Research Communications*, 36(5), 838-843.

Rawat, J., Biswas, D., & Sindhwani, G. (2011). Effect of age on presentation with diabetes: Comparison of nondiabetic patients with new smear-positive pulmonary tuberculosis patients. *Lung India*, 28(3), 187.

Rayfield, E. J., Ault, M. J., Keusch, G. T., Brothers, M. J., Nechemias, C., & Smith, H. (1982). Infection and diabetes: The case for glucose control. *The American Journal of Medicine*, 72(3), 439-450.

Reid, M., McFadden, N., & Tsimba, B. (2013). Clinical challenges in the co-management of diabetes mellitus and tuberculosis in southern Africa. *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, 18(3), 135-140.

Restrepo, B. I. (2016). Diabetes and tuberculosis. *Microbiology spectrum*, 4(6). Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5240796/>

Restrepo, B. I., & Schlesinger, L. S. (2014). Impact of diabetes on the natural history of tuberculosis. *Diabetes Research and Clinical Practice*, 106(2), 191-199.

Riza, A. L., Pearson, F., Ugarte-Gil, C., Alisjahbana, B., Van de Vijver, S., Panduru, N. M., ... Van Crevel, R. (2014). Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *The Lancet Diabetes & Endocrinology*, 2(9), 740-753.

Roche distributors Mannheim, Germany. (2018, February). Tina-quant Hemoglobin A1c Gen.3 - Hemolysate and Whole Blood Application package insert. Mannheim, Germany: Roche distributors.

Ronacher, K., Alisjahbana, B., Riza, A. L., Koesoemadinata, R. C., Malherbe, S. T., & Ugarte-Gil, C. (2019). Diabetes mellitus among pulmonary tuberculosis patients from four Tuberculosis-endemic Countries: The TANDEM Study. *Clinical Infectious Diseases*.

Ruslami, R., Aarnoutse, R. E., Alisjahbana, B., Van Der Ven, A. J., & Van Crevel, R. (2010). Implications of the global increase of diabetes for tuberculosis control and patient care. *Tropical Medicine & International Health*, 15(11), 1289-1299.

Ryu, Y. J. (2015). Diagnosis of Pulmonary Tuberculosis: Recent Advances and Diagnostic Algorithms. *Tuberculosis and Respiratory Diseases*, 78(2), 64.

Saunders, M. J., Tovar, M. A., Collier, D., Baldwin, M. R., Montoya, R., Valencia, T. R., ... Evans, C. A. (2019). Active and passive case-finding in tuberculosis-affected households in Peru: a 10-year prospective cohort study. *The Lancet Infectious Diseases*, 19(5), 519-528.

Shah, M., Hanrahan, C., Wang, Z. Y., Dendukuri, N., Lawn, S. D., Denking, C. M., & Steingart, K. R. (2016). Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. *Cochrane Database of Systematic Reviews*, 5.

Shariff, N. M., & Safian, N. (2015). Diabetes mellitus and its influence on sputum smear positivity at the 2nd month of treatment among pulmonary tuberculosis patients in Kuala Lumpur, Malaysia: A case control study. *International Journal of Mycobacteriology*, 4(4), 323-329.

Sharma, D., Goel, N. K., Sharma, M. K., Walia, D. K., Thakare, M. M., & Khaneja, R. (2018). Prevalence of diabetes mellitus and its predictors among tuberculosis patients currently on treatment. *Indian Journal of Community Medicine*, 43(4), 302-306.

Shiraiahi, R. (2010). *Excel sample calculation tool Beta 1, 0. Ho Chi Minh City, Vietnam* [PDF].

Siddiqui, A. N., Khayyam, K. U., & Sharma, M. (2016). Effect of Diabetes Mellitus on Tuberculosis Treatment Outcome and Adverse Reactions in Patients Receiving Directly Observed Treatment Strategy in India: A Prospective Study. *BioMed Research International*, 2016, 1-11.

Singla, R., Khan, N., Al-Sharif, N., Al-Sayegh, M. O., Shaikh, M. A., & Osman, M. M. (2006). Influence of diabetes on manifestations and treatment outcome of pulmonary TB patients. *International Journal of Tuberculosis and Lung Disease*, 10(1), 74-79.

- Small, P. M., & Pai, M. (2010). Tuberculosis Diagnosis — Time for a Game Change. *New England Journal of Medicine*, 363(11), 1070-1071.
- Stalenhoef, J. E., Alisjahbana, B., Nelwan, E. J., Ven-Jongekrijg, J., Ottenhoff, T. H., Meer, J. W., ... Crevel, R. (2007). The role of interferon-gamma in the increased tuberculosis risk in type 2 diabetes mellitus. *European Journal of Clinical Microbiology & Infectious Diseases*, 27(2), 97-103.
- TBFACTS.org. (2019, March 19). *Latent TB vs active TB* [image]. Retrieved from <https://www.tbfacts.org/wp-content/uploads/2018/07/latent-tb-1.jpg>
- Todar, K. (2012). Mycobacterium tuberculosis and Tuberculosis. In *Todar's Online Textbook of Bacteriology*. Retrieved from <http://textbookofbacteriology.net/tuberculosis.html>
- Trinh, Q. M., Nguyen, H. L., Nguyen, V. N., & Nguyen, T. V. (2015). Tuberculosis and HIV co-infection—focus on the Asia-Pacific region. *International Journal of Infectious Diseases*, 32, 170-178.
- Tsukaguchi, K., Okamura, H., Ikuno, M., Kobayashi, A., Fukuoka, A., Takenaka, H., ... Yamamoto, C. (1997). The relation between diabetes mellitus and IFN-gamma, IL-12 and IL-10 productions by CD4 α beta T cells and monocytes in patients with pulmonary tuberculosis. *Kekkaku*, 72, 1799-1801. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/9423299>
- Uplekar, M., Weil, D., Lonnroth, K., Jaramillo, E., Lienhardt, C., Dias, H. M., ... Raviglione, M. (2015). WHO's new End TB Strategy. *The Lancet*, 385(9979), 1799-1801.
- US Embassy Namibia. (2019, March 29). World TB Day Commemoration. Retrieved from <https://na.usembassy.gov/world-tb-day-commemoration/>
- Viardot, A., Grey, S. T., Mackay, F., & Chisholm, D. (2007). Potential Antiinflammatory Role of Insulin via the Preferential Polarization of Effector T Cells toward a T Helper 2 Phenotype. *Endocrinology*, 148(1), 346-353. doi:10.1210/en.2006-0686
- Webb, E. A., Hesselning, A. C., Schaaf, H. S., Gie, R. P., Lombard, C. J., Spitaels, A., ... Delport, S. (2009). High prevalence of Mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus. *Int J Tuberc Lung Dis*, 13(7), 868-874. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/19555537>
- WHO. (2004). *Toman's tuberculosis: case detection, treatment and monitoring* (9241546034). Retrieved from <https://www.who.int/tb/publications/toman-2004-334/en/>

WHO. (2017, June 7). Speeches & Messages. Retrieved from <https://www.afro.who.int/regional-director/speeches-messages>

Workneh, M. H., Bjune, G. A., & Yimer, S. A. (2016). Prevalence and Associated Factors of Diabetes Mellitus among Tuberculosis Patients in South-Eastern Amhara Region, Ethiopia: A Cross Sectional Study. *PLOS ONE*, 11(1), e0147621.

Workneh, M. H., Bjune, G. A., & Yimer, S. A. (2017). Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review. *PLOS ONE*, 12(4), e0175925.

World Health Organization. (2005, August 26). WHO declares TB an emergency in Africa. Retrieved from https://www.who.int/mediacentre/news/releases/2005/africa_emergency/en/

World Health Organization. (2007). *Diabetes prevention and control: a strategy for the WHO African region: Report of the Regional Director*. Retrieved from <https://apps.who.int/iris/handle/10665/19997>

World Health Organization. (2011). *Collaborative Framework for Care and Control of Tuberculosis and Diabetes*. Retrieved from <https://www.who.int/tb/publications/tb-diabetes-framework/en/>

World Health Organization. (2011). *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings* (ISBN 978 92 4 150070 8). https://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf;jsessionid=C5D8616A6511615AB2D9E7A24CD26576?sequence=1

World Health Organization. (2011). *Use of glycated hemoglobin (HbA1c) in the diagnosis of diabetes mellitus*. Retrieved from https://www.who.int/diabetes/publications/report-HbA1c_2011.pdf

World Health Organization. (2014). *Definitions and reporting framework for tuberculosis 2013 revision, updated December 2014* (ISBN: 9789241505345). Retrieved from <https://www.who.int/tb/publications/definitions/en/>

World Health Organization. (2015). *WHO End TB Strategy*. Retrieved from https://www.who.int/tb/post2015_strategy/en/

World Health Organization. (2016). *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Retrieved from <https://apps.who.int/iris/handle/10665/208825>

World Health Organization. (2016). *Diabetes Country Profile Namibia*. Retrieved from https://www.who.int/diabetes/country-profiles/nam_en.pdf?ua=1

World Health Organization. (2017). TB comorbidities and risk factors. Retrieved from <https://www.who.int/tb/areas-of-work/treatment/risk-factors/en/>

World Health Organization. (2018, July 3). Tuberculosis (TB). Retrieved from <https://www.afro.who.int/health-topics/tuberculosis-tb>

World Health Organization. (2019). *Global tuberculosis report 2018*. Retrieved from https://www.who.int/tb/publications/global_report/en/

World Health Organization. (2019, March 1). Active case finding: Systematic screening for active tuberculosis. Retrieved from <https://www.who.int/tb/areas-of-work/laboratory/active-case-finding/en/>

World Health Organization. (2019, April 4). Treatment: background. Retrieved from <https://www.who.int/tb/areas-of-work/treatment/background/en>

World Health Organization. (2019, March 25). Universal antiretroviral therapy (ART) for all HIV-infected TB patients. Retrieved from https://www.who.int/hiv/topics/tb/art_hivpatients/en/

World Health Organization. (2019, March 19). WHO endorses new rapid tuberculosis test. Retrieved from https://www.who.int/tb/features_archive/new_rapid_test/en/

World Health Organization. (2019, June 20). Diagnosis and treatment of TB, HIV-associated TB and drug-resistant TB. Retrieved from <https://www.who.int/gho/tb/epidemic/diagnosis/en/>

Zeratsky, K. (2017, June 30). Diabetes: Does alcohol and tobacco use increase my risk? Retrieved from <https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/expert-answers/diabetes/faq-20058540>

Zheng, C., Hu, M., & Gao, F. (2017). Diabetes and pulmonary tuberculosis: a global overview with special focus on the situation in Asian countries with high TB-DM burden. *Global Health Action*, 10(1), 1264702. doi:10.1080/16549716.2016.1264702

Annexure I- Participant Questionnaire

Study Name: Impact of Diabetes on the TB treatment outcomes among TB patients in Khomas Region

Facility Name:	Interviewer Name
Participant Name:	Participant Unique Identifier
Date of interview:	

Step 1 Demographic Information

CORE: Demographic Information		
Question	Response	Code
Sex (<i>Record Male / Female as observed</i>)	Male 1 Female 2	
What is your date of birth? <i>Don't Know</i>	dd mm year <i>If known, Go to C4</i>	
How old are you?	Years	

Step 1 Behavioral Measurements

CORE: Tobacco Use		
Now I am going to ask you some questions about tobacco use.		
Question	Response	
Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes?	Yes	1
	No	2
Do you currently smoke tobacco products daily ?	Yes	1
	No	2
CORE: Alcohol Consumption		
The next questions ask about the consumption of alcohol.		
Question	Response	Code
Have you ever consumed any alcohol such as beer, wine, spirits or <i>[add other local examples]</i> ?	Yes	
	No	
Have you consumed any alcohol within the past 12 months ?	Yes	
	No	
Have you stopped drinking due to health reasons, such as a negative impact on your health or on the advice of your doctor or other health worker?		
CORE: History of TB		

Final treatment outcomes	Cured		
	Completed		
	LTFU		
	Treatment failure		
	Died		
CORE: History of Diabetes			
Have you ever had your blood sugar measured by a doctor or other health	Yes	1	
	No	2 <i>If No, go to H12</i>	
Have you ever been told by a doctor or other health worker that you have raised blood sugar or diabetes?	Yes	1	
	No	2 <i>If No, go to H12</i>	
Have you been told in the past 12 months?	Yes	1	
	No	2	
In the past two weeks, have you taken any drugs (medication) for diabetes prescribed by a doctor or other health worker?	Yes	1	
	No	2	
Are you currently taking insulin for diabetes prescribed by a doctor or other health worker?	Yes	1	
	No	2	
Have you ever seen a traditional healer for diabetes or raised blood sugar?	Yes	1	
	No	2	
Are you currently taking any herbal or traditional remedy for your diabetes?	Yes	1	
	No	2	

Step 3 Biochemical Measurements

CORE: Blood Glucose		
Question	Response	
During the past 12 hours have you had anything to eat or drink, other than water?	Yes 1 No 2	
Time of day blood specimen taken (24 hour clock)	Hours : minutes : hrs mins	
HbA1c result		
Today, have you taken insulin or other drugs (medication) that have been prescribed by a doctor or other health worker for raised blood glucose?	Yes 1	
	No 2	

Annexure II - Participant information and consent form

Dear participant:

My name is Anita Beukes, a Master student from the Namibia University of Science and Technology.

You are invited to take part in a study to find out how many tuberculosis (TB) patients in the Khomas Region also have diabetes. You are living in the area that has been selected to participate in the study, therefore you and all other adults TB patients in this area, have been selected.

If you agree to participate in the study, the following procedure will be taken:

- We will ask you to assist us to complete a questionnaire by answering a few questions regarding your TB, diabetes and HIV history.
- A phlebotomist will also ask you to draw blood for diabetes diagnosis.

The benefit for you to participate in the study, is that you will receive assistance for disease conditions you might have. Your participation will also provide information that will help the Ministry of Health and Social Services to improve health services for everyone in the country. The risks of participation are minimal

All results will be kept confidential and your name will only be used to assist us to contact you regarding the care you might need. Participation in this study is voluntary. If you choose not to participate, it will not affect in any way the provision of health services to you. You can withdraw yourself from the study at any moment.

We will highly appreciate your participation in the study.

If you have any question please contact the Principal Investigator at this telephone number: +264 811223812

I have read/understood the Information Sheet concerning the study about the prevalence of diabetes among TB patients in the Khomas region and the impact of diabetes on TB treatment outcomes.

I have had the opportunity to ask questions about the study and the questions that I have asked have been answered to my satisfaction.

I now understand what will be required of me and what procedures I will have to go through during this study.

I understand that I may withdraw from this study at any time without giving a reason and withdrawal will not affect my usual care and treatment.

I consent voluntarily to participate in this study.

Signature / thumb impression:Date:

Name of participant:

Witness Signature / thumb impression:Date:

Name of witness:

For individuals aged less than 16 years, ask consent from the parent or other adult identified as responsible for the individual before asking the adolescent for his/her consent. Enroll into survey only if both the parent (or guardian) and the adolescent consent to participating

Annexure III - Confidentiality Form

OATH/AFFIRMATION OF SECRECY BY THE STUDY STAFF MEMBERS

I (Block letters).....

Do hereby make oath/solemnly affirm that I am conversant with the provision of the Protection of Information Act, 1982 (Act 84 of 1992) as amended by the Proclamation AG.29/1985 dated 15 June 1985 and unless duly authorized I will not at any time during my service as a staff member of the study or when I have left the said service, divulge in any way to the media, general public, or unauthorized person any form of classified or sensitive information or any other information and/or material that is or was within my knowledge or is or was in my possession relative of the Public Service or Government of Namibia.

.....

Signature of Deponent

Sworn/Affirmed before me at.....thisday of.....20.....

.....

Signature

.....

NAME AND RANK

COMMISSIONER OF OATH

(EX OFFICIO)

.....

SIGNATURE OF WITNESS

.....

NAME AND RANK

Annexure IV- MoHSS approval letter



REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13198	Ministerial Building	Tel: 061- 2032150
Windhoek	Harvey Street	Fax: 061- 222558
Namibia	Windhoek	Email: shimenghipangelwa71@gmail.com

OFFICE OF THE PERMANENT SECRETARY

Ref: 17/3/3 AM
Enquiries: Mr. J. Nghipangelwa

Date: 19 October 2017

Ms. Anita Beukes
University of Science and Technology
Windhoek

Dear Ms. Beukes

Re: Impact of diabetes on Treatment of TB patients in Khomas Region.

1. Reference is made to your application to conduct the above-mentioned study.
2. The proposal has been evaluated and found to have merit.
3. Kindly be informed that permission to conduct the study has been granted under the following conditions:
 - 3.1 The data to be collected must only be used for academic purposes;
 - 3.2 No other data should be collected other than the data stated in the proposal;
 - 3.3 Stipulated ethical considerations in the protocol related to the protection of Human Subjects' should be observed and adhered to, any violation thereof will lead to termination of the study at any stage;
 - 3.4 A quarterly report to be submitted to the Ministry's Research Unit;
 - 3.5 Preliminary findings to be submitted upon completion of the study;
 - 3.6 Final report to be submitted upon completion of the study;

Annexure V- NUST approval letter



**NAMIBIA UNIVERSITY
OF SCIENCE AND TECHNOLOGY**

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Windhoek
NAMIBIA

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W: www.nust.na

FACULTY OF HEALTH AND APPLIED SCIENCES

DECISION/FEEDBACK ON RESEARCH PROPOSAL ETHICAL CLEARANCE

Dear Prof/Dr/Mr/Ms/Other(s):

Anita Beukes

Student No (if applicable): 217076629

Research Topic:	Impact of Diabetes on the treatment of TB patients in Khomas Region, Namibia
Supervisor (if applicable):	Mrs C de Waal-Miller
Co-supervisor(s) if applicable:	Prof SR Moye
Qualification registered for (if applicable):	Master of Health Sciences

Re: Ethical screening application No:

REC - 00015/2017

The Research Ethics Screening Committee has reviewed your application for the above-mentioned research project. Based on the recommendation of the expert reviewer, the research as set out in the application is hereby:

(Indicate with an X)

Approved: i.e. may proceed with the project:	
Approved provisionally: i.e. may proceed but subject to compliance with recommendation(s) listed below	X
Not approved: Not to proceed with the project until compliance with recommendation(s) listed below and resubmit ethics application for consideration	
IS MINISTRY OF HEALTH & SOCIAL SERVICES (MoHSS) APPROVAL REQUIRED?	YES: X NO:

It is important to note that as a researcher, you are expected to maintain ethical integrity of your research, strictly adhere to the ethical policy of NUST, and remain within the scope of your research proposal and supporting evidence as submitted to the REC. Should any aspect of your research change from the information as presented, which could have an impact or effect on any research participants/subjects/environment, you are to report this immediately to your supervisor or REC as applicable in writing. Failure to do so may result in withdrawal of approval. Kindly consult your supervisor or HoD if you need further clarification.

We wish you success in your research endeavour and are of the belief that it will have positive impact on your career as well as the development of NUST and the society in general.

Ethical Issues that require compliance/ must be addressed		
No.	Ethical Issues	Comment/recommendation
1.	Involves collection of identifiable information about people	To provide confidentiality strategy to FHAS-REC
2.	Collection of information from TB patients through hospital records and facilities.	To obtain MoHSS approval and submit copy to FHAS-REC secretariat*.

NB: May attach additional page as required; * Failure to do so will invalidate research outcome

Full Name (reviewer): ...Dr SYLVANUS ONJEFU... Signature: *[Signature]* Date: 4/9/2017

Full Name: PROF...OMDTAYO AWOFOLU... Signature: *[Signature]* Date: 2/9/2017

Chair: Ethics Screening Committee

Annexure VI- NIP Approval Letter



NAMIBIA INSTITUTE OF PATHOLOGY LIMITED

Reg. No. 2002431
Tel: +264 61 295 4500 • Fax: +264 61 255 566 • P.O. Box 777 • Windhoek • Namibia • info@nip.com.na • www.nip.com.na

OFFICE OF THE CHIEF OPERATIONS OFFICER

Enclosures: Mr Boniface Makumbi; Tel: 061-295 4210

20 March 2019

Ms Anita Boukes
University of Science and Technology
Windhoek

Dear Madam,

RE: Impact of diabetes on Treatment of TB patients in Khomas Region

1. The above mentioned research proposal was referred to the Research/Ethics Committee of the Namibia Institute of Pathology Limited for review.
2. After review, it is a pleasure to inform you that approval was granted for you to proceed with the research on condition that the following be complied with:
3. Observe and adhere to all ethical considerations and confidentiality to protect clientele and Namibia Institute of Pathology Limited (NIP) information.
4. Adhere to all terms and conditions as stipulated by the Ministry of Health and Social Services
5. Final report to be shared with the Namibia Institute of Pathology Limited.

Yours Sincerely

Boniface Makumbi
Acting Chief Operations Officer

Directors: Dr. D. Shauluka (Chairperson); S. Van Rijen (Vice Chairperson); A. Avela; M. Kapere; Dr. E. Kapwewongo; E. Kwela; E. Ujavu.
M. Ngaprasanthu (Acting CEO); G. Imhof (Company Secretary)

Annexure VII- Khomas Directorate Approval Letter



9 - 00001

REPUBLIC OF NAMIBIA

Ministry of Health and Social Services

Private Bag 13322
Windhoek
Namibia

Khomas Region Directorate
Florence Nightingale Street,
Windhoek

Tel: 061 - 2035911
Fax: 061 - 235997

Eqq: Mr. B. Isaacs

Ref: S49

Date: 8 May 2019

OFFICE OF THE DIRECTOR

STAFF MATTER: CONFIDENTIAL

MS. ANITA BEUKES
NAMIBIA UNIVERSITY OF SCIENCE AND TECHNOLOGY
WINDHOEK
NAMIBIA

Dear Ms. Beukes

I have the pleasure to inform you that as per Executive Director's approval permission to conduct a study of "prevalence of diabetes among TB patients in the Khomas Region has been extended from 13 May – 30 June 2019.

The office wishes you success with your research.

Yours sincerely


MS. ELIZABETH MUREMI
DIRECTOR: KHOMAS REGION

"Health for All"

Annexure VIII – Study Data file



Diabetes dataset
update 10 July.csv