AN INVESTIGATION OF ISONIAZID MONO-RESISTANCE TUBERCULOSIS IN TSHWANE DISTRICT, GAUTENG, IN 2009

By

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SUPERVISOR: Professor Paul Chelule

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DECLARATION

I, Sonwabo Lindani hereby declare that the work on which this dissertation is based, An investigation of Isoniazid mono-drug resistance tuberculosis in Tshwane district, Gauteng, in 2009, is original (except where acknowledgements indicate otherwise) and that neither the whole work nor part of it has been, is being, or shall be submitted for another degree at this or any other university, institution for tertiary education or examining body.

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Sonwabo Lindani                                 Date
ACKNOWLEDGEMENTS

Firstly, I give thanks and praises to the almighty God for strengthening me from the beginning of this work to its completion.

I would like to appreciate and thank my supervisor, Professor. Paul Chelule, for his guidance, support, encouragement and contributions from the conception to completion of my research project.

I also wish to thank the following institutions and people:
- NHLS for providing data used.
- ETR.net Johannesburg team for providing additional data.

To all healthcare professionals who participated in the study, I thank you. Without your participation, this study would not have been possible to conduct and accomplish.

To everybody that I have not mentioned above, your support was a blessing.

Thank you.
ABSTRACT

**Background:** Tuberculosis (TB) is a global challenge and South Africa is one of the countries that are still battling with the management and control of this disease. To manage tuberculosis better, it is important to document the prevalence on INH mono-drug resistant TB and determine treatment outcomes on these patients as compared to those who have drug susceptible tuberculosis (TB) and identify associated risk factors.

**Study Aim:** The aim of the study was to determine the prevalence and investigate the associated factors of Isoniazid mono-drug resistance tuberculosis in Tshwane district, Gauteng, in 2009.

**Methods:** This is a descriptive retrospective records review study on Isoniazid (INH) mono-resistant TB patients in Tshwane in year 2009. During the first phase, a review of electronic registers including socio-demographic and other characteristics of patients that were on tuberculosis treatment in year 2009 within the Tshwane District and the whole National Health Laboratory Service (NHLS) Corporate data warehouse (CDW) database for 2009.

During the second phase a matched case-control study was conducted based on the information from the CDW. Cases were patients with INH culture confirmed mono-resistance TB who were matched by sex, name, date of birth and diagnosis date with controls, patients with drug susceptible TB. For comparison, data was converted into categorical variables and bi-variant analysis was done by running a two by two table of association. The Odds ratio (OR) and 95% confidence interval were calculated to determine the statistical significance. A p-value of ≤ 0.05 was considered significant.

**Results:** Of the 349 study patient’s records selected for the study, 55% of them were males and the mean age was 36.6 years. Although most of the patients were newly diagnosed with tuberculosis (94%), few of them had a known HIV status (31%). Out of the total patients with known HIV status, sixteen percent (16%) of them were HIV negative, 34% had INH mono-resistant TB and HIV positive. A total 25% of patients sampled were under directly observed treatment (DOT). Bivariate analysis showed that participating in DOT support reduces the risk to developing resistant TB compared
to those not participating (OR=0.50, 95% CI=0.30-0.83, p=0.01). Seventy-two percent (72%) of the patients had positive final outcomes with a total of 58.6% having sensitive TB and 93% were on treatment regimen 1.

**Conclusion and recommendations:** The study has shown that the prevalence of INH mono-resistant TB patients is relatively high among patients studied, with district 1 having more prevalence (n=85, 55.1%) than other regions. Participating in DOT program greatly enhances positive treatment outcome and is highly recommended in managing Isoniazid mono-resistant tuberculosis (INHMr TB) patients.
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over 30 years. Similarly, INHMr TB was also higher in males (55%) than females, although this was not statistically significant. Only one hundred and thirty-two (n=132, 37.8%) of patients had recorded HIV status and out of these 65.9% of them were HIV positive. Although not statistically significant results show that being HIV positive increases the risk of developing TB resistance as compared to the HIV negative patients (OR=0.8, 95%CI=0.28-2.1 and p=0.6).

Out of the 349 selected patients a total of eighty-six (N=86, 24.6%) patients were on DOT system and majority of these were from the INH sensitive TB group (N=58, 17%). In a bivariate analysis being under DOT support reduces the risk to developing resistant TB compared to those not on DOT support (OR=0.50, 95%CI=0.30-0.83, p=0.01). About sixteen percent (N=58; 16%) of total patients were not recorded whether were on DOT support or not, with nine percent (N=35, 9%) of these being INHMr TB patients.

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DISCUSSION, CONCLUSION AND RECOMMENDATIONS

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CHAPTER 1
STUDY BACKGROUND

1.1 Introduction

Tuberculosis (TB) is one of the top 10 causes of patient deaths and the leading cause from a single infectious disease, surpassing HIV/AIDS (WHO, 2018). Tuberculosis is an infectious disease with an estimated 9 million cases and nearly 2 million deaths annually (Wang et al, 2014). For example, in the year 2016, an estimated total of 1.3 million people, who were HIV negative, died of TB globally (WHO, 2017). In addition, there were 374,000 deaths resulting from TB disease among people who were HIV positive. Thus, a total of 1,674,000 TB patient deaths were reported. An estimated 250,000 children died of TB in 2016 and this number includes that of children with HIV associated TB. People who have both TB and HIV, when they die, are internationally classified as having died from HIV (Cain et al, 2009). It is also reported that, forty percent (40%) of HIV deaths were associated with TB (WHO, 2017). In South Africa an estimated 438,000 people were diagnosed with TB in 2016, 19,000 were drug resistant and out of the total estimate, 258,000 were HIV positive. The total of 23,000 of those who died, were HIV negative, while 101,000 were HIV positive (WHO, 2017).

Tuberculosis infected patients get acquired drug-resistant TB when their TB treatment is inadequately prescribed, or drugs are substandard or not the correct regimen or when the patient fails to take treatment regularly or appropriately. Secondly, transmitted or primary drug-resistant TB, occurs from the direct transmission of drug-resistant TB from one infected person to another person who is not infected (Department of Health, 2014).

Isoniazid is a potent anti-tuberculosis drug, which forms one of the main components of the recommended first line tuberculosis (TB) treatment regimen. Treatment of patients infected with INH-mono resistant TB strains using standardized therapy has been associated with increased risk of treatment failure and further acquired resistance such as multi-drug resistant tuberculosis (MDR-TB) (WHO, 2011). Isoniazid is the most important first-line drug for treatment of tuberculosis due to its potent early bacterial activity (Tsai-Yu et al, 2014).
Resistance to anti-tuberculosis drugs is reported to be a global problem and is a consequence of poor tuberculosis (TB) control programmes (Hughes, 2014). The impact of drug resistance following tuberculosis treatment depends on the pattern of the drug resistance and the treatment regimen applied. Resistance to Isoniazid (INH) is reported to be very common with a prevalence rate of 20% amongst previously treated cases and 10% amongst new cases (Cattamanchi et al, 2009). Other studies report INH resistance among new cases to be 10.3% and even higher in retreatment patients (Chiang, 2010; Churchyard, 2014). In another study conducted in South Africa, a 48.8% treatment success rate on INH mono-resistant patients was achieved (Marais et al., 2014; Menzies et al, 2009). Yet another study conducted in Cape Town, showed that 65% of patients completed therapy successfully, 15% of patients had treatment failure, 1% died, 16% defaulted, and 61% of those who failed therapy progressed to MDR TB (Jacobson et al, 2011; Ebomwu et al, 2013). These findings are not unique to South Africa as similar results have been reported elsewhere (Chien et al, 2015; Varahram et al, 2014; Wang et al, 2009; Cattamanchi et al, 2009).

1.2 Problem statement

Isoniazid mono-drug resistant tuberculosis (INHMr TB) prevalence is much higher than Rifampicin resistance but diagnosis of INH mono-resistance has received less attention largely because its clinical impact has not been reported intensively and treatment outcomes extent, recurrence patterns in patients with INH mono-resistance are not widely known (WHO, 2014).

In patients with primary INH mono-resistant TB, MDR-TB may emerge if the four standard drugs are not given in the intensive phase for the treatment of new patients (Chiang, 2010; Churchyard, 2014). Some studies have shown that INH monoresistance TB reduces the probability of achieving high cure rate when INH is a core drug in the regimen used for treatment of TB in that patient. To address this problem, it is imperative to understand the prevalence and factors that are associated with INH-monotherapy resistance in TB patients. Although recent report on the national survey show the prevalence of Isoniazid mono-resistance in South Africa as 9.3% and rifampicin mono-resistance is said to be at 4.6% (Ismail et al, 2016), this survey
although it also covered Gauteng province, showed national average there are no reports showing this prevalence for all districts in Gauteng province. This study focused on the investigation of INH mono-drug resistance tuberculosis in Tshwane district.

This study is the first showing the prevalent and the state of isoniazid (INH) resistance in the whole of Tshwane district. The study findings will inform on formulating better strategies that can implemented for better management of TB epidemic (Brink, 1996). The study period is restricted to the year 2009 because it is the year when Line Probe Assay (LPA) was introduced by National Health Laboratory Services (NHLS) and Tshwane region was one of the first districts to be fully covered.

1.3 Study aim

The purpose of this study is to investigate the state of INH mono-resistant TB in Tshwane district in year 2009 in South Africa.

1.4 Research question

1. What is the prevalence of INH mono-resistance among TB patients in Tshwane district?

2. What are the factors associated with INH mono-resistance?

3. What is difference in treatment outcomes between mono-resistant and controls patients?

1.5 Objectives

The specific objectives are to:

1. Determine the prevalence of INH mono-resistance among TB patients in Tshwane district in 2009

2. Determine the factors associated with INH mono-resistance in cases and their controls
3. Determine the difference in treatment outcomes among patients with INH mono-resistance how they differ from their controls in Tshwane district

1.6 Study significance

This study sought to determine prevalence of INH mono-resistance in Tshwane district and how treatment outcomes of patients with INH mono-resistance differ from the other TB patients in Tshwane district. The results will be communicated to the relevant authorities in TB management to inform policy and TB management strategy.

1.7 Conclusion

This chapter has presented the research problem, the study aims, the research questions we sought to investigate, the objectives of the study, and the significance of the study are also discussed. The next chapter will discuss the literature review of the study.
CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter presents a review of literature on and summarizes relevant published reports on Isoniazid mono-resistant tuberculosis (INHMr TB) and articulates gaps and similarities found in the published reports. The aim of this chapter is to critically analyse what is known about this resistance phenomenon (Brink, 1996), and to lay down the background for the current study. The search was done on google scholar using key word Isoniazid mono-resistance Tuberculosis.

2.2 Prevalence tuberculosis

Pulmonary tuberculosis and drug-resistant tuberculosis are a big concern for public health professionals globally; with an estimated 8.6 million new cases and 1.3 – 1.6 million deaths in year 2012, it is a high burden disease (WHO, 2013; Ramonowski et al., 2017). A systemic review of the studies in low and middle income countries reported tuberculosis infection rate amongst health care workers (HCWs) ranging from 3.9% to 14.3% (Joshi et al, 2006). In year 2017 World Health Organization (WHO) reported that 558 000 people (range, 483 000–639 000) developed TB that was resistant to rifampicin (RR-TB), and of these, 82% had multidrug-resistant TB (MDR-TB). Sadly, South Africa is one of the 22 high-burden TB countries in the world and has second highest TB incidents in the world (WHO, 2012; Ismail et al 2014).

2.3 Diagnosis and types of TB regimens used in TB management

In South Africa tuberculosis is routinely screened and diagnosed with GeneXpert machine which only detects rifampicin resistance or sensitivity. To determine whether patients have drug susceptible TB or drug resistant TB histological drug susceptibility testing is done through culturing bacteria. This is done using Line Probe Assay (LPA), a Drug Sensitivity Testing (DST) kit which takes about six weeks to give results (Kim,
In principle, LPA are tests that use polymerase chain reaction (PCR) and reverse hybridization methods to detection of mutations associated with drug resistance. This test was approved for rapid drug resistance testing by WHO in 2008.

With Drug Sensitivity Testing (DST) being reserved for patients who have treatment failure, it means patient who are solely resistant to Isoniazid (INH) can only be diagnosed later during treatment and many studies mention this as a challenge in the overall tuberculosis (TB) treatment outcomes in patients (Wang et al, 2014). In the absence of routine DST, patients receive an initial regimen of 4-drug therapy, if found to be sensitive to Rifampicin.

Anti-TB drugs used to treat patients generally depends on the type of TB that the patient present with in the facility or to the treating clinician. Patients that are susceptible to Rifampicin and Isoniazid are managed with regimen 1 (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide). The patients that are resistant to both isoniazide (INH) and Rifampicin (R), are managed following multi-drug resistant regimen with additional drugs and over a long duration. Regimen 3A (Isoniazid, rifampicin, and pyrazinamide) are used on children <8 years and <30 kg, who have uncomplicated TB disease. Regimen 3B (Isoniazid, rifampicin, pyrazinamide and ethambutol) for children <8 years and <30 kg, having complicated TB disease (Department of Health, 2014).

2.4 TB drug resistance and how it arises

A person with active TB disease has drug resistant TB if the TB bacteria that the person is infected with, will not respond to, and are therefore resistant to at least one of the main TB drugs. Drug resistance to a single agent is reported to be the most common type of resistance (Jean et al, 2003). MDR (multi drug resistant) TB is the name given to TB when the bacteria that are causing it are resistant to at least isoniazid and rifampicin, two of the most effective TB drugs.

The World Health Organization (WHO) reported an increasing trends of drug-resistant tuberculosis (TB). Resistance to anti-tuberculosis drugs is a global problem and is a
consequence of poor tuberculosis (TB) control programs (WHO, 2004; Department of Health, 2014; Hughes, 2014).

### 2.5 Mono-drug resistance and multi-drug resistance therapy

Multi-drug resistant therapy is a more costly regimen and requires patients to be kept on medication for a longer duration (over 6 months).

Prolonged duration of treatment is reported as a contributor to patient defaulting in treatment, leading to poor treatment outcomes. Mono-drug resistant therapy is less expensive as compared to multi-drug resistance therapy (Hughes, 2014). In South Africa, with the introduction of GeneXpert test, the algorithm has made it easier to diagnose Rifampicin resistance, but Isoniazid resistance is usually missed until later when TB culture is done due to positive smear after two months of intensive phase. Sputum culture results takes up to six (6) weeks to be ready, which further prolongs the time the patient is kept on ineffective regimen (Department of Health, 2014).

### 2.6 Prevalence of INH mono-resistant TB

Isoniazid is a potent anti-tuberculosis drug which forms one of the main components of the recommended first line tuberculosis (TB) treatment regimen. Treatment of patients infected with INH-mono resistant TB strains using standardised therapy has been associated with increased risk of treatment failure and further acquired resistance such as MDR-TB (WHO, 2011). Isoniazid is an important first line anti-TB agent given its potent early bacterial activity and extensive evidence base as a first line therapy for drug susceptible TB, (Romanowski et al, 2017). Isoniazid (INH) is one of the most key first line TB treatment drugs largely because of its potent bacterial activity (WHO, 2008; Varahram el et, 2014; Wang et al, 2014; Chien et al, 2014). It is noted that INH mono-resistance risk factors and treatment outcomes have not been well described (Cattamanchi et al, 2009).

The prevalence of INH mono-resistant TB varies widely across most parts of the world. INH is the most common form of mono-resistance, its world prevalence is estimated to range from 4% to 12 % globally and there is no consensus on how these patients
should be treated (Beaz-Saldana et al, 2016; WHO, 2016; Villegas et al, 2016). Seven percent (7%) of TB patients reported in USA TB surveillance in 2005 were INH mono-resistant (Hoopes et al, 2008). WHO (2008), reported that INH mono resistant TB is the most common form of resistance with the prevalence of 10% amongst new cases and 28% on the retreated cases reported in 2009 globally. Some years later, a Taiwanese study has reported that resistance to INH is said to be 13% globally making it the most common form of TB resistance, this makes the effects of INH resistance to be of high interest (Chien et al, 2014).

In South Africa, the prevalence of INH mono-resistance is reportedly standing at 9.3% (INH mono-resistance is 6.1%) higher than rifampicin resistance which is at 4.6% (rifampicin mono-resistance is at 1.7%) (SANAC, 2014). Concerns have been raised in the country about the increased number on INH mono-resistant cases and the current South African algorithm for management of TB may lead to missed early detection of INH resistant tuberculosis in South Africa (Ismail et al, 2016).

2.7 Factors associated with INH Mono-resistant patient poor outcomes

It has been reported in literature, that several factors may contribute to the onset of INH resistance. These include the use of illicit substances and drugs, coming from low socio-economic backgrounds, as well as being HIV-positive (WHO, 2014).

Furthermore, in terms of demographic characteristics, INH mono-resistance tuberculosis was found to be high among men, the middle aged, those with low income levels, and those with previous history of TB (Renata et al 2016; Chien et al, 2014). Different reasons are given for this global phenomenon ranges from biological factors, health seeking behaviour, access of health facilities by different gender, under reporting of TB in women (Nhamoyebonde et al, 2014; Rhines, 2012).

Moreover, alcoholism has been noted as one of the predictors of Isoniazid (INH) mono-drug resistant tuberculosis (TB) (Villegas et al 2016). Substance abuse has been also found to be associated with Isoniazid (INH) mono-resistant TB. Studies shows that patients with a history of substance abuse were more likely to have INH mono-resistant TB compared to those with no such history (Baez-Saldana et al 2016; Fox et al, 2011; Villegas et al, 2016).
The HIV positive status in TB patents has been highlighted as one of the predictors of Isoniazid (INH) mono-resistant tuberculosis. Patients who were HIV positive had a higher percentage of INH mono-resistant TB as compared to HIV negative patients (Villegas et al, 2016). Isoniazid mono-resistant TB patient’s outcomes were worse amongst patient with unknown HIV status, which indicates that this group may require additional attention to obtain more data on the reasons (Deepa et al 2013). However studies conducted in USA and South Africa reported no negative associations between INH mono-drug TB resistance and being HIV positive (Hopes et al 2008; Jacobson et al, 2011).

2.8 Treatment regimens for INH mono-resistant TB

Management of INH mono-resistant TB patients has been widely debated. The current 9 months regimen was based in trials done in low TB rates and low TB resistance areas (Gegia et al, 2012). The regimen is made of daily doses of rifampicin, pyrazinamide, and ethambutol (Bang et al, 2010).

It should be noted that, although MDR and rifampicin resistant are well described in TB treatment guidelines, there is no specific guidelines for management of INH mono-resistant TB patients. There has been a concern that the standard 8 months treatment regimen currently being used in India may be inadequate to treat patients with INHMr TB (Deepa et al, 2013). It is understandable that some authors have declared that the optimal regimen for INH mono-resistant TB is still unknown (Chien et al, 2014). In South Africa, it is the first regimen consisting of RHZE for six (6) months to nine (9) months that is used for INH mono-resistant TB (National Department of Health, 2014).

There is strong association between INH mono resistance and poor treatment outcomes. Literature reviewed showed that patient with INH mono-resistance TB were more likely to default treatment, being lost to follow up, or even later develop multi-drug resistant TB (Chien et al, 2014; Leonela et al, 2016; Karen et al, 2011). This includes high treatment failure and death rates. The only way of mitigating for this will be early diagnosis and ensuring that patients are managed on the correct and adequate treatment regimen.
2.9 Conclusion

The prevalence of INH mono drug-resistant TB is evidently high across the world confirming the fact that this form of resistance is most common. What seems to be clear in most studies, is that INH mono drug-resistant TB is linked to unfavorable treatment outcomes.

In South Africa, there are no reported similar studies that cover the whole district as this study did. Hence, the exact extent of INH mono-resistant TB is widely unknown. The findings of this study will be of utmost importance in getting information that can be used to design relevant interventions.
CHAPTER 3
RESEARCH METHODOLOGY

3.1 Introduction

Research methods refer to the manner of a procedure, techniques, and processes used in implementing research design (Babbie, 2001). This chapter presents the methods used in conducting the study. It describes the study design, study setting, study population, inclusion and exclusion criteria, sample size, as well as the sampling procedure, data collection and analysis, measures taken to ensure validity and reliability and ethical considerations.

3.2 Study design

This was a descriptive, cross-sectional study on isoniazid (INH) mono-resistant TB patients in Tshwane in year 2009. A retrospective records review was done on TB patient’s records. The records review involved the collection of data from electronic registers that included socio-demographic and other characteristics of patients that were on tuberculosis treatment in year 2009 within the Tshwane District.

3.3 Study setting and population

This study was conducted using data from Tshwane district facilities, Gauteng in South Africa. Study population included all TB patients within the district during the study period, first January 2009 – 31 December 2009. TB Records of patients with culture confirmed INH mono drug-resistant TB from 1 January 2009 to 31 December 2009 were identified. The sourced list of patients comprised all patients diagnosed with isoniazid mono-resistant TB and susceptible TB in Tshwane district.

3.4 Inclusion Criteria

All records of TB patients who have been treated for TB in Tshwane District from 1 January 2009 to 31 December 2009 were recruited into the study.
3.5 Exclusion criteria

The following exclusion criteria was applied:

- Patients diagnosed outside or resident in other areas outside Tshwane district.
- Patients will be excluded if they had been on treatment for less than 2 months.

3.6 Sampling and sampling technique

As mixed design, for Phase 1, a census of all patients will be performed as data will be simply extracted from the databases. For the second phase, the number of cases determined the final sample size. In the first phase a census was used in order to calculate the prevalence of INH mono-drug resistance. The whole National Health Laboratory Service (NHLS) Corporate data warehouse (CDW) database for 2009 was used. The Electronic TB resistant TB register (ETR.net) treatment register was used for triangulation purposes and any other relevant data not found on the CDW database.

In the second phase, stratified random sampling was used to obtain samples from both sensitive and resistant groups of patients. A computer generated random numbers comprising cases and controls was used to sample the records. The sample size was calculated using Epi-info 3.0 (CDC, 2017) based on a worst expected frequency of 3.9%, 5% precision and a confidence interval of 95%. The sample size of 149 patients was obtained from resistant group. A matched case-control study was conducted based on the information from the CDW. Cases were patients with culture confirmed INH mono-resistance TB who were matched by sex, name, date of birth and diagnosis date with controls, patients with normal susceptible TB; on a ratio of 1:1.2. Thus, a matched control group of 200 patients was randomly selected from the sensitive group. The control group was taken for the purpose of comparing the final treatment outcomes. This gave a total sample size of 349.
3.7 Data collection

A standard checklist was used for data collection. The checklist had this information: Patient identity, hospital or clinic number, centre where these patients were treated, whether these patients were ever previously diagnosed with TB before this current episode, treatment regimens, treatment doses, duration of treatment, date of birth and documented adverse effect (mild or serious).

3.8 Data analysis

Data extracted were consolidated in Microsoft Excel (Ms, 2010) where it was captured, cleaned and made ready for data analysis with STATA 10 (College Station, USA). Since the data had a normal distribution, parametric tests were used. For comparison, data was converted into categorical variables and bi-variant analysis was done by running a two by two table of association. Logistic regression model were used to determine factors associated with INH mono-resistance TB and predictors of successful treatment outcome. The Odds ratio (OR) and 95% confidence interval were calculated to determine the statistical significance. A p-value ≤ 0.05 was considered statistically significant (Gordis, 2009).

3.9 Validity and reliability

To ensure reliability of data collected, the tool, in form of data extraction form, was adapted from previously validated ones in previous publications on similar research on Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with mono-resistance to Isoniazid (Menzies et al, 2009). Records with more than five missing data were excluded from the data to further improve validity.

3.10 Bias

Selection and missing data biases were issues which could arise in this study. Patients to be included in the study needed to appear in two databases for matching purposes (NHLS or ETR.net), if not appearing on both databases a patient was not included for the study. This was minimized by double checking every selected name in the match
database to an extent of asking for the name to be rechecked in the big database by either NHLS or ETR.net. Selection bias was addressed by using simple random sampling technique for eligible patient’s records (Degu, 2006).

3.11 Ethical issues

Study ethical clearance was obtained from School Research Ethics Committee (SREC) and Sefako Makgatho Health Science University Research Ethics Committee (SMUREC) and the Project reference number (SMUREC/H/216/2016: PG) (see Appendix 1). To gain entrance to the study setting and to the study population, permission from the Tshwane District authorities was sought and obtained prior to the commencement of the study.

This was a record review with no direct contact with the patients, so individual consent form were not required but managerial permission were obtained from the university and City of Tshwane research authorities.

Records were kept confidential to avoid any risk of being seen by unauthorised individuals this was done by ensuring that information was stored in the computer that is password protected with limited access. Patient’s identities were protected and all participants were assigned a unique study identity (ID) number through use of a “linking file,” or study register, and were identified through these study ID numbers.

3.12 Conclusions

This chapter has given a summary on the research design, study setting and site, sampling target, data collection methods, and analysis plan. Ethical considerations relating to data collection are also described in detail. The next chapter will be on presentation and interpretation of the results.
CHAPTER 4
PRESENTATION OF RESULTS

4.1 Introduction

This chapter presents the findings of the study in descriptive and inferential forms. The results are presented beginning with the participants’ characteristics. Data reported include patient characteristics, prevalence of INH mono-resistant TB, treatment regimens used, and impact of INH mono-resistance on treatment outcomes.

4.2 Patients’ demographics and treatment profile

A total of 349 study patients’ records were selected for the study, in which 55% of them were for the males and the mean age was 36.6 years (age ranged between 1-80 years). Although most of the patients were newly diagnosed with tuberculosis (n=331, 94.8%), few of them had a known HIV status (n=132, 37.8%). Most of the study participants had unknown HIV status (n=217, 62.2%). For those with known HIV status (n=132), sixteen percent (16.9%) were HIV negative and 38.6% had INH mono-resistant TB. A total 24.9% of patients sampled were under directly observed treatment (DOT) system. Seventy-three percent (72.8%) of all patients sampled had positive final outcomes which is either cured or completed treatment. Amongst patients with positive final outcomes, 58.6% had sensitive TB and 93% were on regimen 1 treatment (Table 4.1).
Table 4.1: Sociodemographic characteristics of study patients (N=349)

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<th>INH TB Mono-resistant- Cases</th>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75 (21.5%)</td>
<td>80 (22.9%)</td>
</tr>
<tr>
<td>Male</td>
<td>86 (24.6%)</td>
<td>108 (30.9%)</td>
</tr>
<tr>
<td><strong>Age in years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19</td>
<td>6 (1.7%)</td>
<td>11 (3.2%)</td>
</tr>
<tr>
<td>20-29</td>
<td>40 (11.5%)</td>
<td>46 (13.2%)</td>
</tr>
<tr>
<td>30 and above</td>
<td>110 (31.5%)</td>
<td>136 (38.9%)</td>
</tr>
<tr>
<td><strong>Treatment outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured</td>
<td>55 (15.7%)</td>
<td>94 (26.9%)</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>50 (14.3%)</td>
<td>55 (15.7%)</td>
</tr>
<tr>
<td>Transfer</td>
<td>14 (4.0%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>Failed</td>
<td>18 (5.2%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Died</td>
<td>13 (3.7%)</td>
<td>15 (4.4%)</td>
</tr>
<tr>
<td>Defaulted</td>
<td>11 (3.1%)</td>
<td>15 (4.4%)</td>
</tr>
<tr>
<td><strong>DOT Support</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (8.3%)</td>
<td>58 (16.6%)</td>
</tr>
<tr>
<td>No</td>
<td>97 (27.8%)</td>
<td>107 (30.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>35 (10.0%)</td>
<td>23 (6.6%)</td>
</tr>
<tr>
<td><strong>HIV-status</strong></td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
<td>45 (12.9%)</td>
<td>66 (18.9%)</td>
</tr>
<tr>
<td>Negative</td>
<td>6 (1.7%)</td>
<td>15 (4.3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>110 (31.5%)</td>
<td>107 (30.7%)</td>
</tr>
<tr>
<td><strong>TB treatment Regimens</strong></td>
<td></td>
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</tr>
<tr>
<td>Regimen 1</td>
<td>144 (41.3%)</td>
<td>178 (51.0%)</td>
</tr>
<tr>
<td>Regimen 3A</td>
<td>13 (3.7%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>Regimen 3B</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>Test Specimen Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sputum</td>
<td>122 (34.9%)</td>
<td>170 (48.7%)</td>
</tr>
<tr>
<td>Aspirate</td>
<td>4 (1.1%)</td>
<td>10 (2.9%)</td>
</tr>
<tr>
<td>Patient category</td>
<td>Bloods</td>
<td>Fluid</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>New</td>
<td>4 (1.1%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>2 (0.6%)</td>
<td>3 (0.9%)</td>
</tr>
<tr>
<td>Retreatment</td>
<td>0 (0%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Moved In</td>
<td>29 (8.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Transferred out</td>
<td>3 (0.9%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ARV treatment</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>6 (1.7%)</td>
<td>0 (0%)</td>
<td>155 (44.4%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>2 (0.6%)</td>
<td>2 (0.6%)</td>
<td>183 (52.3%)</td>
</tr>
<tr>
<td>Retreatment</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>148 (42.4%)</td>
</tr>
<tr>
<td>Moved In</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>183 (52.3%)</td>
</tr>
<tr>
<td>Transferred out</td>
<td>2 (0.6%)</td>
<td>2 (0.6%)</td>
<td>148 (42.4%)</td>
</tr>
</tbody>
</table>

### 4.3 Prevalence of INH TB mono-resistance

One of the objectives of this study was to determine the prevalence of IMR IN Tswane District. Based on the data obtained using a data extraction sheet, Tshwane district had 5347 patients, diagnosed with tuberculosis in year 2009. Out of these, 631 (11.8%) patients were on INH mono-resistant therapy. The INH mono-resistant patients comprised 55.5% males and 44.4% females.
Figure 4.1: Prevalence of INHMr TB

4.4 Gender versus INH mono-resistance (N=161)

Of the 349 patients sampled 24.6% (n=86) of males were INH mono-resistant, 21% (n=75) of females had INH mono-resistant TB. Based on the frequencies, the results showed that males are more likely to have INH mono-resistant tuberculosis (TB) compared to females, but this is not statistically significant (OR=1.18, 95%CI =0.78-1.80, p=0.45). Refer to Figure 4.2 below:

Figure 4.2: INH Mono-resistance versus gender
4.5 Types of TB regimens used

In this study, all patients selected were managed with different treatment regimens. These patients were put on one of the three treatment regimens (1, 3A and 3B). Majority of them were on regimen 1 (n=322, 92.2%) (Isoniazid, rifampicin, pyrazinamide, and ethambutol). Regimen 1 is used for new and previously treated adults and children more than 8 years old (weighing more than 30 kilograms).

A total of 21 (6.0%) of patients were on regimen 3A made of rifampicin, pyrazinamide, and ethambutol which is used for children less than 8 years old weighing less than 30 kilograms with uncomplicated TB. The least used regimen was 3B (n=3, 0.7%) which is made of Isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Details of the treatment schedule are shown in Figure 4.4 below.

![Figure 4.3: Treatment regimens used to manage INH mono-resistance (N= 349).](image)

4.6 Treatment outcomes

Successful treatment outcome was noted in 254 (73%) of patients who were either cured or completed treatment. A few number of patients (n=4, 1.2%) were transferred out to other facilities adjacent to where they resided, to promote compliance. The study also showed that 5.5% of patients failed treatment (mostly died) while 7.4% of the
patients defaulted (most lost to follow-up). Death was the outcome determined in about 8% of the patients. Figure 4.4 below gives more details.

![Figure 4.4: Treatment outcomes of isoniazid (INH) mono-resistance tuberculosis (TB) patients (N=349)](image)

4.7 Factors associated with INH mono-resistant TB

A logistic regression analysis was carried out to determine if independent variables such as patient’s district, age, gender, DOT support, HIV, factors were associated with INH mono-resistant tuberculosis.

The factor associated significantly with INH mono-resistance TB was being a patient from District 1, which is an urban district in Tshwane as shown in Table 4.2 below.

No difference noticed in risk of INH mono-resistant (INHMr) TB between various age groups. Although not significant, it should be noted that INH mono-resistant (INHMr)TB was increasing with age with people less than 20 years old having less than those over 30 years. Similarly, INHMr TB was also higher in males (55%) than females, although this was not statistically significant. Only one hundred and thirty-two (n=132, 37.8%) of patients had recorded HIV status and out of these 65.9% of them were HIV positive. Although not statistically significant results show that being HIV positive

20
increases the risk of developing TB resistance as compared to the HIV negative patients (OR=0.8, 95%CI=0.28-2.1 and p=0.6).

Out of the 349 selected patients a total of eighty-six (N=86, 24.6%) patients were on DOT system and majority of these were from the INH sensitive TB group (N=58, 17%). In a bivariate analysis being under DOT support reduces the risk to developing resistant TB compared to those not on DOT support (OR=0.50, 95%CI=0.30-0.83, p=0.01). About sixteen percent (N=58; 16%) of total patients were not recorded whether were on DOT support or not, with nine percent (N=35, 9%) of these being INHMr TB patients.

Table 4.2: Factors associated with INH mono-resistant TB

<table>
<thead>
<tr>
<th></th>
<th>TB mono-resistant</th>
<th>Non-Resistant</th>
<th>OR</th>
<th>95%CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>09 (2.57%)</td>
<td>6 (1.72%)</td>
<td>Ref.</td>
<td>-</td>
<td>-</td>
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<tr>
<td>20-29 years</td>
<td>44 (12.61%)</td>
<td>47 (13.45%)</td>
<td>0.47</td>
<td>0.16-1.40</td>
<td>0.18</td>
</tr>
<tr>
<td>30+ years</td>
<td>108 (30.95%)</td>
<td>135 (38.68%)</td>
<td>0.44</td>
<td>0.16-1.23</td>
<td>0.12</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>75 (21.49%)</td>
<td>80 (22.92%)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Males</td>
<td>86 (24.64%)</td>
<td>108 (30.95%)</td>
<td>1.2</td>
<td>0.77-1.79</td>
<td>0.45</td>
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<tr>
<td>Patient’s district</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>District 1</td>
<td>85 (24%)</td>
<td>44 (13%)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>District 2</td>
<td>19 (5.4%)</td>
<td>18 (5.2%)</td>
<td>0.55</td>
<td>0.26-1.14</td>
<td>0.11</td>
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<tr>
<td>District 3</td>
<td>29 (8.3%)</td>
<td>43 (12.3%)</td>
<td>0.35</td>
<td>0.19-0.63</td>
<td>0.00</td>
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<tr>
<td>District 4</td>
<td>8 (2.3%)</td>
<td>14 (4.0)</td>
<td>0.29</td>
<td>0.11-0.76</td>
<td>0.01</td>
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<tr>
<td>District 5</td>
<td>1 (0.3)</td>
<td>5 (1.4)</td>
<td>0.10</td>
<td>0.01-0.91</td>
<td>0.04</td>
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<td>District 6</td>
<td>14 (4.0)</td>
<td>53 (15.2)</td>
<td>0.13</td>
<td>0.07-0.27</td>
<td>0.00</td>
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<td>District 7</td>
<td>3 (0.9)</td>
<td>4 (1.1)</td>
<td>0.39</td>
<td>0.08-1.81</td>
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<td>District 8</td>
<td>2 (0.6)</td>
<td>7 (5.0)</td>
<td>0.15</td>
<td>0.03-0.74</td>
<td>0.02</td>
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<td>HIV status</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Negative</td>
<td>6 (4.54%)</td>
<td>15 (11.36%)</td>
<td>Ref</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>66 (50%)</td>
<td>0.8</td>
<td>0.29-2.10</td>
<td>0.61</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>----------</td>
<td>------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td><strong>DOT Support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>45 (34.09%)</td>
<td>66 (50%)</td>
<td>0.8</td>
<td>0.29-2.10</td>
<td>0.61</td>
</tr>
<tr>
<td>Yes</td>
<td>29 (8.3%)</td>
<td>58 (16.6%)</td>
<td>0.50</td>
<td>0.30-0.84</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### 4.8 Conclusion

This chapter has discussed the research results including demographic characteristics of the research participants, prevalence and associated factors of INH mono drug-resistant TB. The chapter further discussed the association between demographic and associated factors as well as multivariate logistic regression of other important variables.
CHAPTER 5
DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Introduction

This chapter discusses the findings in line with the current literature related to the study. This study investigated Isoniazid (INH) mono-resistant TB in Tshwane district, in South Africa. The study focused on determining the prevalence and investigating the associated factors of Isoniazid (INH) mono-resistant TB in Tshwane district. In this chapter, the findings, conclusions as well as recommendations are discussed.

5.2 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Majority (55%) of the study records were for were males patients of the middle age. This is reflective of the male’s health seeking behavior in the country whereby males tend to seek health late and are more likely not to comply or/ finish full course of treatment reported in other studies (Thompson et al, 2016). Some studies that even rare diseases that equally affects males and females, confounding factors such as access to care, which may lead to bias in reporting and there is a need to establish whether biological nature plays a role (Nhamoyebonde et al, 2014; Rhines, 2013).

Majority of these patients were newly diagnosed (94%) and some patients had resistant form of tuberculosis although this was their first episode. This finding is reflective of the fact that some patients do inherit a resistant strain of tuberculosis as some of the people who are TB infected, are within communities without treatment putting most people at risk of contracting TB resistant strains (SA TB guidelines, 2014). In the cases sampled (349) only 38% had a known HIV status (comprising 32% HIV negative versus 6% who were positive). This may be suggestive of the fact that some patients may not have been having HIV test done which is an optional requirement or/ this may accredited a gap in recording or capturing of this information.
5.3 PREVALENCE OF INH MONO-RESISTANT TB PATIENTS

The prevalence of 11.8% is in line with other global studies (Beaz-Saldana et al, 2016; WHO 2016; Villegas et al, 2016).

The findings in this study show that the prevalence of isoniazid mono-resistant tuberculosis is 11.8%. These findings are similar to those reported by other researchers across the world and in South Africa. The range is usually between 4%-12% globally (Beaz-Saldana et al, 2016; WHO 2016; Villegas et al, 2016). INH monoresistance tuberculosis was reported to be seven percent (7%) in USA TB surveillance in 2005 (Hoopes et al, 2008), and was at 13% in Taiwanian (Chien et al, 2014) which is higher than observed in South Africa National Institute for Communicable Diseases (NICD) of 9.3% in their National Wide Survey, 2012-2014 (Ismail et al, 2016). The prevalence of isoniazid mono-resistant tuberculosis as reported in most studies, is constantly around and just above 10% rate, which indicates the extent of this form of tuberculosis resistance across the world.

The reported prevalence of isoniazid mono-resistant tuberculosis (INHMr TB) of thirteen percent (13%) globally is making it the most common form of TB resistance, this makes the effects of INH resistance to be of high interest for further exploration to get more information (Chien et al, 2014). In addition, INH mono resistant TB has been reported as the most common form of resistance worldwide in 2009 with the prevalence of 28% on the retreated cases (WHO, 2016).

5.4 TYPES OF TREATMENT REGIMENS USED

Patients that are susceptible to Rifampicin and Isoniazid are managed with regimen 1 (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide). Most patients in this study were treated with regimen 1 (93%) and less of the other 2 regimens. Regimen 1 seems to be the preferred regimen as most patients were sensitive to it in this study setting. South African recommended regimen for INH mono-resistant TB is first line drugs for RHZE for six (6) months to nine (9) months (National Tuberculosis Management Guidelines, 2014). Anti-TB drugs used to treat patients generally depends on the type of TB that the patient presents with in the facility or to the treating clinician. However, the recommended 9 months global regimen is based on clinical trials (Bang et al 2010;

Recommended guidelines may not work well if they are not designed to meet the needs of the local patients. It has been reported in India, for example, that the 8 months treatment regimen was not adequate for treatment and they didn’t have local guidelines for management of the anti-TB resistant patients (Deepa et al, 2013). Thus, the optimal regimen for INH mono-resistant TB is still unknown (Chien et al, 2014).

What became clear with the literature review is that there is no general standardized worldly accepted guidelines for management of INH mono-resistant patients, which is the matter of concern.

5.5 FACTORS ASSOCIATED TO INH MONO-RESISTANT TB

In this study, a number of factors were examined statistically to determine if they played any significant role in contributing to INH mono-resistance. None of the sociodemographic (age categories, gender and the HIV status) seemed to play any role. This is contrary to other studies findings where INH mono-resistance tuberculosis was found to be high among men, the middle aged, those with low income levels, and those with previous history of TB (Renata et al 2016; Chien et al, 2014). Furthermore, use of illicit substances and drugs, coming from low socio-economic backgrounds, as well as being HIV-positive (WHO, 2014), have been reported to play a significant role. This discrepancy could have arisen due to unconfirmed issues that may need further investigation.

Lack of association of HIV status to mono-drug resistance in this current study could be attributable to low numbers of those that had known HIV status. The HIV positive status in TB patents has been highlighted as one of the predictors of Isoniazid (INH) mono-resistant tuberculosis. For example, having unknown HIV status has been associated with INH mono-resistant tuberculosis in a study conducted in India (Deepa et al 2013).

In this current study, it was found that being under DOT support significantly reduced the risk to developing resistant TB compared to those not participating in the program.
Directly observed treatment (DOT) is the system recommended by WHO for effective tuberculosis management. In this current study, in the selected sample, only 25% of patients sampled were under directly observed treatment (DOT) system. Studies do support the fact that effective DOT support system tend to yield positive TB treatment outcomes, as it has been shown to be effective strategy to improve outcomes of tuberculosis infected patients (Nachega et al, 2003; Thiam et al 2007).

Drug resistance patterns in this study also differed per sub-district with some areas having higher percentage of cases than others. This suggests that we may need targeted TB management for selected areas as the pattern and burden may not be the same for different districts and sub-districts. The difference in TB spread or prevalence per district shown in this study is in line with other studies that report that areas that are populous have high prevalence of TB, (Nachega et al, 2003). In this study we were only able to confirm HIV status in very few patients, out of those confirmed the resistance patterns differed based on HIV status. The fact that we were able to confirm HIV status in few number of patients is of concern as it may indicate poor compliance with the TB management guidelines. These guidelines advocates for all tuberculosis positive patients to be offered HIV testing on a voluntary basis or this missing information may be attributed to poor recording of data. It may be either some patients are refusing or/ service is not offered or poor recording of the results by the health professionals.

5.5 STUDY LIMITATIONS

This study being a retrospective study review, missed to investigate other factors that have been shown to worsen the resistance. For example, alcoholism and substance abuse have been noted as some of the predictors of Isoniazid (INH) mono-drug resistant tuberculosis (TB) (Villegas et al 2016; Baez-Saldana et al 2016; Fox et al, 2011; Villegas et al, 2016). These factors were missing in the records studied in this research. Some information that is important when conducting TB study such as weight, educational status, and other medical history is not part of routine data captured in the data bases such as ETR.net and NHLS corporate data warehouse (CDW).
5.6 CONCLUSIONS

The findings of this study show that the prevalence of INHMr TB is relatively high among patients studied. This prevalence was more common in District 1 than the other health districts. This study has also confirmed previous findings that INHMr affects overall TB treatment outcomes. Participating in DOT program greatly enhances positive treatment outcome and is highly recommended in managing INHMr patients.

5.7 RECOMMENDATIONS

Because District 1 had more INHMr TB than the other districts, reasons for this should be investigated later. Moreover, due to poor treatment success and high treatment failure in INHMr TB patients, other regimens including new drugs such as Bedaquiline should be envisaged. Furthermore, although adherence to treatment was not and could not be assessed in this study, further studies should explore the factors associated to low DOT support and the level of adherence to treatment.
REFERENCES


of Smear Positive Re-Treatment Tuberculosis Patients in the State of Andhra Pradesh, India. PLoS ONE 8(10); e76189.doi:10.1371/journal.pone.0076189


Menzies D at al., 2009. Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with mono-resistance to Isoniazid: A Systematic Review and Meta-analysis. Plos Medicine, 6, Issue 9


National Health Laboratory Service (NHLS) and Corporate data warehouse (CDW) database for 2009 was used. And The Electronic Drug resistant TB register (EDR.net)


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APPENDICES

APPENDIX 1: Medunsa Research and Ethics Committee (MREC)

Clearance Certificate

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Molotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@emu.ac.za
P.O. Box 163 Medunsa 0204

APPROVAL NOTICE - NEW APPLICATION

01 September 2016

L. Sonwabo
Department of Public Health
P.O. Box 215
Medunsa, 0204

MEETING: 07/2016

SMUREC Ethics Reference Number: SMURECH2162/2016: PG

The New Application received on 15 August 2016, was reviewed by members of Sefako Makgatho University Research Ethics Committee 01 September 2016 and was approved on 01 September 2016.

Title: An investigation of isoniazid mono-resistant tuberculosis in Tshwane District, Gauteng, in 2009

Researcher: L. Sonwabo
Supervisor: Prof NG Mabugu
Department: Public Health
School: Health Care Sciences
Degree: MPH

Please note the following information about your approved research protocol:

Protocol Approval Period: 01 September 2016 – 01 September 2017

Please remember to use your protocol number (SMURECH2162/2016: PG) on any documents or correspondence with the REC concerning your research protocol.

Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation (ICRG20008461), Institutional Review Board (IRB2000070088) Expiry date: 05 December 2016, Federal Wildlife Assurance (FWA2000030843) Expiry date: 31 August 2017 and NHREC No: REC 210448-003

Sincerely,

[Signature]
DR C BAKER
DEPUTY CHAIRPERSON SMUREC

[Seal]
SEFAKO MAKGATHO
HEALTH SCIENCES UNIVERSITY
SMU Research Ethics Committee
Chairperson

Date: 01072016
31 October 2016

Applicant: Mr Sonwabo Lindani
Institution: Gauteng Department of Health
Department: Quality Assurance
Email: sonwabo.lindani2@gauteng.gov.za / lindanisonwabo@yahoo.com
Tel: 011 555 0412
Cell: 062 673 5999

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "An Investigation of Isoniazid Mono-Resistance Tuberculosis in Tehwane District, Gauteng in 2009" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you to conduct the proposed study as outlined in the submitted application.

Please note that the approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met:

- Ethics approval is obtained from a recognised SA Health Research Ethics Committee.
- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Department) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
Good day Lindani

Your protocol was approved by the research committee. Kindly, fill the attach form and revert back to the office.

Best regards,

Dr Razwiedani
**ANNEXURE A: Data Collection Form for CDW Database Extraction**

**Data Collection Form for Database Extraction 2016**

Sefako Makgatho University A Research TB Project

**LEARNER NAME:** Sonwabo Lindani

**An Investigation of Isoniazid Mono-Resistance Tuberculosis in Tshwane District, Gauteng, in 2009**

<table>
<thead>
<tr>
<th>data collection/extraction date:</th>
<th>(dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>collection conducted by (name):</td>
<td>Signature:</td>
</tr>
<tr>
<td>Database Records</td>
<td>Yes</td>
</tr>
<tr>
<td>ETR/EDR records</td>
<td>Yes</td>
</tr>
<tr>
<td>Database record review was done:</td>
<td>Hospital / Clinic number:</td>
</tr>
<tr>
<td>Name of facility where specimen was collected:</td>
<td>Lab TB Specimen number:</td>
</tr>
<tr>
<td>Date of TB Specimen collection:</td>
<td>(dd/mm/yyyy)</td>
</tr>
<tr>
<td>Gender:</td>
<td>Male</td>
</tr>
<tr>
<td>Race:</td>
<td>Asian</td>
</tr>
<tr>
<td>Date of Birth:</td>
<td>(dd/mm/yyyy)</td>
</tr>
<tr>
<td>Identity No:</td>
<td>Identity No Unk</td>
</tr>
<tr>
<td>Address:</td>
<td>Town / City:</td>
</tr>
<tr>
<td>Telephone No [List]:</td>
<td></td>
</tr>
<tr>
<td>Treatment initiated at time of review:</td>
<td>Yes</td>
</tr>
<tr>
<td>What is a status of tx:</td>
<td>Died</td>
</tr>
<tr>
<td>Where was treatment collected:</td>
<td>Name of facility:</td>
</tr>
</tbody>
</table>

**INFORMATION REGARDING HIV STATUS:**

<table>
<thead>
<tr>
<th>HIV status during review (documented):</th>
<th>Positive</th>
<th>Negative</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notes:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Data Collection Form for Records Review 2016

Sefako Makgatho University A Research TB Project

**LEARNER NAME:** Sonwabo Lindani

### An Investigation of Isoniazid Mono-Resistance Tuberculosis in Tshwane District, Gauteng, in 2009

<table>
<thead>
<tr>
<th>Data collection date:</th>
<th>(dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>collection conducted by (name):</td>
<td>Signature:</td>
</tr>
</tbody>
</table>

- Medical Records: [ ] Yes [ ] No

Medical record review was done: [ ] Yes [ ] No

- Hospital / Clinic number:

Name of facility where specimen was collected:

<table>
<thead>
<tr>
<th>Date of TB Specimen collection:</th>
<th>(dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab TB Specimen number:</td>
<td>(dd/mm/yyyy)</td>
</tr>
</tbody>
</table>

- Gender: [ ] Male [ ] Female [ ] Unk

- Race: [ ] Asian [ ] Black [ ] Coloured [ ] White [ ] Unk

Date of Birth: [ ] (dd/mm/yyyy) DOB Unk [ ] Age: [ ] Days [ ] Months [ ] Years [ ] Age Unk [ ]

- Identity No: [ ] (dd/mm/yyyy)
- Identity No Unk [ ]

Address:

- Town / City: [ ] Province: [ ]

Telephone No (List):

- Treatment completed at time of review: [ ] Yes [ ] No
- If Yes, date completed: [ ] (dd/mm/yyyy)

If No, what is a status of tx:

- Treatment on-going [ ] completed
- Died [ ]
- Lost to follow up [ ]
- Unknown [ ]

Where was treatment collected:

- Name of facility:

TB treatment regimen given:

- If Yes, name facility:
  - Clinic [ ]
  - Hospital [ ]
  - MDR Unit [ ]
  - Unknown [ ]

---

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### RISK FACTORS FOR TB:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was patient ever been previously diagnosed with TB before this episode?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes, how many times? _______</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was patient diagnosed with TB after this episode?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If Yes, how many treatment episodes?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did the last treatment last for &gt; 1 month?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**: dd/mm/yyyy**

Notes:

### INFORMATION REGARDING HIV STATUS:

<table>
<thead>
<tr>
<th>HIV status during review (documented):</th>
<th>Positive</th>
<th>Negative</th>
<th>Unknown</th>
</tr>
</thead>
</table>

If Yes, what was the date of initiation of HAART? **dd/mm/yyyy**