FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

by

HENOCK BEKELE KETO

Submitted in accordance with the requirements For the degree of

DOCTOR OF LITERATURE AND PHILOSOPHY

In the subject

Health Studies

At the

UNIVERSITY OF SOUTH AFRICA

SUPERVISOR: PROFESSOR PETER THOMAS SANDY

January 2020
DECLARATION
I declare that this study entitled “FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA” is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

Name and Signature

Date

January 2020
ACKNOWLEDGEMENTS

I would like to acknowledge and thank:

- My advisor, Professor Peter Thomas Sandy, for his unreserved support and guidance throughout the study years.

- University of South Africa for providing a learning opportunity to Ethiopians in need.

- The study respondents whose willingness to participate in the study and to give information to the best of their knowledge made this study a reality.

- The Administrators of the hospitals where the study was conducted for giving me permission to collect data from patients under treatment and follow-up.

- Dr Rosamund Southgate, from Doctors Without Borders-London Office, for reading the thesis and giving valuable comments.

- My wife, Sosina Tegenu, and my sons, Abenezer, Fanuel, Sofonias and Samuel, for their encouragement and for giving me their precious family time.
FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

STUDENT NUMBER: 57661049
STUDENT: HENOCK BEKELE KETO
DEGREE: DOCTOR OF LITERATURE AND PHILOSOPHY
DEPARTMENT: HEALTH STUDIES, UNIVERSITY OF SOUTH AFRICA
SUPERVISOR: PROFESSOR PETER THOMAS SANDY
ABSTRACT

PURPOSE: The purpose of this study was to assess factors associated with the development of drug resistant tuberculosis in Ethiopia.

DESIGN: A quantitative case-control study was conducted to determine if there were any significant differences in prevalence of pre-defined factors between cases and controls.

METHODS: Cases were patients with drug resistant tuberculosis who had a confirmed diagnosis by culture drug-susceptibility or gene expert tests. Successfully treated, tuberculosis symptom free patients who had been on first-line tuberculosis treatment and who were registered as cured or treatment completed were taken as controls. An equal number of cases (N=181) and controls (N=181) was selected using a systematic random sampling method and was used in the study. A structured questionnaire developed by the researcher was used to collect data. Odds ratio and multiple logistic regression were used to quantify the strength of association between dependent and independent variables.

RESULTS: The development of drug resistant tuberculosis was significantly associated with two or more previous episodes of tuberculosis illness (adjusted odds ratio (AOR): 14.84; 95% CI 8.90 – 24.75), previous first-line tuberculosis treatment not directly observed by a health worker for 7 to 8 weeks (AOR: 13.41; 95% CI 8.06 – 22.29) and previous first-line tuberculosis treatment outcome of failure (AOR: 39.19; 95% CI 12.05 -127.46). Interruption of first-line tuberculosis treatment for one day or more (AOR = 4.28; 95% CI 2.76 – 6.64) and history of treatment in the first-line tuberculosis treatment category for previously treated patients (AOR: 3.70; 95% CI 2.40 – 5.72) were also significantly associated with the development of drug resistant tuberculosis in the current study.

CONCLUSION: Patients with a history of previous first-line tuberculosis treatment, patients who interrupted previous first-line tuberculosis treatment and patients with previous first-line tuberculosis treatment outcome of failure were at high risk of developing drug resistant tuberculosis. Therefore, the full course of first-line tuberculosis treatment should be given, following the Directly Observed Treatment (DOT) guide. Patients with recurrent tuberculosis and unfavourable first-line tuberculosis treatment outcome should be tested for drug susceptibility.

KEY CONCEPTS: Case-control study, Directly Observed Treatment, Drug resistant tuberculosis
# TABLE OF CONTENTS

DECLARATION ................................................................................................................................. ii

ACKNOWLEDGEMENTS .................................................................................................................. iii

ABSTRACT ........................................................................................................................................ v

ABBREVIATIONS ............................................................................................................................. xix

CHAPTER 1 ......................................................................................................................................... 1

ORIENTATION TO THE STUDY ........................................................................................................... 1

1.1 INTRODUCTION .......................................................................................................................... 1

1.2 BACKGROUND OF THE RESEARCH PROBLEM ........................................................................ 3

1.3 MOTIVATION OF THE STUDY ...................................................................................................... 6

1.4 STATEMENT OF THE RESEARCH PROBLEM ............................................................................ 7

1.5 AIMS, OBJECTIVES AND HYPOTHESIS OF THE STUDY ........................................................ 10

1.5.1 Aim of the study ...................................................................................................................... 10

1.5.2 Objectives of the study .......................................................................................................... 10

1.5.3 Research questions and hypothesis ...................................................................................... 11

1.5.3.1 Research questions ........................................................................................................... 11

1.5.3.2 Research hypothesis ......................................................................................................... 11

1.6 SIGNIFICANCE OF THE STUDY ............................................................................................... 11

1.7 DEFINITIONS OF KEY CONCEPTS ............................................................................................ 12

1.7.1 Conceptual definitions ......................................................................................................... 12

1.7.2 Operational definitions ........................................................................................................ 14

1.8 THEORETICAL FOUNDATIONS OF THE STUDY .................................................................... 16

1.8.1 Precede–proceed model ....................................................................................................... 16
1.8.2 Reasons for choosing precede–proceed model.................................................................19
1.8.3 Development of drug resistant tuberculosis ......................................................................21
  1.8.3.1 Healthcare provider related causes of drug resistant tuberculosis.................................21
  1.8.3.2 Patient related causes of drug resistant tuberculosis ..........................................................22
  1.8.3.3 Drug related causes of drug resistant tuberculosis ............................................................22

1.9 RESEARCH PARADIGM .........................................................................................................25
  1.9.1 Epistemology ....................................................................................................................26
  1.9.2 Ontology ..........................................................................................................................27
  1.9.3 Methodology ......................................................................................................................27
  1.9.4 Axiology ................................................................................................................................28

1.10 RESEARCH METHODOLOGY AND RESEARCH DESIGN ..................................................29
  1.10.1 Research methodology ......................................................................................................29
  1.10.2 Research design ...............................................................................................................29
  1.10.3 Setting and population of the study ...................................................................................30
  1.10.4 Sample and sampling methods ..........................................................................................31
  1.10.5 Data collection methods and procedures ...........................................................................33
  1.10.6 Data management and analysis ..........................................................................................33
  1.10.7 Ethical considerations ........................................................................................................34

1.11 SCOPE AND LIMITATIONS OF THE STUDY .................................................................35

CHAPTER 2 ..................................................................................................................................36

LITERATURE REVIEW ....................................................................................................................39
2.1 INTRODUCTION ..................................................................................................................39
2.2 CONCEPT OF DRUG RESISTANT TUBERCULOSIS .......................................................40
2.3 DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS ...................................................41
2.4 DRUG RESISTANT TUBERCULOSIS VERSUS DRUG SUSCEPTIBLE TUBERCULOSIS 42
2.5 DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS ............................................43
  2.5.1 Factors associated with the development of drug resistant tuberculosis in Europe and North America ........................................................................................................43
  2.5.2 Factors associated with the development of drug resistant tuberculosis in South America 44
  2.5.3 Factors associated with development of drug resistant tuberculosis in Asia ...............45
  2.5.4 Factors associated with the development of drug resistant tuberculosis in Africa ........47
  2.5.5 Factors associated with the development of drug resistant tuberculosis in Ethiopia ......49
2.6 SUMMARY ................................................................................................................................54

CHAPTER 3 ..................................................................................................................................55
RESEARCH METHODOLOGY AND RESEARCH DESIGN .......................................................55
3.1 INTRODUCTION ..................................................................................................................55
3.2 RESEARCH METHODOLOGY ............................................................................................56
3.3 RESEARCH DESIGN ............................................................................................................58
  3.3.1 Reasoning Strategies .......................................................................................................61
    3.3.1.1 Inductive reasoning ...................................................................................................61
    3.3.1.2 Deductive reasoning .................................................................................................62
3.4 RESEARCH PARADIGM .......................................................................................................62
  3.4.1 Epistemology of a Paradigm ..........................................................................................63
  3.4.2 Ontology of a Paradigm ..................................................................................................65
3.4.3 Methodology of a Paradigm .................................................................................................................. 66
3.4.4 Axiology .................................................................................................................................................. 66
3.4.5 Positivism: Paradigm of the study ....................................................................................................... 67
3.5 RESEARCH METHOD .............................................................................................................................. 71
3.5.1 Research population and study settings ............................................................................................. 73
3.5.1.1 Eligibility criteria .............................................................................................................................. 76
3.5.1.1.1 Inclusion criteria ............................................................................................................................ 76
3.5.1.1.2 Exclusion Criteria .......................................................................................................................... 77
3.5.2 Sampling ............................................................................................................................................... 77
3.5.2.1 Sample size determination ................................................................................................................. 78
3.5.2.2 Sampling methods ............................................................................................................................. 80
3.5.3 Data collection ..................................................................................................................................... 81
3.5.3.1 Data collection method ..................................................................................................................... 81
3.5.3.2 Development and testing of the data collection questionnaire ....................................................... 82
3.5.3.3 Characteristics of the data collection questionnaire ...................................................................... 83
3.5.4 Data analysis ....................................................................................................................................... 84
3.5.5 Ethical considerations ........................................................................................................................... 86
3.5.5.1 Beneficence (Do good) ..................................................................................................................... 87
3.5.5.2 Non-malfeasance (do no harm) ......................................................................................................... 88
3.5.5.3 Respect for autonomy (Respect for persons) .................................................................................. 88
3.5.5.4 Justice ............................................................................................................................................... 90
3.5.5.5 Informed consent .............................................................................................................................. 90
3.5.5.6 Respect for anonymity, confidentiality and privacy ...................................................................... 93
4.3.3.3 Contact with patient with drug resistant tuberculosis .......................................................... 113
4.3.3.4 Chronic illness .......................................................................................................................... 115
4.3.4 Tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment .......................................................................................................................... 116
4.3.4.1 Tuberculosis treatment interruption ......................................................................................... 116
4.3.4.2 Anti-tuberculosis drug side effect ............................................................................................ 117
4.3.4.3 Cigarette and alcohol .............................................................................................................. 119
4.3.4.4 Directly observed tuberculosis treatment ................................................................................. 120
4.3.5 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment .......................................................................................................................... 122
4.3.5.1 First-line tuberculosis treatment category ............................................................................... 123
4.3.5.2 First-line tuberculosis treatment outcome .............................................................................. 124
4.3.5.3 HIV status during first-line tuberculosis treatment ................................................................. 125
4.3.6 Results from logistic regression analysis .................................................................................... 126
4.3.6.1 Logistic regression analysis of the sociodemographic characteristics of the study respondents ........................................................................................................................................ 127
4.3.6.2 Logistic regression analysis of the tuberculosis disease related conditions .............................. 129
4.3.6.3 Logistic regression analysis of the tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment ......................................................... 131
4.3.6.4 Logistic regression analysis of the first-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment ......................................................... 134
4.4 SUMMARY ..................................................................................................................................... 135

CHAPTER 5 ........................................................................................................................................ 136
DEVELOPMENT OF CONCEPTUAL MODEL ................................................................................ 136
5.1 INTRODUCTION ........................................................................................................... 136
5.2 GENERAL ASPECTS OF MODEL ............................................................................... 137
  5.2.1 Concept synthesis ................................................................................................. 140
  5.2.2 Statement Synthesis ............................................................................................ 142
  5.2.3 Theory synthesis ................................................................................................ 144
5.3 MODEL FOR THE PREVENTION OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA ................................................................................................................................. 147
5.4 EVALUATION OF MODEL FOR THE PREVENTION OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA ................................................................................................................................. 152
  5.4.1 Theory description ............................................................................................... 153
  5.4.2 Critical reflection ................................................................................................ 154
5.5 SUMMARY .................................................................................................................. 157

CHAPTER 6 ....................................................................................................................... 158
DISCUSSION ..................................................................................................................... 158
  6.1 INTRODUCTION ....................................................................................................... 158
  6.2 DISCUSSION OF THE STUDY RESULTS ................................................................. 158
    6.2.1 Sociodemographic characteristics of the study respondents .............................. 158
      6.2.1.1 Gender ......................................................................................................... 159
      6.2.1.2 Age ............................................................................................................. 160
      6.2.1.3 Marital status .............................................................................................. 161
      6.2.1.4 Educational status ..................................................................................... 161
      6.2.1.5 Occupation ................................................................................................ 161
    6.2.2 Tuberculosis disease related conditions ............................................................ 162
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2.2.1 Number of previous tuberculosis episodes</td>
<td>162</td>
</tr>
<tr>
<td>6.2.2.2 Previous hospitalization</td>
<td>163</td>
</tr>
<tr>
<td>6.2.2.3 Contact with a patient with drug resistant tuberculosis</td>
<td>164</td>
</tr>
<tr>
<td>6.2.2.4 Chronic illness</td>
<td>165</td>
</tr>
<tr>
<td>6.2.3 Tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment</td>
<td>166</td>
</tr>
<tr>
<td>6.2.3.1 Tuberculosis treatment interruption</td>
<td>166</td>
</tr>
<tr>
<td>6.2.3.2 Anti-tuberculosis drug side effects</td>
<td>167</td>
</tr>
<tr>
<td>6.2.3.3 Cigarette and alcohol</td>
<td>168</td>
</tr>
<tr>
<td>6.2.3.4 Directly observed tuberculosis treatment</td>
<td>169</td>
</tr>
<tr>
<td>6.2.4 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment</td>
<td>170</td>
</tr>
<tr>
<td>6.2.4.1 First-line tuberculosis treatment category</td>
<td>170</td>
</tr>
<tr>
<td>6.2.4.2 First-line tuberculosis treatment outcome</td>
<td>172</td>
</tr>
<tr>
<td>6.2.4.3 HIV status during first-line tuberculosis treatment</td>
<td>175</td>
</tr>
<tr>
<td>6.3 SUMMARY</td>
<td>176</td>
</tr>
<tr>
<td>CHAPTER 7</td>
<td>177</td>
</tr>
<tr>
<td>CONCLUSIONS AND RECOMMENDATIONS</td>
<td>177</td>
</tr>
<tr>
<td>7.1 INTRODUCTION</td>
<td>177</td>
</tr>
<tr>
<td>7.2 SUMMARY AND INTERPRETATION OF THE RESEARCH RESULTS</td>
<td>178</td>
</tr>
<tr>
<td>7.2.1 Sociodemographic characteristics of study respondents</td>
<td>178</td>
</tr>
<tr>
<td>7.2.2 Tuberculosis disease related conditions</td>
<td>178</td>
</tr>
<tr>
<td>7.2.3 Tuberculosis treatment adherence related conditions during the most recent first line tuberculosis treatment</td>
<td>179</td>
</tr>
</tbody>
</table>
7.2.4 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment................................................................................................................180

7.3 CONCLUSIONS..................................................................................................................................................................................181

7.4 RECOMMENDATIONS........................................................................................................................................................................182

7.4.1 Recommendations for practice ......................................................................................................................................................182

7.4.2 Recommendations for future research ........................................................................................................................................183

7.5 CONTRIBUTIONS OF THE STUDY ..................................................................................................................................................183

7.6 LIMITATIONS OF THE STUDY .........................................................................................................................................................184

7.7 CONCLUDING REMARKS .................................................................................................................................................................185

LIST OF REFERENCES..............................................................................................................................................................................186
LIST OF TABLES

Table 1.1: Causes of drug resistant tuberculosis ................................................................. 23
Table 3.1: The population of the study regions projected for 2019 and the number of patients with drug resistant tuberculosis detected by the study regions from July 1 2017 to June 30 2018 .................................................................................................................................................. 75
Table 4.1: Number of study respondents per hospital ............................................................ 104
Table 4.2: Frequency distribution of the age groups of the study respondents ..................... 107
Table 4.3: Occupation of the study respondents .................................................................... 110
Table 4.4: Cigarette smoking and alcohol drinking habits of the study respondents ................ 119
Table 4.5: Directly observed tuberculosis treatment of the study respondents ..................... 121
Table 4.6: The first-line tuberculosis treatment outcome of the study respondents .............. 124
Table 4.7: Logistic regression analysis of the sociodemographic characteristics of the study respondents .................................................................................................................. 129
Table 4.8: Logistic regression analysis of the tuberculosis disease related conditions .......... 131
Table 4.9: Logistic regression analysis of the tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment ............................................ 133
Table 4.10: Logistic regression analysis of the first-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment ...................................................... 135
Table 5.1 Process of theoretical model development ................................................................ 138
LIST OF FIGURES

Figure 1.1 The nine phases of PRECEDE-PROCEED theoretical framework .........................18
Figure 1.2 Theoretical framework for the development and prevention of drug resistant tuberculosis based on the nine phases of PRECEDE-PROCEED theoretical framework ..........20
Figure 1.3 The relationship of the three categories of presumed causes of the development of drug resistant tuberculosis with each other and with development of drug resistant tuberculosis. ..................................................................................................................................................24
Figure 3.1 Elements of paradigm and the relationship between them. ................................63
Figure 3.2 Regional administrations of Ethiopia ........................................................................76
Figure 4.1: Number of the study respondents by gender and with case or control group ....105
Figure 4.2: Proportion of the study respondents by gender ........................................................106
Figure 4.3: Marital status of the study respondents .....................................................................108
Figure 4.4: Educational status of the study respondents ..............................................................109
Figure 4.5: Number of previous illness with tuberculosis ............................................................111
Figure 4.6: Proportion of the study respondents with two or more episodes of previous tuberculosis ..............................................................................................................................................112
Figure 4.7: History of previous hospitalization of the study respondents ................................113
Figure 4.8: History of household or close contact with a patient with drug resistant tuberculosis .............................................................................................................................................114
Figure 4.9: The presence of chronic illness in the study respondents .......................................115
Figure 4.10: Tuberculosis treatment interruption for one day or more by the study respondents ..................................................................................................................................................117
Figure 4.11: The presence of anti-tuberculosis drug side effects and the percentage of patients with vomiting during the study respondents’ most recent first-line tuberculosis treatment .................................................................118

Figure 4.12: Cigarette smoking alcohol drinking habit of the study respondents during most recent first-line tuberculosis treatment .................................................................................................................120

Figure 4.13: Number of weeks of directly observed tuberculosis treatment provided to the study respondents during their most recent first-line tuberculosis treatment ........................................122

Figure 4.14: The first-line tuberculosis treatment category of the study respondents during their most recent first-line tuberculosis treatment .........................................................................................123

Figure 4.15: The proportions of the first-line tuberculosis treatment outcomes of the study respondents during their most recent first-line tuberculosis treatment .........................................................125

Figure 4.16: The proportions of the HIV status of the study respondents during their most recent first-line tuberculosis treatment ..............................................................................................................126

Figure 5.1 Model for the prevention of drug resistant tuberculosis in Ethiopia .................................................146
ANNEXES

Annexe A: Data collection tool ................................................................. 206
Annexe B: Consent form ................................................................. 217
Annexe C: Assent form ................................................................. 220
Annexe D: Ethical clearance certificate ........................................... 223
Annexe E: Letter of support ................................................................. 224
ABBREVIATIONS

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immune Deficiency Syndrome

CI: Confidence Interval

COR: Crude Odds Ratio

AOR: Adjusted Odds Ratio

SPSS: Statistical packages for social sciences

WHO: World Health Organization

FMOH: Federal Ministry of Health of Ethiopia

CDC: Centres for Disease Control
CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION

“A bacterium called mycobacterium tuberculosis often affects the lungs and causes the disease known as tuberculosis (TB)” (World Health Organization (WHO) 2019a). Tuberculosis is transmitted from person to person through droplet inhalation. “When patients with pulmonary tuberculosis sneeze, cough or spit, they release the tuberculosis bacteria into their surroundings. A person inhaling these bacteria gets infection of the lungs” (Kanabus 2019).

One-third of the world's population is infected by the mycobacterium tuberculosis bacteria but does not transmit the bacteria to other individuals. These individuals infected by mycobacterium tuberculosis bacteria are not ill with tuberculosis disease but have latent tuberculosis (WHO 2019a). About 10% of people with latent tuberculosis develop active tuberculosis disease throughout their lifetime. “However, persons with compromised immune systems, such as people living with Human Immunodeficiency Virus (HIV), malnutrition or diabetes, or people who use tobacco, have a much higher risk of falling ill” (Centres for Disease Control (CDC) 2018).

A person with active tuberculosis disease can have mild symptoms for many months. This favours the transmission of the bacteria to others due to delay in diagnosis (Netherlands Tuberculosis Foundation 2019). A person with active tuberculosis can infect up to fifteen other individuals through close contact in one year. Up to two thirds of individuals with active tuberculosis will die if they are not treated. However, the majority of patients with tuberculosis can be cured if they take anti-tuberculosis drugs properly. “Generally, tuberculosis is a disease that can be cured and prevented” (WHO 2019b).
“Drug resistant tuberculosis is tuberculosis, which is either multidrug-resistant or rifampicin resistant” (WHO 2019c). “Multidrug- resistant tuberculosis is tuberculosis that is resistant to at least two first-line anti-tuberculosis drugs, rifampicin and isoniazid. The second form of drug resistant tuberculosis is rifampicin resistant tuberculosis, which is tuberculosis resistant to the anti-tuberculosis drug rifampicin” (WHO 2019c). The laboratory diagnosis of multidrug-resistant tuberculosis is made by culture and drug susceptibility testing while rifampicin resistant tuberculosis is diagnosed by gene x-pert test (Federal Ministry of Health of Ethiopia (FMOHOE 2014a:43; WHO 2019d).

One of the reasons given for the development of drug resistant tuberculosis is infection by anti-tuberculosis drug resistant strains of mycobacterium tuberculosis bacteria. The second reason is the increase in number of naturally occurring drug resistant mutants due to incorrect treatment (WHO 2019c). Individuals who have never taken first-line tuberculosis treatment develop primary drug resistant tuberculosis, while Individuals who took first-line tuberculosis treatment incorrectly develop secondary drug resistant tuberculosis (European Centre for Disease Prevention and Control 2019).

The occurrence of drug resistant tuberculosis is primarily due to mistake by the patient or health professionals leading to inadequate treatment. The human genomes have some impact but not significant (FMOHOE 2014b:12). These potential causes of inadequate treatment can be broadly categorized into healthcare factors (like poor follow-up by the provider or a weak tuberculosis programme), medicinal (ineffective drugs), and patient related factors (like non-adherence to treatment) (FMOHOE 2014b:14; Tuberculosis Alliance 2019).

This introduction section gives an overview of the current study. It presents the objectives and hypothesis of the study, details of the research problem, the theoretical framework and a summary of the research paradigm applied in the study. It also summarizes the research methodology and research design of the study.
1.2 BACKGROUND OF THE RESEARCH PROBLEM

Tuberculosis is the number one killer of human beings from infectious diseases. When compared with all types of diseases, tuberculosis is again among the fatal diseases that kill large number of people worldwide (WHO 2018a). “In 2017, tuberculosis caused an estimated 1.3 million deaths (range, 1.2 - 1.4 million) among human immunodeficiency virus (HIV) negative people and 300,000 deaths (range, 266,000 – 335,000) among people living with HIV” (WHO 2018a). According to the WHO’s global tuberculosis report (2018a), in 2017, an estimated 1.7 billion people had a latent tuberculosis infection that did not progress to disease. This accounted for nearly a quarter of the world’s population who were at risk of developing the active tuberculosis disease during their lifetime.

WHO’s global tuberculosis report (2018a) stated that about 10 million people had tuberculosis disease worldwide in 2017. From these people with tuberculosis nearly 6 million were men, while the rest 3 million and 1 million were women and children respectively. Individuals from all age groups got tuberculosis, but 90% of them were 15 years and older. Nine percent of patients with tuberculosis were HIV positive and of these 72% of them were from Africa. There was no country of the world, which was free of tuberculosis. However, India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa were the top high burden countries having the larger proportion of patients with tuberculosis. Eighty seven percent of the world’s patients with tuberculosis lived in just 30 countries. Europe and the Americas had the lowest proportion of patients with tuberculosis with each contributing only to 3% of the worldwide burden (Medical Xpress 2019; WHO 2018a).

Drug resistant tuberculosis has been one of the major health hazards to people of the world. “Worldwide in 2017, an estimated 558,000 people (range, 483,000 – 639,000) developed tuberculosis that was resistant to rifampicin, and of these, 82% had multidrug-resistant
From these estimated people, 160,684 patients with drug resistant tuberculosis were diagnosed and reported in 2017. There was a slight increment of case identification in 2017 when compared with the 153,119 cases identified the previous year (WHO 2018a). From all patients with drug resistant tuberculosis diagnosed in 2017, 139,114 (87%) of them were treated. This represents a quarter of the estimated number of patients who had drug resistant tuberculosis in that year (WHO 2018a).

From all patients with drug resistant tuberculosis diagnosed in 2017, 3.5% of them had no history of treatment with first-line anti-tuberculosis drugs while 18% of them were treated for drug susceptible tuberculosis sometime in the past (WHO 2018a). Treatment completion and cure rates of patients with drug resistant tuberculosis were low in the majority of countries averaging 55%. Few countries had good drug resistant tuberculosis treatment outcome. More than 70% of patients with drug resistant tuberculosis treated in Ethiopia, Viet Nam, Bangladesh, Myanmar, Kazakhstan, and Bangladesh completed their treatment and some of them had a laboratory result that confirmed that they were cured of their illness (WHO 2018a).

“Africa, with an estimated population of 1.1 billion, had a total tuberculosis incidence of 2.5 million (range, 2.2 - 2.8 million) in 2017, of which 0.7 million (range, 0.6 - 0.8 million) were HIV positive” (WHO 2018a). In 2017, there were 413,000 (range, 348,000 – 485,000) deaths due to tuberculosis in HIV negative people while 252,000 (range, 219,000 – 287,000) patients with tuberculosis who died had HIV coinfection (WHO 2018a).

In 2017, an estimated 2.7% (range, 1.7 - 4.0) of patients in Africa who were diagnosed to have tuberculosis for the first time were drug resistant. The estimate for patients with drug resistant tuberculosis who had history of previous first-line tuberculosis treatment for the same year in Africa was 14% (range, 0.49% - 43%) (WHO 2018a). The WHO’s global tuberculosis report (2018a), also estimated new patients with drug resistant tuberculosis in Africa in 2017 to be 90,000 (range, 76,000 – 106,000). Multidrug-resistant tuberculosis was estimated to represent
68% of these African patients with drug resistant tuberculosis and the rest 32% were estimated to be rifampicin resistant tuberculosis.

Ethiopia is an east African country with an estimated population of 105 million and an estimated annual tuberculosis incidence of 172,000 new cases per year (range, 121,000 – 232,000) in 2017, equivalent to 164 (range, 115–221) new tuberculosis patients per 100,000 populations per year (WHO 2018a). However, the number of cases actually notified to the Ethiopian ministry of health in 2017 was 117,705, giving a tuberculosis case detection rate (notified divided by estimated incidence) of 68% (range, 50% - 96%). The 2017 Ethiopian tuberculosis mortality rate, excluding those with HIV, was 24 (range, 15 – 35) deaths per 100,000 populations, which adds up to 25,000 (range, 16,000 – 37,000) deaths per year according to the WHO’s global tuberculosis report (2018a).

The WHO’s global tuberculosis report (2018a) on all countries’ tuberculosis profile ranked Ethiopia as the 17th high drug resistant tuberculosis burden country of the world in 2017. Ethiopia was ranked the fifth highest country in Africa for the burden of drug resistant tuberculosis following South Africa, Nigeria, Mozambique and Democratic Republic of Congo in 2017 (in this decreasing order). From the tuberculosis cases reported by Ethiopia for the year 2017, an estimated 2700 were patients with drug resistant tuberculosis with a minimum and maximum range of 1,700 and 3,700 respectively (WHO 2018a).

The results of the second round of the Ethiopian national tuberculosis drug resistance survey, conducted from 2011 to 2014, showed a drug resistant tuberculosis prevalence of 2.3% in tuberculosis treatment naive patients and 17.8% in patients who took first-line tuberculosis treatment previously (WHO 2015a). The 2017 incidence of drug resistant tuberculosis in Ethiopia was estimated to be 5,500 (range, 2,900 – 8,900) cases per year or 5.2 (range, 2.8 - 8.4) patients out of 100,000 populations in one year. However, only 680 (12.4%) laboratory-confirmed patients with drug resistant tuberculosis were diagnosed and treated in 2017 in
Ethiopia (WHO 2018a). The WHO’s global tuberculosis report (2018a) also indicated that, in 2017, Ethiopia had cases of drug resistant tuberculosis in an estimated 2.7% (range, 1.6% – 4.1%) of tuberculosis treatment naïve patients and 14% (range, 6.7% – 25%) of patients who took first-line tuberculosis treatment previously.

The fact that only 680 (12.4%) of the estimated 5,500 overall incident drug resistant tuberculosis cases in 2017 were detected indicates the need to adopt a more rigorous case finding approach for drug resistant tuberculosis in Ethiopia. The case detection rate of drug resistant tuberculosis needs to be increased alongside with preventive approaches to combat the incidence of new patients with drug resistant tuberculosis. This study aims to contribute to the insight into the strategies and activities for improving the detection of new patients with drug resistant tuberculosis as well as preventing its person-to-person transmission. Added to this, the outcomes of this study can serve as baseline information for further studies and program implementations on drug resistant tuberculosis in Ethiopia.

1.3 MOTIVATION OF THE STUDY

Addressing the gaps in case detection of drug resistant tuberculosis requires having the capacity for first-line tuberculosis drug susceptibility testing so that early diagnosis is made (WHO 2018a). Added to this, increasing the case detection rate of drug resistant tuberculosis has to be followed by improving the treatment and follow-up provided to patients with drug resistant tuberculosis to achieve good treatment outcome. This improvement in quality of care provided requires better access to treatment, better laboratory capacity and effective medicines. Continued scientific researches on tuberculosis in general and drug resistant tuberculosis specifically are the basics to fulfil these requirements for improving case detection and treatment outcome of drug resistant tuberculosis (WHO 2018a).
Drug resistant tuberculosis is one of the emerging challenges of health service delivery in Ethiopia (FMOHOE 2014a:12). The researcher also noted this fact during medical practice as a medical doctor and tuberculosis programme manager. The researcher used to be a project coordinator for the tuberculosis control programme run by a non-governmental organization in Ethiopia for five years. During this period, the researcher noted the knowledge gap on why patients with drug resistant tuberculosis developed the disease. Thus, the researcher started to assess factors associated with the development of drug resistant tuberculosis. The researcher conducted this study in the belief that knowing the factors, which lead to the development of drug resistant tuberculosis, is the key to devising effective preventive measures.

Ethiopia has high morbidity from drug resistant tuberculosis with an incidence estimated to be 5,500 cases per year, ranking the 17th highest burden country in the world (WHO 2018a). Despite this high disease burden, a few studies have been undertaken in Ethiopia on determinants of drug resistant tuberculosis. This information gap was the main motive for conducting this study.

1.4 STATEMENT OF THE RESEARCH PROBLEM

Mycobacterium tuberculosis strains resistant to the most active core anti-tuberculosis drugs emerged decades after tuberculosis became a curable illness in nearly all cases (WHO 2014a). The creation of these drug resistant mycobacteria has made the control of tuberculosis a significant menace to global public health. Mycobacterium tuberculosis bacteria, which developed resistance to first-line anti-tuberculosis drugs, require long duration of highly expensive treatment when compared with those mycobacteria, which are susceptible to these drugs. This may hamper the achievement of the goals of WHO’s end tuberculosis strategy (WHO 2019c). First-line anti-tuberculosis drugs cannot treat tuberculosis caused by drug resistant mycobacterium tuberculosis bacteria. Drug resistant tuberculosis is treated by a
combination of drugs like capreomycine, protheonamide, cycloserine, pyrazinamide, bedaquiline and levofloxacin (Global Tuberculosis Community Advisory Board 2019; WHO 2019c).

When mycobacterium tuberculosis bacteria develop resistance to these second-line anti-tuberculosis drugs, the disease progresses to extensively drug resistant tuberculosis. “Extensively drug-resistant tuberculosis is a form of multidrug-resistant tuberculosis that does not respond to the most effective second-line anti-tuberculosis drugs capreomycine (injectable group) and levofloxacin (quinolone group)” (WHO 2015b).

The increase in prevalence of drug resistant tuberculosis is challenging for the health systems of the poor countries of the world. This challenge is apparent in Ethiopia where this study was done. As Ethiopia is one of the poor countries of the world, the limited resources the country has cannot cope with the increase in prevalence of drug resistant tuberculosis. Thus, drug resistant tuberculosis adds to the burden of the staggering health system of the country (FMOHOE 2014b:16; Hiruy, Melese, Habte, Jerene, Gashu, Alem, Jemal, Tessema, Belayneh & Suarez 2018:4). Treatment failure or defaulting from treatment is common in treatment of drug resistant tuberculosis due to the two yearlong treatment with expensive second-line anti-tuberculosis drugs, which have many side effects. First-line anti-tuberculosis drugs used for the treatment of drug susceptible tuberculosis on the other hand are more effective with less side effects, cheap and have a short treatment duration of 6 months (FMOHOE 2017:16; WHO 2019a).

In most resource-limited countries, there are no or limited number of laboratories capable of doing first-line anti-tuberculosis drugs susceptibility testing. This results in very small number of patients with tuberculosis whose drug susceptibility to first-line anti-tuberculosis drug is known lowering the case detection rate of drug resistant tuberculosis (WHO 2019c). For instance, there are only two laboratories with a capacity of doing line probe gene assay and mycobacterial culture and drug susceptibility test to diagnose drug resistant tuberculosis in Ethiopia, which give
service to more than 105 million people residing in the eleven regions of the country. This results in a high number of undiagnosed patients with drug resistant tuberculosis in the community, which will transmit the disease to others (FMOHOE 2017).

The introduction of a new diagnostic technology in 2014, the gene x-pert test, which detects mycobacterium tuberculosis and rifampicin resistance, has helped to increase the number of patients with drug resistant tuberculosis diagnosed in Ethiopia (Ethiopian Public Health Institute 2017; WHO 2015c). However, this increase in case detection is only a relative increase and the case detection is still below the expected level, which necessitates a study on the causes of the problem for timely detection of drug resistant tuberculosis.

In Ethiopia, there are a few studies conducted on determinants of drug resistant tuberculosis. One such study carried out at a sub-city level, assessed factors that might determine the occurrence of drug resistant tuberculosis in Addis Ababa. The study by Selamawit, Girmay, Belaineh, Muluken, Alemayehu, Pedro and Gobena (2013:782), found out that not adhering to tuberculosis treatment, more than one pulmonary tuberculosis episode, tuberculosis retreatment and drug side effect, had a significant association with the development of drug resistant tuberculosis.

To date, there is very limited empirical evidence in Ethiopia on factors leading to the acquisition of drug resistance tuberculosis. The significant gap in knowledge on drug resistance tuberculosis needs to be filled by studies like this study, which deeply looked into different sociodemographic and clinical factors that might predict drug resistance tuberculosis by raising the index of suspicion. In addition to the customary social and demographic variables, the study assessed tuberculosis disease related conditions, tuberculosis treatment adherence related conditions and first-line tuberculosis treatment related conditions of the study respondents.
1.5 AIMS, OBJECTIVES AND HYPOTHESIS OF THE STUDY

1.5.1 Aim of the study

The aims of this study were twofold; it intended to:

1. Determine factors leading to the acquisition of drug resistant tuberculosis in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia.

2. Develop a conceptual model for drug resistant tuberculosis in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia.

1.5.2 Objectives of the study

1. Assess sociodemographic characteristics predicting the occurrence of drug resistant tuberculosis in confirmed patients with drug resistant tuberculosis.

2. Assess tuberculosis disease related conditions predicting the occurrence of drug resistant tuberculosis in confirmed patients with drug resistant tuberculosis.

3. Assess tuberculosis treatment adherence related conditions predicting the occurrence of drug resistant tuberculosis in confirmed patients with drug resistant tuberculosis.

4. Assess first-line tuberculosis treatment related conditions predicting the occurrence of drug resistant tuberculosis in confirmed patients with drug resistant tuberculosis.
1.5.3 Research questions and hypothesis

1.5.3.1 Research questions

1. Why do patients in the Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia, develop drug resistant tuberculosis?
2. How can the occurrence of drug resistant tuberculosis be prevented in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia?

1.5.3.2 Research hypothesis

1. There is no association between the occurrence of drug resistant tuberculosis and the sociodemographic characteristics of patients with drug resistant tuberculosis.
2. There is no association between the occurrence of drug resistant tuberculosis and tuberculosis disease related conditions of patients with drug resistant tuberculosis.
3. There is no association between the occurrence of drug resistant tuberculosis and tuberculosis treatment adherence related conditions of patients with drug resistant tuberculosis.
4. There is no association between the occurrence of drug resistant tuberculosis and first-line tuberculosis treatment related conditions of patients with drug resistant tuberculosis.

1.6 SIGNIFICANCE OF THE STUDY

The significance of this study relates to the fact that it led to the identification of determinants of the occurrence of drug resistant tuberculosis. The identified factors contributed to the development of the conceptual model for drug resistant tuberculosis, which is one of the major
public health problems affecting the people of Ethiopia. There were no similar studies done in Ethiopia. This study is unique in the factors it assessed and the geographical area it covered.

Currently, Ethiopia uses a very broad preventive approach to prevent the development of drug resistant tuberculosis (FMOHOE 2017). This prevention modality is resource intensive as it primarily focuses on alleviating all factors presumed to be the determinants of the occurrence of drug resistant tuberculosis. However, the conceptual model will enable health practitioners to adopt a more focused preventive strategy. A focused strategy ensures that more resources are allocated for addressing the most important determinants of the occurrence of drug resistant tuberculosis. Added to this, the study findings can serve as a baseline information for future evaluation of the implementation of drug resistant tuberculosis programmes.

1.7 DEFINITIONS OF KEY CONCEPTS

1.7.1 Conceptual definitions

**Tuberculosis (TB):** “Tuberculosis is an infectious disease caused by a bacterium called mycobacterium tuberculosis, which is a rod-shaped bacillus” (WHO 2014b). Mycobacterium tuberculosis usually affects the lungs and pulmonary tuberculosis is the name given to this lung tuberculosis (FMOHOE 2014c). Pulmonary tuberculosis is a significant cause of illness and death in the world as it is the commonest type of tuberculosis (WHO 2014b). Pulmonary tuberculosis is transmitted from one person to another by the inhalation of the dried residue of larger respiratory droplets, which are released into the air during the coughing or sneezing of an infectious pulmonary tuberculosis patient (FMOHOE 2014c).

**Rifampicin resistant tuberculosis (RR-TB):** “Rifampicin resistant tuberculosis is tuberculosis caused by mycobacterium tuberculosis bacteria resistant to the anti-tuberculosis drug rifampicin” (WHO 2014b; WHO 2018b). The resistance to rifampicin can be detected using culture and a
drug sensitivity test or genotypic methods like gene x-pert and line probe assay (FMOHOE 2014b).

**Multidrug-resistant tuberculosis (MDR-TB):** “Multidrug-resistant tuberculosis is tuberculosis caused by mycobacterium tuberculosis bacteria resistant to at least both anti-tuberculosis drugs isoniazid and rifampicin” (WHO 2014b). Isoniazid and rifampicin resistance can be detected using culture and a drug sensitivity test and line probe assay (FMOHOE 2014b; WHO 2018b).

**Drug resistant tuberculosis (DR-TB):** “Drug resistant tuberculosis refers to either rifampicin resistant tuberculosis or multidrug-resistant tuberculosis in broad terms” (WHO 2014b). Drug resistance among new patients with tuberculosis refers to resistance in patients who have no prior history of treatment with first-line anti-tuberculosis drugs for a period longer than one month. This reflects the degree of ongoing infection by drug resistant strains in the population. Drug resistance among patients who were previously treated with first-line anti-tuberculosis drugs refers to resistance in patients who took standardized tuberculosis treatment for a period of one or more month. This is an indirect indicator of inappropriate treatment (FMOHOE 2014c).

**Extensively drug resistance tuberculosis (XDR-TB):** “Extensively drug resistance tuberculosis is tuberculosis caused by mycobacterium tuberculosis bacteria resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin) detected by culture and sensitivity test, in addition to multidrug-resistance” (WHO 2014b; WHO 2018b).

**Pulmonary tuberculosis (PTB):** “Pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis involving the lung parenchyma or the tracheobronchial tree.” A patient with extra pulmonary and pulmonary tuberculosis is grouped under pulmonary tuberculosis (WHO 2014b).
Extra pulmonary tuberculosis (EPTB): “Extra pulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of tuberculosis involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges” (WHO 2014b).

Tuberculosis treatment adherence: “In terms of tuberculosis control, adherence to treatment is defined as the extent to which the patient's history of therapeutic drug taking coincides with the prescribed treatment” (WHO 2018c). The process can assess adherence to tuberculosis treatment during treatment like counting the pills remaining or the number of days the patient presented during appointments. The outcome of poor or good tuberculosis treatment adherence can also be assessed by the end treatment outcome (WHO 2018c).

1.7.2 Operational definitions

Directly Observed Treatment (DOT): “Directly observed treatment implies standardized short-course tuberculosis treatment given under direct and supportive observation by health workers, community volunteers or family members.” Directly observed treatment ascertains that the patient takes anti-tuberculosis drugs correctly and this improves adherence (WHO 2019e).

Drug side effect: “Side effects, also known as adverse events, are unwanted or unexpected events or reactions to a drug.” Adverse events of drugs range from mild discomforts to life-threatening events (United States Food and Drug Administration 2018).

Treatment outcomes: For patients with tuberculosis who are taking first-line anti-tuberculosis drugs, their outcomes of treatment are classified as follows: (WHO 2014b).
“Cured: A patient with bacteriologically confirmed pulmonary tuberculosis at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion” (WHO 2014b).

“Treatment completed: A patient with tuberculosis who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable” (WHO 2014b).

“Treatment failed: A patient with tuberculosis whose sputum smear or culture is positive at month 5 or later during treatment” (WHO 2014b).

“Died: A patient with tuberculosis who dies for any reason before starting or during the course of treatment” (WHO 2014b).

“Lost to follow-up (Defaulter): A patient with tuberculosis who did not start treatment or whose treatment was interrupted for two consecutive months or more” (WHO 2014b).

“Not evaluated: A patient with tuberculosis for whom no treatment outcome is assigned. This includes cases transferred out to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit” (WHO 2014b).

“Treatment success: The sum of cured and treatment completed (WHO 2014b).

“New patient: A patient with tuberculosis who has never been treated for tuberculosis or has taken anti-tuberculosis drugs for less than 1 month” (WHO 2014b).
“Previously treated patient: A patient with tuberculosis who has received 1 month or more of anti-tuberculosis drugs in the past” (WHO 2014b).

1.8 THEORETICAL FOUNDATIONS OF THE STUDY

Theories give explanation that help in understanding of an event or phenomena. Theories anticipate, assume and challenge an existing knowledge (University of Southern California 2019a). A theoretical framework is a pillar that supports the theory of a study. A theoretical framework explains why the problem studied exists (University of Southern California 2019a). This study used precede–proceed theoretical framework which is discussed below in detail.

1.8.1 Precede–proceed model

“The precede–proceed model is a cost–benefit evaluation framework proposed in 1974 by Dr Lawrence Green, that can help health programme planners, policy makers, and other evaluators analyse situations and design health programmes efficiently” (Crosby & Noar 2011:7-15; Rural Health Information Hub 2019). It gives a guidance that helps in the assessment, planning, implementation and evaluation of health related activities. The precede–proceed model encompasses planning and evaluation (Crosby & Noar 2011:7-15; Rural Health Information Hub 2019).

Crosby and Noar (2011:7-15) divide the precede–proceed theory into two parts with nine phases or steps (see figure 1.1). The first part is composed of five phases, which are stepwise assessments that result in a knowledge that helps to make informed decisions. “These phases are called “PRECEDE” which is an acronym for “Predisposing, Reinforcing and Enabling Constructs in Educational or Ecological Diagnosis and Evaluation” (Crosby & Noar 2011:7-15). The second part has four phases that base the knowledge gained from the first part. “This
second part is called “PROCEED”, which stands for “Policy, Regulatory and Organizational Constructs in Educational and Environmental Development” (Crosby & Noar 2011:7-15).

PRECEDE lays out the guide to plan a public health programme with visible aim and target. It involves assessing the following community factors: (Crosby & Noar 2011:7-15; Rural Health Information Hub 2019).

*Phase 1: Social assessment:* What is the problem of the society? What does the community need? What should be the outcome?

*Phase 2: Epidemiological assessment:* What are the health related factors affecting the existing problems? What should be done first and what follows? What is the aim?

*Phase 3: Behavioural and environmental assessment:* What are the main environmental and behavioural determinants?

*Phase 4: Educational and ecological assessment:* What are the behavioural and environmental factors that predispose, reinforce, and enable the behaviours?

*Phase 5: Administrative policy assessment:* What are the administrative and policy issues that affect the implementation?

PRECEED aids a public health programme on its implementation and evaluation. It includes setting the result and implementation of the programme: (Crosby & Noar 2011:7-15; Rural Health Information Hub 2019).

*Phase 6: Implementation:* How do we intervene? What resources are there? How do we run the programme? How do we evaluate the programme?

*Phase 7: Process Evaluation:* Is the programme serving the population in need? Where are we in terms of achieving our aim? What corrective measures should be taken?

*Phase 8: Impact Evaluation:* Does the programme achieved its behavioural and environmental objectives?
Phase 9: Outcome Evaluation: Does the programme achieved its objecting of boosting the positive behaviour? Does the programme stopped or minimized the negative behaviour?

Figure 1.1 below summarizes the nine phases of PRECEDE-PROCEED theoretical framework.

Figure 1.1 “The nine phases of PRECEDE-PROCEED theoretical framework”
(Adapted from: Crosby & Noar 2011:7-15; University of Kansas 2018).

The precede–proceed model guides disease prevention programmes like prevention of drug resistant tuberculosis starting from the planning phase to implementation and evaluation. The precede–proceed model has been used in many public health programmes and was found to be effective both for short and long term interventions (Rural Health Information Hub 2019). The precede–proceed model is community oriented and aims to achieve community ownership of a public health program, which is of paramount importance for permanent change of behaviour, which passes to the generations to come (Rural Health Information Hub 2019).
Precede–proceed model assumes the points listed below when structuring a public health programme: (University of Kansas 2018).

1. Voluntary community participation and multisector collaboration.

2. Influence of the community.

3. Health is affected many factors.

4. Healthy implies a good quality of the lives of individuals and communities.

1.8.2 Reasons for choosing precede–proceed model

The researcher chose the precede–proceed model as a theoretical framework for this study on drug resistant tuberculosis in Ethiopia for the following reasons: (University of Kansas 2018)

- Precede–proceed model can be used for prevention of drug resistant tuberculosis at community level from planning to implementation and evaluation.

- Precede–proceed model involves community participation. This gives better understanding of the burden of drug resistant tuberculosis in the community.

- Community involvement builds community ownership of the prevention activities of drug resistant tuberculosis, which can result in successful intervention.

- Precede–proceed model takes into consideration the administrative and policy issues that can affect the prevention activities of drug resistant tuberculosis.
- Precede–proceed model encompasses monitoring and evaluation of the prevention activities of drug resistant tuberculosis as the activities go on, when the intervention is implemented and when the desired result is reached.

- Precede–proceed model allows to adapt the prevention activities of drug resistant tuberculosis the existing environment and the demands of the community.

Figure 1.2 Theoretical framework for the development and prevention of drug resistant tuberculosis based on the nine phases of the PRECEDE-PROCEED theoretical framework
(Adapted from Crosby & Noar 2011:7-15; University of Kansas 2018).
1.8.3 Development of drug resistant tuberculosis

The WHO classifies factors, which precede the occurrence of drug resistant tuberculosis into drug related, patient related and healthcare provider related causes (WHO 2015b). These factors are described below and are incorporated in the theoretical framework for the development and prevention of drug resistant tuberculosis and the design is based on the nine phases of PRECEDE-PROCEED theoretical framework (See figure 1.2 above).

1.8.3.1 Healthcare provider related causes of drug resistant tuberculosis

Mismanagement of first-line tuberculosis treatment is one of the main reasons assumed to be responsible for the development of drug resistance tuberculosis (WHO 2017). Healthcare provider mistakes, which include improper use of first-line anti-tuberculosis drugs and early discontinuation of first-line tuberculosis treatment, can make mycobacterium tuberculosis bacteria resistant to these drugs. Examples of this malpractice by health workers include not giving the full 6 month course of first-line tuberculosis treatment and prescribing incorrect treatment (incorrect dose or duration of treatment) (WHO 2017).

The healthcare provision system can also be a cause for the occurrence of drug resistant tuberculosis (Huber 2014). Weak tuberculosis control programmes of countries can cause drug resistance due to inappropriate first-line tuberculosis treatment. Direct observation of tuberculosis treatment by health workers is the core of tuberculosis control programmes due to the risk that patients may not finish the first-line tuberculosis treatment. However, some developing countries cannot implement this strategy due to resource constraints (Huber 2014). The faults in the healthcare system can be due to faulty guidelines, not following guidelines, no guidelines, no training and poor supervision, not following treatment provision, disorganized control programmes, inadequate regimens, lack of drug sensitivity test and poor access to healthcare (CDC 2017).
1.8.3.2 Patient related causes of drug resistant tuberculosis

Drug resistant tuberculosis arises from the human error of not giving adequate first-line anti-tuberculosis drugs properly for patients with tuberculosis (Huber 2014). Because of the six months needed for treatment of drug susceptible tuberculosis, patients tend not to take the drugs properly. After two weeks of treatment most patients with drug susceptible tuberculosis will not have the symptoms of their illness, which makes some of them to interrupt taking their drugs from false sense of wellbeing. However, the mycobacterium tuberculosis bacteria in the bodies of these patients are not yet completely killed. Therefore, these mycobacterium tuberculosis bacteria become resistant to the first-line anti-tuberculosis drugs the patient took (Huber 2014).

Patients with tuberculosis can by themselves cause the occurrence of drug resistant tuberculosis from poor adherence to treatment or default from treatment and alcohol dependence (FMOHOE 2014b). Social barriers in the community like stigma and discrimination imposed on patients with tuberculosis have their own impact on making these patients default from treatment or not to take their tuberculosis drugs regularly. Other conditions of the patient like drug adverse effects or drug interactions and mal-absorption also contribute to poor treatment adherence and suboptimal ineffective drug level in the blood, which creates a fertile ground for flourishing of drug resistance (FMOHOE 2014b).

1.8.3.3 Drug related causes of drug resistant tuberculosis

The use of inappropriate combination of drugs like taking only one drug, a drug of low quality or improperly stored drug can also cause to the occurrence of drug resistant tuberculosis from the incapacity of the drug to kill the mycobacterium tuberculosis bacteria (FMOHOE 2014b). A combination of drugs is required to cure tuberculosis. However, tuberculosis medication may not contain the complete combination of drugs due to wrong doses or combinations by the
manufacturer. Certain drugs may not be available for various reasons. This incomplete combination may facilitate the creation of drug resistant tuberculosis (FMOHOE 2014b).

Table 1.1 below summarizes the three categories of presumed determinants of the development of drug resistant tuberculosis.

<table>
<thead>
<tr>
<th>Health-care provider or programme related factors</th>
<th>Drug related factors</th>
<th>Patient- related factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Inappropriate guidelines</td>
<td>• Poor quality</td>
<td>• Poor adherence or default</td>
</tr>
<tr>
<td>• Non-compliance with guidelines</td>
<td>• Unavailability of certain drugs due to stock-outs or delivery disruptions</td>
<td>• Lack of or inadequate patient information</td>
</tr>
<tr>
<td>• Absence of guidelines</td>
<td>• Poor storage conditions</td>
<td>• If treatment is not given for free</td>
</tr>
<tr>
<td>• Poor training</td>
<td>• Wrong doses or combinations (manufacture related)</td>
<td>• Lack of transportation or money or support</td>
</tr>
<tr>
<td>• Poor supervision</td>
<td></td>
<td>• Drug adverse effects or interaction,</td>
</tr>
<tr>
<td>• No monitoring of treatment provision</td>
<td></td>
<td>• Social barriers</td>
</tr>
<tr>
<td>• Poorly organized or funded control programme</td>
<td></td>
<td>• Mal-absorption</td>
</tr>
<tr>
<td>• Inadequate regimens</td>
<td></td>
<td>• Substance or alcohol dependence</td>
</tr>
<tr>
<td>• Lack of drug sensitivity testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Poor access to healthcare</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“Table 1.1 Causes of drug resistant tuberculosis”
(FMOHOE 2014b).

Figure 1.3 below is designed to show the relationship of between the three categories of presumed determinants of the occurrence of drug resistant tuberculosis and the development of drug resistant tuberculosis. As an example from the figure, the poor quality of a first-line anti-tuberculosis drug may lead to the increased incidence of drug side effects. A patient with tuberculosis suffering from a first-line anti-tuberculosis drug side effect may be prone to poor
Poor treatment adherence leads to inadequate first-line tuberculosis treatment, which favours an increase in the number of naturally occurring mutant mycobacterium tuberculosis bacteria resistant to first-line anti-tuberculosis drugs leading to the development of drug resistant tuberculosis (FMOHOE 2014b).

**Figure 1.3 The relationship of the three categories of presumed causes of the occurrence of drug resistant tuberculosis with each other and with development of drug resistant tuberculosis.**

(Adapted from “guidelines on programmatic management of drug resistant Tuberculosis in Ethiopia, 2nd edition”, FMOHOE 2014b)
1.9 RESEARCH PARADIGM

“Research paradigm is an approach to conducting a research that has been verified by the research community for long and that has been in practice for many years” (Stephen & Kasim 2015). A scientific research philosophy is defined by research paradigm. Researcher can be equipped with the basics of philosophy, theory, instrument and methodology if he has a clear research paradigm (Žukauskas, Vveinhardt & Andriukaitienė 2018).

“The three basic paradigms are positivism, constructivism or interpretivism and pragmatism” (Bartleby 2017). These three paradigms are further divided into ontology, epistemology and methodology. Ontology deals with the nature of reality, epistemology explains the connection between the investigator and his version of reality, and methodology is technique used to analyse research (Bartleby 2017).

The researcher of this study chose a positivist paradigm, as the aim of the study was to determine associations between specific independent factors and drug resistant tuberculosis. According to Rehman and Alharthi (2016:54) positivist paradigm often uses quantitative data. The use of quantitative data to represent and analyse features of a study entity is consistent with a positivist paradigm. Thus, positivist paradigm is appropriate for this current quantitative study, which looked into determinants of drug resistant tuberculosis. Further explanations on positivist epistemology paradigm are briefly given in the sections below and detailed in chapter 3.

“A paradigm is composed of four different types of assumptions, namely, epistemology, ontology, methodology and axiology” (Kivunja & Kuyini 2017:26).
1.9.1 Epistemology

“Epistemology is concerned with the nature of human knowledge that the researcher can acquire for extending, broadening and deepening the understanding in the field of research” (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:52). Epistemology describes the way one knows a certain thing; or the way the knowledge we have was acquired (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:51). Epistemology ascertains the trust researcher has on the information collected. It has direct impact on the method of acquiring new understanding of unknown things (Kivunja & Kuyini 2017:26; Rehman & Alharthi 2016:52).

As described in Kivunja and Kuyini (2017:27) and Rehman and Alharthi (2016:52), epistemology focuses on the following:
1. The type and kind of knowledge.
2. The way of acquiring knowledge.
3. The mechanism of transferring knowledge to other individuals.

This study assessed determinants of the development of drug resistant tuberculosis in Ethiopia. In order to know these factors, the study respondents were asked about their experiences during the most recent first-line tuberculosis treatment. Added to this, objective facts were looked for by collecting data from the first-line tuberculosis treatment registers of the study respondents. This shows that the current study put emphasis on the understanding that knowledge on determinants of the development of drug resistant tuberculosis is best derived from the experiences of patients with all forms of tuberculosis and from the objective facts documented in their first-line tuberculosis treatment registers. Thus, the approach of the current study leans towards empirical epistemology. In other words, the source of knowledge for the current study on determinants of the development of drug resistant tuberculosis was empirical knowledge.
1.9.2 Ontology

“Ontology is a section of philosophy that studies the nature of existence, of being, as well as the basic groups of things that exist and the relationship between them” (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:51). It examines one’s understanding of the world we live in. It focuses on what one thinks of to believe the existence of one thing. Ontology is important to understand the interpretation of the findings of a study (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:51).

Ontology incorporates one’s thinking towards believing the existence of an entity under investigation (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:51). Ontology explains the constituents of the environment we live in, as they exist. It looks into the knowledge that helps to understand the implications of findings of a study (Kivunja & Kuyini 2017:27).

The following ontological assumptions were used in the current study to investigate determinants of the occurrence of drug resistant tuberculosis in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia.
- Adherence to first-line tuberculosis treatment is key prevention mechanism from occurrence of drug resistant tuberculosis.
- Provision of proper first-line tuberculosis treatment and follow-up to patients with drug susceptible tuberculosis can protect them from developing drug resistant tuberculosis.

1.9.3 Methodology

“Methodology refers to the research design, methods, approaches and procedures used in a study that is planned to find out something” (Kivunja & Kuyini 2017:28). Data collection, study subjects, questionnaire and data management make up the study methodology (Kivunja & Kuyini 2017:28).
Methodology entails the mechanism by which the knowledge we have about the world is acquired (Kivunja & Kuyini 2017:28; Rehman & Alharthi 2016:52). Kivunja and Kuyini (2017:28) and Rehman and Alharthi (2016:52) state that, the methodology of a study guides the researcher how to reach to the goal of acquiring new knowledge.

The current study was quantitative research as the study had an objective of assessing the degree of relationship between different independent variables and the development of drug resistant tuberculosis numerically. The quantitative approach is a kind of research approach, which quantifies the relationships between variables (Babbie 2014:87). The following methodological assumptions were used in the current study.
- Comparing the first-line tuberculosis treatment related conditions of drug resistant tuberculosis and successful first-line tuberculosis treatment outcome can identify determinants of the occurrence of drug resistant tuberculosis.
- The quantitative finding from primary and secondary data collected can generate information that helps to understand determinants of the occurrence of drug resistant tuberculosis.

1.9.4 Axiology

“Axiology is concerned with the ethical issues that need to be considered when planning research study” (Kivunja & Kuyini 2017:28). It instructs the conduction of studies in an ethical way and advocates the practice of ethical behaviour. Studies involving humans should strictly follow ethical research principles (Kivunja & Kuyini 2017:28).

All the necessary ethical precautions were considered when planning the current study. The ethical considerations were made with regard to the study respondents, the data and the way of reporting study findings.
1.10 RESEARCH METHODOLOGY AND RESEARCH DESIGN

This section presents a brief summary of the research methodology and research design. A detailed explanation is given in chapter 3.

1.10.1 Research methodology

“Research methodology is the way researchers have to follow to conduct their research.” It guides researchers on identifying a problem, setting an objective and analysing the result from the data collected (Sileyew 2019). The steps researchers follow to predict, describe and explain a study finding are called research methodology (Rajasekar, Philominathan & Chinnathambi 2013:5).

Creswell (2014:32) divides research methodologies into three types, which are qualitative, quantitative and mixed methods. This study aimed to assess the relationships between different pre-defined factors and the development of drug resistant tuberculosis and produce generalizable knowledge. It planned to examine these relationships by using numbers and closed-ended questions. The best methodology to examine relationships between different variables by using numbers and closed-ended questions is quantitative methodology, which was used in this study.

1.10.2 Research design

Research design provides the necessary framework for conducting a study (Sileyew 2019). A case-control design was used in the current study. “Case-control research is a type of observational research in which two existing groups differing in outcomes are identified and compared on the basis of some supposed causal attribute” (Salazar, Crosby & DiClemente 2015:107). “Case-control researches identify factors that may be associated with a disease by
comparing subjects which have that disease (the “cases”) with subjects who do not have the disease but are otherwise similar (the “controls”)” (Salazar, Crosby & DiClemente 2015:107).

The purpose of case-control research is to find out the degree of association between an exposure and an outcome (Lamorte 2015: 5). The current study used case-control research design whereby it enrolled patients who had developed drug resistant tuberculosis and tried to assess the magnitude of relationship between the development of drug resistant tuberculosis and the different assumed causative factors.

In the current study, the two differing groups of cases and controls had an outcome of drug resistant tuberculosis and successful first-line tuberculosis treatment respectively. Cases were patients with drug resistant tuberculosis who include patients with multidrug-resistant tuberculosis and rifampicin resistant tuberculosis. These cases had a confirmed diagnosis by culture drug-susceptibility or gene expert tests. Symptom free successfully treated patients with tuberculosis who completed their treatment or were cured of their illness after taking first-line tuberculosis treatment were taken as controls. Drug resistant tuberculosis patients (the cases) follow their treatment as inpatient for the first 8 months and as outpatient for the next 12 months (FMOHOE 2014b). Therefore, both inpatients and outpatients were used when sampling the cases. The controls (Patients successfully treated by first-line tuberculosis treatment) were all outpatients as the treatment modality of drug susceptible tuberculosis is outpatient care (FMOHOE 2014a).

1.10.3 Setting and population of the study

The current study was conducted at referral drug resistant tuberculosis treatment hospitals located in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia. The hospitals where the study was conducted provide treatment-initiating service to patients with drug resistant tuberculosis. These hospitals also treat patients with drug
susceptible tuberculosis. The six hospitals used as a study setting were Gondar University Hospital, Adama Hospital, Hawasa Hospital, Mekele Hospital, Dire Dawa Hospital and Saint Peter Hospital.

The study population was composed of patients with drug resistant tuberculosis and patients with successful first-line tuberculosis treatment outcome. Patients with drug resistant tuberculosis who took at least one first-line tuberculosis treatment in the past and were on treatment at the treatment initiating hospitals during the study period, were used as cases. Controls were patients treated with first-line tuberculosis treatment at the same hospitals giving treatment for the cases. These controls were tuberculosis symptom free patients who were cured of tuberculosis or had successfully completed first-line tuberculosis treatment during the study period. Drug resistant tuberculosis patients (the cases) follow their treatment as inpatient for the first 8 months and as outpatient for the next 12 months (FMOHOE 2014b). Therefore, both inpatients and outpatients were used when sampling the cases. The controls (Patients successfully treated by first-line tuberculosis treatment) were all outpatients as the treatment modality of drug susceptible tuberculosis is outpatient care (FMOHOE 2014a).

1.10.4 Sample and sampling methods

The sample size was determined based on the needed statistical power of the study, expected odds, size of the exposure and desired significance level (Keogh & Cox 2014:20). The current study had an 80% statistical power or probability of finding the real causes of the development of drug resistant tuberculosis. The significant factor determining the occurrence of drug resistant tuberculosis was expected to have an odds ratio (OR) of two or more. The current study assumed that 20% of the controls might have an exposure similar to the cases. A 0.05 significance level was used.
Taking into consideration the above statistical factors, 181 cases and 181 controls were enrolled into the study after a scientific calculation, which is described in detail in chapter 3. In the study regions, the number of patients with drug resistant tuberculosis enrolled into treatment annually was larger than the calculated sample size. Thus, an adequate number of cases were obtained. The controls were also enrolled in the study regions in larger proportion. A 10% increment in sample size was considered taking into consideration the non-respondents from the study population.

Systematic random sampling technique was used to select the respondents of the study (Salazar, Crosby & DiClemente 2015:155). The next person listed on the treatment and follow-up register was enrolled into the study whenever a selected person refused to be part of the study. Patients who were willing to be enrolled into the study and gave written consent were interviewed.

1.10.5 Data collection methods and procedures

Data asking for information on the possible determinants of the occurrence of drug resistant tuberculosis were collected using a structured questionnaire developed by the researcher. Primary data from the study respondents and secondary data from their treatment follow-up registers were collected using this questionnaire. The main variables in the questionnaire included socio-demographic characteristics, factors affecting treatment adherence and tuberculosis treatment follow-up indicators.

Trained physicians, nurses and health officers under the direct supervision of the principal researcher collected the data. A one full day training was given to these health professionals who collected the data. To ascertain the validity and reliability of information gathered by the questionnaire, the data collectors were given an explanation on each question. The data collectors were made to know the meaning of technical words used, purpose of each question or
what it intended to measure and the sources of information or data. Instructions on the questionnaire reminded the data collectors how to proceed while collecting the data. To minimize recall bias, the respondents mother tongue (first) language was used, the questionnaire was carefully designed though it could not be totally avoided and guiding events like holidays and national events were used by the data collectors to help the respondents remember the time of past occurrences.

A pre-test was performed on the questionnaire before it was used for the large-scale study. The researcher conducted a sample data collection on 40 patients involving both cases and controls equally. These 40 patients used for pretesting the questionnaire were not included in the sample of the main study. Based on the knowledge acquired from sample data collected, the questionnaire was modified to make it feasible.

1.10.6 Data management and analysis

Data collected was entered into data entry software of Epi-data version 7. The SPSS (Statistical packages for social sciences) Statistics version 23 software was used for data analysis. The frequencies of each variable was initially tabulated. This ascertained data completeness and consistency.

Categorical variables were selected and analysed with bivariate analysis. This is to test the relationship between the dependent variable drug resistant tuberculosis and the independent presumed risk factors. The strength of this relationship between the probable risk factors and drug resistant tuberculosis was measured using odds ratio (Lamorte 2015: 5).
Multiple logistic regression analysis was used to take out the confounding effect of different variables on the result. Then the effect of each variable on determining of the occurrence of drug resistant tuberculosis was assessed. Independent study variables having a p-value of less than or equal to 0.05 in bivariate analysis were added in the multivariate logistic regression analysis (Keogh & Cox 2014:84).

1.10.7 Ethical considerations

Before filling in the questionnaire, the data collectors informed the respondents of the study who were 18 years and older about the aim of the study. Additionally, the study patients were ascertained that their identity would not be documented and the information they gave would be kept confidential. A pre-prepared information leaflet about the aim of the study and confidentiality was read for every study patient to address these issues.

If a patient agreed to be enrolled into the study and gave verbal and written consent, the data collector proceeded to the interview. If any patient declined to participate, his or her decision was respected and he or she was excluded from the study. For study respondents whose age were below 18 years, parental or guardian consent was obtained. The steps followed while obtaining parental or guardian permission were similar to those followed for those who were 18 years and older.

The major risk associated with drug resistant tuberculosis is stigma and discrimination. A patient with drug resistant tuberculosis is stigmatised and discriminated in Ethiopia because of fear (FMOHOE 2014b). The fear is created by the aerosol transmission and the difficult treatment modality of drug resistant tuberculosis. All the necessary precautions were taken in the current study not to document the name and home address of study respondents on the questionnaire to ensure confidentiality. Study respondents were interviewed privately. All the information given by the study respondents was solely used for the study purpose.
An informative letter about the aim of the study was submitted to all health facilities included in the study together with the ethical clearance from University of South Africa with reference number of “REC-012714-039; HSHDC/448/2015”. A support letter written to tuberculosis clinics of the health facilities to allow conducting the study was also obtained from the medical directors of each health facility.

1.11 SCOPE AND LIMITATIONS OF THE STUDY

The study was conducted in six of the eleven administrative regions of Ethiopia. The study revealed the situation of drug resistant tuberculosis in these six regions. The study findings can be taken as reference for drug resistant tuberculosis prevention activities in the rest of the five regions of Ethiopia. The study finding can also serve as baseline information for future country level national study by the Ethiopian government.

The six study regions have a relatively higher burden of drug resistant tuberculosis than the other regions in Ethiopia. However, it is still not the exact representation of the Ethiopian or other Ethiopian regions’ drug resistant tuberculosis burden. The determinants of the occurrence of drug resistant tuberculosis in the study regions might not have necessarily reflected the exact picture in the other regions not included in the study.

The eleven regions in Ethiopia have many similar features with regard to drug resistant tuberculosis. However, it cannot be said that they have absolutely the same features. These factors of representativeness can be taken as limitations of the study.
1.12 CHAPTER LAYOUT OF THE THESIS

This thesis has seven chapters and the bibliography. The contents of each section are briefly explained here.

CHAPTER 1: ORIENTATION TO THE STUDY

This chapter introduces the thesis and gives an overview of the entire study. It gives the background information on drug resistant tuberculosis from worldwide, African and Ethiopian perspectives. It also incorporates the statement of the problem, research aim and questions, objectives of the study and paradigms of the research. A brief description of the research design and methodology is also included in this chapter.

CHAPTER 2: LITERATURE REVIEW

This chapter presents the different literature sources reviewed on determinants of the occurrence of drug resistant tuberculosis. Peer reviewed research from international journals, books, websites and other publications was used to write the literature review. The literature review was organized in such a way that it starts by reviewing the general knowledge on drug resistant tuberculosis, proceeds to literature from global studies, the Americas, Europe, Asia and Africa. Finally, the chapter closes by reviewing literature sources from studies conducted in Ethiopia.

CHAPTER 3: RESEARCH METHODOLOGY AND RESEARCH DESIGN

Chapter 3 focuses on the research design and methodology used by the researcher to conduct the current study. The study setting, study population and sampling methods are
explained in this chapter. Data collection and data analysis methods are also elaborated here. Ethical considerations constitute the final section of this chapter.

CHAPTER 4: RESEARCH RESULTS

Chapter 4 presents the results of the current study. The research results are presented in narrative and table form. The number and percentage of each independent variable is displayed for the cases and controls. The reporting of the results was organized in such a way that it first displays different factors presumed to cause the development of drug resistant tuberculosis separately and then together in the analysis section.

CHAPTER 5: THE DEVELOPMENT OF CONCEPTUAL MODEL

This chapter describes how the conceptual model for drug resistance tuberculosis was developed.

CHAPTER 6: DISCUSSION

This chapter gives an explanation on the research results on the presumed causes of the development of drug resistant tuberculosis. It explains the results of the research by comparing it with literature, which has results similar or dissimilar to the current study’s results. It reasons out why the study results were the same as or different from the results of other studies conducted in Ethiopia, Africa and the rest of the world.
CHAPTER 7: CONCLUSIONS AND RECOMMENDATIONS

Chapter 7 concludes the study by summarizing the statistically significant determinants of the occurrence of drug resistant tuberculosis. Based on the conclusions, recommendations are presented for future action. This chapter also contains the contributions and limitations of the study.

LIST OF REFERENCES

All literature sources used in the current study are documented here in alphabetical order. The writings and the contents of each reference line were carefully organized following the instructions of University of South Africa’s manual for thesis writing.

1.13 SUMMARY

This chapter gave an orientation to the main aspects of the current study. It gave background information on drug resistant tuberculosis and outlined the objectives of the current study. A summary of the research methodology and design used in the current study were also given. The current study looked into factors making Ethiopian patients develop drug resistant tuberculosis with the goal of showing ways of tackling this public health catastrophe effectively. It was conducted taking into consideration, places where the burden of drug-resistant tuberculosis was higher by relative comparison. All necessary scientific methods and ethical principles were strictly followed during the whole course of the study.
2.1 INTRODUCTION

Drug resistant tuberculosis is a type of tuberculosis, which is either multidrug-resistant or rifampicin resistant. Multidrug-resistant tuberculosis is tuberculosis resistant to at least both first line anti-tuberculosis drugs, rifampicin and isoniazid. Rifampicin resistant tuberculosis is tuberculosis resistant to the anti-tuberculosis drug rifampicin detected using phenotypic or genotypic methods (WHO 2018a). Drug-resistant tuberculosis is confirmed by the phenotypic method using culture and drug susceptibility testing or genotypic method using gene x-pert test (CDC 2017).

The main reasons for emergence and spread of drug resistance tuberculosis are mismanagement of tuberculosis treatment and person-to-person transmission (WHO 2018d). Inappropriate use of antimicrobial drugs and premature treatment discontinuation can cause drug resistance that can then be transmitted from person-to-person (WHO 2018d). Although there are advances in other areas of medicine, the control of tuberculosis remains challenging and in 2016 tuberculosis was the leading infectious cause of death worldwide (Wright, Tomlinson, Rangaka & Fletcher 2018:217).

Different literature sources reviewed on the basic known facts about drug resistant tuberculosis and on determinants of the occurrence of drug resistant tuberculosis are presented in this chapter. Peer reviewed researches on drug resistant tuberculosis from international journals, books, websites and other publications are included in this literature review. This literature review chapter started by reviewing the general knowledge on drug resistant tuberculosis and proceeds to literature sources from global studies, the Americas,
Europe, Asia and Africa. The chapter ends by reviewing literature sources from studies conducted on drug resistant tuberculosis in Ethiopia.

2.2 CONCEPT OF DRUG RESISTANT TUBERCULOSIS

“Drug resistant tuberculosis is a disease caused by mycobacterium tuberculosis bacteria that are spread from person to person through droplet inhalation” (CDC 2017). Drug resistant tuberculosis usually affects the lungs, but it can also infect any part of the body, like the bones and intestine. Drug resistant tuberculosis develops when mycobacterium tuberculosis bacteria become non-susceptible to the drugs used to treat tuberculosis. This means that the anti-tuberculosis drugs are not able to kill mycobacterium tuberculosis bacteria (CDC 2017).

Resistance to anti-tuberculosis drugs is a natural phenomenon occurring in all wild type populations of mycobacterium tuberculosis by spontaneous chromosomal mutations (FMOHOE 2014b). This means through time the chromosomes of mycobacterium tuberculosis bacteria develop change in their Deoxyribonucleic acid (DNA) structure by nature. The selection of naturally occurring drug resistant mutant bacteria by inadequate tuberculosis treatment is the main reason for the population of mycobacterium tuberculosis bacteria to become increasingly drug resistant. As the drug-susceptible bacteria are killed by sub-optimal treatment, the drug resistant mutant bacteria gradually become an increasing proportion of the bacteria, and this result in the emergence of a drug resistant form of tuberculosis (FMOHOE 2014b).

“Drug resistance among new tuberculosis patients refers to resistance in patients who have no history of treatment for tuberculosis for a period longer than one month. This is also called primary drug resistance” (FMOHOE 2017). The patient acquires the mutated drug resistant
“Drug resistance among previously treated tuberculosis patients or secondary drug resistance refers to resistance in patients who have been treated for tuberculosis for a period lasting more than one month” (FMOHOE 2017). Inappropriate sub-optimal treatment leads to the amplification of mutated drug resistant mycobacterium tuberculosis bacteria in these patients (FMOHOE 2017).

2.3 DIAGNOSIS OF DRUG RESISTANT TUBERCULOSIS

“The WHO’s end tuberculosis strategy advocates early diagnosis and initiation of proper treatment of all persons of all ages with any form of drug susceptible tuberculosis or drug resistant tuberculosis” (WHO 2015d). This requires ensuring access to the WHO’s recommended laboratory tests and universal drug susceptibility testing for all patients with signs and symptoms of tuberculosis. There are a number of laboratory tests available for the diagnosis of drug resistant tuberculosis like phenotypic culture-based drug susceptibility testing and molecular methods (WHO 2015d).

“Phenotypic, culture methods are based on the analysis of the ability of mycobacterium tuberculosis to grow in culture media containing a critical concentration of specific anti-tuberculosis agents (which is resistance) or, conversely, its inability to grow in the same media (susceptibility)” (Ängeby, Juréen, Kahlmeter, Hoffner & Schön 2012:693). “A critical concentration is the lowest concentration of anti-tuberculosis drugs that inhibit the growth of wild strains of mycobacterium tuberculosis that have never been exposed to tuberculosis drugs, while at the same time not inhibiting clinical strains of mycobacterium tuberculosis that are considered resistant.” Liquid culture can give result in only 10 days, unlike the 28 to 42 days by solid media (Ängeby, Juréen, Kahlmeter, Hoffner & Schön 2012:693).
“Molecular (genotypic) methods detect specific deoxyribonucleic acid mutations in the genome of the mycobacterium tuberculosis, which leads to resistance to specific anti-tuberculosis drugs.’ These tests currently include gene x-pert and line probe assays. Line probe assays have the advantage of detecting mutations causing resistance to both isoniazid and rifampicin but are done only on sputum smear–positive specimens or cultured isolates of mycobacterium tuberculosis. Gene x-pert detects mutations in the rifampicin resistance-determining region, which are associated with rifampicin resistance with very high sensitivity (WHO 2016a).

2.4 DRUG RESISTANT TUBERCULOSIS VERSUS DRUG SUSCEPTIBLE TUBERCULOSIS

Drug resistant tuberculosis is transmitted in a similar way that drug susceptible tuberculosis is transmitted (CDC 2017). Tuberculosis is spread through the air from one person to another. The tuberculosis bacteria are released into the air when a patient with tuberculosis disease of the lungs or throat coughs or sneezes. Persons nearby may inhale these bacteria and become infected (CDC 2017).

There are no differences in the clinical manifestations of drug resistant tuberculosis from the susceptible ones (Laborín 2018:18). A cough of two or more weeks is the main symptom with or without fever, chest pain, haemoptysis, and significant weight loss. Patients with the drug resistant form of tuberculosis can never be differentiated from those with the drug susceptible tuberculosis using clinical evaluation, smear acid fast bacilli tests or chest x-ray (Laborín 2018:18).

The main differences between drug resistant tuberculosis and drug susceptible tuberculosis lie in their diagnostic and treatment modalities (Gupta 2015:32). An acid-fast bacilli test and chest x-ray confirm the presence of mycobacterium tuberculosis bacteria and the tuberculosis disease respectively but do not tell if it is resistant or sensitive to anti-tuberculosis drugs. Phenotypic
(culture tests) and genotypic (molecular tests) are needed to diagnose drug resistant mycobacterium tuberculosis bacteria (Gupta 2015:32).

Drug susceptible tuberculosis treatment takes from 6 to 12 months depending on the site of the disease and the outcome of the previous tuberculosis treatment (WHO 2017). Drug resistant tuberculosis treatment on the other hand, may take from 20 to 36 months until a complete cure is achieved. Drug susceptible tuberculosis treatment uses the drugs isoniazid, rifampicin, pyrazinamide and ethambutol, which are called first-line drugs. Second-line drugs like capreomycine, levofloxacin, prothionamide and cycloserine are used in the treatment of drug resistant tuberculosis (WHO 2016b, WHO 2017).

2.5 DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS

2.5.1 Determinants of the occurrence of drug resistant tuberculosis in Europe and North America

Gomes, Correia, Mendonça and Duarte (2014:111) studied the determinants of the occurrence of drug resistant tuberculosis on tuberculosis patients in northern Portugal. Multivariate conditional logistic regression identified the independent predictors for drug resistant tuberculosis. Diabetes mellitus, intra-venous drug use and previous tuberculosis treatment were found to be determinants of the occurrence of drug resistant tuberculosis.

Scientists from United States of America and Europe, Sergeev, Colijn, Murray and Cohen (2012:67), studied the association between HIV and the risk of drug resistant tuberculosis. “Whereas HIV facilitates the emergence of multidrug-resistant tuberculosis within a community over several decades, HIV seropositive individuals presenting with tuberculosis may counterintuitively, be at a lower risk of drug resistant tuberculosis at the early stages of the co-epidemic”. This is due to many individuals with incident HIV infection already harbouring latent
mycobacterium tuberculosis infection acquired at an earlier time when drug resistance was less prevalent. The study found that the rise of HIV could increase the prevalence of multidrug-resistant tuberculosis within populations. “Social mixing among individuals with similar HIV status and lower average CD4 (Cluster of Differentiation 4) counts among HIV-seropositive individuals further increases the expected burden of multidrug-resistant tuberculosis.”

Faustini, Hall and Perucci (2006:158) conducted a systematic review of 29 papers on risk factors associated with multidrug-resistant tuberculosis in Europe. “The pooled risk of multidrug-resistant tuberculosis was 10.23 times higher in previously treated than in never treated cases, with wide heterogeneity between studies.” The risk was higher in cohort studies carried out in Western Europe than in Eastern Europe. “Multidrug-resistant tuberculosis cases were more likely to be foreign born, younger than 65 years, male and HIV positive.”

**2.5.2 Determinants of the occurrence of drug resistant tuberculosis in South America**

Jacobs, Pelissari and Pinto studied (2018:675) factors associated with the drug resistant tuberculosis incidence rate in Brazil. In the multilevel model, males and black persons had a higher risk of drug resistant tuberculosis. “Compared with those aged above 60 years, persons aged 15-59 years also had a higher risk.” The following contextual factors were also associated with the incidence rate of drug resistant tuberculosis: proportion of previously treated patients and acquired immune-deficiency syndrome.

An ecological study was conducted in 26 Latin American countries that had data on 38 selected variables. “Tuberculosis-HIV co-infection and multidrug-resistant tuberculosis in previously treated tuberculosis cases were found to be positively associated with tuberculosis” (Bergonzoli, Castellanos, Rodríguez & García 2016:101).
A team of experts directly investigated the impact of HIV co-infection on the evolution of drug resistant tuberculosis emergence and on the transmission dynamics in South America. The study found that HIV co-infection does not affect the transmission or the mutation rate of mycobacterium tuberculosis. It was not associated with an increased drug resistance within patients. The study results indicated that HIV is an amplifier of tuberculosis outbreaks by making individuals susceptible, but that HIV co-infection does not have impact the emergence and transmission of resistant strains (Eldholm, Rieux, Monteserin, Lopez, Palmero, Lopez, Ritacco, Didelot & Balloux 2016:5).

A study in Peru assessed the epidemiological characteristics of patients with multidrug-resistant tuberculosis with and without diabetes. The study found out that patients aged over 35 years and being overweight or obese were significantly associated with the development of drug resistant tuberculosis in diabetic patients (Gil, Alarcon, Figueroa, Moore & Golub 2016:313).

2.5.3 Determinants of the occurrence of drug resistant tuberculosis in Asia

The significant risk factors for multidrug-resistant tuberculosis identified in a study in Nepal included HIV sero-positivity, travel cost, contact history of tuberculosis, living in a nuclear family and non-adherence to tuberculosis treatment. Distance to treatment centres more than 5 Kilometers, previous history of tuberculosis, living in a rural area, unmarried and un-employment were also other positive significant predictors for multidrug-resistant tuberculosis in Nepal (Bichha, Jha, Salhotra, Weerakoon, Karki & Bichha 2017:31).

Another study conducted in Nepal, Sita (2017:548), identified irregularity in taking medicine, large family size, farming as an occupation, past history of tuberculosis and bovine at home as statistically significant risk factors for multidrug-resistant tuberculosis. Males and individuals in the age group 21 to 30 years were also found to be highly prone to multidrug-resistant tuberculosis. On the contrary to this finding, another study conducted in the same country of
Nepal by Maharjan, Singh, Khadka & Aryal (2017:106), showed that females were significantly associated multidrug-resistant tuberculosis.

Patterns of drug resistance and risk factors associated with the development of drug resistant mycobacterium tuberculosis were studied in Pakistan. “The risk factors for the development of multidrug-resistant tuberculosis were in the early age range from 10 to 25 years and previously treated tuberculosis patients” (Ullah, Javaid, Tahir, Ullah, Shah, Hasan & Ayub 2016:11).

Determinants of multidrug-resistant tuberculosis among patients with pulmonary tuberculosis were assessed at the Central Chest Institute of Thailand. Multivariate analysis identified the independent risk factors for multidrug-resistant tuberculosis to be 2 or more episodes of prior pulmonary tuberculosis, a duration of illness of more than 60 days and a sputum acid fast bacilli smear 3 plus. “Added to this, the presence of lung cavities and pleural effusion, prior pulmonary tuberculosis management with a non-category 1 regimen and having treatment failure or default as treatment outcomes were observed in a higher proportion among patients with multidrug-resistant tuberculosis” (Chuchottaworn, Thanachartwet, Sangsayunh, Than, Sahassananda, Surabotsophon & Desakorn 2015:10).

A retrospective review of data was conducted from follow-up documents of 3552 patients attending a tuberculosis clinic in Dalian, China between 2012 and 2015. These patients were smear positive for mycobacterium tuberculosis. The review showed that the history of previous tuberculosis treatment and older age of 60 or more were associated with multidrug-resistant tuberculosis (Lv, Lu, Shi & Zhou 2017:1779).

A case-control study was conducted on risk factors for the development of multidrug-resistant tuberculosis in Bangladesh. History tuberculosis treatment was found to be the main determinant of multidrug-resistant tuberculosis. “The study also identified age 18 to 45 years, some education up to secondary level, service and business as the occupation, past smoking
status, and type 2 diabetes as well as comorbid illness as risk factors” (Rifat, Milton, Hall, Oldmeadow, Islam, Husain, Akhanda & Siddiquea 2014:8).

A retrospective study on epidemiological trends of drug resistant tuberculosis in China conducted from 2007 to 2014 identified a previous tuberculosis treatment history as one significant factor for the development of multidrug-resistant tuberculosis. Patients with multidrug-resistant tuberculosis were more likely to be female, aged 25 to 44 years, having prior tuberculosis contact and having cavity or bilateral disease on chest radiology. (Xiao-chun, Xian-xin, Jiang-nan, Yao, Chun-bao, Guo-ru & Huai-chen 2016:15)

The trend of drug resistance and determinants of the occurrence of drug resistant mycobacterium tuberculosis were studied in Pakistan. “Risk factors for the development of multidrug-resistant tuberculosis were early age (ranges between 10–25 years) and previous tuberculosis treatment” (Ullah, Javaid, Tahir, Ullah, Shah, Hasan & Ayub 2016:1).

2.5.4 Determinants of the occurrence of drug resistant tuberculosis in Africa

Berhan, Berhan and Yizengaw (2013:271) conducted a meta-analysis of 30 articles on drug resistant tuberculosis in Sub-Saharan Africa. “The pooled analysis showed that the risk of developing drug resistant tuberculosis to at least one anti-tuberculosis drug was about 3 times higher in individuals who had a previous history of tuberculosis treatment than new tuberculosis cases.” The likelihood of having drug resistant tuberculosis in previously tuberculosis treated cases was more than five times higher than that of new tuberculosis cases. However, HIV infection was not the determinant of the occurrence of drug resistant tuberculosis.

A study assessed the risk factors associated with drug resistant tuberculosis in rural Eastern Cape, South Africa. “High rates of drug resistant tuberculosis among treatment-naive patients, compounded with prevalent cases of relapses and defaulters among previously treated patients
raise the importance of drug resistant tuberculosis acquisition through direct transmission rather than the evolution of resistance.” Females were more likely to contract and develop extensively drug-resistant tuberculosis than males (Fotso, Vasaikar & Apalata 2018:384).

A national survey conducted in South Africa, one of the high burden drug resistant tuberculosis countries in Africa, assessed the determinants of multidrug-resistant tuberculosis (Weyer, Brand, Lancaster, Levin and Van der Walt 2007:1120). This study states that previous tuberculosis treatment or retreatment, tuberculosis treatment failure, tuberculosis treatment defaulting and previous hospitalizations were significantly associated with the development of drug resistant tuberculosis.

A study conducted in a rural community in the Tugela Ferry district of South Africa, Andrews (2010:12), states that a history of prolonged hospitalization and previous tuberculosis treatment failure were risk factors for both multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. Philip, Farai, Surbhi, Rosalia, Abbas, Lauren, Nick, Jamie, Allyn and Timothy’s (2012:385) study on the characteristics of multidrug-resistant tuberculosis echoes the findings of previous studies by Weyer et al (2007:1120) and Andrews (2010:12). According to Philip et al (2012:385), previous TB treatment, previous hospitalization and household contact with a drug-resistant tuberculosis case were associated with drug-resistant tuberculosis.

A case-control study was conducted on 102 drug-resistant tuberculosis cases and an equal number of drug susceptible tuberculosis control patients at the Kibong’oto Infectious Disease Hospital in northern Tanzania. The statistically significant risk factors associated with multidrug-resistant tuberculosis were a previous history of treatment with first-line anti-tuberculosis drugs, smoking, contact with tuberculosis case and a history of tuberculosis (Lema, Majigo, Mbelele, Abade & Matee 2016:4).
Pires, Folgosa, Nquobile, Gitta and Cadir (2014:142) analysed secondary data from the national tuberculosis referral laboratory, in the city of Maputo, Mozambique, and from the Beira regional tuberculosis referral laboratory, in the city of Beira, Mozambique. “Multidrug-resistant tuberculosis was most common in males, particularly those in the 21-40 year age bracket.” Multidrug-resistant tuberculosis was also high in previously treated patients.

A systematic review and meta-analysis of 27 articles was conducted on risk factors of drug-resistant tuberculosis in sub-Saharan Africa. The study reviewed the drug susceptibility testing results for a total of 13,465 new and 1,776 previously treated tuberculosis patients. Pooled estimates of any drug-resistant tuberculosis prevalence among previously treated tuberculosis patients was significantly higher than drug-resistant tuberculosis prevalence among new tuberculosis patients. Multidrug-resistant tuberculosis in this region was not driven by the high HIV prevalence rates (Lukoye, Sengooba, Musisi, Kasule, Cobelens, Joloba & Gomez 2015:291).

2.5.5 Determinants of the occurrence of drug-resistant tuberculosis in Ethiopia

Biadglegne, Sack and Rodloff (2014:31) conducted a systematic review of 23 articles on drug-resistant tuberculosis in Ethiopia. Some of these articles tried to assess determinants of the occurrence of drug-resistant tuberculosis in Ethiopia. HIV/AIDS (Human immunodeficiency virus/Acquired Immune Deficiency Syndrome), previous exposure to tuberculosis treatment and exposure to a known drug-resistant tuberculosis case were the determinants of the occurrence of drug-resistant tuberculosis. “Added to this, a history of using poor quality tuberculosis drugs, treatment in a poorly performing control programme, mal-absorption, treatment not directly observed by a health worker, being male and failure of first-line short-course chemotherapy were found to be associated with the increased risk of drug-resistant tuberculosis in Ethiopia.” History of exposure to anti-tuberculosis drug treatment was found to be the most powerful predictor of drug-resistant tuberculosis incidence reported, followed by HIV/AIDS.
A study conducted in Addis Ababa, Ethiopia, assessed factors that might determine the development of multidrug-resistant tuberculosis in patients 5 years old and above. “According to Hirpa, Medhin, Girma, Melese, Mekonen, Suarez and Ameni (2013:782), drug side effects during first-line treatment, treatment not directly observed by a health worker, interruption of treatment for at least a day, duration of treatment between 2 and 7 months and retreatment with the category II regimen were significantly associated with the development of drug-resistant tuberculosis.” In this study, HIV infection was not the determinant of the occurrence of drug-resistant tuberculosis.

Assefa, Seyoum and Oljira (2017:209) identified independent determinants for multidrug-resistant tuberculosis in two hospitals in Addis Ababa. “The study states that determinants for multidrug-resistant tuberculosis were a history of previous tuberculosis treatment, failure to disclose tuberculosis disease to others or social stigma, a history of hospitalization due to tuberculosis, contact history with a known tuberculosis patient and sputum smear positivity.” Whereas, HIV co-infection and diabetes were not associated with multidrug-resistant tuberculosis. The history of previous tuberculosis treatment was the only statistically significant risk factor for drug-resistant tuberculosis in the districts of Metemma and west Armachiho, Northwest Ethiopia (Mekonen, Tessema, Moges, Gelaw, Eshetie & Kumera 2015:461). A systematic review and meta-analysis of studies conducted on multidrug-resistant tuberculosis in the Ethiopian settings also found out that previous tuberculosis treatment was the most powerful predictor for multidrug-resistant tuberculosis infection (Eshetie, Gizachew, Dagnew, Kumera, Woldie, Ambaw, Tessema & Moges 2017:219).

Desissa, Workineh and Beyene (2018:422) assessed the risk factors for the development of multidrug-resistant tuberculosis among patients undergoing multidrug-resistant tuberculosis treatment in East Shoa, Ethiopia. “The study states that a history of contact with known tuberculosis patient, previous first-line tuberculosis treatment, being a rural resident, being
unemployed and alcohol drinking were determinants of the occurrence of multidrug-resistant tuberculosis.”

Being a farmer by occupation, tuberculosis contact history, alcohol use, HIV infection, a previous tuberculosis history and a previous unfavourable tuberculosis treatment outcome were predictors of multidrug-resistant tuberculosis in a study conducted in the Oromia region of Ethiopia (Mulisa, Workneh, Hordofa, Suaudi, Abebe & Jarso 2015:57). Tuberculosis treatment failure and defaulting from tuberculosis treatment were taken as unfavourable tuberculosis treatment outcomes in this study conducted in Oromia region, which is the largest region in Ethiopia.

Another study assessed the determinants of the occurrence of multidrug-resistant tuberculosis in armed force hospital in Ethiopia. “The study found out that being a civilian and tuberculosis contact history were strong predictors of multidrug-resistant tuberculosis in armed force and civilian patients.” Moreover, HIV infection was also identified as determinant of the occurrence of multidrug-resistant tuberculosis among armed force members (Demile, Zenebu, Shewaye, Xia & Guadie 2018:249).

Predictors of multidrug-resistant tuberculosis in the south-western part of Ethiopia were assessed in a case control study. “Not disclosing tuberculosis infection to relatives, insufficient instructions on how to take anti-tuberculosis drug, contact history with multidrug-resistant tuberculosis, interruption of first-line tuberculosis treatment for at least 1 day and having alcohol drinking habits were identified predictors for multidrug-resistant tuberculosis infection in study area” (Gobena, Ameya, Haile, Abreha, Worku & Debela 2018:30).

Mulu, Mekonnen, Yimer, Admassu and Abera (2015:368) studied the risk factors for multidrug-resistant tuberculosis patients in the Amhara National Regional State. A total of 153 multidrug-resistant tuberculosis cases and an equal number of non-multidrug-resistant tuberculosis control
patients participated in the study. Patients who had tuberculosis treatment failure, cavitation on chest x-ray and contact with patients with multidrug-resistant tuberculosis were more likely to be patients with multidrug-resistant tuberculosis. Low monthly income, alcohol consumption and young age were the other risk factors of multidrug-resistant tuberculosis.

Workicho, Kassahun and Alemseged (2017:91) studied the risk factors for multidrug-resistant tuberculosis among patients with tuberculosis at the Saint Peter’s tuberculosis Specialized Hospital, Addis Ababa, Ethiopia. The case-control study conducted on 90 cases and 90 controls showed that the young age of 30 or less years, living in a household with only one room, a history of previous tuberculosis treatment and being HIV infected were statistically significant independent predictors of multidrug-resistant tuberculosis.

Dessalegn, Daniel, Behailu, Wagnew and Nyagero (2016:5) analysed the predictors of multidrug-resistant tuberculosis among adult patients at Saint Peter Hospital in Addis Ababa, Ethiopia. “The likelihood of having multidrug-resistant tuberculosis was 20.3 times higher among those who had a previous history of tuberculosis treatment than those with no previous history of tuberculosis treatment.” Added to this, having tuberculosis illness more than once, pulmonary tuberculosis and treatment with a category II regimen were associated with the development of multidrug-resistant tuberculosis. HIV infection was less prevalent among cases than controls.

Fikre, Tewelde and Shaweno (2019:1) conducted a case control study on determinants of multidrug-resistant tuberculosis among tuberculosis patients in Southern Ethiopia. Factors that independently predicted multidrug-resistant tuberculosis were time to reach a health facility taking more than three hours, history of contact with known patients with multidrug-resistant tuberculosis, patients with no formal education, patients who did not get counselling and patients who did not hear about multidrug resistant tuberculosis.
A systematic review and meta-analysis of 34 studies conducted in Ethiopia analysed the data of 7461 patients with tuberculosis or multidrug resistant tuberculosis. The study states that the history of previous tuberculosis treatment was the major determinant of the development of multidrug resistant tuberculosis. Contact history with a known patient with multidrug resistant tuberculosis and poor adherence to treatment of drug susceptible tuberculosis also significantly contributed to the development of multidrug resistant tuberculosis (Girum, Muktar, Lentiro, Wondiye & Shewangizaw (2018:5). Asgedom, Teweldemedhin and Gebreyesus (2018:8) also found previous exposure to tuberculosis treatment to be the most commonly identified risk factor of multidrug resistant tuberculosis in Ethiopia on a systematic review of 22 articles.

Worku, Getinet, Mohammed and Yang (2018:167) conducted a study, which characterized drug resistant tuberculosis cases in All Africa Leprosy, Tuberculosis, Rehabilitation and Training Hospital in Addis Ababa, Ethiopia. They found out that there was a significant age disparity between male and female cases with a high impact of drug resistant tuberculosis on productive adult male population in the age group of 25 to 44 years. A history of prior treatment with first-line anti-tuberculosis drugs and positive sputum smear microscopy results were the other factors, which were found to be significantly associated with the development of drug-resistant tuberculosis.

A cross-sectional study was conducted in Addis Ababa, Ethiopia, from June 2015 to December 2016. In this study, the prevalence of multidrug-resistant tuberculosis in the study population was of a significantly high level among previously treated patients with tuberculosis in the age group of 25 to 34. “HIV co-infection, smoking of cigarette, alcohol drinking, hospital admission and health facility visiting were identified as risk factors for developing multidrug resistant tuberculosis” (Mesfin, Beyene, Tesfaye, Admasu, Addise, Amare, Dagne, Yaregal, Tesfaye & Tessema 2018:6).
In contrast to the above studies, Biadglegne, Tessema, Rodloff and Sack (2013:1589) reported that newly treated patients with tuberculosis harbour multidrug-resistant tuberculosis in Ethiopia in a significant proportion. The study concluded that the development of multidrug-resistant tuberculosis had no significant association with a history of previous tuberculosis treatment. This study also showed that being male was a significant risk factor for the development of multidrug-resistant tuberculosis, which was not confirmed by other studies, conducted in Ethiopia.

2.6 SUMMARY

As can be summarized from the literature review presented in this chapter, drug resistant tuberculosis is a major public health problem in developing countries in Africa, Asia and South America although the extent of burden varies from country to country. Different factors were found to be predictors of the development of drug resistant tuberculosis in studies conducted in the 5 continents of the world as reviewed in this chapter. However, previous tuberculosis treatment history was the most common significant determinant of the occurrence of drug resistant tuberculosis in the majority of the literature sources reviewed.

In Ethiopia, studies were conducted to assess factors leading to the development of drug resistant tuberculosis. These studies also found different predictors of development of drug resistant tuberculosis with previous tuberculosis treatment history being the most common significant finding. The studies conducted in Ethiopia were limited to either a specific health facility or a specific district of the country. The current study was different in that it assessed the determinants of the occurrence of drug resistant tuberculosis in a wider perspective from the different regions of Ethiopia.
CHAPTER 3
RESEARCH METHODOLOGY AND RESEARCH DESIGN

3.1 INTRODUCTION

This chapter explains in detail the research methodology and the research design used in the current study. There are sections in this chapter, which show how sampling was done from the study population. The study settings, the study population and the sample population used in the current study are elaborated on in specific sections of this chapter.

All the steps from data collection to data analysis are elaborated on in this chapter section by section. It chapter also includes a description of the data collection instrument with regards to its characteristics. It also explains how the data collection instrument was tested before it was used for the current study. There is a section in this chapter on the data collection process, which explains how and by whom the data was collected during the current study. The statistical methods used in the current study to analyse the data collected also make a section in this chapter.

Ethical issues related to both sampling and data collection received due attention in the current study. These ethical issues are explained in this chapter. Added to this, the validity and reliability of this study is discussed based on scientific explanations. Different reasoning strategies and research paradigms are discussed in detail in the separate sections of this chapter. The reasoning strategy and the research paradigm used in the current study are also discussed with regard to the reasons for choosing the specific reasoning strategy and research paradigm.

This chapter ends by summarizing the detailed explanations given on the research methodology and the research design used in the current study.
3.2 RESEARCH METHODOLOGY

“According to Rajasekar, Philominathan and Chinnathambi (2013:5), research methodology is a systematic way to solve a problem. It is a science of studying how research is to be carried out.” Essentially, the steps researchers follow to describe, explain and predict a phenomena are called research methodology. “Research methodology is also defined as the study of methods by which knowledge is gained” (Rajasekar, Philominathan & Chinnathambi 2013:5). Creswell (2014:31) describes research methodology as a way of conducting a study including data collection, analysis, and interpretation.

“The aim of research methodology is to give the work plan of research. This plan involves several decisions like which approach should be used to study a topic, the philosophical assumptions the researcher brings to the study, procedures of inquiry and specific research methods of data collection, analysis, and interpretation” (Creswell 2014:31; Rajasekar, Philominathan & Chinnathambi 2013:5). The selection of research method depends on the type of the problem studied, the researcher and the study subjects (Creswell 2014:31).

As stated in Rajasekar, Philominathan and Chinnathambi (2013:6), research methodology is different from research method. “Research methodology refers to which method, formula or algorithm has to be used out of the various existing methods, formulae, or algorithms, while research methods help the researcher get a solution to a problem.” The study of research methods trains the researcher. The study of research methodology guides in choosing methods, materials, scientific tools and training for the research.

“According to Rajasekar, Philominathan and Chinnathambi (2013:6), research methodology is concerned with the explanation of the following:
1. Why is a particular research study undertaken?
2. How did one formulate research problem?
3. What types of data were collected?
4. What particular method has been used?
5. Why was a particular technique of analysis of data used?”

Creswell (2014:32) divides research methodologies into three types, which are qualitative, quantitative and mixed methods. These methodologies are not as discrete as they appear. A study tends to be qualitative than quantitative or vice versa. Mixed methods research incorporates elements of both qualitative and quantitative approaches (Creswell 2014:32).

“Qualitative research is an approach for exploring and understanding the meaning individuals or groups ascribe to a social or human problem” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9). The process of research involves questions and procedures, data collection, data analysis and the researcher making interpretations of the meaning of the data. The final written report is variable. Some use an inductive style; focus on an individual meaning and the importance of the situation. “Qualitative research uses words and open-ended questions. Qualitative methods like interviews are best for describing, interpreting, contextualizing, and gaining in-depth insight into specific concepts or phenomena. It investigates the why and how of decision-making” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9).

“Quantitative research is an approach for testing objective theories by examining the relationship among variables” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9). These variables are being measured on instruments and numbered data are analysed using statistical procedures. It tests theories deductively building in protections against bias, controlling for alternative explanations, and being able to generalize and replicate the findings. “Quantitative research uses numbers and closed-ended questions. Quantitative methods like surveys are best for measuring, ranking, categorizing, identifying patterns and generalizing. It investigates the what, where and when of decision-making” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9).
“Mixed methods research is an approach to inquiry involving collecting both quantitative and qualitative data, integrating the two forms of data, and using distinct designs that may involve philosophical assumptions and theoretical frameworks” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9). It assumes that that the combination of qualitative and quantitative approaches provides a more complete understanding of research problem. “Mixed methods allow for a combination of numerical measurement and in-depth exploration” (Creswell 2014:32; McCombes 2019; Rajasekar, Philominathan & Chinnathambi 2013:9).

This study aimed to examine the relationships between different pre-defined factors and the development of drug resistant tuberculosis. It planned to examine these relationships by using numbers and closed-ended questions to produce generalizable knowledge on the development of drug resistant tuberculosis. Thus, the quantitative research methodology was used in the current study.

3.3 RESEARCH DESIGN

“Research design is a framework of methods and techniques chosen by researcher to combine various components of research in a reasonably logical manner so that the research problem is efficiently handled” (Bhat 2019; University of Southern California 2019b). It provides insights about how to conduct research using a particular methodology and constitutes the blueprint for the collection, measurement, and analysis of data. The research problem determines the type of design researcher should use (Bhat 2019; University of Southern California 2019b).

“According to research guides, there are different types of research designs and some of them are briefly defined below (Georgia State University 2019). “
“Meta-Analysis: A way of combining data from many different research studies. A meta-analysis is a statistical process that combines the findings from individual studies.”

“Systematic Review: A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue.”

“Randomized Controlled Trial: A controlled clinical trial that randomly (by chance) assigns participants to two or more groups.”

“Cohort Study (Prospective Observational Study): Clinical research study in which people who presently have a certain condition or receive a particular treatment are followed over time and compared with another group of people who are not affected by the condition.”

“Case-control Study: Case-control studies begin with the outcomes and do not follow people over time. Researchers choose people with a particular result (the cases) and interview the groups or check their records to ascertain what different experiences they had. They compare the odds of having an experience with the outcome to the odds of having an experience without the outcome.”

“Cross-sectional study: The observation of a defined population at a single point in time or time interval. Exposure and outcome are determined simultaneously.”

The current study used case-control research design, as it was found to be the best design to find determinants of the occurrence of drug resistant tuberculosis. The study began with the outcome of drug resistant tuberculosis. The researcher chose patients with drug resistant tuberculosis (the cases), interviewed them and checked their records to ascertain what different experiences they had. The researcher compared the odds of having an experience with drug
resistant tuberculosis to the odds of having an experience without drug resistant tuberculosis or patients with successful first-line tuberculosis treatment outcome (the controls).

“Case-control study is a type of observational study in which two existing groups differing in outcomes are identified and compared on the basis of some supposed causal attribute” (Salazar, Crosby & DiClemente 2015:107). Case-control studies are often used to identify factors that may contribute to a disease by comparing subjects who have disease (the cases) with patients who do not have the disease but are otherwise similar (the controls)” (Salazar, Crosby & DiClemente 2015:107).

“The case-control design is a powerful method for investigating factors that may explain a particular event. It is extensively used in epidemiology to study disease incidence, one of the best known examples being Bradford Hill and Doll's investigation of the possible connection between cigarette smoking and lung cancer” (Keogh & Cox 2014:8).

The goal of a case-control study is to estimate the magnitude of the association between an exposure and an outcome (Lamorte 2015: 5). The current study used case-control research design, as its goal was to assess the magnitude of association between different pre-defined factors and the development of drug resistant tuberculosis.

In the current study, the two different groups of cases and controls had an outcome of drug resistant tuberculosis and successful first-line tuberculosis treatment outcome respectively. Cases were patients with drug resistant tuberculosis who include patients with multidrug-resistant tuberculosis and patients with rifampicin resistant tuberculosis. The patients with drug resistant tuberculosis had a diagnosis confirmed by culture drug-susceptibility or gene expert tests. Patients who were successfully treated by first-line anti-tuberculosis drugs became symptom free after getting cured or having completed treatment were taken as controls.
3.3.1 Reasoning Strategies

“Reasoning is the action of constructing thoughts into a valid argument” (Jackson 2019). When an argument is constructed, that argument will be either valid or invalid. “A valid argument is reasoning that is comprehensive on the foundation of logic or fact.” Inductive and deductive reasoning are types of propositional logic. “Propositional logic is the branch of logic that studies ways of joining or modifying entire propositions, statements or sentences to form propositions that are more complicated, statements or sentences.” This means that propositional logic develops a conclusion based on facts and reasoning (Jackson 2019; Miessler 2019).

“Inductive and deductive reasoning use propositional logic to develop valid arguments based on fact and reasoning” (Jackson 2019; Miessler 2019). Inductive and deductive reasoning have a premise and a conclusion; how each type of reasoning reaches to the conclusion is different. Deductive reasoning starts with a hypothesis and then tests if it is true observation, while inductive reasoning starts with observations and goes back to theories (Jackson 2019; Miessler 2019).

The current study used inductive reasoning to construct a valid argument based on the findings of the study. Inductive reasoning was used as the current study needed to give cause and effect reasoning or bottom-up reasoning because it intended to prove that certain factors determining the occurrence of drug resistant tuberculosis.

3.3.1.1 Inductive reasoning

“Inductive reasoning is reasoning where the premises support the conclusion” (Jackson 2019). The conclusion is the hypothesis, which is the part of reasoning that it is trying to prove. “Inductive reasoning is also referred to as cause and effect reasoning or bottom-up reasoning because it seeks to prove a conclusion first.” This comes from specific instances to develop a
general conclusion. “Inductive reasoning is bottom-up reasoning; it started with a probable conclusion and induces premises” (Jackson 2019; Miessler 2019).

Induction makes observations that lead to generalizations. If the premises are true in induction, the conclusion is probably true. Induction is used all the time in everyday life because most of the world is based on partial knowledge, probabilities, and the usefulness of a theory (Jackson 2019; Miessler 2019).

### 3.3.1.2 Deductive reasoning

“Deductive reasoning is reasoning where true premises develop a true and valid conclusion” (Jackson 2019). In the case of deductive reasoning, the conclusion must be true if the premises are also true. Deductive reasoning uses principles for a specific conclusion. “Deductive reasoning is also known as top-down reasoning because it goes from general and works its way down to more specific” (Jackson 2019; Miessler 2019).

Deduction has theories for an outcome, which are tested by studies. "If the premises are true in deduction, the conclusion is definitely true. “Deduction is not used in everyday life, as it requires a sequential set of facts (Jackson 2019; Miessler 2019).

### 3.4 RESEARCH PARADIGM

“In educational research, the term paradigm is used to describe researcher's worldview. This worldview is the perspective, or thinking, or school of thought, or set of shared beliefs, that informs the meaning or interpretation of research data” (Kivunja & Kuyini 2017:26). Paradigms are used to provide beliefs and dictates for researchers and give guidance on what needs to be be studied, how is it studied and how the study findings are interpreted (Kivunja & Kuyini 2017:26).
“Most of the research paradigms emerge from one of the two of the approaches to research that are positivist approach and interpretivism approach” (Stephen & Kasim 2015). Each of these can be grouped by examining their ontology, epistemology and methodology (Bartleby 2017).

Figure 3.1, adapted from Patel (2015) and displayed below, shows elements of a paradigm. The figure also gives a summary of the basic question behind each element of a paradigm and the relationship between them.

A paradigm comprises four basic sets of assumptions, namely, epistemology, ontology, methodology and axiology (Kivunja & Kuyini 2017:26).

### 3.4.1 Epistemology of a Paradigm

“Epistemology is the philosophical view to seek the reality” (Makombe 2017:22; Shah & Abdullah 2013:252). It seeks the truth, which is ontology. Epistemology and ontology are interwoven and are impossible without each other. Realism, rationalism, relativism, and irrationalism types of epistemology. Epistemology shows the reality (Makombe 2017:22; Shah & Abdullah 2013:252).
“Epistemology explains the knowledge of mankind to the researcher so that he will extend, broaden and deepen understanding of nature” (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:52).

Kivunja and Kuyini (2017:27), define the sources of knowledge as follows:

“1. Intuitive knowledge: If one relies on forms of knowledge such as beliefs, faith and intuition, then the epistemological basis of the research is intuitive knowledge.”

“2. Authoritative knowledge: If one relies on data gathered from people in the know, books, leaders in organisations, then the epistemology is grounded on authoritative knowledge.”

“3. Rationalist epistemology or logical knowledge: If one puts emphasis on reason as the surest path to knowing the truth, then this approach is called rationalist epistemology or logical knowledge. “

“4. Empirical epistemology: If one puts emphasis on the understanding that knowledge is best derived from sense experiences and demonstrable, objective facts, then the approach leans towards empirical epistemology.”

The current study assessed determinants of the occurrence of drug resistant tuberculosis in Ethiopia. For knowing the determinants of the occurrence of drug resistant tuberculosis, the study respondents were asked about their experiences during the most recent first-line tuberculosis treatment. Added to this, objective facts were looked for by collecting data from the first-line tuberculosis treatment registers of the study respondents. This shows that the current study put emphasis on the understanding that knowledge on determinants of the occurrence of drug resistant tuberculosis is best derived from the experiences of patients with drug resistant tuberculosis and from the objective facts documented on their first-line tuberculosis treatment
registers. Thus, the approach of the current study leans towards empirical epistemology. In other words, the source of knowledge for the current study on determinants of the occurrence of drug resistant tuberculosis was empirical knowledge.

3.4.2 Ontology of a Paradigm

“The ontology is the reality of knowledge that exist and that the research wants to seek” (Makombe 2017:22; Shah & Abdullah 2013:252). Research paradigms have an ontological view that the researcher tries to know by studying. “Monism, pluralism, idealism, dualism, materialism are few of the ontological views. The ontology of research is known when the epistemology is understood. “Researchers use objectivity as an epistemological view when applying quantitative methods as the methodology” (Makombe 2017:22; Shah & Abdullah 2013:252).

Ontology focuses on the belief to be real, the behaviours of an entity has to be investigated (Kivunja & Kuyini 2017:27; Rehman & Alharthi 2016:51). Ontology provides knowledge on entities that make up the world. It investigates the real environment that makes up the themes that scientists analyse to get a true meaning, embedded in study data (Kivunja & Kuyini 2017:27).

“As described in Kivunja and Kuyini (2017:27), ontology makes researcher ask questions such as:”
“1. Is there reality out there in the social world or is it a construction, created by one’s own mind?
“2. What is the nature of reality? In other words, is reality of an objective nature, or the result of individual cognition?”
“3. What is the character of the situation being studied?”
3.4.3 Methodology of a Paradigm

“Methodology refers to the research design, methods, approaches and procedures used in a study” (Kivunja & Kuyini 2017:28). The methodology can be quantitative or qualitative along with the different mechanisms of study it encompasses (Makombe 2017:22; Shah & Abdullah 2013:252). In natural sciences, quantitative research methodology is commonly used while in social sciences, qualitative research methodology is more common in use. Mixed-method methodology is used in both pure sciences and social sciences (Makombe 2017:22; Shah & Abdullah 2013:252).

“For a positivist, quantitative research methodology is more suitable” (Makombe 2017:22; Shah & Abdullah 2013:252). Data collection, study subjects, questionnaire used and data management are all components of methodology. “The methodology includes the logic and flow of the systematic processes followed in conducting research project, to gain knowledge about research problem” (Kivunja & Kuyini 2017:28).

“According to Kivunja and Kuyini (2017:28) and Rehman and Alharthi (2016:52), in considering the methodology for research, one should ask the question on how to go about obtaining the desired data, knowledge and understandings that will enable one to answer research question.” Methodology includes assumptions, limitations and the way they were managed. It focuses on how we come to know the world (Kivunja & Kuyini 2017:28; Rehman & Alharthi 2016:52).

3.4.4 Axiology of a paradigm

“Axiology of a paradigm is concerned with the ethical issues that need to be considered when planning research” (Kivunja & Kuyini 2017:28). It is the philosophical way of making decisions of that include defining, evaluating and understanding concepts of behaviour. It considers what
value one shall attribute to the participants, the data and the researchers (Kivunja & Kuyini 2017:28).

Axiology of a paradigm tells the nature of ethics or ethical behaviour. It considers the regard for human values of everyone that will be involved with or participate in the research project (Kivunja & Kuyini 2017:28). Axiology is guided by four criteria of ethical conduct namely, teleology, deontology, morality and fairness (Kivunja & Kuyini 2017:28). Kivunja and Kuyini (2017:28) explain these four criteria of ethical conduct as follows:

“1. Teleology: Technically, teleology is the theory of morality, which postulates that doing what is intrinsically good or desirable, is a moral obligation that should be pursued.”

“2. Deontology: Deontology is the understanding that every action that will be undertaken during the research will have its own consequence intended to benefit participants, the researcher, the scholastic community or the public at large” (Kivunja & Kuyini 2017:28).

“3. Morality: According to Kivunja and Kuyini (2017:28), the morality criterion refers to the intrinsic moral values that will be upheld during the research. For example, that the researcher will be truthful in their interpretation of the data.”

“4. Fairness: The criterion of fairness draws the researcher’s attention to the need to be fair to all research participants and to ensure that their rights are upheld” (Kivunja & Kuyini 2017:28).

3.4.5 Positivism: Paradigm of the study

“Positivist research philosophy claims that the social world can be understood in an objective way” (Žukauskas, Vveinhardt & Andriukaitienė 2018). In this research philosophy, the researcher is an objective analyst and, based on it, dissociates himself from personal values and works

“Quantitative research always follows positivist approach because positivists believe in the empirical hypothesis testing.” In natural sciences, positivism is preferred because of its empirical nature to study facts. In quantitative research, the research follows a probabilistic model that is determined by previous research. “Positivists believe that the findings of one study can be generalized to another study of a similar kind regardless of it is conducted in a different environment and situations.” This is true of scientific variables like volume, speed, density, strength, and weight (Makombe 2017:22; Shah & Abdullah 2013:252).

Positivism assumes that reality exists independently of humans (Rehman & Alharthi 2016:53). It is not mediated by our senses and immutable laws govern it. “The ontological position of positivists is that of realism.” Positivists strive to understand the social world like the natural world. “In nature, there is a cause-effect relationship between phenomena, and once established, they can be predicted with certainty in the future.” For positivists, the same applies to the social world. Reality is context free, which means that different researchers working in different times and places will converge to the same conclusions about a given phenomenon” (Rehman & Alharthi 2016:53).

“The epistemological position of positivists is that of objectivism” (Rehman & Alharthi 2016:53). “Researchers come in as objective observers to study phenomena that exist independently of them and they do not affect or disturb what is being observed.” They will use language and symbols to describe phenomena in their real form, as they exist, without any interference whatsoever. Positivists view the world as being out there, and available for study in a more or less static form. Positivists believe that there are laws governing social phenomena, and by
applying scientific methods, it is possible to formulate these laws and present them through factual statements (Rehman & Alharthi 2016:53).

The current study also shares the epistemological position of positivists, as the researcher objectively observed factors associated with the development of drug resistant tuberculosis, independently of them and without affecting or disturbing what was being observed.

“The positivist methodology relies heavily on experimentation. Hypotheses are put forward in propositional or question form about the causal relation between phenomena. Empirical evidence is gathered; the mass of empirical evidence is then analysed and formulated in the form of a theory that explains the effect of the independent variable on the dependent variable” (Rehman & Alharthi 2016:51).

“The approach to analysing data in positivist research is deductive; first, a hypothesis is proposed, then it is either confirmed or rejected depending on the results of statistical analysis” (Rehman & Alharthi 2016:54). “The purpose is to measure, control, predict, construct laws and ascribe causality if it could be proved that A caused B, then a theory will be formulated for wider applicability which will illustrate the causal relation between A and B: ‘A causes B’ or ‘A leads to B’. To be able to do this, the researcher has to make sure that it was indeed A that caused B, not anything else. To make sure no other variables caused the effect, positivist researchers try to control extraneous variables, with two or more groups being subjected to the same conditions with the only difference being the independent variable” (Rehman & Alharthi 2016:54).

The current study had two groups categorized as cases and controls, which were compared for the proportion of the same factors with different values of the independent variables. The current study explained the effect of the independent factors on the dependent variable drug resistant tuberculosis. Certain factors were found to lead to the development of drug resistant tuberculosis in the current study.
“According to Rehman and Alharthi, (2016:54) positivist research often generates numerical data. The use of quantification to represent and analyse features of social reality is consistent with positivist epistemology. Because this epistemology assumes that features of social reality have a constancy across time and settings, a particular feature can be isolated and it can be conceptualized as a variable, that is, as an entity that can take on different values. These values can be expressed as numerical scales” (Rehman & Alharthi 2016:54). In a similar way, the current study generated numerical data, which quantified the association between the independent factors and the dependent variable drug resistant tuberculosis.

“The quantitative data that positivist researchers use to answer research questions and formulate theories can be collected through true experiments or less rigorous quasi-experiments, standardized tests and large or small scale surveys using closed ended questionnaires. The numeric data that are generated through these methods are subjected to descriptive or inferential statistical analysis” (Rehman & Alharthi 2016:54).

The current study collected quantitative data using closed ended questionnaires. In the same way as positivist researchers do, the numeric data that were generated through closed ended questionnaires were subjected to descriptive and inferential statistical analysis.

According to the positivist approach, research is deemed to be of good quality if it has internal validity, external validity, reliability and objectivity (Rehman & Alharthi 2016:54). Rehman and Alharthi (2016:54) define these measures of quality of research as follows:

“1. Internal validity: If the researcher proves that it is the independent variable (and not other variables) that had an effect on the dependent variable, the study is considered to have internal validity.”
“2. External validity: If the results thus arrived at are generalizable, it has external validity.”

“3. Reliability: If different researchers conduct the study in different times, places and contexts and arrive at the same results, it has reliability.”

“4. Objectivity: If researchers study phenomena without contaminating their apprehension, they are considered objective."

The current study is a quantitative research as the study had an objective of assessing the degree of association between different factors and the development of drug resistant tuberculosis numerically. Quantitative approach is a type of research approach, which quantifies the relationships between variables (Babbie 2014:87). “Quantitative research is used to quantify a problem by way of generating numerical data or data that can be transformed into useable statistics. In quantitative research the aim is to determine the relationship between one thing (an independent variable) and another (a dependent or outcome variable) in a population” (Babbie 2014:87).

The researcher chose a positivist paradigm, as the purpose of the study was to measure, control, predict and ascribe causality between specific independent factors and drug resistant tuberculosis. “According to Rehman and Alharthi (2016:54) positivist research often uses quantitative data. “The use of quantification to represent and analyse features of social reality is consistent with positivist epistemology. Thus, the positivist paradigm is consistent with the current quantitative study, which looked into determinants of drug resistant tuberculosis.

3.5 RESEARCH METHOD

“Research methods are the strategies, processes or techniques utilized in the collection of data or evidence for analysis in order to uncover new information or create better understanding of a
topic" (Dudovskiy 2019a; University of Newcastle 2019). While methods of data collection and data analysis represent the core of research methods, researchers have to address a range of additional elements within the scope of the research (Dudovskiy 2019a; University of Newcastle 2019).

“According to Creswell (2014:45), research methods involve the forms of data collection, analysis, and interpretation that researchers propose for their studies”. Researchers collect data on an instrument or gather information on a behavioural checklist. “On the other end of the continuum, collecting data might involve visiting research site and observing the behaviour of individuals without predetermined questions or conducting an interview in which the individual is allowed to talk openly about a topic, largely without the use of specific questions” (Creswell 2014:45).

“The type of data analysed may be numeric information gathered on scales of instruments or text information recording and reporting the voice of the participants” (Creswell 2014:45; Dudovskiy 2019a). “Researchers make interpretations of the statistical results, or they interpret the themes or patterns that emerge from the data. In some forms of research, both quantitative and qualitative data are collected, analysed, and interpreted. Instrument data may be augmented with open-ended observations or census data and may be followed by in-depth exploratory interviews. In this case, of mixing methods, the researcher makes inferences across both the quantitative and qualitative databases” (Creswell 2014:45; Dudovskiy 2019a).

The methods used in the current study to collect, analyse and interpret the quantitative data on determinants of the occurrence of drug resistant tuberculosis in Ethiopia are described below.
3.5.1 Research population and study settings

“Research population is a comprehensive group of individuals, institutions, objects and so forth, which have common characteristics that are of an interest to researcher” (Rafeedali 2019). The common characteristics of the groups distinguish them from other individual, institutions, objects and so forth. All individuals or objects within a certain population usually have a common, binding characteristic or trait. Usually, the description of the population and the common binding characteristic of its members are the same. It is for the benefit of the population that research is conducted. “Research population represents the entire group of people or objects to which the researcher wishes to generalize the study findings” (Rafeedali 2019).

The research population of the current study was composed of patients with drug resistant tuberculosis and patients with successful outcome of first-line tuberculosis treatment. Patients with drug resistant tuberculosis who had a history of taking at least one course of first-line tuberculosis treatment and those on second-line tuberculosis treatment at the treatment initiating hospitals during the study period were used as cases. Controls were selected from patients with successful outcome of first-line tuberculosis treatment who were on follow-up at the same hospitals giving treatment for the cases. These controls were tuberculosis symptom free patients who were cured of tuberculosis or successfully completed first-line tuberculosis treatment during the study period. Drug resistant tuberculosis patients (the cases) follow their treatment as inpatient for the first 8 months and as outpatient for the next 12 months (FMOHOE 2014b). Therefore, both inpatients and outpatients were used when sampling the cases. The controls (patients successfully treated by first-line tuberculosis treatment) were all outpatients as the treatment modality of drug susceptible tuberculosis is outpatient care (FMOHOE 2014a).

The study was conducted in six referral hospitals found in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia. The geographical map of these regions is shown in figure 3.2 below. The Central Statistical Agency of Ethiopia (2013:47) projected the population of these six regions for the year 2019 to be 88,738,000. As displayed in table 3.1, this
accounts for 88.84% of the total population of Ethiopia, which was projected to be 99,880,000 for the year 2019 (Central Statistical Agency of Ethiopia 2013:47).

As displayed in table 3.1, Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions together detected 705 patients with drug resistant tuberculosis in the Ethiopian fiscal year, which covers the dates from July 1 2017 to June 30 2018 (Ministry of Health of Ethiopia 2019). This accounts for 86.93% of the 811 patients with drug resistant tuberculosis detected nationally in the same Ethiopian fiscal year (Ministry of Health of Ethiopia 2019).

One hospital from each of the six regions was included in the current study. The hospitals where the current study was conducted provide treatment-initiating service to patients with drug resistant tuberculosis. These hospitals also provide first-line tuberculosis treatment. The six hospitals used as a study setting were Gondar University Hospital from Amhara region, Adama Hospital from Oromia region, Hawasa Hospital from South people region, Mekele Hospital from Tigray region, Dire Dawa Hospital from Dire Dawa region and Saint Peter Hospital from Addis Ababa region.
Table 3.1 The population of the study regions projected for 2019 and the number of patients with drug resistant tuberculosis detected by the study regions from July 1 2017 to June 30 2018.

<table>
<thead>
<tr>
<th>Region</th>
<th>Population*</th>
<th>Patients with drug resistant tuberculosis**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>% of national</td>
</tr>
<tr>
<td>Oromia</td>
<td>37,267,000</td>
<td>37.31%</td>
</tr>
<tr>
<td>Amhara</td>
<td>21,844,000</td>
<td>21.87%</td>
</tr>
<tr>
<td>South people</td>
<td>20,087,000</td>
<td>20.11%</td>
</tr>
<tr>
<td>Tigray</td>
<td>5,443,000</td>
<td>5.45%</td>
</tr>
<tr>
<td>Addis Ababa</td>
<td>3,604,000</td>
<td>3.61%</td>
</tr>
<tr>
<td>Dire Dawa</td>
<td>493,000</td>
<td>0.49%</td>
</tr>
<tr>
<td>Total</td>
<td>88,738,000</td>
<td>88.84%</td>
</tr>
</tbody>
</table>

*Ethiopia’s projected population for the year 2019 is 99,880,000 (Central Statistical Agency of Ethiopia 2013:47).

**Number of patients with drug resistant tuberculosis detected nationally in the Ethiopian fiscal year, from July 1 2017 to June 30 2018, was 811 (Ministry of Health of Ethiopia 2019).
3.5.1.1. Eligibility criteria

3.5.1.1.1 Inclusion criteria

1. Patients with drug resistant tuberculosis who had a history of previous first-line tuberculosis treatment and were on treatment at the study hospitals during the study period.

2. Tuberculosis symptom free patients with successful first-line tuberculosis treatment outcome of cured or treatment completed at the study hospitals during the study period.

3. Patient with drug resistant tuberculosis who are five years old or older.
3.5.1.1.2 Exclusion Criteria

1. Patients with drug resistant tuberculosis who had no history of previous first-line tuberculosis treatment but were on treatment at the study hospitals during the study period.

2. Patients with drug resistant tuberculosis who were not on treatment at the study hospitals during the study period.

3. Patients with tuberculosis treated with first-line tuberculosis treatment but did not have outcomes of cured or treatment completed at the study hospitals during the study period.

4. Patients with tuberculosis treated with first-line tuberculosis treatment but still had symptoms of tuberculosis after completing treatment at the study hospitals during the study period.

5. Patients with extra-pulmonary tuberculosis including those treated with first-line tuberculosis treatment and those on treatment for drug resistant tuberculosis.

6. Patients with drug resistant tuberculosis who are less than five years of age. These group of patients were excluded from the study as drug resistant tuberculosis in children less than five years of age is from transmission of drug resistant tuberculosis to the child from household contacts, rather than acquired from prior exposure to tuberculosis treatment (WHO 2014c).

3.5.2 Sampling

“Sampling is a process used in statistical analysis in which a predetermined number of observations are taken from a larger population” (Kenton 2019). “Due to the large sizes of populations, researchers often cannot test every individual in the population because it is too expensive and time-consuming.” This is the reason why researchers rely on sampling
techniques (Creswell 2014:204). “In sampling, researchers assume that samples are drawn from the population and sample means and population means are equal. Researchers therefore make inferences about the population with the help of samples” (Statistics Solutions 2019).

3.5.2.1 Sample size determination

“The sample size is a significant feature of any empirical study in which the goal is to make inferences about a population from a sample” (Taherdoost 2017). In order to generalize from a random sample and avoid sampling errors or biases, a random sample needs to be of adequate size (Smith 2019; Taherdoost 2017). According to Creswell (2014:205) and Smith (2019) before calculating a sample size, the researcher needs to determine the following things in general about the target population and the sample needed:

“1. Population Size: How many total people fit for the research demographic?”

“2. Margin of Error (Confidence Interval): No sample will be perfect, so the researcher needs to decide how much error to allow. The confidence interval determines how much higher or lower than the population mean the researcher is willing to let the sample mean fall.”

“3. Confidence Level: How confident does the researcher want to be that the actual mean falls within the confidence interval? The most common confidence intervals are 90% confident, 95% confident and 99% confident.”

“4. Standard Deviation: How much variance does the researcher expect in the responses? The safe decision is to use 0.5. This is the most forgiving number and ensures that the sample will be large enough.”

According to Fahim, Negida, and Fahim (2019:20), the requirements for calculating the sample size of a case-control study include the following:

1. Expected odds ratio (OR) between exposed and non-exposed groups.
2. The probability of exposure in cases.
3. The probability of exposure in controls.
4. Statistical power: 0.8, 0.85, or 0.9
5. Alpha: usually 0.05
6. Number of controls per subject in the cases group (1 in case of equal groups).

In the current study, the size of the sample was determined based on the needed statistical power of the study, the expected odds, the size of the exposure and the desired significance level (Keogh & Cox 2014:20). The study had an 80% statistical power or probability of finding the real determinants of the development of drug resistant tuberculosis. The significant determinant of the occurrence of drug resistant tuberculosis was expected to have an odds ratio (OR) of two or more. The study assumed that 20% of the controls might have an exposure similar to the cases. A 0.05 significance level was used. Considering a binary exposure, difference in proportions formula described in Keogh and Cox (2014:20) was used to calculate the sample size (n). Difference in proportions formula is as described below:

\[ n = \left( \frac{r + 1}{r} \right) \frac{(\bar{p})(1 - \bar{p})(Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2} \]

- \( r = \) the ratio of controls to cases which is 1 as they will be equal in number
- \( p_1 = \) the proportion of cases with exposure = \( \text{odds ratio} \times \text{proportion exposed in controls} \)
  \[
  p_1 = \frac{2 \times 0.2}{0.2 (2-1) + 1} = 0.33
  \]
- \( p_2 = \) the proportion of controls with exposure = 0.2
- \( \bar{p} = \) the average proportion of cases and controls with exposure = \( (0.33+0.2)/2 = 0.265 \)
- \( Z_\beta = 0.84 \) for 80% statistical power
- \( Z_{\alpha/2} = 1.96 \) for 0.05 significance level

\[
\begin{align*}
n &= 2 \frac{(0.265)(1-0.265)(0.84+1.96)^2}{(0.33-0.20)^2} \\
&= 181
\end{align*}
\]
Therefore, 181 cases and 181 controls were included in the study. A 10% increment in sample size was considered taking into consideration the non-respondents from the study population. The 181 cases and 181 controls were divided into equivalent proportions to the six study sites.

### 3.5.2.2 Sampling methods

“Sampling method refers to the way that observations are selected from a population to be in the sample for a sample survey “(Stat Trek 2019). “The main types of probability sampling methods are simple random sampling, stratified sampling, cluster sampling, multistage sampling and systematic random sampling.” The importance of probability sampling methods is that they guarantee that the sample chosen is representative of the population. This ensures that the statistical conclusions will be acceptable (Salazar, Crosby & DiClemente 2015:153; Stat Trek 2019).

Patients who participated in the current study were selected using the systematic random sampling method. As described in Salazar, Crosby and DiClemente (2015:155), “with systematic random sampling, we create a list of every member of the population. From the list, we randomly select the first sample element from the first k elements on the population list. Thereafter, we select every kth element on the list.” The systematic random sampling of the current study begun with selecting the first patient from the cases to be enrolled into the study at random from the treatment follow-up register of patients with drug resistant tuberculosis at each study site. The first patient from the controls was also selected at random from the first-line tuberculosis treatment follow-up register of patients with tuberculosis at each study site. However, from this first patient onward, the rest of the patients were enrolled into the current study systematically by selecting every other patient from the treatment follow-up registers.

When a selected patient was not willing to be enrolled into the study, the next patient on the register was taken and enrolled in the study, as long as the patient was willing to participate. If
this next patient on the register also refused to be enrolled into the study, the patient next to him or her on the register picked by systematic random sampling was enrolled in the study and a similar procedure was followed with every selection of patients who participated in the current study.

All patients enrolled into the current study were found in the sampling frame, which was limited by the study period. Sampling frame is an existing list of some sort that essentially represents the entire population under study (Salazar, Crosby & DiClemente 2015:53). The sampling frame of the current study included patients who were on treatment of drug resistant tuberculosis during the study period for the cases. The sampling frame for the controls included patients who finished first-line tuberculosis treatment during the study period. Drug resistant tuberculosis patients (the cases) follow their treatment as inpatient for the first 8 months and as outpatient for the next 12 months (FMOHOE 2014b). Therefore, both inpatients and outpatients were used when sampling the cases. The controls (patients successfully treated by first-line tuberculosis treatment) were all outpatients as the treatment modality of drug susceptible tuberculosis is outpatient care (FMOHOE 2014a)

3.5.3 Data collection

“Data collection is the systematic approach to gathering and measuring information from a variety of sources to get a complete and accurate picture of an area of interest” (McLaughlin 2016). “Data collection enables the researcher to answer relevant questions, evaluate outcomes and make predictions about future probabilities and trends” (McLaughlin 2016).

3.5.3.1 Data collection method

A structured questionnaire developed by the researcher was used to look into the determinants of the occurrence of drug resistant tuberculosis. Primary data was collected from the study
respondents and secondary data was collected from the first-line tuberculosis treatment registers. The main variables in the questionnaire included socio-demographic characteristics, factors associated with first-line tuberculosis treatment adherence, tuberculosis disease related conditions and first-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment (see annexe A).

Trained physicians, nurses and health officers under direct supervision of the principal researcher collected the data. One full day training was given to these health professionals collecting the data. To ascertain the validity and reliability of information gathered by the questionnaire, the data collectors were given an explanation on each question. The data collectors were aware of the meaning of technical words used, the purpose of each question or what it intends to measure and the sources of data. Instructions on the questionnaire reminded and guided the data collectors on how to proceed during the data collection process. The principal researcher had a supervisory role and oversaw the activity while the data was being collected. The principal researcher gave guidance and elaboration to the data collectors when needed. To minimize recall bias, the respondents mother tongue (first) language was used, the questionnaire was carefully designed though it could not be totally avoided and guiding events like holidays and national events were used by the data collectors to help the respondents remember the time of past occurrences.

3.5.3.2 Development and testing of the data collection questionnaire

The data collection questionnaire was developed by the researcher taking into consideration possible factors that were presumed to cause the occurrence of drug resistant tuberculosis. Each question was included in the questionnaire, based on the information acquired from the literature review.
A pre-test was performed on the questionnaire before it was used for the large-scale study. The researcher conducted a sample data collection from 40 patients. From these patients, 20 of them were patients with drug resistant tuberculosis or the cases and the rest 20 were patients with successful first-line tuberculosis treatment outcome or the controls. Saint Peter hospital in Addis Ababa, which was one of the study sites, was used to pre-test the data collection questionnaire. These 40 patients used for pretesting the questionnaire were not included in the sample of the main study.

Based on the knowledge acquired from sample data collected during the pre-test, the questionnaire was modified to make it feasible and easy to understand. Some questions, which could not result in reliable information, were omitted. For example, a question asking the patient whether the pulmonary tuberculosis he had previously was bacteriologically confirmed or not was omitted as the patients were not able to give this information during the pre-test data collection. This question was replaced by a simple question asking the patients about the number of previous episodes of tuberculosis treatment they had in general. A question asking about the HIV status of the patients was taken from the questionnaire for primary data to the questionnaire for secondary data to make the data objective and reliable, as the patients were seen to be uncomfortable to give an answer due to the stigma attached with HIV. Information on the first-line tuberculosis treatment registration number was added after pre-testing of the questionnaire to make collection of the primary and secondary data of a specific study respondent a perfect match.

3.5.3.3 Characteristics of the data collection questionnaire

The data collection questionnaire was structured by the researcher in a user friendly way. Clear instructions were written for data collectors to guide them while interviewing the study respondents and collecting secondary data from the first-line tuberculosis treatment registers.
The words and sentences used in the questions were simple and clear. Precautions were taken not to use complex scientific words and elaborations were added in brackets when necessary.

The data collection questionnaire had the following components (see annexe A):

1. **Sociodemographic characteristics of the study respondents:** Age, gender, educational status, marital status and occupation of the study respondents.

2. **Tuberculosis disease related conditions of the study respondents:** Number of previous episodes of tuberculosis treatment, history of previous hospitalization, history of contact with a patient with drug resistant tuberculosis and the presence of other chronic disease.

3. **Tuberculosis treatment adherence related conditions of the study respondents:** Interruption of anti-tuberculosis drugs for at least a day, history of anti-tuberculosis drug side effects, direct observation by health worker while taking anti-tuberculosis drugs, history of cigarette smoking and alcohol drinking. These questions targeted the patients who received the most recent first-line tuberculosis treatment.

4. **First-line tuberculosis treatment related conditions of the study respondents:** First-line tuberculosis treatment category, first-line tuberculosis treatment outcome and HIV status of the study respondents. These data were collected from the most recent first-line tuberculosis treatment registers of the study respondents.

### 3.5.4 Data analysis

“Data analysis is the way of evaluating data using analytical and statistical tools to discover new knowledge” (Sridhar 2018). According to Salazar, Crosby and DiClemente (2015:398) data
analyses need the use of three basic procedures, which are descriptive analysis, bivariate analysis and multivariate analysis.

“First, the data should be described. This initial procedure is nothing more than a representation of the data in the form of frequency counts and, if applicable, means with their standard deviations” (Salazar, Crosby & DiClemente 2015:398). During the current study, the data collected were entered into the data entry software of Epi-info version 7. The SPSS (Statistical packages for social sciences) statistics version 23 software was used for data analysis. Data completeness and consistency was checked by running frequencies of each variable. The mean ages of the study participants with their standard deviations were calculated for the cases and the controls separately in the descriptive analysis.

Second, bivariate associations between variables should be calculated and statistical significance determined. Bivariate refers to a relationship between two variables (Salazar, Crosby & DiClemente 2015:398). In health research, the bivariate association would be between the outcome variable and the predictor variable. When testing whether these bivariate associations are statistically significant, the P-value (the probability that a finding occurred by chance given the null hypothesis is true) must be calculated (Salazar, Crosby & DiClemente 2015:398).

During the current study, bivariate analysis was carried out for categorical variables, to test the association between the dependent variable the development of drug resistant tuberculosis and the independent presumed risk factors. An odds ratio was used to measure the degree of this relationship between the probable risk factors and the development of drug resistant tuberculosis. The cut-off point used to determine a statistically significant association was a p-value of 0.05 (Lamorte 2015: 5).
The third basic procedure is to conduct a multivariate analysis of the data. “Multivariate represents a statistical analysis involving multiple predictors and a single outcome” (Salazar, Crosby & DiClemente 2015:398). Bivariate relationships seldom capture the complexity of health behaviours. “Most health behaviour is rarely, if ever, predicted by only one predictor variable. In fact, health behaviours often have complex determinants that can only be understood when a large number of variables are taken into consideration” Multivariate analysis captures the complexity of health behaviours by taking into consideration a large number of variables (Salazar, Crosby & DiClemente 2015:398).

During the current study, multiple logistic regression analysis was used to control the confounding effect of different variables while assessing the effect of each variable on the likelihood of the development of drug resistant tuberculosis. Variables having a p-value of 0.05 or less in bivariate analysis were added in the multivariate logistic regression analysis (Keogh & Cox 2014:84).

### 3.5.5 Ethical considerations

“Ethics questions about right versus wrong conduct and what constitutes a good or bad life, as well as the justificatory basis for such questions, the situations in which values conflict and the systematic analysis and resolution of these conflicts” (Fouka & Mantzorou 2011:3; Salazar, Crosby & DiClemente 2015:45; WHO 2015e). “Health ethics is the interdisciplinary field of study and practice that seeks specifically to understand the values undergirding decisions and actions in healthcare, health research and health policy, and to provide guidance for action when these values conflict” (Fouka & Mantzorou 2011:3; Salazar, Crosby & DiClemente 2015:45; WHO 2015e).

An informative letter about the aim of the study was submitted to all health facilities included in the study together with the ethical clearance from University of South Africa with reference
number of “REC-012714-039; HSHDC/448/2015”. A support letter written to tuberculosis clinics of the health facilities to allow conducting the study was also obtained from the medical directors of each health facility.

“According to Fouka and Mantzorou (2011:4), Salazar, Crosby and DiClemente (2015:45) and World Health Organization (2015e) the core ethical principles stress the need to do good (known as beneficence) and the need to do no harm (known as non-malfeasance).” “In practice, these ethical principles mean that researchers need to: (a) obtain informed consent from potential research participants; (b) minimise the risk of harm to participants; (c) protect their anonymity and confidentiality; (d) avoid using deceptive practices; and (e) give participants the right to withdraw from the research.” These core ethical principles are briefly discussed below.

3.5.5.1 Beneficence (Do good)

“Beneficence refers to an action performed for the benefit of others. This principle states that persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being” (Salazar, Crosby & DiClemente 2015:54). “Researchers should ensure that they always act in the best interest of the research participant. Stakeholder engagement ensures that the researchers know the research participants’ perspectives, culture and context to avoid any unanticipated harmful consequences, like stigmatization” (WHO 2019f).

Understanding the participants and researchers’ responsiveness to the research study is crucial to minimizing harm (WHO 2019f). The principle of beneficence includes the professional mandate to do effective and significant research to better serve and promote the welfare of our constituents (Fouka & Mantzorou 2011:5).
The current study intended to do good to the society, as its aim was to know determinants of the occurrence of drug resistant tuberculosis and develop a model for the prevention of drug resistant tuberculosis based on the study findings. The model for the prevention of drug resistant tuberculosis developed by the current study can benefit individuals, if used by the Ethiopian government and other stakeholders, by preventing the development of drug resistant tuberculosis and contributing to the promotion of the welfare of communities.

3.5.5.2 Non-malfeasance (do no harm)

Non-malfeasance principle states that researchers have an obligation not to inflict harm on persons intentionally (Salazar, Crosby & DiClemente 2015:54). “Non-maleficence means avoiding the causation of harm. As many treatments involve some degree of harm, the principle of non-maleficence would imply that the harm should not be disproportionate to the benefit of the treatment or inflicting the least harm possible to reach a beneficial outcome” (WHO 2015e).

“According to Jahn (2011:225), the principle of non-maleficence is closely associated with the maxim primum non nocere (first do no harm) and supports the following rules: Do not kill, do not cause pain or suffering, do not incapacitate and do not cause offense.”

The necessary precautions were taken during the current study not to harm the study respondents psychologically. When choosing the words and sentences in the data collection questionnaire, caution was taken so that the question will not offend the study respondents. The data collectors were also made to have a good approach so that the process of data collecting would not cause offense on the study respondents.

3.5.5.3 Respect for autonomy (Respect for persons)

“Respect for autonomy is a norm that obliges researchers to respect the decisions (self-determination) of adults who have decision-making capacity” (Jahn 2011:225). Researchers
should accept a person’s right to choose, to hold views, and to take actions based on personal values and beliefs. “Three conditions must exist for autonomous action by those with capacity to choose: Intentionality, understanding and absence of controlling influences that determine their action” (Jahn 2011:225). “The following moral rules or obligations are derived from the application of the principle of respect for autonomy: Tell the truth, respect the privacy of others, protect confidential information and obtain consent for interventions with patients” (Jahn 2011:225).

“Autonomy is most often considered to refer to the ability of an individual to be his or her own person, to make his or her own choices based on his or her own motivations, without manipulation by external forces” (WHO 2015e). However, others in a more Kantian tradition see autonomy as being firmly related to accepting and acting, based on one’s obligations, that is, acting morally, the precise opposite of doing what one wants (WHO 2015e).

The current study respected the autonomy of the study respondents. The study respondents were told the truth about the aim of the study and their privacy was respected by interviewing them in a room where no one else but the data collector can hear their response. The study respondents gave their consent to be enrolled into the study intentionality after having a good understanding of the study with no controlling influences that determined their decision.

Some study respondents selected by systematic random sampling chose not to respond to the study. In such cases, their decision not to participate was respected and the next patient in the treatment follow-up register was selected. The study respondents were told that they had the right to withdraw from the study at any time during the interview but no one withdrew from the study after starting the interview.
3.5.5.4 Justice

“Justice is a highly contested concept that can, roughly, be thought of as giving people what they deserve” (WHO 2015e). Justice instructs researchers to treat others equitably and distribute benefits or burdens fairly (Jahn 2011:226). The principle of justice states that research should ensure that reasonable, non-exploitative and well-considered procedures are administered fairly and equally (Salazar, Crosby & DiClemente 2015:56).

There was no immediate benefit from the current study that could be distributed to the study respondents. However, the model developed for prevention of drug resistant tuberculosis in the current study was designed in such a way that all individuals would benefit from it equally in being protected from the development of drug resistant tuberculosis.

During the data collection process, all the study respondents were asked of similar questions with no special omission or addition of question for specific individuals. This similarity in the questions asked of all study respondents made the psychological burden of being interviewed the same for each study respondent. However, some replies had follow-up elaborating questions depending on the reply given by the study respondents. For example, study respondents who said yes to the presence of chronic illness were asked to specify the illness while those who said no were not exposed to such questions. This was a minor variation in questions asked and was not seen to cause special discomfort on the study respondents during the data collection process.

3.5.5.5 Informed consent

“Informed consent is an agreement to a certain course of action, such as treatment or participation in research, based on complete and relevant information by a competent individual without coercion” (WHO 2015e). “Informed consent means that a person knowingly, voluntarily
and intelligently, and in a clear and manifest way, gives his consent.” Informed consent is one of the means by which a patient's right to autonomy is respected. Informed consent seeks to incorporate the rights of autonomous individuals through self-determination. It also seeks to prevent assaults on the integrity of the patient and protect personal liberty and veracity (Fouka & Mantzorou 2011:4).

“Informed consent is one of the means by which a patient’s right to autonomy is respected. Informed consent seeks to incorporate the rights of autonomous individuals through self-determination. It also seeks to prevent assaults on the integrity of the patient and protect personal liberty and veracity (Fouka & Mantzorou 2011:4).

“Individuals can make informed decisions in order to participate in research voluntarily only if they have information on the possible risks and benefits of the research. Free and informed consent needs to incorporate an introduction to the study and its purpose as well as an explanation about the selection of the research subjects and the procedures that will be followed” (Salazar, Crosby & DiClemente 2015:57). “It is essential to describe any physical harm or discomfort, any invasion of privacy and any threat to dignity as well as how the subjects will be compensated in that case. Added to this, the subjects need to know any expected benefits either to the subject or to science by gaining new knowledge. A disclosure of alternatives is also required” (Salazar, Crosby & DiClemente 2015:57).

When a minor under 18 years of age is involved, because they are not of legal age, they can provide only their assent or agreement to participate. Assent refers to persons who are not of legal age for providing their agreement to participate in research study. The parent(s) and guardians will have the right to decide whether a child should take part in a given research study (Salazar, Crosby & DiClemente 2015:57).

Before enrolling patients who were 18 years and older into the current study, they were informed about the study and its purpose as well as an explanation about the selection method of the study respondents. These patients were also informed about the category of questions they were to be asked, which were their sociodemographic characteristics, their previous tuberculosis treatment adherence history with related questions and questions on the previous first-line tuberculosis treatment they took. A pre-prepared one-page information paper was used for this
purpose and data collectors read it for all study respondents individually before asking them for their written consent to participate in the study (see annexe B).

After the patients were given all the necessary information, they were asked for their willingness to participate in the study and they decided knowingly and voluntarily. Patients who agreed to respond to the study questions read a written consent form and signed on it to ascertain that they knowingly and willingly participated in the study (see annexe B). The data collectors then proceeded to the questions and documented the study respondent’s response on the questionnaire.

The current study included patients whose age was 5 years and above but under 18 years. Children between 5 and 18 years of age who were old enough to understand the proposed research in general were asked for their willingness (assent) to respond to the study questions during data collection time of this study. The parents/guardians of these children who were in the same data collection room with them gave their consent and signed on the specifically prepared consent form after the children gave their assent for inclusion in the study. According to Ethiopian national ethics guideline, assent will be sought from a study participant under the age of 18 years old (Ethiopian Ministry of Science and Technology 2014:38). The minor child should be given appropriate information based on the child’s level of comprehension whatever the complexity of the research procedures. Then, an assent, a child’s affirmative agreement to participate in research shall be sought from all children 12 years of age and above, in addition to the consent of a parent, next-of-kin, or guardian (Ethiopian Ministry of Science and Technology 2014:38). Children are vulnerable age group due to lack of maturity and understanding that comes with age. As children cannot decide based on good understanding of the benefit or harm of a study, they have to give assent and the parent/guardian signs an informed consent (Ethiopian Ministry of Science and Technology 2014:38). In the current study, since these patients under 18 years of age were not of legal age to be asked of informed consent, a specifically designed assent form was used for these minor age patients (see annexe C). The
parents or guardians of patients with age of 5 years and above but under 18 years were given
the same information given to the adult patients. Parents or guardians who agreed for their
children to respond to the study questions read a written consent form and signed on it to
ascertain that they knowingly and willingly allowed their children’s inclusion in the study.

3.5.5.6 Respect for anonymity, confidentiality and privacy

“The issue of confidentiality and anonymity is closely connected with the rights of beneficence,
respect for the dignity and fidelity. Anonymity is protected when the subject's identity cannot be
linked with personal responses” (Fouka & Mantzorou 2011:6; WHO 2015e). “If the researcher
cannot promise anonymity, he has to address confidentiality or the management of private
information by the researcher in order to protect the subject's identity” (Fouka & Mantzorou
2011:6; WHO 2015e). “Confidentiality means that the researcher is obliged to keep information
secret unless its disclosure has been appropriately authorized by the person concerned or, in
extraordinary circumstances, by the appropriate authorities to protect the society” (Fouka &

According to WHO (2019f), privacy protects a person from discrimination by others. Respect for
privacy implies that a person should not be expected to share personal information if he chose
not to do so. Any violation of privacy requires ethical justification unless there is consideration in
like for the protection of the community (WHO 2019f).

In the current study, the study respondents remained anonymous to any individual who was not
part of the data collection. The data collection questionnaire did not document the study
respondents’ name and residential address that can identify them. Therefore, no one reading the
data collection questionnaire could identify who the study respondents were except the data
collectors and the principal researcher. The data collectors and the principal researcher vowed
to the study respondents to keep whatever information they gave confidentially and this was documented in the informed consent and assent forms.

The major ethical challenge associated with drug resistant tuberculosis in Ethiopia is stigma and discrimination patients with drug resistant tuberculosis are facing from the community (FMOHOE 2014b). A patient with drug resistant tuberculosis is stigmatised and discriminated in Ethiopia for there is a fear among the community. The fear is created by the aerosol mode of transmission and the difficult treatment modality of drug resistant tuberculosis. Added to this, some communities believe that all patients with tuberculosis are HIV positive from lack awareness, which adds to the stigma and discrimination patients with drug resistant tuberculosis are facing (FMOHOE 2014b).

During the current study, the following precautions were taken to keep the confidentiality of the study respondents. The study respondents were interviewed at a place where other individuals could not overhear the replies the study respondents gave. All the study respondents in the current study shared their information to data collectors only because they chose to do so and they were not obliged to give information in any way. The study respondents had the right to ask elaboration on any unclear question. A one-day training was given to the data collectors by the principal researcher on the details of the study, on ethical issues in general and specific to the study, the questionnaires and how to address any question that might arise from the study respondents. The data collection process ended by thanking the study respondents and reassuring them of the confidentiality of all the information they gave.
3.6 QUALITY OF THE STUDY: VALIDITY AND RELIABILITY

3.6.1 Validity and reliability

“The principles of validity and reliability are fundamental cornerstones of the scientific method. Together, they are at the core of what is accepted as scientific proof by scientist and philosopher alike. Validity and reliability are the quality criteria used to evaluate quantitative research studies” (Shuttleworth 2019; Surbhi 2017). As the current study was a quantitative study, the criteria for evaluating the quality of the study were its validity and reliability.

“Simply, the validity of the measuring instrument represents the degree to which the scale measures what it is expected to measure. It is not same as reliability, which refers to the degree to which measurement produces consistent outcomes” (Shuttleworth 2019; Surbhi 2017). Validity is all about the genuineness of the research, whereas reliability is nothing but the repeatability of the outcomes. The difference between validity and reliability is that, validity is related to accuracy, while reliability is related to precision. A valid instrument is always reliable, whereas reliable instrument need not be a valid instrument. These characteristics give validity more value than reliability (Shuttleworth 2019; Surbhi 2017).

3.6.1.1 Validity

“Validity explains how well the collected data covers the actual area of investigation. Validity means measure what is intended to measure or an instrument is accurately measuring what it is supposed to measure” (Stephanie 2016; Taherdoost 2016:29). Validity includes experimental idea and ascertains the results obtained meet all of the requirements of the scientific study. There should be randomization of the study participants and the necessary precaution taken in assignment of controls (Shuttleworth 2019).
According to Dudovskiy (2019b), measures to ensure validity of research include, but not limited to the following points:

a) Appropriate time scale for the study has to be selected. The current study’s time duration was adequate to collect data reaching the sample size in the allocated time. Adequate number of patients were following their treatment at the study site during the study period.

b) Appropriate methodology has to be chosen, taking into account the characteristics of the study. Taking into consideration the characteristics of drug resistant tuberculosis, a quantitative case-control study method was chosen. This study method identified the necessary information on determinants of the occurrence of drug resistant tuberculosis in Ethiopia.

c) The most suitable sample method for the study has to be selected. Systematic random sampling method used in the current study was suitable to get representative sample of study respondents.

d) The respondents must not be pressured in any ways to select specific choices among the answer sets. There was no pressure imposed on the study respondents by data collectors or the principal researcher. The study respondents chose answers, which they believe were the correct answers for the questions they were asked.

According to Dudovskiy (2019b), it is important to understand that although threats to research validity can never be avoided, researchers need to try their best to lessen this threat. Simply, validity measures the point to which differences discovered with the scale reflect true differences, among objects on the characteristics under study. To be taken as valid, it must not have any measurement error. “Validity in quantitative research tells whether one can draw meaningful and useful conclusion from measurements on particular instruments” (Creswell
Scientific research is expected to have internal validity and external validity, which are described below.

3.6.1.1.1 Internal validity

“Internal validity tells how an experimental design is structured and includes all of the steps of the scientific research method” (Shuttleworth 2019). Internal validity of research is measured by its ability to test what it was intended to test. Even if the research results are great, sloppy and inconsistent design will compromise its integrity in the eyes of the scientific community (Shuttleworth 2019).

The following precautions were taken to make the current study find what it was intended to find, which were determinants of the occurrence of drug resistant tuberculosis in Ethiopia. The questionnaire used for data collection in the current study was designed in easily understandable way to make it collect the information intended to be collected from the study respondents. The questionnaire used for data collection was made to include as many factors as possible, which were presumed to be associated with the development of drug resistant tuberculosis after extensive literature review. This questionnaire was pre-tested before it was used for the main study and modifications were made on its contents to make it collect valid information from the study respondents. Pre-testing of the data collection questionnaire made the questionnaire capture quality and important data, which were obtainable.

The data collectors were given extensive one-day training by the principal researcher on the details of the study, on ethical issues in general and specific to the study, the questionnaires and how to address any question that might arise from the study respondents and were closely monitored by the principal researcher to make them collect the information intended to be collected from the study respondents of the current study. All of the necessary steps of the scientific research methods were followed during data entry, data analysis and interpretation of
the study findings. These measures taken and scientific methods used can give the current study internal validity.

3.6.1.1.2 External validity

“External validity is the process of examining the results and questioning whether there are any other possible causal relationships” (Shuttleworth 2019). Control groups and randomization will minimize external validity problems but no method is perfect. “This is why the statistical proofs of a hypothesis are called significant, not absolute truth” (Shuttleworth 2019). “Any scientific research design only puts forward a possible cause for the studied effect. There is always the chance that another unknown factor contributed to the results and findings. This extraneous causal relationship may become more apparent, as techniques are refined and honed” (Shuttleworth 2019). Eliminating confounding factors, by using controls and duplicate samples, is the best way to ascertain that study results are acceptable (Shuttleworth 2019).

The current study used a case-control study design and randomization (systematic random sampling) in selecting the study respondents, which can give the study external validity. The cases had drug resistant tuberculosis while the controls were free from drug resistant tuberculosis and had successful first-line tuberculosis treatment outcome. This case-control study design lessened the external validity problems the current study might have faced. The use of controls in the current study helped to eliminate other potential causal relationships with the development of drug resistant tuberculosis, which were actually not true causal relationships. This increased the probability that only significant factors leading to the development of drug resistant tuberculosis were identified, which could give the current study external validity.
3.6.1.2 Reliability

“Reliability concerns the extent to which a measurement of a phenomenon provides stable and consistent result” (Taherdoost 2016:33; Surbhi 2017). Reliability implies repeatability. A test is said to be reliable if repeat measurement made by it under constant conditions gives the same finding (Taherdoost 2016:33; Surbhi 2017). Reliability is the ability of study results to be repeatable (Stephanie 2016). For instance, a blood pressure apparatus is a reliable tool that would measure the correct blood pressure each time it is used. In the same way, reliable research findings can be replicated repeatedly (Stephanie 2016). Degree of stability of a study result is ascertained by making a comparison of the results of repeated measurement while equivalence of a study result can be measured when two researchers compare the observations of the same studies (Shuttleworth 2019; Surbhi 2017).

“Reliability refers to whether scores to items on an instrument are internally consistent (that is, are the item responses consistent across constructs?), stable over time (test-retest correlations), and whether there was consistency in test administration and scoring” (Creswell 2014:295). A research is expected to have internal reliability and external reliability (Stephanie 2016). “Internal reliability, or internal consistency, is a measure of how well research is actually measuring what the researcher wants it to measure” (Stephanie 2016). External reliability means that the test or measure can be generalized beyond the researcher (Stephanie 2016). For example, a test for drug resistant tuberculosis should be able to detect drug resistant tuberculosis in different groups of people.

The reliability of the current study will be tested by similar studies that will be done in the future. “The idea behind reliability is that any significant results must be more than a onetime result and be repeatable at any time” (Shuttleworth 2019). The statistically significant results of the current study are expected to be repeatable in the future by similar studies. “Other researchers must be able to replicate the same research, under the same conditions and generate the same results.” Without the duplication of statistically significant results, the study has not completed the
demands of testability (Dudovskiy 2019b; Shuttleworth 2019). So as to make the current study reliable scientific methods detailed above in this methodology chapter were used from data collection to data analysis and interpretation to make the results of the current study inherently repeatable. The sociodemographic and clinical questions included in the data collection questionnaire were obtainable information based on previous scientific studies detailed in literature review. The data obtained were carefully entered into and analysed by internationally accepted scientific software.

3.7 SUMMARY

This chapter presented the research methodology and the research design used in the current study. The current study was a quantitative case-control study. It elaborated reasoning strategies and discussed the different types of research paradigms. The specific reasoning strategy and research paradigm used by the current study was also indicated. The research method section of this chapter gave a detailed explanation on the research population and study settings, the sampling method used, the data collection process and the way of data analysis. Ethical considerations were given due attention in this chapter and discussed in detail. This chapter ended by discussing the quality of the current study. As the current study was a quantitative study, the discussion focused on elaborating the study’s validity and reliability.
CHAPTER 4
RESEARCH RESULTS

4.1 INTRODUCTION

Patients with tuberculosis were enrolled into a case-control study with equal number of cases and controls to assess determinants of the occurrence of drug resistant tuberculosis after taking first-line tuberculosis treatment in Ethiopia. One hundred and eighty-one (181) cases and 181 controls were enrolled into the study. The study respondents were patients with drug resistant tuberculosis and patients with successful first-line tuberculosis treatment outcome, which were used as cases and controls respectively. The study respondents were selected from Gondar University Hospital, Adama Hospital, Hawasa Hospital, Mekele Hospital, Dire Dawa Hospital and Saint Peter Hospital. Data were collected in the period from September 1, 2018 to December 31, 2018.

Primary data were collected by interviewing the study respondents. Patient follow-up registers were used to collect secondary data. Trained data collectors collected the data following ethical principles. Descriptive and inferential statistical methods were used to manage and analyse collected data as summarized in section 4.2 below.

This chapter presents the analysed study results in a table form with a preceding paragraph summarizing important results. The tables present the frequency distribution of study variables in absolute numbers and percentages. A table that displays the possible risk factors associated with the development of drug resistant tuberculosis presents the results of statistical analysis in the form of crude odds ratio, adjusted odds ratio and p-value.
4.2 DATA MANAGEMENT AND ANALYSIS

A pre-tested structured questionnaire developed by the researcher was used to collect data on determinants of the occurrence of drug resistant tuberculosis. It was used to collect primary data from the patients who participated in the study and secondary data from patient follow-up registers. Trained physicians, nurses and health officers with supportive supervision of the principal researcher collected the data.

Data collected were entered into data entry software of Epi-info version 7. Data entered into Epi-info version 7 were exported to SPSS Statistics version 23 software, which was used for data analysis. Data completeness was confirmed by analysing frequency table on Epi-info version 7 and SPSS Statistics version 23 software.

Binary logistic regression was used to test the association between the dependent variable drug resistant tuberculosis and each independent presumed risk factor. The result of this binary logistic regression was crude odds ratio that quantified the strength of this association between each potential risk factor and drug resistant tuberculosis (Lamorte 2015: 5).

Multiple logistic regression analysis was used to control the confounding effect of the independent variables by analysing the impact of each variable on the probability of the occurrence of drug resistant tuberculosis. The result of this analysis was adjusted odds ratio. A p-value of 0.05 was used to determine a significant degree of association. Independent variables having a p-value 0.05 or less in binary logistic regression were analysed again by the multiple logistic regression analysis (Keogh & Cox 2014:84).

Study variables that had an odds ratio of two or more after adjusting for confounding factors and a p-value of less than 0.05 were considered significantly associated with the development of drug resistant tuberculosis.
4.2.1 Data Reliability Analysis: Cronbach’s alpha scores

It is possible to objectively measure the reliability of a data using Cronbach's alpha, the most widely used objective measure of reliability. “Alpha was developed by Lee Cronbach in 1951 to provide a measure of the internal consistency of a test or scale; it is expressed as a number between 0 and 1” (Tavakol & Dennick 2011:53). “Internal consistency describes the extent to which all the items in a test measure the same concept and hence it is connected to the interrelatedness of the items within the test. Internal consistency should be determined before a test can be employed for study purposes to ensure validity” (Regents 2019; Tavakol & Dennick 2011:53).

Reliability estimates also show the amount of measurement error in a test (Lund 2018; Tavakol & Dennick 2011:53). This interpretation of reliability is the correlation of test with itself. “Squaring this correlation and subtracting from 1.00 produces the index of measurement error. For example, if a test has a reliability of 0.80, there is 0.36 error variance (random error) in the scores (0.80×0.80 = 0.64; 1.00 – 0.64 = 0.36). As the estimate of reliability increases, the fraction of a test score that is attributable to error will decrease. If the items in a test are correlated to each other, the value of alpha is increased” (Glen 2019; Tavakol & Dennick 2011:53). However, a high coefficient alpha is not necessarily a high degree of internal consistency as the length of the test affects alpha. “If the test length is too short, the value of alpha is reduced. Thus, to increase alpha, more related items testing the same concept should be added to the test” (Goforth 2015; Tavakol & Dennick 2011:53).

“According to Glen (2019) and Goforth (2015), the internal consistency of research graded as follows depending on the result of Cronbach’s alpha: 0.9 ≤ α is excellent, 0.8 ≤ α < 0.9 Good, 0.7 ≤ α < 0.8 Acceptable, 0.6 ≤ α < 0.7 Questionable, 0.5 ≤ α < 0.6 Poor and α < 0.5 is Unacceptable.”
Data reliability analysis was done for the current study by adding all the study variables except the sociodemographic variables into SPSS Statistics version 23 software and running the reliability analysis. On this reliability analysis, the result of Cronbach's alpha for the current study was found to be 0.80. This result shows that the reliability or internal consistency of the current study is good.

4.3 PRESENTATION OF RESULTS

4.3.1 Study setting characteristics

A total of 181 cases who were patients with drug resistant tuberculosis and an equal number of controls who were patients successfully treated by first-line anti-tuberculosis treatment, were selected from six hospitals in Ethiopia. Equivalent proportion of study respondents were included from Gondar University Hospital, Adama Hospital, Hawasa Hospital, Mekele Hospital, Dire Dawa Hospital and Saint Peter Hospital (Table 4.1).

<table>
<thead>
<tr>
<th>Hospital’s Name</th>
<th>Number of cases</th>
<th>Number of controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gondar University Hospital</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Adama Hospital</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Hawasa Hospital</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Mekele Hospital</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Dire Dawa Hospital</td>
<td>30</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Saint Peter Hospital</td>
<td>31</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>181</strong></td>
<td><strong>181</strong></td>
<td><strong>362</strong></td>
</tr>
</tbody>
</table>
4.3.2 Sociodemographic characteristics of the study respondents

The study respondents gave information on their specific sociodemographic characteristics. These personal information collected from the study respondents were their gender, age, marital status, educational status and occupation.

4.3.2.1 Gender

As figure 4.1 shows, the majority of the study respondents were males, representing 101 (55.80%) and 97 (53.59%) of the cases and the controls respectively. Females accounted for 80 (44.20%) of the cases and 84 (46.41%) of the controls. From the whole study respondents, 198 (54.70%) were males, while 164 (45.30%) of them were females (figure 4.2).
4.3.2.2 Age

The majority of patients with drug resistant tuberculosis who responded in the study, accounting for 124 (68.51%) of the cases, had an age in the range of 15 to 34 years. A higher proportion patients with successful first-line anti-tuberculosis treatment outcome, which made up 103 (56.90%) of the controls, also had an age between 15 and 34 years. The mean age was 30.2 years for the cases and 34.2 years for the controls. Table 4.2 shows the frequency distribution of the age groups of the study respondents. The ages of the study respondents were grouped at 10 years interval. The grouping of the ages of the study respondents started from 5 years, as under 5 years old children were excluded from the study.
Table 4.2: Frequency distribution of the age groups of the study respondents

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CASES N = 181</th>
<th></th>
<th>CONTROLS N = 181</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Age (years)</td>
<td>5 - 14</td>
<td>4</td>
<td>2.21%</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>15 - 24</td>
<td>54</td>
<td>29.83%</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>25 - 34</td>
<td>70</td>
<td>38.68%</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>35 - 44</td>
<td>33</td>
<td>18.23%</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>45 – 54</td>
<td>13</td>
<td>7.18%</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>55 - 64</td>
<td>5</td>
<td>2.77%</td>
<td>7</td>
</tr>
<tr>
<td>≥ 65</td>
<td>2</td>
<td>1.10%</td>
<td>13</td>
<td>7.18%</td>
</tr>
</tbody>
</table>

4.3.2.3 Marital status

The study respondents were asked of the marital status they had at the time of the interview. A larger proportion of both the cases and the controls were single accounting for 99 (54.70%) and 92 (50.83%) of the study respondents in their group respectively. Married study respondents had the second highest proportion representing 62 (34.25%) of the cases and 71 (39.23%) of the controls. Divorced individuals were 16 (8.84%) in the cases and 10 (5.52%) in the controls. Widow was the lowest marital status in the study respondents, accounting for only 4 (2.21%) of the cases and 8 (4.42%) of the controls (figure 4.3).
4.3.2.4 Educational status

The study respondents had a level of education varying from individuals with no formal education to those who had a college and above education. Study respondents educated to high school level, which were nearly equal in number in the cases and the controls, had the higher proportion followed by students and graduates of college and above. There were 81 (44.75%) of the cases of educated up to 9th to 12th grade, while 82 (45.30%) of the controls also had a similar level of education. Study respondents with no formal education accounted for the lowest proportion of 7.18% in the cases and 6.63% in the controls.
4.3.2.5 Occupation

The study respondents included jobless individuals and people who were privately employed, working for the government or self-employed. Full time students and farmers were also among the study respondents. Privately employed workers made up the biggest proportion of the cases with 49 (27.07%) of the study respondents in the group making a living on it. However, students constituted the biggest proportion in the controls, as 53 (29.28%) of the study respondents in the control group were going to school at the time of the study (Table 4.3).
Table 4.3: Occupation of the study respondents

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CASES N = 181</th>
<th></th>
<th>CONTROLS N = 181</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Occupation</td>
<td>No work</td>
<td>30</td>
<td>16.57%</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Student</td>
<td>42</td>
<td>23.20%</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Farmer</td>
<td>16</td>
<td>8.84%</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Government Employed</td>
<td>36</td>
<td>19.90%</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Private Employed</td>
<td>49</td>
<td>27.07%</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Self employed</td>
<td>8</td>
<td>4.42%</td>
<td>12</td>
</tr>
</tbody>
</table>

4.3.3 Tuberculosis disease related conditions

The current study looked into certain conditions that might be related with the acquisition of tuberculosis disease in general. The study respondents were asked about their past medical history with regard to the number of times they were ill with tuberculosis previously and a history of previous hospitalization for any illness. Added to these, the study respondents were asked for the presence of household or close contact with patient with drug resistant tuberculosis and other chronic disease.

4.3.3.1 Number of previous tuberculosis episodes

The study respondents were asked to give information on the number of times they were diagnosed to have any form of tuberculosis disease and first-line tuberculosis treatment started in the past by a health facility. The study respondents in the case group gave the information excluding the drug resistant tuberculosis they had at the time of the study. The study respondents in the control group were interviewed after completing the first-line anti-tuberculosis treatment and they counted their recent illness as a previous tuberculosis.
As shown in figure 4.5, the majority of the study respondents in the control group, accounting for 143 (79.00%) of them, had only one episode of tuberculosis in their lifetime. However, only a quarter of the study respondents in the case group, which were 47 (25.97%), had one episode of diagnosed previous tuberculosis, for which first-line tuberculosis treatment was started at a health facility. From the 181 patients with drug resistant tuberculosis in the case group, 63 (34.81%) and 54 (29.83%) of them had two and three episodes of previous tuberculosis respectively. Whereas in the control group, 23 (12.71%) of the study respondents had two episodes of previous tuberculosis and 12 (6.63%) of them had three episodes of previous tuberculosis. History of four or more episodes of previous tuberculosis was given by 17 (9.39%) of the study respondents in the case group and by 3 (1.66%) of the study respondents in the control group.

![Figure 4.5: Number of previous illness with tuberculosis per cases and controls (N=181 cases and 181 controls)](image-url)
Figure 4.6 shows the proportion of the study respondents in the case and the control groups with two or more episodes of previous tuberculosis in comparison with those who only had one episode of previous tuberculosis. When assessing the history of previous tuberculosis in the case group, a majority or 134 (74.03%) of the study respondents with drug resistant tuberculosis had two or more episodes of previous tuberculosis. Whereas, in the control group, only 38 (21.00%) of the study respondents had two or more episodes of tuberculosis.

Figure 4.6: Proportion of the study respondents with two or more episodes of previous tuberculosis per cases and controls (N=181 cases and 181 controls)

4.3.3.2 Previous hospitalization

History of previous hospitalization for any medical, surgical, gynaecologic or other types of illnesses was one of the study questions forwarded to the study respondents.
As shown in figure 4.7, the larger proportions of the study respondents in the case group, as well as those in the control group, had no history of previous hospitalization. Study respondents representing 64 (35.36%) of the cases were hospitalized sometime in the past, while 117 (64.64%) of them were not. From the control group, 132 (72.93%) of the study respondents were never hospitalized for any illness and only 49 (27.07%) of them had history of previous hospitalization.

![Figure 4.7: History of previous hospitalization per cases and controls (N=181 cases and 181 controls)](image)

4.3.3.3 Contact with patient with drug resistant tuberculosis

The role of air born transmission in acquisition of drug resistant tuberculosis was assessed by asking the study respondents if they ever had a household or close contact with a patient with drug resistant tuberculosis.
The majority of the study respondents in both the case and the control group did not have history of household or close contact with a patient with drug resistant tuberculosis. From the study respondents interviewed, 159 (87.85%) of the cases and 163 (90.06%) of the controls replied that, they never lived in the same household or had close contact with a patient with drug resistant tuberculosis. There was history of either living together or having close contact with a patient with drug resistant tuberculosis in 22 (12.15%) the cases and 18 (9.94%) of the controls (Figure 4.8).

Figure 4.8: History of household or close contact with a patient with drug resistant tuberculosis (N=181 cases and 181 controls)
4.3.3.4 Chronic illness

The presence of any illness with chronic nature and ongoing at the time of the study was asked. The chronic illnesses the study respondents had included diabetes mellitus, hypertension, asthma, heart failure and other diseases as well. HIV/AIDS was not included here even though it was one of the chronic illnesses the study respondents had. HIV/AIDS was assessed separately by a specific study question.

At the time the study, 77 (42.54%) the study respondents in the case group and 64 (35.36%) of those in the control group were having certain kind of chronic illness. No chronic illness was reported by 104 (57.46%) of the study respondents in the case group. The larger proportion or 117 (64.64%) of the study respondents in the control group did not have any form of chronic illness as well, excluding HIV/AIDS (Figure 4.9).

Figure 4.9: The presence of chronic illness per cases and controls (N=181 cases and 181 controls)
4.3.4 Tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment

The current study assessed factors that were expected to affect the study respondents’ adherence to tuberculosis treatment during their most recent first-line tuberculosis treatment. Tuberculosis treatment interruption was assessed along with the side effects of anti-tuberculosis drugs in general and vomiting specifically. Cigarette smoking and alcohol drinking habits of the study respondents were the other factors assessed. The provision of directly observed tuberculosis treatment to the study respondents was also assessed together with the number of weeks the treatment was directly observed by a health worker.

4.3.4.1 Tuberculosis treatment interruption

The study respondents were asked if they had ever interrupted taking anti-tuberculosis drugs during their most recent first-line tuberculosis treatment. Tuberculosis treatment interruption by the study respondents for one or more days was taken into consideration and compared with those who completed the treatment without any interruption.

The larger proportion of the study respondents in the case group, accounting for 117 (64.64%) of them, interrupted taking anti-tuberculosis drugs for at least one day. Whereas in the control group, only 60 (33.15%) of the study respondents gave history of tuberculosis treatment interruption for one or more days. The most recent first-line tuberculosis treatment was completed without a single day interruption by 64 (35.36%) of the study respondents in the case group and 121 (66.85%) of the study respondents in the control group (Figure 4.10).
4.3.4.2 Anti-tuberculosis drug side effect

One of the study questions the current study asked the study respondents was the occurrence of any kind of the side effects of anti-tuberculosis drugs. Vomiting, which is the commonest side effect of anti-tuberculosis drugs, was asked separately and its impact on tuberculosis treatment adherence assessed.

Figure 4.11 shows the proportion of study respondents in the case and the control group with and without anti-tuberculosis drug side effects during the most recent first-line tuberculosis treatment. A third bar was added in this figure to show the percentage of study respondents with vomiting during their most recent first-line tuberculosis treatment.
The current study found out that 94 (51.93%) of the study respondents in the case group encountered anti-tuberculosis drug side effects during the most recent first-line tuberculosis treatment. From these study respondents 77 (42.54%) of them had vomiting as an anti-tuberculosis drug side effect. The occurrence of anti-tuberculosis drug side effects generally and vomiting specifically during the most recent first-line tuberculosis treatment was reported by 87 (48.07%) and 72 (39.78%) of the study respondents in the control group respectively. No anti-tuberculosis drug side effect occurred during the most recent first-line tuberculosis treatment of 87 (48.07%) of the cases and 94 (51.93%) of the controls. There was also no vomiting reported by 104 (57.46%) of the cases and 109 (60.22%) of the controls.

Figure 4.11: The presence of anti-tuberculosis drug side effects and the percentage of patients with vomiting during the study respondents’ most recent first-line tuberculosis treatment (N=181 cases and 181 controls)
4.3.4.3 Cigarette and alcohol

Cigarette smoking was assessed by asking the study respondents if they smoked one or more cigarettes daily during their most recent first-line tuberculosis treatment. Alcohol intake was assessed by asking the study respondents the number of any type of alcohol drinks they took on daily basis during their most recent first-line tuberculosis treatment.

As table 4.4 shows, a small proportion of the study respondents in both the case and the control group were smoking cigarettes or consuming alcohol during their most recent first-line tuberculosis treatment. Only 26 (14.36%) of the cases and 17 (9.39%) of the controls smoked cigarettes. From all the study respondents, 150 (82.87%) of the cases and 155 (85.63%) of the controls never took alcohol or took less than one drink per day during their most recent first-line tuberculosis treatment.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES N = 181</th>
<th></th>
<th>CONTROLS N = 181</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
<td>Number</td>
</tr>
<tr>
<td>Smoked cigarettes daily (1 cigarette or more)</td>
<td>No</td>
<td>155</td>
<td>85.64%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>26</td>
<td>14.36%</td>
</tr>
<tr>
<td>Alcohol intake on daily basis (irrespective of type)</td>
<td>Never or &lt; 1 drink per day</td>
<td>150</td>
<td>82.87%</td>
</tr>
<tr>
<td></td>
<td>1 – 4 drinks per day</td>
<td>26</td>
<td>14.37%</td>
</tr>
<tr>
<td></td>
<td>≥ 5 drinks per day</td>
<td>5</td>
<td>2.76%</td>
</tr>
</tbody>
</table>

Figure 4.12 shows the proportion of the study respondents with regard to their cigarette smoking and alcohol drinking habits during their most recent first-line tuberculosis treatment. For alcohol
drinking, the study respondents who took one or more drinks per day were categorized as ‘Yes’ and those who never drunk or drunk less than one drink per day were categorized as ‘No’.

Figure 4.12: Cigarette smoking alcohol drinking habit of the study respondents during most recent first-line tuberculosis treatment (N=181 cases and 181 controls)

4.3.4.4 Directly observed tuberculosis treatment

Table 4.5 shows whether a health worker directly observed the most recent first-line tuberculosis treatment of the study respondents. It also shows the number of weeks the tuberculosis treatment was directly observed by a health worker.

The majority of the study respondents in both the case group and the control group confirmed that a health worker directly observed their recent first-line tuberculosis treatment. From the
study respondents in the case group, 159 (87.85%) of them said, they got a directly observed first-line tuberculosis treatment. Similarly, from the control group, 175 (96.69%) of the study respondents confirmed that a health worker directly observed their most recent first-line tuberculosis treatment.

Table 4.5: Directly observed tuberculosis treatment of the study respondents

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES N = 181</th>
<th></th>
<th>CONTROLS N = 181</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Directly observed by health worker while taking anti-tuberculosis drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22</td>
<td>12.15%</td>
<td>6</td>
<td>3.31%</td>
</tr>
<tr>
<td>Yes</td>
<td>159</td>
<td>87.85%</td>
<td>175</td>
<td>96.69%</td>
</tr>
<tr>
<td>For how many weeks was treatment directly observed by health worker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 2 weeks</td>
<td>29</td>
<td>16.03%</td>
<td>6</td>
<td>3.32%</td>
</tr>
<tr>
<td>3 – 4 weeks</td>
<td>65</td>
<td>35.91%</td>
<td>12</td>
<td>6.63%</td>
</tr>
<tr>
<td>5 – 6 weeks</td>
<td>50</td>
<td>27.62%</td>
<td>33</td>
<td>18.23%</td>
</tr>
<tr>
<td>7 - 8 weeks</td>
<td>37</td>
<td>20.44%</td>
<td>130</td>
<td>71.82%</td>
</tr>
</tbody>
</table>

Figure 4.13 summarizes the number of weeks of directly observed tuberculosis treatment provided to the study respondents during their most recent first-line tuberculosis. It compares the optimal seven to eight weeks of directly observed tuberculosis treatment to the sub-optimal less than seven weeks of directly observed tuberculosis treatment.

Even though the majority of the study respondents in the case group and the control group confirmed to get directly observed tuberculosis treatment, there was discrepancy between the two groups when comparing the number of weeks their treatment was observed. Only 37 (20.44%) of the study respondents in the case group got the optimal seven to eight weeks of directly observed tuberculosis treatment. Whereas in the control group, 130 (71.82%) of the study respondents had a first-line tuberculosis treatment, which was directly observed by a
health worker for seven to eight weeks. The most recent first-line tuberculosis treatment of 144 (79.56%) of the study respondents in the case group was directly observed by a health worker for less than seven weeks. In contrast to this, only 51 (28.18%) of the study respondents in the control group got the sub-optimal less than seven weeks of directly observed tuberculosis treatment.

Figure 4.13: Number of weeks of directly observed tuberculosis treatment provided to the study respondents during their most recent first-line tuberculosis treatment (N=181 cases and 181 controls)

4.3.5 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment

The current study looked into the most recent first-line tuberculosis treatment of the study respondents and assessed certain factors in relation with the treatment given. These assessed factors included the first-line tuberculosis treatment category, the first-line tuberculosis treatment outcome and the HIV status of the patient.
4.3.5.1 First-line tuberculosis treatment category

As shown in figure 4.14, the secondary data collected from the tuberculosis treatment follow-up registers of the study respondents revealed that the larger proportion of study respondents in the case group were treated as previously treated patients while the larger proportion of study respondents in the control group were treated as new patients. The documentation on the tuberculosis treatment follow-up registers showed that 60 (33.15%) of the cases and 112 (61.88%) of the controls were treated with the first-line tuberculosis treatment category for new patients with tuberculosis. Study respondents treated with the first-line tuberculosis treatment category for previously treated patients with tuberculosis accounted for 121 (66.85%) of the cases and 69 (38.12%) of the controls.

Figure 4.14: The first-line tuberculosis treatment category of the study respondents during their most recent first-line tuberculosis treatment (N=181 cases and 181 controls)
4.3.5.2 First-line tuberculosis treatment outcome

The final treatment outcomes of the study respondents’ most recent first-line tuberculosis treatment were documented on tuberculosis treatment follow-up registers as cured, completed, failed or defaulted. As shown on table 4.6, a relatively higher proportion of tuberculosis treatment failure was documented in the case group whereby 69 (38.12%) of the study respondents had a failed first-line tuberculosis treatment outcome. The majority of the study respondents in the control group accounting for 156 (86.19%) of them had a first-line tuberculosis treatment outcome of either cured or treatment completed.

Table 4.6: The first-line tuberculosis treatment outcome of the study respondents

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CASES N = 181</th>
<th>CONTROLS N = 181</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percentage</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure/complete</td>
<td>80</td>
<td>44.20%</td>
</tr>
<tr>
<td>Failure</td>
<td>69</td>
<td>38.12%</td>
</tr>
<tr>
<td>Default</td>
<td>32</td>
<td>17.68%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

Figure 4.15 shows that the proportion of the study respondents failing or defaulting first-line tuberculosis treatment was higher in the case group when compared to those in the control group. Study respondents in the control group on the other hand had higher cure or treatment completion rate than those in the case group.
4.3.5.3 HIV status during first-line tuberculosis treatment

During the current study, it was noted that all respondents were tested for HIV and the results were documented on tuberculosis treatment follow-up registers. As shown in figure 4.16, from all the study respondents, 26 (14.36%) of the cases and 22 (12.15%) of the controls were found to be HIV positive. An HIV negative result was documented for 155 (85.64%) of the study respondents in the case group and for 159 (87.85%) of the study respondents in the control group.
Figure 4.16: The proportions of the HIV status of the study respondents during their most recent first-line tuberculosis treatment (N=181 cases and 181 controls)

4.3.6 Results from logistic regression analysis

After adjusting for possible confounding factors with multivariate analysis, the current study analysed the data from the study results to identify the significant factors leading to the development of drug resistant tuberculosis in Ethiopia. These significant factors were identified using Odds Ratio (OR) and a chi square test, which gave a p-value.

The odds of a sub-division of a study variable occurring on study respondents in the case group when compared with study respondents the control group was analysed. Crude Odds Ratio (COR) was calculated by comparing sub-divisions of a single variable only. Adjusted Odds Ratio (AOR) was calculated to assess the level of significance of the association of a single study variable with the development of drug resistant tuberculosis, when adjusted with other study
variables. A 95% Confidence Interval (CI) was taken as a range for the study result, when calculating the crude odds ratios and the adjusted odds ratios.

4.3.6.1 Logistic regression analysis of the sociodemographic characteristics of the study respondents

As shown on table 4.7, being male or female by gender had no significant association with the development of drug resistant tuberculosis. Males and females had almost equivalent proportion with the odds of male gender being associated with the development of drug resistant tuberculosis calculated as adjusted odds ratio of 1.22 (95% CI: 0.81 – 1.86) and p-value of 0.40.

The current study also found out that belonging to different age groups had no impact on the development of drug resistant tuberculosis. Taking study respondents who had an age of 45 and above as constant, there was no significant risk of developing drug resistant tuberculosis in study respondents in the age groups 5 to 24 (AOR: 1.42, 95% CI: 0.92 – 2.22) and 25 to 44 (AOR: 1.40, 95% CI: 0.92 – 2.12) with p-values of 0.15 and 0.14 respectively (Table 4.7).

According to the current study, the study respondents’ marital status had nothing to do with the development of drug resistant tuberculosis. The study respondents with drug resistant tuberculosis who were single at the time of the study, had an adjusted odds ratio of 1.34 (95% CI: 0.88 – 2.02) and p-value of 0.21. The odds of being divorced or widowed and having drug resistant tuberculosis was also an insignificant study result (AOR: 1.25, 95% CI: 0.65 – 2.43) with a p-value of 0.62 (Table 4.7).

The fact that the study respondents were better educated or not did not have impact on their acquisition of drug resistant tuberculosis. The risk of developing drug resistant tuberculosis in the study respondents who were not educated at all or who were educated to 8th grade and below was found to be with an adjusted odds ratio of 1.12 (95% CI: 0.65 – 1.93) and a p-value of
Based on the criteria of the current study, this result showed insignificant difference in the risk of developing drug resistant tuberculosis between in the study respondents who were not educated at all or who were educated to 8\textsuperscript{th} grade and below and those study respondents educated to the level of 9\textsuperscript{th} to 12\textsuperscript{th} grade, college or above (Table 4.7).

As shown in table 4.7, the study respondents with no work and those who were students or farmers at the time of the study were categorised as unemployed. Employed category included those study respondents who were government employed, private employed and self-employed. The adjusted odds ratio of unemployed study respondents who had drug resistant tuberculosis was 1.12 (95\% CI: 0.74 – 1.69) with a p-value of 0.67. In other words, this study result showed that there was no significant difference in occupation status between the study respondents in the case group and the study respondents in the control group.

In general, the current study found out that there was no significant association between the sociodemographic characteristics of the study respondents and the development of drug resistant tuberculosis in Ethiopia (Table 4.7).
Table 4.7: Logistic regression analysis of the sociodemographic characteristics of the study respondents

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES N=181</th>
<th>CONTROLS N=181</th>
<th>CRUDE OR* (95% CI**)</th>
<th>P-VALUE</th>
<th>ADJUSTED OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>101</td>
<td>97</td>
<td>1.09 (0.72 - 1.65)</td>
<td>0.40</td>
<td>1.22 (0.81 – 1.86)</td>
</tr>
<tr>
<td>Female</td>
<td>80</td>
<td>84</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 - 24</td>
<td>58</td>
<td>52</td>
<td>1.170 (0.75 – 1.83)</td>
<td>0.15</td>
<td>1.42 (0.92 – 2.22)</td>
</tr>
<tr>
<td>25 - 44</td>
<td>103</td>
<td>93</td>
<td>1.250 (0.83 – 1.89)</td>
<td>0.14</td>
<td>1.40 (0.92 – 2.12)</td>
</tr>
<tr>
<td>≥ 45</td>
<td>20</td>
<td>36</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>99</td>
<td>92</td>
<td>1.17 (0.77 – 1.77)</td>
<td>0.21</td>
<td>1.34 (0.88 – 2.02)</td>
</tr>
<tr>
<td>Married</td>
<td>62</td>
<td>71</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Divorced/Widow</td>
<td>20</td>
<td>18</td>
<td>1.13 (0.57 – 2.21)</td>
<td>0.62</td>
<td>1.25 (0.65 – 2.43)</td>
</tr>
<tr>
<td>Educational status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Grade and below</td>
<td>37</td>
<td>30</td>
<td>1.29 (0.76 – 2.20)</td>
<td>0.78</td>
<td>1.12 (0.65 – 1.93)</td>
</tr>
<tr>
<td>9th Grade and above</td>
<td>144</td>
<td>151</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>88</td>
<td>77</td>
<td>1.28 (0.84 – 1.93)</td>
<td>0.67</td>
<td>1.12 (0.74 – 1.69)</td>
</tr>
<tr>
<td>Employed</td>
<td>93</td>
<td>104</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*OR = Odds Ratio; **CI = Confidence Interval

4.3.6.2 Logistic regression analysis of the tuberculosis disease related conditions

As shown in table 4.8, the current study found out that the development of drug resistant tuberculosis was strongly associated with the presence of history of two or more previous episodes of illness with tuberculosis. The odds of having history of two or more previous episodes of illness with tuberculosis was nearly 15 times higher in the study respondents in the case group than the study respondents in the control group with adjusted odds ratio of 14.84 (95% CI: 8.90 –24.75) and a p-value of 0.00.

History of previous hospitalization for any illness did not show significant difference between the patients with drug resistant tuberculosis in the case group and patients with successful first-line
tuberculosis treatment outcome in the control group. The adjusted odds ratio of patients with drug resistant tuberculosis to be hospitalized prior to their illness at the time of the study was 1.31 (95% CI: 0.96 – 1.78) with a p-value of 0.11. Thus, previous hospitalization was not associated with the development of drug resistant tuberculosis according to the current study finding (Table 4.8).

Table 4.8 shows that direct transmission of drug resistant mycobacterium tuberculosis bacteria from a patient with drug resistant tuberculosis did not have strong evidence in the current study. The odds of the study respondents in the case group having a household or close contact with a patient with drug resistant tuberculosis was insignificant. The adjusted odds ratio of the study respondents in the case group who lived in the same household or in close contact with a patient with drug resistant tuberculosis was 1.38 (95% CI: 0.72 – 2.65) with a p-value of 0.41.

As shown in table 4.8, the presence of chronic diseases other than tuberculosis and HIV, had an adjusted odds ratio of 1.41 (95% CI: 0.93 – 2.16) with a p-value of 0.13. This result showed that the presence of chronic diseases like hypertension and diabetes mellitus in the study respondents in the case group was not a significant factor that led to the development of drug resistant tuberculosis.
Table 4.8: Logistic regression analysis of the tuberculosis disease related conditions

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES N=181</th>
<th>CONTROLS N=181</th>
<th>CRUDE OR* (95% CI**)</th>
<th>P-VALUE</th>
<th>ADJUSTED OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tuberculosis episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>47</td>
<td>143</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Two or more</td>
<td>134</td>
<td>38</td>
<td>10.73 (6.59 – 17.48)</td>
<td>0.00</td>
<td>14.84 (8.90 – 24.75)</td>
</tr>
<tr>
<td>Previously hospitalized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117</td>
<td>132</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>64</td>
<td>49</td>
<td>1.47 (0.94 – 2.31)</td>
<td>0.11</td>
<td>1.31 (0.96 – 1.78)</td>
</tr>
<tr>
<td>Household or close contact drug resistant tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>159</td>
<td>163</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>18</td>
<td>1.25 (0.65 – 2.43)</td>
<td>0.41</td>
<td>1.38 (0.72 – 2.65)</td>
</tr>
<tr>
<td>Presence of other chronic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>104</td>
<td>117</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>64</td>
<td>1.35 (0.89 – 2.07)</td>
<td>0.13</td>
<td>1.41 (0.93 – 2.16)</td>
</tr>
</tbody>
</table>

*OR = Odds Ratio; **CI = Confidence Interval

4.3.6.3 Logistic regression analysis of the tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment

According to the current study results, neither the side effects of anti-tuberculosis drugs in general nor the commonest anti-tuberculosis drugs side effect vomiting specifically, were associated with the development of drug resistant tuberculosis. As shown in table 4.9, the adjusted odds ratio for patients with drug resistant tuberculosis to have any kind of the side effects of anti-tuberculosis drugs during the most recent first-line tuberculosis treatment was 1.08 (95% CI: 0.88 – 1.33) with a p-value of 0.53. There was also no significant difference in the occurrence of the anti-tuberculosis drugs side effect vomiting between the cases and the controls during their most recent first-line tuberculosis treatment (AOR: 1.07; 95% CI: 0.84 – 1.37 and p-value: 0.67).

Interruption of taking first-line anti-tuberculosis drugs for one day or more was significantly associated with the development of drug resistant tuberculosis with an adjusted odds ratio of
4.28 (95% CI: 2.76 – 6.64) and a p-value of 0.00. In other words, the current study showed that patients with drug resistant tuberculosis had interrupted taking first-line anti-tuberculosis drugs for one day or more during their most recent first-line tuberculosis treatment with an adjusted odds ratio of more than four times when compared with those patients with successful first-line tuberculosis treatment outcome (Table 4.9).

The personal habit of the study respondents shown in table 4.9, which was cigarette smoking during their most recent first-line tuberculosis treatment did not have association with the development of drug resistant tuberculosis (AOR: 1.17; 95% CI: 0.62 – 2.22 and p-value: 0.75). The odds of having drug resistant tuberculosis from taking one or more alcohol drinks per day during the most recent first-line tuberculosis treatment was also insignificant (AOR: 1.46; 95% CI: 0.82 – 2.58 and a p-value: 0.25).

The most recent first-line tuberculosis treatment, which was not directly observed by a health worker for 7 to 8 weeks was a significant factor associated with the development of drug resistant tuberculosis. A health worker did not directly observe the most recent first-line tuberculosis treatment of the study respondents in the case group for 7 to 8 weeks with an adjusted odds ratio of 13.41 (95% CI: 8.06 – 22.29) and a p-value of 0.00 (Table 4.9).
Table 4.9: Logistic regression analysis of the tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>CRUDE OR* (95% CI**)</th>
<th>P-VALUE</th>
<th>ADJUSTED OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-tuberculosis drug side effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>87</td>
<td>94</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>94</td>
<td>87</td>
<td>1.17 (0.77 – 1.76)</td>
<td>0.53</td>
<td>1.08 (0.88 – 1.33)</td>
</tr>
<tr>
<td><strong>Suffered drug side effect vomiting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>104</td>
<td>109</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>72</td>
<td>1.12 (0.74 – 1.70)</td>
<td>0.67</td>
<td>1.07 (0.84 – 1.37)</td>
</tr>
<tr>
<td><strong>Interrupted anti-tuberculosis for at least a day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>64</td>
<td>121</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>117</td>
<td>60</td>
<td>3.69 (2.39 – 5.69)</td>
<td>0.00</td>
<td>4.28 (2.76 – 6.64)</td>
</tr>
<tr>
<td><strong>Daily smoked cigarettes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>155</td>
<td>164</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>26</td>
<td>17</td>
<td>1.62 (0.85 – 3.10)</td>
<td>0.75</td>
<td>1.17 (0.62 – 2.22)</td>
</tr>
<tr>
<td><strong>Alcohol on daily basis during tuberculosis treatment (irrespective of type):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never or &lt; 1 drink per day</td>
<td>150</td>
<td>155</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>≥ 1 drinks per day</td>
<td>31</td>
<td>26</td>
<td>1.23 (0.70 – 2.17)</td>
<td>0.25</td>
<td>1.46 (0.82 – 2.58)</td>
</tr>
<tr>
<td><strong>Directly observed by health worker while taking anti-tuberculosis for 7 – 8 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>144</td>
<td>51</td>
<td>9.92 (6.11 – 16.12)</td>
<td>0.00</td>
<td>13.41 (8.06 – 22.29)</td>
</tr>
<tr>
<td>Yes</td>
<td>37</td>
<td>130</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*OR = Odds Ratio; **CI = Confidence Interval
4.3.6.4 Logistic regression analysis of the first-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment

As shown in table 4.10, being treated with the treatment category for previously treated patients during the most recent first-line tuberculosis treatment had significant association with the development of drug resistant tuberculosis with an adjusted odds ratio of 3.70 (95% CI: 2.40 – 5.72) and a p-value of 0.00.

Table 4.10 shows that the most recent first-line tuberculosis treatment outcome of treatment failure was significantly associated with the development of drug resistant tuberculosis (AOR: 39.19; 95% CI: 12.05 - 127.46 and p-value 0.00). The other unfavourable treatment outcome of defaulting the most recent first-line tuberculosis treatment was not found to have significant association with the development of drug resistant tuberculosis in the current study (AOR: 1.45; 95% CI: 0.88 – 2.40 and p-value 0.18).

The current study found out that being HIV positive did not increase the chance of developing drug resistant tuberculosis. The adjusted odds ratio for patients with drug resistant tuberculosis who were HIV positive was just 0.91 (95% CI: 0.50 – 1.67) with a p-value of 0.88 (Table 4.10).
Table 4.10: Logistic regression analysis of the first-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>CASES</th>
<th>CONTROLS</th>
<th>CRUDE OR* (95% CI**)</th>
<th>P-VALUE</th>
<th>ADJUSTED OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment category during the recent tuberculosis treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>60</td>
<td>112</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Previously treated</td>
<td>121</td>
<td>69</td>
<td>3.27 (2.13 – 5.04)</td>
<td>0.00</td>
<td>3.70 (2.40 – 5.72)</td>
</tr>
<tr>
<td>Treatment outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cure/complete</td>
<td>80</td>
<td>156</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Failure</td>
<td>69</td>
<td>3</td>
<td>36.55 (11.23 – 118.94)</td>
<td>0.00</td>
<td>39.19 (12.05 -127.46)</td>
</tr>
<tr>
<td>Default</td>
<td>32</td>
<td>22</td>
<td>1.55 (0.86 – 2.79)</td>
<td>0.18</td>
<td>1.45 (0.88 – 2.40)</td>
</tr>
<tr>
<td>HIV test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>155</td>
<td>159</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>26</td>
<td>22</td>
<td>1.21 (0.66 – 2.23)</td>
<td>0.88</td>
<td>0.91 (0.50 – 1.67)</td>
</tr>
</tbody>
</table>

*OR = Odds Ratio; **CI = Confidence Interval

4.4 SUMMARY

This research result chapter presented the study results of the current study. It presented the quantitative results of the current study by categorizing them into sociodemographic characteristics, tuberculosis disease related conditions, tuberculosis treatment adherence related conditions and first-line tuberculosis treatment related conditions. Logistic regression analysis of the study results in these categories were presented in the final section of this chapter.
CHAPTER 5
DEVELOPMENT OF CONCEPTUAL MODEL

5.1 INTRODUCTION

When doing research, the researcher can discover a new result. The result of research can also be proving or disproving an existing result. Whatever the result of research is, it should be able to contribute to the betterment of a specific phenomenon like disease in the field of health sciences. The use of research result to bring about change may require the development of a conceptual model. “According to McEwen and Wills (2019:87), a conceptual model includes a group of interrelated ideas that represent and convey a picture of a phenomenon.” Conceptual models outline concepts and explain the relationship between phenomena under study.

Based on the results of the current study the researcher developed a conceptual model, which can be used for prevention of drug resistant tuberculosis in Ethiopia. Literature sources written on implementation sciences and drug resistant tuberculosis were reviewed in the process of developing this model. Added to this was personal input by the researcher from knowledge acquired during many years of work experience on drug resistant tuberculosis. This chapter is allocated to describe the model for drug resistant tuberculosis in Ethiopia. The chapter includes the general perspective of developing a model and the specific model developed by the researcher. The model was developed following the steps of PRECEDE-PROCEED theoretical framework from phase 1 (social assessment) to phase 9 (outcome evaluation).
5.2 GENERAL ASPECTS OF MODEL

“According to Nilsen (2015:53), models are approaches used in implementation science to describe and guide the process of translating research into practice.” Models need not be the exact representations of reality to have value. “Models are theories with a more narrowly defined scope of explanation; a model is descriptive, whereas a theory is explanatory as well as descriptive” (Nilsen 2015:53). Models are graphic representations of phenomena that objectify and present study results (McEwen & Wills 2019:88). “McEwen and Wills (2019:88) divide models as theoretical and empirical.”

“There are three main levels used to develop theoretical model called concept development, statement development, and theory construction” (McEwen & Wills 2019:192). “Chinn and Kramer (2015) add two levels that involve validating the theory and applying theory in practice.”

Table 5.1 below summarizes the theoretical model development process.
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Concept development”</td>
<td>“Specifying, defining, and clarifying the concepts used to describe a phenomenon of interest”</td>
</tr>
<tr>
<td>“Statement development”</td>
<td>“Formulating and analysing statements explaining relationships between concepts; also involves determining empirical referents that can validate them”</td>
</tr>
<tr>
<td>“Theory construction”</td>
<td>“Structuring and contextualizing the components of the theory; includes identifying assumptions and organizing linkages between and among the concepts and statements to form a theoretical structure”</td>
</tr>
<tr>
<td>“Testing theoretical relationships”</td>
<td>“Validating theoretical relationships through empirical Testing”</td>
</tr>
<tr>
<td>“Application of theory in practice”</td>
<td>“Using research methods to assess how the theory can be applied in practice; research should provide evidence to evaluate the theory’s usefulness”</td>
</tr>
</tbody>
</table>

According to Walker and Avant (2019:61), there are three basic approaches to model development: synthesis strategy, derivation strategy and analysis strategy for each of the three levels (concepts, statements, and theory). Thus, in total, there are nine model development strategies, which are concept synthesis, statement synthesis, theory synthesis, concept derivation, statement derivation, theory derivation, concept analysis, statement analysis and theory analysis.
“Synthesis strategy focuses on the process of transforming practice related research about phenomena of interest into an integrated form, which allows to bring bits and pieces of knowledge together in a more useful and coherent form” (Walker & Avant 2019:111).” Derivation strategy uses analogy to obtain explanations or predictions about a phenomenon in one field from the explanations or predictions in another field” (Walker & Avant 2019:75). “Analysis strategy is the systematic evaluation of the theory for meaning, logical adequacy, usefulness, generality, parsimony, and testability “(Walker & Avant 2019:165).

The current study used synthesis strategy since the three specific aims of synthesis are similar with the aims of the study as detailed below (Walker & Avant 2019:152).

“1. Synthesis strategy aims to represent the factors that precede or influence a particular event. The current study also aimed to find factors that precede the development of drug resistant tuberculosis”.

“2. Synthesis strategy aims to represent effects that occur after some event. The current study also looked into the development of drug resistant tuberculosis after predisposing factors.

“3. Synthesis strategy aims to put related, but discrete scientific information into a more theoretically organized form. The aim of developing this model was also to put determinants of the occurrence of drug resistant tuberculosis in an organized form to devise an effective prevention strategy.”

According to Walker and Avant (2019:112), synthesis strategy has three components, which are concept synthesis, statement synthesis and theory synthesis. Each component is described below.
5.2.1 Concept synthesis

“Concept synthesis is used when concepts require development based on study findings” (McEwen & Wills 2019:145). The researcher has to design a mechanism to arrange the study finding about the study problem from his own perspective. According to Walker and Avant (2019:113), methods of synthesizing concepts follow:

“1. Qualitative synthesis—depends on sensory data and looking for similarities, differences, and patterns among the data to identify the new finding.”

“2. Quantitative synthesis—needs numbers to delineate those attributes that represent the concept and those that do not.

“3. Literary synthesis—includes reviewing literature to have new understanding about the concept or to find new concepts.”

“4. Mixed methods—use of any of the above ways either sequentially or concurrently.”

In the current study, the researcher used quantitative method to synthesize concepts. The concepts were derived from the numerical data of the study findings. Factors, which were significantly associated with the development of drug resistant tuberculosis in the current study, served as a foundation for synthesizing concepts of the model developed. The concepts created were grouped hierarchically starting from the basic requirements to prevent the development of drug resistant tuberculosis, proceeding to the processes and showing the ultimate result.

The concepts synthesized include building the capacity of health workers on drug susceptible tuberculosis and drug resistant tuberculosis and ascertaining the use of standard guidelines and follow-up formats by all health facilities. Increasing community awareness on drug susceptible tuberculosis and drug resistant tuberculosis was the other core concept. Access to quality
assured diagnostic laboratory, adequate drug supply and infection prevention mechanisms were the additional basic concepts synthesized to prevent the development of drug resistant tuberculosis in Ethiopia.

The concepts synthesized were grouped into inputs, activities, outputs and outcomes. The concepts incorporated into inputs were knowledge gap of health workers, low utilization of standard guidelines and formats, community unawareness, poor access to diagnostic laboratory service, inadequate drug supply and lack of infection prevention materials. The activities were synthesized conceptualizing poor case finding effort, poor counselling, lack of health education, poor treatment follow-up and poor infection prevention practice. The output concepts were synthesized aiming to better poor treatment adherence, high number of treatment interruption and a very low case finding effort with regard to both drug susceptible tuberculosis and drug resistant tuberculosis.

The outcomes were divided into immediate, intermediate and final. The output concepts were synthesized aiming to result in immediate outcomes of improving unwanted treatment outcomes and alleviating the high transmission of drug susceptible tuberculosis and drug resistant tuberculosis. These in turn were expected to produce intermediate outcome of addressing the high morbidity and mortality from drug susceptible tuberculosis and drug resistant tuberculosis. The final expected outcome of the model was to tackle the high burden of drug susceptible tuberculosis and drug resistant tuberculosis in Ethiopia.
5.2.2 Statement Synthesis

Statement synthesis is the second step in the development of model using synthesis strategy (Walker & Avant, 2019:127). “Relational statements are the basics of theory, as they are the ways by which the theory comes together. The process of synthesis and validation of relational statements includes developing relational statements and determining empirical” (McEwen & Wills 2019:194).

In the current study, the researcher used the statement synthesis strategy to show the relationship between two or more concepts using the current study’s findings as a base and adding personal clinical and public health experience. The following relational statements were developed to serve as a link during theory synthesis stage.

1. Lack of basic knowledge on programmatic management of drug susceptible tuberculosis by health workers can lead to incorrect treatment and follow-up of patients with drug susceptible tuberculosis. This in turn causes the conversion of drug susceptible mycobacterium tuberculosis to drug resistant strain. Health workers with inadequate knowledge on drug resistant tuberculosis as well can contribute to spread of drug resistant tuberculosis from not applying proper infection prevention methods and sub-optimal treatment and follow-up.

2. Availing standard national guidelines on programmatic management of drug susceptible tuberculosis and drug resistant tuberculosis at all health facilities to serve as a reference for health workers can improve the quality of care provided to patients with tuberculosis. All health facilities should also use the same standard treatment and follow-up formats to have a uniform system, which is easy to monitor and evaluate.

3. As tuberculosis is an illness that can easily be transmitted by droplet inhalation, lack of community awareness on preventive mechanisms can have a significant impact on increasing
the spread of both drug susceptible tuberculosis and drug resistant tuberculosis. Patients with tuberculosis and the communities they live with should be educated on ways of breaking the transmission cycle.

1. Shortage of supplies can contribute to an increase in prevalence of drug susceptible tuberculosis and drug resistant tuberculosis. A health facility should have its own laboratory or close access to another diagnostic laboratory to confirm the presence or absence of drug susceptible tuberculosis and drug resistant tuberculosis. Adequate drug supplies another resource that should be available to cure patients with confirmed drug susceptible tuberculosis and drug resistant tuberculosis. To prevent the air born spread of mycobacterium tuberculosis bacteria, supplies like masks and mechanical ventilators are required.

2. Finding cases of drug susceptible tuberculosis and drug resistant tuberculosis requires active search with high index of suspicion. Active house-to-house search for individuals with cough of two weeks or more by health extension workers is implemented in some parts of Ethiopia. However, it needs to be escalated to make it a nationwide activity. This strategy finds patients with chronic cough who did not go to a health facility. For those patients who are at a health facility for any reason, health workers should screen them for the presence of symptoms of tuberculosis. This strategy finds tuberculosis in patients who come to a health facility but are not complaining of the tuberculosis symptoms they have due to the chronic nature of the illness. These active case finding strategies lead to early diagnosis and treatment of drug susceptible tuberculosis and drug resistant tuberculosis, which halts the spread of the disease to other individuals.

3. Poor tuberculosis treatment adherence by a patient with drug susceptible tuberculosis is one contributing factor changing drug susceptible mycobacterium tuberculosis bacteria to drug resistant strain. Non-adherent patients with drug resistant tuberculosis can also have a failed treatment outcome or progress to extensively drug-resistant tuberculosis. Poor counselling and inadequate health education given to patients by health workers can be the reason that makes
patients not to adhere to treatment, as they are not well informed. Not providing directly observed tuberculosis treatment by health workers breaches the main mechanism for ascertaining whether the tablets are swallowed by the patient or not, which predisposes the patient to poor treatment adherence.

4. Apart from providing drug therapy, both drug susceptible tuberculosis and drug resistant tuberculosis require close follow-up by a health worker with regard to laboratory monitoring, drug side effect identification and management, psychosocial support and defaulter tracing. Failure to provide the necessary follow-up to patients with drug susceptible tuberculosis can result in the occurrence of drug resistant tuberculosis. Patients with drug resistant tuberculosis can also advance to the more difficult to treat, extensively drug-resistant tuberculosis, if not properly followed.

5.2.3 Theory synthesis

“Theory synthesis is a theory development strategy designed by Walker and Avant” (2019:149). In theory synthesis, concepts and statements are developed into a network (McEwen & Wills 2019:195). According to McEwen and Wills (2019:195), the aims of theory synthesis are to represent a study finding through a set of concepts and statements, to describe the entities that precede a particular finding, to predict effects of some event, or to organize research findings into theoretically organized structure.

In the current study, the researcher organized pre-outlined concepts and statements into a form of network to synthesize a comprehensive theory entitled “Model for the prevention of drug resistant tuberculosis in Ethiopia” displayed on figure 5.1 below. The theory was synthesized taking into consideration factors, which were significantly associated with the development of
drug resistant tuberculosis in the current study. These significant factors were used, as pillars of the model and ways of addressing them were incorporated as key components of the theory synthesized to prevent the development of drug resistant tuberculosis in Ethiopia.

The theory synthesized to prevent the occurrence of drug resistant tuberculosis was designed as a compact and informative graphic representation of the current study findings expressed in a model form. In developing the model, the researcher followed the three steps of theory synthesis described by McEwen and Wills (2019:195) as follows:

1. Selected the prevention of drug resistant tuberculosis as a topic of interest and specified focal concepts that lead to materialization of the selected topic.

2. Conducted a review of the literature to identify related factors and noted their relationships. Identified and recorded relationships indicating whether they are bidirectional, unidirectional, positive, neutral or negative, weak or ambiguous, or strong in support evidence.

3. Organized concepts and relational statements into an integrated representation of the prevention of drug resistant tuberculosis. Arrows were used to express the relationships among the concepts.
Figure 5.1 Model for the prevention of drug resistant tuberculosis in Ethiopia

- Adequate standard registers supply
- Provision of standard guidelines
- Tuberculosis diagnosis and drug sensitivity test access
- Personal protective equipment
- Training for health workers
- Defaulter tracing
- Linkage to treatment
- Using health extension workers
- Increased drug susceptible tuberculosis and drug resistant tuberculosis case finding
- Decreased transmission of drug susceptible tuberculosis and drug resistant tuberculosis
- Drug resistant tuberculosis free Ethiopia

INPUT

ACTIVITIES

OUTPUT

IMMEDIATE OUTCOME

INTERMEDIATE OUTCOME

OUTCOME

- Tuberculosis screening
- Tuberculosis test and drug sensitivity test
- Infection prevention
- Directly observed treatment
- Counseling and health education
- Defaulter tracing
- Linkage to treatment
- Using health extension workers
- Good treatment outcome
- Decreased treatment interruption
- Better treatment adherence
- Decreased morbidity and mortality
- Increased drug susceptible tuberculosis and drug resistant tuberculosis case finding
- Decreased transmission of drug susceptible tuberculosis and drug resistant tuberculosis
- Good treatment outcome
- Decreased treatment interruption
- Better treatment adherence
- Decreased morbidity and mortality
5.3 MODEL FOR THE PREVENTION OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

Taking into consideration the findings of the current study as pillars and adding knowledge from literature and personal experience, the researcher developed a model (see figure 5.1 above). The aim of the model developed was to point out ways of preventing the development of drug resistant tuberculosis in Ethiopia. These ways of drug resistant tuberculosis prevention were derived from determinants of the occurrence of drug resistant tuberculosis in Ethiopia according to the current study.

The model developed also incorporated issues associated with drug susceptible tuberculosis for the following reasons:

1. The clinical presentations of drug susceptible tuberculosis and drug resistant tuberculosis are similar. Thus, symptom and sign screening can detect both cases.

2. Drug susceptible tuberculosis can change to drug resistant tuberculosis if not properly treated. Thus, issues associated with treatment of drug susceptible tuberculosis have direct impact on the development of drug resistant tuberculosis.

3. Drug susceptible tuberculosis and drug resistant tuberculosis have similar mode of aerosol transmission that require the same prevention mechanisms.

The model was developed by conceptualizing the possible ways of preventing the occurrence of the statistically significant determinants of the development of drug resistant tuberculosis in the current study. The statistically significant findings of the study, which were taken as pillars of the model include, two or more episodes of tuberculosis illness, treatment not directly observed by health worker, previous first-line tuberculosis treatment outcome of failure, interruption of first-line tuberculosis treatment and previously treated first-line tuberculosis treatment category.
The inputs of the model were carefully selected aiming to answer the question, what is needed to run activities for preventing the development of drug resistant tuberculosis smoothly and effectively. A quality and adequate anti-tuberculosis drug supply is one of the basic resources needed, as a diagnosed patient with tuberculosis should start treatment immediately. Health workers should be trained on drug susceptible tuberculosis and drug resistant tuberculosis. They should also be provided with adequate standard registers for recording purposes and standard guidelines to use as a reference. Diagnosing drug susceptible tuberculosis and drug-resistant tuberculosis is the key requirement for case finding. Thus, health facilities should have the access or capacity to do microscopy, radiology and drug sensitivity tests. To prevent the transmission of drug susceptible tuberculosis and drug resistant tuberculosis, personal protective equipment and materials for patient education are of paramount importance.

The activities needed to prevent drug resistant tuberculosis focus on proper drug susceptible tuberculosis and drug-resistant tuberculosis suspect identification, diagnosing and confirming the presence of these diseases and ultimately providing the patients with proper treatment and follow-up. If patients with drug susceptible tuberculosis and patients with drug-resistant tuberculosis are identified early, diagnosed and are well treated, these patients will no longer be infectious and further transmission from these patients is halted. This in turn has direct impact on the occurrence of drug susceptible tuberculosis and drug-resistant tuberculosis as the number of people with new infection is decreased. Infection prevention is also another activity implemented during drug susceptible tuberculosis and drug-resistant tuberculosis suspect identification, diagnosis and treatment. Infection prevention aims to stop the aerosol transmission of mycobacterium tuberculosis from the patient to other individuals like health workers treating the patient, household contacts living with the patient and close contacts working with the patient.
High index of suspicion is required to identify patients who might have drug susceptible tuberculosis or drug resistant tuberculosis. Tuberculosis symptom screening should be conducted for all patients coming to a health facility at the place of triage. The triage health personnel then send all patients having a cough of two weeks or more to a specifically assigned outpatient clinic. The outpatient clinic clinician further evaluates the patient for signs and symptoms of tuberculosis as well as for determinants of the occurrence of drug resistant tuberculosis.

The clinician then orders investigations for drug susceptible tuberculosis only or for both drug susceptible tuberculosis and drug resistant tuberculosis according to the findings. Tuberculosis symptom screening should also be conducted at other patient entries like HIV clinic, paediatric clinic, antenatal clinic, chronic care clinic and specialty clinics. Tuberculosis symptom screening for contacts of patients with drug susceptible tuberculosis or drug resistant tuberculosis by clinicians following them is another way of suspect identification. House to house, tuberculosis symptom screening by health extension workers is another means of identifying tuberculosis patients in the community.

All tuberculosis suspects identified by screening should be tested for the presence of mycobacterium tuberculosis bacteria either by direct microscopy or by gene x-pert test. Chest x-ray can be supplemental investigation if available. All drug resistant tuberculosis suspects identified should be tested for anti-tuberculosis drug sensitivity. Drug sensitivity testing should be done preferably by gene x-pert for quick result. Culture and line probe assay are the other options if gene x-pert is not available. The standard laboratory procedures should be followed while doing these tests to get a reliable result.
Patients diagnosed to have drug susceptible tuberculosis or drug resistant tuberculosis should be linked to treating health facilities as soon as possible. These treating health facilities should be geographically closer to the patients’ residence as much as possible for adherence reason. The treating health facilities should do baseline laboratory investigations and decide on initiation of treatment as early as possible.

Once a decision is made to start treatment, the first thing to do is provision of detailed counselling and health education to the patient and caretaker. The counselling focuses on treatment adherence detailing how the treatment will be given and what is expected of the patient and caretaker. It also includes explaining the benefits of adhering to treatment and the negative consequences of non-adherence. Health education on symptoms of the disease, modes of disease transmission, ways of infection prevention and common drug side effects should be given to the patient and caretaker.

Health professionals and treatment supporters should directly observe the treatment of patients with drug susceptible tuberculosis and patients with drug resistant tuberculosis throughout the treatment course. The health professional providing the drugs should directly observe when the patient swallows the tablets during the intensive phase of treatment. This intensive phase of treatment is the first two months of treatment in drug susceptible tuberculosis and the first eight months of treatment in drug resistant tuberculosis.

In the continuation phase after these months, the caretaker can be trained as treatment supporter at home to observe when the patient swallows the tablet and to put mark on the patient follow-up card accordingly. Health extension workers who work at health posts, which are the nearest health structures to many Ethiopians living in rural areas, can also be used to
observe treatment. The use of health extension workers improves treatment adherence as it decreases the distance the patients have to travel daily to take their medicines.

Patients with drug susceptible tuberculosis or patients with drug resistant tuberculosis may discontinue treatment and follow-up for various reasons. Tracing the patients who defaulted from treatment and continuing their follow-up is one of the activities done by health professionals following them. The patients who are lost to follow-up can be traced by their permanent address and through their caretakers. Health extension workers who work closer to the patients can go to the patients’ home, provide counselling and convince them to resume their treatment and follow-up. This will enable the patients to complete their treatment and have a good treatment outcome.

As the mode of transmission of mycobacterium tuberculosis bacteria is by droplet inhalation, infection prevention has a key role in the prevention of the occurrence of drug resistant tuberculosis. The infection prevention measures focus on ways of preventing the bacteria from being inhaled by un-infected individuals. Covering the mouth and nose while sneezing and coughing is the first measure of infection prevention taken by the patient. Health workers, caretakers and patients need to wear specific types of protective masks. Good natural ventilation at health facilities and the patients’ home can wipe out the bacteria from the rooms. Inpatient treatment facilities for drug resistant tuberculosis patients should additionally have mechanical ventilation mechanisms.

The overall output of providing counselling and health education as well as directly observing treatment is better adherence to treatment of drug susceptible tuberculosis and drug resistant tuberculosis. Proper linkage to treating health facility, defaulter tracing and using health extension workers for treatment follow-up can result in significant decrease in treatment
interruption. Regular symptom screening followed by proper laboratory diagnosis can result in increase in case finding of both drug susceptible tuberculosis and drug resistant tuberculosis.

Better treatment adherence and decreased treatment interruption will have an immediate outcome of good treatment outcome. Increased drug susceptible tuberculosis and drug resistant tuberculosis case finding with early treatment initiation and infection prevention will result in decreased transmission of both drug susceptible tuberculosis and drug resistant tuberculosis. The good treatment outcome and reduced transmission will in turn result in decreased morbidity and mortality from drug susceptible tuberculosis and drug resistant tuberculosis as an intermediate outcome. If the prevention activities of this model are regularly implemented, the ultimate outcome will be a country free of drug susceptible tuberculosis and drug resistant tuberculosis. The information in this model developed will be distributed to health workers in Ethiopia through government, non-government and private health structures after presenting the study findings and the model developed to relevant stakeholders overseeing these health structures.

5.4 EVALUATION OF MODEL FOR THE PREVENTION OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

The model developed for the prevention of drug resistant tuberculosis in Ethiopia was evaluated by systematically examining the theory synthesized. The intent of the evaluation was to determine how well the theory guides implementation of strategies for the prevention of drug resistant tuberculosis in Ethiopia. "Chinn and Kramer (2015) outlined a two-phase process of evaluating a model the final outcome of which is a decision whether to use the theory or not." Basic components of this process are theory description and critical reflection, which are described below.
5.4.1 Theory description

“According to Chinn and Kramer (2015), theory description has six components, which are purpose, concepts, definitions, relationships, structure, and assumptions.”

“1. The purpose of the theory should be stated explicitly or at least be identifiable in the text of the theory.” The purpose of the model developed in the current study was clearly stated, which was to prevent the occurrence of drug resistant tuberculosis in Ethiopia.

2. The concepts of the theory should be linguistically expressed. The concepts of the model synthesized based on evidence from the current study’s statistically significant findings were explained with clear and adequately detailed statements.

3. Definitions or meanings of concepts should be conveyed to give character to the theory. The main purposes of the concepts synthesized for developing the current model were detailed for each concept. While explaining what the concept synthesized aimed to achieve, the meaning of the concept was made clear.

4. Relationships is a term given to an element, which states that concepts should be structured into a systematic form that links each concept with others. The current model was also structured in a way that showed interlinkage between different concepts. For example, building the capacity of health workers on drug susceptible tuberculosis and drug resistant tuberculosis ascertains the use of standard guidelines and formats. It also has a direct impact on increasing community awareness on drug susceptible tuberculosis and drug resistant tuberculosis as trained health workers can use the knowledge they gained to give all the necessary counselling and health education to the community. Added to this, a health worker trained on updated
standard guidelines provides clinical care and diagnostic laboratory service to patients with better quality than those who are not trained.

“5. Structure implies that the relationships should be linked to form a whole when the ideas of the theory interconnect.” Structure facilitates application of reasoning of theory. When the ideas of the current model interconnect, they give a structure that is linked to form one idea, which is preventing the development of drug resistant tuberculosis.

“6. Assumptions are concerned with truths determining the types of concepts, definitions, purpose, relationship, and structure.” The facts that determined the nature of concepts synthesized for the current model were factors significantly determining the occurrence of drug resistant tuberculosis in the current study. These factors also shaped the definitions, purpose, relationship, and structure of the model for the prevention of drug resistant tuberculosis in Ethiopia.

5.4.2 Critical reflection

“According to Chinn and Kramer (2015), critical reflection of a theory determines how well a theory serves its purpose.” “Critical reflection analyses clarity, consistency, complexity, generality, accessibility, and importance of the theory”. In assessing clarity and consistency, Chinn and Kramer’s (2015) critical reflection would examine:

“1. Semantic clarity: Are the concepts defined? Do the concepts establish empirical meaning?” The concepts synthesized for the current model were well defined at the initial stage of its development. All the concepts used to construct the model had an empirical meaning, which elaborated specific activities that aimed at preventing the development of drug resistant tuberculosis in Ethiopia.
“2. Semantic consistency: Are the concepts used consistently? Are the concepts congruent with their definitions?” All the concepts synthesized were used consistently throughout the development process of the current model. The concepts written at the stage of concept synthesis were reflected while writing statement synthesis and theory synthesis stages as well. These concepts were also used in a manner congruent with their initial definition during each step of constructing the current model.

“3. Structural clarity: Are the connections and reasoning within the theory understandable?” The model for the prevention of drug resistant tuberculosis in Ethiopia started from initial inputs and systematically proceeded to activities and their outputs before showing immediate, intermediate and ultimate outcomes. These distinctive steps followed while developing the current model can give it structural clarity. These clear connections and the reasoning stated in the current model can make it easily understandable.

“4. Structural consistency: Is the structure of the theory consistent in its form?” All the necessary precautions were taken to keep a consistent structure while developing the model for the prevention of drug resistant tuberculosis. The concepts of the model for the prevention of drug resistant tuberculosis in Ethiopia are interrelated with each other and structured in a coherent way. These qualities of the current model give it structural consistency.

“5. Simplicity or complexity: Is the theory simple? Is the theory complex?” Chinn & Kramer (2015) evaluate simplicity of a model by the number of concepts and their interrelationships, which should be minimal. A model should be as simple as possible with a small number of concepts. The model for the prevention of drug resistant tuberculosis in Ethiopia has five basic concepts, which are interrelated in a specific limited way. These characteristics of the model make it a simple one.

“6. Generality: Does the theory cover a wide scope of experiences and phenomena?”
Even though the current study was on factors associated with the development of drug resistant tuberculosis in Ethiopia, the model developed widened its scope to include drug susceptible tuberculosis. The model for the prevention of drug resistant tuberculosis in Ethiopia also included ways for prevention of drug susceptible tuberculosis. The wide scope of the current model, which includes the prevention mechanisms of both drug resistant tuberculosis and drug susceptible tuberculosis, gives the model more generality. Generally, the current model can be used to design a good strategy for the prevention of drug susceptible tuberculosis alone at places where drug resistant tuberculosis is not a problem. In places where drug resistant tuberculosis is a challenge, it can be used to design a combined strategy as decreasing the number of drug susceptible tuberculosis cases and treating them properly decreases the number of drug susceptible mycobacterium tuberculosis bacteria that change into a drug resistant strain. Though the current model is developed for Ethiopia, it can be adopted by other countries with modification according to their local context. The model can also be modified to be used in designing strategies for the prevention of other airway diseases like pneumonia, bronchitis and asthma.

“7. Accessibility: How accessible is the theory?”

The researcher believes that the empirical grounding of the concepts of the model for the prevention of drug resistant tuberculosis in Ethiopia is clear. Hard copies of the current model can be distributed to governmental and non-governmental organizations working on tuberculosis programmes in Ethiopia. These organizations can use the current model as a base while designing or updating strategies for the prevention of drug resistant tuberculosis and drug susceptible tuberculosis. Electronic copies of the model can be distributed to all stakeholders working on health so that they will be able to adapt and modify it to fit for designing strategies for the prevention of other diseases.

“8. Importance: How can the theory support the medical practice, research and education?”
The model for the prevention of drug resistant tuberculosis in Ethiopia can contribute to medical practice by providing clear guidance to health professionals on a model to follow to prevent the development of drug resistant tuberculosis in the community they are serving. Following the current model, health facility managers can plan for training health workers and acquisition of adequate supplies. Clinicians can implement regular tuberculosis case finding activities besides providing proper treatment and follow-up for tuberculosis patients. Counsellors and health educators can increase awareness of the community on tuberculosis. In general, the current model can bring about change in medical practice that can ultimately prevent the development of drug resistant tuberculosis in Ethiopia. The current model can also serve as a reference to researches on tuberculosis or other diseases who may need to refer it. The model for the prevention of drug resistant tuberculosis in Ethiopia can be part of a short training or formal education on programmatic management of drug resistant tuberculosis if accepted by authorities responsible for preparing training manuals.

5.5. SUMMARY

This chapter focused on development of conceptual model based on the study results. The current study used synthesis strategy, which starts from concept synthesis, proceeds to statement synthesis and ends up synthesizing a theory or model. A model termed “model for the prevention of drug resistant tuberculosis in Ethiopia” was ultimately developed. A graphic representation of this model was displayed followed by a detailed explanation. Finally, the model developed for the prevention of drug resistant tuberculosis in Ethiopia was evaluated by systematically examining the theory synthesized. This model can also be used for the prevention of drug susceptible tuberculosis by itself or as part of the prevention of drug resistant tuberculosis.
CHAPTER 6
DISCUSSION

6.1. INTRODUCTION

This chapter discusses the current study’s results by comparing them with results of studies carried out in Ethiopia, Africa and elsewhere in the world. The discussion in this chapter follows the sequence of the results presented in chapter 4. Thus, this discussion chapter has sub-headings similar to those in the result chapter.

6.2. DISCUSSION OF THE STUDY RESULTS

6.2.1 Sociodemographic characteristics of the study respondents

Sociodemographic characteristics of the study respondents were not significantly determining the occurrence of drug resistant tuberculosis in the current study. Assefa, Seyoum and Oljira (2017:209) also concluded that sociodemographic characteristics of the study respondents were not determinants for the occurrence of drug resistant tuberculosis in a study done in Addis Ababa, Ethiopia.

However, different studies indicate different sociodemographic determinants of the development of drug resistant tuberculosis. There is no single sociodemographic factor identified as a common predictor of drug resistant tuberculosis by majority of studies.
6.2.1.1 Gender

The majority of the respondents of this study were males, representing 101 (55.80%) and 97 (53.59%) of the cases and the controls respectively. However, being male or female by gender was not a significant determinant for the development of drug resistant tuberculosis in the current study. This was due to the small difference in male-to-male and female-to-female proportion between the cases and the controls. A study conducted in Ethiopia had similar finding with the current study, which found the gender of a patient not to be a determinant factor for the development of drug resistant tuberculosis (Demile, Zenebu, Shewaye, Xia & Guadie 2018:249). Another study conducted in Mali also did not find any significant association between the gender of an individual and the development of drug resistant tuberculosis (Bayaa, Achenbachc, Konea & Tolobab 2019:149).

There were also studies, which had a finding different from the current study. A study carried out in Addis Ababa, Ethiopia found out that there was a high impact of drug resistant tuberculosis on the male population (Worku, Getinet, Mohammed & Yang 2018:167). Another study carried out in Maputo, Mozambique also found out that multidrug-resistant tuberculosis was most common in males (Pires, Folgosa, Nquobile, Gitta & Cadir 2014:142).

On the contrary, another study conducted in Nepal showed that female gender was significantly associated multidrug-resistant tuberculosis (Maharjan, Singh, Khadka & Aryal 2017:106). “A retrospective study on epidemiological trends of drug resistant tuberculosis in China from 2007 to 2014 identified that multidrug-resistant tuberculosis patients were more likely to be female, aged 25 to 44 years (Xiao-chun, Xian-xin, Jiang-nan, Yao, Chun-bao, Guo-ru & Huai-chen 2016:15).”
This variation in results of association of gender of an individual with drug resistant tuberculosis can be due to difference in geographical, cultural and economic situation of study respondents.

6.2.1.2 Age

The majority of patients with drug resistant tuberculosis who participated in the current study, accounting for 124 (68.51%) of the cases, had an age in the range of 15 to 34 years. However, a similarly higher proportion patients with successful first-line tuberculosis treatment outcome, which made up 103 (56.90%) of the controls, also had an age between 15 and 34 years. This similarity in age range between the cases and the controls made age an insignificant determinant of the occurrence of drug resistant tuberculosis. Age was also not a significant determinant of the occurrence of drug resistant tuberculosis in a study carried out in Addis Ababa, Ethiopia (Hirpa, Medhin, Girma, Melese, Mekonen, Suarez & Ameni 2013:782). There was also a similar finding by a study done in Sudan, which ruled out age from being a determinant of the occurrence of drug resistant tuberculosis (Elduma, Mansournia, Foroushani, Hamdan, Elegail, Elsone & Naie 2019:41).

There were also studies, which found out that individuals of specific age groups were significantly vulnerable to develop drug resistant tuberculosis. A study conducted in Addis Ababa, Ethiopia found out that there was a high impact of drug resistant tuberculosis in the age group of 25–44 years (Worku et al 2018:167). Similarly, a study conducted in Maputo, Mozambique, found out that drug resistant tuberculosis was most common in the 21-40 year age bracket (Pires et al 2014:142).
6.2.1.3 Marital status

The study respondents’ marital status had no significant relationship with the occurrence of drug resistant tuberculosis in the current study. In other words, being single, married, divorced or widowed was not a determinant factor for acquisition of drug resistant tuberculosis in the current study. A similar study finding was indicated in Desissa, Workineh and Beyene' study (2018:422), where marital status was not found to determinant of the occurrence of drug resistant tuberculosis in East Shoa, Ethiopia.

6.2.1.4 Educational status

A previous study conducted in the south-western part of Ethiopia found out that the educational status of the patients was not a predictor of the occurrence of drug resistant tuberculosis (Gobena, Ameya, Haile, Abreha, Worku, & Debela 2018:30). The current study also did not find a significant relationship between the occurrence of drug resistant tuberculosis and the educational status of the study respondents. This shows that having a lower level of academic knowledge did not predispose the study respondents to the occurrence of drug resistant tuberculosis at a significant level. The other way round, higher level of education was not preventing the study respondents from developing drug resistant tuberculosis.

6.2.1.5 Occupation

The current study found out that whether the study respondent was an individual with no work, student, farmer, government employed, private employed or self-employed had no impact on the occurrence of drug resistant tuberculosis. A study conducted in Addis Ababa, Ethiopia also showed that there was no significant difference in occupation status between patients with drug resistant tuberculosis and patients with successful treatment outcome of first-line tuberculosis treatment (Hirpa et al 2013:782).
6.2.2 Tuberculosis disease related conditions

6.2.2.1 Number of previous tuberculosis episodes

The current study found out that the occurrence of drug resistant tuberculosis was strongly associated with history of first-line treatment for two or more previous episodes of illness with tuberculosis. According to the current study, history of two or more previous first-line treatments for illness with tuberculosis was nearly 15 times more common in patients with drug resistant tuberculosis than in patients with successful treatment outcome of first-line tuberculosis treatment. There were studies done in Ethiopia and other countries, which had similar finding.

A study conducted at Saint Peter Hospital in Addis Ababa, Ethiopia also found out that the likelihood of history of two or more previous first-line treatments for illness with tuberculosis was 15.7 times higher among patients with drug resistant tuberculosis than in patients with successful treatment outcome of first-line tuberculosis treatment (Dessalegn, Daniel, Behailu, Wagnew & Nyagero 2016:5). Another study conducted in Addis Ababa, Ethiopia also found history of two or more previous first-line treatments for illness with tuberculosis to be nearly 32 times more common in patients with drug resistant tuberculosis than in patients with successful treatment outcome of first-line tuberculosis treatment (Hirpa et al 2013:782).

A case-control study conducted in Sudan, East Africa, also showed strong association between history of two or more previous first-line treatments for illness with tuberculosis and the occurrence of drug resistant tuberculosis with an adjusted odds ratio of 54.85 (95% confidence interval, 30.48 - 98.69) (Elduma, Mansournia, Foroushani, Hamdan, Elegail, Elsony & Naienen 2019:41). Another study conducted in Mali, West Africa, also found out that two courses of prior first-line treatments for illness with tuberculosis was significantly associated with the occurrence
of drug resistant tuberculosis with an adjusted odds ratio of 3.25 (95% confidence interval, 1.44 - 7.30) (Baya, Achenbach, Kone & Toloba 2019:149).

There were also studies conducted in Asia, which had similar result as the current study. History of two or more previous first-line treatments for illness with tuberculosis was found to have significant association with the occurrence of drug resistant tuberculosis by studies done in Thailand, Malaysia and China (Chuchottaworn, Thanachartwet, Sangsayunh, Than, Sahassananda, Surabotsophon & Desakorn 2015:10; Elmi, Hasan, Abdullah, Jeab, Alwi & Naing 2015:1076; Lv, Lu, Shi & Zhou 2017:1779).

Resistance to anti-tuberculosis drugs is a natural phenomenon occurring in all wild-type populations of mycobacterium tuberculosis by spontaneous chromosomal mutations (Kanabus 2018). Within wild-type mycobacterium tuberculosis populations, small populations of mutants are found to be resistant to anti-tuberculosis drugs. However, repeated exposure to anti-tuberculosis drugs increases the number of these small populations of mutant bacteria leading to the occurrence of drug resistant tuberculosis (Kanabus 2018). This explains why repeated exposure to first-line anti-tuberculosis drugs, due to treatment of two or more episodes of tuberculosis illness, was more common in patients with drug resistant tuberculosis than in patients with successful treatment outcome of first-line tuberculosis treatment in the current study.

6.2.2.2 Previous hospitalization

According to the current study, previous hospitalization was not associated with the development of drug resistant tuberculosis. This implies that hospital acquired infection with drug resistant mycobacterium tuberculosis bacteria, which is categorized as primary drug resistant tuberculosis, was not a significant cause for the development of drug resistant
tuberculosis in the current study. A case-control study on the risk factors for the development of drug resistant tuberculosis in Bangladesh also found no association between previous hospitalization and the development of drug resistant tuberculosis (Rifat, Milton, Hall, Oldmeadow, Islam, Husain, Akhanda & Siddiquea 2014:8).

However, previous hospitalization was one of the risk factors with significant association with the development of drug resistant tuberculosis in some other studies. As stated in Assefa, Seyoum and Oljira (2017:209), history of hospitalization was an independent determinant for drug resistant tuberculosis in two hospitals in Addis Ababa, Ethiopia. “A cross-sectional study conducted in Addis Ababa, Ethiopia, from June 2015 to December 2016 also found that the prevalence of drug resistant tuberculosis in the study population was of a significantly high level among patients with history of hospital admission” (Mesfin, Beyene, Tesfaye, Admasu, Addise, Amare, Dagne, Yaregal, Tesfaye & Tessema 2018:6).

This difference in study finding with regard to history of previous hospitalization can be due to difference in the areas covered by the studies. The above two studies were conducted only in Addis Ababa, while the current study covered five other regions of Ethiopia in addition to Addis Ababa. Thus, the current study gave a bigger picture of the risk of acquiring drug resistant tuberculosis from hospitalization into Ethiopian hospitals, which was found to be not significant.

6.2.2.3 Contact with a patient with drug resistant tuberculosis

There was no significant difference in proportion between the cases and the controls of the current study with regard to history of contact with a patient with drug resistant tuberculosis. The presence of history of household or close contact with a patient with drug resistant tuberculosis was not found to be a predictor of drug resistant tuberculosis in the current study. A similar result was stated in Hirpa et al (2013:782), whereby the study did not find any relationship between the
presence of household or close contact with a patient with drug resistant tuberculosis and the development of drug resistant tuberculosis in Addis Ababa, Ethiopia.

This is evidence that indicates that the occurrence of drug resistant tuberculosis in the current study’s settings was mainly through mutation of mycobacterium tuberculosis bacteria to drug resistant strain and not by breathing in drug resistant mycobacterium tuberculosis bacteria released into air when a patient with drug resistant tuberculosis coughed or sneezed. In other words, secondary drug resistant tuberculosis after exposure to the first-line anti-tuberculosis drugs was the commoner type of disease in the current study than primary drug resistant tuberculosis. Primary drug resistant tuberculosis is found in first-line tuberculosis treatment-naïve patients who are infected by inhaling drug resistant mycobacterium tuberculosis bacteria released into air when a patient with drug resistant tuberculosis coughed or sneezed (World Health Organization 2018d).

However, a study which assessed determinants of the occurrence drug resistant tuberculosis in armed force referral and teaching hospital in Addis Ababa, Ethiopia, found out that history of contact with a patient with drug resistant tuberculosis was a strong predictor of drug resistant tuberculosis in armed force and civilian patients (Demile, Zenebu, Shewaye, Xia & Guadie 2018:249). Nevertheless, the finding of the study at this armed force referral and teaching hospital was not repeated by other studies in Ethiopia.

6.2.2.4 Chronic illness

According to the current study, the presence of chronic diseases like hypertension, asthma and diabetes mellitus in the study respondents was not a significant determinant of the occurrence of drug resistant tuberculosis. Hirpa et al (2013:782) and Assefa et al (2017:209) corroborate this
result by indicating that these two studies conducted in Addis Ababa, Ethiopia, did not find any association between the presence of chronic diseases and the occurrence of drug resistant tuberculosis.

However, studies conducted in Peru, Portugal and Bangladesh found diabetes mellitus to be related with the occurrence of drug resistant tuberculosis (Gil, Alarcon, Figueroa, Moore & Golub 2016:313; Gomes, Correia, Mendonça & Duarte 2014:111; Rifat et al 2014:8). Nevertheless, these studies’ results cannot imply that all chronic diseases were a risk factor for the development of drug resistant tuberculosis, as the findings were only for diabetes mellitus and not exhaustively inclusive of other chronic diseases like the current study.

6.2.3 Tuberculosis treatment adherence related conditions during the most recent first-line tuberculosis treatment

6.2.3.1 Tuberculosis treatment interruption

Interruption of taking first-line anti-tuberculosis drugs for one day or more was a significant determinant of the occurrence of drug resistant tuberculosis in the current study. The current study showed that adjusted odds ratio of patients who interrupted taking their first-line anti-tuberculosis drugs for one day or more during their most recent first-line tuberculosis treatment was more than four times for patients with drug resistant tuberculosis when compared with patients with successful first-line tuberculosis treatment outcome.

A case-control study conducted in south western Ethiopia also identified the interruption of first-line anti-tuberculosis treatment for at least one day to be a predictor for drug resistant tuberculosis infection (Gobena, Ameya, Haile, Abreha, Worku & Debela 2018:30). Hirpa et al (2013:782) also found that the interruption of first-line tuberculosis treatment for at least one day during the most recent first-line tuberculosis treatment was a significant determinant of the
occurrence of drug resistant tuberculosis with an adjusted odds ratio of 13.1 (95% confidence interval: 3.0 – 56.6), in a case-control study done in Addis Ababa, Ethiopia.

In a study conducted in Sudan, East Africa, the interruption of first-line tuberculosis treatment was associated with the occurrence of drug resistant tuberculosis with an adjusted odds ratio of 7.62 (95% confidence interval: 3.16 – 18.34) (Elduma et al 2019:41). Another study conducted in Myanmar, Asia, also found out that those who missed taking first-line anti-tuberculosis drugs during the initial treatment more than once weekly were at a higher risk of developing drug resistant tuberculosis with an adjusted odds ratio of 2.35 (95% confidence interval: 1.18 – 4.65) (Khan, Hutchison, Coker, Yoong, Hane, Innes, Khaing & Aung 2017:13).

It is easy for patients to remember whether they interrupted tuberculosis treatment for at least one day or not though they may not recall the exact number for many days of treatment interruption. Therefore, one day of treatment interruption was used as a cut of point and the study finding showed that any tuberculosis treatment interruption could lead to the occurrence of drug resistant tuberculosis. Inadequate tuberculosis treatment that results from interruption of taking first-line anti-tuberculosis drugs favours the increase in the number of mutant drug resistant mycobacteria by killing only the drug susceptible mycobacteria, which ultimately results in the occurrence of drug resistant tuberculosis (Kanabus 2018).

6.2.3.2 Anti-tuberculosis drug side effect

According to the current study, the occurrence of drug resistant tuberculosis was not associated with the presence of the side effects of anti-tuberculosis drugs, including the most common anti-tuberculosis drugs side effect vomiting, during the most recent first-line tuberculosis treatment. The researcher did not come across a study with a similar finding and this can be a new finding.
However, according to Hirpa et al (2013:782), drug side effects during first-line treatment were significant determinants of the occurrence of drug resistant tuberculosis in a study conducted in Addis Ababa, Ethiopia. The effect of drug side effects including vomiting during first-line tuberculosis treatment interferes with the regular intake of drug and treatment adherence. A patient with drug side effects can be ordered to stop treatment temporarily by clinicians or he might stop taking drugs by himself for fear of the side effects. Vomiting can also take out the drugs before being absorbed. These conditions in turn lead to inadequate treatment that causes resistance to anti-tuberculosis drugs from increase in the number of mutant strains of mycobacterium tuberculosis.

However, with proper medical treatment and close follow-up, the side effects of first-line anti-tuberculosis drugs can be managed before exposing the patient to the occurrence of drug resistant tuberculosis. The reason behind current study result of no association between the side effects of first-line anti-tuberculosis drugs and the occurrence of drug resistant tuberculosis can be due to early and effective management of the side effects of the drugs by clinicians. The other possible reason can be the relatively lesser severity of the side effects of first-line anti-tuberculosis drugs encountered by the study respondents in the case group and the control group that did not lead to treatment interruption causing inadequate treatment and the occurrence of drug resistant tuberculosis.

### 6.2.3.3 Cigarette and alcohol

The personal habits of the study respondents with regard to smoking cigarette and drinking alcohol was not related with development of drug resistant tuberculosis in the current study. Two different studies conducted in Addis Ababa, Ethiopia, Hirpa et al (2013:782) and Assefa et al
(2017:209), also did not find any association between smoking cigarette and drinking alcohol and the occurrence of drug resistant tuberculosis.

However, a study conducted in East Shoa, Ethiopia, found that alcohol consumption was a potential determinant of the occurrence of drug resistant tuberculosis (Desissa, Workineh & Beyene 2018:422). Another case-control study conducted in Kibong’oto Infectious Disease Hospital in northern Tanzania found a statistically significant association between drug resistant tuberculosis and cigarette smoking (Lema, Majigo, Mbelele, Abade & Matee 2016:4).

These differences in the study findings can be explained by the variation in culture and economic capability of the study respondents as some communities might have greater habit and capability of using alcohol and cigarette than other communities of a different set up.

6.2.3.4 Directly observed tuberculosis treatment

The presence of a most recent first-line tuberculosis treatment, which was not directly observed by a health worker for 7 to 8 weeks was a significant factor associated with the occurrence of drug resistant tuberculosis in the current study. According to the current study, a health worker did not directly observe the most recent first-line tuberculosis treatment of patients with drug resistant tuberculosis for 7 to 8 weeks with an adjusted odds ratio of 13.41 (95% confidence interval: 8.06 – 22.29).

A study carried out in Addis Ababa, Ethiopia, also concluded that treatment not directly observed by a health worker was a significant determinant of the occurrence of drug resistant tuberculosis (Hirpa et al 2013:782). “A systematic review and meta-analysis of 129 studies published in international journals also found out that not directly observing tuberculosis treatment was a risk factor that led to the occurrence of drug resistant tuberculosis in different countries where the studies were conducted” (Alipanah, Jarlsberg, Miller, Linh, Falzon, Jaramillo & Nahid 2018:15).
Direct observation by a health professional when a patient swallows anti-tuberculosis drugs ascertains that there is no treatment interruption. However, a patient may not take anti-tuberculosis drugs regularly for different reasons if not observed by a health professional while taking the drugs. This in turn causes sub-optimal or inadequate tuberculosis treatment, which leads to the development of drug resistant tuberculosis (Kanabus 2018).

6.2.4 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment

6.2.4.1 First-line tuberculosis treatment category

According to the current study, being treated with the first-line tuberculosis treatment category for previously treated patients during the most recent first-line tuberculosis treatment, had a significant association with the development of drug resistant tuberculosis with an adjusted odds ratio of 3.70 (95% confidence interval: 2.40 – 5.72) and p-value of 0.00. This analysis was performed with patients with tuberculosis who were treated by the first-line tuberculosis treatment category for new patients during the most recent first-line tuberculosis treatment and the result found was statistically compared between the cases and the controls. New patients are patients who have never been treated for tuberculosis or have taken anti-tuberculosis drugs for less than one month, while previously treated patients are patients who have received one month or more of anti-tuberculosis drugs in the past (WHO 2014b).

Systematic reviews and meta-analysis of a number of studies were conducted on drug resistant tuberculosis in Ethiopia. These studies found out that being treated with the first-line tuberculosis treatment category for previously treated patients was the most powerful predictor for multidrug-resistant tuberculosis infection (Asgedom, Teweldemedhin & Gebreyesus 2018:8; Eshetie,
Gizachew, Dagnew, Kumera, Woldie, Ambaw, Tessema & Moges 2017:219; Girum, Muktar, Lentiro, Wondiye & Shewangizaw 2018:5). A history of previous tuberculosis treatment, which made patients to be treated by the first-line tuberculosis treatment category was also the only statistically significant risk factor for drug resistant tuberculosis in the districts of Metema and West Armachiho, Northwest Ethiopia (Mekonnen, Tessema, Moges, Gelaw, Eshetie & Kumera 2015:461).

Berhan, Berhan and Yizengaw (2013:271) conducted a meta-analysis of 30 articles on drug resistant tuberculosis in Sub-Saharan Africa. The meta-analysis conducted showed that the risk of having drug resistant tuberculosis in previously tuberculosis treated patients with tuberculosis was more than 5-fold higher than that of new tuberculosis cases. Faustini, Hall and Perucci (2006:158) also reviewed 29 papers on risk factors associated with drug resistant tuberculosis in Europe. “The systematic review concluded that the pooled risk of drug resistant tuberculosis was 10.23 times higher in previously treated cases than in never treated cases.” This implies that, the previously tuberculosis treated patients with tuberculosis in these studies were treated by the first-line tuberculosis treatment category for previously treated patients, which is the standard treatment category for such kind of patients (WHO 2017).

A similar result was reported by a study in Belarus. It reported that, being treated by the first-line tuberculosis treatment category for previously treated patients was a significant determinant of the occurrence of drug resistant tuberculosis as compared to being treated by the first-line tuberculosis treatment category for new patients. It had an adjusted odds ratio of 6.1 (95% confidence interval: 4.8 – 7.7) and p-value of 0.00 (Skrahina, Hurevich, Zalutskaya, Sahalchyk, Astrauko, Hoffner, Rusovich, Dadu, Colombani, Dara, Gemert & Zignol 2013:36). In another study in Nanjing, China, with an equal number of cases and controls, reported that re-treatment or being treated by the first-line tuberculosis treatment category for previously treated patients was determinant of the occurrence of drug resistant tuberculosis with an adjusted odds ratio of
This association could be function of repeated exposure to anti-tuberculosis drugs, which increases the number of populations of naturally occurring mutant mycobacterium tuberculosis bacteria leading to the development of drug resistant tuberculosis (Kanabus 2018).

According to Biadglegne, Tessema, Rodloff and Sack (2013:1589), newly treated patients with tuberculosis harbour drug resistant tuberculosis in Ethiopia in a significant proportion, which contradicts the findings of the above studies and the current study. The study concluded that the development of drug resistant tuberculosis had no significant association with a history of previous tuberculosis treatment. However, this finding was not confirmed by other studies in Ethiopia. Another study, which assessed determinant of the occurrence of drug resistant tuberculosis in rural Eastern Cape, South Africa also identified high rates of drug resistant tuberculosis among treatment-naive patients (Fotso, Vasaikar & Apalata 2018:384). These findings were the opposite of most study findings in Ethiopia and other countries whereby the occurrence of drug resistant tuberculosis was significantly associated with being treated by the first-line tuberculosis treatment category for previously treated patients during the most recent first-line tuberculosis treatment.

6.2.4.2 First-line tuberculosis treatment outcome

The current study identified previous first-line tuberculosis treatment outcome of failure as the strongest risk factor for the occurrence of drug resistant tuberculosis. The most recent first-line tuberculosis treatment outcome of treatment failure was a significant determinant of the
occurrence of drug resistant tuberculosis with an adjusted odds ratio of 39.19 (95% confidence interval: 12.05 - 127.46) and p-value of 0.00.

A similar finding of significant association of previous first-line tuberculosis treatment outcome of failure with the occurrence of drug resistant tuberculosis was found by a systematic review of 23 articles on drug resistant tuberculosis in Ethiopia (Biadglegne, Sack & Rodloff 2014:31). A case-control study conducted in the Amhara National Regional State also found failure of first-line tuberculosis treatment to be associated with an increased risk of drug resistant tuberculosis (Mulu, Mekonnen, Yimer, Admassu & Abera 2015:368).

Another study carried out at the central chest institute of Thailand identified that having treatment failure as first-line tuberculosis treatment outcome, was a determinant factor for the occurrence of drug resistant tuberculosis (Chuchottaworn, Thanachartwet, Sangsayunh, Than, Sahassananda, Surabotsophon & Desakorn 2015:10).

The result of tuberculosis treatment failure as a cause of drug resistant tuberculosis in the current study can be explained by the fact that the main cause of tuberculosis treatment failure is an inadequate treatment from not taking first-line anti-tuberculosis drugs correctly, incorrect drug regimens or the poor quality of drugs (WHO 2017). Inadequate tuberculosis treatment in turn leads to the selection of naturally occurring drug resistant mutant bacteria, which become increasingly drug resistant (Kanabus 2018). As the drug susceptible organisms are killed during sub-optimal treatment, the drug resistant mutants gradually become an increasing proportion of the disease burden, and result in an emergence of a drug resistant form of tuberculosis. Tuberculosis treatment failure can also result if the patient already has drug resistant tuberculosis even if the treatment is taken correctly (Kanabus 2018).
The other unfavourable treatment outcome of defaulting on the most recent first-line tuberculosis treatment was not found to have a significant association with the occurrence of drug resistant tuberculosis in the current study with an adjusted odds ratio of 1.45 (95% confidence interval: 0.88 – 2.40 and p-value 0.18). Workicho, Kassahun and Alemseged (2017:91) corroborate on this finding of the current study by indicating that no significant association between defaulting in the most recent first-line tuberculosis treatment and the occurrence of drug resistant tuberculosis. It had an adjusted odds ratio of 1.60 (95% confidence interval: 0.67 – 3.78) in a case-control study conducted at Saint Peter's Tuberculosis Specialized Hospital, in Addis Ababa, Ethiopia. Another study conducted in Sudan also did not find defaulting in the most recent first-line tuberculosis to be a predictor of the occurrence of drug resistant tuberculosis (Ali, Ablasheedy, Hassali, Kibuule & Godman 2019:90).

On the contrary, defaulting in previous first-line tuberculosis treatment was one of the significant risk factors for the occurrence of drug resistant tuberculosis in a study conducted in the Oromia region of Ethiopia (Mulisa, Workneh, Hordofa, Suaudi, Abebe & Jarso 2015:57). The Central Chest Institute of Thailand also carried out a study that identified tuberculosis treatment default as an independent risk factor for drug resistant tuberculosis (Chuchottaworn, Thanachartwet, Sangsayunh, Than, Sahassananda, Surabotsophon & Desakorn 2015:10).

This discrepancy in the study results can be due to an increased effort in defaulter tracing being implemented in Ethiopia in recent years (Ministry of Health of Ethiopia 2019). The decrease in the number of patients defaulting in first-line tuberculosis treatment in Ethiopia can be the reason for the non-association of defaulting in the most recent first-line tuberculosis treatment with the occurrence of drug resistant tuberculosis.
6.2.4.3 HIV status during first-line tuberculosis treatment

The current study found out that being HIV positive did not increase the chance of developing drug resistant tuberculosis. The HIV status of study respondents had no significant predicting relationship with drug resistant tuberculosis in the current study with an adjusted odds ratio of 0.91 (95% confidence interval: 0.50 – 1.67) and a p-value of 0.88.

There were studies with a result similar to the current study. The HIV status of study respondents was not a determinant of the occurrence of drug resistant tuberculosis in a case-control study conducted in Addis Ababa, Ethiopia (Hirpa et al 2013:782). Studies conducted in Sub-Saharan Africa also did not find a significant association between the HIV status of patients and the occurrence of drug resistant tuberculosis (Berhan, Berhan & Yizengaw 2013:271; Lukoye, Ssengooba, Musisi, Kasule, Cobelens, Joloba & Gomez 2015:291).

The HIV status of patients was also not associated with the occurrence of drug resistant tuberculosis in studies conducted in South America and India (Eldholm, Rieux, Monteserin, Lopez, Palmero, Lopez, Ritacco, Didelot & Balloux 2016:5; Shah, Shah & Dave 2018:1463).

In contrast, studies conducted in Latin America, Nepal, Malaysia and Ethiopia, showed that being HIV infected was a statistically significant independent predictor of drug resistant tuberculosis (Bergonzoli, Castellanos, Rodríguez & Garcia 2016:101; Bichha, Jha, Salhotra, Weerakoon, Karki & Bichha 2017:31; Elmi, Hasan, Abdullah, Jeab, Alwi & Naing 2015:1076; Workicho, Kassahun & Alemseged 2017:91).

“However, a micro-level laboratory based study confirmed that, HIV co-infection does not significantly affect the transmissibility or the mutation rate of mycobacterium tuberculosis within patients and was not associated with an increased emergence of resistance within patients”
“The study results showed that the HIV epidemic serves as an amplifier of tuberculosis outbreaks by providing a reservoir of susceptible hosts, but that HIV co-infection is not a direct driver for the emergence and transmission of resistant strains” (Eldholm, Rieux, Monteserin, Lopez, Palmero, Lopez, Ritacco, Didelot & Balloux 2016:5). This laboratory research finding gives further backing to the finding of the current study which rules out HIV status as a predictor of drug resistant tuberculosis.

6.3 SUMMARY

This chapter discussed the results of the current study by comparing with the results of studies conducted in Ethiopia, Africa, Asia, Europe and the Americas using the extant literature. Some of the studies referred to for comparison had results that were similar with and supported the results of the current study. There were also studies referred to for comparison, which had results that were different from the results of the current study. Explanations were given on the possible reasons for the differences in results between the current study and studies referred to for comparison.
CHAPTER 7
CONCLUSIONS AND RECOMMENDATIONS

7.1 INTRODUCTION

This chapter presents the conclusions made on factors associated with the occurrence of drug resistant tuberculosis in Ethiopia from the analysis and the interpretation of the results of the current study. The chapter also gives recommendations on ways of preventing the acquisition of drug resistant tuberculosis by tackling factors, which lead to the development of drug resistant mutant mycobacterium tuberculosis bacteria based on the conclusions made.

This chapter also elaborates on the possible contributions the current study can provide in an effort to prevent the development of drug resistant tuberculosis in Ethiopia and elsewhere. The current study also had its own limitations. These limitations are presented in a specifically assigned section in this chapter.

This chapter ascertains that the current study achieved the two main purposes it was conducted for, which were to:
1. Determine factors associated with the development drug resistant tuberculosis in Ethiopia.
2. Develop a conceptual model for preventing the development of drug resistant tuberculosis in Ethiopia.
7.2 SUMMARY AND INTERPRETATION OF THE RESEARCH FINDINGS

7.2.1 Sociodemographic characteristics of study respondents

According to the results of the current study, on sociodemographic characteristics, the majority of study respondents were males and belonged to the age group 15 to 34 years in both cases and controls. The majority of cases and controls who responded in the study were also single, educated above 8th grade and employed. The mean age of study respondents was 30.2 years for the cases and 34.2 years for the controls, which indicated that individuals affected by both drug resistant tuberculosis and drug susceptible tuberculosis were on average around the middle age category.

Even though male gender, age group of 15 to 34 years, single marital status, higher education and employment were variables which represent the majority of study respondents, none of them were associated with the development of drug resistant tuberculosis in a statistically significant way. Thus, in the six hospitals found in six regions of Ethiopia where the current study was conducted, the soiodemographic characteristics of study respondents were not determinants of the occurrence of drug resistant tuberculosis.

7.2.2 Tuberculosis disease related conditions

The majority of patients with drug resistant tuberculosis had two or more previous tuberculosis illnesses for which they were treated. On the other hand, only a few patients with successful first-line tuberculosis treatment outcomes had two or more episodes of tuberculosis. The greater proportion, both the cases and the controls, had neither close contact with a patient with drug resistant tuberculosis nor history of chronic illness, which made both factors to be insignificant determinants of drug resistant tuberculosis. A history of hospitalization was also an insignificant factor and was not determinant of the occurrence of drug resistant tuberculosis.
After the adjusting for possible confounding factors with multivariate analysis, the current study found that the development of drug resistant tuberculosis was strongly associated with two or more episodes of the previous tuberculosis illness with an adjusted odds ratio of nearly 15. Therefore, having two or more previous tuberculosis illness was a significant risk factor leading to the development of drug resistant tuberculosis in the current study. This result can be interpreted in line with the repeated exposure of patients with two or more previous bouts of the tuberculosis illness to first-line anti-tuberculosis drugs that favour the increase in the number of naturally existing drug resistant mutant mycobacterium tuberculosis bacteria.

7.2.3 Tuberculosis treatment adherence related conditions during the most recent first line tuberculosis treatment

Interruption of first-line tuberculosis treatment for at least one day was a statistically significant factor that led to the occurrence of drug resistant tuberculosis in the current study. Interruption of first-line tuberculosis treatment for at least one day was nearly fourfold prevalent in patients with drug resistant tuberculosis when compared with patients with a successful first-line tuberculosis treatment outcome. Thus, not taking first-line anti-tuberculosis drugs for one day or more can cause drug resistant tuberculosis because of inadequate treatment according to the current study.

Patients who were not directly observed by a health worker for 7 to 8 weeks while taking first-line tuberculosis treatment, which were nearly thirteen fold in the cases as compared to the controls, developed drug resistant tuberculosis at a statistically significant level in the current study. This entails that first-line tuberculosis treatment not directly observed by a health worker throughout the intensive phase of treatment ends up in poor treatment adherence. Therefore,
poor treatment adherence leads to inadequate treatment, which causes the development of drug resistant tuberculosis.

From factors presumed to affect first-line tuberculosis treatment adherence, cigarette smoking, alcohol consumption and anti-tuberculosis drug side effects were statistically insignificant factors that were not determinant of the occurrence of drug resistant tuberculosis in the current study.

7.2.4 First-line tuberculosis treatment related conditions during the most recent first-line tuberculosis treatment

The first-line tuberculosis treatment category for previously treated patients with tuberculosis was significant determinant of the occurrence of drug resistant tuberculosis in the current study. The more frequently a patient is exposed to first-line anti-tuberculosis drugs, the higher the chances of developing resistance to the drugs. Added to this, these patients with tuberculosis treated by the first-line tuberculosis treatment category for previously treated patients, had unfavourable treatment outcomes of failure, relapse or default during the previous first-line tuberculosis treatment, which favour the occurrence of drug resistant tuberculosis.

Previous first-line tuberculosis treatment outcome of failure was the strongest predictor of the occurrence of drug resistant tuberculosis in the current study. The interpretation of this result is that the tuberculosis treatment failed because first-line tuberculosis treatment was given to a patient harbouring a drug resistant mutant strain of mycobacterium tuberculosis bacteria. This is because first-line anti-tuberculosis drugs cannot kill drug resistant mutant strain of mycobacterium tuberculosis bacteria. Thus, giving first-line tuberculosis treatment to a patient with drug resistant tuberculosis leads to treatment failure, which makes tuberculosis treatment failure a predictor of the occurrence of drug resistant tuberculosis according to the current study.
Defaulting from previous first-line tuberculosis treatment and being HIV positive were not determinants of the occurrence of drug resistant tuberculosis according to the current study.

7.3 CONCLUSIONS

Based on the findings of the current study which assessed factors associated with the development of drug resistant tuberculosis in patients with drug resistant tuberculosis as compared to patients with successful first-line tuberculosis treatment outcome, in Oromia, Amhara, South people, Tigray, Addis Ababa and Dire Dawa regions of Ethiopia, the following conclusions were made:

1. The unfavourable first-line tuberculosis treatment outcome of failure was associated with the development of drug-resistant tuberculosis.

2. Having two or more episodes of previous tuberculosis illness was associated with the development of drug-resistant tuberculosis.

3. First-line tuberculosis treatment not directly observed by a health worker for seven to eight weeks during the intensive phase of treatment was associated with the development of drug-resistant tuberculosis.

4. Interruption of first-line tuberculosis treatment for one day or more was associated with the development of drug resistant tuberculosis.

5. A history of treatment by the first-line tuberculosis treatment category for previously treated patients was associated with the development of drug-resistant tuberculosis.
7.4 RECOMMENDATIONS

7.4.1 Recommendations for practice

1. The full course of first-line tuberculosis treatment should be administered following the Directly Observed Treatment (DOTs) programme guide. That is, treatment should be under direct observation of a health professional during the intensive phase of treatment and a treatment supporter during continuation phase of treatment to enhance patient adherence to tuberculosis treatment.

2. Regular screening of patients for symptoms of tuberculosis at all outpatient departments of health facilities and house-to-house screening for a cough of two weeks or more by health extension workers for early and increased detection of patients with tuberculosis.

3. Regular identification of suspects of drug-resistant tuberculosis, like patients with recurrent tuberculosis and unfavourable first-line tuberculosis treatment outcome at health facilities, and there should be drug sensitivity testing for them for early and increased detection of patients with drug-resistant tuberculosis.

4. Tuberculosis infection prevention measures should be strengthened and regularly practiced in health facilities to prevent aerosol transmission of mycobacterium tuberculosis bacteria.

5. Close follow-up and proper treatment of first-line tuberculosis drug side effects should be continued as regular practice at health facilities to avoid treatment interruption because of the side effects from tuberculosis drugs.

6. Access to anti-tuberculosis drug sensitivity testing should be improved to enhance the early diagnosis of patients with drug-resistant tuberculosis.
7.4.2 Recommendations for future research

1. Even though, the current study was conducted in six different regions of Ethiopia, further broader studies, which include other regions of Ethiopia, need to be conducted.

2. Laboratory based research to identify the magnitude of primary drug resistant tuberculosis and secondary drug resistant tuberculosis in Ethiopia is recommended.

7.5 CONTRIBUTIONS OF THE STUDY

The current study contributes to the betterment of the health system with regard to addressing the challenge posed by drug-resistant tuberculosis. Its contributions are outlined as follows:

1. It identified factors associated with the development of drug-resistant tuberculosis. It findings can be used as baseline information to devise an effective and efficient strategy for the prevention of the development of drug-resistant tuberculosis.

2. It showed that first-line tuberculosis treatment directly observed by a health worker for seven to eight weeks at the intensive phase of treatment, regular uninterrupted first-line tuberculosis treatment and the absence of repeated tuberculosis illness were factors preventing the development of drug-resistant tuberculosis in patients with successful first-line tuberculosis treatment outcome.

3. It developed a model for the prevention of the development of drug-resistant tuberculosis based on its findings. This model could be adopted for the prevention of the development of drug-resistant tuberculosis in different contexts.
4. It could be used as reference for future studies aiming to widen the knowledge on factors associated with the development of drug-resistant tuberculosis.

7.6 LIMITATIONS OF THE STUDY

The following points can be considered as limitations of the study:

1. The current study was conducted in six different regions out of the eleven regions of Ethiopia. Thus, it might not reflect the exact situations in all regions of Ethiopia with regard to factors associated with the development of drug-resistant tuberculosis.

2. The current study was a hospital-based study and it might not exactly reflect the picture at health facilities below a hospital level.

3. The current study asked the study respondents for information on the first-line tuberculosis treatment they took years back. The information the study respondents gave to data collectors could have memory bias.
7.7 CONCLUDING REMARKS

A key factor associated with the development of drug-resistant tuberculosis was not taking first-line tuberculosis treatment properly. Thus, healthcare workers should strictly follow the Directly Observed Treatment (DOTs) strategy and make sure that tuberculosis patients are taking their first-line tuberculosis treatment appropriately.
LIST OF REFERENCES


Jahn, WT. 2011. The 4 basic ethical principles that apply to forensic activities are respect for autonomy, beneficence, non-maleficence, and justice. *Journal of Chiropractic Medicine* 10(3):225–226.


Annexe A: Data collection tool

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA.

Research for Doctor of Literature and Philosophy, University of South Africa.
Principal researcher: Henock Bekele, MD, MPH.

QUESTIONNAIRE FOR INTERVIEWING STUDY RESPONDENTS

INSTRUCTION TO DATA COLLECTOR:

1. Call the study respondent to a place where privacy can be kept, explain about the study, obtain written informed consent for respondents 18 years old and above or assent plus parental/guardian informed consent for respondents under the age of 18 years and conduct the interview individually.

2. Circle the response of the study respondent and fill in the blanks where necessary.

Study respondent’s code number: ________

First-line tuberculosis treatment registration number: ________________

Treating health facility’s name: ________________

The study respondent is:

A. Patient with drug resistant tuberculosis (Case)
B. Patient with successful first-line tuberculosis treatment outcome (Control)

1. **Gender:**
   - A. Male
   - B. Female

2. **Age** (in years): __________

3. **Marital status:**
   - A. Single
   - B. Married
   - C. Divorced
   - D. Widow/widower

4. **Educational status:**
   - A. No formal education
   - B. 1st – 8th Grade
   - C. 9th – 12th Grade
E. College and above

5. **Occupation:**

A. No work

B. Student

C. Farmer

D. Government Employed

E. Private Employed

F. Self-employed

6. **Were you previously hospitalized for any illness?**

   (Note: This does not include the current admission for treatment of drug resistant tuberculosis at the time of the study).

   A. No

   B. Yes
7. How many episodes of previous tuberculosis illness did you have?

(Note: The current drug resistant tuberculosis illness is not counted for the cases. The tuberculosis illness for which first-line tuberculosis treatment was completed is counted for the controls).

A. One  
B. Two  
C. Three  
D. Four or more

8. Have you ever had a household or close contact with a patient with drug resistant tuberculosis?

A. No  
B. Yes

9. Did you have other chronic diseases while on the most recent first-line tuberculosis treatment? (Note: HIV/AIDS is excluded from the chronic disease list here).

A. No  
B. Yes, Specify ____________
10. Did you encounter any anti-tuberculosis drug side effects during the most recent first-line tuberculosis treatment?

A. No

B. Yes, Specify ____________

11. Did you suffer from the drug side effects of vomiting during the most recent first-line tuberculosis treatment?

A. No

B. Yes

12. Have you ever interrupted taking anti-tuberculosis drugs for at least one day during the most recent first-line tuberculosis treatment?

A. No

B. Yes
13. Were you smoking cigarettes daily during the most recent first-line tuberculosis treatment?

A. Yes

B. No

14. Were you drinking alcohol on a daily basis during the most recent first-line tuberculosis treatment (irrespective of type)?

A. Never or < 1 drink per day

B. 1 – 4 drinks per day

C. ≥ 5 drinks per day

15. Were you directly observed by a health worker while taking anti-tuberculosis drugs during the most recent first-line tuberculosis treatment?

A. No

B. Yes
16. If yes, for how many weeks were you directly observed by a health worker while taking anti-tuberculosis drugs during the most recent first-line tuberculosis treatment?

A. 1 – 2 weeks

B. 3 – 4 weeks

C. 5 – 6 weeks

D. 7 – 8 weeks
FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA.

Research for Doctor of Literature and Philosophy, University of South Africa.
Principal researcher: Henock Bekele, MD, MPH.

QUESTIONNAIRE FOR COLLECTING SECONDARY DATA FROM REGISTERS

INSTRUCTION TO DATA COLLECTOR:

Circle the appropriate information found documented in the first-line tuberculosis treatment register. Data is collected for the most recent first-line tuberculosis treatment.

Study respondent’s code number: _________

First-line tuberculosis treatment registration number: _____________________

Treating health facility’s name: ___________________

The study respondent is:

A. Patient with drug resistant tuberculosis (Case)
B. Patient with successful first-line tuberculosis treatment outcome (Control)

17. Treatment category during the most recent first-line tuberculosis treatment:

A. New patient

B. Previously treated patient
18. Treatment outcome of the most recent first-line tuberculosis treatment:

A. Cured

B. Completed for bacteriologically confirmed pulmonary tuberculosis

C. Completed for clinically diagnosed pulmonary tuberculosis and extra pulmonary tuberculosis

D. Failure

E. Default

F. Unknown

19. HIV status during the most recent first-line tuberculosis treatment:

A. Negative

B. Positive

C. Not tested
Data collector's name: _________________________

Data collector's signature: _______________________

Place of data collection: _________________________

Date of data collection: _________________________

Principal researcher's name: _____________________

Principal researcher's signature: ___________________
Annexe B: Consent form

CONSENT FORM

TITLE OF RESEARCH PROJECT

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF DRUG RESISTANT TUBERCULOSIS IN ETHIOPIA

Date…./…../20...

Dear Mr/Mrs/Miss/Ms

This is research being conducted to know/investigate what is leading to the development of drug resistant tuberculosis in Ethiopia. Dr Henock Bekele is the principal researcher under supervision of University of South Africa. The University of South Africa research ethics committee gave ethical approval for the study to be conducted.

You are requested to respond to 16 questions, which may take about 10 minutes. You are selected randomly to participate in the study. About 362 similar patients with tuberculosis will also participate in this study. No photographic material, video recordings or tape recordings will be required.

The information you give will be used for the study purposes only. The information given will also be kept confidentially. You will not be asked for your identification including name and address.
Only a code number will be given to you, which is different from that of other study respondents. You can ask any question before; during or after the interview and clarification will be given to you by the interviewer.

Your participation is voluntary. Your decision to participate or not to participate will not affect the care given to you and your family or your relationship with the healthcare providers. You are allowed to withdraw from the study at any time during the data collection process without any consequences being harmful to you.

Your participation in the study will benefit the community at large by contributing to prevention of the development of drug resistant tuberculosis. The study will identify factors leading to drug resistant tuberculosis. These predisposing factors can be addressed accordingly, ultimately preventing the development of drug resistant tuberculosis.

If you want to communicate with the principal researcher, you can use the address below:

Dr. Henock Bekele Mobile: +251911406458
Deputy Medical Coordinator Office: +251966215643
Doctors Without Borders E-mail: henockbkb@yahoo.com
P.O. Box 21423 code 1000
Addis Ababa, Ethiopia

If you agree to participate in the study, would you please read the statements below and sign in the space provided? Thank you for your participation.
CONSENT

I, the undersigned, ……………………………………………………………………… (Full name) have read the above information relating to the research and have also heard the verbal version, and declare that I understand it. I have been afforded the opportunity to discuss relevant aspects of the research with the research leader, and hereby declare that I agree voluntarily to participate in the project.

I indemnify the university and any employee or student of the university against any liability that I may incur during the course of the research.

I further undertake to make no claim against the university in respect of damages to my person or reputation that may be incurred because of the research or through the fault of other respondents, unless resulting from negligence on the part of the university, its employees or students.

I have received a signed copy of this consent form.

Signature of respondent…………………………………………………………………………

Signed at …………………………………. on ………………………………………

Signature of researcher: ………………………………………………………………………

Signed at …………………………………. on ………………………………………
Dear parent or guardian,

This research is being conducted to know what is leading to the development of drug resistant tuberculosis in Ethiopia. The name of the principal researcher is Dr. Henock Bekele and the study is being conducted under supervision of University of South Africa (UNISA). The study has received ethical approval and permission for conducting it by University of South Africa Research Ethics Committee.

You are asked for permission on behalf of your child for your child’s participation in the study. You and/or your child are required to respond to 16 questions, which may take about 10 minutes. Your child is selected randomly to participate in the study. About 362 similar patients with tuberculosis will also participate in this study. No photographic material, video recordings or tape recordings will be required.

The information you and/or your child give will be used for the study purposes only. The information given will also be kept confidentially. You will not be asked for your child’s identification including the name and address. Only a code number will be given to your child,
which is different from other study respondents. You can ask any question before; during or after the interview and clarification will be given to you by the interviewer.

Your child’s participation is voluntary. Your decision for your child to participate or not to participate will not affect the care given to the child, you and your family or your relationship with the healthcare providers. You are allowed to withdraw your child from the study at any time during the data collection process without any harmful consequences to you or your child.

Your child’s participation in the study will benefit the community at large by contributing to the prevention of the development of drug resistant tuberculosis. The information gathered from your child and other respondents will identify factors leading to drug resistant tuberculosis. These identified predisposing factors can be subsequently addressed accordingly and the development of drug-resistant tuberculosis can be prevented.

If you want to communicate the principal researcher, you can use the address below:

Dr. Henock Bekele
Mobile: +251911406458
Deputy medical coordinator
Office: +251966215643
Doctors Without Borders
E-mail: henockbkb@yahoo.com
P.O.Box 21423 code 1000
Addis Ababa, Ethiopia

If you agree for your child to participate in the study, would you please read the statements below and sign in the space provided?

Thank you for allowing your child’s participation in the study.
ASSENT

I, the undersigned, …………………………………………………………………...(Full name) have read the above information relating to the research and have also heard the verbal version, and declare that I understand it. I have been afforded the opportunity to discuss relevant aspects of the research with the research leader, and hereby declare that I agree voluntarily for my child…………………………………..(Full name) to participate in the research project.

I indemnify the university and any employee or student of the university against any liability that my child or I may incur during the course of the research.

I further undertake to make no claim against the university in respect of damages to my or my child’s reputation that may be incurred because of the research or through the fault of other respondents, unless resulting from negligence on the part of the university, its employees or students.

I have received a signed copy of this assent form.

Signature of parent or guardian: ……………………………………………………………...

Signed at …………………………………. on ………………………………………...

Signature of researcher: ……………………………………………………………...

Signed at …………………………………. on …………………………………………...
Annexe D: Ethical clearance certificate

UNIVERSITY OF SOUTH AFRICA
Health Studies Higher Degrees Committee
College of Human Sciences
ETHICAL CLEARANCE CERTIFICATE
REC-012714-039

HSHDC/448/2015

Date: 25 November 2015
Student No: 5766-104-9

Project Title: Factors associated with the development of drug-resistant tuberculosis in Ethiopia.

Researcher: Henock Bekele Keto
Degree: D Lit et Phil Code: DPCHS04
Supervisor: Prof PT Sandy
Qualification: PhD
Joint Supervisor: Prof ON Makhubela-Nkondo

DECISION OF COMMITTEE
Approved

Prof L Roets
CHAIRPERSON: HEALTH STUDIES HIGHER DEGREES COMMITTEE

Prof MM Moleki
ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES
PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES
29 AUGUST, 2018
UNISA-ET/KA/ST/29/29-08-17

ST. PETER HOSPITAL
ADDIS ABABA

Dear Madam/Sir,

The University of South Africa (UNISA) extends warm greetings. By this letter, we want to confirm that Dr. Henock Bekele Keto (student number 57661049) is a PhD student in the Department of Health Studies at UNISA. Currently, he is at the stage of data collection on his doctoral research entitled “Factors associated with development of drug resistant tuberculosis in Ethiopia”.

This is therefore to kindly request you to assist the student in any way that you can. Attached, please find the ethical clearance that she has secured from the Department of Health Studies. We would like to thank you in advance for all the assistance that you will provide to the student.

Sincerely,

Dr. TsiGe GebreMeskel Aberra
Deputy Director – Academic and ICT Support