Economic Analysis of the Health Care Intervention: A Case Study of the Hospitalization and Ambulatory Treatment of MDR-TB in Pakistan

By

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School of Economics
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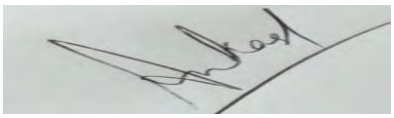

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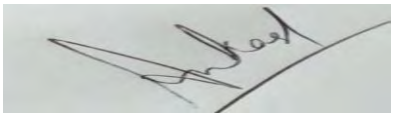

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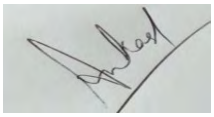

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Dedicated to

My parents, Akif and Arsal

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List of Abbreviation

HC	Hospital Care
AC	Ambulatory Care
MDR-TB	Multi Drug Resistant Tuberculosis
NTP	National Tuberculosis Program
WHO	World Health Organization
UHC	Universal Health Coverage
GDP	Gross Domestic Product
DALYs	Disability Adjusted Life Years
YLL	Years of Live Lost
YLD	Years of Life Lived with Disability
ICER	Incremental Cost-Effectiveness Ratio
LTFU	Loss to Follow-Up
CPHM	Cox Proportional Hazard Model
SDGs	Sustainable Development Goals
PSDP	Public Sector Development Program
WHO-CHOICE	Choosing Interventions that are Cost-Effective
CUA	Cost and Utility Analysis
CBA	Cost and Benefit Analysis
CEA	Cost-Effectiveness Analysis
HIC	High-Income Countries
UMIC	Upper-Middle-Income Countries
LIC	Low-Income Countries
I$	International Dollars
PKR	Pakistani Rupee
RCT	Randomized Control Trials
USD	United States Dollars
OECD	Organisation For Economic Co-Operation and Development
AIH	Absolute Income Hypothesis
RIH	Relative Income Hypothesis
IIH	Income Inequality Hypothesis
TPD	Theory Of Polarized Development
KM	Kaplan-Meier Curve
OOP	Out-of-Pocket Expenditures
CHE	Catastrophic Health Care Expenditure

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Abstract

This study analyses the cost-effectiveness of treatment arms of multi-drug resistance tuberculosis (MDR-TB) namely hospital and ambulatory care in Pakistan. Alongside that a number of factors that correlate with the outcome of cure and loss to follow-up of MDR-TB patients in Pakistan are analyzed. We have collected the data of 438 MDR-TB patients registered for the treatment of MDR-TB by the National Tuberculosis Program (NTP) of Pakistan from 2012 to 2017 from three regions of Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital, Lahore, and Ojha Institute of Chest Disease, Karachi. The results indicate that no treatment care shows a continuous dominance in the cost effectiveness analysis and both arms have played an important role in the reduction of disease burden for the patients. Hence, both treatment cares can be accepted simultaneously as appropriate strategies for the treatment of MDR-TB in Pakistan. The outcome of cure is not related to the treatment care and is positively related to the medical and time expenditure. The loss to follow-up has an insignificant relation with the treatment care, significantly increases with the catastrophic health care expenditure and reduces with the financial incentives Moreover when the patients facing catastrophic expenditure are given financial incentives then the loss to follow-up reduces significantly. Our study supports the use ambulatory care for the treatment of MDR-TB in Pakistan alongside a hospital arm. The financial impediments need to be reduced for the patients and financial incentives may be continued and ensured by the health programs to support the patients.

Keywords: Multi-drug resistance tuberculosis, cost-effectiveness, Hospital care, Ambulatory care, Catastrophic health care expenditure, Financial incentives

Chapter 1

Introduction

The substantial improvement in the standard of living of human beings is the key to economic development (Sen, 1983 and 1998). Development leads to more freedom and good health is an important freedom that all human beings should be entitled to everywhere in the world. Health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" as explained by the World Health Organization (WHO, 2020)[1]. Human beings should be able to attain a high quality of life irrespective of their socio-economic status, political and religious beliefs. But despite being recognized as a basic human right, all individuals do not have equal access to health services.

The state is responsible for the provision of health care as among other factors, the strength of a state is also recognized by the health status of individuals (Ibañez and Dekanoside, 2017). But the provision of health services as a public good creates an additional burden on the budget of government. If the health expenses keep on growing at a higher rate, then the health care might become inaccessible for most individuals in the future (Chernew *et al*., 2009 b). According to an estimate by Chernew *et al*. (2009 a), if the health care expenditure will continue to grow at the current pace then around 40 percent of GDP of the industrialized countries would be engulfed by this expenditure by the end of 2050. Many countries are trying to manage their budgets to maximize the coverage of health services under resource-scarce settings. The management of ever-increasing demand for health care under scarce economic resources gives rise to the field of health economics according to Zweifel *et al*. (2009).

[1] https://www.who.int/about/governance/constitution

The field of health economics has evolved that relates the application of the "economic theory to the phenomenon and problems associated with health and health care" (Zweifel *et al*., 2009). It deals with efficiency, effectiveness, value, management, behavior in the production and consumption of health and health care, allocation of resources in the health care system of an economy as well as the functioning of the health care markets. The interlinkages between health care and economics have become more pronounced over time and the monetary and non-monetary burden of disease is usually assessed to ensure effective and efficient treatment mechanisms (Salkeld *et al*., 1995, Culyer & Newhouse, 2000, Murray *et al*., 2002, Branning &Vater, 2016, Jakovljevic & Ogura, 2016, Arif *et al*., 2021).

The incidence, prevalence, and treatment of disease are influenced not only by the medical conditions but also by non-medical factors. Therefore, along with the medical expenditures, the treatment expenditures also involve non-medical expenditures i.e., transportation, psychological pressures, loss of productivity, working hours and income, etc. (Wilkinson and Pickett, 2006 and Modi *et al*., 2020). The disease can lead a household into the 'poverty ratchet[2]' (Chambers, 1983) or the 'medical poverty trap[3]' (Whitehead *et al*., 2001). The suffering of a bread runner of the family due to disease translates into the financial sufferings of a household. More expenditure on acquiring health services leads to a reduction of investment in human capital and consumption of health care that traps the household into the intergenerational poverty cycle. In this situation, sometimes the patient makes a decision of not undertaking the treatment as health care is not equally accessible and affordable to him/her although health is considered as a basic

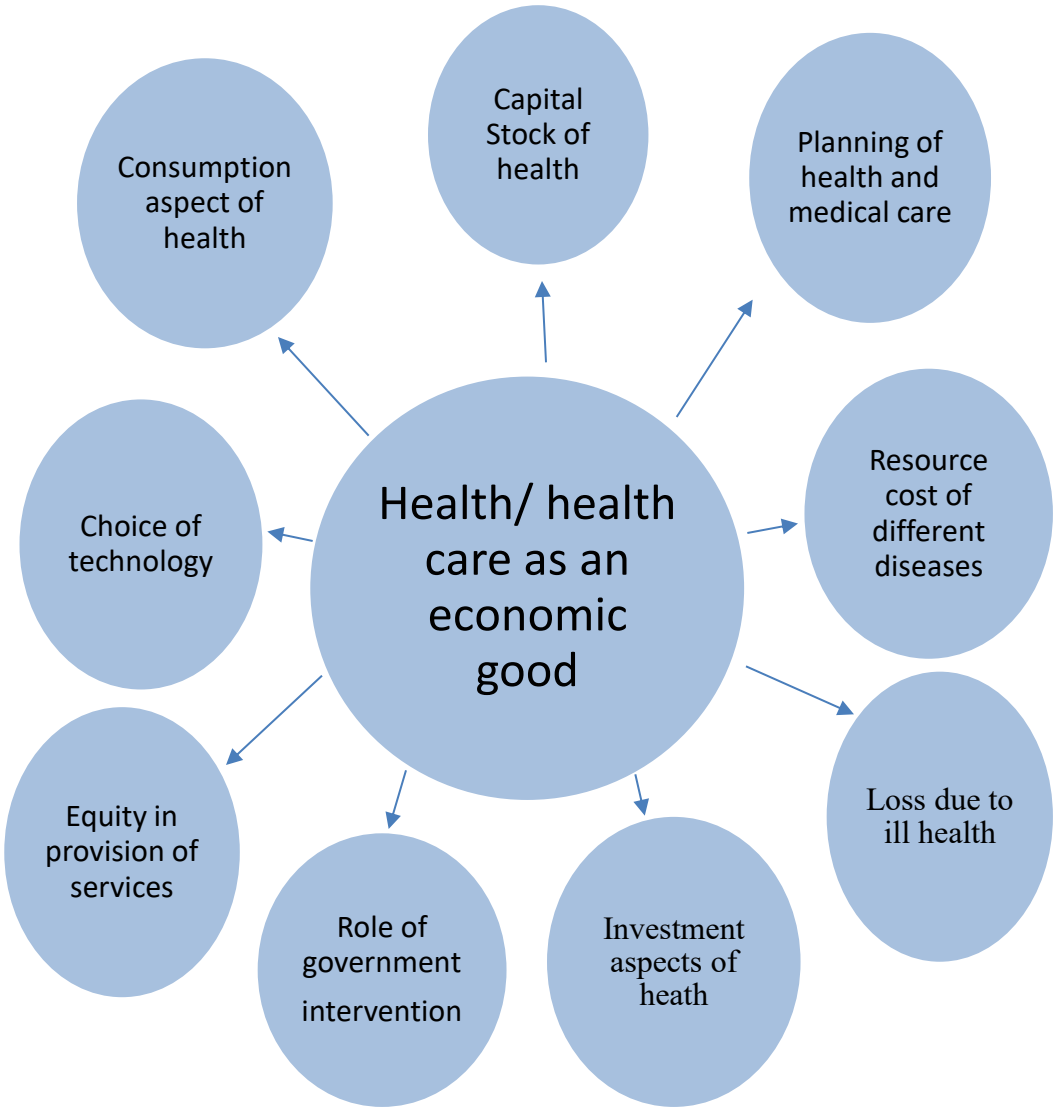
[2] The poverty ratchet means that the household suffers from the reduction in assets resulting from the need to sell the assets to finance the expenditures which leads to further impoverishment

[3] The poor health condition and the medical expenditures trap the patients and household into the cob-web of poverty as the potential to bear the medical expenditure is low.

human right. Hence, health economics has a fundamental role in defining strategies for the provision of cost-effective health care services to all individuals.

Therefore, the Commission on Macroeconomics and Health report by WHO (2001) strengthens the idea of the inclusion of economic analysis in health care decisions and financing as good health is an important contributor to economic development as it increases the productivity of the labor force and national income of the country (also see *Economic Survey of Pakistan*, 2018). There is evidence that the provision of health care can be improved with lesser spending by opting for better strategies (Fisher and Wennberg, 2003, Zweifel *et al*., 2009, Sorenson *et al*., 2013 and Agha, 2015). The analysis of the factors affecting the supply and demand of health services, the factors affecting health outcomes and the success of strategies designed by the health programs in any country are important to be studied for efficient allocation of resources (Hayes et al., 2010 and Chandra et al., 2010). The multi-dimensionality of the health care is shown in Figure 1.1.

Figure 1.1. Various Dimensions of Health Care



Source: Author's own creation

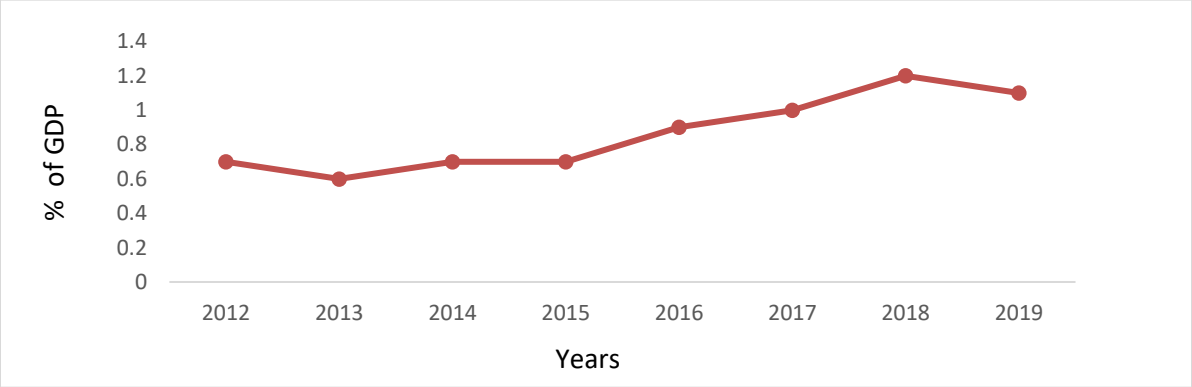
1.1. Provision of Health Care in Pakistan

The health care provision has become a challenge over time and Pakistan is facing the issue of the scarcity of resources with rapidly increasing population and increasing cost of medical care. However, different health programs are launched by the Governments of Pakistan to make the health of individuals better. Sehat Sahulat Programme is launched by the government to identify underprivileged individuals and to provide them with indoor patient service. The Dengue control program, Ehsaas Programme, and Expanded Program for Immunization are also launched by different governments. The public health sector is also working closely with World Health Organization (WHO) to eradicate the diseases like malaria, tuberculosis, and polio through Malaria Control Programme, Tuberculosis (TB) Control Programme, and Polio Eradication Initiative (PEI) programs. In addition, Human Immunodeficiency Virus (HIV)/Acquired Immune Deficiency Syndrome (AIDS) Control Programme, Maternal, and Child Health (MCH) Programme, and Cancer Treatment Programme are also working that are initiated by the governments. Alongside that, the health sector is also trying to control the Covid-19 pandemic.

The government is trying to take multiple initiatives to achieve the target of Universal Health Coverage (UHC) by WHO (2015) to make health care accessible to all individuals that would save them from financial catastrophe by 2030. The National Health Vision 2016-2025 is introduced as an effort to ensure UHC. Technical assistance is also taken from the World Bank as an arrangement of the health funds in Pakistan. But despite all the efforts, the health funding in Pakistan is very low and the health challenges have been increasing over time in Pakistan (*Economic Survey of Pakistan,* 2020).

The increase in the health budget is not promising as can be seen in Figure 1.2 where an increase from 0.7 to 1.1 as the percentage of the GDP has taken place from 2012 to 2019. It is a big challenge for the health sector to cater to all the health issues in a scarce resource setting with a population that is the 6th largest in the world.

Figure 1.2: Health Expenditure as a Percentage of GDP



Source: Economic Survey of Pakistan, Ministry of Finance, Pakistan (2020)

The performance of other health indicators, shown in Table A1 in the appendix, also depicts that the health sector condition is compromised in Pakistan. According to the Economic Survey of Pakistan (2019), the life expectancy in Pakistan is 67.3 years which is the lowest in the South Asian region which shows the need for substantial health policy initiatives to be taken in order to improve the health indicators. The population per bed is 1608 which is low, especially under the Covid-19 pandemic where medical care needs might not be fulfilled in case of an emergency because of insufficient bed spaces.

Pakistan has not been able to experience a smooth growth path over time and has faced high fiscal deficits (*Economic Survey of Pakistan*, 2019). Under the resource scare setting, it is not easy for the government to make provision of funds for the broader spectrum of the health

sector. The promise of national and governmental organizations about a safe and disease-free environment is yet seen as an unaccomplished task. But despite all these issues, the provision of medical facilities needs to be prioritized to ensure improvement in the quality of life of individuals. Hence, the government needs to find alternate strategies and ways through which people can be the ultimate beneficiaries of policies and maximum gains can be attained without causing waste of resources.

1.1. MDR-TB: A Challenge for the Health System in Pakistan

World Health Organization has ranked countries according to the burden of disease. Pakistan is ranked 6th amongst 22 high disease burden countries of the world where 40 percent of the burden of disease in Pakistan is in the form of communicable diseases such as malaria and tuberculosis (TB). The TB cases are increasing by 510,000 each year. According to WHO (2020), the incidence of TB (number of new cases) stands at 230 per 100,000 population, and prevalence (existing cases) of TB is about 310 per 100,000 population and the deaths are 39 per 100,000 population. Amid the scarcity of resources and multiple health issues prevailing in the country, high incidence rate (new cases) of tuberculosis (TB) has made the government to declare TB as a national emergency (*Economic Survey of Pakistan*, 2019). Then a major health threat exists in the form of multi-drug resistance tuberculosis (MDR-TB) where resistance from at least one of the two most powerful first-line anti-TB medications i.e., isoniazid and rifampin are observed globally (WHO, 2020). Pakistan ranks 4th in the high disease burden of MDR-TB in the world where 15,000 people are affected each year.

The WHO's End TB strategy (2015) targets to eradicate TB by the year 2035 and it is also one of the agendas of the Sustainable Development Goals (SDGs). Thus, it is need of time to focus on:

I. Strategies of government that are undertaken to control communicable diseases i.e. multi-drug resistance tuberculosis (MDR-TB).

II. Interlinkages among the various socio-economic, demographic, and spatial factors that lead to the incidence and prevalence of MDR-TB that may be associated with the treatment outcomes so that health policy can be defined accordingly.

The inclusion of economic analysis in health care decision-making is vital as careful economic evaluation will help the policymakers to allocate the resources optimally for the treatment of MDR-TB. The competing healthcare intervention strategies can be evaluated in detail in this regard which has the potential to provide important insight into the relative gains and cost of the respective strategy with considerable policy implications (Salkeld *et al*., 1995, Wagstaff, 2002, Hutubessy *et al*., 2003 and Rahman, 2020).

MDR-TB is particularly challenging for the health programs as the second-line TB drugs are expensive and less effective not only in Pakistan but also around the world (Ramachandra and Swaminathan, 2015). The expenditure on treatment is an important determinant of the commitment and success of the treatment as it creates a financial burden on the health program and patients. It is important to define the policies that are beneficial for both stakeholders in the process of improving the MDR-TB treatment outcomes. The demographic, socio-economic, and spatial factors also need to be considered along with the selection of effective strategies to achieve the desired health outcomes. The choice of treatment care selection should be taken into account carefully while dealing with MDR-TB patients. The treatment can be imparted in different ways i.e. ambulatory care where patients are treated in the community with the help of the family and community health workers which may involve hospital admission for two weeks only (Berman, 2000, Nathanson, 2006 and Ho *et al*., 2017) versus hospital care where the

patient is entitled to hospital admission for two months for treatment in an early phase of the disease and later treatment is carried out in the community (Bassili *et al*., 2013).

According to WHO (2009) report "the choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds with adequate infection control measures, the availability of trained personnel to administer treatment and manage adverse drug reactions; a social support network to facilitate adherence to ambulatory treatment; and the presence of other clinical or social conditions for in-patients". Hence understanding the burden of the MDR-TB disease and the multi-dimensional spectrum of the factors that affect the treatment outcomes of MDR-TB is essential for effective and efficient policymaking.

1.2. Background and Motivation

The health system of Pakistan is struggling to reduce the financial burden on hospitals and patients and to improve health outcomes with limited resources. On the other hand, the new cases of MDR-TB are increasing by 4.2% in Pakistan (WHO, 2020). MDR-TB is a communicable disease hence it is important to treat it timely to avoid person-to-person transmission. If one case of MDR-TB is left untreated or partially treated then the patient can infect 10 to 15 people in a year which spreads the disease further (WHO, 2002). If the treatment protocols are not properly followed or the patient does not adhere to the treatment then further resistance strains are developed in the body of the MDR-TB patients which is not easy to be treated (WHO, 2019). Hence, it is the utmost requirement to focus on the factors that affect the treatment of the MDR-TB and to define efficient strategies.

The economic evaluation of the strategies outlined by the health program to combat MDR-TB and to understand the factors that affect the treatment outcomes will help the policymakers to take the health care financing decisions which will optimize the health outcomes with the limited budget. A shift towards the ambulatory regime in a resource-scarce setting to lessen the burden on hospitals (WHO, 2009, Berman, 2000 and Ho *et al*., 2017) but the feasibility of this recommendation in the case of MDR-TB in Pakistan is not studied to the best of our knowledge and it needs to be addressed. Alongside it will help to analyze whether the burden on the hospitals can be reduced by providing treatment to the MDR-TB patients in the home environment instead delaying treatment waiting for the hospital beds. A study on this subject is also important for addressing some of the targets on health indicators prescribed in SDGs, the End TB Strategy and Universal Health Coverage by WHO.

The policy initiatives are undertaken by the National TB Control Program (NTP), Ministry of Health, Pakistan to improve the treatment outcomes of the patients i.e. selection of the treatment care strategies and provision of financial incentives to the patients which are not evaluated by far in detail in case of MDR-TB. Though researches are available in the literature about the medical perspectives of MDR-TB outcomes in Pakistan but literature gap exists related to the cost-effectiveness analysis of the treatment strategies of hospital and ambulatory care and detailed analysis of the association of socio-economic, spatial, and health policy-related factors with the treatment outcomes of MDR-TB patients. Hence, there is a need for an in-depth analysis to find if better health care can be provided with lower health spending and factors that can lead to better treatment outcomes for MDR-TB. Keeping in view the importance of these factors, we are motivated to undertake this research.

1.3. Objectives and Contribution

The basic research questions examined in this study are as follows: if there is a difference in cost-effectiveness of ambulatory and hospitalization care for the multi-drug resistance tuberculosis and which one is more effective?, do the demographic, socio-economic, and spatial factors have an association with the treatment outcomes of MDR-TB patients, and how policy initiatives undertaken by the health programs are associated with the health outcomes?

Based on the research questions, the following objectives are defined in our study.

i. To evaluate the cost-effectiveness of two health care treatment arms i.e. hospital versus ambulatory care arm for the treatment of MDR-TB in Pakistan.

ii. To analyze the association of the outcome of the cure for MDR-TB patients in Pakistan with their socio-economic and spatial characteristics and the treatment regimens followed.

iii. To analyze the association of the loss to follow-up of MDR-TB patients with the catastrophic healthcare expenditure and health policy interventions of health program.

The use of an ambulatory care for MDR-TB treatment is recommended as it is likely to have a positive relationship with the cure rate and reduces the resource burden on hospitals as the treatment is carried at the doorsteps of the patients (WHO, 2009). In order to see the viability of the treatment arm for Pakistan, we will do a cost-effectiveness analysis of the treatment arms of hospital and ambulatory care. We will calculate the incremental cost-effectiveness ratio (ICER) where the incremental cost is in monetary units and the incremental benefit is in the non-monetary units. In global health studies, a threshold used for comparison of cost-effective strategy is Cost per DALYs averted and ICER being less than one and three times annual GDP per capita which will be applied in our analysis also. After analyzing the ICER, we would be

applying the sensitivity analysis, etc. to check the robustness of our results and the relevant policy implications will be drawn.

In order to establish the relationship between the demographic, socio-economic, spatial, and policy-related factors with the outcome of cure, we would be analyzing multiple variables in our study. The demographic variables included in our model are age and gender and the socio-economic factors are education and family income of patients. The medical expenditures are also included to see the association with the outcome of cure. The spatial factors included in the analysis are time and travel expenditures endured in commuting to health care facilities which also capture the non-medical domain of health care. The policy-related factor is the selection of the treatment care i.e. hospital versus the ambulatory care whose association is established with the outcome of cure. We would be using the survival analysis in our study by applying the Cox proportional hazard technique.

According to WHO (2010), the loss to follow-up is the treatment outcome of "a patient whose treatment is interrupted for 2 consecutive months or more". WHO (2019) has emphasized the need to identify the factors that lead to loss to follow-up as it increases the drug resistance and person-to-person transmission of the disease. National Tuberculosis Program (NTP), Ministry of Health, Pakistan, has taken different initiatives to improve the treatment outcomes of MDR-TB. We would be analyzing the association of policy initiatives i.e. selection of treatment care strategies and provision of financial incentives to the patients of MDR-TB by the NTP, with the treatment outcome of MDR-TB. The patients have to bear the financial burden which is sometimes a high proportion of the annual income of the household known as catastrophic health care expenditure. The association of the catastrophic health care expenditure with the treatment outcome of loss to follow-up is also studied. Moreover, it is also studied if the financial

incentives given to the patients facing the catastrophic health care expenditure reduces the loss to follow up. The logistic regression technique is used in our analysis.

We have collected the secondary data of 438 patients registered at three main MDR-TB centers in Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital, Lahore, and Ojha Institute of Chest Disease, Karachi from 2012 to 2017.

This study will provide an important insight into the cost-effectiveness of the intervention strategies, i.e. selection of the treatment care as a health policy variable, undertaken by NTP, Pakistan. This study will contribute to the literature by providing an important insight from a health policy perspective by testing the feasibility of using ambulatory care for the treatment of TB to contribute in analyzing the health provisions in the scare resource settings that can reduce the burden on the hospitals without compromising the quality of treatment and treatment can be immediately started in the home environment of patients without having to wait for the hospital beds. The analysis of the demographic, spatial, and socio-economic determinants associated with the health outcomes of MDR-TB patients will also provide evidence-based policy implications for the health sector to achieve the SDG's target of a disease-free environment which will be an important contribution in literature.

Our study finds that there is no difference in the cost-effectiveness of the hospital and ambulatory care hence both strategies can be used simultaneously for the treatment of MDR-TB in Pakistan. Our study supports the WHO's proposition about the viability of using the ambulatory arm. The patient's age, family income, education level, and treatment care are not associated with the outcome of the cure. Whereas, the medical expenditure and time expenditure increases the chance to be cured. In our analysis of the factors associated with the loss to follow-up (LTFU) of the MDR-TB patients in the process of treatment, the treatment care strategies do

not show association with the LTFU showing that hospital and ambulatory care are not related to the unfavorable outcome of the treatment. This finding also provides the support for WHO proposition that the treatment for the MDR-TB can be conducted in ambulatory care alongside hospital care and the financial incentives given by NTP reduce the financial catastrophe for the patients that decreases the loss to follow-up during treatment of MDR-TB.

1.4. Plan of study

In order to pursue the objectives of the study, the second chapter is based on the economic evaluation of the hospital vs. ambulatory care of the MDR-TB program in Pakistan. The thesis is written in the essay theme consisting of three essays given in Chapter 3, 4 and 5.The third chapter is based on a study that analyzes the association of the socioeconomic and spatial characteristics alongside treatment regimens with the outcome of cure of MDR-TB patients in Pakistan. The fourth chapter deals with the analysis of catastrophic expenditure and policy interventions of health programs on the loss to follow-up of MDR-TB patients in Pakistan. Finally, in the last chapter 5, we will conclude the analysis followed by policy implications.

Appendix A

Table A1: Health Indicators in Pakistan

Health Indicator	2016	2017	2018	2019
Hospitals	1,243	1,264	1,279	1,282
Dispensaries	5,971	5,654	5,671	5,743
Basic health units	5,473	5,505	5,527	5,472
Maternity and child health care centres	755	727	747	752
Rural health centres	688	688	686	670
Tuberculosis centres	345	431	441	412
Total beds	124,821	131,049	132,227	133,707
Registered doctors	195,896	208,007	220,829	233,261
Life expectancy at birth (years)	66.8	66.9	67.1	67.3
Registered dentists	18,333	20,463	22,595	24,930
Registered midwives	36,326	38,060	40,272	41,810
Population per bed	1,565	1,585	1,608	1,608
Registered lady health workers	17,384	18,400	19,910	20,565
Population per doctor	997	957	963	963
Population per dentist	10,658	9,730	9,413	9,413
Average consultation fee of doctor	140.83	155.38	178.59	228.16
Infant Mortality Rate (per 1,000 live births)	62.4	61.4	60.5	59.5

Note: All indicators are given as total numbers and the average consultation fee of a doctor is given in the Pakistani rupee.
Source: Economic Survey of Pakistan (2020-2021)

Chapter 2

Economic Evaluation of the Hospital vs. Ambulatory Care of MDR-TB Program in Pakistan

ABSTRACT

The study analyses the cost-effectiveness of treatment arms of multi-drug resistance tuberculosis (MDR-TB) namely hospital and ambulatory care in Pakistan. The decision tree model is used in the cost-effectiveness analysis (CEA) and incremental cost-effectiveness ratios are calculated. Disability-adjusted life years (DALYs) averted is used as a measure of health outcome and social cost is calculated by using data of 342 MDR-TB patients registered between the years 2012 to 2017 during the randomized control trials in the health care facilities of Lahore, Murree, and Karachi. Five different scenarios are analyzed for the calculation of DALYs by incorporating various combinations of discount rates and age weights that allow us to compare and contrast different scenarios for the robustness of the results through sensitivity analysis. The result of CEA indicates that no arm shows continuous dominance in all the categories and both arms have played an important role in the reduction of disease burden for the patients. Hence, both arms can be accepted simultaneously as appropriate strategies for the treatment of MDR-TB in Pakistan. Hence, our study supports to use ambulatory care for the treatment as the long waiting list in hospitals can be avoided and treatment can be started without any delay at the door-steps of MDR-TB patients.

Keywords: Cost-effectiveness, Ambulatory care arm, Hospital Care, MDR-TB, Pakistan

2.1. Introduction

The inclusion of economic analysis in health care decisions and financing has gained importance over the past few decades. The structure of development expenditure and rules indicating resource allocation are vital in explaining the economic aspect of achieving maximum satisfaction with the minimum resources (Zweifel *et al*., 2009). Hence, economic evaluation of health care programs is required for rational decision-making for resource allocation so as to enhance the information set for policymakers (Salkeld *et al*., 1995). Such evaluation provides an important insight into the relative gains and costs of competing intervention strategies (Hutubessy *et al*., 2003) and important policy implications may as well be drawn.

Tuberculosis (TB) is the seventh most important cause of global disabilities and premature mortality in the world according to the World Health Organization (WHO, 2016). The report of WHO (2020) shows that every year about 482,683 new cases of multi-drug resistance TB (MDR-TB) are being observed worldwide where the first-line TB drugs i.e. isoniazid or rifampin have failed to cure patients globally. The End TB Strategy (2014) and Sustainable Development Goal (SDG) of 'good health and wellbeing' by the United Nations emphasize attaining the target of remission of TB disease by the year 2035. However, a financing gap of 2.3 billion dollars exists in the supply and demand of medical services globally according to WHO (2017) along with non-adherence to international standards of treatment protocols in most of the countries.[4]

Pakistan is ranked fifth among the high TB burden countries and fourth for MDR-TB in the world (WHO, 2020). The country's TB incidence rate is 268 per 100,000 with an annual increase of 510,000 cases each year, amongst which 15,000 are MDR-TB patients (WHO, 2016).

[4] http://www.emro.who.int/pak/programmes/stop-tuberculosis.html

Ramachandra and Swaminathan (2015) state that MDR-TB is a major issue faced by public health systems as the second-line TB drugs are expensive and less effective not only in Pakistan but also globally. Proper allocation of the scarce resources along with efficient and effective policy intervention strategies are required to enhance the range of affordable services provided at national and regional levels to eradicate this disease and to achieve WHO and SDGs targets.

The cost burden born by health programs and patients is a very important determinant of commitment and success of treatment as these costs determine the financial burden on the economy under the scarce resource settings. Pakistan is not able to experience a smooth growth path over time because of high current account and fiscal deficits according to the *Economic Survey of Pakistan* (2018). While facing the deficits and scarcity of resources, it is not an easy task for the government to allocate resources in a multi-dimensional development spectrum. The Public Sector Development Program (PSDP) expenditure has declined over time and budgetary allocation in the health sector is also low and indicators of health infrastructure have not shown sound and promising improvements compared to the population size of Pakistan.

The promise of national and governmental organizations about a safe and disease-free environment is yet seen as an unaccomplished task under scarce resources in Pakistan. But despite all these issues, the provision of medical facilities needs to be prioritized to ensure betterment in the quality of life of individuals. Hence, the government needs to find ways through which people can be the ultimate beneficiaries of policies and maximum gains can be attained without causing waste of resources.

Adaptation of evidence-based interventionist policies by the government is considered very important for disease eradication hence it acts as a motivation for this study to undertake the economic evaluation of strategies opted by health programs in order to combat MDR-TB in the

resource-scarce setting in Pakistan where health expenditure is only 1.1% of the annual gross domestic product in 2018-19 (*Economic Survey of Pakistan*, 2021). This study will provide important policy implications for efficient health resource allocation.

There are different intervention strategies for MDR-TB treatment, amongst which hospital care and ambulatory care are predominant. The standard definition of hospital care involves admission of a patient in the hospital for two months followed by treatment in the community whereas ambulatory care refers to treatment in the community by health workers or family members and may include initial hospitalization of the maximum of two weeks (Bassili *et al*., 2013). The use of ambulatory care for MDR-TB treatment is recommended as it is likely to have a positive impact on the cure rate and reduces the resource burden on hospitals as treatment is carried in the home environment (WHO, 2009, Berman, 2000, Nathanson, 2006, and Ho *et al*., 2017). This recommendation is expedient in resource-scarce settings in Pakistan where there is a need to reduce the burden on hospitals without forgoing treatment quality as only one hospital bed is available for 1608 people according to the *Economic Survey of Pakistan* (2019). Hence, in order to ensure that the patients and community do not suffer because of resource constraints, it is very important to see the viability of the alternate treatment regime of ambulatory care in Pakistan that ensures the treatment at the doorsteps of the patients. Cost-effectiveness analysis (CEA) of randomized control trials (RCT) (i.e. random allocation of MDR-TB patients in groups of ambulatory and hospital care arms to avoid biases in decision making in the selection of intervention cost-effectiveness) has not been performed for Pakistan to the best of our knowledge. Alongside it will help to analyze whether the burden on the hospitals can be reduced by providing treatment to the MDR-TB patients in the home environment instead delaying treatment waiting for the hospital beds. The present study attempts to fill this gap in the literature

and analyze the cost-effectiveness of these two treatment arms of the MDR-TB program in Pakistan and it is the primary objective of the present study.

WHO-CHOICE (Choosing Interventions that are Cost-Effective) states that "the term allocative efficiency, on the other hand, is typically used in health economics to refer to the distribution of resources among different programs or interventions to achieve the maximum possible socially desired outcome for the available resources". So, our study estimates the incremental cost-effectiveness ratio (hereafter ICER) of the two treatment arms (ambulatory and hospital care) of MDR-TB in order to determine which treatment arm is more effective in the case of Pakistan. For this purpose, the study analyses the disability-adjusted life years (hereafter, DALYs) averted followed by social cost in both arms from a sample of 342 MDR-TB patients registered at the National Tuberculosis Program of Pakistan in the three TB centers in Lahore, Karachi, and Murree from 2012 to 2017.

The incremental cost in monetary units refers to the difference in social cost i.e. program and patient costs on medical and non-medical (e.g. transport, etc.) expenditures in both arms. On the other hand, incremental effectiveness is the difference in the effectiveness of interventions in a non-monetary unit. The measure of effectiveness is the difference in DALYs in the hospital and ambulatory care arm (Brent, 2011). DALYs provide a measuring unit for the loss of life caused by disease i.e. 'One DALY is thus one lost year of healthy life' (Murray and Lopez, 1996), economically valued equivalent to gross domestic product (GDP) per capita per year (Institute for Health Metrics and Evaluation, 2013) and decrease in DALYs is a measure of benefit which shows a reduction in loss i.e. DALYs averted and hence the difference in DALYs refers to incremental effectiveness. In global health studies, a threshold used for the comparison of cost-effective strategy is the cost per DALYs averted or ICER less than one and three times annual

GDP per capita (Marseille *et al*., 2014 and Daroudi *et al*., 2021) The economic rationale behind this threshold is that it measures the value of available resources in a country and value of years of life as derived from the estimated willingness to pay of an individual for risk averaged for the respective population (Robinson *et al*., 2019). This benchmark aid in comparing and contrasting alternative treatment schemes in terms of cost-effectiveness analysis (Murray and Acharya, 1997).

Secondary objectives of the study include the analysis of the proportion of patients who are cured, died, failed to cure, and lost to follow-up, and the cost incurred by the patients along with the assessment of cost per DALY averted in each arm. We would also test the robustness of our results by various methods mentioned in the methodology section.

The structure of the study is as follows. The literature review is presented in Section 2.2 while the methodology is explained in Section 2.3. The data and variables are discussed in Section 2.4. Results are presented and discussed in Section 2.5 followed by a conclusion in Section 2.6.

2.2. Literature Review

2.2.1. Introduction

Evaluation of the health program is important not only from a clinical perspective but also for the policymakers as economic evaluation can help them to manage scarce resources efficiently. Petrou (2012) suggests that economic evaluation is beneficial not only at the national level but also at the local government levels as the pathways shown by such analysis provide evidence and motivate the policymakers to act according to the observation-based assessment. Different approaches are used in the economic evaluation of heath programs and they have their

benefits and drawbacks which are discussed in Section 2.2.2. According to Zweifel *et al*. (2009) the handling of health care data needs attention for efficient policy implications hence we have given a broader overview of some common data handling issues in Section 2.2.3 followed by the empirical literature in Section 2.2.4.

2.2.2. Theoretical and Methodological Background and Issues

The Commission on Macroeconomics and Health Report by WHO (2001) emphasizes the idea of inclusion of economic analysis in health care decisions and financing. According to Drummond (2005), economic evaluation integrates the costs and advantages attached to a strategy and help to give monetary value to it. For example, it may involve cost minimization where the desired outcome may be achieved by the least costly procedure which is possible in the case of trial-based analysis where the health outcomes are the same and the cost can be evaluated based on the minimization principle. Petrou (2012) explains that in order to compare the impact of a strategy, a threshold should be set to decide whether the intervention is desirable. For example, the willingness to pay is estimated by inquiring individuals about the rate at which they are ready to pay for a particular treatment care of a health program or willingness to make a tradeoff between the health and non-health outcomes. Alternatively, the threshold can also be set by health and economic experts based on the technique used for the evaluation.

Philips *et al*. (2006) and Weinstein (2006) explain that commonly used methodologies in the economic evaluation of health data are decision-analytic modeling and trial-based economic evaluation. Decision analytic modeling computes results by applying various mathematical tools in software by using data of cost and consequences collected and compiled from various sources. Trial-based evaluation is based on randomized control trial (hereafter RCT), which deals with the allocation of patients randomly in groups called control and comparison groups. The Control

group comprises of standard treatment regime and the comparison group is a new or alternate treatment strategy at a particular time. Petrou (2012) says RCT provides a wide range of patients' data on which various statistical and econometric tools can be applied to see the relationship between health and economic indicators. A few studies like Sculpher *et al*. (2006) argue that decision-analytic modeling and trial-based economic evaluation techniques are not much reliable as truncation of data occurs when the study period is over but other studies like Buxton *et al*. (2006) say that decision-analytic modeling and trial-based economic evaluation techniques reinforce each other and enrich information set for policymakers.

Zweifel *et al*. (2009) and Round *et al*. (2014) explain that there are different approaches for the economic evaluation of health indicators and programs which can measure the advantage of health care intervention against the cost units. The advantage of intervention can be presented in cardinal utility function units featuring health variables in the scalar index in the case of Cost and Utility Analysis (CUA), or monetary units in Cost and Benefit Analysis (CBA), or a natural unit of health like body temperature measured or length of life in the Cost-effectiveness Analysis (CEA) while the cost is in the monetary term in all three strategies.

In the case of cardinal utility measure of health, the analysis is called Cost and Utility Analysis (CUA) of treatment strategies, which shows multiple dimensions of health i.e. expansion of the length of life and side effects of medications, etc. in the utility units by assigning different weights to health states and cost of treatment is considered. Here, the incremental cost-utility ratio is calculated with incremental cost in monetary units and incremental benefit in utility terms, and a threshold for comparison is assigned, for instance, willingness to pay for a particular treatment strategy by the patients, etc. The advantage of using this strategy is that it involves both qualitative and quantitative measures in the calculation but at

the same time this strategy is criticized because of its subjective measurement of benefits that involves a value judgment of the quality of life instead of a clinical measure.

Another strategy explained by Robinson (1993) and Culyer and Chalkidou (2019) is the Cost and Benefit Analysis (CBA) of treatment strategies where both measures are in monetary units. So, if net cost is less than net benefit then the intervention is said to be beneficial. Here, the ease of assessment is that each intervention can be evaluated individually. When there are several mutually exclusive intervention strategies then one with the highest net benefit is adapted. The incremental cost-benefit ratio can be found with numerator and denominator both in monetary terms. This strategy has the advantage that it is unbiased as being free from value judgments about the health outcomes. The drawback of this strategy is the potential for error in the quantification of the benefits and costs as some of the costs and benefits are subjective that may mislead the results.

Levin and McEwan (2001) and Suwantika *et al*. (2020) explain another measure that is the Cost-Effectiveness Analysis (CEA) of treatment strategies where the health measure is in the natural units e.g. length of life and the cost of treatment is in monetary units. Incremental cost-effectiveness ratio (ICER) can be calculated as a ratio of the difference between the cost known as incremental cost and the difference between effectiveness known as incremental effectiveness of the competing strategies. The advantage of using ICER is the ease of calculation for quantifying the effectiveness measure which is in the natural units of health and the clinical measures that can easily be incorporated into the analysis, unlike the incremental cost-benefit ratio where monetary units are required in order to see the advantage of the strategy and data related to benefit may not be readily available for the policy making process to compare the economic cost and economic benefit of the health intervention strategy or incremental cost-utility

ratio where the advantage involves the subjective evaluation. WHO (1993) has formulated a measure to quantify the disease burden, risk factors, and injuries known as disability-adjusted life years (DALYs) which captures the loss of life years comprising premature death and years of life not spent in full health and reduction in DALYs is taken as a measure of effectiveness.

Global Burden of Disease Study (2004) uses DALYs to address ethical criteria for quantifying the burden of disease and injury as mentioned by Murray (1994 & 1996). It is a measure opted to compare and contrast the health status and health service provision in different countries. It gives a comparison of time lost in two states i.e. years of life lost due to death (YLLs) and years lived with disability due to disease (YLDs). Murray *et al*. (1994) and Murray and Acharya (1997) explain that DALYs provide an opportunity to consider the patients with similar health conditions as the same group with the consideration of gender and age. The difference in DALYs of the two competing strategies is treated as incremental effectiveness. The incremental cost is calculated by taking the difference of total cost (direct and indirect cost) endured by the patients and their households in the two competing strategies. Then the incremental cost-effectiveness ratio (ICER) is calculated as the ratio of incremental cost and incremental effectiveness of competing treatment strategies. The drawback of the strategy is that it depends heavily on the assumptions about the discount rates, age weights and expected life expectancy and assumptions need to be handled carefully.

According to Weinstein (1990), Zweifel *et al*. (2009), and Suwantika *et al*. (2020) in all the above-mentioned approaches where interventions are mutually exclusive, the dominated strategies which are more costly with less effectiveness are excluded and incremental cost and benefit/effectiveness ratios are recalculated. Zweifel *et al*. (2009) further explain that if an intervention is found to be more expensive as compared to other expensive strategies based on

the threshold then the intervention strategy can be rejected due to extended dominance when interventions can be scaled down proportionally. These approaches have the benefit of providing information to the policymakers related to a more effective strategy but not about whether the highest cost-effective strategy should be undertaken or not. So, the budget size has to be kept in view in order to be specific about how many strategies should be undertaken till the budget is exhausted.

All the above-mentioned approaches can be used for the evaluation of health interventions. However, the costs and the advantages of interventions should be calculated carefully.

2.2.3. Data-Related Issues in Health Care

WHO (2017) mentions that evaluation of health care intervention programs is important for the eradication of the disease. It will help the health programs to select a better strategy. Various tools are used to find the effectiveness of the intervention strategies and DALYs is one such tool that is commonly applied at sectoral and micro-level decision making but many studies do not clearly specify the assumptions taken during the calculation of DALYs. For example, according to Fox-Rushby and Hanson (2001), the use of a correct measure of life expectancy, disability weights, and other assumptions are not clearly mentioned in nine studies out of a sample of sixteen studies published from the year 1993 to 2000. The study raises the concern that if assumptions are not clearly mentioned then studies cannot be compared with each other. Sensitivity analysis is applied in only a few of the studies and detailed calculations are not provided which creates confusion among readers and more importantly for the policymakers.

The availability of data for the calculation of the cost in CEA analysis is another issue (WHO, 2009). It includes dimensions of health care program cost, personal cost on health care,

and indirect non-health care cost. Health care program cost is related to technology, program, laboratory test, treatment and adverse effects of medications, etc. Alongside that non-health care costs that are not directly related to health outcomes but they support the health program like the cost of running awareness programs in communities have to be borne by the health program. Direct personal costs include home care cost of services, supplementary equipment, food supplies, and transportation cost, etc. Indirect non-medical costs include the opportunity cost of time spent in traveling or hospitalization, etc., and the productivity and work loss. Even in the case of free provision of treatment by public sectors, the indirect cost has to be incurred by patients as well as family members i.e. transport cost and loss of working days due to time spent for acquiring treatment. The availability and accuracy of all these costs, discount factor, and inflation adjustment along with the consideration of uncertainty across the cost data are very important factors in the analysis of health care programs and policymaking.

Given that researcher has to be cautious about all the factors mentioned above, Zweifel *et al*. (2009) explain that CEA provides a comprehensive picture of health outputs and scarce resources available at the disposal of government through the incorporation of social perspectives either through direct intervention by centralized decision or through decentralized ones in the provision of health services.

2.2.4. Empirical Literature

A wide range of studies focused on the success of different treatment regimens of MDR-TB based on 'outcomes' but very few of them have focused on the cost-effectiveness of the strategies. The standard clinical outcomes are defined by WHO (2010). Treatment completed refers to "a patient who completed treatment but who did not have a negative sputum smear or

culture result in the last month of treatment and on at least one previous occasion". Cured refers to "a patient whose sputum smear or culture is positive at the beginning of the treatment but who is smear or culture test is negative in the last month of treatment and on at least one previous occasion". Treatment failure refers to "a patient whose sputum smear or culture is positive at 5 months or later during treatment". Default means "a patient whose treatment is interrupted for 2 consecutive months or more". The outcome 'died' is for "a patient who died for any reason during the course of treatment". The term 'not evaluated" refers to the patient whose outcome is not declared till the end of the analysis, while 'still under treatment' refers to a patient whose treatment is still in process.

Some of the empirical studies show viability of both treatment care strategies i.e. ambulatory hospital care as there is no significant difference in the outcomes of hospital and ambulatory care in Thailand (Kamolratanakul *et al*., 1999), Tanzania (Lwilla *et al*., 2003), Zambia (Miti, 2003), Machakos district of Kenya (Kangangi *et al*., 2003) and Haryana, North India (Singh *et al*., 2004). A lot of research related to CEA is available for the medicines used for the treatment and health outcomes. But only a few studies are available that analyze the difference in cost and cost-effectiveness of ambulatory and hospital care strategies.

Various studies have used the systematic review of literature and meta-analysis to identify the relationship between the treatment regimens and the health outcomes. These studies provide an in-depth insight into various trends that are available in literature about the feasibility of the treatment regimens. For the success of the health care intervention of ambulatory care along with the support from policymakers and government, strong coordination is required from the society and community as WHO (2003) reports "organized community groups, peer groups, chosen members of the community, and family members all have the potential to act as supervisors to

ensure completion of treatment and hence cure. Kangovi *et al*. (2009) explain in a meta-analysis of studies about the treatment outcomes that community-based workers play an important role in determining their commitment to the program especially if they are given incentives in developing countries and empathetic behavior of the healthcare workers makes patients more comfortable with the treatment procedures (Kangovi *et al.,* 2009).

Barter *et al*. (2012) did a systematic review of 30 articles to access the cost of TB treatment in sub-Saharan Africa. The medication, hospitalization, transportation, and caregiving in the private sector are major cost contributors to the treatment. The portion of the cost as a percentage of the average income earners varied from a small proportion of the income to 10 times the income for the poorest of 20% of the population. The study has suggested serious policy actions by the health sector to save the patients from the financial burden.

Fitzpatrick and Floyd (2012) conduct a systematic review of the literature and concluded that MDR-TB patients should be treated in ambulatory care, as outpatient care has a lower cost per DALYs averted as compared to hospital care in 14 WHO sub-regions. Few studies have found support for the ambulatory care in South Asian countries also. The visit to health facilities daily in the initial phase of treatment leads to more monetary and time costs along with the loss of working hours for the working patients and accompanied fellows which act as a hurdle in the treatment process in Pakistan hence treatment in community in ambulatory care may be helpful in reducing such burdens (Khan *et al*., 2002) and cost saving nature of ambulatory/community care is also found by John *et al*. (2018) for India and Gomez *et al*. (2016) for Bangladesh.

Bassili *et al*. (2013) conduct a meta-analysis of treatment outcomes of the patients by using 35 published studies for the ambulatory and hospital-based models and find pooled treatment success rate of 66.4%. The study finds that there is no statistical difference in the outcomes of

the two arms hence the ambulatory arm can be used along with the availability of services in-hospital care for patients in dire need. Weiss *et al*. (2014) perform a systematic review and meta-analysis of 10 studies to access the treatment outcomes of community-based TB treatment and find that the treatment success rate is 65%, loss to follow-up is 15%, deaths are 13% and 6% failure rate has occurred where the treatment regimens did not show a relationship with the treatment success rate. Laurence *et al*. (2015) performed a systematic review of the literature to analyze the cost of treatment incurred by the providers and patients in case of drug-susceptible TB and MDR-TB by using 71 research papers. The cost of treatment for MDR-TB is US$ 83,365 in high-income countries (HIC), US $ 5284 in upper-middle-income countries (UMIC), US $6313 for the lower-middle-income countries (LMIC), and US $1218 for low-income countries (LIC).

William *et al*. (2016) perform a systematic review of the 16 studies for the countries including China, Bangladesh, Ethiopia, India, Kenya, South Africa, Russia Uzbekistan, and Philippines to observe the treatment success rate in the community and hospital care and found a better treatment success rate and lower failure rate for the community care than the hospital care. Tran *et al*. (2018) perform a systematic review of the literature by using 12 papers and recommended that MDR-TB treatment to be conducted in ambulatory care instead of hospital care. The cost per patient is more for the MDR-TB than the drug-sensitive TB by almost 40% whereas inpatient cost is about US $16300 comprising ninety-five percent of per-patient total cost (Schnippel *et al*., 2013). Byun *et al*. (2021) perform a systematic review of literature of seventeen studies that include the cost evaluation of the treatment strategies for tuberculosis in low, middle, and higher-income countries. The results suggest that the short regimes of 2-4 months are more desirable than 6 months of treatment regimens along with the use of the new medicines with existing

drugs. In the low and middle-income countries, community-based care, home-based care, and mobile-device-based care are found to be more cost-effective than the hospital care and self-administered care regime. The short treatment regimens have the potential to reduce the disruptions in the work-life of the patients which increases treatment adherence.

Some other studies also focus on the short term and long term regimens. Owens *et al*. (2013) applied the decision analysis in order to find the cost-effectiveness of the treatment regime comprising treatment provision with the first line of the treatment regime for six months versus shorter duration in the public sector by using the parameters from the studies about TB globally. Among the 100 patients, movement to the shorter duration regime from the standard 6-month therapy resulted in the aversion of 8 to 14 disability-adjusted life years; DALYs. The main cost-effectiveness factors are prices of the drugs, cost of the treatment delivery, and deaths prevented. For the cases like Brazil, the delivery cost of treatment is higher than the cost of the drug, making the 6-month regime more cost-saving. For the cases like Philippines, the cost per DALYs averted is US $88 if the cost of drug is US $66 per patient hence if the drugs cost per day is less than US $0.37 then the shorter treatment regime becomes more cost-saving. Manabe *et al*. (2012) use the decision tree model to analyze the cost of a 6-month treatment regime with 4 months of treatment with first line TB drugs for Uganda. The drug price for daily dosage came out to be US $0.115 for the two months and US $0.069 for the 6-month treatment regime. The average per-patient treatment cost is US $23.64 for a 4-month regime and $26.07 for a 6-month regime. Death, failure, and relapse rates are less in a 4-month regime than in a 6-month regime.

The studies have also focused on the feasibility of treatment regimens for the TB treatment. Hunchangsith *et al*. (2012) analyze the cost-effectiveness of multiple treatment regimens by using the decision tree model for Thailand. The strategies under consideration are direct

treatment strategy provision by the health worker, community worker, and health worker, mobile phone reminder strategy along with self-administered therapy. Cost is taken in the international dollar for 2005 and DALYs as the outcome of health. The results of the cost-effectiveness analysis did not show a preference for any strategy. The advantage gained in terms of health with health workers is 7900 DALYs, a family member is 9400 DALYs, and a community member is 13,000 DALYs. The failure rate was higher in the self-administered strategy. However, the mobile phone reminder strategy did not appear to be effective as more dead rates are reported in this case.

Nsengiyumva *et al*. (2012) analyze the relationship of digital technologies with the MDR-TB in Brazil by using a decision analysis framework and finds that digital technologies can be cost savings in the case of MDR-TB by 15 to 18 percent in comparison to the standard treatment conducted thorough the health or community worker. The study for India shows that the home based care came out to be US $ 404 and the facility-based care is US $2310 indicating a saving of 80% in home-based care. The hospital stay charges are more in facility-based care which is a major cost burden for the patients (John and Chatterjee, 2016). John *et al*. (2018) explain that ambulatory care eases the burden on the patients and hospitals in India and will increase the equity to access to health services by using the decision tree model. The treatment can be initiated timely in the community at the doorsteps of the patients. The overall discussion shows that the treatment in ambulatory care can reduce the disease burden for patients as compared to hospital care. In the hospital care, an average estimated cost of treatment is US $3390.56 and for decentralized care, it is US $17241.1. Decentralized caregiving is more cost-saving and ICER per Quality Adjusted Life Years (QALYs) gained is US $2382.68. Bada *et al*. (2019) calculated the costs of provision of the TB treatment in the hospital for 8 months, hospital for 2 months, and

ambulatory care in Nigeria. The cost of treatment for 8-month hospitalization is US $18,528, 2-month hospitalization, it is US $15,159 and for ambulatory care, it is US $9425 and concludes that ambulatory care is a reasonable option in case of treatment of TB in Nigeria. The Cost per DALY averted in ambulatory care came to be US $579 in Estonia and US $429 in Tomsk Oblast (Floyd *et al*., 2012) which is less than the annual per capita GDP of these countries hence viable to use for TB treatment.

Macedo *et al*. (2020) analyze the cost-effectiveness of the regimens for the MDR-TB treatment in Brazil by using the Markov method. The regimens included the medication with current drugs, only oral drug with bedaquiline and a long term standard regime. The regime with only oral drugs with bedaquiline is found to be cost-reducing by US $ 10,186 as compared to US $10,503 for the regime with current drugs and US $ 21,035 for the long term regime. Alemayehu *et al*. (2020) perform the cost-effectiveness analysis by using Markov based model for the treatment provisions in the initiative centers and follow-up centers in Ethiopia. The average cost-effectiveness ratio per DALYs averted is US $671 for the follow-up centers and US $1471 in initiative centers. The ICER of MDR-TB treatment came out to be US $1641 per DALYs averted for the initiative center showing that the strategy is cost-effective.

2.2.5. Concluding remarks

Countries are shifting towards the use of ambulatory care regime for the treatment of MDR-TB because of its advantages of service provision at the doorsteps of the patients and reduction of burden for the hospitals. A lot of research has been done related to the outcomes of the strategy but cost-effectiveness is addressed by a few of them. The literature review identifies that it is important to explicitly mention all the assumptions that are used in cost-effectiveness

analysis. It will make the results and policy recommendations more robust. The policymakers will also have a clear picture of which intervention strategy is most viable and policy can be designed accordingly. For Pakistan, only one study (Khan *et al*., 2002) explores the cost-effectiveness of alternative treatment strategies, though it does not explicitly analyze the ambulatory care in the study. This leaves the caveat in the literature and gives us a margin to fill the research gap for Pakistan by analyzing the cost-effectiveness of ambulatory and hospital care for MDR-TB treatment in Pakistan. The assumptions used in the analysis are explicitly explained in our study as discussed in sub-sections 2.3.1 and 2.3.2.

2.3. Methodology for the Evaluation of Health Intervention Strategies

In order to evaluate the two treatment arms for MDR-TB, the study employs cost-effectiveness analysis (CEA). The measure of effectiveness considered here is the reduction in the life-year loss i.e. DALYs averted and cost measured in monetary units. The CEA is helpful in determining the relative importance of one health intervention as compared to other interventions based on disease-related clinical measures and information can be used along with the cost consideration to determine how much of the cost has to be born for a health outcome gain. The discussion of methodology is as under.

2.3.1. Effectiveness Measure of Health Intervention Strategies

The study uses DALYs as a measure of effectiveness of the health care program. The difference in the DALYs of treatment strategies of hospital care and ambulatory care is taken as incremental effectiveness. DALYs is a combined measure of mortality (early death) and morbidity (ill health). DALYs is the weighted sum of the years of life lost (YLL) and years of life lived with disability (YLD), wherein the weights assigned to YLL and YLD are set as equal

to one and less than one respectively. The reduction in DALYs or DALYs averted/saved by adopting treatment arm rather than hospital care is an effectiveness measure as discussed in Section 2.2.2. We adopt the methodology proposed by Fox-Rushby and Hanson (2001). DALYs are calculated for both arms separately to compare the effectiveness of treatment strategies of hospital and ambulatory care arms.

In order to calculate DALYs, we use a number of statistics. The onset of disability (denoted as 'ao') refers to the age at which a patient is diagnosed with MDR-TB. The age of death (ad) is recorded as the age of the patient at the time of death. Duration of disability (Ld) is the time spent in an ill state calculated as the time duration from initial diagnosis of MDR-TB till outcome is determined as cured or died by the health program. Gender-specific local life expectancy at a given age is used to measure standard expectation of life at the age of death (Le). Data are extracted from WHO Life Tables for Pakistan (2012-2016). The disability weight reflects the intensity of disease ranging from 0 (perfect health) to 1 (death). We take the disability weight of 0.29 for MDR-TB as proposed by the Global Burden of Disease Study (2004) (also see Salomon *et al.*, 2012).

According to Murray and Achaarya (1997) in the calculation of DALYs, the inclusion of the age of patients provides information about the life cycle of individuals based on their age cohorts and reduces the chance of discrimination among lives of individuals therefore; the DALYs of different age groups may be assigned different weights. The reason behind taking age weights is the perception that adults have more contribution to family and community life and are economically more active than other age groups. Therefore, the value of life is considered to increase from zero at birth to the highest in the early twenties and then decreases again as a person gets older. But Anand and Hanson (1997) have criticized the allocation of resources

based on DALYs where one specific age group is given more importance, as ethically the lives of the individuals who do not have a higher contribution to economic activities should not be valued less by the policy makers. So, following this argument uniform age weights are also included in our analysis to nullify social preferences related to the age of patients and the importance of the potential economically active part of the population on ethical grounds. This study incorporates uniform and non-uniform age weights to see how effectiveness measure is affected by them and it will also help us to compare and contrast various scenarios.

Moreover, Anand and Hanson (1997) argue that standard life expectancy might not be the correct measure since socio-economic factors also affect life expectancy and the standard measure does not capture the difference in the life expectancy across different regions. So this study caters to these differences by incorporating gender-based local life expectancy for Pakistan instead of standard life expectancy as proposed by Murray (1996). A discount rate is also used which shows the rate at which the economy is willing to trade off present with future consumption. As the inflation rates changes over time, hence the real interest rate is taken in the analysis to adjust the interest rate for inflation. The discount rate of zero, 3, and 5.96 percent are considered. The discount rate of zero refers to equal weights to future and present time, 3% refers to the U.S treasury real interest rate considered to be a risk-free rate and 5.96% is the average real interest rate in Pakistan over the period 2011-2017 (*Economic Survey of Pakistan*, 2018).

The years of life lived with disability (YLD) and the years of life lost (YLL) are calculated by using Equations 2.1 and 2.2 respectively as proposed by Fox-Rushby and Hanson (2001).

$$YLD_i(r, M, \alpha) = D\left[\frac{MZe^{rao}}{(r+\alpha)^2}\left\{e^{-(r+\alpha)(Ld+ao)}[-(r+\alpha)(Ld+ao)-1]\right.\right.$$

$$\left.\left. - e^{-(r+\alpha)ao}[-(r+\alpha)ao-1]\right\} + \frac{1-M}{r}\left(1-\mathrm{e}^{-\mathrm{rLd}}\right)\right] \quad 2.1$$

$$YLL_i(r, M, \alpha) = \frac{MZe^{rad}}{(r+\alpha)^2}\left\{e^{-(r+\alpha)(Le+ad)}[-(r+\alpha)(Le+ad)-1]\right.$$

$$\left. - e^{-(r+\alpha)ad}[-(r+\alpha)ad-1]\right\} + \frac{1-M}{r}(1-\mathrm{e}^{-\mathrm{rLe}})\Big] \quad 2.2$$

Here,

M = age weighting modulation factor, 0 for uniform weights and 1 for non-uniform weights

Z = 0.1658= Age weighing adjustment constant to normalize the impact of non-uniform age weights so they do not disturb the total number of DALYs

Le = Loss function of years of life loss estimated by gender-based local life expectation at age ad

ad = age of death

r = discount rate

α = 0.04 = age weighting constant

ao = age of onset of disability

Ld = duration of disability

D = disability weight

i = i^{th} number of patient

YLD = years of life lived with disability

YLL = years of life lost

The calculation of years of life lost (YLL) involves the time of death of the patient compared to the expectation of life a person would have lived without the disease. Hence, it requires two

steps of calculation. First, YLL is calculated from age of death by using Equation 2.2 as proposed by Fox-Rushby and Hanson (2001).

Then, in the second step, the value of YLL obtained in Equation 2.2 is converted into the expectation of a loss of life at the onset of disability to ensure that all DALYs from years of life lost are added up from the onset of disability by taking a common matric as proposed by Fox-Rushby and Hanson (2001). The total life year lost from the age of death is converted into life years lost at the age of onset of disability. So, the value obtained from Equation 2.3 will give the final value of loss due to premature death i.e. YLL.

The left side of the Equation 2.3 shows years of life lost at the age of death (YLL_i at age ad) and the right had side shows $YLL_i\ (r\ M,\ \alpha)$ from Equation 2.2, s is the duration of disease found from the age of death (ad) and the age of onset of disease of MDR-TB for a patient which is discounted at the rate r to obtain the variable of YLL_i at the age of death.

$$YLL_i\ at\ age\ ad = YLL_i(r\ M, \alpha)e^{-rs} \qquad 2.3$$

where s= number of discounted years (ad-ao)

The summation of YLD from Equation 2.1 and YLL from Equation 2.3 will yield the value of DALYs for one patient in Equation 2.4.

$$DALYs_i = YLL_i + YLD_i \qquad 2.4$$

DALYs for each patient in the hospital arm are calculated and then summation is done for all the values for DALYs for this arm. Similarly, summation of DALYs is also performed for the ambulatory arm as shown in Equation 2.5.

$$DALYs = \sum_{i=1}^{n} DALYs_i \qquad 2.5$$

where index *i* refers to a patient from 1 to 171 in each arm in Equation 2.5.

The main purpose of effectiveness analysis is to see which intervention results in decreasing the DALYs as given in Equation 2.5. Different scenarios are analyzed by incorporating various combinations of the discount rate (r), age weighing modulation factor (M), and age weighing constant (α) in the calculation of DALYs. It allows us to compare and contrast the results and to draw conclusions related to the robustness of the effectiveness analysis through sensitivity. In category 1, all weights are set equal to zero as proposed by Murray *et al*. (2013a). In category 2, the discount rate is taken as 3% and the age weighing modulation factor and age weighing constant are set equal to 1 and 0.04 respectively. In category 3, the discount rate is set equal to 3% while age weighing modulation factor and age weighing constant are set equal to zero. In category 4, the discount rate of 5.96% is considered with age weighing modulation factor equal to 1 and age weighing constant equal to 0.04. Finally, in category 5, the discount rate of 5.96% is considered along with the values of age weighing modulation factor and age weighing constant being set equal to zero.

2.3.2. Cost Measure of Health Intervention Strategies

We assess the cost by using a social perspective i.e. cost incurred by health program and patients along with their families for the treatment of MDR-TB to explore the efficient allocation of resources proposed by WHO (2000). The cost of treatment per patient incurred by the National Tuberculosis Program of Pakistan includes the cost of medical services along with the provision of food baskets to treatment supporters which is estimated to be equal to US $1000 for

each arm. Though the health program bears a major share of the cost, nonetheless patients also have to bear different types of costs, and this social cost[5] incurred by the patients is included in our analysis.

Different types of costs are incurred by the patients along with their families in the MDR-TB treatment process. The costs categories included in our analysis from the patients' perspective are the total cost of traveling to various health facilities by the patient, treatment of adverse effects, medicines/drugs, laboratory tests, preventive measures to control infection at home, for example, use of masks, etc., two-way home visits cost if the patient has relocated for treatment, and accompanying fellow travel, fellow rent as the accompanying fellow often has to rent a separate room as a precaution because of the communicable nature of the MDR-TB disease and other miscellaneous expenditures. The indirect cost of fellow's income loss due to taking time off from work is also included. Each category is first converted from monthly to yearly data and then summed up to find the total cost for patients in both arms separately. We would be using this cost of each arm as a baseline case for the sensitivity analysis which is explained in the next section.

Cost is reported in international dollars (I$), US dollars ($), and the Pakistani Rupee (PKR). The I$ is a standard representation of local currency purchasing power parity and its value is same as one US dollar has in the United States (US) at a particular point in time representing values adjusted for purchasing power. Augustovski *et al*. (2018) explain that WHO has proposed to take a benchmark of a year in the analysis to make a comparison across the currencies of different countries based on purchasing power parity in comparison to the US in the year 2017 when US had the highest level of GDP in the world, so 2017 is used as a base year and the value

[5] Social cost i.e. program and patient costs on medical and non-medical (e.g. transport, etc.) expenditures

proposed by International Monetary Fund[6] and World Bank[7] is one I$ equivalent to 33.59 Pakistani Rupee which is used in our study. Further explaining the information about the cost and the years, the average rate of one US dollar was equal to 104 as an average Pakistani Rupee during the years 2012-2017 which is used in this study.

2.3.3. Cost-Effectiveness Measure of Health Intervention Strategies

Cost per DALYs averted is calculated for each arm. The ratio of cost per DALYs averted is an important indicator in the cost-effectiveness analysis as it provides information about the cost of saving a year of life for each treatment arm. The cost-effective strategy is the one that has a cost per DALYs less than the GDP per capita per year, that is, the cost of saving a life year is less than per capita income per year. Moreover, cost per DALYs averted less than three times GDP per capita is also accepted as cost-effective as explained by Marseille *et al*. (2015).

Then another cost-effectiveness measure which is ICER is calculated following Hutubessy *et al*. (2003) and Edoka and Stacey (2020). This measure is given by using Equation 2.6 which is the ratio of incremental cost i.e. difference in the cost of the ambulatory arm over the hospital care arm, and incremental effectiveness of treatment which is the difference between the DALYs averted/saved in the ambulatory arm over the hospital arm. Note that the DALYs is the summation of years of life lost (YLL) and years of life lived with disability (YLD); hence the difference in DALYs is an effectiveness measure.

$$ICER = \frac{Cost\ of\ ambulatory\ care\ arm - Cost\ of\ hospital\ care\ arm}{DALYs\ of ambulatory\ \ care - DALYs\ of\ hospital\ care} \qquad 2.6$$

[6] https://www.imf.org/external/datamapper/PPPEX@WEO/OEMDC/ADVEC/WEOWORLD/DA/PAK
[7] https://data.worldbank.org/indicator/PA.NUS.PPP?locations=PK

Cost is discounted at 3% in categories 2 and 3 and 5.96% in categories 4 and 5 to make it compatible with DALYs in the calculation of ICER. The additional cost of saving a life year would be analyzed by this ratio.

Deterministic one-way sensitivity analysis is performed to address the question of 'what if the key inputs or assumptions changed' as applied by Goldsmith *et al*. (1987), Saltelli *et al*. (2004), Schneeweiss *et al*. (2006), Hunink *et al*. (2008), and Vreman *et al*. (2020). Along with the application of different sets of assumptions for the DALYs, sensitivity analysis is also performed on patients' cost but not on program cost as it is constant. The variation in patients' costs includes an increase or decrease of 10% to 40% from the cost of each arm (calculated from the data collected from the MDR-TB centers) taken as baseline case and results are inferred.

The final check of the robustness of our results will be the application of a t-test with unequal variances to check if there is a significant difference in the series of DALYs of hospital and ambulatory care arms in each category as well as among the costs of these treatment strategies.

2.3.4. Data

To find ICER as mentioned in Equation 2.6, we collected the secondary data from a pool of 438 patients diagnosed and registered for the treatment of MDR-TB at the National Tuberculosis Program (NTP) of Pakistan from 2012 to 2017. In a randomized control trial carried out by NTP during 2012 to 2017, the MDR-TB patients were asked to participate in the random control trial and those who volunteered to participate were randomly assigned to the hospital care arm (H) and ambulatory care arm (A) irrespective of the intensity of the disease. The trial was carried out in three regions of Pakistan namely Gulab Devi hospital, Lahore, TB Samli Sanatorium Hospital, Murree, and Ojha Institute of Chest Diseases, Karachi. The data is recorded in the original

survey /questionnaire that is used as the primary data collection instrument by NTP and we have used that as a secondary source of data in this study. The record of data about the socio-demographics factors, economic factors, medicines, transport cost, loss of work, need for accommodation of care givers, etc. was maintained by the NTP centers by using the questionnaire instrument that was filled / self-reported by patient at each monthly visit of NTP center. This instrument is used as a monthly follow-up visit form by NTP. Different questions were written in the survey questionnaire related to the various type of costs incurred by the patients and accompanied fellows that were filled by the patients on each monthly follow-up visit. We have collected all the data from the records of the NTP centers. The trial enrolled a total of 438 patients during the time period 2012 to 2017 and we have collected the data of 438 patients for these years and the distribution of patients is shown in Table 2.1.

Table 2.1: Distribution of Patients

Facility	Number of Patients	Male	Female
Ojha Institute of Chest Diseases, Karachi	190	107	83
Gulab Devi hospital, Lahore	202	113	89
TB Samli Sanatorrium Hospital, Murree	46	24	22
Total	438	244	194

Seven outcomes of 438 patients are observed in the analysis i.e. completed, cured, failed to recover, lost to follow-up, not evaluated till the end of the trial, still under treatment, and died as mentioned in Table 2.2. The table shows that the gender ratio is quite similar across the three hospitals.

Table 2.2: Outcomes of Patients

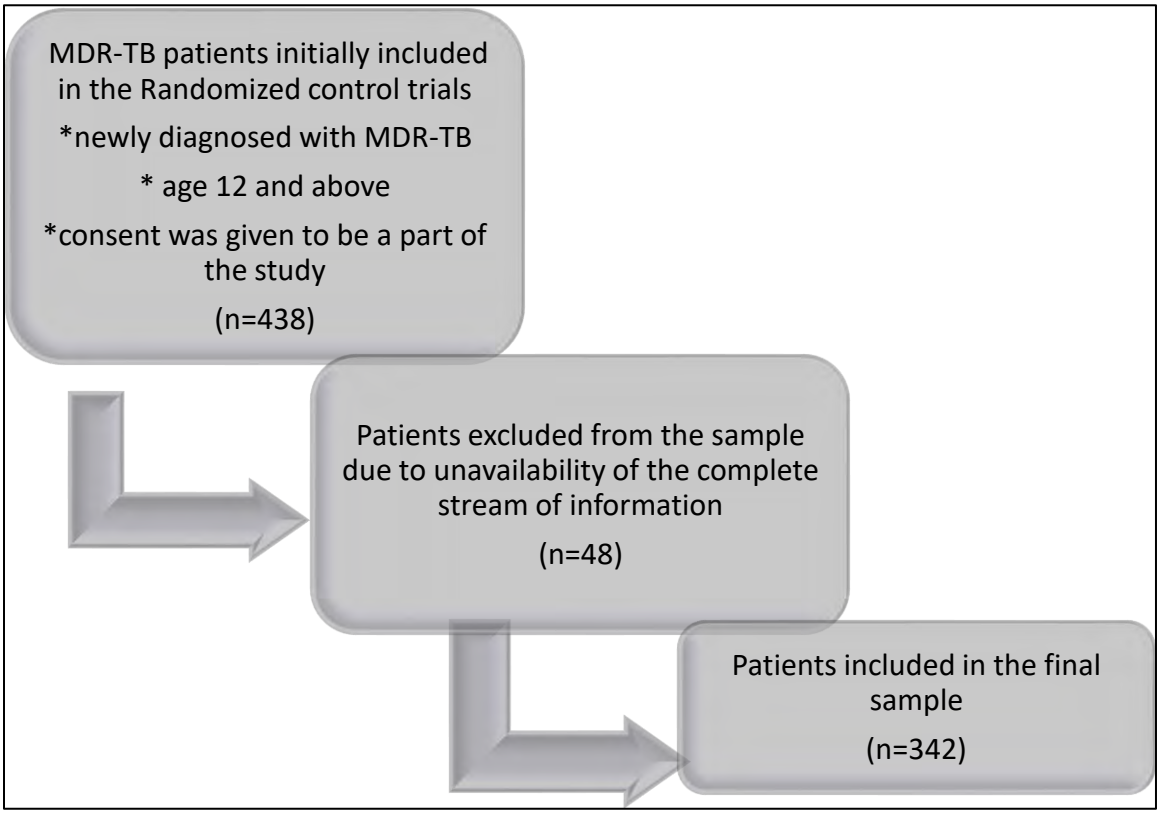
Outcome	Number of Patients
Completed	2
Cured	302
Failed	12
Lost to follow up	46
Not evaluated	8
Still under treatment	6
Died	62

Retrospectively data is collected with the pool of 438 patients in total with 219 patients in each arm. The information about the basic criteria for the eligibility to be part of the study is the patients who are newly diagnosed with the MDR-TB for the first time. Moreover, the eligibility criterion taken by NTP is to include the patients aged 12 and above that we have also followed. The patients were introduced to the concept of RCT and the patients who agreed to take part in the trial are registered in the RCT and randomly allocated to the treatment care. The data of the potential patients who were eligible for the RCT but declined to participate in the RCT is not available at the NTP record at all the three TB centers from where we have collected the data for this study. The data requirement for the variables for the cost effectiveness analysis is seen and the patients for whom the required data is not available are excluded from the sample. In the end, we have 342 patients that are part of this study.

The data requirement of the cost-effectiveness analysis is given in the study and the patients for whom the required data is not available are excluded from the sample. In the end, we have 342 patients that are part of this study with 171 patients in each arm out of a larger number who were in the study. Apparently this may appear as the arbitrary action that may lead to biases but if we look into the socio-demographic profile of the patients shown in the Table

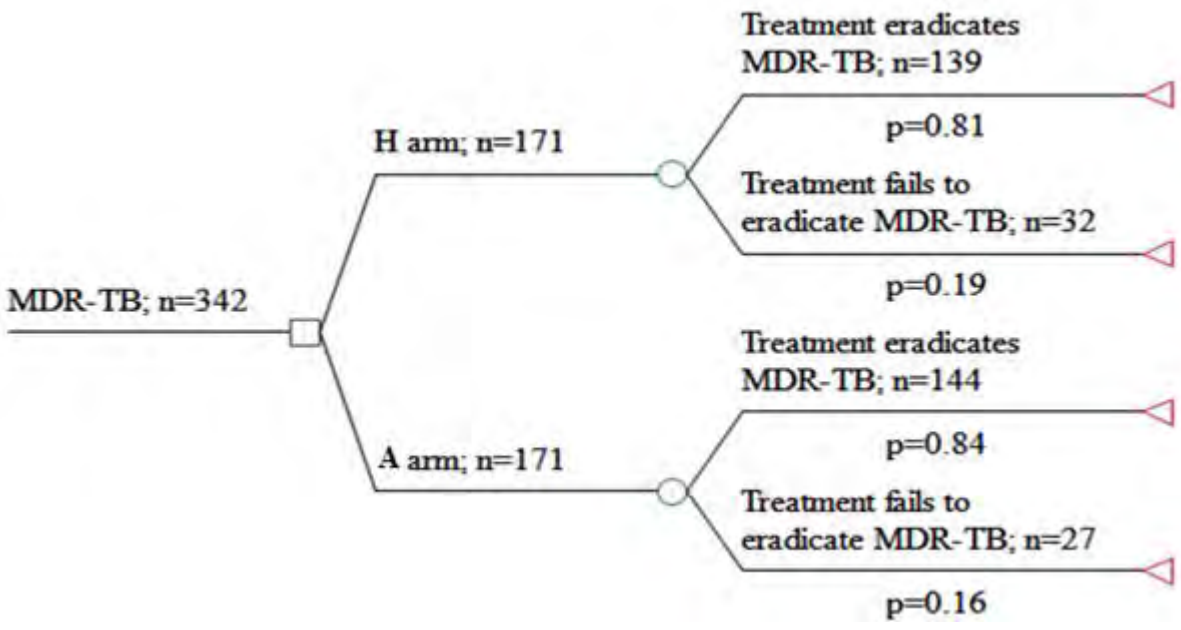
B1 in Appendix B then it indicates that the patients characteristics are not too dissimilar hence it provides us the rationale to perform the cost effectiveness analysis with the given sample size with 171 patients in each arm and the sample from each treatment care can be compared for the cost-effectiveness. Medication and follow-up visit protocols are same in both arms. The test of significance does not show a difference within the age group of these arms. The Fisher exact test is applied to nominal variables of marital status and gender and the Wilcoxon rank-sum is applied to an ordered categorical variable which shows there is no significant difference within the groups. As other characteristics of patients are the same hence RCT with the given sample provides a sound ground for CEA and using the sample with 171 patients in each arm.

Figure 2.1: Inclusion and Exclusion Criteria



The decision tree model is used as an initial framework of cost-effectiveness in our analysis. The outcomes of cured and died are the relevant outcomes for our study as the cure rate shows life-years saved from the disability, indicating the true success of health intervention and premature deaths lead to loss of potentially productive years (Srinath *et al*., 2005). The distribution of patients in each arm is shown in Figure 2.2 by using the software TreeAge Pro 2018. Same sample size of the competing treatment strategies is taken in the CEA (Biau, 2008) and we have 171 observations of patients for the hospital care arm who are cured and died hence the same sample size is taken for the patients of the ambulatory care also with the rationale that patients' characteristics are same as discussed above.

Figure 2.2: Decision Tree Diagram of MDR-TB Control Strategies



H = hospital arm, A = ambulatory arm, n = total number of patients & p = probability of cure and death.

The decision tree in Figure 2.2 starts with a total of 342 patients who are divided into H and A arms (171 each). The probability of eradication of MDR-TB of disease is slightly higher in the A arm as compared to the hospital arm showing that if the treatment protocols are followed properly by the patients then A arm provides a chance of getting cured as the treatment is immediately available at the door-step of the patient. The number of patients who are cured in the A arm is more as compared to H arm while the death rate is lower in the A arm than H care showing a sound execution of the treatment in A arm. Demographic and Socioeconomic factors are shown in Appendix B and along with the cost-effectiveness analysis for the treatment strategies, a brief discussion based on the cost of the three health care centers will be given in the results and discussion section.

2.4. Results and Discussions

Our sample of 342 patients shows that the cure rate is 81% and 84% in hospital and ambulatory arms respectively as shown in Figure 2.2, which falls within the desired target of 75-90% success rate set by WHO (2015), reflecting a high rate of treatment success in each treatment arm and indicating sound execution of the treatment strategies in hospital and ambulatory arms in Pakistan.

These statistics show better monitoring and counseling are provided to the patients and their families in ambulatory care along with conventional hospital care treatment. Among the cities in our sample, Murree and Lahore are part of Punjab, a province of Pakistan that received a major share of the health budget i.e. 1472.8 million USD whereas Karachi is part of Sindh, a province that received 968.6 million USD in the federal budget of 2017-2018. In our sample, the health facilities of Punjab i.e. Gulab Devi hospital, Lahore, and TB Samli Sanatorium Hospital, Murree

show better cure rates and fewer death rates as shown by the medical records. The cure rate recorded in the health facility of Lahore is 84%. In Murree, the cure rate is slightly better at 86%. In the facility of Karachi, the biggest metropolitan city in Pakistan the cure rate is 81.7%.

The values of YLL presented in Table 2.3 show that years of life lost are less in ambulatory care as compared to hospital care for all categories. The reason is the lesser death rates in ambulatory care than the hospital care so fewer entries are recorded for the age of death in the formula of YLL for ambulatory care. The result indicates that appreciable medical literacy is provided by health experts to the patients and households that have led to adherence to treatment protocols.

Table 2.3: Years of Life Lost (YLL)

Category	**1**		**2**		**3**		**4**		**5**	
r, M , α	**0, 0, 0**		**0.03, 1, 0.04**		**0.03, 0, 0**		**0.0596, 1, 0.04**		**0.0596, 0, 0**	
Treatment Arm	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**
Total YLL*	1214.4	996.2	71.1	63.34	20.08	16.54	79.32	67.62	26.71	21.23
YLL per patient	7.10	5.83	0.42	0.37	0.12	0.10	0.46	0.40	0.16	0.12
Standard Error	1.23	0.95	0.17	0.13	0.02	0.02	0.14	0.11	0.03	0.02
Minimum value	0	0	-4.17	-3.47	0	0	-2.89	-2.48	0	0
Maximum value	58.6	50.75	9.38	7.7	0.83	0.72	7.32	6.21	0.96	0.84
C.I (at 95%)	4.67 to 9.52	3.4 to 8.26	0.08 to 0.75	0.04 to 0.70	0.08 to 0.16	0.06 to 0.14	0.18 to 0.74	0.13 to 0.67	0.11 to 0.21	0.07 to 0.17

H=hospital Arm, A= ambulatory arm, r =discount rate, M= age weighting modulation factor, α= age weighting constant, and C. I (at 95%) = values of upper and lower bound of 95% confidence interval around mean, * Total YLL of 171 patients in each arm.

The years of life lived with a disability are shown in Table 2.4. Total YLD is less in the hospital care as compared to ambulatory care in all categories. The reason for this difference is that the average duration of disability is less in the hospital arm i.e. 1.14 years as compared to 1.29 years in ambulatory care as analyzed when the values of YLD are calculated for each arm which incorporates the value of the duration of the disability. The initial phase of treatment of

the patients has been catered by medical experts under specific protocols. Timely provision of medicines by health experts during the initial phase of treatment and constant guidance to patients and families may have aided in the reduction of the duration of disability in the hospital care arm.

Table 2.4: Years of Life Lived with Disability (YLD)

Category	**1**		**2**		**3**		**4**		**5**	
r, M, α	**0, 0, 0**		**0.03, 1, 0.04**		**0.03, 0, 0**		**0.0596, 1, 0.04**		**0.0596, 0, 0**	
Treatment Arm	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**
Total YLD*	65.04	72.09	85	99.28	190.6	216.46	86.59	97.06	187.2	211.6
YLL per patient	0.38	0.42	0.50	0.58	1.11	1.27	0.51	0.57	1.09	1.24
Standard Error	0.02	0.01	0.03	0.02	0.04	0.03	0.02	0.02	0.04	0.03
Minimum value	0.03	0.02	-2.86	0.02	0.08	0.07	0.02	0.02	0.08	0.07
Maximum value	0.72	0.71	1.06	1.03	2.1	2.07	1.03	1	2.03	1.99
C.I (at 95%)	0.35 to 0.41	0.39 to 0.45	0.45 to 0.55	0.53 to 0.63	1.03 to 1.19	1.19-1.34	0.46-0.56	0.52 to 0.62	1.01 to 1.18	1.17 to 1.31

H=hospital Arm, A= ambulatory arm, r =discount rate, M= age weighting modulation factor, α= age weighting constant, and C. I (at 95%)= values of upper and lower bound of 95% confidence interval around mean, * Total YLD of 171 patients in each arm

Total DALYs as shown in Table 2.5, are less in ambulatory care in category 1 where time is not discounted and age weights are set equal to zero to nullify the social preference according to age. DALYs for the hospital arm and ambulatory arm are 1279.45 and 1069.9 respectively. The values of DALYs are larger in this category as compared to other categories because the DALYs are not discounted based on the current and future value and equal value is given to future and present time and age weights are also not included. Considering assumptions of the model regarding discount rates and age weights, ambulatory care becomes less effective than hospital care in categories 2, 3, and 5 owing to more duration of disease in ambulatory care overshadowing the fewer deaths and better cure rates.

In categories 3 and 5 in Table 2.5, when the age weight based on the society's preferences for the potential economically active part of the population is not included on ethical grounds and real interest rates are included then during the high inflation periods when the real interest rate is low then hospital care is a preferable strategy in terms of lesser DALYS than ambulatory care. In categories 2 and 4, the age weights are included in the human capital consideration that younger individuals will be valued more and society's norms about giving more importance to the young people as compared to old ones based on the more active participation of the young people in the economic activities along with the real interest rate. In category 2, the real interest rate is lower indicting high inflation then the present value of the healthy year of life will be higher and along with age weights, the DALYs of the hospital care become lower but category 4 shows that when high-interest rate and age weights are considered then ambulatory care becomes a slightly better strategy.

Table 2.5: Disability Adjusted Life Years (DALYs)

Category	**1**		**2**		**3**		**4**		**5**	
r, M , α	**0,0,0**		**0.03,1,0.04**		**0.03,0,0**		**0.0596,1,0.04**		**0.0596,0,0**	
Treatment Arm	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**
Total DALYs*	1279.45	1069.9	159.44	162.62	210.66	233	165.9	164.68	213.88	232.88
DALYs per patient	7.48	6.26	0.93	0.95	1.23	1.36	0.97	0.96	1.25	1.36
Standard Error	1.22	0.95	0.94	0.13	1.23	0.03	0.14	0.11	0.03	0.03
Minimum value	0.03	0.02	-4.14	-3.26	0.083	0.07	-2.83	-2.3	0.08	0.07
Maximum value	58.63	52.09	9.42	7.95	2.17	2.25	7.36	6.45	2.25	2.29
C.I (at 95%)	5.07 to 9.89	3.85 to 8.67	0.60 to 1.26	0.62 to 1.28	0.16 to 1.30	1.29 to 1.43	0.70 to 1.24	0.69 to 1.23	1.18 to 1.32	1.29 to 1.43

H=hospital Arm, A= ambulatory arm, r =discount rate, M= age weighting modulation factor, α= age weighting constant, and C. I (at 95%)= values of upper and lower bound of 95% confidence interval around mean, * Total DALYs of 171 patients in each arm.

The cost of treatment shown in Table 2.6 provides an important insight into budgetary allocation and affordability of health services and systems. The data of cost of treatment shown

in Table 2.6 provides an important insight into budgetary allocation and affordability of health services and systems. The cost presented in Table 2.6 is representing social perspective which we have collected from the monthly follow-up visit forms of the patients available at the NTP centers. The section 2.4 shows that though the program has shared the cost burden of the patients in each arm ($1000 in both regimes) but none the less, the patients had to manage different direct and in-direct expenditures in the process of treatment on their own. Patients sometimes had to go to the local pharmacies to purchase medicines and labs for medical tests as reported in the follow-up forms of the patients which are the reason of difference in per patient cost. In-patient hospitalization is done initially in the hospital care for 2 months and in ambulatory care the treatment is given in the ambulatory care that may include initial 2 weeks of hospitalization as mentioned in the Introduction Chapter 1, section 1.2. Brief outpatient episodes are also experienced by few patients who needed urgent medical help because of bad health condition during the treatment period but do not require overnight stay that is also included in our study. Moreover, the costs presented in Table 2.6 are representing social perspective. Moreover, the duration of treatment until cure is different between the two regimes and hence is the cost.

Table 2.6 shows the economic burden of the disease on the patients and their families. Total traveling cost is more in the ambulatory arm as the initial phase of treatment is completed in the community. So, the patients and fellow care-takers have to make frequent trips to the health facilities and labs which have commuting costs. Such traveling costs are less in the hospital care as compared to ambulatory arm i.e. US $21242.78 vs. US $23392 as in the hospital care due to inpatient care where the patient is hospitalized for the initial two months; the patients do not have to travel during this time and service provision within the hospital. One of the reasons for the high traveling cost in both the treatment arms is related to the general social setting in Pakistan

where females are usually accompanied by male members during their visits to health facilities as shown by the record of patients' follow-up forms to health facilities.

MDR-TB can also be transmitted in the community; so strong preventive measures have to be taken, which increases the cost of prevention in the community. The uses of masks, extra ventilation facilities, and fumigations, etc. are adopted as preventive measures by the patients and households in our sample, which create an additional financial burden in both arms but the cost of preventive measures is more in ambulatory care (US $2432.63) as compared to the hospital care arm (US $1729.17) as in the initial two months of an intense phase of treatment of MDR-TB, the patient stays at home so members of the family have to take more cautions to control the person to person spread of disease. Cost of medicines, treatment of side effects, and lab tests are more in the ambulatory arm as compared to the hospital arm as shown in Table 2.6 below. The hospitals ensure provisions of medicine and lab tests and treatment of side effects by mostly covering such costs themselves but some instances have been reported by the patients in the record forms that they had to do out of pocket expenditure for the medicine in the hospital care once they are discharged from the hospital. On the other hand, in the case of ambulatory care, though services are provided by the health facility units the coverage is less and patients had to go to the private labs and pharmacies for the tests and medicines

Table 2.6: Different Types of Cost Burdens During Treatment of MDR-TB

Type of costs		Cost in PKR		Cost in I$		Cost in US$	
		H	A	H	A	H	A
Travelling Cost	All patients	2,209,249	2,432,768	65,771.03	72,425.36	21,242.78	23,392
	Per patient	12,919.58	14,226.71	384.63	423.54	124.23	136.80
	C.I (at 95%)	9,925.3 to 15,913.8	11,761.1to 16,692.3	295.48 to 473.77	350.13 to 496.92	95.4 to 153.0	113.0 to 160.5
Hospitalization Cost	All patients	286,541.8	141,691.6	8,530.57	4,218.27	2,755.20	1,362.41
	Per patient	1675.68	828.61	49.89	24.67	16.11	7.97
	C.I (at 95%)	1,329.2 to 2,022.1	679.6 to 977.5	39.57 to 60.199	20.23 to 29.10	12.78 to 19.44	6.53 to 9.39
Side Effects Treatment Cost	All patients	108,587	162,689.4	3,232.72	4,843.39	1,044.10	1,564.32
	Per patient	635.01	951.40	18.90	28.32	6.11	9.15
	C.I (at 95%)	327.7 to 942.7	490.73 to 1412.0	9.76 to 28.06	14.61 to 42.04	3.15 to 9.06	4.7 to 13.5
Medicine Cost	All patients	234,38.8	46,561.4	697.79	1,386.17	225.4	447.7
	Per patient	137.07	272.29	4.08	8.11	1.32	2.62
	C.I (at 95%)	9.06 to 265.0	47.06 to 591.6	0.27 to 7.89	1.40 to 17.61	0.08 to 2.54	0.45 to 5.68
Lab test Cost	All patients	79,260.48	91,887.8	2,359.65	2,735.57	762.12	883.5365
	Per patient	463.51	537.36	13.80	16.00	4.46	5.17
	C.I (at 95%)	273.3 to 653.6	328.03 to 746.6	8.14 to 19.46	9.76 to 22.23	2.62 to 6.28	3.15 to 7.17
Preventive Measure Cost	All patients	179,834.2	252,994.5	5,353.80	7,531.84	1,729.2	2,432.6
	Per patient	1,051.66	1,479.50	31.31	44.05	10.11	14.23
	C.I (at 95%)	901.4 to 1,201.6	673.5 to 2,285.4	26.84 to 35.78	20.05 to 68.04	8.66 to 12.5	6.4 to 21.9
Patients Relocation Cost	All patients	5,625.3	2,042.5	167.47	60.81	54.089	19.639
	Per patient	32.90	11.94	0.98	0.36	0.32	0.11
	C.I (at 95%)	12.8 to 52.8	16.1 to 40.0	0.38 to 1.52	0.48 to 1.19	0.12 to 0.50	0.15 to 0.38
Room rent	All patients	260,749.2	417,620	7,762.70	12,432.87	2,507.204	4,015.577
	Per patient	1,524.85	2,442.22	45.40	72.71	14.66	23.48
	C.I (at 95%)	234.8 to 2814.8	112.4 to 4771.9	6.99 to 83.79	3.35 to 142.06	2.25 to 27.0	1.08 to 45.8
Home Visits Cost	All patients	43,458.2	91,485	1,293.78	2,723.58	417.867	879.663
	Per patient	254.14	535.00	7.57	15.93	2.44	5.14
	C.I (at 95%)	81.7 to 426.5	251.49 to 818.5	2.43 to 12.69	7.48 to 24.37	0.78 to 4.100	2.41 to 7.87
Fellows Room Rent	All patients	227,990.1	438,528.6	6,787.44	13,055.33	2,192.213	4,216.621
	Per patient	1,333.28	2,564.49	39.69	76.35	12.82	24.66
	C.I (at 95%)	33.27 to 2,633.2	2,503.5 to 6,465.3	58.99 to 78.39	74.53 to 192.47	1.94-30.79	-7.40-39.44

Type of costs		Cost in PKR		Cost in I$		Cost in US$	
		H	A	H	A	H	A
Fellow Transport and Others Cost	All patients	674,362.1	766,854.3	20,076.28	22,829.84	6,484.251	7,373.599
	Per patient	3,943.64	4,484.53	117.41	133.51	37.92	43.12
	C.I (at 95%)	2,363.3 to 5,523.9	3,044.53 to 5,447.8	70.36 to 164.46	90.64 to 162.19	22.7 to 53.1	29.2 to 52.3
Income Loss of Fellows	All patients	285,414.5	351,673.9	8,497.01	10,469.60	2,744.37	3,381.479
	Per patient	1,669.09	2,056.57	49.69	61.23	16.05	19.77
	C.I (at 95%)	1,276 to 2,062.1	1,589.7 to 2,523.4	37.99 to 61.39	47.33 to 75.12	12.69 to 19.8	15.2 to 24.2
Transport Cost of Supporter	All patients	1,045,967	1,210,261	31,139.24	36,030.40	10,057.38	11,637.13
	Per patient	6,116.77	7077.55	182.10	210.70	58.82	68.05
	C.I (at 95%)	5,211.4 to 7,012	6,224.2 to 7,930.8	155.15 to 208.75	185.29 to 236.11	50.1 to 67.4	59.8 to 76.2
Total cost	All patients	5,430,478.21	6,407,057	161,669.5	190,743.0	52,216.14	61,606.32
	Per patient	31,757.2	37,468.2	945.4	1,115.5	305.4	360.3
	C.I (at 95%)	26,305.8 to 37,208.5	32,120.96 to 42,815.37	783.14 to 11.7.75	956.26 to 1274.65	252.9 to 357.7	308.8 to 411.6

H=hospital Arm, A= ambulatory arm, PKR shows the cost in Pakistani Rupee; I$ in international dollar and USD in US dollar whereas C. I (at 95%) = values of upper and lower bound of 95% confidence interval around mean.

Ambulatory care is laden with two-way commuting, thereby burdening the distant patients with an additional room rental to stay near a health facility. Hospitalization cost is more in hospital care i.e. US $2755.2 as compared to US $1362.4 in ambulatory care in our sample as shown in Table 2.6, as the patients are registered for in-patient care. Relocation from home town to another city for the purpose of treatment is experienced less in ambulatory care, as medical provisions are given at the time of visits to health facilities so fewer numbers of patients have to bear relocation costs. The loss of working days of accompanying fellows represents an additional burden as it often leads to a deduction of income, especially if a person belongs to the service

sector or is self-employed. It is comparable to WHO (2000) findings that the indirect cost burden often becomes more than the direct one which can be applied in our analysis also where 50.29% of patients are not working during the treatment period. Most of the patients belong to the lower-income group (please see Appendix B). Hence these expenditures put extra financial constraints on the patients and families in the treatment of MDR-TB which needs to be monitored by the health system.

Overall, the treatment in ambulatory care shows a higher burden of cost for the patients and the household. Despite substantial saving in hospitalization cost, ambulatory care ends up resulting in higher costs because of higher traveling cost that has to be borne by the patients and the accompanying fellow and a need for more preventive measures at home in the initial phase of treatment. Moreover, sometimes the patients and their fellows have to take the room on rent for the follow-up visits and lab tests, etc. if the health facilities are far from home which increases the total expenditure along with the expense of the medicines and the lab tests which are sometimes born by the patients in the ambulatory care from their pocket, especially in the early phase of treatment that is mostly covered by the hospital in the hospital care. The duration of the disease is also more in the ambulatory care hence more cost has to be incurred in the ambulatory care.

The total cost burden for the patients in Karachi, Lahore, and Murree is US $44283.45, US $34887.23, and US $34651.7 respectively. In our sample, Murree being a hilly area has to face harsh weather in winters which creates difficulties in daily life chores and availability of employment opportunities. The income loss for the fellow who accompanies the patient during

visits to health facilities is 8.9% of total cost in Murree as compared to 4% in Lahore[8] where areas with better endowments experience the better living condition. Karachi and Lahore, being the metropolitan cities, have more employment opportunities and better transport systems, etc.

The cost per DALYs averted is shown in Table 2.7. The ratio of cost per DALYs averted is an important indicator in the cost-effectiveness analysis as it provides information about the cost of saving a year of life for each treatment arm. The cost-effective strategy is the one that has cost per DALYs averted less than GDP per capita per year, that is, the cost of saving a life year is less than per capita income per year. Moreover, cost per DALYs less than three times GDP per capita is also accepted as cost-effective as explained by Marseille *et al*. (2015).

In category 1, the cost of saving a healthy year of life is US $40.8 in hospital care and US $57.6 in ambulatory care. If we compare the ratios of both arms then the hospital care is more cost-saving as compared to ambulatory care. The cost per DALYs ratio is much lower in category 1 than in other categories because of the larger values of the DALYs obtained when age weighting and discounting are not considered. Category 2, 3, 4, and 5 also show that the cost per DALYs averted is lower in hospital care as compared to ambulatory care showing that the hospital care is more cost-saving. However, if we compare the cost per DALYs with the GDP per capita of Pakistan (PKR 169416, I$ 5043.64, and US $1629, *Economic Survey of Pakistan,* 2017) then Table 2.7 shows that all the ratios for hospital care and ambulatory care are less the GDP per capita showing that the cost of saving a life year is less than per capita income per year hence both strategies are cost-effective in case of Pakistan though hospital care is more cost-saving.

[8]This also indicates the geographical poverty trap, a term used by Knight and Lina (1993) that refers to a disadvantage related to the location of a place leading to a low level of geographical capital like human, physical and social capital accompanied by high poverty level.

Table 2.7: Cost per DALYs Averted in Hospital and Ambulatory Arm

Category	1		2		3		4		5	
r, M , α	0,0,0		0.03,1,0.04		0.03,0,0		0.0596,1,0.04		0.0596,0,0	
Treatment Arm	H	A	H	A	H	A	H	A	H	A
PKR	4,244.4	5,988	34,059.7	39,398.9	25,778.4	27,498.1	32,731.5	38,906.1	25,390.3	27,512.3
I$	126.4	178.3	1,014	1172.9	767.4	818.6	974.4	1158.3	755.9	819.1
US $	40.8	57.6	327.5	378.8	247.9	264.4	314.7	374.1	244.1	264.5

H=hospital Arm, A= ambulatory arm, r =discount rate, M= age weighting modulation factor, α= age weighting constant, PKR shows the cost per DALYs in Pakistani Rupee, I$ in the international dollar, US $ in US Dollars.

Now, we will discuss the ICER as shown in Table 2.8 below which is calculated by using Equation 2.6. The incremental cost of PKR 976579, I$ 29073.49, or US $9390.18 is calculated by using the numerator of Equation 2.6. The incremental effectiveness is found as the difference in the DALYs of hospital care and ambulatory care arms by using the values mentioned in Table 2.5 for each category and then ICER is calculated for each category The ICER values for category 1 and 4 shows that the ambulatory care is more costly and more effective having lower DALYs than the hospital care where the additional cost of saving the life is lesser than the threshold of GDP per capita.

Whereas other categories 2, 3, and 5 where discounting and age weights (or both) are considered, the DALYs of the hospital arm become less and the cost of the hospital care is also less thus, the hospital care arm is more attractive in the respective categories making hospital care a dominant strategy and ambulatory care as the dominated strategy being more costly and less effective. So, overall results of CEA indicate that no arm shows continuous dominance in all the categories and it depends upon the assumptions used in the analysis. Hence, both arms can be used as effective treatment strategies and are acceptable and appropriate to be used in the case of Pakistan.

Table 2.8: Incremental Cost-Effectiveness Ratio

Category	1	2	3	4	5
r, M, α	**0,0,0**	**0.03,1,0.04**	**0.03,0,0**	**0.0596,1,0.04**	**0.0596,0,0**
ICER in PKR	-4,491.69	8,875.75	1,263.42	-45,437.2	2,950.27
ICER in I$	-133.72	264.24	37.61	-1,352.70	87.83
ICER US $	-43.19	85.34	12.1	-437	28.37
Result	The ambulatory arm is cost-effective	The ambulatory care is more costly and less effective	The ambulatory care is more costly and less effective	The ambulatory arm is cost-effective	The ambulatory care is more costly and less effective

ICER=Incremental cost-effectiveness ratio, PKR shows ICER in Pakistani Rupee, I$ in the international dollar; US $ in the United States Dollar and comparison is made with a benchmark of GDP per Capita with respective currency denomination, AC is ambulatory care

The results of the Table 2.8 show that no arm has shown a continuous dominance. We would check the robustness of the results obtained in Table 2.8 by applying a one-way sensitivity analysis on the cost of both arms. The results for the change in hospital care cost are shown in Table 2.9 and ambulatory care cost is shown in Table 2.10. Table 2.9 shows that when the cost of the hospital care arm increases up to 10% or decreases from 10% to 40% from the total hospital cost values of baseline case (baseline values are mentioned in Table 2.6) then still the ambulatory care arm appears to be a dominant strategy in categories 1 and 4 where though the cost is high for the ambulatory care but effectiveness is also more than the hospital care. When the cost of hospital care increases by 20%, 30%, and 40% then ambulatory care becomes less costly and more effective than the hospital care in categories 1 and 4. In categories 2, 3, and 5, when the cost of hospital care increases by 10% and decreases from 10 to 40% from the total hospital cost values of baseline case then the hospital care remains the dominant strategy in the sensitivity analysis and ambulatory care becomes the dominated strategy being more costly and less effective. The trend of results differs slightly when the hospital care arm's cost increases from 20% to 40% as the ambulatory arm becomes less costly and less effective while the hospital arm

retains its dominance being more costly and more effective in categories 2, 3, and 5. The results again show that unconditional continuous dominance is not shown by ambulatory or hospital arms.

Table 2.9: Results of Sensitivity Analysis with Variation in Hospital Care Costs

Category	% Change in Hospital Care Arm Cost as Compared to the Baseline Case	Incremental cost			ICER			Overall Results
		PKR	I$	US $	PKR	I$	US $	
1	Baseline case	976,578.7	29,073.49	9,390.18	-4,491.69	-133.72	-43.19	AC is cost effective
	Increase by 10%	433,531.40	12,906.56	4,168.60	-2074.3	-61.753	-19.9	
	Increase by 20%	-109,516.40	-3,260.39	-1,053	524	15.599	5	
	Increase by 30%	-652,564.20	-19,427.34	-6,274.70	3122.3	92.95	30	
	Increase by 40%	-1,195,612	-35,594.28	-11,496.3	5720.6	170.30	55	
	Decrease by 10%	1,519,627.10	45,240.46	14,611.80	-7270.9	-216.46	-69.9	
	Decrease by 20%	2,062,674.90	61,407.41	19,833.40	-9869.3	-293.82	-94.9	
	Decrease by 30%	2,605,722.70	77,574.36	25,055	-12467.6	-371.17	-119.9	
	Decrease by 40%	3,148,770.50	93,741.31	30,276.60	-15065.9	-448.52	-144.9	
2	Baseline case	976578.79	29073.498	9390.18	8875.75	264.24	85.34	HC is cost effective
	Increase by 10%	13,005.90	387.19559	125.1	4089.9	121.76	39.3	
	Increase by 20%	-3,285.50	-97.811849	-31.6	-1033.2	-30.759	-9.9	
	Increase by 30%	-19,576.90	-582.82	-188.2	-6156.3	-183.28	-59.2	
	Increase by 40%	-35,868.40	-1,067.83	-344.9	-11279.4	-335.79	-108.5	
	Decrease by 10%	45,588.80	1,357.21	438.4	14336.1	426.79	137.8	
	Decrease by 20%	61,880.20	1,842.22	595	19459.2	579.31	187.1	
	Decrease by 30%	78,171.70	2,327.23	751.7	24582.3	731.8338	236.4	
	Decrease by 40%	94,463.10	2,812.24	908.3	29705.4	884.35	285.6	
3	Baseline case	976578.79	29073.498	9390.18	1263.42	37.61	12.1	HC is cost effective
	Increase by 10%	13,005.90	387.19559	125.1	582.2	17.33	5.6	
	Increase by 20%	-3,285.50	-97.811849	-31.6	-147.1	-4.3792	1.4	
	Increase by 30%	-19,576.90	-582.82	-188.2	-876.3	-26.088	-8.4	
	Increase by 40%	-35,868.40	-1,067.83	-344.9	-1605.6	-47.799	-15.4	
	Decrease by 10%	45,588.80	1,357.21	438.4	2040.7	60.753	19.6	
	Decrease by 20%	61,880.20	1,842.22	595	2769.9	82.462	26.6	

Category	% Change in Hospital Care Arm Cost as Compared to the Baseline Case	Incremental cost			ICER			Overall Results
		PKR	I$	US $	PKR	I$	US $	
	Decrease by 30%	78,171.70	2,327.23	751.7	3499.2	104.17386	33.6	
	Decrease by 40%	94,463.10	2,812.24	908.3	4228.4	125.882	40.7	
4	Baseline case	976578.79	29073.498	9390.1	-45437.2	-1352.70	-437	AC is cost effective
	Increase by 10%	24,277.80	722.77	233.4	-19899.8	-592.43	-191.3	
	Increase by 20%	-6,132.90	-182.58113	-59	5027	149.6576	48.3	
	Increase by 30%	-36,543.60	-1,087.93	-351.4	29953.8	891.74	288	
	Increase by 40%	-66,954.30	-1,993.28	-643.8	54880.6	1633.83	527.7	
	Decrease by 10%	85,099.10	2,533.47	818.3	-69753.4	-2076.6	-670.7	
	Decrease by 20%	115,509.80	3,438.82	1,110.70	-94680.2	-2818.70	-910.4	
	Decrease by 30%	145,920.50	4,344.16	1,403.10	-119606.9	-3560.7	-1150.1	
	Decrease by 40%	176,331.10	5,249.51	1,695.50	-144533.7	-4302.87	-1389.7	
5	Baseline case	976578.79	29073.498	9390.18	2950.27	87.8317	28.37	HC is cost effective
	Increase by 10%	24,277.80	722.77	233.4	1277.8	38.041	12.3	
	Increase by 20%	-6,132.90	-182.58113	-59	-322.8	-9.61	-3.1	
	Increase by 30%	-36,543.60	-1,087.93	-351.4	-1923.3	-57.25	-18.5	
	Increase by 40%	-66,954.30	-1,993.28	-643.8	-3523.9	-104.90	-33.9	
	Decrease by 10%	85,099.10	2,533.47	818.3	4478.9	133.340	43.1	
	Decrease by 20%	115,509.80	3,438.82	1,110.70	6079.5	180.99	58.5	
	Decrease by 30%	145,920.50	4,344.16	1,403.10	7680	228.6	73.8	
	Decrease by 40%	176,331.10	5,249.51	1,695.50	9280.6	276.2	89.2	

PKR shows Pakistani Rupee, I$ is the international dollar, US$ is the US Dollar, ICER is the incremental cost-effectiveness ratio and comparison is made with a benchmark of GDP per Capita with respective currency denomination. The incremental effectiveness in category 1 is -209.5, category 2 is 3.18, category 3 is 2.34, category 4 is -1.22 and category 5 is 19. Dominated refers to ambulatory care being less cost-effective than hospital care in respective categories.

Table 2.10 shows that when the cost of the ambulatory care arm increases from 10% to 40% or reduces by 10% from the total ambulatory cost values of the baseline case (baseline values are mentioned in Table 2.6) then the ambulatory care arm becomes the dominant strategy in categories 1 and 4, being costly but having more effectiveness. When the ambulatory care cost reduces by 20% to 40%, then the ambulatory care arm becomes less costly and more effective in categories 1 and 4. In the case of categories 2, 3, and 5, when the cost of ambulatory care increases from 10% to 40% or reduces up to 10% than the baseline case then the ambulatory care becomes even more costly than the hospital care with lower effectiveness hence ambulatory care arm becomes the dominated strategy. When the ambulatory care arm's cost reduces from 20% to 40%, then the ambulatory arm becomes less costly but still, it is less effective hence it remains the dominated strategy and the hospital care arm still is the dominant strategy. Overall, the results of sensitivity analysis concerning costs also do not show a preference for any arm.

Table 2.10: Results of Sensitivity Analysis with Variation in Ambulatory Care Costs

Category	% Change in Ambulatory Care Arm Cost as Compared to the Baseline Case	Incremental cost			ICER			Overall Results
		PKR	I$	US$	PKR	I$	US$	
1	Baseline case	976578.7	29073.495	9390.18	-4491.69	-133.72	-43.19	AC is cost effective
	Increase by 10%	16,172,849	481,478.09	15,550.8	-7738.2	-230.37	-74.4	
	Increase by 20%	2,257,990.7	67,222.11	21,711.4	-10803.8	-321.64	-103.9	
	Increase by 30%	2,898,696.4	86,296.41	27,872	-13869.4	-412.90	-133.4	
	Increase by 40%	3,539,402.2	105,370.71	34,032.7	-16934.9	-504.16	-162.8	
	Decrease by 10%	335,873.40	9,999.21	3,229.50	-1607.1	-47.84	-15.5	
	Decrease by 20%	-304,832.20	-9,075	-2,931.0	1458.5	43.42	14	
	Decrease by 30%	-945,538.00	-28,149.39	-9,091.7	4524.1	134.69	43.5	
	Decrease by 40%	-15862	-472.22	-15,252	7589.7	225.95	73	
2	Baseline case	976578.8	29073.498	9390.2	8875.75	264.24	85.34	HC is cost effective
	Increase by 10%	48,518.50	1,444.43	466.5	15257.4	454.22	146.7	
	Increase by 20%	67,739.70	2,016.66	651.3	21301.8	634.17	204.8	
	Increase by 30%	86,960.80	2,588.89	836.1	27346.2	814.12	262.9	
	Increase by 40%	106,182	3,161	1,020.90	33390.6	994.06	321.1	
	Decrease by 10%	10,076.20	299.97618	96.8	3168.6	94.33	30.5	
	Decrease by 20%	-9,144.90	-272.25067	-87.9	-2875.8	-85.61	-27.7	
	Decrease by 30%	-28,366.10	-844.48	-272.7	-8920.2	-265.56	-85.8	
	Decrease by 40%	-47,587.30	-1,416.71	-457.5	-14964.6	-445.51	-143.9	
3	Baseline case	976578.8	29073.498	9390.2	1263.42	37.61	12.1	HC is cost effective
	Increase by 10%	48,518.50	1,444.43	466.5	2171.8	64.66	20.9	
	Increase by 20%	67,739.70	2,016.66	651.3	3032.2	90.27	29.2	
	Increase by 30%	86,960.80	2,588.89	836.1	3892.6	115.89	37.4	
	Increase by 40%	106,182	3,161	1,020.90	4753	141.50	45.7	
	Decrease by 10%	10,076.20	299.97618	96.8	451	13.43	4.3	
	Decrease by 20%	-9,144.90	-272.25067	-87.9	-409.4	-12.19	-3.9	
	Decrease by 30%	-28,366.10	-844.48	-272.7	-1269.7	-37.80	-12.2	
	Decrease by 40%	-47,587.30	-1,416.71	-457.5	-2130.1	-63.41	-20.5	
4	Baseline case	976578.79	29073.498	9390.2	-45437.2	-1352.70	-437	AC is cost effective
	Increase by 10%	90,567.90	2,696.28	870.8	-74236	-2210.06	-713.8	
	Increase by 20%	126,447.4	3,764.44	1,215.80	-103645.5	-3085.61	-996.6	

Category	% Change in Ambulatory Care Arm Cost as Compared to the Baseline Case	Incremental cost			ICER			Overall Results
		PKR	I$	US$	PKR	I$	US$	
	Increase by 30%	162,327.00	4,832.60	1,560.80	-133054.9	-3961.15	-1279.4	
	Increase by 40%	198,206.50	5,900.76	1,905.80	-162464.4	-4836.69	-1562.2	
	Decrease by 10%	18,808.90	559.96	180.8	-15417.1	-458.98	-148.2	
	Decrease by 20%	-17,070.60	-508.20482	-164.1	13992.3	416.56	134.5	
	Decrease by 30%	-52,950.10	-1,576.36	-509.1	43401.7	1292.10	417.3	
	Decrease by 40%	-88,829.60	-2,644.53	-854	72811.2	2167.65	700.1	
	Baseline case	976578.79	29073.498	9390.18	2950.27	87.83	28.37	
	Increase by 10%	90,567.90	2,696.28	870.8	4766.7	141.91	45.8	
	Increase by 20%	126,447.40	3,764.44	1,215.80	6655.1	198.13	64	
	Increase by 30%	162,327.00	4,832.60	1,560.80	8543.5	254.35	82.1	
5	Increase by 40%	198,206.00	5,900.74	1,905.80	10431.9	310.57	100.3	HC is cost effective
	Decrease by 10%	18,808.90	559.96	180.8	989.9	29.47	9.5	
	Decrease by 20%	-17,070.60	-508.20482	-164.1	-898.5	-26.75	-8.6	
	Decrease by 30%	-52,950.10	-1,576.36	-509.1	-2786.8	-82.97	-26.8	
	Decrease by 40%	-88,829.60	-2,644.53	-854.1	-4675.2	-139.18	-45	

PKR shows Pakistani Rupee, I$ is the international dollar, US$ is the US Dollar, ICER is the incremental cost-effectiveness ratio and comparison is made with a benchmark of GDP per Capita with respective currency denomination. The incremental effectiveness in category 1 is -209.5, category 2 is 3.18, category 3 is 2.34, category 4 is -1.22 and category 5 is 19. Dominated refers to ambulatory care being less cost-effective than hospital care in respective categories.

Finally, sample descriptive using t-test for equality of means between DALYs of hospital and ambulatory arm for each category and between costs of the two arms are shown in Table 2.11. DALYs of categories 3 and 4 showed a statistically significant difference between the DALYs of ambulatory and hospital care arms ($p \leq 0.01$). But for the remaining categories i.e. 1, 2, and 5, and costs series, we fail to reject the null hypothesis that there is no difference between the respective series.

Table 2.11: Sample Descriptive Using t-test for Equality of Means

Category	**1**		**2**		**3**		**4**		**5**		**Cost of H and A**	
r, M, α	**0,0,0**		**0.03,1,0.04**		**0.03,0,0**		**0.0596,1,0.04**		**0.0596,0,0**			
Treatment Arm	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**	**H**	**A**
Mean	7.48	6.26	0.95	0.94	1.24	1.36	1.25	1.36	0.97	0.96	31080.3	36553.5
The t value	0.75		0.02		-2.43***		-2.3***		0.04		-1.42	

H=hospital Arm, A= ambulatory arm, r =discount rate, M= age weighting modulation factor, α= age weighting constant and *** =significant at 1% level of significance & SD=standard deviation

So, results of sensitivity analysis and hypothesis testing of statistical significance between DALYs of hospital and ambulatory arm for each category, and cost series of both arms show that overall there is not much difference in the impact of these treatment strategies. Hence, both arms have played an important role in the reduction of loss for patients. Our results reflect that alongside hospital care, the ambulatory care arm can also be used for the treatment of MDR-TB in Pakistan.

2.5. Conclusion

This study employs the cost-effectiveness analysis (CEA) for the evaluation of the two MDR-TB treatment arms in Pakistan namely hospital care and ambulatory care arms. Our study estimates the incremental cost-effectiveness ratio (ICER) of the two treatment arms of MDR-TB to investigate which treatment arm is more effective in the case of Pakistan. Alongside that cost per DALYS is also calculated for each arm. For this purpose, the study analyses the disability-adjusted life years averted followed by social cost in both the arms from a sample of 342 MDR-TB patients registered at the National Tuberculosis Program of Pakistan in the three TB centers in Lahore, Karachi, and Murree from 2012 to 2017.

The study finds that the overall success rate of treatment is 82.5% in a sample of 342 patients where the cure rates are higher in the ambulatory care and death rates are lesser as compared to the hospital arm. The cost per DALYs is less for hospital care as compared to the ambulatory care arm showing that hospital care is more cost-saving but the cost per DALYs averted is less than GDP per capita per year in both arms showing both arms can be used efficiently. The analysis of the ICERs shows that there is no difference between the cost-effectiveness of hospital care and ambulatory care arms for the treatment of MDR-TB in Pakistan as continuous dominance is not shown by any arm in the analysis. Both arms show their strengths as per the baseline assumption taken in the analysis so they can be used simultaneously to provide access to treatment to patients. Our study supports the WHO recommendation to use the ambulatory care arm for treatment as long waiting lists in hospitals can be avoided and treatment can be started immediately in a home environment.

The initial phase of treatment completed in a hospital under the supervision of qualified experts results in less duration of disability and can be more cost-saving for the patients but it applied more pressure on hospitals with less cure rates. We can derive some important policy conclusions from our results. The ambulatory care arm can play a very important role in reducing the burden of disease as we have seen that the number of deaths is less and the cure rate is more in ambulatory care as compared to hospital care, despite being more costly. Awareness regarding curative and preventive measures needs to be improved further to reduce the duration of disability and it will help the patients to increase their productivity. Government should focus more on community care by providing better facilities at the community level ranging from the easy availability of medicines to awareness related to timely administration of medicines and

other preventive measures to reduce the spread of disease, which will reduce the medical and non-medical costs of treatment.

The role of community health workers and other treatment supporters has to be enhanced in this regard. The incentives given to treatment supporters can also improve their performance which will lead to better treatment adherence on part of patients. These measures will also help in minimizing disease duration and the total cost of treatment. Proper vocational training centers for community health workers would help the health system to provide more out-patient care thereby relieving the hospitals of excessive burden and availability of the treatment at the door-steps of the patients.

Appendix B

Table B1: Demographic and Socioeconomic Factors

Variables		Number of patients	
		Ambulatory Arm	Hospital Arm
Education	Illiterate	54	58
	Literate	13	25
	Primary	28	32
	Lower secondary	31	25
	Secondary	26	16
	Higher secondary	13	12
	University degree	6	3
Marital status	Currently married	109	111
	Separated	2	3
	Divorced	2	2
	Unmarried	56	54
	Widowed	2	1
Occupation and employment status	Not working currently	76	96
	Agriculture	8	4
	Housewives	35	27
	Student	19	15
	Labor	6	12
	Service	13	7
	Business	1	2
	Others	13	8
Gender	Male	95	92
	Female	76	79
Income groups	less than 500,00 PKR	21	18
	50001- 100,000 PKR	26	34
	100,001- 150,000 PKR	41	34
	150,001- 200,000 PKR	21	24
	200,001-250,000 PKR	20	18
	greater than 250000 PKR	42	43
Duration of cure	Average in years	1.29	1.14

Variables		Arm	
		Ambulatory Arm	Hospital Arm
Age	patients between age 12-16	7	10
	patients between age 17-34	105	103
	patients between age 35-52	42	40
	patients above 52	17	18

PKR=Pakistani Rupee

Chapter 3

Analyzing the Association of the Outcome of Cure for MDR-TB Patients in Pakistan with their Socioeconomic and Spatial characteristics and the treatment regimens followed

Abstract

This study identifies and analyzes a number of factors that correlate with the outcome of the cure of multi-drug resistance tuberculosis (MDR-TB) patients in Pakistan. Survival analysis is carried out by applying the multivariable Cox Proportional Hazard model on the data taken from the three main MDR-TB sites (Murree, Karachi, and Lahore) in Pakistan. The results show that there is no difference in the survival of patients between the two treatment care strategies of hospital and ambulatory care. Male gender is negatively associated with the outcome of the cure while medical expenditure and spatial characteristic of time expenditure are positively related to the outcome of cure of MDR-TB patients. The study concludes that the availability of affordable and accessible health services, ambulatory care alongside hospital care should be ensured to improve the treatment outcomes of MDR-TB patients in Pakistan.

Key Words: MDR-TB, Spatial, Policy, Socio-economic, Survival analysis

3.1. Introduction

Interlinkages between health care and economics have become more pronounced over time. The incidence, prevalence, and treatment of disease are affected not only by the medical conditions but also by non-medical factors. Various environmental, socio-economic, socio-cultural, and biological factors affect the health status of people residing in different geographical regions and belonging to different social groups (Marmot and Wilkinson, 2006 and Oliver *et al*., 2008). Some of the differences in health status are contributed by natural factors like genes and old age but many of them are related to socio-economic disparities (Evans and Stoddart, 1990 and Galama and Kippersluis, 2010). The socio-economic burden on patients seeking treatment, spatial factors, and selection of treatment strategies may play important roles in determining the outcome of treatment for different diseases. In this context, the present study plans to analyze the association of socioeconomic and spatial characteristics alongside treatment regimens with the outcome of cure of multi-drug resistance tuberculosis (MDR-TB) patients in Pakistan.

Every year about 0.4 million new cases of MDR-TB are being observed across the globe where resistance to treatment from at least one of the two most powerful first-line anti-TB medications i.e. isoniazid or rifampin is observed universally (WHO, 2020). The prevalence rate of disease among the new MDR-TB patients is 3.1% compared to 10% among already treated TB patients worldwide (WHO, 2012). WHO (2003, 2008) has raised a concern that first-line drugs have failed over the years worldwide and the second-line drugs are more expensive and less effective which create a major challenge for the health systems in different countries. Since one of the targets of Sustainable Development Goals (SDGs) of ‘good health and wellbeing’ focuses on TB free environment by the year 2035, the medical experts are exploring the

development of such frameworks that can help to achieve the target of the eradication of TB (WHO: End TB strategy, 2015). Two alternate regimens exist for the treatment of TB i.e. ambulatory care and hospital care. In the former regime, treatment is carried out in the community with the support of family and healthcare workers with hospitalization in the early phase for a maximum of two weeks if required. In the latter regime, patients are hospitalized for two months, followed by treatment in the community (Bassili *et al*., 2013). A shift towards the ambulatory regime in the resource-scarce settings to lessen the burden on hospitals as it is expected that treatment can be efficiently given in ambulatory care also (WHO, 2009, Berman, 2000 and Ho *et al*., 2017, Arif *et al*, 2021).

According to a report of the National Tuberculosis Program (NTP) of Pakistan (NTP, 2015), Pakistan has the fourth highest burden of MDR-TB across the globe and the new cases of MDR-TB are increasing annually by 4.2% in Pakistan (WHO, 2020). Therefore, understanding the factors that are correlated with the cure rate of MDR-TB patients is vital to improve the treatment outcome and quality of life of the patient as well as to prevent person-to-person transmission of the disease. A disease-free environment is vital for a healthy population which in return offers a healthy labor force that increases the labor force participation rate and enhances productivity along with increasing the chances of more investment in health and education. A study on this subject is also important for addressing some of the targets on health indicators prescribed in SDGs. The association of spatial factors and treatment strategies for MDR-TB patients has not been studied in detail for Pakistan. Keeping in view the importance of these factors, the objective of our present study is to identify and analyze the socio-economic, spatial factors, and policy-related factors in the selection of treatment strategies for MDR-TB patients that are associated with the outcome of cure of the MDR-TB disease in Pakistan.

A number of demographic and socio-economic factors such as age, gender, education, and the poverty level of patients are studied to see their association with the cure rate of MDR-TB patients. In addition, medical expenditure incurred by patients is included to analyze its association with the cure rates. The spatial factors are captured by time and travel expenditure on the commute to health facilities encompassing the non-medical domains that are related to the treatment outcome. The availability of health facilities in the nearby location and low expense on the commute is expected to reduce the burden of patients and family members, thereby leading to better adherence to treatment. The policy-related variable is the provision of two treatment strategies i.e. ambulatory and hospital care. As explained above, the policymakers are trying to analyze the feasibility of a shift toward ambulatory care. Hence, this study can provide an important insight from a health policy perspective by testing the feasibility of WHO's (2009) recommendation in favor of ambulatory care while analyzing the cure rates of MDR-TB patients in Pakistan.

The study is based on the data of MDR-TB patients registered at three sites of the National Tuberculosis Program (NTP) in Karachi, Lahore and Murree collected during the time period 2012 to 2017. The methodology adopted is survival analysis which will help us to analyze the outcome of cure from the perspective of the above-mentioned covariates.

The rest of the chapter is organized as follows. The literature review is presented in Section 3.2 and the methodology and data are described in Section 3.3. Results and discussion are mentioned in Section 3.4 followed by a conclusion in Section 3.5.

3.2. Literature Review

3.2.1. Introduction

The development of the frameworks that encompass the domains of health and economics has gained importance over time. According to OECD (2002, 2004), health policy needs to be efficient to encompass the microeconomic efficiency i.e. to minimize the expenditure on a given level of health outcome, and macroeconomic efficiency that deals with an adequate level of public expenditure on health.

Smith *et al*. (2015) and Bloom *et al*. (2018) state that a disease-free environment leads to a better standard of living for people by increasing their productivity and many researchers are exploring the domain of health economics to develop the inter-linkages between health, and socio-economic and spatial indicators. So, in this section multi-dimensionality of the health and factors associated with the health outcomes are explored in the theoretical and empirical perspectives from the existing literature.

3.2.2. Socio-economic and Spatial Perspectives

Public health literature has discussed the relationship between socio-economic and spatial factors, and health outcomes from the perspectives of social inequality and political economy. The social inequality perspective shows that inequality exists in the socio-economic status and social standings of the individuals in a society that leads to the differential in health status. Whereas Szreter and Woolcock (2004) and McCartney *et al*. (2019) explain the political economy argument that poorly augmented policies and inclination of policies in favor of only a few social classes or geographical areas lead to the exclusion of other groups from the resource utilization in an economy and creates negative health outcomes. Together the differences in the

social settings and non-uniform policies for all the segments of society lead to differentials in the health outcome across the population.

A. **Social Inequality Perspective**

The differential in the health status of the individuals (or groups) is called health inequality and the avoidable differences in health based on the race or ethnicity that can be controlled by sound policies is termed as health inequity. Kawachi *et al*. (2002), CSCP (2011) and Emily *et al*. (2020) explain that health difference based on age is not health inequity but the difference in the infant mortality rate based on ethnicity and race is considered as health inequity as it indicates an unfair distribution of resources.

Different approaches like utilitarianism, hypotheses related to absolute income, relative income, income inequalities, neo-materialism, social capital, and status anxiety hypotheses, etc. exist in the economic literature on health care. Bentham (1789) and Mill (1861) propose the utilitarian approach which is a society-centric approach postulating that maximum benefit obtained from a given cost should be attained in the course of action that is morally right as it increases the happiness and satisfaction level of the individuals. Various researchers like Shiell and Hawe (1996), Mackay (2017), and Hilsenrath and Borders (2020) have applied this approach in health economics to focus on achieving maximum net benefits in attaining healthcare. This approach also indicates that inequalities exist in societies and health systems that affect health outcomes. The discussion about the inequality in health and the impact of the socio-economic perspective became more pronounced later in the literature where the inequality was explained in the context of absolute income, relative income, and the income inequalities hypotheses.

Keynes' (1936) concept of absolute income is also applied in health economics and the relationship between income and health is explained by the absolute income hypothesis (AIH). AIH states that the health status depends upon the individual's income only and does not vary with the differences in the earning of the overall population. Hence, if income does not change then health status should remain the same irrespective of the earning level in the neighborhood (also see Preston, 1975 and Rogers, 1979). But this hypothesis does not incorporate the aspect that if the income of an individual is not changing as compared to the earnings of other individuals, then the changes in the material needs over time would not be fulfilled. This will cause a negative impact on health by creating distress and psychological issues when the individuals are not able to manage the average consumption patterns prevailing in the society (also see Kawachi *et al*., 2002).

Duesenberry **(**1949**)** caters to the differential in income level in the relative income hypothesis (RIH) which suggests that health status is associated with the relative income differential that is the income of others as compared to a person's income in the society. The studies of Rodgers (1979), Kosicki (1987), Hsieh and Pugh (1993), Kawachi and Kennedy (1997), Layte (2011), Adeline and Delattre (2017), and Drakopoulos (2021) explain that relative poverty leads to more impoverishment and bad health in the population. The RIH provides a better picture in the analysis of income and health by incorporating the perception of people in ranking themselves in a society in comparison to others and the impact of income on their health status. For example, there may emerge the feeling of social exclusion in one income group as compared to another income group. It can also entail a larger perspective by incorporating the role of businesses and the government in the betterment of impoverished segments of society through income redistribution.

Wilkinson (1996) extends the RIH and explains the income inequality hypothesis (IIH) in the context of differential in the health status of individuals. IIH postulates that health differential is associated with income inequality based on social and economic differences prevailing in an area of residence. The linkages between income, mortality, and health become weak after a certain income level in a country and income distribution takes lead in determining the health outcome. The importance of civic inclusion and social justice becomes less meaningful for the people due to the increasing maldistribution of the resources which leads to more stress and lower life expectancy.

The AIH deals with the direct effect of income on health, and the RIH talks about the difference in income of a person as compared to other people in the society, for example, the difference of a person's income from the mean income of the population and the IIH states that health is affected not only by the own income but also by the income inequality prevailing in the region.

Another dimension of the association between health and socio-economic factors is described by studies by Smith and Egger (1996), Kaplan *et al*. (1996), Lynch *et al*. (1997), and Bernard *et al*. (2007) by using the neo-materialistic approach stating that more economic, political and social disparities in the presence of scarcity of resources would lead to more income inequality and more will be the individuals with lower income and poor health. The investment in the building of social and community infrastructure like physical capital, human capital, education, transport and health services, etc. will be low leading to a reduction of better-earning chances in the future. The neo-materialistic hypothesis takes the discussion ahead in literature by bringing the focus towards the reasons for differences in socioeconomics disparities which leads to a

lower level of income that ultimately deteriorates the health status while IIH focused only on the income inequality in the region that affects health.

A few more concepts explain that differential in health outcomes can occur because of socio-economic factors that lead to the reduction of trust and confidence levels in the society and this discussion originates from the work of Bourdieu (1985). For example, the social capital hypothesis shows that differences in the income level lead to less social capital such as less social interaction and inter-personal trust among groups. This concept is used in multiple studies like Kaplan *et al*. (1996), Kennedy *et al*. (1996), Kawachi and Berkman (2000), and Majeed and Tahseen (2018) that centered the discussion on social capital. Then status anxiety hypothesis is introduced and discussed by Wilkinson and Pickett (2009) and Layte and Whelan (2014) explains the concept of social capital and social interaction further by incorporating the medical reason and anxiety related to the social status, stating that psycho-social processes are affected by inequality which has a harmful effect on health that was ignored by the social capital hypothesis. The feelings like distrust and inferiority are experienced by individuals, which damage the psycho-endocrine mechanisms, leading to bad health outcomes and a fall in the level of social capital development in a society.

The discussion in this sub-section suggests that multiple socio-economic factors such as income level, distribution of resources and human capital, etc. tend to affect health outcomes through multiple channels, and these need to be addressed by the health policymakers to attain better health outcomes in a society.

B. **Political Economy Perspective**

In the context of the political theory, the concept of dependency of one region on the other regions originates with the work of dependency theory by Prebish (1949) stating that the peripheries (i.e., the sub-urban or the rural areas) are dependent on the core (urban areas) for their growth and development. With the evolution of neo-classical theories by Marshal (1890) and Solow (1956), the concept of regions converging to a common level of productivity and wealth emerged. But Myrdal (1957) and Hirschman (1958) discussed the theory of polarization as a critical response to the neo-classical theory stating that growth in the centers (core) will lead to lower chances of growth in the peripheries as the flow of human and physical capital will take place towards the center instead of regions that are supposed to be converging to the higher level of productivity.

Later, Friedman (1972) used the concept of core and periphery in the theory of polarized development (TPD) stating that the spatial system focuses more on the core regions which are the center of social, economic, and technological innovation than the peripheral regions. TPD explains the concept of underdevelopment in the context of a capitalistic system where the benefit is not equally enjoyed by all economic groups and all groups are not able to get an equal advantage because of the privileged group. Lasuén (1973) explains that TPD is expanded by the incorporation of theories of growth poles and growth centers in the spatial context during the 1960s and 1970s. The agglomerations develop because of more innovation and production in the cities which attracts the further flow of capital in the cities and thus rural growth is compromised which makes peripheries experience lower innovation. Keim (2006) introduced the idea of a knowledge economy stating that the metropolitan regions (core) have more concentration of the service-based sector like financial, banking, and legal services which attract more business and

economic activities, and health care units like hospitals and labs, etc. are also better developed in the metropolitans.

Various studies like Kuhn (2015), Damian *et al*. (2018), Janevic *et al*. (2020), Stoica *et al*. (2020), and Popescu *et al*. (2021) have applied TPD in the healthcare analysis. The health policies oriented towards the center like metropolitan and urban areas make the periphery (sub-urban and rural areas) face exclusion in attaining health care services. The health systems and services are better developed in the core hence people from peripheral areas have to travel to the core for acquiring health facilities. The awareness about good health practices and treatment of diseases is also better in cities as compared to peripheries as information accessibility is easy in the areas where hospital and health care units are well established. Innovation in the production methods to reduce the cost and expansion of health markets are also more pronounced in the core that makes the services more readily available in the urban areas, thereby improving the health outcomes.

When the health facilities are concentrated in the core then the health facilities and outcomes in the peripheries are compromised as the patients may have to travel long distances and have to put extra effort to get information about the disease and treatment, which leads to extra out-of-pocket expenditure putting the peripheries at disadvantage. The difference in the health facilities can occur in cities also where the spatial effect can be prominent with the development of slums in urban settlements. The hygiene and health facilities are better in the main urban centers as compared to slums. For example, the people living in slums in India and Pakistan experienced only a marginal increase in income over the years, hence cannot afford a better quality of health, water, sanitation, and ventilation facilities (Usmani and Ahmad, 2018 and Samuel and Nisar, 2021).

Krugman (1991) emphasizes the importance of transportation costs in economic decision-making as it increases the total cost of the activity. Copus (2001) stated that the peripheries have to bear high transport expenditure and fewer economic benefits that need the attention of policy makers to incorporate spatial proximity in the decision-making. Two concepts exist in the discussion of location in healthcare i.e. space and place. Arcaya *et al*. (2015) define space as the location of the individual in the proximity of the health risk (like polluted water streams) and the protective factors (like health facilities) that are spatially distributed. The concept of place is related to the administrative perspective i.e. districts, states, and cities. Roxberg *et al*. (2020) explain that health differences can occur based on spatial and place perspectives and need to be addressed by governments while taking health initiatives.

Along with the transportation cost to health facilities, another spatial factor that has been studied in literature is the level of transport accessibility to health facilities proxied by the variables of distances from home to health facility or the transport time. Lenhard *et al*. (1987) have shown that patients who have to travel long distances for treatment often show better treatment outcomes than patients who do not travel much, a hypothesis often termed as distance bias or referral bias. Kelly *et al*. (2016) found the support of distance bias in the systematic review of literature encompassing the regions of North America, West Europe, and Australia. Similar results are previously found by Goodman *et al*. (1997) for England. On the other hand, studies like Haynes *et al*. (2003) for New Zealand and Robsky *et al*. (2020) for Uganda show the distance-decay mechanism that if the distance is more from a health facility then the patients are more likely to suffer from the disease. There are also some studies that find no association between distance and health outcomes like Lankila *et al.* (2016) for Northern Finland.

The disparities in health care can occur in the context of culture, social role, structure of society, poverty, rich economic status of neighborhoods, and health status. The policies that focus on one segment of the society lead to the creation of the core (segment focused by policy) and periphery (the segment neglected by policy) and the peripheries suffer because of the non-availability of sufficient services and facilities and have to bear the transport and time expenditures in attaining health services. The socio-economic and spatial factors need to be given due importance in policy-making for better health outcomes.

3.2.3. The Health Policy Intervention: Selection of Treatment care

An important perspective in the provision of health services is the determination of treatment strategies. Institute of Medicine (2012) reports that most patients do not get hospital beds timely and have to be kept in concentration in small hospital wards which lead to further contamination and spread of disease. Hence, alternate treatment strategies, for example, ambulatory care needs to be explored for the treatment of diseases that can be managed in the community. Berman (2000), Bassili *et al*. (2013), and Ho *et al*. (2017) explain that in the ambulatory care, treatment of the MDR-TB is carried out in the community with the support of family and healthcare workers with hospitalization in the early phase for a maximum of two weeks if required. In hospital care, patients are hospitalized for two months, followed by treatment in the community.

A shift is proposed towards the ambulatory care for the treatment of the communicable disease of tuberculosis and stated "the choice between hospitalization and ambulatory treatment depends on several factors in addition to the severity of the disease. Such factors include the availability of hospital beds with adequate infection control measures, the availability of trained personnel to administer treatment and manage adverse drug reactions, a social support network

to facilitate adherence to ambulatory, and the presence of other clinical or social conditions for in-patients" (WHO, 2009). Hence, if the treatment protocols are managed properly in ambulatory care then the ambulatory care is expected to increase the efficiency of the health care system and yield favorable outcomes of treatment in two dimensions (also see Berman 2000, De Vries *et al*., 2017, Ho *et al*. 2017 and Chavan *et al*., 2020). Firstly, it will reduce the burden on the hospital, and secondly, the treatment can be started immediately at home with the help of family and community health supporters without waiting for the bed space for a long time and treatment outcomes can be improved. Hence, it is important for the policymakers to focus on the evidence-based implication to ensure that the best health outcomes are achieved with the given availability of resources.

3.2.4. Empirical Linkages

Pakistan is one of the countries that experienced a sharp increase in the spread of MDR-TB in recent years. Ahmad *et al.* (2015) have reported three times to increase in the MDR-TB cases in Pakistan from 2005 to 2015. According to the estimates given by Khan *et al*. (2016), the highest number of cases are reported in Punjab (51%), followed by Sindh (23%), Khyber Pakhtunkhwa (15%) and Baluchistan (3.5%).

The struggle with the treatment of MDR-TB does not lie only in the medical domain. A stigma is attached to the disease and the patients tend to avoid TB tests because of the fear of social exclusion in Pakistan. For example, Liefooghe *et al*. (1995) show that the fear of social stigma is highly prevalent in Sialkot (Pakistan), which indicates the need for improvement of health literacy to reduce the stigma and to educate people about the curability of MDR-TB. Agboatwalla *et al*. (2003) show that the people in the rural and urban Sindh lack knowledge

about the symptoms of TB and the importance of completion and duration of the treatment which leads to non-adherence to treatment, especially when the patient starts to feel slightly better. Akhtar *et al*. (2016) indicate that MDR-TB is seen to be more prevalent in the urban settings of Punjab where women did not know the importance of follow-ups to health centers and completion of the treatment. Khan *et al*. (2006) find that increased awareness about the disease and treatment protocols lead to a greater willingness of patients to undertake treatment.

WHO (2005) states that the main causes of the incidence of MDR-TB are lack of social support framework for the population at risk, lack of understanding about the treatment protocols with 100% commitment along with the delays in the diagnosis and identification of the MDR-TB in Pakistan. The disease of TB is associated with various social, economic, demographic, and biological factors in Pakistan. Low-income level, illiteracy, poverty, place where people are residing, proximity to the toxic environment, unavailability of the health facility in the residing areas, long waiting list in the hospital to start the treatment, and smoking habits are common risks indicators in Pakistan (Khan, 2017).

Ullah *et al*. (2015), Khan *et al*. (2015), Ahmed *et al*. (2016), Hashmi *et al*. (2017), Khan (2017) and Imran *et al*. (2019) find that aging and lower body weight lead to more deaths during the treatment of MDR-TB in Pakistan. However, Ullah *et al*. (2015) and Laghari *et al.* (2019) find that young people are more prone to the incidence of diseases because of unhealthy dietary habits which compromise the immunity system though the death rate is lower for young people than the elderly people. Javaid *et al*. (2016) state that poor socio-economic status, rural settings, and unfriendly behaviour of the family members and treatment providers are also reported by the patients as reasons for the irregular follow-up visits to the health facilities.

WHO (2016) has reported that though Pakistan has a high MDR-TB burden, yet disperses a very small amount of the health budget in this category given the scarcity of resources and multiple health problems prevailing in Pakistan. The prevalence rate of the MDR-TB is high in patients who are already treated for pulmonary TB in Pakistan. This is an indication of non-compliance to the TB treatment protocols by the medical experts and patients. Javaid *et al*. (2016) highlight that the easy availability of TB medicines over the counter at the pharmacies leads to self-medication by the patients that create further issues. Atif *et al*. (2017) find that even in the case of a free treatment provided by the government for the MDR-TB patients during the time of April 1, 2014, and December 31, 2015, in Bahawalpur, Punjab, the treatment outcomes were not promising, indicating that the health experts need to pay more attention to the high-risk patients and management of the clinical protocols.

Rizvi *et al*. (2015) state that an important issue is the financial constraints that the patients and family members have to face during the treatment procedures. The medicines for TB are very expensive and even in the case of the free provision of the medication by the National Tuberculosis Program of Pakistan, sometimes patients have to buy medicines from the commercial pharmacies because of the disruption of the supply chain of medicines in the public TB centers. Along with the direct cost, indirect cost is also borne by the patients and households in the treatment of TB. The direct cost involves the purchase of medicines, hospitalization, transport cost, etc. and the indirect cost involves the loss of income and time cost, etc. Rizvi *et al*. (2015) report that the average direct and the indirect costs are reported as 1714 and 3445 rupees per month respectively showing that the indirect cost burden is high in Pakistan.

The expenditure on commuting is a financial burden. Sometimes the patients have to travel to distant areas for the treatment which involves the travel expenditure. For example, a survey

conducted in Lahore by Rehman *et al*. (2018) shows that the average expenditure borne by the patients is 807.3 rupees per visit to a health facility for the treatment. The median value is 350 rupees while the range is 60 to 6000 rupees per visit to a health facility and the travel distance has a mean value of 44.9 km. The patients reported that they have to face hurdles in the treatment such as the high cost of transport, meals, and other expenditures because of the non-availability of health facilities near their homes.

Zageye *et al*. (2019) perform a systematic review of literature by using 13 studies and found that the long traveling time is a reason for the nonadherence to the treatment in Ethiopia. Tola *et al*. (2019) find in a systematic review that travelling cost and more time of traveling are important risk factors that create hurdle in the treatment. Teferi *et al*. (2021) find that economic burden of disease leads to unsuccessful treatment outcomes in Africa. Johnston *et al*. (2009) find in the systematic review that male gender is more prone to TB because of biological and behavioral factors.

The neighboring country of India is also struggling with the MDR-TB which is reported to have the highest global burden of MDR-TB in the world (27%) as per WHO (2020) which is followed by another neighbor China having the second-highest global burden of MDR-TB (14%) globally. WHO (2010) report that China is struggling with a low treatment success rate of 40.95% and the situation has not changed much over time (WHO, 2020). WHO (2005), Flora (2013), and Saha *et al*. (2015) state that Bangladesh has a current MDR-TB rate of 3.6% in the new case and it has a higher rate of 19% in the patients who are re-treated for TB. Fewer laboratories and diagnostic material, less training of the treatment supporters, distortions in the continuous supply of the second-line drugs, and the unwillingness of the patients to undergo hospitalization for one month in the early phase of treatment are the common risks factors in

India, China, and Bangladesh. It is often seen that after the discharge of the patient from the hospital, it is difficult to keep a track of them for follow-up visits. The transport of the sputum samples from the remote areas to the laboratory for testing, the high cost of transport for the patients, and geographical constraints are yet some more challenges.

Raazi *et al. (2017),* Saldanha *et al*. (2019), and Shivekar *et al*. (2020) find that male patients belonging to the working-age group are more prone to MDR-TB though it can vary among different areas in a country. Kaul (1998), Phadake (1998), and Shringarpure *et al*. (2013) report that people in India prefer private health facilities over public ones because of more data privacy in private health facilities as stigma is attached to the disease. The unfriendly behavior of the health workers with the patients, socio-economic disparity, and caste system are also common risk factors in India. The issue of traditional healers is common who lack medical knowledge, which leads to an increase in drug resistance. The patients who experience betterment in health due to treatment or those who develop the side effect stop the medication, which leads to further drug resistance. The studies have suggested the provision of more accessible health facilities in different geographical locations. Atre and Mistry (2005) find that the vertical health programs only focus on a few treatment regimens which might be shortsighted so more government focus is required for effective treatment regimes. To endure the challenges of MDR-TB treatment, the Government of India is working on developing a partnership with the private sector to join hands against this disease. The decentralization of the treatment of TB is helping India in monitoring the burden of TB but access to remote areas is still a big challenge (Duggal *et al*., 1992, NCAER, 1995 and Uplekar *et al*., 2001).

According to WHO (2020), Ethiopia, Kazakhstan and Myanmar are able to manage the burden of MDR-TB disease in a better manner and they have reached the target of 75% treatment

success rate for MDR-TB where training the family members related to treatment protocols, focus on the preventive measures and public-private partnership have improved the treatment success rate despite poor medical infrastructure and high traveling costs for treatment (also see Tadesse *et al*., 2013 and Meressa *et al*., 2015). Pakistan can also learn from these experiences by undertaking private-public partnerships and engaging the community to ensure that all the stakeholders play their role in the fight against TB and to achieve the SDGs.

3.2.5. Concluding Remarks

Based on the above discussion, it can be concluded that different socio-economic, spatial, and policy-related factors are associated with the treatment of MDR-TB. The countries bearing the burden of this disease are striving hard to improve the treatment outcomes. Many types of researches have been presented for Pakistan related to TB and MDR-TB treatment outcomes but a gap exists in the literature related to the identification of the spatial and health policy-related factors that can have a potential association with the treatment outcome. Hence, this study will contribute by providing evidence on the association of socio-economic, spatial, and health policy-related factors with the cure rate of MDR-TB patients in Pakistan.

3.3. Methodology

We will discuss the model, data collection method, estimation technique, and model diagnosis in this section.

3.3.1. Model

The health outcome of the MDR-TB patients is determined by various medical and non-medical factors. In our model, we will determine the association of the health outcome of cure with demographic, socio-economic, spatial, and health policy factors. The health outcome of

cure is taken as the duration of treatment in months till the outcome of cure is experienced by the MDR-TB patient measured from the origin when the patient is diagnosed with MDR-TB. The demographic variables included in the model are the age and gender of the MDR-TB patients. The age of MDR-TB patients is taken as a continuous variable in the number of years. Gender is a categorical variable set equal to 1 for males and 0 for females.

The socio-economic factors are education, family income, and medical expenditure. Education of the patient is an important social construct that may play a vital role in understanding the importance of treatment. The education variable is taken as the number of years of education of the patients. Then family income is constructed by converting the total annual family income into family income per month which is then divided by the number of household members of the MDR-TB patient. The flow variables of medical, travel and time expenditure are taken in monthly averages. Medical expenditure is defined as average medical expenditure that creates an additional burden on the family's budget as funding for expensive treatments and medicines creates an extra out-of-pocket expenditure which may act as a disincentive for the continuation of treatment without breaks. Medical expenditure is calculated in our study as expenditures on preventive measures, side effects, and hospitalization that are taken as an average medical expenditure per month in US dollars units (total medical expenditures in US$ during the treatment divided by the number of treatment months).

The spatial factors are captured by the travel and time expenditure. The patients have to travel to health facilities i.e. district tuberculosis health centers and laboratories for follow-ups and medical tests which entail time and travel expenditures. We have defined travel expenditure as the average expenditure per month on two ways traveling to health facilities by public or own transport and is calculated as total monthly expenditure of return trip in US$ during the treatment

divided by the number of treatment months. The average rate of one US dollar was equal to 104 Pakistani Rupee during the years 2012-2017 which is used as the currency conversion rate for medical and travel expenditures which was available in the medical record in Pakistani Rupee. Time expenditure is another spatial factor that is defined as the average hourly time spent by the patient per month in two-way travel to health facilities i.e. from home to health facility and back to home and calculated/ measured as the total time of travel in hours during the treatment divided by the number of treatment months. The average time spent on travelling by the patients is relatively less in the initial two months when they are in the hospital care as compared to ambulatory care as hospitalization is involved more in HC and patient has to stay back in the hospital. Only after the discharge, travelling has to be done for the follow-up visits in the outpatient care. In the ambulatory care, the travelling time is slightly higher as from the first month, the follow-up visits start and two way travelling is observed from the beginning of the treatment period. The average time spent on travelling is 3.2 hours per month for hospital care and 4.5 for ambulatory where AC mainly involves the outpatient care.

The health policy-related variable is the selection of the treatment care i.e. hospital care versus ambulatory care. This is a categorical variable set equal to 1 for the hospital care and 0 for the ambulatory care. Based on the description of the variables, we can write the functional relationship of the outcome of cure with various factors as follows.

$$Outcome\ of\ cure_{i} = f(Age_i, Gender_i, Education_i, Family\ Income_i, Medical\ Expenditure_i \\ Travel\ expenditure_i, Time\ expenditure_i, Treatment\ care\ _i) \qquad 3.1$$

3.3.2. Data, Censoring, and Handling of Censored data

We have collected the data of 438 newly diagnosed and registered patients for MDR-TB treatment (2012-2017) from three sites of Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital, Lahore, and Ojha Institute of Chest Disease, Karachi. Secondary data of all the variables i.e. socioeconomic and spatial characteristics and treatment regimens is recorded from the registration and monthly follow-up forms of the patients available at the NTP centers. The self-reported data upon the enrollment in the study from the patients is gathered at the time of registration and also on each month at the time of follow-up to the NTP center that we have collected from the NTP centers. An important issue in health-related data exists where incomplete records are observed in the data collection process. Some of the patients do not complete their treatment and it is not possible to know what happened to them afterward. The event of interest of cure may not have occurred at the end of the study period of 2017 where it is not possible to analyze if the patients are cured of the MDR-TB afterward or what happens to them when they did not appear for the follow-up visits for treatment at the health centers. The patients may also die before the end of the study period. Hence, partial information is available and this situation is called censoring which is applicable in our study. Therefore, the inclusion criterion comprises of including patients who are diagnosed with MDR-TB for the first time at the age 12 and above. The exclusion criterion involves an incomplete stream of information provided by the patients for a major part of the study period. Based on the availability of relevant information, 369 patients are included in the final sample as shown in Figure 3.1.

Another issue exists that all the patients would not enter the study at the same time. This pattern is known as the staggered entry. Some of the patients are diagnosed with the disease at

the start of the study period 2012 and some develop the disease later on hence the entry point of the patients varies in this study.

Multiple treatment outcomes exist for the treatment as per the description of WHO (2010) which are cured, completed, died, lost to follow-up, failed to recover, not evaluated till the end of the study, and still under treatment. One of the treatment outcomes is declared by the health providers in the process of the treatment. The patient is said to be 'cured' if the sputum smear or cultural test becomes negative. Sometimes the treatment is 'completed' but the patient does not recover from the disease. Treatment can 'fail' for the patient when the sputum smear or cultural test is positive for 5 consecutive months. The treatment may be interrupted for two consecutive months or more and the health outcome of 'loss to follow-up' is declared in this case. The patient may have 'died' in the course of treatment. The patient whose outcome is not declared till the end of the study period falls under the category of 'not evaluated, while 'still under treatment' and is referred to as the patient whose treatment is still in the process. These outcomes are used as standard outcomes.

The treatment outcomes of the MDR-TB patients are shown in Table 3.1. In our sample, some of the patients died for whom further perspectives of treatment could not take place. The treatment failed for 11 patients, while 30 patients did not complete the whole treatment, which led to the loss of follow-up. Males have shown more loss to follow-up than females. The socio-economic pressures, the stigma of the disease, work burden, less time off from work, and fear of income loss are some common factors related to the treatment that can possibly lead to the loss to follow up (also see Javaid *et al*., 2017). Table 3.1 shows that 4 patients were still under treatment by the end of the study period 2017. One patient completed the treatment but could not recover from MDR-TB and the treatment outcomes of 6 patients were not evaluated by the

health program. The cure rate of patients in our sample is 77.24 % (see Table 3.1) and the overall treatment success rate i.e. cure and completed is 77.51% which falls within the desired target of 75-90% (WHO, 2015 and Kibret *et al*., 2017). The cure rate in the sample of male patients is less than that in the sample of female patients, though it also falls (marginally) in the desired range.

Table 3.1: Treatment Outcomes of MDR-TB Patients

Outcomes	All Patients	Females Patients	Males Patients
Cured	285 (77.24)	125 (80.13)	160 (75.12)
Died	32 (8.67)	17 (10.9)	15 (7.04)
Failed	11 (2.98)	5 (3.21)	6 (2.82)
Loss to follow up	30 (8.13)	7 (4.49)	23 (10.8)
Still under treatment	4 (1.08)	1 (0.64)	3 (1.41)
Completed	1 (0.27)	0 (0)	1 (0.47)
Not evaluated	6 (1.63)	1 (0.64)	5 (2.35)
Total	369	156	213

Note: The numbers in brackets are the percentages from column total.

The questions of when or whether the treatment outcome of cure occurs for the patient need to be addressed. The treatment outcome of cure has occurred for 285 MDR-TB patients in our study and other patients have not experienced cure hence we have defined all other outcomes as censored in our analysis. Different patients were diagnosed with MDR-TB and registered with the National Tuberculosis Program (NTP) centers at different points of time from 2012 to 2017.

The staggered entry data points for the patients are recorded carefully from the record of the hospitals.

The next step is to identify the appropriate technique for the analysis of such data. The survival analysis is a useful method that helps to cater to censoring and staggered entry simultaneously and deals with the time of an event. The survival analysis shows that the chance of the occurrence of an event is the same among all the observations. The survival analysis is a better option to use here as the conventional linear model and other (non-linear) probability models like logit and probit do not entertain the censoring and staggered entry issues. We will discuss the estimation technique in the next sub-section.

3.3.3. Econometric Model

For the application of survival analysis in our model mentioned in Equation 3.1, we will use the Cox proportional hazard method (Cox, 1972) for the multivariate analysis to identify the factors that are associated with the cure of MDR-TB patients. This is an appropriate modeling technique as it deals with censoring and staggered entry issues in the data (Sy and Taylor, 2000, Stepanova and Thomas, 2000, Kim *et al*., 2016, Ngari *et al*., 2021). We will focus on the time to event of cure in the treatment of MDR-TB. For this purpose, we will first define some basic terms for this study:

i. **Event:** Treatment outcome of the cure

ii. **Time to origin:** The time when the study begins and when all the patients are alive (2012 in our case)

iii. **Time scale:** The measurement of the time is done in months

iv. **Time to event:** Duration of time from the start of treatment till the occurrence of the event 'cure' in months

vi. **Survival time:** Duration of time from the start of treatment till the end of the study if the event does not.

v. **Failure time:** The time when the event of cure happens for a patient.

We define the dependent variable as the time to event of the outcome of cure. Now, assume a random variable at time T for the event cure to happen in our model. Then hazard function is used to define the distribution of time T in Equation 3.2:

$$H(t) = \lim_{\Delta t \to 0} \left\{ \frac{P_0(t \leq T \leq t + \Delta t) \,|\, T \geq t}{\Delta t} \right\} \qquad 3.2$$

Equation 3.2 shows that hazard function H(t) is the conditional probability of the occurrence of the event cure between the time t and Δt, given that the patient continues the treatment by time t, divided by Δt, as Δt approaches zero and the patient is declared as cured medically. In the survival analysis approach, we will employ the Cox proportional hazard model (CPM) to address the duration of the event, the probability of occurrence of an event, and the issue of right censoring. An advantage of using CPM is that one does not need to specify the distribution of baseline hazard H_0(t), the baseline is the value of hazard when all the covariate values are equal to zero, as it considers a common value for all units in the population. Here CPM is used to analyze the association of the occurrence of cure with demographic, socio-economic, spatial, and health policy factors. Hence, we specify the following econometric model based on the theoretical model given in Equation 3.1(see Altman, 1991).

$$H(t, \gamma) = e^{(z\gamma)} H_o(t) \qquad 3.3$$

The left-hand side is the hazard function and the right-hand side is its specific form indicating that the hazard function at time t is specified as some baseline hazard function multiplied by a factor $e^{(Z\gamma)}$ that depends upon a vector of variables Z, consisting of the same variables that appear on the right-hand side of Equation 3.1 with γ as the vector of parameters. Here H_o refers to an unknown function of hazard under standard baseline conditions which does not depend on covariates (Wang *et al*., 1993).

Proportional hazard, as the name signifies, means that the hazard of an individual related to a specific covariate is proportional to the baseline hazard giving relative estimates rather than an absolute one. So, γ can be estimated by using the rank order of the occurrence of cure or censoring times without the knowledge of H_0(t) by ranking n^{th} order event time. An individual who has survived a second period t_2 must have survived a previous time period t_1. Hence, an n^{th} order cure time is given by $t_1 < t_2 < t_3 \ldots\ldots t_n$. Denoting the set of patients at risk to cure at time t_i by $Q_{(t_i)}$, the likelihood function for the vector of parameters is given in Equation 3.4:

$$L(\gamma) = \prod_{i=1}^{n} \frac{\exp\,(Z_{(i)}\gamma)}{\Sigma_{g\epsilon Q_{(t_i)}} \exp\,(Z_{(i)}\gamma)} \qquad 3.4$$

The estimates of γ are derived from the maximization of the logarithm function of Equation 3.5. Equation 3.5 can be converted into the discrete hazard as shown in Equation 3.5 given below because data for patients are recorded on a monthly basis so that multiple patients can be cured in a given month. Hence, multiple events of cure can occur, a situation referred to as tied failure for which likelihood function needs to be altered as it becomes difficult to comprehend which patient to incorporate in the risk set of cure time t_1, t_2, (Stepanova and Thomas,2000). Let the

number of the event of cure at time t_i be denoted by f_i. Let $Q_{(t_i,f_i)}$ be the set of all subset of f_i patients from the set $Q_{(t_i)}$ of patients at risk to cure. So, $Q \epsilon Q_{(t_i,f_i)}$ now represents the set of f_i patients who might have experienced cure at t_i. Let $C_Q = \sum_{g \epsilon Q} Z_g$ where C_Q denotes the summation of covariates vector Z of patients in set Q and g is the element of Q. Let F_i be the set of f_i patients that cure at t_i, so the sum of covariates vector of these patients is given by $C_{Fi} = \Sigma_{g \epsilon F_i} Z_g$. The Likelihood function is given as Equation 3.5:

$$L_{cox}\gamma = \prod_{i=1}^{n} \frac{\exp\left(C_{F_i}\gamma\right)}{\sum_{Q \epsilon Q_{(t_i,f_i)}} \exp\left(C_Q\gamma\right)} \qquad 3.5$$

The continuous hazard functions are assumed in the CPM. Our health data are recorded on a monthly basis in which tied failures can also occur. As mentioned above the likelihood function involving tied failures needs modification as it becomes difficult to identify the patient to be included in the risk set at each time of cure t_1, t_2, t_3…… The use of tied failure and the ordering is not easy to compute; hence approximations are developed for this purpose. We use Breslow's method (Breslow, 1974) which provides a reasonable approximation of the function mentioned in Equation 3.5 which works well when the number of the patients getting cured f_i at time t_i is small compared to the patients in the risk set. Breslow's method has suggested the modification of the denominator term of Equation 3.6 to be replaced by $[\sum_{g \epsilon Q_{(t_i)}} \exp(Z_g\gamma)\,]^{f_i}$ for computational ease. The modified partial likelihood function is given in Equation 3.6.

$$L_\gamma\gamma = \prod_{i=1}^{n} \frac{\exp\left(C_{F_i}\gamma\right)}{\left[\sum_{g \epsilon Q_{(t_i)}} \exp(Z_g\gamma)\,\right]^{f_i}} \qquad 3.6$$

The Cox proportional technique would be applied by using the stepwise backward elimination method for variable selection that involves dropping variables with Z-Value ≤ 1.65

until all the remaining variables are significant in our final model. This process helps to analyze the predictive power of the variables by adding all the variables in the model and then the variables which are not significant to the model are dropped leaving behind the most important variables. This method is opted to focus on variables that have a significant impact on the response variable in our model.

We would also analyze if there is any difference between the categories of the policy variable of treatment by using the Kaplan-Meier (1958) curves known as KM curves. KM curve is a step function that indicates whether the survival function of one group is above the other, that is its survival chances are higher. We will also test the null hypothesis that there is no difference in the survival between the categories of treatment care by using the Log-rank test.

3.3.4. Model Diagnosis

Diagnostic tests are applied to check whether the Cox proportional hazard model is correctly fitted. In the diagnostic tests, residuals of the model provide important information and are examined carefully as censoring is involved in the data. We would test the model fit, transformation of covariates for correct functional form, and presence of the outliers which might create abnormalities in the regression results.

I. Test of Model Fit and KM Curves

Firstly, we will examine if the model is correctly fitted and if the residuals of the model can be used for this purpose. If the model fits correctly, then the residuals will not show any specific pattern. Here we use Cox Snell residuals (Cox and Snell, 1968), which are:

$$rd_{(cs_i)} = \exp(\hat{\gamma} Z_i)\, \widehat{H}_o(t_i) = \widehat{H}_i(t_i) = -\log\left(\hat{S}_i(t_i)\right) \quad 3.7$$

Here $\widehat{H}_o(t)$ is the estimated cumulated baseline hazard, $\widehat{H}_i(t_i)$ is the estimated cumulative hazard for an ith individual at time t_i and $\hat{S}_i(t_i)$ is estimated survival function for an i^{th} individual at time t_i. Exponential distribution exists for -log S(t) with a mean equal to one irrespective of the form of S(t) as described by Collet (1994). A good fit shows that estimated values $\hat{S}_i(t_i)$ and actual value $S(t_i)$ are close hence -log $\hat{S}_i(t_i)$ where *i*= 1 to *n* acts as an *n* number of observations having an exponential distribution with unit mean which are treated as the Cox-Snell residuals hence negative log of the estimated survival function -log$\hat{S}(t_i)$ could be set equal to the $rd_{(cs_i)}$ constituting the residuals having an exponential distribution with unit mean[9]. Then a graph is plotted with the cumulative hazard function on the Y-axis and Cox Snell residuals on the X-axis and if the model fits well then the unit slope and zero intercepts of the straight line would appear.

II. Identification of Functional Forms and Covariate Transformation

The identification of true functional form and the need for the covariate transformation are explored in the analysis. Sometimes the data set shows non-linearity and skewness and hence needs to be transformed to make the data handling and interpretation easier. This can be identified by transforming the Cox Snell residuals into martingale residuals $rd_{(mr_i)}$ (Therneau *et al*., 1990) as shown in Equation 3.8 below.

$$rd_{(mr_i)} = \Delta_i - rd_{cs_i} \qquad 3.8$$

where martingale residuals $rd_{(mr_i)}$ is the difference between observed numbers of failures for a patient in the interval (0, t_i), denoted by Δ and the expected number of failures, taken as rd_{cs_i}. The residuals $rd_{(mr_i)}$ are then plotted against the rank order of time. The absence of any

[9] The detailed derivation of the relationship between $rd_{(cs_i)} = -\log\left(\hat{S}_i(t_i)\right)$ can be seen in Collett (1994).

particular pattern in the graph shows that functional form is appropriate and covariate transformation is not required (Qin and Shen, 2010).

III. Identification of Outliers

Identification of outliers plays an important role in regression analysis as a single abnormal value can have enough potential to distort the results (Rousseeuw and Leroy, 1987). Therefore, the martingale residuals are transformed into deviance residuals rd_{dv_i}, shown in Equation 3.9, as proposed by Therneau *et al*. (1990), that makes the distribution symmetrical around zero as shown below.

$$rd_{dv_i} = sgn(rd_{mr_i})[-2\{\{-rd_{mr_i} + \Delta_i \, log(\Delta_i - rd_{mr_i}\}] \quad 3.9$$

where $sgn(rd_{mr_i})$ is the sign of $rd_{(mr_i)}$

We would be able to identify the outlier if some large values in the residual graph lie far away from symmetrical distribution around zero.

IV. Time Dependency

Time dependency can also arise when the variable of interest changes over time i.e. it shows the interaction among the covariate and time. In the CPM, time dependency should not occur as its absence is one of the features of the hazard function. Hence, in order to identify this issue, we will use Schoenfeld residuals (Schoenfeld, 1982) derived and this will also be set as an important base for testing the proportionality assumption in the CPM.

Given the vector of the set of covariates for the i^{th} patient $Z_i = (Z_{i1}, Z_{i2}, \ldots. Z_{ik})$ and the set of patients at risk to cure Q_i, the vector of Schoenfeld residuals at time t_i, hat is $rs_i = (rs_{i1}, \ldots.., rs_{ik})$ at time t_i is shown below.

$$rs_{in} = Z_{in} - E(Z_{in}|Q_i) \quad 3.10$$

Thus, the residual is defined as observed values of covariates for the i^{th} patient i.e. Z_i minus its expected values that are conditional on the risk set Q_i which removes time dependency as the temporal effect is not present. Equation 3.10 shows that patients having covariates values similar to those in the risk set are less likely to cure with a smaller absolute value of residuals and the ones having a larger absolute value of residuals relative to the risk set are more likely to cure. The residuals are plotted against time of the treatment. If there are a random pattern of residuals against time, then it shows that time dependency does not exist.

V. Test of Proportionality Assumption

The Schoenfeld residuals can be scaled by using the estimator of variance which gives residuals more diagnostic power (Grambsch and Therneau, 1994). These residuals, also called scaled residuals, are used to test proportionality assumptions and are given by:

$$rss_{in} = [Var(rs_{in})\,]^{-1}\, rs_{in} \quad 3.11$$

Equation 3.11 shows that the vector of Scaled Schoenfeld residuals is the inverse of the residuals covariance matrix multiplied by the vector of residuals. The plot should be centered around zero if the proportionality assumption holds.

3.4. Results and Discussions

Summary statistics of MDR-TB patients are reported in Table 3.2, which indicate that female patients show a greater percentage of cure than male patients. One of the reasons is that male patients show inconsistent behavior in managing the protocols of taking medicines timely as

compared to females and males are medically more prone to TB and less likely to cure as indicated by WHO (2020).

The percentage of cure is less in older patients (aged 60 or more years) and more censoring is experienced by them in our study as shown in Table 3.2. The older patients show low cure rates as the immunity level declines with age. In our sample, 94.3% of the patients belong to the age group 15-59 years showing that a large percentage of the MDR-TB patients belong to an economically active population thereby indicating the need for the government's focus on this segment of the society to avoid loss of income in the future. This percentage is higher than the estimate of 75% for this age group in Pakistan by WHO (2002).

Table 3.2: Summary Statistics of the Characteristics of MDR-TB Patients

Patients' characteristics		All patients	Cured	Censored
Gender	Male	213 (57.72)	160 (75.12)	53 (24.88)
	Female	156 (42.28)	125 (80.13)	31 (19.87)
Age	≤14	3 (0.82)	3 (100)	0 (0)
	15-36	254 (68.83)	204 (80.31)	50 (19.69)
	37-59	94 (25.47)	69 (73.4)	25 (26.6)
	≥60	18 (4.88)	9 (50)	9 (50)
Education	Illiterate	110 (29.81)	85 (77.27)	25 (22.73)
	Secondary School	174 (47.15)	136 (78.16)	38 (21.84)
	Higher Education	85 (23.04)	64 (75.29)	21 (24.71)
Treatment care	Hospital Care	172 (46.61)	132 (76.74)	40 (23.26)
	Ambulatory Care	197 (53.39)	153 (77.66)	44 (22.34)

Note: The numbers in the brackets in the third column are the percentages from the total number of patients (i.e. 369), while those in the next two columns are the percentages from the number of patients in the third column in the relevant category.

The patients with higher education show a lower percentage of cure and a higher percentage of censoring in our sample. This trend shows that education alone is not sufficient to explain better chances of cure. Complementary factors i.e. good medical counseling, family and community support, and other socio-economic factors may also be vital in the determination of the final health outcome. This trend differs from Ahmad *et al*. (2012) for Pakistan where a fewer number of schooling years leads to adverse effects on the health status.

The ambulatory care shows a relatively greater percentage of cure and less censoring relative to the hospital care, though the difference is rather small. Patients find it more convenient to be

treated at home, leading to better treatment adherence even though the treatment is supervised in the hospital care and continuous and timely administration of medicines is ensured by health experts in the initial intensive phase of treatment.

The results of the backward elimination method are shown in Table 3.3. The Cox proportional hazard analysis shows that age does not have a significant association with the outcome of cure in our sample. The family income also does not show an association with cure. The health program contributed to sharing of financial burden by providing basic medicines and food baskets to MDR-TB patients who are included in our study, which might have resulted in an insignificant role of family income in the cure of patients.

The education status of patients does not have a significant relationship with the outcome of cure. A possible explanation for this result is that the medical practitioners are able to deliver substantial information to patients and their families regarding the importance of adherence to treatment and timely administration of medicines and, therefore, the level of formal education might not play much role in the treatment of MDR-TB (also see WHO, 2013).

Table 3.3: Variable Selection through Backward Elimination Process based on Z-Statistics

Variables	Z-statistics				
	Step 1	Step 2	Step 3	Step 4	Step 5
Age	0.73	Dropped	Dropped	Dropped	Dropped
Family income	-0.77	-0.84	Dropped	Dropped	Dropped
Education	-0.81	-0.86	Dropped	Dropped	Dropped
Treatment care	1.13	1.14	1.14	Dropped	Dropped
Travel expenditure	-1.75	-1.74	-1.62	-1.61	-1.72^
Gender	-1.94	-1.98	-1.97	-2.03	-2.05
Medical expenditure	4.64	4.61	4.65	4.73	4.78
Time expenditure	4.97	4.99	4.98	5.03	5.17

^The Z-Value> 1.65 but the confidence interval spans from 0.853 to 1.011 showing the non-significant association of Travel expenditure with the duration of cure and null hypothesis of no relationship of travel expenditure on time of cure cannot be ruled out.

In our model, the choice of hospitalization and ambulatory care for treatment has no significant association with the outcome of cure. This result provides support for WHO's the proposition that health care provision can be shifted towards ambulatory care. Proper provision of medicines and guidance to patients and their families can reduce the burden on hospitals and treatment can be started immediately without delays in ambulatory care at the door-steps of the patients. However, gender, medical expenditure and time expenditure are significantly associated with the health outcome of cure (see Appendix C for the descriptive statistics of the final model).

The results of the final model are shown in Table 3.4. The hazard ratio for gender (HR = 0.77, p = 0.04) shows that male patients are 23 percent less likely to be cured than female patients as shown by the negative value of the coefficient of gender dummy (-0.23). As discussed earlier, men are biologically more prone to TB and their behavioral patterns affect the incidence and outcome of the MDR-TB. Both diagnosis and death rates for men are higher than for

women. Our results differ from Ullah *et al*. (2010) findings that female patients are more at risk for MDR-TB in Punjab, Pakistan but the reason for this pattern is not provided in that study.

Table 3.4: Results of Cox proportional Hazard Model

Covariate	Parameter Estimate	HR	C. I (95%)
Gender	-0.23	0.77	0.610 to 0.990
Medical expenditure	0.09	1.09	1.055 to 1.128
Time expenditure	0.04	1.04	1.012 to 1.079

C.I shows value at 95% confidence interval and HR shows hazard ratio

The patients are 9% more likely to cure when the average monthly medical expenditure increase by one dollar (HR = 1.09, $p < 0.001$). If we reconsider the nature of the medical expenditures included in the calculation of the medical expenditure then these are expenditures on preventive measures, side effects, and hospitalization. The expenditures done to acquire the better preventive measures to control the spread of disease may have created sound environment around the patient which prevented further spread of disease and led to reduction in time of recovery. Similarly, timely management of the side effect by effective medications also increases the chance to cure. The hospitalization based upon the recommendation of medical experts also leads to improve the chance of cure hence; the average monthly medical expenditure is associated with the improvement in the time to cure in our analysis. According to the study of Balkhi *et al*. (2021) different studies have reported different results about the association of the health care spending with the health outcome. There is no specific and/or single direction of relationship that exists in literature about the relationship between medical expenditure and health outcome. Hence, our result that increase in medical expenditure is associated with an improvement in the time to cure seems to be supported by the literature. Moreover, our results

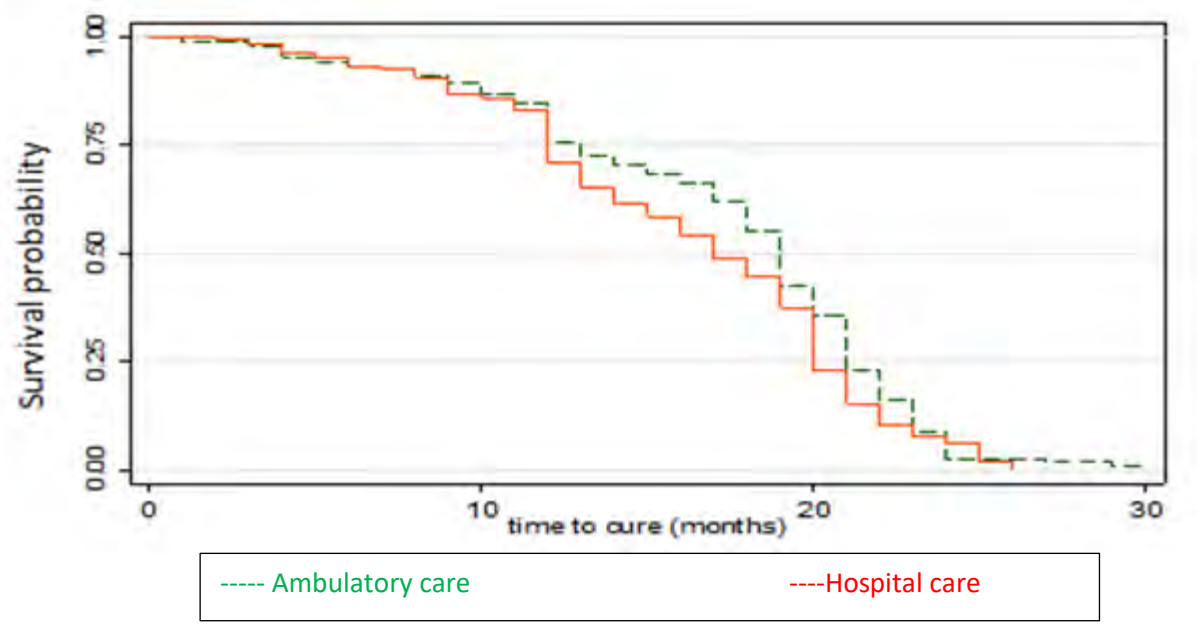
also find support from the recent publication of WHO (2022) that shows that new regimens are shortening the duration of cure really significantly for TB however, the healthcare expenditure on them is more than the previous regimens which took longer time to act.

However, when the average monthly time expenditure increases by one hour then the patients are 4% more likely to be cured (HR = 1.04, $p < 0.001$). The spatial impact captured by time expenditure shows that an increase in time expenditure leads to a better chance to experience the outcome of cure. Increased time expenditure in the present study seems to be associated with a more rapid cure. The time spent depends primarily on distance travelled to obtain care, then it implies that patients living further away gets cure faster, showing patients are less concerned about time expenditure endured during the treatment (also see Goodman *et al*., 1997 and Kelly *et al*., 2016). Hospitalization episodes are also experienced by some patients and hospitalized patients have to spend more time in treatment in the first two months which leads to better chances of cure with shorter duration of cure and if the patients are satisfied with health service provision at follow-up at district health facilities and laboratories, and transport facilities are available easily there then treatment outcome will become better. This positive relation between the distance and cure is called as distance bias in literature which is supported for Pakistan in our analysis. Similar results are reported by Buhn *et al*. (2020) and Kelly *et al*. (2016) and Goodman *et al*. (1997).

The Kaplan-Meier curve (Figure 3.1) reflects the difference in survival chances i.e. chance of non-occurrence of event cure between the categories of treatment care. The difference in survival curves between the two treatments is shown where the X-axis in the KM curve shows the time to cure in months and Y-axis is showing the survival probability. The KM is a step function where the horizontal line of each step shows the patients who have been cured or

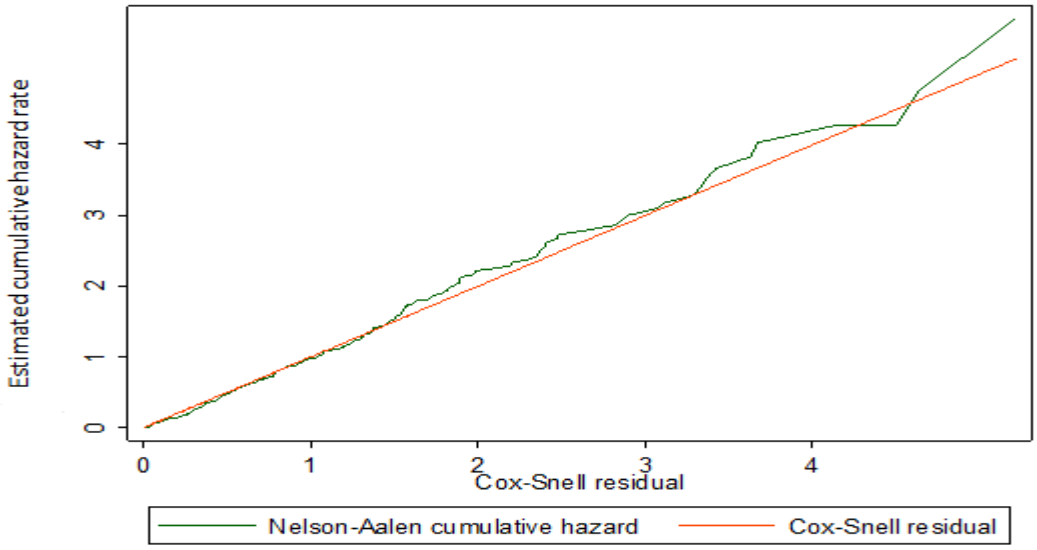
censored at a point in time. Duration of cure is less in hospital care than in the early phase of the disease; the treatment is carried out in the hospital under specific protocols. But visually there is no distinct pattern in the curves of the two treatment strategies. We have cross-checked this finding by using the log-rank test and the result shows that difference in survival curves between the two treatment care is insignificant (p = 0.12, log-rank test).

Figure 3.1: Kaplan -Meier Survival Curves for the Treatment Care



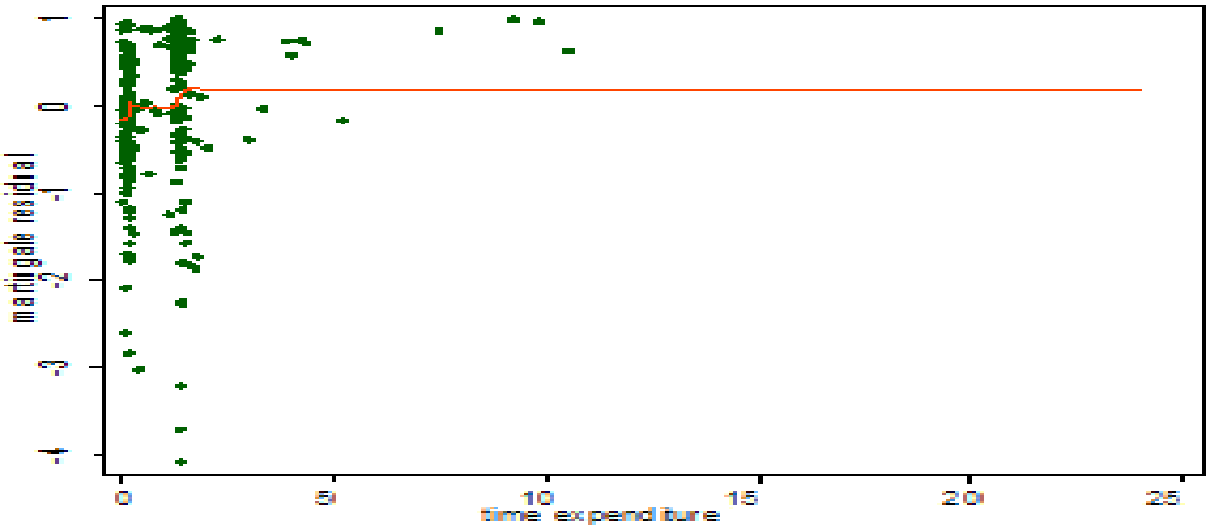
Various diagnostic tests are applied in our analysis to check the reliability of the model and results. The Cox Snell residuals (Figure 3.2) show that model has a good fit as being close to the reference line of Nelson Aelon cumulative hazard portrayed by the 45-degree line.

Figure 3.2: Cox-Snell Residuals for the Cox Proportional Hazard Model

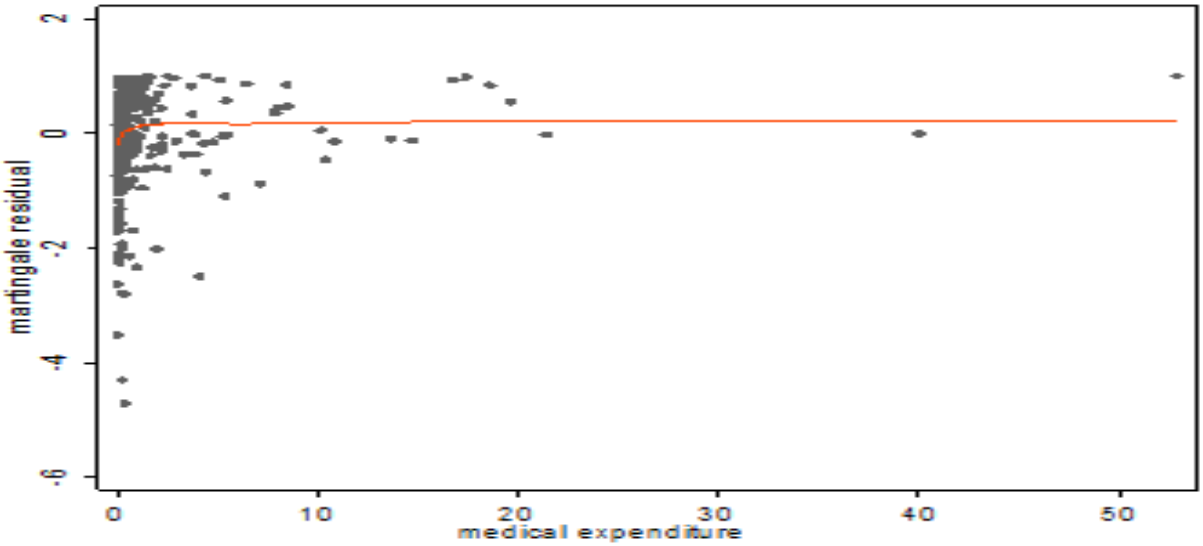


The examination of martingale residuals shows that our model passes the test for correct functional form and covariates transformation is not required (Figure 3.3). The graphs show that the distribution of all three continuous expenditure variables is random and the LOESS smooth curve (locally estimated scatterplot smoothing) is passing through zero, showing that the functional form is correct.

Figure 3.3: Martingale Residuals of the Covariates



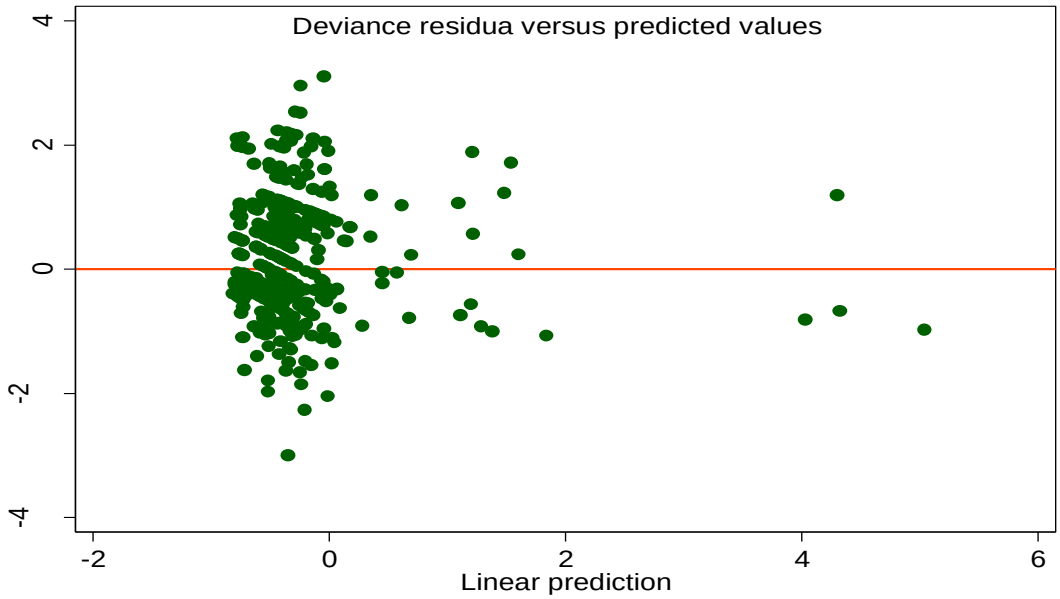
a. Martingale residuals versus Time expenditure



b. Martingale residuals versus Medical expenditure

The deviance residuals (Figure 3.4) confirm the absence of outliers in the dataset.

Figure 3.4: Deviance Residuals



The results of the test of proportionality assumption are shown in Table 3.5; we fail to reject the null hypothesis that the hazards are proportional.

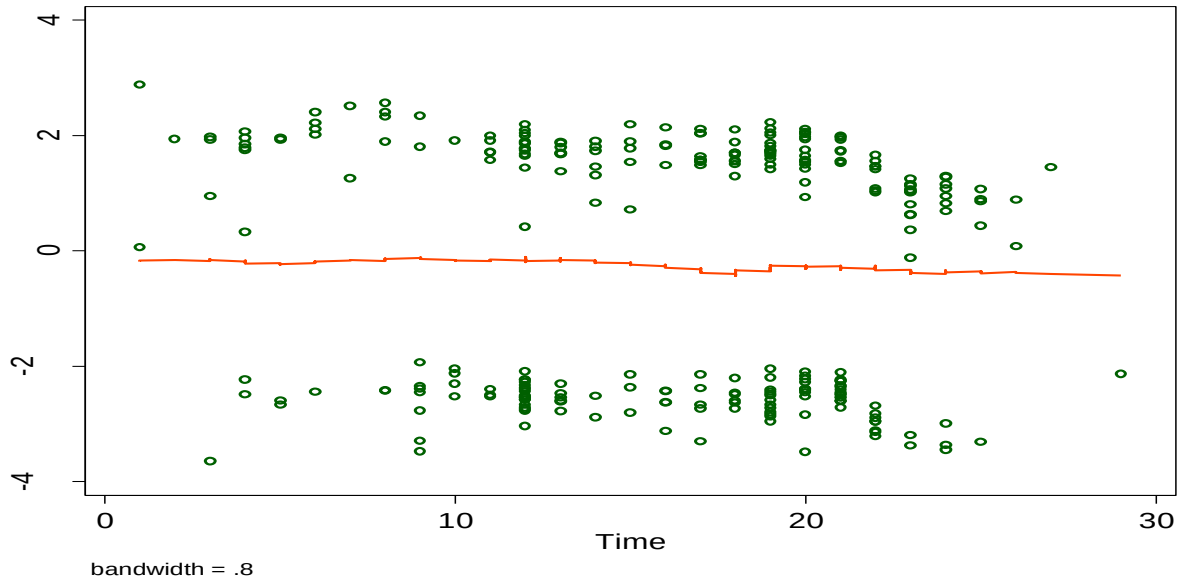
Table 3.5: Results of test of Proportionality Assumption

Covariates	**DF**	**Chi-Square statistic**	**Prob (χ^2 > observed value)**
Gender	1	1.78	0.18
Time expenditure	1	0.55	0.46
Medical expenditure	1	1.54	0.21
Global Test of proportionality			0.21

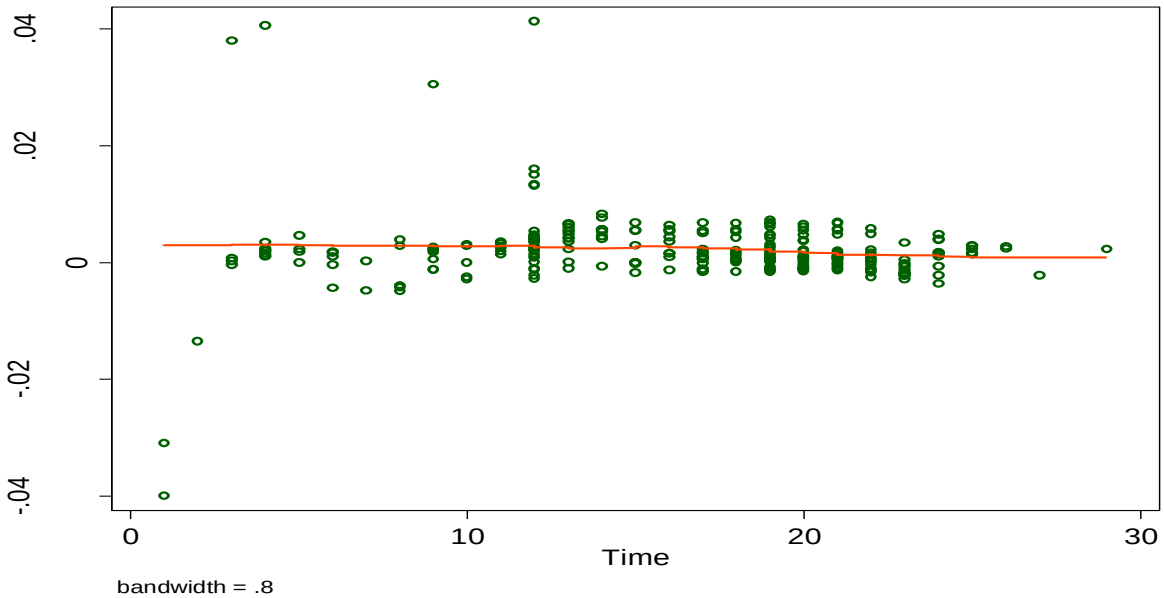
The evaluation of Scaled Schoenfeld residuals and their Loess smooth curve also indicates that the proportionality assumption holds in our model and there is no indication of the time

dependency in our model. The distribution of the residuals is random and the LOESS curve is an approximately straight line with zero slopes (Figure 3.5).

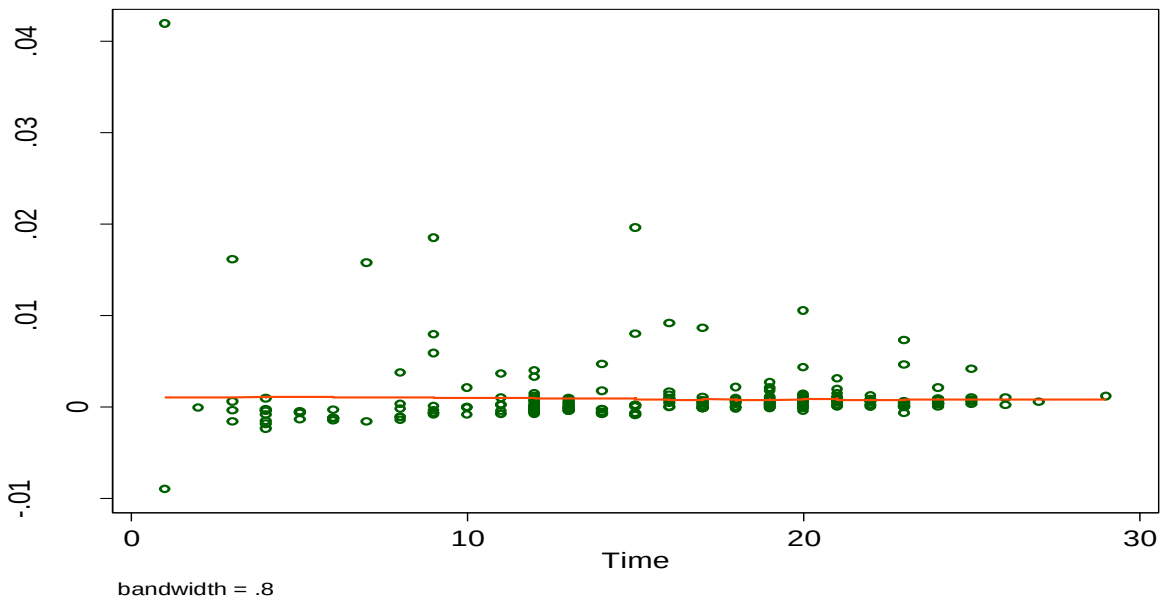
Figure 3.5: Scaled Schoenfeld Residuals and their LOESS Smooth Curve



a. Gender



b. Time expenditure



c. Medical expenditure

Our analysis shows that age, family income, education, and selection of treatment care and travel expenditure have no significant association with the outcome of cure. Gender, medical and time expenditures have a significant relationship with the outcome of cure among the patients with MDR-TB. The spatial factor of time to travel to health facilities improves the chance to experience the outcome of cure in our analysis supporting the distance bias approach (also see Buhn *et al*., 2020 and Kelly *et al*., 2016 and Goodman *et al*., 1997). The medical expenditures on preventive measures, treatment of side effects, and hospitalization improve the chance to experience the outcome of cure.

3.5. Conclusion

The study aims to identify and analyze demographic, socio-economic, spatial and health policy characteristics that are associated with the treatment outcome of cure of MDR-TB patients by using the data of the MDR-TB patients registered at the National Tuberculosis Program from

2012-2017 in Pakistan. Survival analysis is carried out by applying the multivariable Cox proportional hazard model and the study finds that age and family income do not have a significant association with the outcome of cure. Likewise, the level of education has no significant relationship with the duration of cure indicating that the health program seems efficient in the provision of sufficient information to the patients during the follow-up.

The insignificance of the policy intervention variable of hospital and ambulatory care adds to the importance of our research. Our study supports the use of ambulatory care to reduce the burden on hospitals by providing community support to MDR-TB patients as it increases the chance of cure through the timely provision of treatment. The travel expenditure is also not associated with the outcome of cure. The male gender is at more risk of not being cured whereas; time expenditure and medical expenditures have a positive association with the outcome of cure.

The important policy implication that can be drawn from this study is that health policymakers may focus on ambulatory care alongside the hospital care as it can play a substantial role in reducing the burden on hospitals and patients alongside ensuring facilities in hospitals for patients with urgent treatment needs.

Appendix C:

C1 : Description of the variables of the final model

Variables	Mean	Minimum value	Maximum value	Total
Duration of cure (in months)	14.70	9.00	24.00	
Travel expenditure (US $)	6.97	0.84	25.48	
Time expenditure (in hours)	3.94	0.68	6.97	
Gender Male Female				213^ 156^

*^total number of females and males in the sample of 369 MDR-TB patients; US $=United states dollar

Chapter 4

Relationship of Loss to Follow-up of patients with the Catastrophic Expenditure and Policy Interventions of Health Program: A Case Study of MDR-TB treatment in Pakistan

Abstract

This study analyzes the association of health policy initiatives undertaken by the National Tuberculosis Program (NTP), Ministry of health Pakistan, and catastrophic health care expenditure incurred by the patients for the treatment of Multi-Drug Resistance Tuberculosis (MDR-TB) with the loss to follow-up (LTFU) of patients. We have used the data of 358 patients who are diagnosed with MDR-TB for the first time and are registered at TB health care centers for treatment in three cities of Pakistan namely Lahore, Karachi, and Murree from 2012-2017 and we have applied logit regression technique. The results show that the selection of the hospital care is not associated with the LTFU. However, our findings suggest that the patients who face catastrophic expenditure suffer more LTFU than the patients not experiencing this expenditure. On the other hand, financial incentives provided by the health program significantly reduce LTFU. When the patients facing catastrophic expenditure are given financial incentives for more time then there is a significant reduction in LTFU. Our study suggests that both treatment care strategies can be used for the treatment of MDR-TB as both are not associated with the unfavorable treatment outcome of loss to follow-up. Ambulatory care alongside hospital care is a viable option for the treatment of MDR-TB patients in Pakistan to provide the treatment at the doorsteps of the patients. The financial incentive given by NTP improves the patient's commitment to the treatment so it should be continued and ensured as the catastrophic expenditure burden will be reduced for the patients and it will reduce the LTFU and will enhance the success rate of the health program.

Keywords: Multi-Drug Resistance Tuberculosis, National Tuberculosis Program, Hospital care, Ambulatory and hospital care, Catastrophic health care expenditure, Financial incentives

4.1. Introduction

According to Nobel Laureate Amartya Sen development is a process in which real freedoms can be enjoyed by people (Sen, 1983, 1998). The concept of development incorporates the removal of various kinds of non-freedoms that restrict individuals from exercising their reasoned agency to their full potential. It incorporates improvisation of capabilities along with the chance to live the life people have a reason to value and to be able to do things that they like 'doing'. 'Being' able to be well-nourished, without morbidities, educated, healthy, happy, mobile, and actively participating in community life, etc. are valued by individuals, and these doings and beings are called 'functionings' achieved by people which in return mean more wellbeing (Sen, 1998).

This well-being of people is often compromised if financial constraints suppress their functionings, especially in case of bad health. The incidence of disease creates emotional, physical and financial stress not only for the patients but also for the whole household. Incidence of the disease may lead to 'poverty ratchet[10]' (Chambers, 1983) or 'medical poverty trap[11]' (Whitehead *et al*., 2001) as ailment often leads to death or disability of the income earners in a household that restricts the flow of finances. This might reduce the future consumption patterns of households and investment in health and human capital, leading to the 'intergenerational poverty cycle' (see Curie *et al*., 2007 and Wu *et al*., 2019).

Sometimes lack of financial resources forces patients to be disengaged from regular follow-ups to health care units for treatment or even to discontinuation of treatment. WHO (2017)

[10] Poverty ratchet refers to the situation when assets of the household are depleted resulting from the need to sell the assets in order to make both ends meet and ultimately the lack of resources leads to further impoverishment.
[11] The trap of poverty which is created because of the ill-health and high medical expenditures as compared to the potential of bearing the direct and indirect expenses of treatment by the household.

indicates that in the case of multi-drug resistance tuberculosis (MDR-TB), loss to follow-up (LTFU) or non-adherence to treatment is a worrisome situation as a patient will not be able to recover and the disease can be transmitted to other members of the household and community as well. According to WHO (2010), the loss to follow-up is the treatment outcome of "a patient whose treatment is interrupted for 2 consecutive months or more". Almost 4 hundred thousand cases of MDR-TB are reported worldwide each year and this incidence of MDR-TB is particularly challenging for the health system and policymakers as the failure of first-line drugs have occurred and second-line drugs are not only less effective but also more expensive across the globe where resistance to treatment from at least one of the two most powerful first-line anti-TB medications, i.e., isoniazid or rifampin is observed universally (WHO, 2017).

WHO (2010) recommends that the poor and most vulnerable section of the society should be financially protected so that they can bear the burden of disease with less discomfort which will lead them to the completion of treatment. Therefore, WHO's End TB Strategy 2016-2035 (WHO, 2015) focuses on the removal of catastrophic expenditure by 2020 for households suffering from TB. This goal is yet to be achieved. Catastrophic expenditure is measured by WHO (2005) as health care expenditure exceeding 40% of the effective income whereas WHO: End TB Strategy (2015) has defined the threshold expenditure level at 20% of the household income.

Sustainable Development Goals (SDGs) also have an agenda of 'Ensuring healthy lives and promoting the well-being for all at all ages'. Hence, various steps have been taken through public health programs in various countries to facilitate their people to combat diseases. Pakistan is ranked 4th among the high disease burden countries for MDR-TB (WHO, 2020). To save MDR-TB patients from the financial catastrophe, the National Tuberculosis Program (NTP), Ministry

of Health, Pakistan has done various interventions for assisting patients between the years 2012 and 2017. One of the policy measures is the provision of financial aid or food basket to the patients. It is estimated that globally work time of three to four months per household with patients lost due to disease and treatment, which creates income loss of 20 to 30 percent for the household annually.[12] So the provision of financial aid is expected to support these households. Another step taken by NTP is the application of the WHO's (2009) recommendation that treatment can be conducted in ambulatory care effectively instead of putting the complete burden on the health care system by providing treatment in hospital care in a scarce resource setting. This might be an important initiative as *Economic Survey of Pakistan* (2019) has indicated the availability of only one hospital bed for 1608 persons in 2018. Moreover, the health expenditure is only 1.1% of the annual gross domestic product in 2018-19 (*Economic Survey of Pakistan,* 2021) so there is a need to devise efficient health policies with a limited budget.

To the best of our knowledge, the association of the above-mentioned policy initiatives undertaken by the National Tuberculosis Program of Pakistan in the context of treatment outcomes of loss to follow-up of MDR-TB patients has not been formally analyzed in Pakistan. It is important to focus on loss to follow-up as one untreated case of TB has the potential of infecting ten to fifteen people in a year (WHO, 2002), which creates further difficulties for the health system in controlling the disease. Hence, WHO (2019) has emphasized the need to identify the factors that lead to loss to follow-up. The loss to follow-up brings a lot of challenges to the health systems. Firstly, a higher loss to follow-up reduces the success rate of the program which is the total number of patients who are declared to be cured medically and the completed ones (patients whose treatment is completed but the disease could not be eradicated). Secondly,

[12] https://www.who.int/trade/distance_learning/gpgh/gpgh3/en/index6.html

MDR-TB is a communicable disease where the chance of person-to-person transmission is high; hence the treatment protocols need to be followed carefully. Moreover, WHO (2021) states that in case of loss to follow-up, the partial treatment may lead to the development of further resistant strains in the immune system of the patients, which is hard to be treated.

Hence, keeping in view the importance of factors associated with the loss to follow-up, this study analyzes the relationship of health policy interventions with the treatment outcome of loss to follow-up (LTFU) of the MDR-TB patients in Pakistan. Therefore, the first specific objective of the present study is to analyze the association of treatment outcome of loss to follow-up of the MDR-TB patients with the treatment care strategies in Pakistan. The second objective is to quantify and analyze the role of catastrophic health care expenditure endured by the patients as well as the financial incentives received by the patients from the National Tuberculosis Program in the context of treatment outcome of loss to follow-up of the MDR-TB patients. The third and the last objective is to study whether the financial incentives provided to the patients experiencing the catastrophic health care expenditure reduce the loss to follow-up of the MDR-TB patients in Pakistan.

The sample of 358 MDR-TB patients is included in this study based on the availability of the data relevant to this study for the patients who participated in the trials conducted by the National Tuberculosis Program (NTP), Ministry of Health, Pakistan. The data collection is done from the three MDR-TB centers in Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital, Lahore, and Ojha Institute of Chest Diseases, Karachi. The patients were randomly allocated to the hospitals and treatment care in the trials between the period 2012 to 2017 in order to analyze which treatment care is more beneficial in improving the outcomes of MDR-TB

for our cohort-based analysis.[13] The participation of patients in this program with the consent of patients but they were not told beforehand what treatment care they will be allocated.

The rest of the chapter is organized as follows: Section 4.2 presents a brief review of literature and Section 4.3 explains the methodological framework and data. Section 4.4 deals with the results and discussions and, finally, Section 4.5 concludes the study.

4.2. Literature Review

The literature on health economics is vast and has many dimensions. First, health is an economic 'good' like other goods that have a price due to scarcity and willingness to pay and are exchanged in markets. Second, health also has a strong grounding in welfare economics because, unlike many other consumer goods, health is considered a merit good that citizens are supposed to have access to irrespective of their ability to pay. Third, health is not a pure private good because good and bad health statuses have externalities that are not priced in free markets. Fourth, health care and health products carry information asymmetry and are subject to moral hazards, adverse selection, and associated agency problems.

The characteristics of health products as outlined above indicate that the healthcare market is generally not efficient. According to Breyer *et al*. (2012), health care provisions through the private or public sector and health insurances in the private or public sector are subject to various peculiar distortions that make this market difficult to analyze. Because of this reason, health care policies and interventions are to be analyzed carefully. In this section we will present a brief account of existing literature on health economics, keeping in view the above dimensions.

[13] The term cohort refers to a group of participants which are MDR-TB patients in our analysis.

4.2.1. Provision of Health Care through Private and Public Sectors

There is a debate in health economics about the role of the public and the private sectors. The proponents of public health care believe that if health care is heavily regulated then it yields better services as this would ensure universal health coverage either through government insurance or by subsidizing private insurance plans that will increase health equity as everyone will have equal access to health services (Basu *et al*., 2012). The proponents of private health care like Rosenthal and Newbrander (1996) and Berendes *et al*. (2011) believe that if the health sector is left to private insurance and service providers then the competition would increase in the market. It would result in lower prices and better quality of service provision by the private sector without overburdening the government's budget.

Muhuri *et al*. (1996) and CMH (2019) raise the concern that sometimes treatment protocols may not be strictly followed in the private health sector and the health care market has a chance of high price distortions and even the structure of oligopoly and cartels exist though the government tries to break these structures. Hence, the public sector enters the health care market whenever it finds deficiencies in the private sector and the two sectors become complementary to each other. Barros and Siciliani (2012) explain that quite often public and private sectors provide similar services which make them the substitutes for each other.

Health care is not free from externalities. Starc and Town (2020) explain that externalities occur where the actions of some persons affect others but there is no compensation or penalty for such actions and the effects of these actions go beyond just the buyers and sellers to the whole society. Hence the role of the government emerges to control the externalities. For example, if the person takes a vaccine then not only he/she gets protection from the disease but also the

chance of becoming the carrier of the disease reduces, creating a positive externality. But if the cost of vaccination is high or side effects are more then people may not get vaccinated, and here the government may have to intervene by subsidizing and making regulations for the better quality of vaccines. Also, medical research improves the knowledge base for the health care providers but this research is expensive. Hence, the grants given by the government can improve research and development that create positive externalities and increase the welfare of the society. A similar trend is seen in the case of the patients belonging to the bigger household size as arranging out-of-pocket health expenditure might not be possible for households, especially in case of limited income and more expenditure on subsistence-level living.

4.2.2. Catastrophic Health Care Expenditure, Treatment care and Loss to Follow-Up

WHO (2016) states that in the treatment process of diseases out-of-pocket expenditures (OOP) occur, which are categorized as direct expenditure on medical services, transportation, food, and accommodation and indirect expenditure as a result of loss of productivity, income loss, days off from work, etc. It is important to focus on OOP expenditures as the purchase of healthcare services becomes difficult if the household does not have the ability to cope with the financial burden of treatment and this can may lead to a poverty trap (also see WHO, 2000). A survey conducted by Xu *et al.* (2007) for 89 countries indicates that high OOP expenditures are making more than 150 million individuals to suffer from financial problems worldwide.

The OOP expenditure becomes more troublesome if it is a greater proportion of total household income termed as ‘catastrophic health care expenditure’ (CHE). Berki (1986), Xu *et al*. (2003), and Ekman (2007) explain that a method to measure the CHE is ‘capacity to pay’ for primary or any advanced health care service opted for by the household. According to this method, CHE is the amount of OOP expenditure that exceeds the potential threshold to pay and

makes the affected households reduce their necessities over time and can be proxied by consumption expenditure (Garvy, 1948). According to Weinstein *et al.* (2013), another method to measure the CHE is the loss of potential working hours and income loss per hour due to disease or treatment. Initially, WHO (2005) states that the health care expenditure is called catastrophic if it exceeds 40% of the effective income of the household. Then in another study by WHO (2015), this threshold is set at 20% of household income. Hailemichael *et al*. (2019) and Kockaya *et al*. (2021) state that different studies in the literature have opted for thresholds ranging from 5 to 20% of household income.

Paluzzi (2004) states that tuberculosis is one such disease that causes serious financial constraints not only for the household but also for the country. The OOP expenditures that MDR-TB patients have to bear for a long time lead to a reduction in the standard of living and welfare of a country (Berki, 1986, Xu *et al*., 2007, Doorslaer *et al*. 2007 and Wagstaff, 2007). Therefore, the provision of healthcare services to MDR-TB patients becomes a matter of concern to the policymakers when the households lack the ability to cope with the financial burden of treatment (WHO, 2000).

Another area of interest related to disease burden is the selection of the treatment care. WHO (2009) states that the treatment care is called ambulatory care when treatment of patients is conducted in the community with the support of family members or health workers which may include hospitalization for two weeks at the beginning of the treatment. On the other hand, hospitalization care refers to the treatment in hospital for initial two months and then in the community for the remaining duration of disease. Different studies like Toczek (2013) and Ho *et al*. (2017) suggest that community care reduces the loss to follow-up as the barriers like transport costs can be avoided which can be helpful in reducing the CHE as targeted by WHO (2015) and

the social institution like family and community can play an important role in the treatment support to eradicate the disease.

According to Wagstaff and Doorslaer (2003), Sesma *et al*. (2004), Kimani *et al*. (2016), and Sapkota *et al.* (2020) the expensive treatment and catastrophic health expenditure can lead the household to fall into the intergenerational cycle of impoverishment where the generations suffer from the poverty due to lack of resources even in the case of basic primary health care service utilization. The loss to follow-up increases when people do not have the ability to pay for the medical expense which is alarming in the case of MDR-TB as WHO (2017) states that one untreated patient has the potential of infecting 10-15 other individuals in a year. Different studies like Farmer *et al.* (1991), Munro *et al.* (2007), Waitt and Squire (2011), Howse *et al*. (2020) and Arif *et al.* (2021) have stressed the need for effective treatment strategies and policy initiatives, and financial incentives by the government to prevent the spread of disease.

4.2.3. Empirical Analysis

Each year a higher proportion of the patients are missed out on the treatment of TB which increases the total burden of the disease in Pakistan as reported by different studies; for example, 41.2% in Karachi (Rao *et al*., 2009), 18.3% in Multan (Javaid *et al*., 2017) and 7.5% in Baluchistan province (Khan *et al*., 2019). Ali *et al*. (2018) state that the loss to follow-up could be reduced through counseling of patients and family members but some studies like Khan *et al*. (2009) do not find a significant impact of counseling on the loss to follow-up of MDR-TB patients in Pakistan. Soomro *et al*. (2015), Ali *et al*. (2018) and Razzaq *et al.* (2020) find that on average, the loss to follow-up is higher among male patients than female patients because of the higher financial responsibilities of men. On the other hand, delays in the diagnosis of TB for

females are reported in Baluchistan and Khyber Pukhtoonkhwa where the males usually take the decisions for the females, and treatment of females is preferred at home in some instances.

Although, the public sector provides free medication for TB, which has improved the MDR-TB treatment outcomes in Pakistan but Rao *et al.* (2009), Javaid *et al*. (2017) and Kanwal and Akhter (2020) mention that over-the-counter provision of TB drugs is an issue that leads to self-medication by the patients in Pakistan, which can create further drug resistance if the medicine is not administered appropriately. The behavioral patterns of patients might play an important role in determining the outcomes. As soon as patients start to feel better, they just stop the follow-up. Similar trends are observed in the study of Khan *et al.* (2000) for Pakistan. If the recovery is not quick or the condition becomes the worst then patients discontinue the treatment. Sometimes the patients believe that they do not have TB and are just concerned about the remedy to the bad health symptoms that they are facing which increase the LTFU. If the health program is able to make the required arrangements to provide medical literacy to the patients then LTFU can be reduced.

Lomtadze *et al*. (2009) and Codlin *et al. (*2011) state that stigma is attached to TB disease which makes the situation worst not only in Pakistan but also in the neighboring countries. Regarding the loss to follow-up, similar trends are seen in the neighboring countries of China and India where the percentage rate of loss to follow-up among the TB patients is around 30-60%. Zhou *et al.* (2016), Parassana *et al.* (2018) and Arif *et al.* (2021) suggest government interventions to reduce loss to follow-up and improve the treatment outcome of TB.

The above discussion shows that there is a need to undertake appropriate policy initiatives to reduce the spread of TB in Pakistan. The health education related to the importance of treatment and curability of TB may be given to the patients by the trained medical worker to boost the

confidence of the patients and family workers. Likewise, financial incentives for the patients and the service providers may reduce loss to follow-up. In particular, social and financial interventions by the government may ease the disease burden of the patients and may improve the treatment outcome of MDR-TB patients in Pakistan.

4.3 Methodology

We will discuss the model, data collection, variable construction, estimation technique, and model diagnosis in this section.

4.3.1. Model

The health outcome of treatment is related to a multi-dimensional spectrum of medical and non-medical factors. The socio-demographic traits of the individuals like gender, education, and household size influence the health status. The level of affordability of the patients and households to manage various direct and indirect expenditures related to the treatment is an important factor that can determine the health outcome hence the poverty level is taken in our model. Sometimes the level of the health care expenditure is high as compared to the annual income of a household called as catastrophic health care expenditure and a high proportion of expenditure out of the total income of the household may act as a disincentive to continue the treatment and this relationship needs to be explored in detail.

The initiative of financial support given to the patients by the health program is expected to improve the commitment to treatment and a reduction in the loss to follow-up. Moreover, the patients facing catastrophic expenditure are expected to adhere to treatment if they get financial support from the health program. Along with the financial support, another policy initiative taken by the health program is the selection of the treatment care for the MDR-TB patients which are hospital and ambulatory care and it has to be analyzed how the treatment care strategies are

related to the health outcome of loss to follow-up. Hence our study plans to investigate the association between catastrophic expenditure and policy interventions of health program with the loss to follow-up of MDR-TB patients in Pakistan. Based on the discussion above, we can write the functional relationship of the outcome of loss to follow-up with various factors as follows.

$$Outcome\ of\ loss\ to\ follow-up_{i} = f(Age_i,\ Gender_i,\ Edu_i,\ HHS_i,\ Pov_i,\ CHE_i,\ FI_i,\ CHE_i * FI_{i,}\ TC_i) \quad 4.1$$

The dependent variable is a binary variable referred of loss to follow-up (LTFU) among the MDR-TB patients in Pakistan, taken as 1 when the patient experienced a loss to follow-up and 0 for any other health outcome experienced by the patient. The variables of patient's age, education (Edu), household size (HHS), and poverty (Pov) are included in the model as the control variables that help to uncover the true relationship among the variables in the model. According to Cantiello *et al*. (2015), the personal traits of individuals can be a deciding factor in adherence to treatment so we have included the above-mentioned control variables which are the demographic traits of individuals that may be associated with the decision-making process of treatment adherence.

The control variable of age of the patient is taken in the number of years. Gender is a binary variable with the value of 1 for male patients and 0 for female patients. Education (Edu) is defined as 1 for the literate patients and 0 otherwise, household size is the total number of individuals in a household, and poverty (Pov) is another binary variable with the value of 1 for the poor income group and 0 otherwise. The annual family income is converted into family income per month which is then divided by the household size (HHS). The self-reported annual household income is cross-checked with all the monthly follow-up surveys conducted at the

health facility to ensure there is no error in the reported income. The study has taken poor and non-poor groups according to the poverty line of 3294 PKR per capita per month (US$31.6) defined in the Household Integrated Economic Survey of Pakistan (2015). The variable of catastrophic expenditure (CHE) is constructed by summing the direct and indirect monthly expenditure on the treatment of MDR-TB. Then total expenditure is measured as a percentage of the total income of the household and the variable is defined as 1 when the health care expenditure exceeds or is equal to 20% of the household's income and 0 if the expenditure is less than 20%. The purpose of incorporating this variable is to analyze how the catastrophic health care expenditure is related to the loss to follow-up. The interactive terms enhance the understanding about the association about the variables in the model and helps to test more specific hypothesis.

The next variable is financial incentives (FI). National Tuberculosis Program of Pakistan has tried to provide a financial incentive to patients at the time of visit to the health facility on monthly basis equivalent to the amount of US$27 to ease out the financial burden on patients that may also increase their commitment to treatment by sharing the financial burden. However, financial incentives could not be provided to all the patients for 100 percent of the visits because of the financial constraints that occurred during the course of treatment. The variable of financial incentives is set equal to one if the patient has received financial incentives from National Tuberculosis Program for more than 80% of the follow-up visits to the MDR-TB health facility and zero otherwise. We have also taken an interactive term of catastrophic expenditure and financial incentives (CHE*FI) as a binary variable to study if the financial incentives provided to the patients experiencing the catastrophic health care expenditure reduce the loss to follow-up of

the MDR-TB patients in Pakistan and the variable is set equal to 1 for the patients experiencing catastrophic expenditure but are provided with the financial incentives and zero otherwise.

The variable of treatment care is denoted as hospital care (HC) is a binary variable where the hospital care is taken as 1 and the ambulatory care as zero. This variable is taken to see how the hospital care is associated with the loss to follow-up as compared to the ambulatory care.

Since the dependent variable is binary, hence we would specify the theoretical model 4.1 as the logit model using as shown in Equation 4.2.

$$Outcome\ of\ loss\ to\ follow\text{-}up_i = \beta_0 + \beta_1 Age_i + \beta_2 Edu_i + \beta_3 HHS_i + \beta_4 Pov_i + \beta_5 CHE_i + \beta_6 FI_i + \beta_7 CHE_i * FI_i + \beta_8 HC_i + \mu_i \quad 4.2$$

Equation 4.2 is estimated and reduced by using the stepwise backward elimination method for variable selection which involves dropping variables with Z-Value $\leq$ 1.65 until all the remaining variables are significant in our final model. This procedure is adopted to focus on the variables that have a significant association with the response variable in our model.

We apply the Wald test to explore the significance level of variables in the model and the log-likelihood ratio test (LR) to explore the joint significance of variables. Then in order to check the goodness of fit, Pearson chi-square goodness of fit test (Pearson, 1900) is applied with the null hypothesis that the model has a good fit.

4.3.2 Data

Initially, we have collected the data of 438 newly diagnosed patients who are diagnosed with MDR-TB for the first time and are registered for MDR-TB treatment between 2012 and 2017 at three sites in Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital,

Lahore, and Ojha Institute of Chest Diseases, Karachi. The inclusion criterion for the sample for this study comprises of including patients who are newly diagnosed with MDR-TB at age 12 and above. The exclusion criterion involves an incomplete stream of information provided by the patients for a major part of the study period and the patients who have died during the treatment of MDR-TB are not included in our sample because treatment procedures cannot be continued in this case.

Based on the availability of relevant information, 358 patients are included in the final sample**.** Out of the sample of 358 patients, 291 (81.28%) are cured showing a reasonable percentage of the people who have been cured. The treatment failed for the patients also where the culture test remains positive for 5 months or more. Some patients are still under treatment and health outcomes are not declared for a few patients by the health programs by the end of the trial. The loss to follow-up (LTFU) occurred for 42 patients that showing 11.73% of the patients are not adhering to the treatment which is a worrisome situation as one untreated case of TB has the potential of infecting ten to fifteen people in a year (WHO, 2002) which is challenging for the health system. Moreover, a high percentage of loss to follow-up also reduces the success rate of the health program and makes the target of Sustainable Development Goals (SDG) of TB-free environment difficult to achieve.

Table 4.1: Treatment Outcome of MDR-TB Patients

Outcomes	Cured	Failed	Loss to follow up	Still under treatment	Not evaluated	Total
No. of patients	291	11	42	6	8	358
Percentage	81.28	3.07	11.74	1.68	2.23	100

4.4. Results and Discussion

The descriptive statistics of the characteristics of MDR-TB patients are given in Table 4.2. Males are more than females in our sample and have experienced more LTFU. Males are more likely to be tested and diagnosed for disease than females[14] as more social preference is given to males' health. Males are also more prone to the advent of disease because of biological factors and more social interactions along with smoking and drinking habits which may aggravate the disease. Moreover, because more burden of financial responsibilities and income losses from work day's loss especially in case of distant traveling for treatment, the loss of follow-up for males can increase (also see WHO, 2020). The patients aged 40 and above (Age ≥40) showed less adherence as the immunity is compromised with age (also see WHO, 2018).

[14] https://www.who.int/trade/distance_learning/gpgh/gpgh3/en/

Table 4.2: Summary Statistics of the Characteristics of MDR-TB Patients

Variables		All patients	Percentage	Loss to follow up	Percentage
Age	<40	297	82.96	27	9.09
	≥40	61	17.04	15	24.59
Gender	Male	211	58.94	32	15.17
	Female	147	41.06	10	6.8
Education	Literate	251	70.11	30	11.95
	Illiterate	107	29.89	12	11.21
Household size	<5	78	21.79	8	10.25
	≥5	280	78.21	34	12.14
Poverty	Poor	297	83	30	10.1
	Non-poor	61	17	12	19.67
Marital status	Married	223	62.29	27	12.11
	Unmarried	135	37.71	15	11.11
Occupation	Business, agriculture Labor& service	79	22.06	12	15.19
	Student, housewife & not working	279	77.94	30	10.75
Catastrophic expenditure	<20%	218	60.89	11	5.05
	≥20%	140	39.11	31	22.14
Financial Incentives	<80%	75	20.95	30	40
	≥80%	283	79.05	12	4.24
Treatment care	Hospital	184	51.4	32	17.39
	Ambulatory	174	48.6	10	5.75

Note: The fourth column shows the percentages from the respective values of all patients column and the total patients (i.e. 358) and the sixth column shows the percentages of loss to follow-up obtained as the ratio of loss to follow-up values from the fifth column and respective all patients column value multiplied by 100.

The literate and illiterate patients have shown almost the same proportion of the LTFU. This shows that literacy alone is not a deciding factor in the level of treatment adherence as shown in Table 4.2. There are more chances of LTFU for patients belonging to the bigger household size as arranging out-of-pocket health expenditure might not be possible for the households, especially in the case of limited income and more expenditure on subsistence-level living. Higher proportions of the patients are poor and have shown a better adherence to the treatment. It shows that medical literacy along with the financial support by NTP may have created the commitment to treatment. The loss to follow-up is almost the same among the married individuals as the unmarried ones and same proportion of each group have LTFU. Patients who belong to the

business, agriculture, labor, and service categories show a higher LTFU which may be because of the work-related commitment. The patients who have to bear a high financial burden of treatment in terms of catastrophic expenditure show a higher percentage of LTFU i.e. 22.14%. The patients who have received more incentives during the treatment period showed more adherence to treatment and lesser LTFU than another group as shown in Table 4.2. The patients in the hospital care have shown more loss to follow-up than ambulatory care indicating a better chance of adherence in the ambulatory care.

Table 4.3 shows the results of the step-wise backward elimination process[15] where the poverty level does not have a significant relationship with the loss to follow-up. This may have happened because of the sharing of the financial burden of the patients by NTP resulting in more commitment to treatment by the poor and non-poor segment of the patients but the association is insignificant. The association of the household size with the loss to follow-up is insignificant but positive. A greater household size leads to more loss to follow-up as the disease increases the financial constraint and the management of out-of-pocket expenditure becomes problematic for the households with more number of individuals when the needs of everyone have to be catered but the relationship is not significant.

[15] Full names of the variables are shown in the tables with regression results.

Table 4.3: Variable Selection through Backward Elimination Process

Variables	Z statistics					
	Step 1	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**
Poverty	-0.31	Dropped	Dropped	Dropped	Dropped	Dropped
Household size	0.39	0.35	Dropped	Dropped	Dropped	Dropped
Education	0.41	0.41	0.4	Dropped	Dropped	Dropped
Gender	0.92	0.91	0.92	0.98	Dropped	Dropped
Hospital care	1.22	1.24	1.21	1.2	1.24	Dropped
Age	2.95	2.95	2.94	2.92	3.03	3.07
Catastrophic expenditure	3.07	3.07	3.06	3.06	3.07	3.21
Financial Incentives	-2.35	-2.35	-2.39	-2.38	-2.4	-2.4
Catastrophic expenditure*Financial Incentives	-3.15	-3.16	-3.15	-3.21	-3.24	-3.35

Education has an insignificant association with the loss to follow-up showing education does not play a role in the adherence to the treatment and awareness about the disease and medical literacy may be more important in determining the commitment towards the medication and treatment protocols. Gender also has an insignificant relationship with the loss to follow-up.

The hospital care has an insignificant association with the loss to follow-up which is an important finding showing that both hospital and ambulatory care can be used for the treatment of MDR-TB in Pakistan as they are not associated with the unfavourable treatment outcome of loss to follow-up. Alongside the hospital care, ambulatory care can be used as it reduces the pressure on the hospitals and hence can be used to provide treatment in the home environment of the patients. This result supports WHO's the proposition that ambulatory care can be used for the

provision of the treatment which can reduce the burden on patients and hospital and the treatment will be available at the doorsteps of the patients. The variable of age, catastrophic expenditure, incentive, and interactive term of catastrophic expenditure and incentive have a significant association with loss to follow-up significant hence will be used in our final model.

The results of our final model are shown in Table 4.4 where the coefficient reported are the marginal effects of age, catastrophic expenditure, incentive, and interactive term of catastrophic expenditure and financial incentives. Age has a significant association with the loss to follow-up showing that as the age increases then there is a greater chance that the loss to follow-up will occur as the ability to have rapid follow-up visits and more independence in the movement declines with age. The recovery speed from the disease is also slow due to a weak immune system that sometimes demotivates the patients to continue the treatment (also see WHO, 2018).

Table 4.4: Results of Logistic Regression Analysis with Loss of Follow-up as a Dependent Variable (The Coefficients reported are Marginal Effects)

Variables	Coefficient	S.E	Wald test
Age	0.004**	0.001	0.0027
Catastrophic expenditure	0.265*	0.08	0.0001
Financial Incentives	-0.184***	0.07	0.0037
Catastrophic expenditure*Incentive	-0.17*	0.05	0.0022
Pseudo R^2	0.24		
Number of observations	358		
F-statistics (p-value)	p<0.0001		
LR Test(p-value)	p<0.0001		
Pearson chi-square goodness of fit (p-value)	p=0.46		

S.E=Standard error, *=1% level of significance, **=5% level of significance, ***=10% level of significance, Catastrophic expenditure*Financial Incentives is the interactive term of the two variables.

The MDR-TB patients having the catastrophic expenditure (health care expenditure exceeds or equal to 20% of the household's income) and not getting the financial incentives will have a

26.5% higher chance of experiencing the loss to follow-up as compared to the patients not experiencing the catastrophic expenditure. The extra out-of-pocket expenditure puts a financial burden on the patients and household in the treatment of MDR-TB and if they are not able to sustain the financial pressure of health care expenditure then the loss to follow-up can occur. The high proportion of expenditure leads to less timely diagnosis and delays in treatment. Out of 140 patients who faced catastrophic expenditure, 31 patients (22.14%) faced loss to follow-up in our study (as shown in Table 4.3) which means that spending a greater share of household income on treatment is a big challenge in Pakistan because of which either they have to curtail their other expenses or have to make a hard decision of not completing the treatment.

The MDR-TB patients who receive the financial incentives for 80% or more follow-up visits but do not have the catastrophic expenditure will have a lower chance of 18.4% to experience the loss to follow-up as compared to the patients who receive the incentives for less than 80% of the follow-up visits. The financial incentives encourage the patients and their families to follow the treatment and complete it by cushioning the pressure of management of finances that reducing the chance of loss to follow-up. This is an important finding from the National Tuberculosis Program perspective also as a reduction of loss to follow-up will increase the success rate of the health program. Incentives given by programs such as financial aid for food and transport reduce the loss of follow-up and increase the commitment to treatment but if the process of financial assistance is weak and lengthy then it loses its influence on the treatment commitment for MDR-TB patients.

When the patients who are struggling with the catastrophic health care expenditure are provided with the financial incentives for more than 80% of the follow-up visits to health care centers then they show a better level of adherence to MDR-TB treatment and the chance of loss

to follow-up reduces significantly for them as compared to patients not receiving the financial incentives[16]. This result proves to be very important concerning the policy implication that if patients suffering from extra out-of-pocket expenditures are financially supported by the health program then they can be engaged in treatment in a better manner. In this way, the success rate of the program can be increased and the chances of development of further drug resistance due to loss to follow-up can be resolved. The effort of the health program to save patients from the medical poverty trap leads to better health outcomes as the patients suffering from high expenditure related to treatment with lesser resources at their disposal are cushioned from the negative consequences of financial burden. This finding is also important in determining the role and commitment of health program in making the outcomes better.

The Wald test and log-likelihood test statistics show that variables taken in the model are significant. The Pearson chi-square test statistics show that the null hypothesis is accepted and the model has a good fit.

Overall, our results show that loss to follow-up is not associated with the treatment strategies of hospital care and ambulatory care. The financial incentives help the patients to complete their treatment with ease which reduces the loss to follow-up. The financial incentives will reduce the pressure of the catastrophic health care expenditure that leads to a reduction in the loss to follow-up. The results show that the National Tuberculosis Program of Pakistan is taking substantial steps in making the outcomes better by taking sound policy initiatives. If these initiatives had not

[16] Holding age constant, the three coefficients of catastrophic expenditure, financial incentives and catastrophic expenditure*Incentive are added and the value obtained is 0.265-0.184-0.17=-0.089 which shows that the patients experiencing the catastrophic expenditure provided with financial incentives will have a lower chance of experiencing the loss to follow-up by 8.9% which is between the value of catastrophic expenditure (26.5%) and financial incentives (18.4%).

been taken then there was a greater possibility that loss of follow-up would have been higher for MDR-TB patients in Pakistan.

4.5. Conclusion

The purpose of this study is to analyze the association between catastrophic health care expenditure endured by the patients and financial incentives received by the MDR-TB patients from the National Tuberculosis Program of Pakistan with the loss to follow-up. We have also studied whether the financial incentives provided to the patients experiencing the catastrophic health care expenditure reduce the loss to follow-up or not. Moreover, we have analyzed the association of hospital care of treatment with the loss to follow-up among the MDR-TB patients in Pakistan.

The logistic regression technique is applied in the study and the results suggest that the selection of a hospital care is not associated with the loss to follow-up hence both treatment care strategies can be used for the treatment of MDR-TB. This finding leads us to support WHO's proposition that ambulatory care is a viable option for the treatment of MDR-TB patients in Pakistan. The patients who face catastrophic expenditure suffer more loss to follow up and the incentives provided by the health program significantly reduced the loss to follow-up. Another important result obtained is that when the patients facing catastrophic costs are given incentives for more follow-up visits then there is a significant reduction in the loss of follow-up.

Our study has some very important findings based on which substantial policy implications can be withdrawn. Alongside hospital care, the ambulatory care may also be used as a viable treatment strategy in Pakistan. The treatment can be started immediately with the support of family and health workers without delays for the hospital beds. The provision of the treatment at

the doorsteps of the patients will ease out the burden on hospitals and households. However, patients who are in critical health with an immediate need for hospitalization can be given due attention.

The policy initiatives of financial incentives may be continued ensuring that incentives are given on every visit as a compulsory practice. Otherwise, all other expenditure that has been incurred by the program and patients during treatment may go in vain. The catastrophic health care expenditure burden needs to be reduced for the patients otherwise the treatment outcome will not be promising. The financial incentives can act as an important factor that can reduce the adverse effect of catastrophic health care expenditure. This will reduce the loss to follow-up and the success rate of the health program will also increase.

Chapter 5

Conclusion

The good health of individuals is an important construct towards the path of development and prosperity. A healthy labor force is expected to be more productive which increases the total output of the nation. But the availability, accessibility, and affordability of health care have become a major challenge over time because of the scarcity of resources at the disposal of the governments. Hence, it is important to devise such treatment strategies which reduce the burden on the hospitals and make health care more accessible and affordable without compromising the quality of health care.

5.1. Summary

Pakistan has a high burden of multi-drug resistance tuberculosis (MDR-TB) and is ranked 4th in the high disease burden of MDR-TB in the world where 15,000 people are affected each year (WHO, 2020). In addition, one untreated patient with TB has the potential to infect ten to fifteen people in a year (WHO, 2002). According to WHO (2019), the partial or incomplete treatment creates resistant strains in the body of the TB patients which are difficult to be treated hence the treatment protocols should be followed carefully. The timely treatment is important for the eradication of diseases and to control person-to-person disease transmission. Therefore, it is important to devise cost-effective strategies for the treatment of MDR-TB that provide good health outcomes at an affordable cost.

The health outcomes of MDR-TB are affected not only by medical factors like the medicines and lab tests, etc. but also by the non-medical factors like the loss of income owing to treatment and time expenditure during the treatment, etc. Different socio-economic and spatial factors may

also play role in determining the health outcome hence it is important to focus on the multi-dimensionality of the factors associated with the treatment outcomes of MDR-TB. Yet another issue is the increasing burden on the hospital as services have to be provided in multiple health domains under scarce resource availability making the timely provision of the treatment difficult. Hence, the ambulatory care is recommended for the treatment of MDR-TB (WHO, 2009). Ambulatory care is one such regime where the MDR-TB patients can be treated in the community and treatment can be started immediately at the door-steps of the patients and timely provision of the medication will reduce the spread of disease in the community. It will also reduce the pressure on the hospitals as the availability of the hospital bed is sometimes difficult in hospitals.

The National Tuberculosis Program (NTP) of Pakistan has taken different measures to control MDR-TB in Pakistan like the provision of the treatment of MDR-TB in ambulatory care alongside the hospital care and financial incentives to the patients of MDR-TB. The viability of these policy initiatives has not been studied by far in literature and the association of the socio-economic and spatial factors with the treatment outcomes of MDR-TB needs to be explored further.

5.2. Conclusion

Hence, the first objective of our study deals with the cost-effectiveness of two health care treatments i.e., hospital versus ambulatory care for the treatment of MDR-TB in Pakistan. While the second objective is to analyze the association of socio-economic and spatial characteristics and treatment regimens with the treatment outcome of cure of MDR-TB patients in Pakistan. The third objective is to investigate the association of the catastrophic expenditure and policy

interventions of NTP i.e., selection of treatment care and financial incentives on the treatment outcome of loss to follow-up and non-adherence to the treatment of MDR-TB patients.

To address the objectives of our study, we have collected the data of 438 patients from three main MDR-TB centers in Pakistan namely TB Samli Sanatorium Hospital, Muree, Gulab Devi Hospital, Lahore, and Ojha Institute of Chest Diseases, Karachi from 2012 to 2017.

Through this study, we have analyzed if there is a difference in the cost-effectiveness of ambulatory and hospital care for the treatment of multi-drug resistance tuberculosis (MDR-TB) and which one is more effective by applying the cost-effectiveness analysis. For the cost-effectiveness analysis, we have calculated the cost per DALYs averted and the incremental cost-effectiveness ratio (ICER) of the treatment care of the hospital and ambulatory care. The cost is taken in the monetary units and effectiveness is taken in the health units of disability-adjusted life years (DALYs) which is a combined measure of mortality and morbidity and the reduction in the DALYs is the measure of effectiveness (Zweifel *et al*., 2009). The treatment strategy is cost-effective if the cost per DALYs or ICER value is less than GDP per capita per year as the cost of saving a life year is less than per capita income per year. Moreover, ICER less than three times GDP per capita is also accepted as cost-effective (Marseille *et al*., 2015). We have tested the robustness of our results by using the sensitivity analysis and cost-effectiveness planes as discussed in Chapter 2. The results of cost-effectiveness analysis indicate that both ambulatory and hospital care have played important role in the reduction of disease burden for the patients but no treatment care showed continuous dominance in our cost-effectiveness analysis. Our findings suggest that both strategies can be accepted simultaneously as appropriate strategies for the treatment of MDR-TB in Pakistan.

The analysis of the factors associated with the outcome of cure is carried out by applying the Cox proportional hazard model. The socio-economic factors, medical expenditure, and spatial factors of time and travel expenditure along with the treatment strategies are studied in association with the treatment outcome of cure. Our findings suggest that ambulatory and hospital care do not show a significant relationship with the outcome of cure. The medical expenditure on preventive measures, treatment of side effects, and hospitalization have a positive association with the outcome of cure. The spatial factor of time expenditure is significantly associated with the outcome of cure whereas travel expenditure does not show an association with the outcome of cure. The use of ambulatory care can reduce the travel expenses for the patients and households. The time expenditure shows a positive association with the outcome of cure showing that if people are getting a good quality of health care then they are less concerned about the time spent on traveling.

We have also analyzed the association of the socio-economic factors, catastrophic expenditure, and policy interventions undertaken by the National Tuberculosis Program (NTP) of Pakistan i.e. selection of treatment care and financial incentives, on the loss to follow-up of treatment of MDR-TB patients by using the logistic regression analysis. When the loss to follow-up (LTFU) is focused in our study then treatment care strategies do not show a significant association with the LTFU indicating the viability of the ambulatory care alongside the hospital care for the treatment of MDR-TB in Pakistan. The catastrophic health care expenditure increases the chance of LTFU as it creates extra financial pressure during the treatment process but the financial incentives that are given by the health program increase the commitment to continue the treatment. When the patients struggling with the catastrophic expenditure are given

financial incentives for more follow-visits then the LTFU is reduced showing that the initiative taken by the health program is fruitful.

Our study finds that treatment care strategies do not show a significant association with the treatment outcomes of cure as well as loss to follow up indicating the viability of the ambulatory care alongside the hospital care for the treatment of MDR-TB in Pakistan. This result is important as it indicates that ambulatory care can be used for the treatment and our study supports WHO recommendation that health systems should focus on the ambulatory care for the treatment of multi-drug resistance tuberculosis as it will reduce the long waiting list in hospitals and the treatment can be made available in the community. The duration of disability is less in the hospital care as compared to ambulatory care as the initial phase of treatment is completed in the hospital under the supervision of qualified experts but the cure rates also came out to be less in the hospital care than in ambulatory care showing support for the ambulatory care with more cure rates. In the case of hospital care, the availability of beds is one major concern and MDR-TB can spread through person-to-person contact so immediate diagnosis and effective treatment are required. Hence, in order to ensure that patients and the community do not suffer because of resource constraints, an alternate treatment i.e. ambulatory care should be adopted alongside the hospital care that will ensure the treatment at the doorsteps of the patients.

5.2. Policy Implications

The evidence-based interventionist policies adopted by the health program are considered to be important to outline the plans to eradicate the disease. Our study provides some important policy implications in this regard. The cost-effectiveness analysis of the alternate treatment strategies for the treatment of MDR-TB provides empirical evidence to the health policymakers

about the usefulness of ambulatory care in Pakistan alongside hospital care. The ambulatory care can reduce the burden of MDR-TB in Pakistan by reducing the number of deaths and increasing the cure rates as compared to the hospital care. The provision of the treatment at the doorsteps of the patients will ease out the burden on hospitals and households. However, patients who are in critical health with the immediate need of hospitalization can be given due attention in the hospitals. Hence the health policymakers may focus on the ambulatory care alongside the hospital care to improve the treatment outcomes. (The implication also finds support from the study of Fitzpatrick and Floyd (2012) and John *et al*., (2018))

The policy initiative of provision of financial incentives to the patients may be ensured with more commitment by the policy makers. The promised financial incentives should be given on each follow-up visit of the patients to the health care centers otherwise the patients would lose their trust in the financial aid provision by the National Tuberculosis Program and the health program would suffer in terms of more loss to follow-up rate. The financial incentives will reduce the catastrophic expenditure burden on the patients and households and the commitment to treatment will increase. (The implication also finds support from the study of Zhou *et al.* (2016), Parassana *et al.* (2018)).

5.3.Limitations of the study

The study has the data constraint that a bigger sample size could not be taken due to the limited number of patients enrolled in the RCT. Some of the medical records were not completely available in the TB treatment centers which also reduced the sample size leading to results more specific to the cohorts under study.

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Questionnaire: Economic evaluation of Hospital Vs Ambulatory care TB-Program in Pakistan

Information:

Date of interview(day/month/year)

Name of interviewee Mr/Ms:

B.Information of the patients:

MDR-registration;

TBMU number

C. Socio demographic characteristics:

1.what is your marital status.

1.currently married

2.seperated

3.Divorced

4.unmarried

5.Wodowed

6.Other (specify)

2.What is your educational status.

1.illiterate

2.Literate

3.Primary

4.lower secondary

5.secondary

6.higher secondary

7.university degree

8.technical course

3.What is your occupation

1.not working currently

2.agriculture

3.housewives

4.student

5.labor

6.service

7.business

8.other(specify)

4.What was/is your annual income(individual)

----------Rs Not working

5.How many people are there in your household.----------including the patient.

6.What is the total annual income of your family from all sources including yours.----------Rs

Section 2. Data collected on monthly basis;

D. Information related to treatment of disease, events and costs.

DOT and follow up visits

7 How many days have you come in total to the treatment District TB center for taking medicine in the last month / or how many days did the treatment supporter visit your house for taking medicine i.e. for Direct Observed treatment:----------days

(If the patient does not remember please refer to the treatment card and count the days the patients has come for taking the medicine. If patient answers, please anyhow refer to treatment card for confirming the number of days.)

Patients donot know ----------days on treatment card.

8. If treated at the District TB center in the last month, were the follow up visits done at the same day(day and time)that you went for DOT?

1.Yes(if yes, go to question 9) 2.No

If No

8.1. how many additional times you needed to come to the district TB center for the follow up visits?----------times

9 if treated at the district TB center, How many times did you go to the MDR-center laboratory for the follow-up in the last month?---------- times

10 if treated at a district TB center, how many times did you go to the intermediate lab for the follow-up in the last month?----------times.

Data details of visit for DOT and follow-up:

Ask both of DOTS and follow up related information

This is multiple answers question, if respondent has used more than one means. In such case ask the frequency of use of different means.

S.N.	Particulars	DOT visit district	Follow up visit district center	Follow up visit district intermediatary laboratory	Follow up visit MDR-center
11	Travel time to center from home	min----------	min----------	min----------	min----------
12	mode of transportation and average travel per visit-return	1=micro/mini bus ----------RS	1=micro/mini bus ----------RS	1=micro/mini bus ----------RS	1=micro/mini bus ----------RS
		2=Taxi ----------Rs	2=Taxi ----------Rs	2=Taxi ----------Rs	2=Taxi ----------Rs
		3=own vehicle ----------rs	3=own vehicle ----------rs	3=own vehicle ----------rs	3=own vehicle ----------rs
		4=Foot	4=Foot	4=Foot	4=Foot
		5=others(specify) ----------Rs	5=others(specify) ----------Rs	5=others(specify) ----------Rs	5=others(specify) ----------Rs
13	Other incedentak cost per visit(average)	rs--------	rs--------	rs--------	rs--------

14.What is the average time duration that you spent at different centers while visiting for DOT and follow up last month?

1.District TB center (DOT visit)----------min

2.follow up visit district TB center----------min

3. follow up visit intermediate laboratory----------min

4. follow up visit per MDR-center

E.Hospitalization and expenses made by patients related to medication and tests.

15.Have you got hospitalized any time during the last month?

1.yes

2.No

If yes. 16

Events	Days stayed in MDR center	cost covered by the patients (Les)
1		
2		
3		
4		
5		
6		
Total		

Please verify the answers of patients with the information in the treatment ard

Side effects, costs faced by the patients

17. Did you have any side effect in the lasts months?

1.yes

2.No

If Yes,

18.Did you incur any expense to manage your side effects in the last month?

1.yes

2.no

If yes, ask for more information

Don't mention the cost incurred for the management of the side effects during hospitalization to avoid double counting

If the patient has purchased medicines several times for similar type of side effects, calculate the total cost incurred for that side effect.

19.

S.N	Type of side effect	cost of medicine covered by the patients	consultation fee	other costs
1		Rs	Rs	Rs
2		Rs	Rs	Rs
3		Rs	Rs	Rs
4		Rs	Rs	Rs
5		Rs	Rs	Rs

(please verify the answers of the patients with information in the treatment card and additional record of side effect management)

Cost incurred for the MDR-TB medicines

20.Have you purchased MDR-TB medicines on your own during the last month due to some reason.

1.yes

2.No

What is the average amount spent on medicines.---------rs

Don’t include the cost of medicine purchased during hospitalization to avoid double counting

Cost incurred for diagnosis and other investigations of MDR-TB

Donot include cost incurred for TB diagnosis and cost incurred on investigations during hospitalization if any

21.Did you incur any expenses related to laboratory tests for the diagnosis and during the treatment of MDR-TB in the last month.

1.yes

2.No

If yes

22.How much did you pay for the diagnosis or any investigation during treatment of MDR-TB in the last month.----------Rs

F.Infection control at home

23.Did you apply any control measures in the last month to prevent infecting other household members.

1.yes

2.no

If yes ;

23.1. Which ones?

1.Masks (surgical, respirators, others)

2.isolation of the patient in the separate room

3. Ventilation measures:fans, UVGI, others

23.2. Did you had any cost due to those infection control measures.

1.Yes.

2.No

Fi yes,

23.3. How much (total cost for the household)?----------Rs

G. Employment and MDR_TB

24. have you left your job due to getting MDR_TB in the last month?(do not include if job has lost prior to having MDR)

1.yes

2.no.

If yes;

24.1.How many days it has been since you los your job?----------days/month

24.2.What is your previous occupation /job

1.Agriculture

2.business

3.housewives

4.student

5.labor

6.service

7.Other(specify)

25.If working currently, have you lost working days due to TB?

1.yes

2.No

If yes,

25.1.How many days have you lost from work(including paid of other leaves)?----------days.

25.2.What is the average amount of income lost per day.

H. Relocation cost for patients.

26.If not a permanent resident of this city, have you rented a room here for your treatment.

1.yes

2.no

If yes,

26.1.For how many day have you been renting the room in last month.

----------days

Full month

26.2. In case you moved last month how much money did you incur in order to settle in this place for your treatment.

26.3.What is your room rent per month.----------Rs

26.4.Are you sharing the rented room with other person?

1.yes

2.No

If yes, with how many people.----------

27.have you visited your hometown in the last month.?

1.yes

2.No

If yes,

27.1.how many times you have visited your hometown in the last month.----------times

27.2.What is the average cost two-way journey(travel and other associated)n to come to come from your hometown to current place?----------(Rs)-

27.3.what is the average travel time from your hometown to the current place of stay?

1.----------day

2.----------hours.

I.Funding sources for treatment

28.What sources have you used for funding your treatment in the last month?

Specify the sources and total amount used till date

S.N	source	amount (RS)
1	Covered by national tuberculosis program	X
2	Household income	
3	Sell/mortgage items. (specify what)	
4	Borrow money	
5	have you paid any interest on the laons? if yes, specify the amount you pay, per month	
6	community support	
7	from own saving/source	
8	Drawing from medical allowances if any	
9	others(specify the source and amount)….	

J.Information relating to accompanying person/family cost.

If accompanying person is staying together with the patient, avoid double counting the room rent or other foods item cost)

29.Is there anyone who accompanying person than directly go to question number 30.

1.yes

2.no

If the accompanying person is relocated:

30.Does the accompanying person rent a room in last month.

1.yes

2.No

If yes,

30.1.For the many months is the accompanying renting/rented a room?----------month.

30.2.what is the room rent per month?----------Rs.9ask the total amount of rent if room isshared with other person)

30.3.If rented room is shared, with how many people?----------

31.How many DOT and follow up visits were accompanying by other persons in the last month.----------Rs

32.What is the average amount spent on transportation and other incidentals of the attendants per visits, excluding the amount paid the the patients?----------rs

33.How many working days did the accompanying person sue to your disease?)if any) -------days in the last month.

34. What is the average amount of income lost per day?----------Rs

35.Who covered the accompanying persons cost?

1.patient

2.Accompanying person

3.other(specify)--------

Data related to the treatment supporters collected on monthly basis

36.Type of treatment supporter

1.HCW

2.Community member

3.other(specify)

37.Treatment cost during last month.----------rs

38.Incentives given during last month----------RS

39.Transportation cost during last month----------Rs

40.Cost of infection control measures per month----------Rs.