

**EXPLORING THE CHALLENGES FOR
PROGRAMMATIC MANAGEMENT OF DRUG-
RESISTANT TUBERCULOSIS IN NEPAL**

Guna Nidhi Sharma

Nepal

48th International Course in Health Development
September 19, 2011 - September 7, 2012

KIT (ROYAL TROPICAL INSTITUTE)
Development Policy and Practice/
Vrije Universiteit Amsterdam

“EXPLORING THE CHALLENGES FOR PROGRAMMATIC MANAGEMENT OF
DRUG-RESISTANT TUBERCULOSIS IN NEPAL”

A thesis submitted in partial fulfilment of the requirement for the degree
of Master of Public Health

By

Guna Nidhi Sharma

Nepal

Declaration:

Where other people’s work has been used (either from a printed source,
internet or any other source) this has been carefully acknowledged and
referenced in accordance with departmental requirements.

The thesis “EXPLORING THE CHALLENGES FOR PROGRAMMATIC
MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS IN NEPAL” is my
own work.

Signature:



48th International Course in Health Development (ICHHD)
September 19, 2011 - September 7, 2012
KIT (Royal Tropical Institute)/ Vrije Universiteit Amsterdam,
Amsterdam, The Netherlands

September 2012

Organised by:

KIT (Royal Tropical Institute), Development Policy & Practice
Amsterdam, The Netherlands

In co-operation with:

Vrije Universiteit Amsterdam/Free University of Amsterdam (VU)
Amsterdam, The Netherlands

TABLE OF CONTENTS

List of Tables	iv
List of Figures	v
Dedication	vi
Acknowledgement	vii
Abbreviation	viii
Abstract	x
Introduction	xi
Chapter I: Country Background	1
1.1 Geography	1
1.2 Demography.....	2
1.3 Current Political Situation	2
1.4 Economy	2
1.5 Education	3
1.6 Culture, Beliefs and Caste System	3
1.7 Health System of Nepal.....	3
1.8 National TB Control Programme Overview	5
1.8.1 History.....	5
1.8.2 Organization and Structure of NTP.....	6
1.8.3 Policy and Strategy.....	7
Chapter II: Problem Statement, Justification and Study Method ...	8
2.1 Historical Perspective of Drug-Resistant Tuberculosis	8
2.2 Problem Statement.....	9
2.3 Justification	12

2.4	General Objective	13
2.5	Specific Objectives	13
2.6	Study Method	13
2.6.1	Search Strategy	13
2.6.2	Keywords	13
2.6.3	Conceptual Framework	14
Chapter III: Study Findings/Results		18
3.1	Service Related Factors for Tackling MDR-TB	18
3.1.1	Political Commitment.....	18
3.1.2	Programme Management	18
3.1.3	Laboratory Aspects.....	21
3.1.4	Case Finding Strategy	23
3.1.5	Treatment Strategy	26
3.1.6	Drug Management-Procurement, Supply and Regulation	31
3.1.7	Infection Control	32
3.1.8	Supervision, Monitoring and Evaluation.....	33
3.1.9	Recording, Reporting and Data Management	33
3.1.10	Responsiveness of Health Care Providers.....	33
3.2	Patient Related Factors Preventing Uptake of TB Care Services ..	34
3.2.1	Socio-cultural Factors	34
3.2.2	Economic Factors	36
Chapter IV: Discussion		38
4.1	Service Related Factors for Tackling MDR-TB	38
4.2	Patient Related Factors Preventing Uptake of TB Care Services ..	43

4.3	Limitation of Study	44
Chapter V:	Conclusion	45
Chapter VI:	Recommendation	46
References	49
Annexes	56
Annex 1:	Glossary of Terms and Definitions	56
Annex 2:	Nepal at a Glance - Major Indicators	57
Annex 3:	NTP Goal, Objectives, Targets and Strategy	58
Annex 4:	NTP Treatment Regimens	59
Annex 5:	Definitions of DR-TB Patient Registration Categories	60
Annex 6:	List of NTP Partner Organizations	61

List of Tables

Table 1: History of Tuberculosis Control Programme in Nepal.....	5
Table 2: Historical Milestone - Fight against Tuberculosis.....	8
Table 3: Prevalence of Anti-TB Drug Resistance in Nepal, 1996 to 2007	10
Table 4: Target group for first line DST	23
Table 5: Target groups for second line DST.....	23
Table 6: Top ten districts for failure and defaulter, 2009 to 2010.....	25
Table 7: MDR-TB regimen in Nepal	27
Table 8: XDR-TB regimen in Nepal.....	27

List of Figures

Figure 1: Map of Nepal	1
Figure 2: Organisational Structure of National TB Control Programme	6
Figure 3: The schematic figure of evolution of drug-resistant TB.....	9
Figure 4: MDR-TB patients registered for treatment, 2005-2011.....	11
Figure 5: Second line drug resistance in 100 MDR-TB cases.....	11
Figure 6: Schematic presentation of Piot model.....	14
Figure 7: Steps involved in development and spread of MDR-TB.....	15
Figure 8: Conceptual Framework	17
Figure 9: MDR-TB Treatment Centres and Sub Treatment Centres	19
Figure 10: NTP Laboratory Network	22
Figure 11: MDR-TB cases registered for treatment among estimated cases	24
Figure 12 : MDR-TB treatment outcomes, 2005-2009	31

Dedication

This work is dedicated to Mr. Bhagirath Kharel who showed me the academic path from where I rose to pursue university degree.

I would also like to dedicate this work to my wife Rupa Sharma Kattel who has acted not only as a supportive spouse but also as my guardian throughout the course of my university education.

Acknowledgement

I would like to thank The Dutch Government and Nuffic for granting me a scholarship, which created the financial possibility for me to pursue Master's degree in Public Health at the renowned Dutch Institute KIT where I got an opportunity to sharpen my academic calibre.

I feel proud of being a scholar at Royal Tropical Institute (KIT) where dedicated and excellent academicians (course coordinators and facilitators) are working hard to make prepare internationally qualified public health professionals every year. I would like to express my sincere gratitude to all the course coordinators and facilitators of KIT. I also would like to appreciate Rinia who has created very smooth academic environment through a perfect administrative coordination.

I would like to express my sincere gratitude to my thesis advisor, senior consultant from KNCV, who provided me a systematic direction from the induction in the thesis process to finalization of the product. I am very much grateful to him.

I would like to express my gratitude to Dr. Kashi Kant Jha, Director at NTC, who has supported me by releasing relevant information of NTP.

I am very much thankful to Dr. Sharad Chandra Verma, Deputy Director of National TB Centre (NTC), who has supported me to get relevant information about national TB control programme (NTP) in Nepal.

I also would like to thank Mrs. Kamala Wagle from NTC, who helped me to gather relevant information even with her busy schedule.

I would like to appreciate Mr. Pradeep Kumar Shrestha, my friend and public health professional, who has coordinated communication between me and National TB control Programme authorities.

I would like to express my gratitude to Dr. Olga Gorbacheva, Chief Migration Health Physician for International Organization for Migration (IOM) at Damak, who has inducted ideas in my mind to initiate the thesis process. I would like to thank Mr. Anit Kumar Mishra, Public Health Coordinator at IOM, who has provided relevant information about TB in refugee population. I also would like to thank Ms. Sangita Acharya, TB nurse at IOM, who has helped me to gather relevant literatures that were not available electronically.

Lastly but not least, I would like to thank Mr. Subarna Prasad Acharya, an English novelist and my friend, who has helped English language editing in my thesis.

Abbreviation

ACSM	Advocacy, Communication and Social Mobilization
AFB	Acid Fast Bacilli
AIDS	Acquired Immuno-deficiency Syndrome
Amx-Clv	Amoxicillin/Clavulanate
BCG	Bacillus Calmette-Guerin
CAT	Category
CBS	Central Bureau of Statistics
CDC	Centres for Disease Control and Prevention
CDR	Case Detection Rate
CI	Confidence Intervals
Cm	Capreomycin
CSDH	Commission on Social Determinants of Health
DALY	Disability Adjusted Life Years
DDA	Department of Drug Administration
DoHS	Department of Health Services
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Short-course, the internationally agreed strategy for TB control
DRS	Drug Resistant Survey
DR-TB	Drug-Resistant TB
DST	Drug Susceptibility Testing
E	Ethambutol
FCHV	Female Community Health Volunteer
GDF	Global Drug Facility
GENETUP	German Nepal Tuberculosis Project
GFATM	Global Fund against AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
H	Isoniazid
HIV	Human Immuno-deficiency Virus
HMIS	Health Management and Information System
HP	Health Post
I/NGO	International/Non-Governmental Organization
IOM	International Organization for Migration
ISTC	International Standards for Tuberculosis Care
IUATLD	International Union against Tuberculosis and Lung Disease
Km	Kanamycin
Lfx	Levofloxacin
MDG	Millennium Developmental Goals
MDR-TB	Multi Drug-Resistant Tuberculosis
MESH	Medical Subject Headings
Mfx	Moxifloxacin
MoHP	Ministry of Health and Populations
MSF	Médecins Sans Frontières

MTB	Mycobacterium Tuberculosis
NDHS	National Demographic and Health Survey
NLSS	Nepal Living Standards Survey
NRL	National Reference Laboratory
NSP	National Strategic Plan
NTC	National Tuberculosis Centre
NTP	National Tuberculosis Programme
Ofx	Ofloxacin
PAS	p-Aminosalicylic acid
PHC	Primary health Care Centre
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PMU	Programme Management Unit
R	Rifampicin
S	Streptomycin
SAARC	South Asia Association for Regional Cooperation
SCC	Short Course Chemotherapy
SEAR	WHO-South East Asia Region
TAG	Technical Advisory Group
TB	Tuberculosis
TBCTA	Tuberculosis Coalition for Technical Assistance
UNDP	United Nations Development Programme
UNHCR	United Nations High Commission for Refugees
VDC	Village Development Committee
WHO	World Health Organisation
XDR-TB	Extensively Drug-Resistant Tuberculosis
Z	Pyrazinamide

Abstract

Background: In Nepal, 45% of general population is infected with tuberculosis (TB) and 49,000 new TB cases occur every year. Latest anti-tuberculosis drug resistance survey 2006-2007 showed that prevalence of multi drug-resistant tuberculosis (MDR-TB) is 2.9% among new cases and 11.7% among previously treated cases. Until July 2011, 1026 MDR-TB and 27 extensively drug-resistant TB (XDR-TB) cases have been registered for treatment. Emergence of MDR-TB with XDR-TB poses a new challenge for effective TB control in Nepal.

Objective: To explore the challenges for programmatic management of drug-resistant tuberculosis in Nepal in order to make recommendations.

Study Method: Literature review was done by internet search. Relevant articles, reports and information were collected in relation to MDR-TB in Nepal.

Findings: Service related challenges for programmatic management of drug-resistant tuberculosis are very low MDR-TB detection, unclear patient tracing mechanism, narrow high risk targeted case findings, lacking MDR-TB rapid diagnostic tool, relatively inflexible directly observed treatment (DOT), inadequate patient support services, poor responsiveness and lack of adequate operational research in relation to MDR-TB. The possible patient related factors are social stigma and discrimination, misconception about TB, financial and geographical inaccessibility and poor awareness that TB services are free.

Conclusions and Recommendation: Emergence of MDR-TB in Nepal is posing a threat which requires an urgent public health response. Recommendations are introduction of rapid diagnostic test, wider high risk targeted case finding strategy, individualized and flexible DOT, scaling up patient support services, stigma and discrimination reduction strategy, patient tracing mechanism and operational research.

Key words: tuberculosis, multi drug-resistant, extensively drug-resistant, anti-tuberculosis drugs, drug susceptibility testing, Nepal

Word count: 13,109

Introduction

Tuberculosis (TB), an airborne communicable disease, caused by *Mycobacterium tuberculosis* (MTB) complex, is a major public health problem worldwide. Globally, it is estimated that approximately 9 million new TB cases and 1.5 million deaths due to TB occur each year. Almost 85% of all TB cases occur in developing world (WHO, 2011a). It is estimated that 40% of all TB cases occurs in WHO-South East Asia Region (WHO, 2012a).

In Nepal, approximately 60% of adult and 45% of general population is infected with TB. World Health Organization has estimated that the prevalence of all forms of TB is 71,000 (238/100,000 population) and incidence of all forms of TB is 49,000 (163/100,000 population) each year. Surveys showed that prevalence of HIV among TB patients is 2.41%. Nepal is low HIV prevalence country where adult prevalence is 0.4%. Latest anti-Tuberculosis drug resistant survey (DRS) 2006-2007 showed that prevalence of multi drug resistant tuberculosis (MDR-TB) is 2.9% among new cases and 11.7% among previously treated cases (NTP, 2011a; GLC, 2010).

In Nepal, DOTS strategy was introduced in 1996 (NTC, 2011). Drug-resistant tuberculosis management was started in September 2005 (GLC, 2010). National Tuberculosis Control Programme (NTP) has adopted Stop TB Strategy since 2006. NTP has been fully incorporated into primary health care services (NTP, 2011a). Main source of funding for NTP is the Global Fund (GLC, 2010). Acid Fast Bacilli (AFB) microscopy is the main diagnostic tool. German Nepal Tuberculosis Project (GENETUP) laboratory and NTP central laboratory can perform culture and Drug Susceptibility Testing (DST). The major achievements of NTP are death rates declined from 51 in 1990 to 21/100,000 population in 2010; case detection rate is increased from 30% in 1995 to 73% in 2011 and the treatment success is 90% in 2010 (NTP, 2011a). However, drug-resistant TB is emerging as a challenge for effective TB control in Nepal.

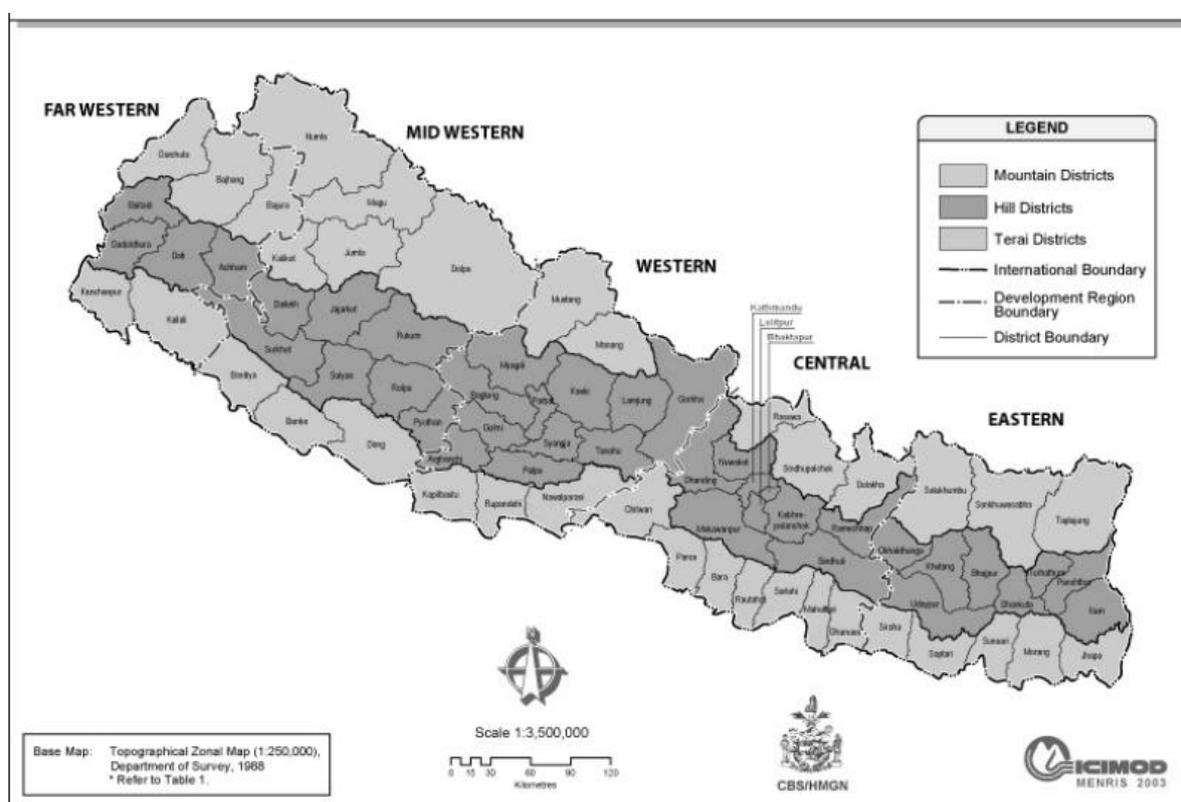
I was working as a medical staff at one of the DOTS demonstration centres in 1996. I also worked in Médecins Sans Frontiers (MSF) supported TB programme in the remote district of Nepal in 2006-2007. In 2010, I got training on "TB Intensive" at Tyler-Texas, USA. Recently in 2011, I worked with MSF as TB doctor in Abkhazia. I am interested to continue my carrier in TB control programmes as a manager or as a researcher in future. Given this professional background, I am interested in doing my thesis in MDR-TB in Nepal. This thesis explores the challenges for programmatic management of drug-resistant TB in Nepal. This thesis is divided into six chapters in following sequence: country background, problem statement and study method, study findings, discussion, conclusion and recommendations.

Chapter I: Country Background

1.1 Geography

Nepal is a landlocked and mountainous country situated between China to the north and India to the east, west and south. It stretches 885 kilometres from east to west and 193 kilometres from north to south. Total area is 147,181 Km². Altitude ranges from 70 meters above sea level to 8,848 meters marking the summit of Mt Everest (CBS, 2010). The map below (Fig.1) shows the ecological and administrative divisions (developmental regions and districts).

Figure 1: Map of Nepal



Source: CBS

Nepal is geographically diverse and famous for its natural beauty. Ecologically, it has been divided into three belts extending from east to west: the Mountains to the north, the Hills along the middle and the Terai plains to the south. Eight of the ten tallest peaks in the world are situated in the mountainous region. The middle Hilly region is largest by land and consists of high hills with rugged terrain. The southern plain, the Terai, is highly fertile and is the main site for agriculture. Many rivers emerge from the Mountains to the north, run through the hills and flow across to India (CBS, 2010).

Mountain and Hilly regions constitute 83% of total land. Geographical accessibility in this part is very difficult because of rugged terrain, dangerous rivers and a poor road network. This poses a big challenge for easier access to health care facilities.

Administratively, Nepal has been divided into 5 developmental regions, 75 districts and, at local level, 58 municipalities and 3,915 Village Development Committees (VDCs). Kathmandu is the capital of the country (CBS, 2010).

1.2 Demography

Nepal's population is 26.4 million and annual population growth rate is 1.4%. Population density is 199 per square kilometres. Total fertility rate decreased from 3.1 in 2006 to 2.6/woman aged 15-49 years in 2011. Eighty-three per cent of people reside in rural areas. Almost 2 million people are out of country for employment. The largest proportion of the population (48.6%) lives in the Terai and only 7.3% live in the Mountains. Remaining 44.3% live in hilly region (CBS, 2011; NDHS, 2006; NDHS, 2011).

There are a large number of refugees and asylum seekers, mainly from Bhutan and Tibet. However, population of Bhutanese refugees is decreasing because many of them have been resettled in developed countries such as Australia, Canada, USA and The Netherlands (UNHCR, 2012).

1.3 Current Political Situation

Nepal has just become a republic state in 2008 after 240 years of monarchy. Before 2007, Nepal went through a decade long armed conflict led by Communist Party of Nepal, Maoists. In 2008, constituent assembly was elected to draft a new constitution to institutionalize republic federalism in the country. However, the constituent assembly ended on 27th May 2012 without drafting a new constitution because of a serious conflict among parties on the modality of federalism. With all this controversy, another constituent assembly election is proposed to be held on November 2012. Hence, current political situation in Nepal is uncertain but stable.

1.4 Economy

Nepal is one of the poorest countries in the world (UNDP, 2009). However, Nepal is rich for its natural resources like water and forest. There is high hydroelectricity potential in the country but it experiences 10-20 hours power outage daily. Almost 25% of people live with less than \$1 daily income per person. Main income source is agriculture, tourism and repatriations from abroad (CBS, 2010).

1.5 Education

Average literacy rate is 61% but there is disparity. Literacy rate is higher in urban areas (77%) than in rural areas (57%). Similarly, male literacy rate is 72%, whereas it is only 51% in females. Almost 95% households can reach primary school in 30 minutes (NLSS, 2011).

1.6 Culture, Beliefs and Caste System

Nepalese society has a rich and diverse cultural heritage. However, some cultural practices and beliefs are counterproductive to people's health.

Superstition, belief in witchcraft, ghosts and curses is still prevalent. There are two effects. For example, a widow with poor personal hygiene from poor socio-economic status is considered a witch and she becomes a victim of violence and social ostracism. On the other hand, people seek primary help from witchdoctors (traditional healers) which delays timely health seeking; the illness becomes complicated and often results in poor outcome (personal observation).

Nepal has a hierarchical social caste system that categorizes people in four major castes: the highest caste-*Brahmin* and lowest caste-*Dalit*. *Dalits* were considered untouchable in the past. However, society is changing with time and it has become less and less a matter of concern, particularly in urban areas. But caste based segregation still exists in rural villages.

1.7 Health System of Nepal

Ministry of Health and Population (MoHP) has the leading and stewardship role in overall health system. Policy-making, planning, budgeting, implementation and coordination among key governmental and non-governmental stakeholders are its main roles and responsibilities. Under the ministry, there are different departments and councils (MoHP, 2012).

1. Department of Health Services (DoHS)
2. Department of Drug Administration (DDA)
3. Department of Ayurveda
4. Medical council, Nursing council, Health Research council

Department of health Services (DoHS) is the largest department responsible for delivering health care services throughout the country. At central level, it has 5 centres including National Tuberculosis Centre (NTC), 7 divisions and 8 central hospitals. At regional level, there are five regional directorates, 3 regional hospitals, 2 sub-regional hospitals and 10 zonal hospitals. At local level, there are 65 district hospitals, 209 Primary Health Care Centres (PHC), 676 Health Posts (HPs) and 3,129 Sub-Health Posts (SHP).

At community level, there are more than 50,000 Female Community Health Volunteers (FCHV). FCHV programme is one of the successful programmes linking community people to the mainstream health system (DoHS, 2011).

Department of Drug Administration (DDA) is a drug regulatory body which regulates all functions related to drugs, in order to make available safe, efficacious and quality drugs to the general public (DDA, 2011).

Nepal has also incorporated some of the alternative traditional medical systems like Ayurveda and has a separate department called Department of Ayurveda. Ayurveda is the most ancient medical system that uses herbs, minerals and animal products. This system also has several health care facilities throughout the country (DoHS, 2011). Although alternative medical system provides some options for people to choose, it also creates confusion among people as to which system is to be chosen for their particular problem.

Health sector decentralisation was attempted in 2002 in accordance with Local Self Governance Act 1999 but it faced several challenges for successful implementation. Health care financing is based on taxation, foreign aid and out of pocket from the people (Collins et al., 2007; DoHS, 2011).

1.8 National TB Control Programme Overview

In this section, a general overview of National TB control programme in Nepal will be presented.

1.8.1 History

The history of TB control programme in Nepal dates back to 1937 when Tokha Sanatorium was established. A brief history of TB control programme in Nepal is outlined in following table.

Table 1: History of Tuberculosis Control Programme in Nepal

1937	Establishment of Tokha Sanatorium
1951	Central Chest Clinic was established to provide curative TB services, Free treatment for the poor
1985	TB Control Project was established Short Course Chemotherapy was introduced in some parts of country
1989	TB Control Project was replaced by National TB Programme Central Chest Clinic was replaced by National Tuberculosis Centre
1993	Short Course Chemotherapy was adopted as the national drug regimen
1995	5 year plan was made based on the WHO framework Policy for DOTS strategy was approved by Government
1996	DOTS was introduced in four demonstration centres ¹ Made a plan to extend DOTS throughout the country in the following 5 years
2005	DOTS Plus program started
2008	Drug-resistant TB management scaled up
2009	NTP adopted six month treatment regimen with rifampicin throughout the course

Source: NTC, 2011

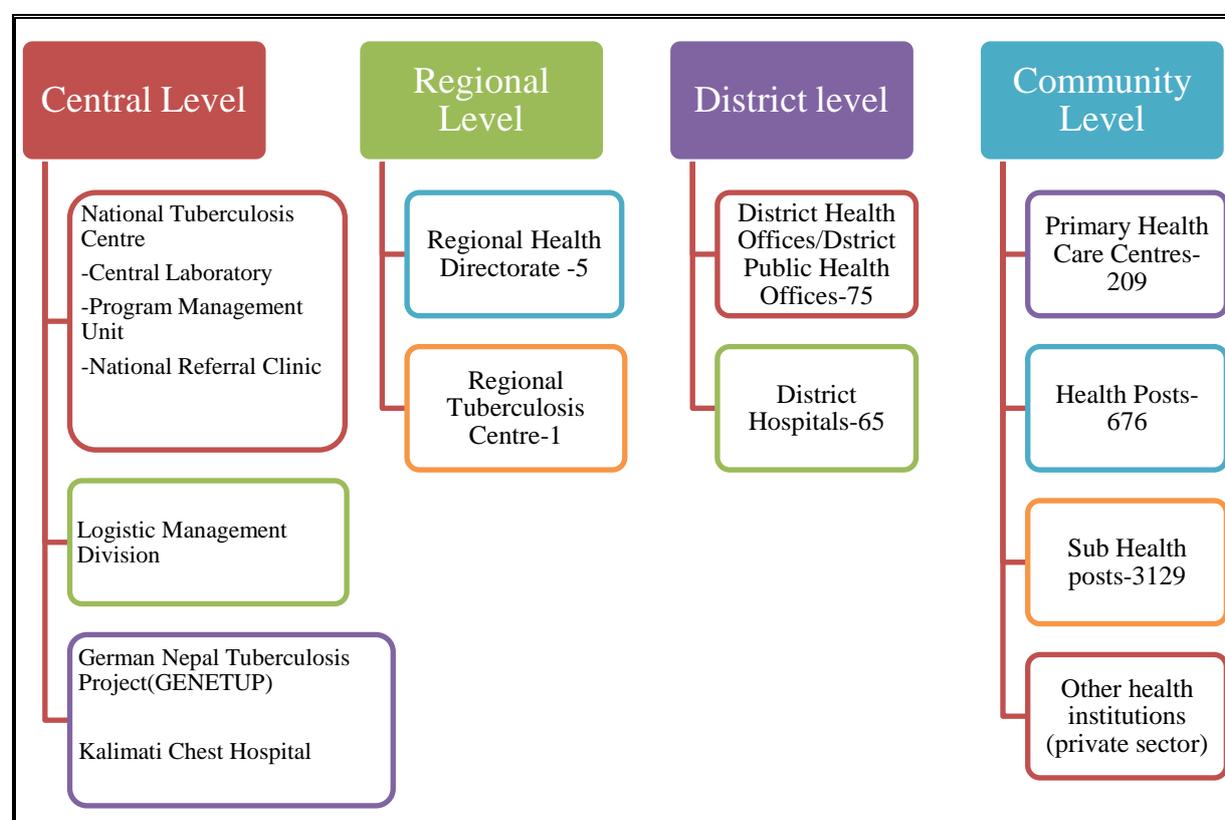
Major intervention was started in 1996 when DOTS strategy was introduced. After that, NTP has been achieving its target of 70% detection rate and 85% success rate. The treatment for MDR-TB was made available through NTP in 2005. Since 2009, NTP has adopted 6 months' treatment regimen with rifampicin throughout the course (NTC, 2011).

¹ Author was working at one of these demonstration centres

1.8.2 Organization and Structure of NTP

At the central level, national tuberculosis centre (NTC) is the focal point of NTP. It is primarily responsible for formulation of policies, strategies and overall planning. NTC also functions as a central level referral hospital with a central laboratory. Central lab is the focal point for NTP laboratory network. German Nepal Tuberculosis Project (GENETUP) is a national reference laboratory. Programme Management Unit (PMU) manages the global fund grants in terms of overall coordination, financing, monitoring and evaluation, procurement and MDR-TB management. Logistics management division of DoHS distributes the drugs (NTP, 2011a).

Figure 2: Organisational Structure of National TB Control Programme



Source: NTP, 2011a

At the regional level, NTP programmes are planned and carried out in coordination with five regional health directorates, which are overseen by permanent regional TB/Leprosy officers. In western development region, there is a regional tuberculosis centre that provides technical support and also works as a regional referral clinic (NTP, 2011a).

At the district level, NTP activities are integrated into general health services. District Health Office or District Public Health Office is responsible for supervision, monitoring & evaluation, training and logistics management of all NTP activities within the district. District TB/Leprosy Officer is a key staff for coordinating all NTP activities. TB case management (diagnosis and treatment) is carried out in the district hospital and primary health care centres. Directly Observed Treatment (DOT) is available at Health Post, Sub Health Post (SHP) and other private institutions (NTP, 2011a).

Almost 99% of SHPs have Sub Treatment Centres. As of July 2011, 1,122 Treatment Centres and 3,126 Sub Treatment Centres are offering DOTS service throughout the country. Similarly, 407 government-run and 98 private sectors (I/NGOs) run microscopy centres are offering microscopy services. Culture and DST services are available at GENETUP and NTC at central level. Culture and DST is also available at International Organisation for Migration (IOM) laboratory in eastern part of Nepal but is limited to Bhutanese refugees. (NTP, 2011a, NTP 2011b; Gorbacheva et al, 2010)

1.8.3 Policy and Strategy

NTP Nepal has adopted the WHO/Stop TB Strategy to achieve the objectives of TB control programme since 2006 (see *Annex 3*). Main policies adopted by NTP are expansion of DOTS throughout the country up to the community level, establishment of microscopic diagnostic facility at PHC level, free diagnostic and treatment services to all TB patients including MDR-TB, passive case finding, use of standardized treatment regimen and DOT. Additionally, NTP policy is to maintain uninterrupted availability of quality assured first and second line drugs at all levels by maintaining the buffer stock as per guideline, to provide TB/HIV services in collaboration with National AIDS programme and to collaborate with public and private sectors (NTP, 2011a). The list of NTP partners are presented in *Annex 6*.

Chapter II: Problem Statement, Justification and Study Method

This chapter presents the outline of the study. It describes historical perspective of drug-resistant TB, problem statement, justification and study method with conceptual framework.

2.1 Historical Perspective of Drug-Resistant Tuberculosis

The causative agent, *Mycobacterium tuberculosis* (MTB), was discovered by Dr. Robert Koch in 1882. Anti-tuberculosis drug was only discovered in the 1940s. As shown in table below, all of the first line drugs were discovered in the 1960s.

Table 2: Historical Milestone - Fight against Tuberculosis

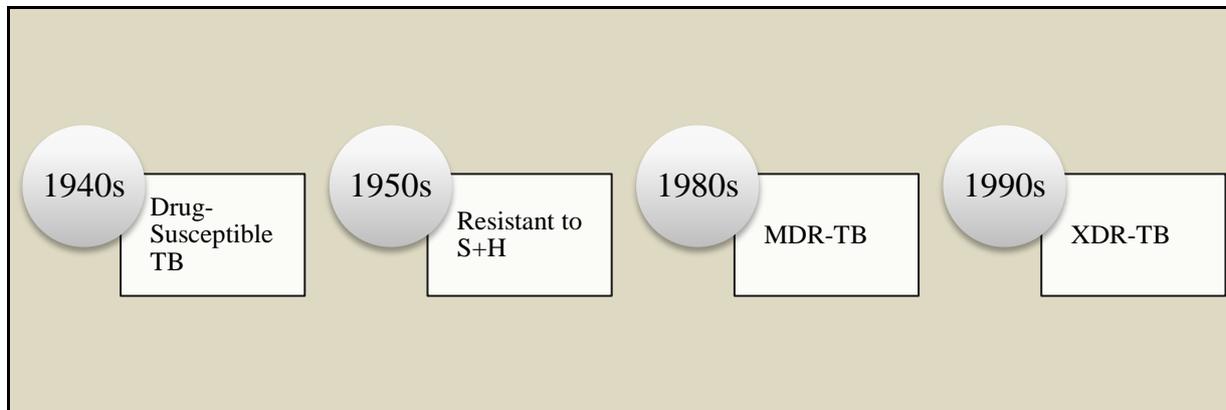
1882, March 24	First time in the history, Robert Koch discovered TB bacilli
1882-1940	Searching for effective and safe anti-tuberculosis drug but unsuccessful
1921	BCG vaccine was first used in humans
1943	Streptomycin(S) was invented
1944, November 20	Streptomycin was administered for the first time to a critically ill TB patient
1952	Isoniazid(H)
1954	Pyrazinamide (Z)
1962	Ethambutol (E)
1963	Rifampicin(R)
1970s-1990s	Fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin) and Second line injectible (amikacin, capreomycin, kanamycin)
2010	Rapid diagnostics e.g. Xpert MTB/RIF (GeneXpert)
2012	New drugs in pipeline: e.g. PA-824, Bedaquiline (TMC-207) New diagnostics in pipeline: e.g. Rapid colorimetric DST New vaccines in pipeline: e.g. MVA85A/AERAS-485

Source: New Jersey Medical School, 2012; Global Alliance for TB, 2012; FDA, 2012, WHO, 2011a

In the meanwhile resistant mutants have developed against anti-TB drugs. Combination therapy was adopted to tackle drug-resistant tuberculosis. However, this strategy has also faced new challenges because multi drug-resistant strains have emerged. The situation has become complicated with the emergence of extensively drug-resistant TB (XDR-TB).

The figure below shows the schematic presentation of evolution of drug resistance tuberculosis.

Figure 3: The schematic figure of evolution of drug-resistant TB



Newer drugs were invented, for example, fluoroquinolones and aminoglycosides, but they are not as effective as first line anti-TB for drug-susceptible TB. Thus, newer drugs are limited to be used in drug-resistant TB. However, there are some positive developments as well. New anti-TB drugs are under developments and some of them are currently in pipeline (New Jersey Medical School 2012; Global Alliance for TB, 2012, WHO, 2011a). Moreover, discovery of rapid diagnostic technology (e.g. Xpert MTB/RIF) is another milestone that could be an effective tool to combat TB (Boehme et al, 2010).

2.2 Problem Statement

Multidrug-resistant TB (MDR-TB) is defined as TB caused by the resistant strains of MTB to at least rifampicin (R) and isoniazid (H). Extensively drug-resistant tuberculosis (XDR-TB) is defined as MDR-TB with additional resistance to second line drugs: at least one injectible out of three (amikacin, capreomycin, kanamycin) and one of fluoroquinolones (Nathanson et al, 2010).

Emergence of multi drug-resistant tuberculosis is a major global threat in public health today. Globally, 650,000 MDR-TB cases were estimated in 2010 and 150,000 deaths due to MDR-TB occurred in 2008. Almost 50% of total MDR-TB cases of the world occur in China and India (WHO, 2011a; WHO, 2010).

As part of a project under World Health Organization (WHO) and International Union against Tuberculosis and Lung Disease (IUATLD), four anti-tuberculosis drug resistance surveys (DRS) were conducted from 1996 to 2007 in Nepal. Survey report showed that MDR in new TB cases (primary MDR-TB) was 1.2% in 1997, 3.6% in 1999, 1.3% in 2002 and 2.9% in 2007. MDR in previously treated patients (acquired MDR-TB) was 12.5% in 1999, 20.5% in 2002 and 11.7% in 2007 (GLC, 2010). The following table shows the summary findings of four DRS with confidence intervals (CI).

Table 3: Prevalence of Anti-TB Drug Resistance in Nepal, 1996 to 2007

	1996-1997		1998-1999		2001-2002		2006-2007	
	Primary	Acquired	Primary	Acquired	Primary	Acquired	Primary	Acquired
No. of TB patients tested	787 (100%)	Not tested	673 (100%)	112 (100%)	755 (100%)	171 (100%)	766 (100%)	162 (100%)
Multi Drug Resistance	9 (1.1%)	-	24 (3.7%)	14 (12.5%)	10 (1.32%)	35 (20.5%)	22 (2.9%)	19 (11.7%)
95% CI	0.52 - 2.16	-	2.00 - 5.26	7.01 - 20.08	0.64 - 2.42%	14.69 - 27.30	1.90 - 4.3	7.20 - 17.7

Source: GLC, 2010; WHO, 2008a

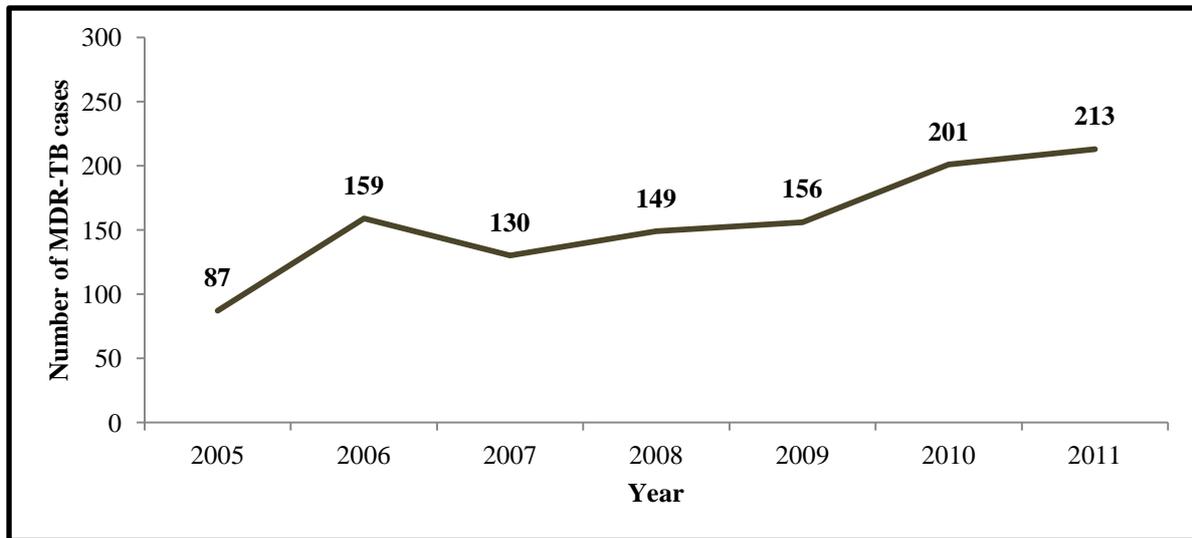
Proportion of primary MDR-TB increased in 2007 as compared to 2002. But the increase is not statistically significant because the confidence intervals are overlapping. However, in WHO-South East Asia Region (SEAR), the proportion of the primary MDR-TB in Nepal is second after Myanmar where it is 4.2% (WHO, 2011b).

Primary MDR-TB in the latest DRS indicates that there is an on-going transmission of MDR-TB. This means acquired MDR-TB cases are spreading MDR-TB in the community. Therefore, appropriate public health response is required to halt transmission.

In Nepal, management of drug resistant tuberculosis was started in 2005 as a DOTS Plus pilot project. NTP has scaled up MDR-TB management in 2008. Now, NTP can treat 300 MDR-TB cases annually.

The annual MDR-TB registration for treatment from 2005 to 2011 is shown in the graph below (NTP, 2011a).

Figure 4: MDR-TB patients registered for treatment, 2005-2011

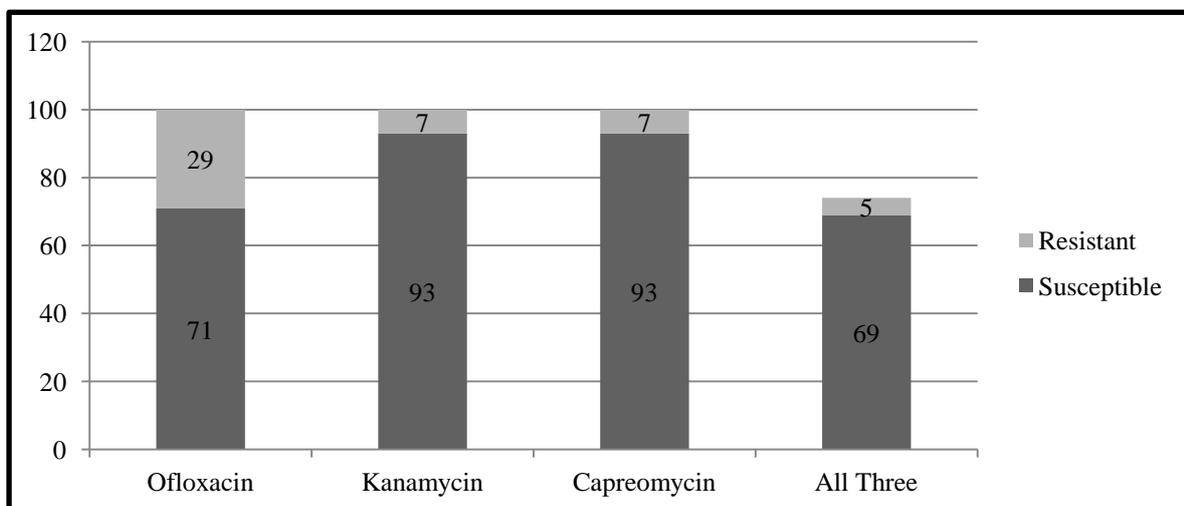


Source: NTP, 2011a; NTP, 2010a

The graph shows that MDR-TB cases registered for treatment are slowly increasing since 2008. The annual number of cases registered for treatment is below NTP’s total capacity to treat (300 MDR-TB cases per year). The data about MDR-TB suspects and MDR-TB diagnosed is not available.

GENETUP conducted a study in randomly selected 100 MDR-TB cases. The pattern of susceptibility of three second-line drugs is as shown in the *graph* below. The prevalence of XDR-TB among MDR-TB is 5% (GLC, 2010).

Figure 5: Second line drug resistance in 100 MDR-TB cases



Source: GLC, 2010

It shows that ofloxacin resistance is very high and it forecasts an additional treatment challenge for MDR-TB cases. In Nepal, first XDR-TB was reported in 2008. As of July 2011, 27 XDR-TB patients are registered for treatment under NTP (NTP, 2011a).

Emergence of MDR-TB along with XDR-TB poses several challenges especially in a poor country like Nepal where almost 25% of people live with less than \$1 daily income per person and TB care financing is largely dependent on external aid. Understanding these challenges is essential for effective TB control.

2.3 Justification

The trend seen in different DRS indicates that NTP Nepal is going to face a new challenge of drug resistance. Emergence of MDR-TB poses several challenges because it is costly and requires long-term treatment with multiple drugs. Similarly, outcome of MDR-TB treatment is poorer than drug-susceptible TB. The cost for treatment of new smear-positive case in DOTS programme in South East Asia Region (SEAR-d)² is \$7 per DALY (Disability Adjusted Life Year) averted, whereas cost for MDR-TB per DALY averted is \$226 (Baltussen et al, 2005). This means treatment of MDR-TB is 32 times costlier than treatment of drug-susceptible TB. TB control is one of the objectives of millennium developmental goal-6 (MDG-6) (UNDP, 2010a). Without addressing the issue of MDR-TB, achieving this goal is also difficult.

The problem of DR-TB should be assessed in country specific context because the problems vary in different settings (Lambregts & Veen, 1995). Context specific strategies can be made to achieve more positive results. Although NTP has set research as an objective, National Strategic Plan (NSP) 2010-2015 has included only DRS as a research issue in relation to MDR-TB (NTP, 2010b). Only a few studies have been conducted concerning MDR-TB in Nepal.

Based on the above-mentioned facts, there is a need for research in MDR-TB. This study explores the challenges for programmatic management of drug-resistant TB in Nepal. The findings of this study will be used to make recommendations for NTP in order to assist appropriate programme response tackling MDR-TB in Nepal.

² Country with high adult and high child mortality: Nepal is one of these.

2.4 General Objective

To explore the challenges for programmatic management of drug-resistant tuberculosis in Nepal in order to make recommendations to NTP for appropriate intervention strategies tackling MDR-TB in Nepal

2.5 Specific Objectives

1. To analyse the current programme response and identify the gaps in tackling MDR-TB in Nepal
2. To explore the patient related factors preventing adequate uptake of TB care services
3. To formulate the recommendation to NTP Nepal for appropriate intervention strategies tackling MDR-TB in Nepal

2.6 Study Method

Literature review was performed in order to collect information as per objectives. Internet search was made with the help of key words. NTP Nepal's reports and guidelines were obtained. Relevant reports and articles were obtained from the official websites of NTP Nepal, WHO, IUATLD, Stop TB Partnership, CDC and KNCV. A conceptual framework adapted from available literature has been used in order to analyse and discuss the findings systematically.

2.6.1 Search Strategy

Literature search was done using different database search engines like PubMed, Google Scholar, Science Direct and Scopus with the help of key words. Literatures available in English from 2000 to 2012 are searched. However, some of the literatures before 2000 are also used because of their relevance in key information. PubMed search was performed using MeSH (Medical Subject Heading) terms and their combinations. Similarly, in other search engines, key words and combinations were used. KIT library was used to search relevant references.

2.6.2 Keywords

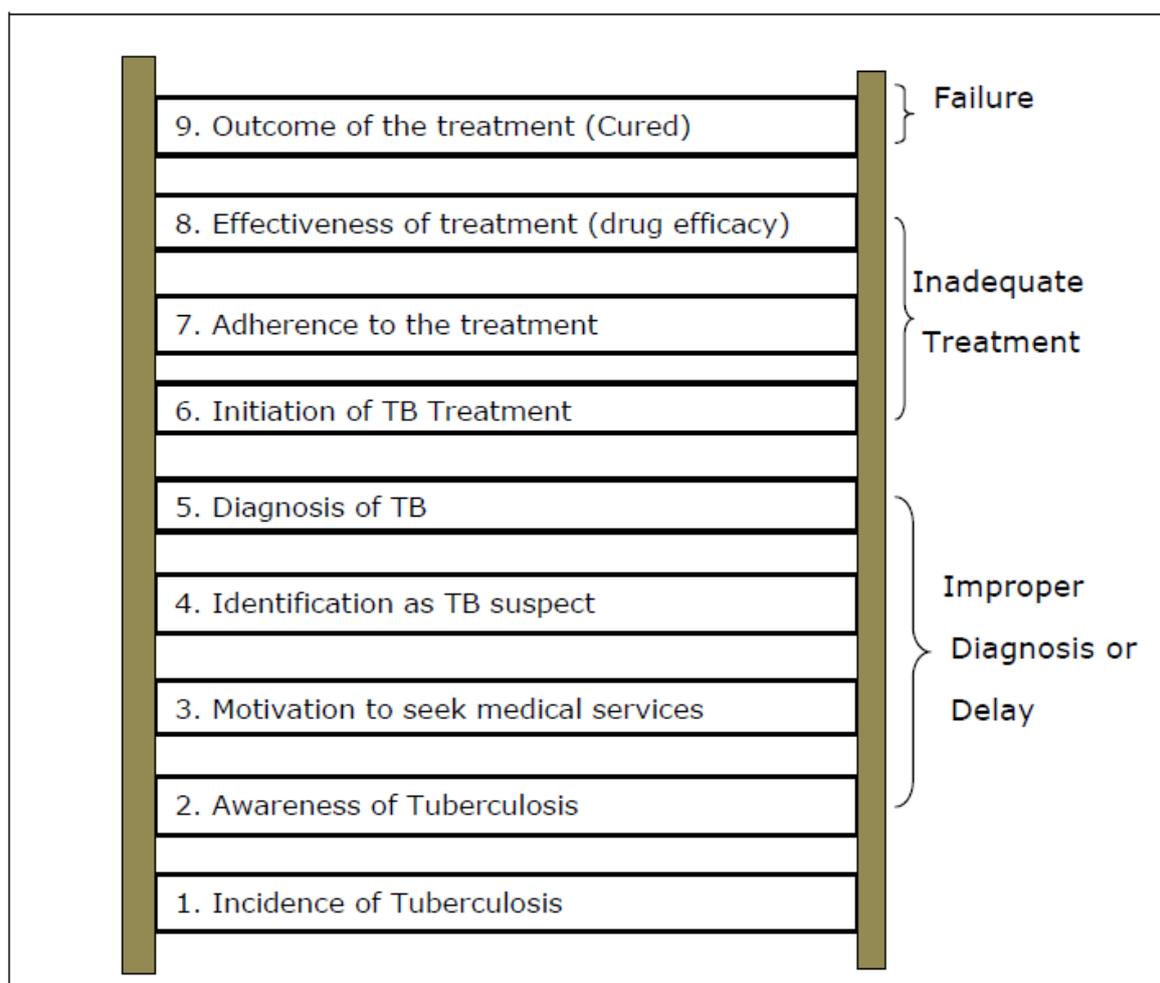
Tuberculosis, multi drug-resistant, extensively drug-resistant, anti-tuberculosis drugs, drug susceptibility testing, Nepal

2.6.3 Conceptual Framework

Conceptual framework is an essential tool in order to explore, describe and analyse information systematically. Relevant literatures concerning tuberculosis control programmes are analysed and a conceptual framework is adapted.

Piot (1967) proposed a conceptual operational model to analyse the overall TB control programme. Piot model is still relevant and it has steps in sequence as shown in *figure 6*. In order to reach the final step (effective outcome as cured), every step should be passed successfully (Piot, 1967; Dujardin et al, 1997).

Figure 6: Schematic presentation of Piot model

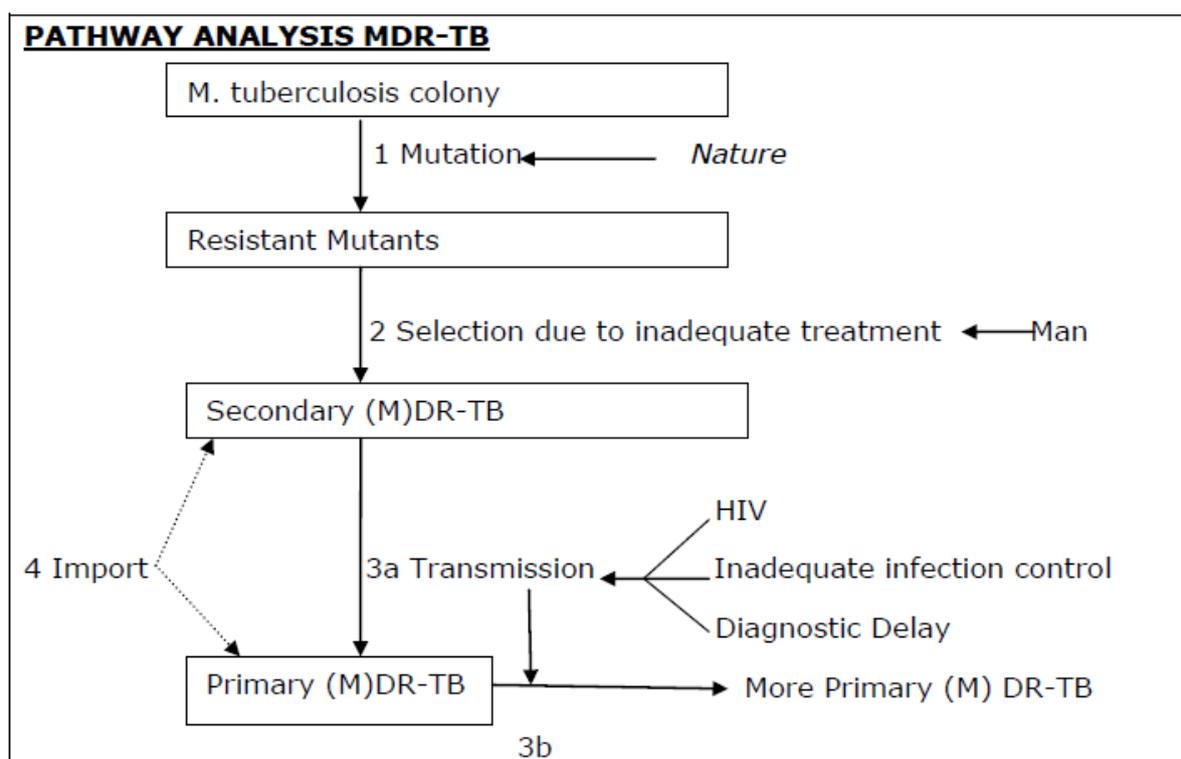


Source: Piot, 1967; Dujardin et al, 1997

Failing to step forward might result in negative outcomes. Challenges for drug-resistant TB might arise from bottlenecks as shown in figure. These obstacles can be grouped into service related factors and patient related factors.

Drug-resistant mutants develop naturally in any large population of bacilli. In untreated patients, the random mutations that confer resistance to anti-tuberculosis drugs occur at predictable frequencies of 1 in 10^6 in isoniazid and 1 in 10^8 in rifampicin. The probability of spontaneous occurrence of resistance to both rifampicin and isoniazid is a product of both, which is $10^8 \times 10^6 = 10^{14}$ (i.e. 1 in 10^{14}). The total number of bacilli rarely reaches 10^{14} even in advanced cavitary disease (Long, 2000; Francis, 2008; Colijn et al, 2011). Hence, MDR-TB development is a manmade problem arising from inadequate treatment. Lambregts & Veen (1995) proposed a pathway for the development and spread of MDR-TB as shown in the schematic figure below (figure 7).

Figure 7: Steps involved in development and spread of MDR-TB



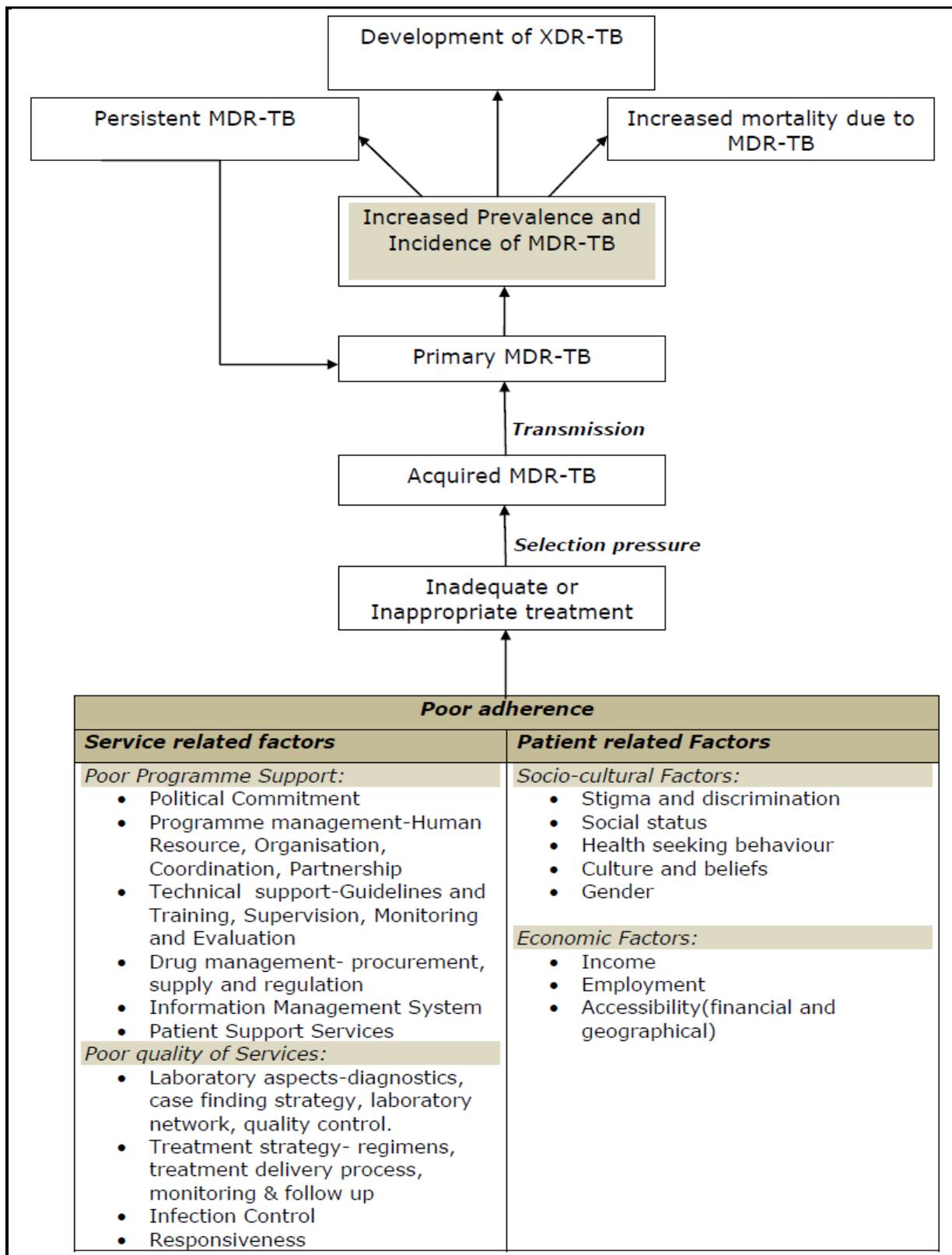
Source: Lambregts & Veen, 1995

In relation to tuberculosis, inadequate treatment creates a selective pressure for development and proliferation of resistant mutants that eventually leads to secondary or acquired MDR-TB. Secondary MDR-TB patients can infect a new individual who is in close contact and then primary MDR-TB develops. Poor infection control measures and improper diagnosis or diagnostic delays often contribute to spread up MDR-TB. Although there is no direct relationship between HIV infection and development of MDR-TB, HIV infected persons are always at high risk for developing active TB. Emergence of MDR-TB in low prevalence country is often contributed by immigrants from the country of high prevalence (Lambregts & Veen, 1995).

The cause of the inadequate treatment are basically related to TB care services or to the factors associated with patients. Country specific explorations of these factors could help to design appropriate interventions to tackle drug-resistant TB (Lambregts & Veen, 1995). The WHO's Programmatic Management of Drug-Resistant TB (PMDT) 2008 emergency update has also cited and emphasized the Lambregts and Veen's concept for causes of inadequate treatment. The WHO has adopted DOTS Strategy as DR-TB control framework since the DOTS components (sustained political commitment, rational case finding strategy, appropriate treatment strategy, uninterrupted supply of quality assured drugs and standardized recording and reporting system) are also applicable in DR-TB control (WHO, 2008b). Thus, the challenges for PMDT should also be explored in these areas.

As discussed above, the selective pressure created due to inadequate treatment is a main cause of the secondary MDR-TB. The major contributing factors for inadequate treatment are either service related or patient related. After reviewing above mentioned literatures, a conceptual framework has been adapted in order to incorporate objectives of the thesis. The adapted conceptual framework shows how different service related factors and patient related factors contribute inadequate treatment which leads to development of acquired MDR-TB. Inadequate and inappropriate management of acquired MDR-TB also leads to primary MDR-TB and so on. Based on this conceptual framework, the challenges of programmatic management of drug-resistant tuberculosis (PMDT) will be analysed and discussed. PMDT is referred as group of activities from different components or units of national TB control programme for the effective management of drug-resistant tuberculosis. The major components are case finding, treatment, prevention, surveillance, and monitoring and evaluation (WHO, 2011c). The adapted conceptual framework used in this thesis is schematically presented in *figure 8*.

Figure 8: Conceptual Framework



Adapted from Lambregts and Veen’s concept, WHO-PMDT and Piot Model

Chapter III: Study Findings/Results

The findings of the study will be presented in two sections: Service related factors for tackling MDR-TB and patient related factors preventing adequate uptake of TB care services. The discussion will be in separate chapter (chapter IV) following this chapter.

3.1 Service Related Factors for Tackling MDR-TB

As outlined in the conceptual framework and specific objective one, this section explores and analyses programmatic responses in tackling MDR-TB to identify the gaps.

3.1.1 Political Commitment

Tuberculosis control programme remains a priority health programme in Nepal. NTP launched DOTS strategy in 1996 and services were made available throughout the country in 2001 (NTP, 2011a). MDR-TB management was made available through DOTS Plus pilot project in 2005. DOTS Plus programme was scaled up in 2008 (NTP, 2010b).

Government of Nepal spends 6.24% of total budget in health care and NTP receives 2.97% of total health budget. The cost for National Strategic Plan (NSP) for 2010-2015 is estimated to be 89 million USD. Global fund contributes 70 million (56 million from this round + 14 million remaining of previous round). Government contributes 16 million (NTP, 2010b). Thus, NTP's budget is largely dependent on Global Fund. If Global Fund stops funding, there will be a serious funding crisis.

3.1.2 Programme Management

Five components of DOTS strategy are also adopted in DR-TB control framework in Nepal. National Tuberculosis Centre (NTC) is responsible for effective implementation of PMDT (NTP, 2011b).

Although NTP started DR-TB treatment in 2005, NTP prepared and released "Drug Resistant Tuberculosis Management Guidelines and Manual" only in November 2011. This DR-TB guideline defines the roles and responsibilities of different institutions for DR-TB management. It also defines coordination mechanisms among central, regional, district and local level institutions involved in DR-TB management. NTP has identified a key focal person as MDR-TB coordinator at central level. MDR-TB Technical Advisory Group (TAG) consists of members from the WHO, SAARC TB & HIV/AIDS Centre, National Association of TB and Chest Physician, GENETUP, senior clinical and section head from NTC and other international non-governmental organizations (I/NGOs). Similarly, programme management unit (PMU) at central level is responsible for dealing with global fund grant (NTP, 2011b).

According to guideline, TAG is supposed to meet at least every quarter to discuss overall DR-TB programme in Nepal. TAG is responsible for providing technical guidance and support to DR-TB management teams from central to community level, especially on management of difficult DR-TB cases. Regional and district TB/Leprosy officers are responsible for proper implementation and coordination of DR-TB activities in their respective working areas.

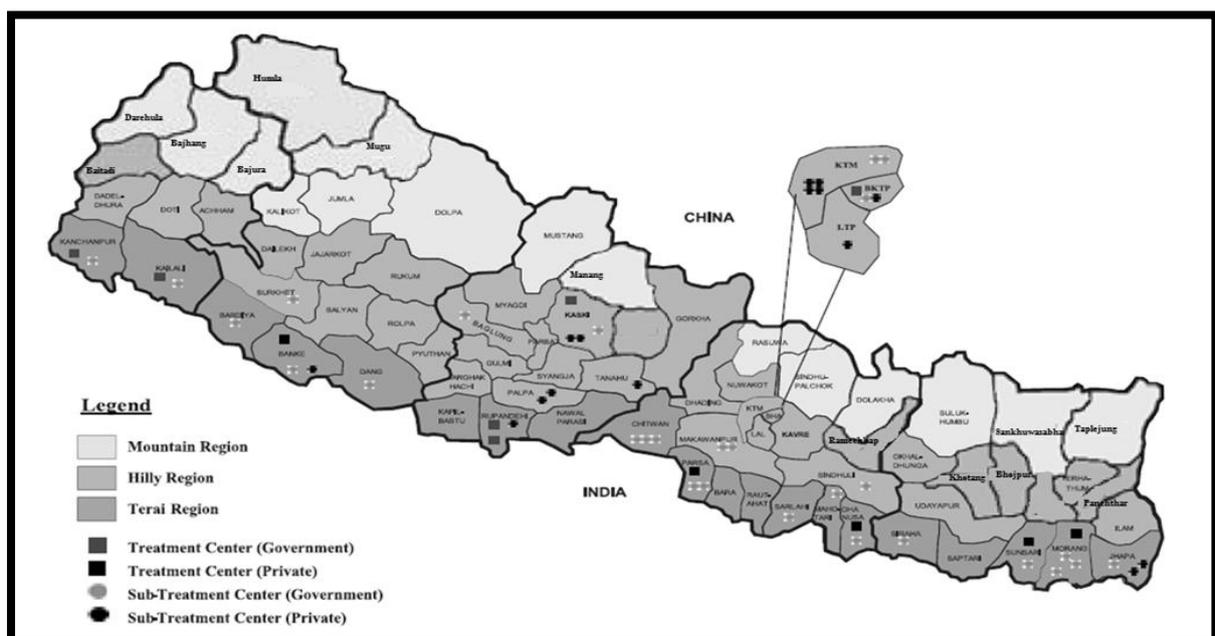
Public private partnership is an approach of DR-TB management. Under guidance of NTP, several partners from private sectors which include medical colleges and I/NGOs are operating almost 50% of DR-TB Treatment Centres and 30% of DR-TB Sub Treatment Centres (NTP, 2011a).

Health Care Facilities for DR-TB service

Tuberculosis care services are claimed to be available all over the country since each VDC has sub health post (SHP) which is supposed to be the sub treatment centre for tuberculosis management (NTP, 2011a).

There are 1,112 Treatment Centres and 3,126 Sub Treatment Centres for drug-susceptible tuberculosis management. For DR-TB, there are 12 treatment centres and 62 Sub Treatment Centres (NTP, 2011a). If the availability of services for drug-susceptible TB is assumed as 100%, the coverage (here, availability) of DR-TB services can be estimated to be less than 1%. The map (*figure 9*) shows DR-TB treatment centres and sub treatment centres throughout the country.

Figure 9: MDR-TB Treatment Centres and Sub Treatment Centres



Source: GLC, 2010

It can be seen in the map that most of the centres are concentrated in Terai region (plain region). Very few facilities are providing DR-TB services in hilly region and almost none in mountain region. Services are available in more accessible parts of the country rather than those parts where geographical accessibility is always a challenge. However, NTP has already planned to scale up the treatment centres and sub treatment centres from 74 to 80 by 2015 (NTP, 2010b).

Human Resource Management

Shortage of human resource for health services in rural areas is a global problem. It is a big challenge in a developing country like Nepal where 83% population lives in rural areas (WHO, 2006; CBS, 2011). Absolute shortage, inadequate competency, uneven distribution and improper human resource management are the main problems in Nepal (WHO, 2008c). Since Tuberculosis control programme is integrated in primary health care services, the human resource for TB programme cannot be seen in isolation.

NTP is responsible for technical support for health care providers involved in its activities whereas department of health services (DoHS) is the main authority for deployment and transfer of the health care providers. Ministry of Health and Population (MOHP) has already adopted the Human Resource Development Information System which records information of human resource for health and links with other health information systems like health management information system (HMIS), logistics and finance for appropriate human resource management (DoHS, 2011).

NTP has defined the roles and responsibilities of health care providers at all levels for TB care services and also regularly conducting trainings, refresher trainings, workshops and meetings on different topics like MDR-TB case management, basic microscopy, logistic management training for MDR-TB, TB/HIV co-infection management, etc (NTP, 2011a). The quality of health care services is also dependent on staff's presence at work, motivation and competency as to how they apply their skills at work (WHO, 2008c). In order to create motivation among staff working in MDR-TB treatment centres, sub treatment centres and laboratories, a financial incentive of \$20/month/staff has been planned in NSP 2010-2015 (GLC, 2010).

3.1.3 Laboratory Aspects

TB Diagnostics

Acid Fast Bacilli (AFB) microscopy is still being used to detect TB worldwide but it does not tell about drug resistance. It cannot differentiate other bacilli like non-tuberculosis mycobacteria and it has only 40-60% sensitivity, meaning that almost 40% of TB cases are being gone undetected. The sensitivity is much lower in HIV infected and in children. However, this technology is cheapest, most feasible and has good specificity of 80-90%. Therefore, AFB microscopy has remained as a widely used TB diagnostic, especially in developing countries (Farnia et al, 2002).

MDR-TB can only be diagnosed by culture and Drug Susceptibility Testing (DST), and it is a gold standard. Culture and DST requires high level of technical expertise, sophisticated laboratory setting and it is labour intensive and time consuming. In recent years, more advanced molecular technologies that can rapidly diagnose drug resistance tuberculosis are emerging. Based on nucleic acid amplification technology, MTBDR^{plus}³ assay can detect both rifampicin and isoniazid resistance and Xpert MTB/RIF⁴ (*GeneXpert*) can detect rifampicin resistance. Xpert MTB/RIF has sensitivity of 97.5% (95% CI 94.4-99) and specificity of 98.1% (95% CI 96.5–98.9) (Boehme et al, 2010; Miotto et al, 2006)

Laboratory Network and Coordination

AFB microscopy centres are available throughout the country. MDR-TB diagnostic is only available in two laboratories that are located in the capital city. Recently in 2010, NTC central laboratory was also authorized to perform culture and DST. GENETUP is National Reference Laboratory (NRL) and is responsible for assisting general organization of NTP laboratory network, performing mycobacterial culture and DST, providing support for quality assurance system for sputum smear microscopy, culture and DST for all laboratories at DR-TB diagnostic sites, liaising with a WHO accredited supranational laboratory for second line DST and External Quality Assurance (NTP, 2011b).

GENETUP laboratory has a capacity to perform 600-700 cultures per month, 500-600 first line DST and 25 second line DST a year.

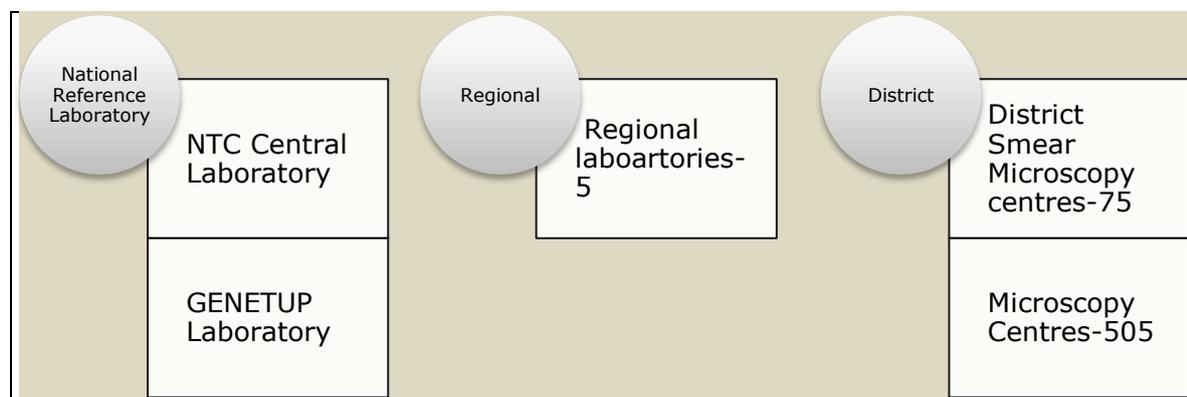
³ MTBDRplus test is a commercially available line-probe assay that rapidly detects Mycobacterium tuberculosis (MTB) complex, as well as the most common mutations associated with rifampicin and isoniazid resistance (Huyen et al., 2010).

⁴ Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance (WHO, 2011c).

According to GLC report, GENETUP has been already overburdened with high number of tests for follow up cultures. NTC central lab can perform 200 cultures per month but the capacity for DST has not been mentioned.

All specimens from suspected DR-TB cases and follow up specimens from DR-patients should be brought to these laboratories. However, 3 regional laboratories (Eastern, Western and Mid-western) are planned to upgrade for performing cultures. NSP 2010-2015 has a plan to upgrade eastern regional laboratory to perform DST. Western regional laboratory has been already upgraded to perform culture (NTP, 2010b; GLC, 2010). The figure below shows NTP laboratory network throughout the country at different levels.

Figure 10: NTP Laboratory Network



Source: NTP, 2011a

The DR-TB management guideline has recommended that culture should be done at 0, 1, 2 months, then every two months until treatment completion. DST should be performed at start and it can be done conditionally, for example, if culture is positive (GLC, 2010 & NTP, 2011b). The result of culture and DST is delivered to the treatment centre by phone so that there is no need to wait to receive the hardcopy for decision making (GLC, 2010).

Laboratory Quality Control

NTP laboratory network has been adopting a quality assurance system that collects samples according to LOT Quality Assurance Sampling system (NTP, 2011a).

National Reference laboratories are affiliated with Supra National Laboratory Gauting, Germany. The external quality control of DST for GENETUP laboratory performed in 2009 showed that result was 100% (GLC, 2010). For AFB microscopy, overall agreement rate is 97.4%. Regular feedback mechanism exists to ensure and maintain quality throughout the country (NTP, 2011a).

3.1.4 Case Finding Strategy

Besides appropriate diagnostic tool and adequate laboratory facilities, case finding strategy is one of the important aspects of MDR-TB control. NTP Nepal has been adopting passive case finding strategy for TB control activities in general (NTP, 2011a). However, NTP has adopted high-risk targeted systematic screening as DR-TB case finding strategy. The table below shows high-risk target groups for first-line DST (NTP, 2011b).

Table 4: Target group for first line DST

1. Failure of Category I(CAT-I)⁵
2. Failure of Category II(CAT-II)⁶
3. CAT-I & CAT-II: failed to convert at 2-3 months and poor clinical response (e.g. persistent fever, cough, weight loss, etc.).
4. TB suspects in HIV infected
5. Any CAT II patients
6. (return after default, relapse, failure)
7. Close contacts of MDR-TB patients

Source: NTP, 2011b

If CAT-I patient is failing to respond the treatment and severely ill that s/he cannot wait for 2-3 months for DST result, MTBDRplus (rapid DST) can be requested at GENETUP. Similarly, if there is suspicion of second line drug resistance, second line DST can be requested at GENETUP. The target groups for second line DST are listed in the table below (NTP, 2011b).

Table 5: Target groups for second line DST

1. Any patient who has had a past history of second line treatment
2. Any patients who has remained culture positive after 4 months of standard MDR-TB treatment or who converts to culture positive after 4 months of the standard MDR-TB treatment
3. Contacts of documented XDR-TB

Source: NTP, 2011b

⁵ CAT I failure: A new patient who is culture or sputum smear microscopy positive at five months or later during treatment (NTP,2009)

⁶ CAT II failure: previously-treated patient who is culture or sputum smear microscopy positive at the end of the re-treatment regimen (NTP, 2009)

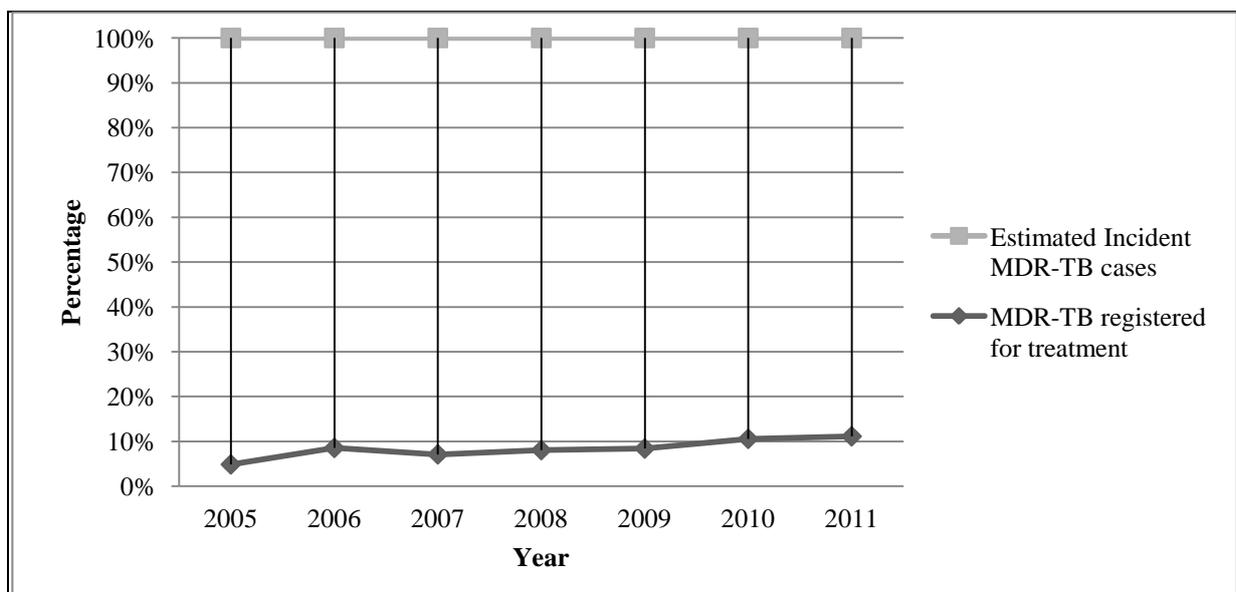
TB diagnosis in paediatric population is challenging since children rarely produce sputum (Brown et al, 2007). Case finding among children aged 0-14 years is 1.6% among all sputum smear positive cases from mid-July 2010 to mid-July 2011. Data for MDR-TB among children's population is not available. National DR-TB guideline mentions that children who are in close contact of DR-TB patients can be diagnosed based on clinical evaluation, chest X-ray findings and tuberculin test (NTP, 2011a; NTP, 2011b). Other sample collection techniques (e.g. Sputum induction, gastric aspiration) for culture and DST are not mentioned.

Case Finding

In Global Plan to Stop TB 2011-2015, case detection rate (CDR) is removed from DOTS component indicator because impact indicators as burden of disease (e.g. prevalence, incidence and mortality) are considered more appropriate targets for the reduction of burden of disease. Therefore, the number of cases diagnosed, notified and treated in DOTS programmes is recommended to use as case finding indicators (WHO, 2011d).

It is estimated that number of MDR-TB among total incident cases in Nepal is 1700 (95% CI 990-2300) (WHO, 2011b). Assuming that estimated incidence as 100%, MDR case findings (here registered for MDR-TB treatment) from 2005-2011 is shown in the graph (*figure 11*) below.

Figure 11: MDR-TB cases registered for treatment among estimated cases



Data Source: NTP, 2009; WHO, 2011b

It can be seen that MDR-TB case finding is very low. If the incidence estimation is true, large proportion (nearly 90%) of MDR-TB cases are either not notified or not on MDR-TB treatment. All these unnoticed MDR-TB cases can continue the spread of MDR-TB in the community if they are alive. Because of unavailability of data, the proportion of treatment initiation among total diagnosed MDR-TB cases could not be presented.

In Bhutanese refugee population, IOM is adopting active case finding strategy. By this strategy, the prevalence of pulmonary TB is 2.7 times higher than previously reported prevalence of all form of TB. The prevalence of MDR-TB among all tested is 2%. (Gorbacheva et al, 2010). Although active case finding strategy can yield an accurate TB prevalence, it might not be feasible to apply it in general population.

The Global Plan to Stop TB 2011–2015 has set a target of 100% to have MDR-TB testing for previously treated TB patients and 20% for newly diagnosed TB patients by 2015 (WHO, 2011d). NTP annual report did not mention these indicators of laboratory testing. Therefore, it is difficult to say how many of previously treated cases and new cases are tested for MDR-TB.

Previously treated cases (defaulters, failures and relapses) of drug-susceptible TB are likely cases for MDR-TB. According to NTP annual report 2011, the top ten districts for failures and defaulters of drug-susceptible TB are presented in the table below.

Table 6: Top ten districts for failure and defaulter, 2009 to 2010

District	Treatment Failure	Defaulter	Combined (Failure+ Defaulter)
Kathmandu	15	31	46
Sunsari	6	40	46
Dhanusa	3	33	36
Rupendehi	16	18	34
Kapilvastu	11	22	33
Morang	4	27	31
Banke	4	24	28
Mahottari	3	23	26
Sarlahi	8	17	25
Jhapa	13	9	22

Data source: NTP, 2011a

This data shows that defaulters and failures are mostly in terai districts and also in the capital city. Probably, MDR-TB cases are also concentrated in these areas although district-wise data are not available. It is interesting to note that the capital city of Kathmandu appears as number one.

A study conducted in Kathmandu among 250 re-treatment cases (relapse, failure and return after default) shows that the occurrence of MDR-TB was found to be 10% (Yoshiyama et al, 2010).

3.1.5 Treatment Strategy

The next step after diagnosis is treatment. The common pathway towards the development of MDR-TB is inadequate treatment of drug-susceptible tuberculosis. Inadequate treatment of DR-TB continues the infection in the community. Therefore, treatment strategies, treatment regimens, model of care and treatment delivery process are important factors for adequate treatment.

Treatment Regimen and Model of Care

There are two types of treatment regimens: standardized and individualised. "Standardized treatment means that all patients in a defined group receive the same treatment regimen". Some advantages of standardized treatment over individualized treatment are decrease in prescription error, ease in estimation of drugs needed and cost effectiveness (WHO, 2009a).

NTP Nepal's guidelines are based on recommendations of International Standards of Tuberculosis Care (ISTC) developed by different international partners including the WHO (NTP, 2011a; TBCTA, 2009). "Tuberculosis Case Management Guideline for health workers and doctors" was developed by NTP in 2009. Since the beginning of DOTS programme, NTP Nepal has been adopting standardized treatment. NTP has grouped patients into different categories for assigning treatment regimens (See *annex 4*). Category I (CAT-I) is for all new TB cases, Category II (CAT-II) is for all re-treatment TB cases and Category IV (CAT-IV) for MDR-TB cases (NTP, 2011b; NTC, 2009).

Although NTP Nepal is also using standardized treatment regimen for MDR-TB, individualisation is permitted based on patient's status in terms of side effects, pregnancy and XDR-TB. As explained in DR-TB guideline, MDR-TB treatment can be started for those patients who have laboratory confirmed MDR-TB or highly suspected MDR-TB (e.g. failure of CAT-II regimen) before DST result (NTP, 2011b). The detail of the registration groups is attached in *Annex 5*.

MDR-TB treatment in Nepal consists of at least four drugs with either certain or almost certain effectiveness. An injectible is used for 8 months. However, it can be extended up to 12 months in case of slow conversion and XDR-TB. The minimum duration of treatment is 20 months and 12 months after culture conversion⁷. The MDR-TB regimen is shown in the table below (NTP, 2011a; NTP 2011b).

Table 7: MDR-TB regimen in Nepal

8 (Km-Z-Lfx-Eto-Cs)/12 (Lfx-Eto-Cs-Z)	
Intensive Phase (8 – 12 months)	Continuation Phase (12 months)
Kanamycin (KM) Pyrazinamide (Z) Levofloxacin (Lfx) Ethionamide (Eto) Cycloserine (Cs)	Pyrazinamide (Z) Levofloxacin (Lfx) Ethionamide (Eto) Cycloserine (Cs)

Source: NTP, 2011a

For XDR-TB, standardized regimen is recommended as shown in the table below (NTP, 2011b).

Table 8: XDR-TB regimen in Nepal

First 12 months	Last 12 months
capreomycin (Cm) + moxifloxacin (Mfx) + p-aminosalicylic acid (PAS) + amoxicillin/clavulanate (Amx/Clv) + pyrazinamide (Z)	moxifloxacin (Mfx) + p-aminosalicylic acid (PAS) + amoxicillin/clavulanate (Amx/Clv)

Source: NTP, 2011b

NTP Nepal has adopted ambulatory-based treatment as model of care for DR-TB. Hospitalisation is limited for very sick patients, severe side effects, adherence problems and vulnerable patients (e.g. disadvantaged orphan, mentally or physically handicapped) (NTP, 2011b).

A study conducted among 175 laboratory-confirmed MDR-TB cases enrolled for treatment from 15 September 2005 to 15 September 2006 found that high cure rate (up to 70%) can be achieved with ambulatory-based standardized MDR-TB treatment (Malla et al, 2009).

⁷ First smear negative and culture negative for two consecutive months

Treatment Delivery Process

Treatment delivery process is a sum of different processes involved in the prescription and delivery of anti-tuberculosis drugs to the diagnosed tuberculosis patient (Lambregts & Veen, 1995).

Directly Observed Treatment (DOT) means a trained or supervised person (treatment supporter) observes the patient swallowing anti-TB drugs. DOT is one of the measures that promotes and assesses adherence to the treatment (WHO, 2002). The treatment supporter could be a health care provider or community health volunteer or any trained person. NTP principally discourages to assign family member as treatment supporter in case of MDR-TB treatment because family member or relative could be more easily manipulated by the patient (NTP, 2011b).

However, one cluster randomized trial conducted in 10 hilly and mountain districts of Nepal showed that there is no significant difference between community DOTS⁸ and family-member DOTS⁹ for achieving positive outcome as cured and treatment completed (adjusted OR¹⁰=0.67, 95% CI 0.41-1.10, p=0.09) (Newell et al, 2006). This study comprised of only drug-susceptible TB patients. Such study for DR-TB has not been conducted yet.

Although DOT has several advantages, it is not devoid of controversy. Based on six clinical trials comparing DOT and SAT (self-administered treatment), a Cochrane systematic review concluded that DOT did not improve outcomes in terms of cure rate and treatment completion. However, there are several other reviews that showed that DOT is associated with high cure and treatment completion rates (TBCTA, 2009 & Jimmy et al, 2000).

ISTC has recommended that DOT should be individualised to a particular patient and it should be mutually acceptable to the patient and service provider (TBCTA, 2009). NTP Nepal has adopted DOT as mode of treatment delivery for drug-susceptible and drug-resistant TB cases and it is clearly explained in national TB treatment guidelines (NTP, 2011b; NTC, 2009).

⁸ Community DOTS: a strategy with drug taking supervised daily by a female community health volunteer or a village health worker, with drugs provided to the supervisor every month (Newell et al, 2006).

⁹ Family-member DOTS: strategy with drug taking supervised daily by a household member selected by the patient, with drugs provided to the patient's supervisor every week (Newell et al, 2006).

¹⁰ OR=Odds Ratio

The treatment for MDR-TB and XDR-TB is mostly clinic based which increases the burden of travelling every day to the clinic for 24 months (NTP, 2011a & GLC, 2010). It can create a difficulty for treatment adherence.

However, DR-TB guideline has some flexibility for community-based DOT for DR-TB, which could be applied only in special situations (e.g. non-ambulatory patient) with the prerequisite that the patient should be at continuation phase of treatment (NTP, 2011b).

Adherence and Patient Support

A systematic review of qualitative studies found that several factors are responsible for adherence to TB treatment and these factors can be grouped as health service factors, personal factors, structural factors and social context (Munro et al., 2007). Trostle (1988, p.1305) said "Non-compliance is an unavoidable by-product of collisions between the clinical world and the other competing worlds of work, play, friendships and family life".

Poor adherence not only increases risk of drug resistance but also increases the risk for morbidity and mortality (WHO, 2003). Adherence to the TB treatment, especially DR-TB treatment is a complex issue. The outcome of the TB control programme largely depends on adherence strategy and its successful implementation.

The importance of treatment adherence is well reflected in DR-TB guideline. Incentives for delivery of DOT, disease education, socio-economic support, emotional support and prompt management of side effects are considered as major measures to ensure treatment adherence (NTP, 2011b).

NTP Nepal has been providing all kinds of TB treatment and diagnostics services free of cost (NTP, 2011a). MDR-TB patients are receiving Nepali Rupees 1500 (about \$20) per month as incentive. Since MDR-TB treatment is mostly clinic based, there is an undue burden on the patient travelling to the treatment centres every day (GLC, 2010). NSP 2010-2015 has planned to rent 10 hostels that could accommodate 100-150 MDR-TB patients (NTP, 2010b). This patient support scheme is not applicable to drug susceptible-TB patients.

Side Effects Management, Monitoring and Follow up

Side effects management for both drug-susceptible and drug-resistant TB is clearly explained in the national guidelines. At the beginning of the treatment, possible side effects and when to seek for medical help is supposed to be explained to the patient and the treatment supporter (NTP 2011b; NTC, 2009). However, how well it is implemented in practice is not known.

One explorative study done in Eastern Terai showed that side effect is one of the important factors contributing to non-adherence to TB treatment. Majority of respondents said that health care providers did not explain what to do if they had side effects (Wares et al., 2003).

Monitoring patient's progress and side effect identification is a key step for appropriate TB case management for a positive outcome. For MDR-TB patient, monthly clinical follow up is recommended (NTP, 2011b & NTC, 2009). Most of the time patients gained weight during treatment and the dose of medication is to be adjusted accordingly but it has not been done until 2010 (GLC, 2010).

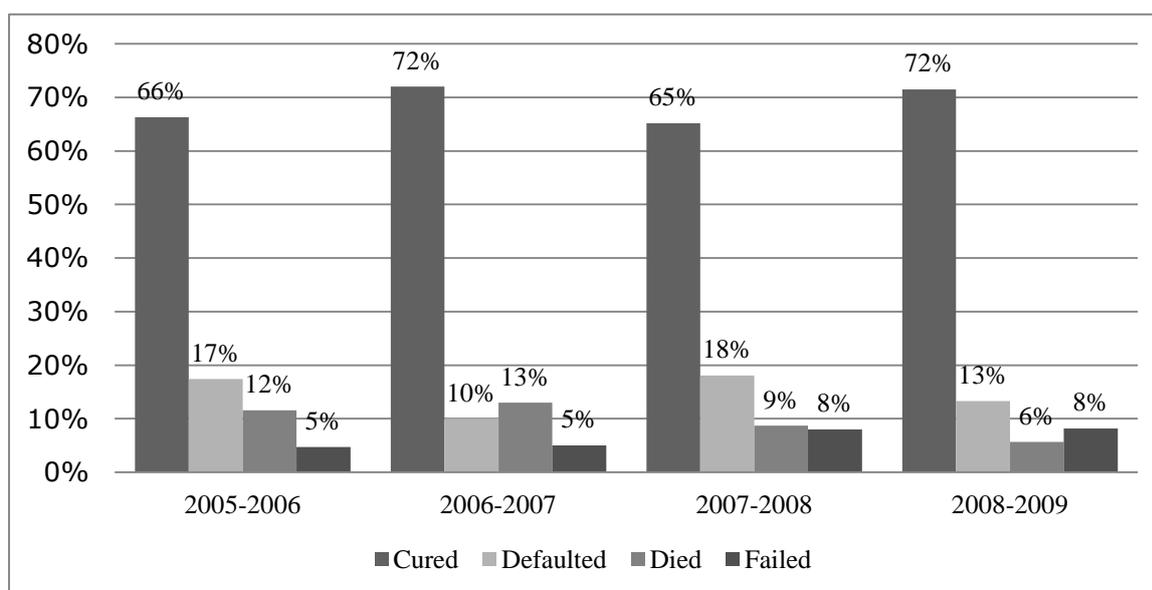
Follow up and contact tracing mechanism of MDR-TB is explained in national DR-TB guideline. During the initial diagnosis, all contacts' list is prepared and home visit is supposed to be done to take full history. Clinical follow up of contacts is supposed be done at least for 2 years but how often it is to be done is not clearly mentioned in the DR-TB guideline (NTP, 2011b).

Defaulter tracing is another important aspect, especially in DR-TB control. Although DR-TB guideline emphasized that there should be system in place for defaulter tracing, clear procedure on defaulter tracing mechanism for both drug-susceptible TB and drug-resistant TB is lacking (NTP, 2011b). Sometimes, patients who are diagnosed as MDR-TB do not show up for treatment. Only 43 patients started treatment out of 58 confirmed MDR-TB cases in 2009 (GLC, 2010). There is also no any mechanism to follow the "no show" cases.

Treatment Outcome of MDR-TB

Based on above-mentioned case finding and treatment strategies, NTP has registered 1026 MDR-TB and 27 XDR-TB cases for treatment until July 2011. Treatment outcome of MDR-TB from 2005 to 2009 is shown in the graph below (NTP, 2011a).

Figure 12 : MDR-TB treatment outcomes, 2005-2009



Data source: NTP, 2011a; NTP, 2010a

The cure rate ranges from 65% to 72%. WHO report 2011 shows that treatment success rate in 14 countries in 2008 cohort ranges from 25%-74% (WHO, 2001a). This means Nepal's MDR-TB treatment outcome seems to be satisfactory but not adequate because Global Plan target is $\geq 75\%$ (WHO, 2011d). Defaulter rate is always more than 10%. Failure rate is also increased in 2008. Defaulters and failures can act as reservoirs for the spread of MDR-TB in the community. Moreover, management of failure cases is challenging because treatment options are limited.

3.1.6 Drug Management-Procurement, Supply and Regulation

Global Drug Facility (GDF) has been procuring drugs for NTP on quarterly basis. Drug supply to different health facilities is carried out by logistic management division of DoHS. Every three months, requirements of the drugs are calculated at clinic level, based on utilization and buffer stock. Each level has 4 months' buffer stock to prevent stock out. At regional level the buffer stock is for 6 months to ensure against any unpredictable delays in supply. Cold chain system exists for PAS storage (GLC, 2010 & NTP, 2011a).

NTP Nepal has claimed that 95% of TB treatment occurs through NTP. NTP itself does not have the authority to regulate the drugs (GLC, 2010). Drug regulatory authority is Department of Drug Administration (DDA).

First line anti-tuberculosis drugs are available in the market. Although these drugs cannot be sold without physician's prescription as a rule, people can still purchase them from private pharmacies. Fluroquinolones, especially ciprofloxacin and ofloxacin are widely used for treatments against conditions other than TB. Similarly, amoxicillin-clauvalunic and amikacin are also widely used in different clinical settings like referral hospitals even in respiratory infections (personal observation). Other second line drugs (cycloserine, capreomycin, PAS, ethionamide, and prothionamide) are not easily available in private pharmacies (GLC, 2010).

3.1.7 Infection Control

Mycobacterium tuberculosis (MTB) is transmitted through airborne particles called droplet nuclei when TB patients with pulmonary or laryngeal TB coughs, sneezes, shouts, sings or talks. Droplet nuclei are expelled to the air and other person inhales them. These droplet nuclei can stay in the air for a prolonged period of time. Probability of getting infection primarily depends on the concentration of infected droplet nuclei in the air, duration of exposure and proximity to the infectious patient (CDC, 2005).

In the era of MDR-TB and XDR-TB, infection control measure is vital for protecting health care providers and community people. There are three major infection control measures: administrative, environmental and personal respiratory protection. The administrative control consists of early diagnosis of infectious TB patient; prompt isolation or separation, early initiation of appropriate treatment and minimization of the time at health care facility. This measure is considered most preferable and feasible (WHO, 2009b). The ratio of notification rate among health care providers and notification rate among general population can be taken for assessment of the quality of infection control measures (WHO, 2011a). NTP does not have data for this indicator.

Currently, NTP Nepal does not have any infection control policy and strategy. Infection control measures are not uniform; laboratory safety standards are also poor and there is no data on occupational risk of TB. However, infection control plan has been included in NSP 2010-2015 (NTP, 2010b).

3.1.8 Supervision, Monitoring and Evaluation

Monitoring and evaluation of NTP activities are carried out by GLC and GDF annually. Internally, supervision and monitoring is carried out at different levels in a regular basis. Findings of these activities are discussed during planning and reporting workshop every four months. Regular monitoring system includes case findings, smear conversion, treatment outcome and programme management (NTP, 2011a). However, NTP report does not mention summary of findings.

3.1.9 Recording, Reporting and Data Management

Data collection method is paper-based and complicated. Although NTP's activities are integrated into primary health care services, health care provider has to fill out separate forms for TB patients. There are three treatment cards: one for TB patient, one for treatment centre or sub treatment centre and one for NTC. For the side effect, a separate form is used (GLC, 2010). The recording system is quite labour intensive and health care provider can get overburdened.

In 2008, WHO supported electronic data collection software (OpenMRS) was installed for DOTS-Plus programme but it did not function well because NTC does not have dedicated IT staff (GLC, 2010).

3.1.10 Responsiveness of Health Care Providers

How the health system responds to the non-medical concerns of the patients is called responsiveness. The components of responsiveness are dignity, confidentiality, autonomy, prompt attention, social support, basic amenities, and choice of provider. Evidence shows that patients whose expectations are met by the services are more likely to adhere to treatment (Darby *et al*, 2012).

Information on responsiveness of health care provider in terms of TB control programme is not available probably because it is rarely studied. However, a study showed that one of the common reasons for interruption of TB treatment is behaviour of health care provider (Wares *et al*, 2003). A qualitative study conducted in Nepal showed that patients expect approachable and supportive health care providers so that patients can feel comfortable discussing their concerns, mostly non-medical issues (Lewis & Newell, 2009).

A case control study showed that poor communication between health care provider and patient is significantly associated with non-adherence to TB treatment (adjusted OR 11.2, 95% CI 2.5-50) (Mishra *et al*, 2006).

3.2 Patient Related Factors Preventing Uptake of TB Care Services

Inadequate uptake of TB care services usually results in poor outcome. Delay in health care seeking result in delaying for diagnosis and treatment, which ultimately leads to poor outcome. As explained earlier in conceptual framework, inadequate treatment of drug-susceptible TB leads to development of MDR-TB. Similarly, inadequate treatment of MDR-TB leads to poor outcome (treatment failure, death, development of XDR-TB). Therefore, adherence is vital for adequate treatment. Understanding of these factors is essential to design appropriate policy, plan and strategies for effective TB control. Considering these facts, this section explores patient related factors that could prevent adequate uptake of TB care services.

3.2.1 Socio-cultural Factors

Achievement in health does not only depend on health system itself; rather it largely depends on socio-economic factors. Existence of inequalities between and within countries is not a natural phenomenon; rather it is a combination of poor social policies, unfair economic distribution and bad politics (CSDH, 2008).

Stigma, Discrimination and Social status

A case control study in patients taking treatment from NTC shows that MDR-TB is significantly associated with social stigma (adjusted OR=2.65, 95% CI 1.22-5.76) and social exclusion (adjusted OR=3.06, 95% CI 1.41-6.67) (Mahato, 2010). Social exclusion is based on caste (e.g. *Dalit*), ethnicity (*Janajatis*¹¹) and gender (UNDP, 2009).

A qualitative study conducted in Kathmandu found that the causes of self-discrimination in relation to TB were expressed by respondents as fear of transmitting TB and fear of gossip in the community. Likewise, causes of discrimination by community members were expressed as fear of perceived risk of infection, perceived link between TB with poverty, low caste, bad behaviour and divine punishment (Baral et al., 2007).

Some respondents also felt that they were discriminated by health care providers. Baral et al. (2007, p.6) cited a quote from one respondent "...I mentioned that I saw blood in my sputum last week and came here for treatment. Suddenly and surprisingly, she asked me to stand far from the window and she covered her mouth, her behaviour was changed. I got surprised and worried I may have got a dangerous disease..."

¹¹ Nepal's indigenous nationalities, popularly called *Janajatis*

Advocacy, Communication and Social Mobilization (ACSM) policy guideline has been already developed by NTP in 2009, especially to combat stigma and discrimination and encourage adherence. It aims to train health care workers, FCHVs, school teachers and community workers. It also aims to mobilize cured TB patients through *TB patient club* (NTP, 2011a).

Health Seeking Behaviour and Beliefs

A study conducted in Nawalparasi found that patients take their consultation route from the private medical shop, pass through multiple providers and lately land in public TB treatment centre. The first health care seeking decision was mainly dependent on factors like perceived seriousness of illness, anticipated level of competence of provider, anticipated quality of care and anticipated cost and economic status of the patient (Ten Asbroek et al., 2008). Knowledge, Attitude and Practice (KAP) survey on TB conducted in a hilly district found that 20% of respondents believe that TB is a hereditary disease (BNMT & NTP, 2009).

Gender and TB

Both men and women have gender related problems to have access to TB care services. For example, fear of losing job often discourages working men for accessing TB care services, results in defaulting. Women are less likely to have access to healthcare service. However, it depends on different setting and socioeconomic strata (WHO, 2005).

Nepal has made significant progress in gender equality in the last decade. Women now have better access to education, politics, economic and social spheres. However, notable disparities still exist across caste and ethnicity, rural and urban settings. Women are grossly under-represented in decision making positions; educational status is poorer than men's and majority of women (77.3%) are engaged in agriculture for livelihood. Domestic violence against women exists throughout the country irrespective of caste, ethnicity, religion and geographical location (UNDP, 2010b). All these factors might affect the women's uptake of TB care services. However, it is difficult to say with certainty because studies are limited exploring gender role in terms of TB care service uptake.

TB Notification rate is always higher in males than females worldwide. In Nepal male to female ratio for case notification in 2011 was 2.2:1, whereas it was 1.9:1 globally (NTP, 2011a; WHO, 2011a). The reason why males have higher notification than females is not well understood. However, sex (biological) and gender differences might have an impact on TB notification (WHO, 2002).

A cross-sectional study in Nepal showed that women have been significantly associated with longer total delay to get diagnosis of TB. Women are more likely to go to traditional healers than men prior to TB diagnosis (Yamasaki et al., 2001). Study does not explain the reasons behind these disparities. However, it might also have some gender impact because women's social status is poorer than men in Nepal.

3.2.2 Economic Factors

Almost a quarter of the population in Nepal live with an income of less than \$1 per person per day (CBS, 2010) and tuberculosis is considered a disease of poverty. One analysis showed that deaths due to TB were decreasing in England before the invention of Bacillus Calmette-Guerin (BCG) vaccine and anti-tuberculosis drugs (McKeown, 1979). It was probably due to improved economic conditions leading to improved living conditions.

Several studies conducted in developed and developing countries found that economically poor and vulnerable people have greater risk of getting TB infection than general population. Similarly poor and vulnerable people are more likely to develop active TB and less likely to complete the TB treatment. Poor TB patient is likely to lose 20-30% of annual wages due to TB (WHO, 2005). In Nepal, large proportion of MDR-TB patients fall in the age group 15-54 years and almost 50% of patients belong to 15-34 years of age (NTP, 2011a). This shows that MDR-TB is affecting economically productive age group.

One case control study conducted in the western region showed that non-adherence to the TB treatment is significantly associated with unemployment (adjusted OR=9.2, 95% CI 3.2-28.5), low status of occupation (adjusted OR=4.4, 95% CI 1.5-12.5), and cost of travel to the treatment centre (adjusted OR=3.0, 95% CI 1.2-7.3) (Mishra et al, 2005). This shows that low socio-economic status is a key factor for non-adherence.

A qualitative study conducted among migrant workers in Kathmandu showed that patients experienced increased economic burden due to TB in terms of illness related costs, living costs and employment related costs. Despite the fact that TB treatment is free of cost, other costs like travel cost to visit treatment centres and cost for supportive medication are also important. Furthermore, many migrant workers were not aware of public health services and landed in private clinic where the service was expensive. Some migrant workers were too ill to go for work, which further cut their income. Treatment centre based DOT had compelled the patients to visit the treatment centre daily. This also cut their working hours. The job nature of migrant workers is usually temporary and daily wage based (Kirwan et al, 2009). These patients are vulnerable to be impoverished due to catastrophic health expenditures. Although this study

was done in specific group (migrant workers), the findings at least reflects the situation of urban poor.

Another qualitative study conducted in eastern Nepal found that all of the defaulter respondents were financially poor, had to leave work and faced difficulty in transportation. Majority of the respondents had stated that distance from the clinic was a major problem (Lamsal et al, 2009).

Chapter IV: Discussion

Tuberculosis has been existing since long in human society. TB bacillus will probably continue to survive in future if more appropriate interventions are not taken. Fight against TB is taking a chronic path. A curable disease is becoming complicated with the emergence of drug resistance. As discussed earlier, MDR-TB is a manmade problem but it is preventable. However, it might go beyond our control if our strategies to tackle it effectively fail.

A pioneer physician fighting against TB, Sir John Crofton (1912-2009) said, "The greatest disaster that can happen to a patient with tuberculosis is that his organisms become resistant to two or more of the standard drugs" (Crofton, 1959, p.1611). The impact of drug-resistance is not contained in a particular patient or a particular community; rather the impact will be large scale and global.

Historically, after introduction of effective chemotherapy, TB was rapidly declining in developed countries. By 1970, several developed countries stopped investment in tuberculosis control. The WHO had only two professional staff for TB control programme in 1989. Resurgence of Tuberculosis with new face of drug resistance compelled many developed countries to rethink about tuberculosis control, and in 1990 they restarted anti-TB drug resistance surveillance. In collaboration with several partners, WHO and IUATLD launched DRS in many countries to understand the Global situation (Espinal, 2003).

This chapter discusses and analyses the findings mentioned in previous chapter in order to indentify the major gaps and possible solutions for tackling drug resistant TB in Nepal.

4.1 Service Related Factors for Tackling MDR-TB

Tuberculosis is remained as priority health programme in Nepal. Government is also willing to contribute 18% of total budget required for TB control. Remaining 82% of NTP budget is from donors but a predominantly donor dependent financing is at risk. Thus, government should think about the sustainable financing.

Political commitment cannot be limited only to prioritization and funding. TB is also a social disease that is often linked to poverty and poor living standards. Wide multi-sectoral collaboration between ministries and private sectors is essential to reduce poverty and improve people's living standards. Achieving MDG-1(poverty reduction) could help to achieve MDG-6(TB control) because they are closely linked.

Programmatic management of DR-TB is articulated in paper. Public-private partnership is well emphasized. It is noticeable that 50% of treatment centres and 30% of sub treatment centres are run by private sectors including I/NGOs. DR-TB management guideline is in hand. MDR-TB coordinator is assigned. Technical Advisory Group is formed. However, the effectiveness of these measures in terms of DR-TB control is yet to be seen.

Health care facilities for DR-TB are mainly located in more accessible regions of the country. It would be justifiable if it was designed based on allocative efficiency. The information on geographical distribution of MDR-TB is not available. Therefore, it is difficult to comment on it. However, if the allocation is based only on the case notification, it might not be equitable because people living in remote parts often have difficulties in accessing healthcare facilities even they are sick.

Since NTP activities are fully incorporated into primary health care service, human resource for TB care services cannot be seen in isolation. It is observed that NTP doesn't have authority for deployment and transfer of the staff involved in TB care services. However, it can be done through coordination mechanism between DoHS and NTC. Financial incentive to the staff working in DR-TB care facilities is a way forward. Since infection control mechanism is inadequate and data on occupational risk is lacking, it is important to think about the occupational risk protection mechanism for health care providers.

How and when a patient is diagnosed is crucial for effective TB control. NTP Nepal has passive case findings strategy which is most cost effective and most appropriate strategy for a developing country like Nepal. In contrast, if this strategy misses cases, NTP needs to invest for long periods of time and if it misses MDR-TB, the epidemic of MDR-TB will be more difficult to tackle as it is 32 times costlier than drug-susceptible TB (Baltussen et al, 2005). NTP has high-risk targeted case finding strategy for MDR-TB, focus on retreatment cases, HIV infected and close contacts. With the current strategy, only about 10% of estimated MDR-TB cases have been detected. High risk groups such as migrant workers, prisoners and people living in congregated settings like urban slums and factories are not targeted. Therefore, MDR-TB case finding strategy seems to be inadequate.

AFB microscopy has remained a main tool for TB diagnosis. As mentioned in the Global Stop TB strategy 2011-2015, there should be at least 1 microscopy centre for 100,000 population, whereas in Nepal, it is almost 2 microscopy centres per 100,000 population (WHO, 2011d; NTP, 2011a). Still many cases may have been missed from being diagnosed because AFB microscopy is notoriously insensitive as it detects only 60% of culture positive pulmonary TB (Young et al, 2008).

Culture and DST is only available at central level in two laboratories. Specimen transportation is a challenge since the country lacks enough good networks of roads. Maintaining cold chain during transportation is another challenge because courier companies used for the transport vary between regions (GLC, 2010). Delay in diagnosis poses an additional risk for patient dying before diagnosis or surviving with disease and continuing transmission. Therefore, rapid diagnosis at the point-of-care is urgent. The alternative would be Xpert MTB/RIF that has far better sensitivity and specificity than AFB microscopy and is relatively fast.

Rapid DST is the most cost effective strategy even in low MDR-TB prevalence setting. The expected benefits by adopting rapid DST are increase in likelihood of early treatment, increased cure rate, decreased mortality, reduced development of additional drug resistance and reduced likelihood of failures and relapses (WHO, 2011c). GLC has recommended NTC central laboratory to have genotyping testing. Although it has not been mentioned in National Strategic Plan (NSP) 2010-2015, there is still possibility because adequate fund is available to have it (GLC, 2010).

Another challenge is paediatric case findings. Existing guidelines do not mention about more invasive techniques like sputum induction or gastric aspiration that could be alternatives to get specimen from children for culture and DST. However, these techniques need a high level of expertise. Application of these techniques is therefore appropriate in referral clinics where high technical expertise is available.

Standardized treatment regimen is the main treatment strategy for both drug-susceptible and drug-resistant tuberculosis. Introduction of rifampicin throughout the course is a step forward. MDR-TB treatment regimen can be individualised in special conditions like pregnancy or side effects and also for XDR-TB. Since second line DST is not feasible for every MDR-TB patients in resource-limited setting like Nepal, standardised treatment for MDR-TB is probably the best choice. A study conducted among 175 laboratory-confirmed MDR-TB patients found that high treatment success can be achieved with fully standardized MDR-TB regimens (Malla et al, 2009).

As mentioned in GLC report, medication was not changed as patient gained weight. If the dose of medication is not adjusted according to body weight, the treatment will be inadequate and risk of developing resistance increases.

Treatment delivery strategy through DOT is controversial. It is a kind of mistrust in the patient and family member. Mutual understanding between patient and health care provider or treatment provider is important. However, there is already a shift from strict health care provider provided DOT to community-based DOT.

Another problem is the impractical clinic-based DOT for DR-TB patient: an MDR-TB patient who, most probably, already tried two treatment regimens, has to attend clinic every day for 24 months. The good intention should be to treat and cure the patient, and also, to ease his/her life. ISTC also recommends that DOT should be individualized with patient's circumstances and decision should be made mutually (TBCTA, 2009).

Here it is noteworthy to quote from "DR-TB management guideline and manual" page number 52, which says, "The patient must live relatively close to the clinic and may need to relocate" (NTP, 2011b). NSP 2010-2015 mentioned that almost 60% of MDR-TB patients are compelled to leave their job and home to receive the treatment (NTP, 2010b). It should be noted that it is not possible for a majority of poor MDR-TB patients from economically productive age group to relocate with a mere sum of 20 US dollars per month provided by NTP. Thus, the psychosocial impact and the opportunity costs of patients compelled to leave their homes and work need to be taken into account. If hostels are arranged as mentioned in NSP 2010-15, it might somehow help with relocation.

Although adherence is well acknowledged as an essential factor for effective DR-TB control, interventions is basically encircling the DOT. We can go further and can explore new options for better adherence. It also can be learned from other chronic diseases as well. For example, a pilot study conducted in India among Type II DM patients found that a reminder sent through SMS has improved treatment outcome (Shetty et al, 2011). "SMS reminder technique" can be further studied whether it increases the adherence among MDR-TB patients or not.

Drug-susceptible TB patient does not get any financial support but most TB patients are from the poor quintiles. Even though drug-susceptible TB treatment is known as short course treatment, 6 months is not a short duration. Some studies already mentioned show that patients perceive financial burden more than the disease itself. Indirect costs like transportation are obstacles in continuing treatment.

There is no clear protocol on patient tracing mechanism for both susceptible-TB and drug-resistant TB patients in national guidelines. A quarter of MDR-TB diagnosed patients do not show up for their treatment initiation. MDR-TB defaulter rate is also high (>10%). Therefore, effective intervention is required to encourage patients for treatment initiation and treatment adherence. Patient tracing mechanism is essential to understand their problems as to why they do default and why they do not show up for treatment initiation.

NTP Nepal has claimed that adequate training, refresher training, supervision, monitoring and evaluation are being conducted on regular basis. Information about the impact of these activities is not readily available except some process indicators like number of staff being trained. However, these process indicators alone do not guarantee that trained staffs are applying their knowledge appropriately.

Drug procurement and supply seems to be well managed. Adequate stock is maintained and quarterly drug order is being practised. If it is true, there should not be any stock outs. Since GDF is responsible for procuring drugs on quarterly basis, there should not be any problem on quality of drugs. As mentioned in GLC report, NTP states that drug regulation is not its area of authority and DDA is responsible for drug regulation. However, it is possible for NTP to coordinate with DDA to regulate anti-TB drugs in the markets.

NTP has already acknowledged that there is no national infection control strategy in hand and infection control measures are inconsistent. This is disheartening for TB control programme, especially in cases of drug resistance. The data on occupational risk is also not available. Good news is that NSP 2010-2015 has already planned to prepare and implement infection control strategy. Administrative measures should be given first priority because it can dramatically reduce the risk of transmission among health care providers and patients and it is most feasible. Personal respiratory protection is also important. Environmental control measure would not be feasible at local level in Nepal because it needs engineering reconstruction. However, it can be done from the beginning if NTP is establishing and constructing new treatment centres.

Service uptake is largely dependent on the responsiveness of the health system. Information related to responsiveness in terms of TB care in Nepal is lacking. However, a couple of studies already indicate that patients expect positive responsiveness from health care providers. This author believes that if we treat TB only through biomedical approach, not addressing the non-medical issues of the patient, it is likely that we will not be able to win the war against tuberculosis.

Regarding service related factors, information system is crucial because it gives us knowledge that can be used to identify problems and address them appropriately. Paper-based and time consuming recording and reporting system exists and electronic system failed because of a lack of IT staff. Reinstatement of electronic system is required at least wherever feasible.

Although operational research has been acknowledged as a necessity for effective TB control programme, only very few studies have been conducted in relation to MDR-TB to explore service related factors. NTP has included operational research in NSP 2010-2015 but area selected for MDR-TB is only DRS (NTP, 2010b).

4.2 Patient Related Factors Preventing Uptake of TB Care Services

In terms of patient related factors, limited studies are conducted in Nepal in relation to Tuberculosis. Most of these studies were conducted in more accessible parts of the country but the reasons for selecting those geographical locations were not clarified. Based on whatever literatures are available, this section will discuss the patient related issues which could prevent uptake of TB care services.

In the community, TB is perceived as a disease of poverty, low social status, divine punishment, low caste disease, result of bad behaviour, etc. This kind of community perception creates a stigma linking to TB. Self-stigmatization and community stigmatisation and discrimination hinder uptake of adequate services. Unfortunately, patients are being stigmatized by health care providers as well. It is quite discouraging for patients to go to the health care facility for services. Although NTP has ASCM policy and guideline, only process indicators are presented in annual report. Thus, effectiveness of ASCM to combat stigma and discrimination is not known. However, it is good to note that NTP is aiming to train health care providers, FCHVs and community volunteers. Aiming to involve cured patients through patient club is a good start. Moreover, cured patient club might help to encourage the patients for adherence as well.

There is still misconception about TB. Studies found that still some people perceive that TB is hereditary disease; TB is result of divine punishment and TB is because of bad behaviour. Such kind of misconception hinders uptake of TB care services.

Although Nepal has made significant improvement to reduce gender inequality in the last decade, it still exists throughout the country. Women and girls are disadvantaged because of gender inequality in terms of education, economic status, representation in decision-making process. Gender usually plays a role in health service uptake. Because of unavailability of literatures, detailed gender analysis in terms of TB could not be made. However, some studies showed that females are more likely to get delayed for getting TB diagnosis and more likely to seek help from traditional healers than males. It is not clear why this happens but it might have some gender impact. Case notification rate in females is almost similar to the global rate. The reasons for less case notification in females than males are not clearly understood.

Some of the studies showed that non-adherence to TB treatment is associated with unemployment and low income. Poor people often discontinue treatment without completion. A qualitative study conducted among migrant workers gives a lot of painful stories about financial inaccessibility to services. Those who need free treatment are not aware of the availability of free services. TB in poor family is one of the causes of catastrophic health expenditure leading to further impoverishment. All these financial factors force poor people to be defaulters. The author has not found the existence of financial risk protection mechanism to prevent catastrophic health expenditures in Nepal. For the effective TB control, pro-poor strategy needs be to in place because poverty and TB are linked through a vicious cycle. Poor people are more likely to develop TB disease and TB disease is likely to further impoverish the poor.

4.3 Limitation of Study

This study is based on literature review. Exploration of the facts largely depended on the availability of the literatures. Literatures found on systematic internet search and information collected from NTP Nepal is limited. Detailed analysis of four anti-TB drug resistance surveys was not possible because of unavailability of detailed reports. The author was also interested to analyse the data of patients who underwent Culture and DST in GENETUP laboratory. Although NTP Nepal agreed to release data, GENETUP laboratory has not released data. More detailed information about MDR-TB patients could not be presented as NTP report does not provide detailed information on it. Exploration of service related factors are largely dependent on NTP reports, guidelines and GLC reports because studies evaluating NTP programmes in different aspects are limited. In terms of patient related factors, studies are limited. The author has adapted a framework from three different concepts to integrate the objectives. The author feels that adapted framework has helped a lot although more detailed exploration would have been possible if more details would have been available.

Chapter V: Conclusion

Tuberculosis is a priority health programme in Nepal. Public private partnership is an example of successful collaboration. Policies, strategies, protocols, guidelines are well articulated in paper. Health facilities for DR-TB are mainly located in geographically accessible locations. Case finding strategy is passive. Culture and DST services are being scaled up. Treatment regimens are in line with international standards. Treatment delivery method is DOT. Patient support services are mainly targeted to drug-resistant TB. Drug procurement and supply is well organized. Infection control strategy is in plan. ASCM policy/guideline is in place. Patient club is already founded. Recording and reporting system is paper-based.

The major challenges for PMDT are reliance on passive case finding strategy, unclear patient tracing mechanism (especially defaulters), limited high-risk targeted case findings for DR-TB, lacking MDR-TB rapid diagnostic tool, poor childhood TB case finding techniques, relatively inflexible DOT method, inadequate patient support services and poor responsiveness. Furthermore, DR-TB services are limited to geographically accessible locations, which hinder the service uptake by patients living in remote parts of the country. Paper-based and time consuming recording system overburdens the health care providers leading to poor quality of care.

Social stigma and discrimination are big obstacles for the uptake of TB care services. Effectiveness of the ASCM to combat these issues is unknown. Sometimes, health care providers themselves discriminate TB patients. Similarly, financial and geographical accessibility is also a barrier for the continuation of treatment. Poor patients are more likely to interrupt treatment before completion and are likely to be impoverished because of catastrophic health expenditure since there is no financial risk protection mechanism. Similarly, poor people tend to be unaware about free TB services. Misconception about TB is prevalent, which creates stigma and also discourages seeking help in time. Gender role in TB is not clearly understood although women are more likely to delay for seeking TB care services and also more likely to seek help from traditional healers.

Based on the findings, it is not time to be satisfied with only meeting targets of drug susceptible TB. Current intervention strategies seem to be inadequate to tackle drug-resistant TB. Thus, urgent public health response is required to fight against new problem emerging as drug-resistant TB in Nepal.

Chapter VI: Recommendation

After analysing the findings, recommendations are made based on feasibility, equity and ethical considerations. Care has been taken not to duplicate the recommendations already provided by GLC. Similarly, recommendations are not made for those issues that are already included in National Strategic Plan 2010-2015. Considering these facts, following recommendations are made.

Recommendation 1:

NTP Nepal should introduce Rapid DST- Xpert MTB/RIF test

Since MDR-TB case detection is very low, it is essential to have rapid DST. Xpert MTB/RIF test is a suitable alternative even in a resource-limited setting. Initially, it can be introduced in some parts of the country as a test and then gradually scaled up at least to the regional level. It should be introduced as soon as possible.

Recommendation 2:

NTP Nepal should introduce wider high-risk targeted active case findings for MDR-TB

Current strategy mainly focuses on the re-treatment cases targeted for MDR-TB diagnosis. Since DRS shows that proportion of MDR-TB among new cases is 2.9%, case findings strategy should also be targeted to pick up primary MDR-TB cases. Therefore, periodic active case finding among high-risk groups (e.g. urban slum dwellers, prisoners, migrant workers, factory workers and health care workers involved in TB care settings) should be done.

Recommendation 3:

NTP Nepal should introduce individualised and flexible DOT

As recommended by ISTC, DOT should be designed based on mutual understanding between patient and health care provider. Such strategy should be applied to both drug-resistant and drug-susceptible TB. National guideline should include the clear procedures for DOT individualization and health care providers should be trained on it.

Recommendation 4:

NTP Nepal should scale up patient support services (psychological and financial)

Patients expect more than diagnosis and some pills for the treatment. Many of their problems and needs have to be addressed to facilitate completion of treatment. Although it is impossible to fulfil all needs, it is possible to address many of their concerns. Patients do not always expect financial support, but expect friendly behaviour from health care providers. This kind of support can be achieved through changes in health care provider's behaviours and establishment of patient-friendly counselling services at treatment centres. Psychosocial and adherence counsellors can be appointed to do this job. It is true that most of the patients need financial support as well but care should be taken that it should not be provided as blanket support. Therefore, piloting is recommended at certain places where the poverty is immense.

Recommendation 5:

NTP Nepal should introduce tracing mechanism for both drug-susceptible and drug-resistant tuberculosis patients

Protocols and procedures on tracing mechanism are not clear in national guidelines. Drug-susceptible TB defaulters are potential cases for MDR-TB development and drug-resistant TB defaulters are reservoirs for transmission of the disease in the community. Sometimes, diagnosed MDR-TB cases do not show up for the initiation of treatment. Therefore, an effective patient tracing mechanism should be established in order to reduce non-initiation of treatment and to prevent defaults by promoting adherence to treatment until completion. In such tracing mechanism, patient's confidentiality should be maintained.

Recommendation 6:

NTP Nepal should collaborate with various stakeholders to combat stigma and discrimination

Stigma and discrimination are seen as major obstacles for service uptake by the patient. Advocacy, Communication and Social Mobilization (ASCM) policy and guideline already exist. The stigma and discrimination reduction activities should be implemented from healthcare facilities to community levels as discrimination exists everywhere along the chain. NTP should take initiative and can collaborate with partner organizations and media houses for implementation of information, education and communication activities.

Recommendation 7:

NTP Nepal should take initiative to encourage researchers for operational research

National TB Control Programme has already set research as one of its objectives, but studies are still few. Knowledge is still lacking on several aspects of DR-TB control programmes, for example, responsiveness of DR-TB services, effectiveness of home-based DOT in MDR-TB treatment, reasons for defaulting, effectiveness of patient support services, testing of new treatment adherence model (e.g. "SMS reminder technique"), etc. Most probably, NTP also does not need to finance it or carry out the research itself, but could encourage and facilitate it by informing about this possibility to students and researchers who are interested.

References

Baltussen, R., Floyd, K., & Dye, C. (2005). Cost effectiveness analysis of strategies for tuberculosis control in developing countries. *BMJ (Clinical research ed.)*, 331(7529), 1364. doi:10.1136/bmj.38645.660093.68

Baral, S. C., Karki, D. K., & Newell, J. N. (2007). Causes of stigma and discrimination associated with tuberculosis in Nepal: a qualitative study. *BMC public health*, 7, 211. doi:10.1186/1471-2458-7-211[Online]. Available at: <http://www.biomedcentral.com/1471-2458/7/211> (Accessed on 07-July-2012).

BNMT & NTP (2009). *Knowledge, Attitude and Practices -Study on Tuberculosis among community People of Sindhupalchowk district*, Kathmandu: British Nepal Medical Trust & National Tuberculosis Control Programme

Boehme C.C., Nabeta P., Hillemann D., Nicol M.P., Shenai S., Krapp F., Allen J., Tahirli R., Blakemore R., Rustomjee B.S.R., Milovic A., Jones M., Brien, S.M.O., Persing, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C., Alland D. and Perkins M.D. (2010). Rapid Molecular Detection of Tuberculosis and Rifampin Resistance. *The New England Journal of Medicine*. 363(11), pp.1005-15

Brown, M., Varia, H., Bassett, P., Davidson, R. N., Wall, R., & Pasvol, G. (2007). Prospective study of sputum induction, gastric washing, and bronchoalveolar lavage for the diagnosis of pulmonary tuberculosis in patients who are unable to expectorate. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 44(11), pp.1415–20. Doi: 10.1086/516782

CBS (2010). *Nepal in Brief*. Thapathali, Kathmandu Nepal: Central Bureau of Statistics

CBS (2011). *National Population and Housing Census 2011, a preliminary report 2011*, Thapathali, Kathmandu Nepal: Central Bureau of Statistics

CDC (2005). *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings, 2005*. MMWR 2005; 54(No. RR-17)

Colijn C, Cohen T, Ganesh A, Murray M. (2011). Spontaneous Emergence of Multiple Drug Resistance in Tuberculosis before and during Therapy. PLoS ONE 6(3):e18327.doi:10.1371/journal.pone.0018327. [Online] Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0018327> (Accessed on 13-Mar-2012)

Collins, C., Omar, M., Adhikari, D., Dhakal, R., Emmel, N., Dhakal, M. R., Chand, P., et al. (2007). Health system decentralisation in Nepal: identifying the issues. *Journal of health organization and management*, 21(6), pp. 535-545.

Crofton John (1959). Chemotherapy of pulmonary tuberculosis. *British Medical Journal*, 1959, 5138(1), pp. 1610–1614.

CSDH (2008). *Closing the gap in a generation: health equity through action on the social determinants of health, Final Report of the Commission on Social Determinants of Health*, Geneva: World Health Organization

Darby, C., Valentine, N., Murray C.J. and L., de Silva A. (2012). *World Health Organization -strategy on measuring responsiveness*, GPE Discussion Paper Series: No. 23, EIP/GPE/FAR, World Health Organization. [Online]. Available at: <http://www.who.int/healthinfo/paper23.pdf> (Accessed on 14-July-2012)

DDA (2011). *Objectives, Department of Drug Administration*. [Online]. Available at: <http://www.dda.gov.np/objectives.php> (Accessed on 09-June-2012)

DoHS (2011). *Department of Health Services-Annual Report 2010-2011*, Teku, Kathmandu, Nepal: Department of Health Services

Dujardin, B., Kegels, G., Buvé, A., Mercenier,(1997). Tuberculosis control: did the programme fail or did we fail the programme? *Tropical Medicine & International Health*, 2: pp. 715–718. doi: 10.1046/j.1365-3156.1997.d01-388.x

Espinal, M. A. (2003). The global situation of MDR-TB. *Tuberculosis*, 83(1-3), pp. 44-51. doi:10.1016/S1472-9792(02)00058-6

Farnia P., Mohammadi F., Zarifi Z., Tabatabee D. J. Ganavi, J., Ghazisaeedi K., Farnia P. K., Gheydi M, Bahadori M, Masjedi M.R., and Velayati A.A. (2002): Improving Sensitivity of Direct Microscopy for Detection of Acid-Fast Bacilli in Sputum : Use of Chitin in Mucus Digestion. *JCM*, 40(2), pp. 508-511. doi:10.1128/JCM.40.2.508

FDA (2012). *Drugs@FDA, US Food and Drug Administration, protecting and promoting your health* [online]. Available at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> (Accessed on 26-July-2012)

Francis J. Curry National Tuberculosis Center and California Department of Public Health (2008). *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Second Ed*. California: Francis J. Curry National Tuberculosis Center

GLC (2010). *Green Light Committee Monitoring Report: Nepal, 22nd February to 26th February 2010*. Kathmandu: Green Light Committee

Global Alliance for TB (2012). *Global Alliance for TB Drug Development, TB Alliance Pipeline* [Online]. Available at: <http://www.tb Alliance.org/downloads/Pipeline/TBA-Pipeline-May-2012.pdf> (Accessed on 17-July-2012)

Gorbacheva, O., Mishra, A. K., Shapovalov, D., & Sudtasay S. (2010). Prevalence of bacteriologically confirmed pulmonary tuberculosis in the Bhutanese refugees in Nepal: Results of active case finding, *International Journal of Infectious Diseases*, 14(1), pp. 150.

Huyen, M. N. T., Tiemersma, E. W., Lan, N. T. N., Cobelens, F. G. J., Dung, N. H., Sy, D. N., Buu, T. N., et al. (2010): Validation of the GenoType MTBDRplus assay for diagnosis of multidrug resistant tuberculosis in South Vietnam, *BMC infectious diseases*, 10, 149. doi:10.1186/1471-2334-10-149 [Online]. Available at: <http://www.biomedcentral.com/content/pdf/1471-2334-10-149.pdf> (Accessed on 09-July-2012)

Jimmy Volmink, Patrice Matchaba and Paul Garner (2000). Directly observed therapy and treatment adherence, *The Lancet*, 355(9212), pp. 1345-1350.

Kirwan, D. E., Nicholson, B. D., Baral, S. C. and Newell, J. N. (2009). The social reality of migrant men with tuberculosis in Kathmandu: implications for DOT in practice. *Tropical Medicine & International Health*, 14(12), pp. 1442-1447. doi: 10.1111/j.1365-3156.2009.02405.x

Lambregts-van Weezenbeek CSB., J. Veen,(1995). Control of drug-resistant tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 76(5), pp. 455-459.

Lamsal DK., Lewis OD, Smith S, Jha N. (2009). Factors Related To Defaulters and Treatment Failure Of Tuberculosis Patients in the DOTS Program in The Sunsari District Of Eastern Nepal. *SAARC Journal of Tuberculosis and Lung Disease & HIV/AIDS* 6(1), pp. 25-30.

Lewis, C.P. & Newell, J.N. (2009). Improving tuberculosis care in low income countries - a qualitative study of patients' understanding of "patient support" in Nepal. *BMC public health*, 9, p.190. [Online]. Available at: <http://www.biomedcentral.com/1471-2458/9/190> [Accessed on 06-July-2012]

Long R. (2000): Drug Resistant Tuberculosis. *CMAJ*, 163 (4), pp. 425- 428.

Mahato R.K. (2010). *Factors associated with the occurrence of Multi Drug-Resistant Tuberculosis*, Degree of Bachelor of Public Health thesis, Biratnagar Nepal: Purbanchal University (Unpublished)

Malla, P., Kanitz, E. E., and Akhtar M. et al., (2009). Ambulatory-based standardized therapy for multi-drug resistant tuberculosis: experience from Nepal, 2005-2006. *PloS one*, 4(12), e8313. doi:10.1371/journal.pone.0008313, [Online]. Available at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008313> (Accessed on 04-July-2012)

McKeon, T. (1979). *Medical Achievement*, Oxford Blackwell Publishers, pp. 58-62

Miotto, P., Piana, F., Penati, V., Canducci, F., Migliori, G. B., & Cirillo, D.M. (2006). Use of genotype MTBDR assay for molecular detection of Rifampin and Isoniazid resistance in Mycobacterium tuberculosis clinical strains isolated in Italy, *Journal of clinical microbiology*, 44(7), pp. 2485-91. doi:10.1128/JCM.00083-06

Mishra, P., Hansen, E. H., Sabroe, S., and Kafle, K. K. (2005). Socio-economic status and adherence to tuberculosis treatment: a case-control study in a district of Nepal. *The international journal of tuberculosis and lung disease*, 9(10):pp. 1134–1139.

Mishra, P., Hansen, E. H., Sabroe, S., & Kafle, K. K. (2006). Adherence is associated with the quality of professional-patient interaction in Directly Observed Treatment Short-course, DOTS. *Patient education and counselling*, 63(1-2), 29-37. doi:10.1016/j.pec.2005.08.006

MoHP (2012). *Roles and Responsibilities of Ministry of Health and Population* [Online], Available at: <http://www.moHP.gov.np/english/function/moHP.php> (Accessed on 08-June-2012)

Munro, S. A, Lewin, S. a, Smith, H. J., Engel, M. E., Fretheim, A., & Volmink, J. (2007). Patient adherence to tuberculosis treatment: a systematic review of qualitative research. *PLoS medicine*, 4(7), e238. doi:10.1371/journal.pmed.0040238. [Online]. Available at: <http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0040238> (Accessed on 03-July-2012)

Nathanson E., Nunn P., Uplekar M., Floyd K., Jaramillo E., Lönnroth K., Weil D., and Raviglione M. (2010). *MDR tuberculosis –critical steps for prevention and control*, *New England Journal of Medicine*, 363(11), pp. 1050-8.

NDHS (2006). *Nepal Demographic and Health Survey 2006*. Kathmandu Nepal: Ministry of Health and Population

NDHS (2011). *Nepal Demographic and Health Survey 2011*. Kathmandu, Nepal: Ministry of Health and Population

New Jersey Medical School (2012): *Global Tuberculosis Institute, History of TB* [Online]. Available at: <http://www.umdnj.edu/ntbc/tbhistory.htm> (Accessed on 27-May-2012)

Newell, J. N., Baral, S. C., Pande, S. B., Bam, D. S., & Malla, P. (2006). Family-member DOTS and community DOTS for tuberculosis control in Nepal: cluster-randomised controlled trial. *Lancet*, 367(9514), pp. 903-9. doi:10.1016/S0140-6736(06)68380-3

NLSS (2011). *Nepal Living Standards Survey Report 2011*. Kathmandu Nepal: Central Bureau of Statistics and National Planning Commission Secretariat.

NTC (2009). *Tuberculosis Case Management Guideline May 2009*. Bhaktapur Nepal: National Tuberculosis Centre.

NTC (2011). *History of Tuberculosis*. [Online]. Available at: <http://www.nepalntp.gov.np/content.php?id=201> (Accessed on 04-Feb-2012)

NTP (2009). *National Tuberculosis Control Programme Nepal-Annual Report 2008-2009*, Bhaktapur, Nepal: National Tuberculosis Center.

NTP (2010a). *National Tuberculosis Control Programme Nepal-Annual Report 2009-2010*. Bhaktapur Nepal: National Tuberculosis Center.

NTP (2010b). *National Strategic Plan-Implementation of Stop TB Strategy (16 July 2010-15 July 2015)*. Kathmandu Nepal: National Tuberculosis Control Programme, Ministry of Health and Population.

NTP (2011a). *National Tuberculosis Control Programme Nepal-Annual Report 2010-2011*. Bhaktapur Nepal: National Tuberculosis Center.

NTP (2011b). *Drug Resistant Tuberculosis Management Guidelines and Manual*. Bhaktapur Nepal: National Tuberculosis Center.

Piot, Dr. M.A. (1967). *A simulation Model of Case Finding and Treatment in Tuberculosis Control Programmes*. Geneva: Tuberculosis Unit of World health organization. (WHO/TB/Tech. Information/67.53)

Shetty, A. S., Chamukuttan, S., and Nanditha, A. Champat Raj R.K., and Ramachandran A. (2011). Reinforcement of Adherence to Prescription Recommendations in Asian Indian Diabetes Patients. *Journal of Association of Physicians of India*, 59(November), pp. 711–714.

TBCTA (2009). *International Standards for Tuberculosis Care (ISTC)*. Second edition. *Tuberculosis Coalition for Technical Assistance*. The Hague, 2009

Ten Asbroek, A. H. a, Bijlsma, M. W., Malla, P., Shrestha, B., & Delnoij, D. M. J. (2008). The road to tuberculosis treatment in rural Nepal: A qualitative assessment of 26 journeys. *BMC health services research*, 8, 7. doi:10.1186/1472-6963-8-7. [Online]. Available at: <http://www.biomedcentral.com/1472-6963/8/7> (Accessed on 14-July-2012)

Trostle, J.A.(1988). Medical compliance as an ideology. *Social Science & Medicine*, 27(12), pp. 1299-1308.

UNDP (2009). *Nepal Human Development Report 2009, State Transformation and Human Development*, Pulchowk Nepal: United Nations Development Programme

UNDP (2010a). *What Will It Take to Achieve the Millennium Development Goals? – An International Assessment*. New York, USA: United Nations Development Programme

UNDP (2010b). *Millennium Development Goals, Assessment for Nepal 2010* [Online]. Available at: <http://www.undp.org.np/2011/08/24/news-updates/millennium-development-goals-needs-assessment-for-nepal-2010-launched--national-commitment-is-the-main-driver-for-meeting-the-mdgs-targets/1342/> (Accessed on 17-June-2012)

UNHCR (2012). *UNHCR country operations profile – Nepal*. [Online]. Available at: <http://www.unhcr.org/pages/49e487856.html> (Accessed on 28-May-2012)

Wares, D. F., Singh, S., Acharya, A K., and Dangi, R. (2003). Non-adherence to tuberculosis treatment in the eastern Terai of Nepal, *The international journal of tuberculosis and lung disease*, 7(4), pp. 327-35.

WHO (2002). *An Expanded DOTS Framework for Effective Tuberculosis Control*. Geneva: World Health Organization, 2002. (WHO/CDS/TB/2002.297)

WHO (2003). *Adherence to long-term therapies: evidence for action- 2003*, Geneva: World Health Organization

WHO (2005). *Addressing poverty in TB control: options for national TB control programmes*. Geneva: World health Organization. (WHO/HTM/TB/2005.352)

WHO (2006). *The world health report 2006: working together for health*. Geneva: World Health Organization

WHO (2008a). *Anti-tuberculosis drug resistance in the world: fourth global report*. Geneva: World Health Organization, 2008. (WHO/HTM/TB/2008.394)

WHO (2008b). *Guidelines for the programmatic management of drug-resistant tuberculosis*, Geneva: World Health Organization. (WHO/HTM/TB/2008.402)

WHO (2008c). *Nepal-Human Resource for Health*. [Online]. Available at: <http://www.nep.searo.who.int/EN/Section4/Section40.htm> (Accessed on 17-June-2012)

WHO (2009a). *Treatment of tuberculosis: Guidelines, 4th edition*. Geneva: World Health Organization. (WHO/HTM/TB/2009.420)

WHO (2009b). *WHO policy on TB infection control in health-care facilities, congregate settings and households, 2009*. Geneva: World Health Organization (WHO/HTM/TB/2009.419)

WHO (2010). *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response*. Geneva: World Health Organization (WHO/HTM/TB/2010.3)

WHO (2011a). *World Health Organization report 2011-Global Tuberculosis Control*. Geneva: World Health Organization. (WHO/HTM/TB/2011.16)

WHO (2011b). *The South-East Asia Regional Response Plan for Drug-resistant TB Care and Control 2011–2015*. New Delhi India: World Health Organization, Regional Office for South-East Asia. (SEA-TB-334)

WHO (2011c). *Guidelines for the programmatic management of drug-resistant tuberculosis 2011 update*. Geneva: World Health Organization, (WHO/HTM/TB/2011.16)

WHO (2011d). *The Global Plan to Stop TB 2011–2015, transforming the fight towards elimination of Tuberculosis*. Geneva: World Health Organization

WHO (2012a). *Tuberculosis in South East Asia Region, The regional Report-2012*. New Delhi India: World Health Organization, Regional Office for South-East Asia. (SEA/TB/338)

WHO (2012b). *Health statistics and health information systems, Metrics: Disability-Adjusted Life Year (DALY)*. [Online]. Available at: http://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/ (Accessed on 10-July-2012)

Yamasaki-Nakagawa, M., Ozasa, K., Yamada, N., Osuga, K., Shimouchi, a, Ishikawa, N., Bam, D. S., Mori, T. (2001). Gender difference in delays to diagnosis and health care seeking behaviour in a rural area of Nepal. *The international journal of tuberculosis and lung disease*, 5(1), pp. 24-31.

Yoshiyama, T., Shrestha, B., & Maharjan, B. (2010). Risk of relapse and failure after retreatment with the Category II regimen in Nepal. *The international journal of tuberculosis and lung disease*, 14(11), pp. 1418-23.

Young, D. B., Perkins, M. D., Duncan, K., & Iii, C. E. B. (2008). *Review series Confronting the scientific obstacles to global control of tuberculosis*, *The Journal of Clinical Investigation*, 118(4). doi:10.1172/JCI34614.

Annexes

Annex 1: Glossary of Terms and Definitions

Disability Adjusted Life Years (DALY): One DALY can be thought of as one lost year of "healthy" life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability. DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost due to premature mortality in the population and the Years Lost due to Disability for incident cases of the health condition (WHO, 2012b).

Directly Observed Treatment (DOT): If trained and supervised person observes the patient swallowing the medication, it is called DOT. DOT is one of a range of measures used to promote and assess adherence to tuberculosis treatment (WHO, 2002).

Directly Observed Treatment Short-Course Strategy (DOTS): The internationally agreed strategy that consists of five components and forms the platform on which tuberculosis control programs are built (WHO, 2002).

Extensively Drug Resistant Tuberculosis (XDR-TB): Resistant to at least Isoniazid and Rifampicin, any fluoroquinolone, and at least one of three injectible second-line drugs (amikacin, kanamycin, or capreomycin) (Francis, 2008).

Individualised Treatment Regimen: A treatment regimen is designed based on Drug Susceptibility Testing (DST) profiles and previous drug history of individual patients, or on local patterns of drug utilization (TBCTA, 2009).

Multi Drug-resistant Tuberculosis (MDR-TB): Resistant to at least Isoniazid (H) and Rifampin (R), considered to be the two most effective anti-tuberculosis drugs (Francis, 2008)

Primary MDR-TB: Presence of multi drug-resistant strain of *M. tuberculosis* in a patient newly diagnosed with TB but who has not previously been treated with TB drugs (or therapy of less than one month duration). These patients were likely to have been infected with a strain that was already drug resistant (Francis, 2008)

Secondary or Acquired MDR-TB: Presence of multi drug-resistant strain in a TB patient who has previously received at least one month of TB therapy. These cases are likely to have been initially infected with a drug-susceptible *M. tuberculosis* strain, but during the course of anti-tuberculosis treatment, drug resistance emerged (Francis, 2008)

Standardized Treatment: Standardized treatment means that all patients in a defined group receive the same treatment regimen (WHO, 2009a).

Annex 2: Nepal at a Glance - Major Indicators

Indicators	Figures	References
Population	26.4 million	CBS, 2011
Population growth rate	1.4%	CBS, 2011
Crude Birth Rate	27.7 per 1000 population	CBS, 2010
Crude Death Rate	8.3 per 1000 population	CBS, 2010
Life Expectancy at Birth	68 years Male: 66, Female: 70	UNDP, 2010
Literacy rate	Average: 61% Male:72% Female:51%	NLSS,2011
Infant Mortality Rate	46 per 1000 live births	NDHS, 2011
Maternal Mortality Ratio	281 per 100,000 live births	NDHS, 2006
Fertility Rate	2.6 per woman aged 15-49 years	NDHS, 2011
% of population under poverty line (daily income < \$1)	25%	CBS, 2010

Annex 3: NTP Goal, Objectives, Targets and Strategy

VISION	A TB-free Nepal	
GOAL	To reduce mortality and morbidity and transmission of tuberculosis until it is no longer a public health problem	
OBJECTIVES	<ul style="list-style-type: none"> To dramatically reduce the National burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets Achieve universal access to high-quality diagnosis and patient-centered treatment Reduce the human suffering and socioeconomic burden associated with TB Protect poor and vulnerable populations from TB, TB/HIV and multi-drug-resistant TB 	
TARGETS	<p>MDG 6, Target 8: ...halted by 2015 and begun to reverse the incidence.</p> <p>Targets linked to the MDGs and endorsed by the Stop TB Partnership:</p> <p>By 2005: detect 70% of new sputum smear positive TB cases and cure at least 85% of these cases</p> <p>By 2015: reduce prevalence of and death due to TB by 50% relative to 1990</p> <p>By 2050: eliminate TB as a public health problem (<1 case per million population)</p>	
COMPONENTS		
<p>1. Pursue high-quality DOTS expansion and enhancement</p> <p>Political commitment with increased and sustained financing</p> <p>Case detection through quality-assured bacteriology Standardized treatment with supervision and patient support</p> <p>An effective drug supply and management system</p> <p>Monitoring and evaluation on system, and impact measurement</p> <p>2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations</p> <p>Implement collaborative TB/HIV activities</p> <p>Prevent and control multi -drug-resistant TB</p> <p>Address prisoners, refugees and other high risk groups and special situations</p>	<p>3. Contribute to health system strengthening based on primary health care</p> <p>Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information on systems</p> <p>Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)</p> <p>Adapt innovations from other fields</p> <p>4. Engage all care providers</p> <p>Public-Public, and Public-Private Mix (PPM) approaches</p> <p>International Standards for Tuberculosis Care (ISTC)</p> <p>5. Empower people with TB, and communities through partnership</p> <p>Advocacy, Communication and Social Mobilization (ACSM)</p> <p>Community participation in TB care</p> <p>Patients' Charter for Tuberculosis Care</p> <p>6. Enable and promote research</p> <p>Programme-based operational research</p>	

Source: NTP, 2011a

Annex 4: NTP Treatment Regimens

Category	Regimen	Type of patients
I	2(HRZE)/4HR(combination)	New sputum smear positive New sputum smear negative New extra-pulmonary
II	2S(HRZE)/1(HRZE)/5HRE (combination)	Re-treatment TB cases including failures, relapses and return after default
MDR-TB regimen		
IV	8-12(Km-Z-Lfx-Eto-Cs)/12(Lfx-Eto-Cs-Z)	<p>Any patients with documented MDR-TB(or XDR-TB) or any patient highly likely to have DR-TB and needs a drug regimen composed of second line anti-tuberculosis drugs in the WHO tuberculosis treatment guideline as "Category IV".</p> <p>These includes:</p> <ul style="list-style-type: none"> • Confirmed MDR-TB or XDR-TB • Highly suspected MDR-TB, this includes any patient who is failure of category II regimen. Failure of Category II patients can directly enter the DR-TB regimen. Other highly suspected cases of MDR-TB should be discussed at the MDR-TB Technical Advisory Group (TAG) meetings, and if approved can enter DR-TB regimen before DST available. These patients may include severely ill close contacts of MDR-TB cases and severely ill category I failure cases. • Poly Resistant TB: Some of the poly-resistant TB will require the full standardized MDR-TB treatment regimen while other cases may require modified use of first line drugs(e.g. any mono or poly-resistant case who has Rifampicin resistance should receive standardized MDR-TB treatment).

Source: NTP, 2011a, NTP, 2011b

Annex 5: Definitions of DR-TB Patient Registration Categories

Type of Category	Definition
New	A patient who has received no or less than one month of anti-tuberculosis treatment. This group includes patients who have confirmed DR TB after DST.
Relapse	A patient whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.
Treatment after Default	A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.
Treatment after failure Category I	A patient who has received Category I treatment for TB and in whom treatment has failed. Failure is defined as sputum smear-positive at five months or later during treatment (However, patients who are doing poorly clinically on Category I and get switched to a DR-TB regimen, on TAG recommendation, or before the time of failure are also placed in this category through rapid DST.
Treatment after failure Category II	A patient who has received Category II treatment for TB and in whom treatment has failed. Failure is defined as sputum smear-positive at five months or later during treatment. (However, patients who are doing poorly clinically on Category II and get switched to a DR-TB regimen, before the time of failure are also placed in this category after confirmation through rapid DST.
Transfer In	A patient who has transferred in from another register for treatment of DR-TB to continue DR-TB treatment.
Other	These are types of patients who may not fit into any of the above categories. Examples include the following: sputum smear-positive patients with unknown previous treatment outcome; sputum smear positive patients who received treatment other than Category I or II (possibly in the private sector); patients who have received several unsuccessful treatments, were considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment (so-called "chronic" patients).

Source: NTP, 2011a; NTP, 2011b

Annex 6: List of NTP Partner Organizations

S.No.	Name of NTP partner Organizations
1	Britain Nepal Medical Trust (BNMT)
2	Family Health International (FHI360)
3	Friends Affected & Infected Together in Hand (FAITH)
4	German Nepal Tuberculosis Project (GENETUP)
5	Health Research and Social Development Forum (HERD)
6	Himalayan Social Welfare Organization (HSWO)
7	International Nepal Fellowship's TLP (Tuberculosis Leprosy Programme)
8	Japan-Nepal Health and Tuberculosis Research Association (JANTRA)
9	National Federation on of Women Living with HIV and AIDS (NFWLHA)
10	Naya Goreto (NG)
11	Nepal Anti-TB Association (NATA)
12	Netherlands Leprosy Relief (NLR)
13	Norwegian Association of Heart and Lung Patients (LHL)
14	SAARC TB and HIV/AIDS Centre (STAC)
15	Stop TB Partnership
16	The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)
17	World Health Organization (WHO)

Source: NTP, 2011a