First Line Non-Multidrug-Resistant Tuberculosis in India: A Neglected Problem

Bhanumati Varghese
India

Master in International Health
10th September 2012 – 05th September 2013

Royal Tropical Institute
Development, Policy and Practice
Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

14th August 2013

Nr of words: 12,041

Intentionally left blank

First Line Non-Multidrug-Resistant Tuberculosis in India:
A Neglected Problem

A thesis submitted in partial fulfillment of the requirement for the degree of

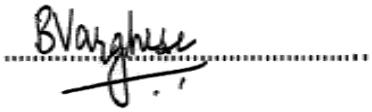
Master in International Health

By

Bhanumati Varghese

India

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 "First Line Non-Multidrug-Resistant Tuberculosis in India: A Neglected Problem" is my own work.

Signature: 

Master in International Health (MIH)
10th September 2012 – 05th September 2013
KIT (Royal Tropical Institute)/Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

August 2013

Organised by:

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

In co-operation with:

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

Intentionally left blank

Table of Contents

Intentionally left blank

List of Tables and Figures

Intentionally left blank

List of Abbreviations

AFB	:	Acid-fast Bacilli
Am	:	Amikacin
Amx/Clv	:	Amoxicillin/Clavulanate
CAL	:	Chronic Airflow Limitation
CB-NAAT	:	Cartridge-Based Nucleic Acid Amplification Test
CFR	:	Case Fatality Rate
Cfz	:	Clofazimine
Clr	:	Clarithromycin
Cm	:	Capreomycin
CP	:	Continuation Phase
Cs	:	Cycloserine
CSF	:	Cerebrospinal fluid
DMC	:	Designated Microscopy Centers
DOT	:	Directly Observed Therapy
DOTS	:	Directly Observed Therapy Short-course
DST	:	Drug Susceptibility Testing
DSTB	:	Drug Sensitive Tuberculosis
E	:	Ethambutol
EPTB	:	Extra Pulmonary Tuberculosis
Eto	:	Ethionamide
EQA	:	External Quality Assurance
FDC	:	Fixed Dose Combination
FQ	:	Fluoroquinolones
F/U	:	Follow up
GDF	:	Global Drug Facility
GDP	:	Gross Domestic Product
GLI	:	Global Laboratory Initiative
H	:	Isoniazid

HIV	:	Human Immunodeficiency virus
HRQoL	:	Health-Related Quality of Life
IP	:	Intensive Phase
Ipm/Cln	:	Imipenem/Cilastatin
IRL	:	Intermediate Reference Laboratory
ISTC	:	International Standards of TB Care
IUATLD	:	International Union Against Tuberculosis and Lung Diseases
Km	:	Kanamycin
Lfx	:	Levofloxacin
LPA	:	Line Probe Assay
LRSI	:	Lala Ram Sarup Institute
Lvx	:	Levofloxacin
Lzd	:	Linezolid
Mfx	:	Moxifloxacin
MDR	:	Multi Drug Resistant
MDR-TB	:	Multi Drug Resistant- Tuberculosis
MoHFW	:	Ministry of Health & Family Welfare
MTb	:	Mycobacterium Tuberculosis
NGO	:	Non- Government Organisation
NRL	:	National Reference Laboratory
NTI	:	National Tuberculosis Institute
OB	:	Obliterative Bronchiolitis
Ofx	:	Ofloxacin
PAS	:	Para-amino salicylic acid
PMDT	:	Programmatic Management of Drug Resistant Tuberculosis
PPM	:	Public-Private Mix
PTB	:	Pulmonary Tuberculosis
Pto	:	Prothionamide
PZA	:	Pyrazinamide

R	:	Rifampicin
Rfb	:	Rifabutin
RNTCP	:	Revised National Tuberculosis Control Program
S	:	Streptomycin
SMR	:	Standard Mortality Ratio
SNRL	:	Supranational Reference Laboratory
TB	:	Tuberculosis
Thz	:	Thiacetazone
TRC	:	Tuberculosis Research Center
Trd	:	Terizidone
USD	:	United States Dollar
WHO	:	World Health Organisation
XDR-TB	:	Extensively Drug Resistant Tuberculosis
Z	:	Pyrazinamide

Intentionally left blank

ABSTRACT

Introduction:
Tuberculosis that shows patterns of first-line drug resistance other than multidrug resistance occurs in large numbers in India. This problem receives relatively less attention compared to the more severe forms of drug-resistant tuberculosis. This thesis aims to explore the causation and consequences of this form of drug-resistant tuberculosis, and make recommendations to improve the management of these patients.

Methods:
The aims of the thesis are addressed by a literature review of the current magnitude of the problem, its current management, and the outcomes of this management for patients and society.

Findings:
First-line non-mutlidrug resistant tuberculosis is mainly created by irrational treatment regimens in the private sector. The enormous, unregulated private sector tuberculosis drug market also contributes to this. The treatment regimens for these patients in the national tuberculosis control program are not very effective as they are not tailored to the specific resistance patterns.

The physical and socioeconomic consequences to individual patients can be severe. The public health consequences are also serious as drug resistant tuberculosis is propagated.

Recommendations:
Patients with first-line drug resistance other than multidrug resistance should be treated based on their DST patterns. The prescribing practices and sale of anti-tuberculosis drugs in the private sector must be strictly regulated.

Keywords: first-line non-mulitdrug resistant tuberculosis, treatment, outcomes

Word count: 12,041

Intentionally left blank

1. BACKGROUND

BRIEF INTRODUCTION TO THE INDIAN HEALTH SYSTEM

India is a low-income country in the world health organization (WHO) south-east Asia region. The health system is three-tiered viz.

- Primary level
- Secondary level
- Tertiary level

The primary health care level consists of a hierarchy of subcenters, primary health centers, and community health centers in rural areas. The secondary health care level for people in rural areas consists of district and sub-district hospitals. These form the primary level for urban areas and there are also urban health centers. The tertiary level consists of referral hospitals in cities (MoHFW 2012-13).

About 4% of the gross domestic product (GDP) was spent on health in 2011. Of the private spending on health, 86% was out-of-pocket spending (WHO. India Statistics Summary).

The Revised National Tuberculosis Control Program (RNTCP) is the government-managed tuberculosis (TB) program in India. There is also a very large private sector involved in TB management (RNTCP 2013).

India is a high-burden country for both tuberculosis (TB) and multidrug-resistant tuberculosis (MDR TB) (WHO 2012).

DRUG-RESISTANT TUBERCULOSIS IN INDIA

The global incidence of TB (tuberculosis) was approximately 8.7 million in 2011, and that of MDR-TB (multi-drug resistant TB) (definition Box 1) was approximately 310,000 cases (220,000-400,000) among cases of pulmonary TB in 2011. Globally, MDR-TB is estimated to occur in 3.7% (2.1%-5.2%) new and 20% (13-26%) previously-treated TB patients. XDR-TB (extensively drug-resistant TB) (definition box 1) has been reported from 84 countries, and is estimated to occur in 9% (6.7%-11.2%) MDR-TB cases (WHO 2012).

India had an estimated 3.1 million (2.1 million-4.3 million) prevalent TB cases in 2011. The estimated TB incidence in 2011 was about 2.2 million (2 million-2.5 million) in 2011. (RNTCP 2013).
In 2011, approximately 2.1 % new TB cases (1.5%-2.7%) and 15% (13%-17%) of previously-treated TB cases were estimated to have MDR-TB in India (RNTCP 2013). The TB notification rate of MDR-TB in India was less than 10% of the estimated cases in 2011. There were about 64,000 (44,000-75,000) MDR-TB cases amongst notified PTB (pulmonary TB) cases in India in 2011 (WHO 2012).

Drug-resistant tuberculosis can be classified as mono, poly, multi, and extensively drug-resistant TB, depending upon the number and groups of anti-TB drugs to which the TB bacillus is resistant [Box 1 (WHO 2013), Box 2 (WHO 2010)].

Box 1 Classification of drug-resistant tuberculosis (WHO 2013)

Mono-drug resistant: resistance to one first line anti-tubercular drug only

Poly-drug resistant: resistance to more than one first line anti-tubercular drugs (not to isoniazid and rifampicin simultaneously)

Multi-drug resistant: resistance to at least isoniazid and rifampicin, with or without resistance to other anti-tubercular drugs

Extensively drug-resistant: multidrug resistance plus resistance to at least one fluoroquinolone and one second-line injectable (kanamycin, amikacin, capreomycin)

Box 2 Groups of anti-TB drugs (WHO 2010)

Group 1: First line oral drugs: H (isoniazid), R (rifampicin), Z (pyrazinamide), E (ethambutol), Rfb (rifabutin)

Group 2: Injectables: first line : S (streptomycin)
second line : Km (Kanamycin), Am (amikacin), Cm (capreomycin)

Group 3: FQ (fluoroquinolones) : Ofx (ofloxacin), Lfx (levofloxacin), Mfx (moxifloxacin)

Group 4: Second line oral bacteriostatic drugs : Eto (ethionamide), Pto (prothionamide), Cs (cycloserine), Trd (terizidone), PAS (para-amino salicylic acid)

Group 5: Cfz (clofazimine), high-dose H (high-dose isoniazid), thiacetazone (Thz),

2. PROBLEM STATEMENT AND JUSTIFICATION

2.1 Magnitude of the problem of first-line non-multidrug-resistant tuberculosis in India

In this thesis, 'first-line non-multidrug-resistant TB' refers to TB with any mono and poly-resistance to first-line drugs, other than MDR TB. Several studies in India document the prevalence of first line mono and poly drug-resistant TB in new and previously-treated cases.

Tables A and B in **Annex II** show results of drug-resistance profile studies with study background described briefly, in new and previously-treated pulmonary TB patients, respectively. Studies that had both new and previously-treated patients are in both tables. Also, though RNTCP treats R resistance as MDR TB (RNTCP 2013), it is shown separately when measured, as R-monoresistance is not typically MDR.

Only studies with culture and drug susceptibility test (DST) done at laboratories accredited by the RNTCP at the time of the study, or those which had external quality assurance (EQA) support of the supranational reference laboratory (SNRL) in Chennai, India, and (2) showing the number and percentage of mono, poly and multi drug resistance separately, are included in the tables in the annexes.

The studies in new patients range from 1997 to 2009, and are conducted in a wide variety of settings. The studies in previously-treated patients range from 1997 to 2008, and are also conducted in several different settings.

Therefore, to give a fairly recent and as large scale as possible picture of resistance in both new and previously-treated patients, one of the surveys from Annex II is considered. This is the 2005-06 state-wide survey in Gujarat state (Ramachandran *et al*, 2009), which includes resistance profiles of both new and previously-treated sputum acid-fast bacilli (AFB) smear positive PTB patients. The percentages of resistance reported in this survey are applied to the numbers of notified new and previously-treated smear positive patients in 2012 (RNTCP 2013), to calculate absolute numbers of patients with a certain resistance pattern (Table 1).
Based on these calculations, the number of non-MDR first line resistant cases of sputum smear positive PTB (175,050) is estimated to be over 2.5x that of notified MDR TB cases of pulmonary TB (64,000).

Table 1: **Estimated non-MDR first-line resistance in new and previously treated Pulmonary TB patients in 2012, India, based on state-wide resistance survey in Gujarat**, **2005-2006**

	Percentage from survey (Number estimated based on 2012 data)	
Type of notified cases by drug resistance pattern (no.)	**New smear positive PTB (629589)****	**Previously-treated smear positive PTB (187645)***
H monores^	5.4 %	11.7%
	(34000)	(21950)
R monores	0.2%	1%
	(1260)	(1900)
E monores	0.2 %	---
	(1260)	---
S monores	10 %	8.4%
	(63000)	(15800)
HE polyres^^	0.2%	0.7%
	(1260)	(1300)
HS polyres	2.9%	6%
	(18250)	(11250)
HES polyres	0.3%	1%
	(1900)	(1900)

*: Previously-treated sputum smear positive PTB cases in 2012 include: relapse 106463 + failure 16400 + default 64782 = 187645
**: New sputum smear positive PTB cases in 2012: 629589
^: monores: monoresistance
^^: polyres: polyresistance

New sm + PTB: monoresistance (H + R + E + S): 99,500
New sm + PTB: polyresistance (non-MDR): 21400
Previously-treated sm + PTB: monoresistance (H + R + S): 39,700
Previously-treated sm + PTB: polyresistance (non-MDR): 14,450
Total non-MDR first line resistance new sm + PTB: 120,900
Total non-MDR first line resistance previously-treated sm + PTB: 54150
Total non-MDR first line resistance (new and previously-treated sm + PTB): 175050

The commonest forms of resistance based on the calculations in Table 1, in decreasing order of frequency are:

- ✓ New patients: S monoresistance, H monoresistance, HS polyresistance
- ✓ Previously-treated patients: H monoresistance, S monoresistance, HS polyresistance

The numbers of new and previously-treated PTB patients with non-MDR first-line resistance are almost certain to be higher than those estimated here as: (1) smear negative PTB cases are not included in this survey (2) These numbers are calculated based on RNTCP-notified number of sputum smear positive new and retreatment cases, and hence do not account for cases from the private sector (3) Pyrazinamide (Z) resistance is not included in the survey.

Z resistance has not been reported in the Gujarat survey, but has been reported from other tertiary level public sector institutes. A study at an institute for chest diseases on 263 Mycobacterium tuberculosis (MTb) isolates from 181 treatment failure sputum smear positive PTB patients treated between 1996-98 showed any PZA resistance of 22% (Dam *et al*, 2005). Another study in north India from 2002-2006 showed any PZA resistance of 2.8% in previously-treated sputum smear positive PTB patients (Rawat *et al*, 2009).

Also, R monoresistance in the Gujarat survey is 0.2% in new and 1% in previously-treated cases. There was no non-MDR R polyresistance reported here. However, other studies [in Annex II] show non-MDR R-polyresistance ranging from 0.1% (Santha *et al*, 2006) to 0.6% (Joseph *et al*, 2007) in new patients and from 0.1% (Paramasivan *et al*, 2010) to 3.5% (Prasad *et al*, 2012) in previously-treated patients. This issue merits consideration in the treatment of R-resistant, H-susceptible TB, as discussed later.

Three studies on resistance in extrapulmonary (EP) samples done in laboratories of tertiary level government institutes are mentioned in Table C in Annex II.
Based on the number of notified new EPTB cases in 2012 (RNTCP 2013) and the resistance prevalence in the most recent study cited of 2007-2010 (Maurya *et al*, 2012), the numbers of non-MDR first line resistance were calculated to be (Table 2):

Table 2: **Estimated burden of non-MDR first-line resistance in new EPTB cases in 2012, India, based on resistance data from 2007-2010**

Drug (s)	H monores	R monores	E monores	S monores	HS polyres	HE polyres	RS polyres	HES polyres	RES polyres
%	9.7	0.8	3.2	4.1	0.8	4.1	1.6	1.6	0.8
No. *	22,700	1900	7500	9600	1900	9600	3800	3800	1900

*Number of notified new extrapulmonary tuberculosis (EPTB) cases in 2012: 234029 (RNTCP 2013)
Estimated non-MDR first-line resistance in notified new EPTB cases: 62700

2.2 Outcomes of Patients with first-line non-multidrug-resistant tuberculosis treated with First Line Drugs

Few studies in India document the treatment outcomes of TB patients treated with first line drugs in the presence of non-MDR first-line drug resistance. Also, as Z DST is often not done, especially previously-treated patients may have undiagnosed Z resistance though they are being treated with this drug.
Studies with culture and DST results from RNTCP-accredited laboratories and involving RNTCP patients only are included. The studies are described in **Annex III** and conclusions of the studies are mentioned here.

- **Studies on new patients**

New sputum smear positive patients treated with Category I regimen (Thomas *et al*, 2005): comparison of relapse rates between patients with H or R resistance and susceptibility.
Relapse rates were almost 2.5 times higher for patients with initial H mono-resistance (26.67%) compared to those susceptible to both H and R (11.2%). There was no pre-treatment sample with any R resistance other than MDR.

New sputum smear positive pulmonary TB patients treated with Category I regimen (Santha *et al,* 2005): Compared to failure rates of HR-sensitive patients (3%), patients with H and R monoresistance had 7 times higher failure rates (21%). Interestingly, failure rate with R monoresistance was the same as that with H monoresistance (20%) and both were less than half that of patients with MDR (44%). Among pre-treatment H-monoresistant patients with sputum samples available at failure, 15% acquired resistance to R at the time of failure, thus becoming MDR, while drug resistance emerged in only 4% of HR-susceptible patients at failure, who became H-monoresistant.

- **Studies on previously-treated patients**

Sputum smear positive patients started on the Category II regimen (Vijay *et al*, 2002):
Patients with non-MDR resistance had more failures and less cure and completion rates than those susceptible to HRES. Pre-treatment drug resistance was identified as a factor associated with Category II treatment failure, in the study.
Emergence of additional drug resistance to H, R, E or S occurred in 1.03% of susceptible patients and 14.7% of pre-treatment resistant patients

572 sputum smear positive PTB patients treated with the Category II regimen were included in the study (Joseph *et al*, 2006).
Patients with non-MDR resistance had nearly 2 times higher unsuccessful outcomes (failure + death = 23%) compared to patients sensitive to HRES (failure + death = 13%).

42 sputum AFB-smear positive patients who were failures on Cat I regimen and started on Cat II regimen were included in the study (Singla *et al*, 2009) .
Non-MDR first-line resistant patients had very poor outcomes on the Category II retreatment regimen, comparable to outcomes of patients with MDR TB. .

Patients in the RNTCP program from seven districts of Andhra Pradesh state covered by RNTCP MDR-TB program(Nagaraja *et al*, 2011): All R-susceptible but had mono or poly resistance to H, E or S.
200 patients who had failed either a Category I, II or III regimen before and were treated with the retreatment regimen (Cat II) were evaluated for treatment outcome in the study. The treatment success was 48% (28/58 patients) in the culture-negative group, 38% (31/81 patients) in the HRES-susceptible group, and only 15% (9/61 patients) in the group non-MDR first-line mono-and-poly resistance. In the group with non-MDR first-line drug resistance, treatment outcomes were almost equally poor in those with monoresitance and polyresistance.

- **Studies in new and previously-treated patients**

In patients without MDR-TB, any H resistance was associated with an increased risk of failure (Santha *et al,* 2002):

Follow up of sputum smear-positive PTB patients treated in the RNTCP, 2-3 years after treatment initiation (Sadacharam et al, 2007): of 1088 patients followed up, 148 had died (15%). There was a significant association between mortality and H or R monoresistance or MDR TB as compared to those with HR-susceptible TB at treatment initiation (12% vs. 28%). Of 840 patients from whom sputum samples were collected at follow up, 156 (18.6%) had relapsed. Relapse was also higher in those with pre-treatment drug resistance.

The poor outcomes of patients with non-MDR first-line resistance treated with first line regimens suggest that these regimens are inadequate to treat such patients.

2.3 Wider impact of poor treatment outcomes in patients with first-line non-MDR TB

Studies also show negative socio-economic as well as long-term physical consequences of TB for individual patients treated for TB. These consequences are very likely to be more severe in patients with poorer response to treatment and increased rates of recurrence.
The consequence to the health system is that there are more patients with active disease and/or increasing resistance, needing more expensive and prolonged treatment, thus increasing the burden on the health system.
Also, as these patients continue to transmit drug-resistant strains in society, there are resultant public health problems of increased primary drug resistance and TB control is jeopardized.
Relevant studies are described in the 'Results' section under 'objective 2.

Summarizing the problem statement: The estimated numbers of patients with first-line non-MDR TB in Tables 1 and 2 show that this is indeed a significant problem in India. The studies on treatment outcomes show that these patients have very poor treatment outcomes with the currently-used first-line treatment regimens. Therefore, this thesis attempts to explore the reasons for occurrence of drug resistance as an objective. It also aims to describe the larger physical, mental and social impact of these poor treatment outcomes on the lives of patients in order to highlight that they need treatment regimens that work for them. Finally, some examples are given from other settings for the treatment of these resistance patterns, and recommendations are made to the Central TB Division of India to improve the management of this form of TB in India.

3. OBJECTIVES

1. Describe the determinants of non-MDR first-line drug resistance in India
2. Describe the consequences to individuals and to society of current suboptimal treatment of non-MDR first-line drug resistance in India
3. Describe interventions to this problem in other countries and consider their application in the Indian setting
4. Formulate recommendations for the Central TB Division for better diagnosis and treatment of non-MDR first-line drug-resistant TB

4. METHODOLOGY & CONCEPTUAL FRAMEWORK

Methodology
Literature search was done in Pubmed using each of the following combinations of terms enumerated below.

- Each main search term was combined with 'tuberculosis' as well as 'TB' separately as both forms are commonly used to name the disease.
- Drug-resistan* was used as a truncated search term to include the words 'resistan**t**' and 'resistan**ce**' in all searches specifically looking for drug resistance.
- Synonyms were used for search terms wherever synonyms related to the aim of the search were found.

The position of hyphens between words was not considered specifically as changes in the position of hyphens did not yield different search results.

Filters applied for each search: studies from 1993-2013, in humans, in the English language.
Studies done 1993 onwards were chosen as that was the year the RNTCP piloted the DOTS program in India.

Search terms:

- Drug-resistan* tuberculosis India
- Treatment (synonyms: therapy, management, regimen, regime) drug-resistan* tuberculosis India
- Determinants (synonyms: causes, factors, determining factors, contributing factors) drug-resistan* tuberculosis India
- Private sector tuberculosis India
- Health-seeking behavior/our (care-seeking behavior/our, health-related behavior/our) tuberculosis India
- Chronic (synonyms: delayed, late, long-term) sequelae tuberculosis
- Post-tuberculosis sequelae
- Impact (synonym: consequences) tuberculosis
- Impairment tuberculosis
- Quality of life tuberculosis
- Standardized treatment (synonyms: therapy, management, regimen, regime) drug-resistan* tuberculosis (standardised)
- Outcome (synonyms: consequence, result, effect) (of) standardised treatment (synonyms: therapy, management, regimen, regime) (for) drug-resistan* tuberculosis

- Acquired (synonym: acquisition) first-line drug-resistan* tuberculosis
- Development (synonym: emergence, appearance, occurrence) first-line drug-resistan* tuberculosis India
- Adherence tuberculosis India
- Default tuberculosis India

The following search terms were also used in ScienceDirect:

- Determinants (synonyms: causes, factors, determining factors, contributing factors) drug-resistan* tuberculosis India
- Private sector tuberculosis India
- Health-seeking behavior/our (care-seeking behavior/our, health-related behavior/our) tuberculosis India
- Quality of life tuberculosis
- Adherence tuberculosis India
- Default tuberculosis India
- Ethics and tuberculosis
- Nosocomial tuberculosis India

TB was used with every search term where 'tuberculosis' was used. However, almost all the results yielded with 'TB' were included in those obtained by using the term 'tuberculosis.'
'India' was used with those search terms that were aimed at giving a picture of the situation in India (prevalence and drug resistance patterns, treatment of drug-resistant TB, determinants of drug-resistant TB, private sector, and health-seeking behavior of Indian TB suspects and patients).
For more universal phenomena (quality of life with TB, post-TB sequelae, use of and outcomes of standardized first-line anti-TB regimens, and the acquisition of drug resistance), 'India' was not part of the words combining to form the search term.

Of the studies from other countries that appeared after any search, those likely to reflect the Indian situation as closely as possible were chosen (eg. high-TB and drug-resistant TB burden countries, same or similar first-line regimens used like the Indian ones, low-middle income countries). For studies from countries with a TB situation not very different from the Indian one but with a much higher HIV prevalence than India, studies were chosen if they explicitly specified that HIV had not confounded the results. However, if a study addressed or discovered a relevant issue not found in Indian studies, it was included. Studies regarding treatment of non-MDR first-line drug resistance with regimens different from the standard first line regimens were found only from developed countries, where the TB burden is very different from that in India. However, as no studies were found in India or close to the Indian context, the studies from developed countries were used.

Articles were chosen from the search results on the basis of their titles, then abstracts, and then full text articles.

Reference chaining was done for articles selected from the primary search.

Websites of the WHO and RNTCP, India were also used to search reports and guidelines.

Conceptual Framework

The framework of Atre and Mistry (2005) shown in Fig1, detailing the determinants of drug-resistant TB in India, is applied in this thesis. The area within the dotted outline in the figure below corresponds to the area shaded in grey in the original framework. That area in the original framework represents targets for interventions by the RNTCP to address drug-resistant TB.
In the figure below, that same shaded area is outlined instead for better clarity in the thesis printout.

This framework is used because it lists the specific factors responsible for causing drug resistance in the Indian context.

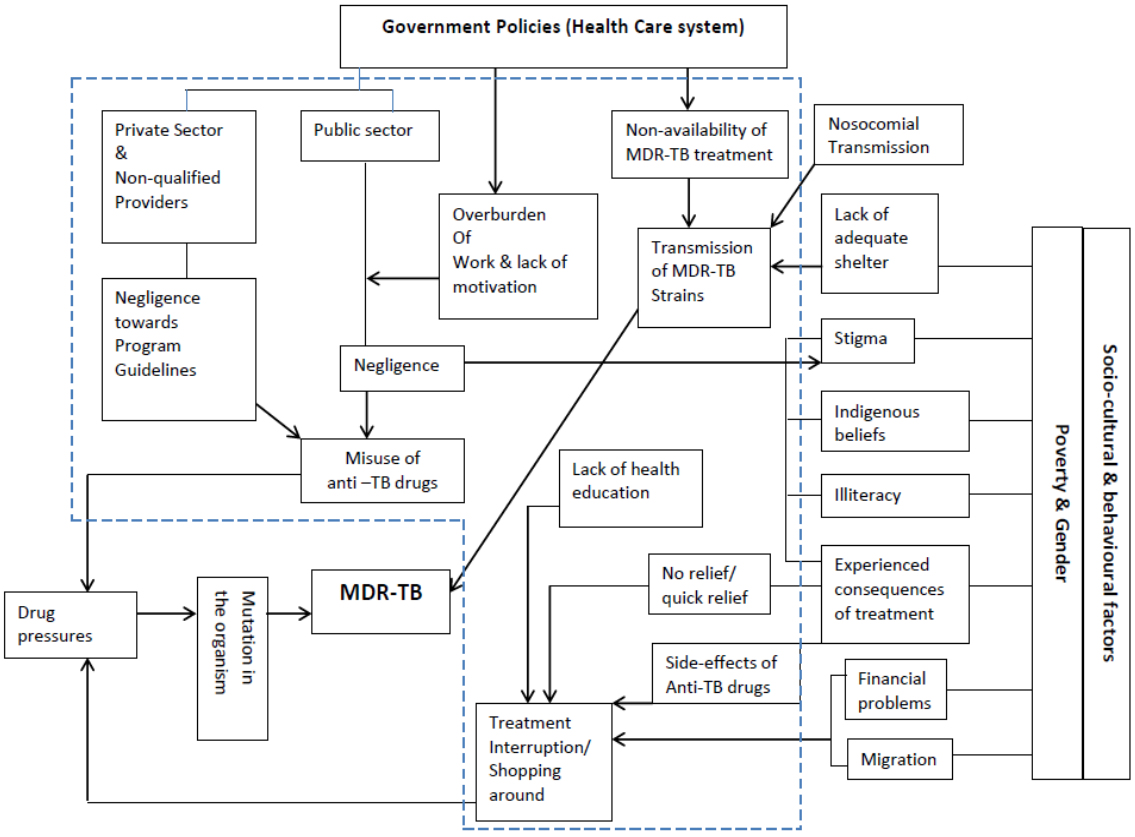


Fig 1: Biomedical, behavioural, and socio-cultural determinants of drug resistant TB. (Atre and Mistry, 2005)

5. STUDY RESULTS

The results of the literature review conducted to explore the issue of non-MDR first line drug resistance in India are described here in line with the first three objectives of the thesis.

5.1 Objective I. Determinants of first line non-MDR TB in India

The first objective, determinants, is described in accordance with the conceptual framework mentioned above.
An overview of the first objective is as follows:

I A. Health care system
- Government Policy
- RNTCP (public sector TB program in India)
    1. Treatment of first-line drug-susceptible and first-line non-MDR TB in RNTCP
    2. Problems in RNTCP implementation
- Private Sector
- Private sector TB drug market

I B. Drug pressures

I C. Socio-cultural and Behavioral Factors that influence health-seeking behavior of patients

5.1.A Health Care System

- Government Policy concerning TB:

The government is committed to providing adequate TB diagnostic and treatment services to all TB patients through the Stop TB Strategy, which incorporates the DOTS strategy, the International Standards of TB Care (ISTC) for all medical practitioners who treat TB, and the Patient Charter for TB Care which includes patients' rights and responsibilities regarding TB treatment (RNTCP 2010; RNTCP 2013).

- RNTCP (public sector TB program in India)
  (Note: 'public sector' and 'government' both refer to the same program in this thesis)

1. Treatment of first-line drug-susceptible and first-line non-MDR TB in RNTCP

The present RNTCP based on the DOTS strategy was piloted in India in 1993 and reached national geographical coverage in 2006. First-line treatment regimens are classified as 'new' for patients who never received anti-TB drugs before or received them for less than one month, and 're-treatment' for patients who received first-line TB drugs for more than one month before. New patients are treated with an intensive phase (IP) of $2(HRZE)_3$ and a continuation phase (CP) of $4(HR)_3$. The regimen is written as $2(HRZE)_3/4(HR)_3$. Previously-treated patients are treated with $2(HRZES)_3/1(HRZE)_3/5(HRE)_3$.regimen (RNTCP 2013). The number before the bracket indicates the duration of the treatment phase in months, and the subscript after the bracket indicates the number of doses of each drug per week (RNTCP 2013).
All drugs in both regimens are given three times per week; all doses of the IP are given as directly-observed therapy (DOT), and at least the first dose of each week in CP is given as DOT. DOT providers can be health system staff, non-government organization (NGO) workers and private medical practitioners allied to the RNTCP, and community volunteers. Monitoring of treatment is done by sputum

smears at IP end, 2 months of CP and at the end of treatment. If smears are positive at IP end, IP is extended by a month and then CP is started irrespective of the smear result (RNTCP 2013).

In the RNTCP, a patient is diagnosed as having MDR TB based on R resistance alone, irrespective of H resistance. Molecular tests such as line probe assay (LPA) which detects resistance to H and R, and GeneXpert, which detects R resistance even in smear negative samples, are used to expedite the diagnosis where available. DST is performed for H (isoniazid), R (rifampicin), E (ethambutol) and S (streptomycin). (RNTCP 2010).

Patients sensitive to rifampicin, irrespective of resistance to other first line drugs, are treated with first line drugs only. If the MDR-TB diagnosis can be obtained early by LPA, the suspects continue whatever first-line regimen they were on if found sensitive to R. If DST results are expected after few weeks or months, those who were on the re-treatment regimen, continue it to completion. Those who were on the treatment regimen for new cases are switched to the re-treatment regimen while awaiting DST results. Contacts of MDR-TB cases who are diagnosed with or suspected to have TB are started on the retreatment regimen if treated for TB before or the regimen for new cases if never treated for TB before. Those resistant to R but sensitive to H are also treated as having MDR TB (RNTCP 2012).

The RNTCP implemented certain significant decisions in 2012: declaring TB a notifiable disease, ban on serology tests for TB diagnosis, and the implementation of the ISTC in India. The RNTCP is also trying, through the drug control authority in India, to prohibit the sale of anti-TB drugs in the drug market. It is also trying to promote the correct use of anti-TB drugs through formal organizations of medical practitioners (RNTCP 2013).

Details of the organization and working of the RNTCP are in **Annex I.** Previously-used terms for regimens (Categroy I, II, III) that are not used in the RNTCP now but are referred to in many studies are also given in the annex.

2. Problems in RNTCP implementation

- Wrong categorization of patients:
  In a study (Atre *et al*, 2007), 13% urban and 9% rural PTB patients had been categorized and treated as ‘new’ patients though they had received anti-TB treatment for at least over a month before the current episode.
  The reasons for this on the part of the health system were: inadequate history-taking by health care personnel due to heavy burden of work or negligence, inadequate records to track previously-treated patients, being focused on attaining program targets, and lack of clarity in classifying patients as ‘new’ or ‘relapse’ if the present and earlier occurrences of TB had happened many years apart.
  On the part of the patients, the reasons for the incorrect classification were: lack of treatment records due to poor understanding of their value or impoverished living conditions, hesitation to reveal information about prior treatment, and being ignorant of the type of drugs they had taken earlier.

- Unsupervised treatment:
  Sometimes in RNTCP-DOTS centers if actually executing DOT is not possible, patients are given drugs to take unsupervised for 1-2 weeks, which may lead to irregular drug intake if patients have not understood the importance and the schedule of the treatment. Also, doctors in the RNTCP sometimes split the drugs instead of once-a-day dosing, due to apprehension that patients may be intolerant to the full dose taken at once.

Both these factors may lead to inadequate drug levels in the serum, favoring the development of drug resistance (Atre and Mistry, 2005).

- Inappropriate referrals within the program:
  A study at a tertiary government hospital in Hyderabad city, south India found that 98% inpatients with first-line sensitive TB received treatment in accordance with RNTCP guidelines. Among those discharged, 96% were appropriately referred to peripheral centers for continuing their DOT. However, information of receiving these patients and continuing their treatment was re-conveyed to the hospital for only 74% patients. Thus, these patients were lost from the RNTCP system, implying that some or all of them defaulted on their treatment (Kondapaka *et al*, 2012).

  A study in 3 medical colleges of 2 states found that only 36% of TB patients diagnosed with TB in the microbiology, radiology and pathology departments of these institutions were referred to the RNTCP in spite of the presence of RNTCP services within these institutions. The authors suggest that this may be due to non-adherence to the RNTCP protocols and also the presence of a large private sector in one of these states, leading to referrals to the private sector (Quazi *et al*, 2012).

- Delayed treatment initiation: A study in 2 rural districts in 2010 examined causes of delay of over 7 days in starting treatment after smear-positive PTB diagnosis (Paul *et al*, 2012). Geographic inaccessibility of patients to allotted DOT center, delay in communication of diagnosis from DMC to referring doctor, and delay in delivery of drugs from RNTCP to DOT providers were identified as factors.

❖ Private sector

Several studies show certain common lacunae in the private sector.

- Diagnostic and monitoring tests:
  There is a great preference for chest X-rays over sputum smear microscopy for PTB diagnosis. This comes across in a study in Delhi in 1995 (Singla *et al*, 1998) where only 12% preferred sputum smear microscopy as a diagnostic test and only 3% for treatment monitoring. In a study in rural areas and an urban slum of Maharashtra state, 15% medical practitioners did not advise sputum examination at all (Uplekar *et al*, 1998). Only 25% doctors in a city in north India used sputum microscopy as one of the tests to decide about treatment completion in 2009-10 (Yadav *et al*, 2012). Only 1 study in Kerala state in 2006 showed that 80% doctors used sputum microscopy as one of the diagnostic tests (Greaves *et al*, 2007).
  12.5% doctors stopped treatment only based on clinical improvement (Singla *et al*, 1998), and 27% stopped treatment only based on completion of the treatment period (Yadav *et al*, 2012)

- Diagnostic delay:
  Site of TB (Kapoor *et al*, 2012. RNTCP patients Oct 2012: average time from onset of symptoms to starting therapy 8.4 months). Diagnostic delay approximately 2 months though 50% patients diagnosed at first private practitioner they consulted (Uplekar *et al*, 1998).

- Use of non-standard regimens:
  94% doctors used 102 different regimens containing 2-5 first line drugs (Singla *et al*, 1998), doctors prescribed 2-5 first line drugs for periods of 3-18 months (Uplekar *et al*, 1998), 20% prescribed 2-3 drug regimens with first line drugs, and about 3% also included levofloxacin (Yadav *et al*, 2012). In a study in Mumbai city, west India, 63 different regimens were prescribed, and only 6/106 (5.7%) wrote a prescription that was correct in terms of drugs, dose and treatment duration (Udwadia *et al*, 2010). The study in Kerala state in 2006 mentioned above showed that a larger proportion, that is 42% doctors, treated their patients based on the DOTS strategy or referred them to the RNTCP (Greaves *et al*, 2007).

- Directly observed therapy:
  No doctor gave directly observed treatment (Singla *et al*, 1998; Uplekar *et al*, 1998; Yadav *et al*, 2012).

- Maintenance of treatment records:
  No doctor kept treatment records (Singla *et al*, 1998; Uplekar *et al*, 1998). Only in one study, 44% kept treatment records (Greaves *et al*, 2007).

- Defaulter tracing:
  No doctor had any system for defaulter tracing (Singla *et al*, 1998). 42% doctors made some attempt to trace a patient who did not follow up (Uplekar *et al*, 1998).

- Referral of seriously ill patients:
  62% doctors referred patients to other private doctors (Singla *et al*, 1998).

- Health education:
  Only 20% doctors stressed the importance of regular treatment, and 41% gave some advice to patients for contact tracing (Singla *et al*, 1998). 64% stressed need for treatment regularity, and 21% gave some advice to avoid transmission to contacts (Yadav *et al*, 2012).

- Other findings:
  For renewing knowledge of TB, 24.6% doctors referred to magazines and 41% referred to representatives of pharmaceutical companies (Singla *et al*, 1998).

  11% doctors did not inform their patients which disease they were diagnosed with, most likely due to TB-related stigma. There were variations between what was prescribed and what the patients consumed, with a few patients taking only mono or dual therapy (Uplekar *et al*, 1998).

  The TB management of doctors trained in western medicine did not differ greatly from those who were not similarly trained (Uplekar et al, 1998). The prescriptions of doctors trained in western medicine were not very different from those trained in the alternative medical systems. 47% prescriptions were correct if only the criteria of prescribing 4 drugs in the intensive phase and minimum treatment duration of 6 months were applied. This was the only silver lining as this was about 4 times higher than the prescriptions in a similar study done in the same area about 20 years ago, when it was 13% (Udwadia et al, 2010).

Comparison of doctors between government and private sectors:

Lucknow city, north India, 2007, assessment of knowledge of PTB among 62 doctors from the private sector and 79 from the public sector (all trained in western medicine): comparison in Table 3.
Correct information about PTB diagnosis and treatment (% indicates % of doctors having correct information)

Table 3: Comparison of knowledge of PTB management between doctors from government and private sectors in Lucknow city

Sector	Symptoms	Diagnostic tests*	No. of samples for microscopy **	Criteria for diagnosis of smear positive PTB	Criteria for diagnosis of smear negative PTB	RNTCP regimen for smear positive PTB	RNTCP regimen for smear negative PTB	Monitoring treatment using smear microscopy	Had received RNTCP training
Private	53%	22%	86%	18%	26%	71%	66%	76%	44%
Public	49%	30%	98%	42%	39%	94%	84%	94%	73%

* 'Correct' response: identifying all 3 tests (sputum AFB smear, sputum culture for MTb and chest Xray) as the preferred tests for PTB diagnosis.
** At this time, the required number was 3 sputum samples
Overall, doctors who had participated in RNTCP trainings had 3.4 times more knowledge about PTB diagnosis and treatment compared to those who had not. Public sector doctors displayed about two times more information than those from the private sector (Vandan *et al*, 2009).

Study in urban and rural areas of Gwalior district, central India, July 2008-June 2009, 100 public sector and 100 private sector doctors trained in western medicine: Comparison in Table 4.
% indicates % of doctors doing the mentioned activity

Table 4: Comparison of knowledge of PTB management between doctors from government and private sectors in Gwalior district

Sector	Sputum smear for diagnosis	Sputum smear for monitoring	Referral of poor patients to RNTCP	Referral of seriously ill patients to RNTCP	Sputum examination in RNTCP-accredited labs	RNTCP guidelines should be followed (agree)	Maintaining treatment records
Private	36%	25%	45%	65%	15%	26%	2%
Public	64%	54%	89%	91%	95%	87%	95%

92% public sector doctors had been trained in the RNTCP guidelines in programs of duration 1-7 days, while only 58% private sector doctors had received a single-day trainings only.
Public sector doctors had a mean score of 9.8/14 and private sector doctors had a mean score of 6.1/14 for TB knowledge (Srivastava *et al*, 2011).

- Private Sector TB drug market, 2004-2009 (Wells *et al*, 2011)

The Indian private drug market (external to RNTCP and other public sector health facilities, and excluding NGOs) for first-line anti-TB drugs (HRZE were included) is among the biggest in TB high-burden countries. The private drug market in India is shared across multiple domestic drug producers.

At least 67% of first-line anti-TB drugs were used for TB in India. Ethambutol use was high in India, with the 2HRZE/6HE regimen being prescribed by 20-40% of the private sector.

The private sector mainly uses FDCs in India, with 3-drug FDCs accounting for 26-37% of first-line drugs used. Loose drugs make 23% of the drugs sold in the private drug market.

Dose strengths were reported for 80% of the drugs sold in India. There was very large variation in the dose of drugs for both loose drugs and FDCs. There were 48 two, three or four-drug FDCs of different dose strengths, with there being 15 variations each for HR and HRZ. There were 22 dose-variant formulations for loose drugs, the largest for E (=8) and Z (=7). 12% drug formulations were in multiples of GDF (global drug facility) or RNTCP-recommended dose strengths and 60% were of non-standard strengths (not the same as nor a multiple of GDF or RNTCP-recommended strengths). Overall, drug strengths in India were greater than the GDF-recommended ones.

First-line regimen cost was calculated assuming a 6-months of 3-1/2 tablets daily with the WHO-recommended 4-drug and 2-drug FDCs for thes IP and CP, respectively. The GDF price of an FDC 2HRZE/4HR daily regimen was about USD 20, and in India it was almost the same (USD 22). The price of the same regimen using loose drugs was 35 USD in India.
Only about 10% FDCs in the private drug market in India conform to WHO-prequalification dosage norms.

To summarize, these studies on the private and public aspects of the health system show how the way each system works can fuel drug resistance. The public sector guidelines try to optimize treatment benefits for patients but sometimes administrative issues cause problems. On the contrary, the private sector does not follow any standard guidelines for TB management. The large private drug market for anti-TB drugs compounds the problems in the private sector.

5.1.B. Drug Pressures

An analysis of resistance to H, R, E and S in 11 countries (India was not part of this study) among 9615 patients (85.5% new and 14.5% previously treated) showed that the risk of having any drug resistance was higher in previously-treated patients. The study also showed that as the length of previous treatment for TB increased, the probability of being resistant to at least one drug also increased (Espinal *et al*, 2001).

Drug resistance can also occur because of suboptimal adherence to treatment. When drugs are taken irregularly, mutant bacilli resistant to the drugs get preferential conditions for growth and continue to multiply. This leads to the creation of a bacillary population resistant to one drug to begin with, later developing resistance to several drugs as erratic adherence continues (Mitchison, 1998).

A study in south India found malabsorption of H and R in HIV (human immunodeficiency virus)-infected TB patients on standard anti-TB therapy. All the patients were male and included both new and previously-treated TB patients. All had advanced HIV infection with an average cluster of differentiation 4 (CD4) count of 61 cells/cu.mm. but none were on anti-retroviral therapy (ART). Of the 26 patients in this group, 20 had diarrhea and of these, 11 had chronic diarrhea. They were being treated for the agents

causing diarrhea based on stool smear examinations, However, there was no significant difference in H and R absorption in those with and without diarrhea (Gurumurthy *et al*, 2004).

Another study in south India (Swaminathan *et al*, 2005) assessed first-line drug resistance in HIV-infected PTB patients. New patients had 4.8% H-monoresistance, 2.4% S-monoresistance, 3.6% HS resistance, 0.6% HES resistance, and 6.6% MDR. Previously-treated patients had 10.8% H-monoresistance, 5.4% had R-monoresistance and S-monoresistance each, 2.7% had HS resistance, and 24.3% had MDR. These results were attributed to recent infections with drugr-resistant bacilli due to increased vulnerability of HIV positive persons to infections. It could also be due to the malabsorption of H and R, as mentioned above.

5.1.C. Health-seeking and health-related behavior of patients

- **Choice of service provider**

  - Non-qualified practitioners (Quacks and pharmacists): The reasons for preferring quacks and pharmacists was that patients felt they recovered fast after the quack's treatment and that the pharmacists did not charge any fee for their advice (Kapoor *et al*, 2012).

  - Seeking care from multiple health-care providers: Patients visited at least 3 providers for treatment **(**Kapoor *et al*, 2012)**.** Patients had consulted a maximum of 8 health-care providers before starting treatment (Uplekar *et al*, 1998).

  - Preference for private sector: Health care-seeking behavior of persons with self-reported TB was explored using data from the National Sample Survey of 2004. At this time, RNTCP services were available to 75% population **(**Hazarika, 2011). About 50% respondents had been treated in the private sector. Individuals of higher educational status and women were more liable to access the private sector. The commonest reason for preferring the private sector was not being content with RNTCP services, which included prolonged waiting periods and financial burden. One of the main reasons for rural residents attending private facilities was non-existence of RNTCP facilities in their vicinity. There were no significant rural-urban or upper-lower economic strata differences in being treated in the private sector. Charles *et al* (2010) also reported that those in a better economic situation preferred the private sector.

    A community-based survey of self-reported TB patients in 30 districts in 2011 found that 54% were receiving treatment from the RNTCP and 46% from private providers. Almost one-third of those with a TB diagnosis from the RNTCP had moved to the private sector for treatment (Satyanarayana *et al*, 2011).

    A survey was done in 36 districts from all over India in 2010 to determine sector of previous TB treatment in 1712 retreatment patients. Forty-four percent patients reported that they had taken their last TB treatment out of the RNTCP (Sachdeva *et al*, 2011).

    A study compared health care seeking-behavior of people with respiratory symptoms before and after RNTCP implementation in the same area of south India, in 1997 and 2008, respectively. Fifty percent patients approached the RNTCP compared to 38% approaching the public sector during the previous TB program. However, 17% moved to a private practitioner subsequent to the first RNTCP visit and 21 % moved to traditional medicine practitioners due to their feeling that RNTCP services were of low quality. This feeling was

created by the delays in the RNTCP, absence of health-care staff, and unresponsiveness of staff to patients' requirements. The most frequent reason for moving from the private to the government sector was economic difficulties (Charles *et al*, 2010). .

These studies show that patients approach multiple health-care providers, often preferring the private ones because of dissatisfaction with the quality of RNTCP services. There is a lack of treatment guidelines in the private sector and treatment regimens may change with each provider, as seen from the section on 'Private sector.' Thus, exposure to different drugs with changing drug pressures puts patients at risk of developing drug resistance.

- **Delayed health-care seeking**

  - Gender: average time from start of symptoms to start of therapy 6.3 months for women and 3.8 months for men (Kapoor *et al*, 2012)

  - Economic status: patients with the lowest economic status sought treatment after about 6 months of symptoms **(**Kapoor *et al*, 2012).

  - Initiation of retreatment regimen: Patients prescribed a retreatment regimen were often reluctant to start treatment due to doubts regarding diagnosis and taking second opinions, hesitation to take frequent S injections, and previous negative episodes associated with TB treatment (Paul et al, 2012). Postponement of care-seeking has also been reported by Charles *et al* (2010) in patients who re-experienced TB symptoms after prior anti-TB therapy.

  These delays in seeking health care may sometimes be inevitable on account of the vulnerable position of women or lack of money. However, this leads to TB transmission in the community. This can be especially dangerous if there is delay in health-care seeking or treatment by those who were treated for TB before. They often have drug-resistant strains which then continue to spread to others in the community.

- **Causes of default**

  - Provider-related factors:

    The following factors were identified in multiple studies:

    1. Long distance from home of patient to allotted DOT center (Jaiswal *et al*, 2003; Gupta *et al*, 2011)
    2. Non-availability of drugs at the DOT center (Jaiswal *et al*, 2003; Gupta *et al*, 2011)
    3. Obstacles in re-entering the DOTS programme after treatment interruption (Jaiswal *et al*, 2003)
    4. Poor communication and support from DOT provider to patient (Jaiswal *et al*, 2003; Gupta *et al*, 2011)
    5. Health-care workers' inability to manage adverse drug effects: It was found that this last reason was sometimes because the DOT providers themselves did not get adequate training and support from the RNTCP (Jaiswal *et al*, 2003; Vijay *et al*, 2010)
    6. Treatment cost in the private sector (Gupta *et al*, 2011)
    7. Treatment not given as DOT (Vijay *et al*, 2010): a study in 20 districts across 6 states revealed that treatment was not observed in 56% new PTB patients who defaulted.

8. Insufficient patient retrieval activities post-treatment interruption (Jha *et al*, 2010): about 40% defaulters had a minimum of 1 treatment interruption in the IP
9. DOT administered at government health facilities (Jha *et al*, 2010): restricted timings of functioning of these facilities makes it inconvenient for some patients to access DOT

- Patient-related factors :

  The following factors were identified in several studies:

  1. Personal and work commitments (Jaiswal *et al*, 2003; Johnson et al, 2003; Vijay *et al*, 2010; Jha *et al*, 2010) which do not allow the matching of schedules of patients and the DOT system
  2. Alcoholism (Jaiswal *et al*, 2003; Vijay *et al*, 2010)
  3. Patients' perception of their response to treatment: non-improvement, worsening, or quick improvement leading them to believe that further treatment was not needed (Johnson *et al*, 2003; Jaiswal *et al*, 2003; Gupta *et al*, 2011), no clinical improvement because of drug resistance and/or widespread lung damage (Jenkins *et al*, 2013)
  4. Not having trust in the treatment (Gupta *et al*, 2011)
  5. Insufficient understanding of the treatment: Ignorance of the long treatment period (Gupta *et al*, 2011), poor knowledge due to illiteracy (Vijay *et al*, 2010), low education levels (Jenkins *et al*, 2013)
  6. Male gender (Jha *et al*, 2010)
  7. Previous default (Jha *et al*, 2010; Jenkins *et al*, 2013)
  8. Adverse drug effects (Jaiswal *et al*, 2003; Johnson *et al*, 2003; Vijay *et a*l, 2010; Jha *et al*, 2010; Jenkins *et al*, 2013)
  9. HIV co-infection (Jha *et al*, 2010), (Jenkins *et al*, 2013): The reasons for this were not elaborated. They could be the inability to attend DOT due to other illnesses associated with HIV or the high pill burden for both HIV and TB treatment together.
  10. Living conditions: homeless, living alone (Jenkins *et al*, 2013)
  11. Length of therapy for drug resistance (Jenkins *et al*, 2013)

Most treatment interruptions or defaults occurred around the third month of treatment (Jaiswal *et a*l, 2003; Gupta *et al*, 2011; Jha *et al*, 2010).

Study on causes and time of default in non-MDR TB patients, Moldova, 2007-2010 (Jenkins *et al*, 2013): This was the only study found that specifically looked at default in patients with first-line non-MDR drug resistance. Default occurred at a median of 110 days on treatment for new patients and 125 days for previously-treated patients. The reasons for default were the reluctance of patients to be treated on account of longer treatment durations needed for drug-resistant TB, increased side-effects due to more drugs in the regimen, and lack of faith in the treatment because they noticed little improvement in their health.

Default due to any cause carries the risk of developing drug resistance as the bacilli are no longer under the suppression of the anti-TB drugs. The study from Moldova highlights the reasons for default in patients with first-line non-MDR resistance. Their interruption of treatment because of the difficulties of treatment further increases resistance, becoming a vicious cycle with increasingly difficult-to-treat resistance.

5.1.D Nosocomial and Occupational Transmission of TB

A review of TB transmission in India in health-care settings in India recognized high risk of TB acquisition for health-care workers (HCW) and patients. The incidence of TB infection and disease in HCWs is more than the average in India, indicative of ongoing transmission in health-care settings, especially hospitals. The very high numbers of TB patients, especially those who are sputum smear positive, and inadequate or absent infection control measures facilitate easy transmission. Unjustified hospitalization, long time lags to TB diagnosis and treatment, poor adherence, and inadequate anti-TB regimens aggravate this problem. The fact that sputum microscopy is often not done in the private sector implies that infectious patients go unrecognized, thus adding to the transmission (Pai *et al*, 2006).

A study in the United States of America also showed that PTB patients with negative sputum smears but positive cultures contributed to 17% of the TB transmission in a certain area (Behr *et al*, 1999).

5.2. Objective II. Consequences of current treatment of first-line Non-MDR drug resistance in India

These consequences are described in patients with presumed drug-susceptible or known MDR TB. However, similar consequences very likely occur in patients first-line non-MDR TB also. They are also very likely to be much more severe than in patients with drug-susceptible TB because of the poorer response to treatment in non-MDR resistance. Thus, these consequences may be similar to if not as severe as those experienced by MDR TB patients.

5.2.A. Economic Consequences

Eleven percent children discontinued education due to parental illness or the associated loss of income. (Geetharamani *et al*, 2001).

Rural south India, 2000(Muniyandi *et al*, 2005):
The total cost related to TB treatment was 19% of the annual family income in patients below the poverty line, and 10% for those above it.

Urban south India, 2005: evaluation of TB-related costs to new patients in the RNTCP and comparison with private sector patients:
All patients, including those treated later in the RNTCP, spent about USD 145 in the private sector before treatment initiation. The cost during treatment in the RNTCP was USD 21 and for patients treated in the private sector it was USD 127. For RNTCP patients, the during-treatment costs were mainly associated with ancillary drugs and supplementary food. Patients in the low standard-of-living category spent 14% of the annual family income for TB-related expenses compared to 9% for those in the middle and high standard-of-living categories (Pantoja *et al*, 2009).

Thus, patients have to spend on treatment or related issues irrespective of the sector they are treated in. Poorer patients have to spend more. It follows that costs will be more for those who respond poorly to treatment, thus aggravating their poverty.

5..2.B. Biological Consequences

- Effect on lung function
  Patients treated for MDR TB showed the following long-term post-treatment sequelae: 78% had productive cough, dyspnea or both. Almost all had persistent lung damage (Singla *et al*, 2009). A study in South Africa showed extensive lung damage in MDR TB patients at treatment completion. In this study, larger extent of lung damage was associated with longer duration of having active TB (Valliere and Barker, 2004).

- Effect on mortality
  A study at a TB unit in a rural area in South India calculated excess mortality in TB patients over that in the general population and risk factors for it. The excess mortality due to TB (measured as SMR: standard mortality ratio) in this population was 4.2, denoting that the mortality rate was 4.2 times more than in the general population. The SMR was especially high in patients treated with the retreatment regimen, in defaulters and in failures (Kolappan *et al*, 2008).

  A similar study was done for TB patients in an urban area in 2002-2003 (Kolappan *et al*, 2006). The SMR for this cohort was 6.1. Here too, patients treated with the retreatment regimen, treatment failures, and defaulters had the maximum mortality.

  A study in China followed new and retreatment PTB patients for 2 years to estimate relapse and mortality rates in cured patients after standard DOTS treatment. Relapse and mortality rates were higher in retreatment cases than in new patients. Among those who died, no patient had had a TB relapse before death. In new patients, all the deaths were due to causes unrelated to the respiratory system. In retreatment patients, 57% had died due to long-term pulmonary consequences of TB, such as cor pulmonale, respiratory failure, and hemoptysis. There was no variation in the mortality rate of new and retreatment cases if retreatment patients who had died due to pulmonary damage caused by TB were left out of the analysis (Cao *et al*, 1998).

Thus, TB patients who have drug resistance often have long-term lung damage. Those who require repeated TB treatment have higher mortality, often from TB-related chronic lung damage.

5.2.C. Consequences to health-related quality of life (HRQoL)

A study in 2 TB units of south India evaluated the effect of TB on physical, mental and social aspects of patients' lives. The commonest response to being diagnosed with TB was to worry (54%) and less frequent but more extreme reactions were suicidal ideation (9%), denial of diagnosis (3%), and depression (8%). About one-third of men and women faced social stigma before treatment, which continued in 20% after treatment end (Rajeswari *et al*, 2005).

TB patients had significantly less average scores on a quality-of-life questionnaire in each domain: physical, psychological, social, and environmental. The physical and psychological domains were most negatively influenced. Women had a lower overall score than men and also in the social domain (Dhuria *et al*, 2008).

New PTB and EPTB patients were assessed for physical, mental, social and economic HRQoL 1 year post-treatment in south India. Forty percent had residual symptoms at the time of the study. These patients had significantly lower physical, mental, and social well-being scores compared to the asymptomatic ones (Muniyandi *et al*, 2007).

A study in Nigeria compared the mental health status of PTB patients with those with lower limb fractures and healthy controls. PTB patients had much higher proportions of psychiatric illness than the other 2 groups. 15% had generalized anxiety disorder, 11% had mild depression, and 4% had adjustment disorder. The presence of psychiatric disorders was inversely related to education, occupational status and incomes levels in PTB patients (Aghanwa and Erhabor, 1998).

5.2.D. Public health consequences

In Peru, 93 new PTB patients treated with the standard regimen 2HRZE/4HR were evaluated for duration of infectiousness post-treatment initiation, based on DST results. DST for PZA was not done. The period required for 90% patients to attain culture negativity was 60 days and 124 days for HRE-susceptible and non-MDR resistant patients, respectively. The smear conversion time was also significantly prolonged for patients with non-MDR resistance as compared to HRE-susceptible ones. Most patients who continued to be infectious for long periods of time were sputum smear negative (Fitzwater *et al*, 2010). These findings mean that patients with non-MDR first-line resistance treated with first-line drugs remain infectious and transmit drug-resistant organisms for a long time. This is because standard first-line regimens do not work well for them.

5.2.E. Social consequences

A study in south India in 2004 looked at felt and enacted stigma at home, in the community and in the work domain for TB patients. It also assessed the perceptions of community and DOT providers regarding stigma. For patients as well as community members and DOT providers, felt stigma was more than enacted stigma. Felt stigma was most prominent in the work place (63%), followed by the community (49%). Difficulties were anticipated in finding a partner for marriage, especially for women (63%). Enacted stigma was the commonest in the community (54%) followed by the workplace (26%) (Jaggarajamma *et al*, 2008).

5.3. <u>Objective III</u>. Interventions to Non-MDR first line resistance in other countries

All the studies below relate to non-MDR H mono or poly resistance. The studies are from developed countries as similar studies from India or settings like India were not found.

A retrospective study in Denmark assessed the treatment outcomes of non-MDR H-resistant patients treated from 2002-2007.
There were 65 patients with H-monoresistance and 46 with H-polyresistance during this period. The commonest polyresistance pattern was HS. 11% patients had had TB before. 74% patients had PTB and 26% had EPTB.
80% patients with H-monoresistance and 78% with H-polyresistance had successful outcome (cure + completion). Long-term survival was 95%. Level of resistance did not affect successful treatment outcome.
The following treatment regimens were most commonly used: 3REZ(H)/3-6RE(Z) and 6-9REZQ [Q denotes a fluoroquinolone]. The mean treatment duration for these and all other regimens was about 9 months, and all were given daily. The study does not specify which type of regimens were used for which resistance patterns or the outcome by resistance pattern separately (Bang *et al*, 2010).

In the USA, 44 patients with H-resistance (39 PTB and 5 EPTB) were treated from 1992-99. 2 patients had been previously treated for TB. Of the 44, 26 had H-monoresistance and 18 had HS resistance. All patients were sensitive to REZ.

They were treated with HRZE daily for 6 months. There were no failures or deaths, and the relapse rate was 4.8% on minimum 2 years follow up. There was no emergence of further resistance on relapse. (Nolan and Goldberg, 2002).

In another study in the USA, treatment regimens and outcomes of 53 patients with H-resistance treated between 1991-1998 were analyzed. Thirty-three patients had H-monoresistance and 20 had HS-polyresistance. Several regimens were used. However, to generalize, 90% regimens had at least RZE given as DOT for minimum 9 months. About one-third patients were given RZE three times a week for 9 months. Average duration of post-treatment follow up was 7 months. Treatment failure occurred in about 2% and relapse in about 6% patients. Thrice-weekly RZE did not have any adverse outcome if all drugs were given for a minimum 9 months (Escalante *et al*, 2001).

A retrospective study was conducted in the United Kingdom of the treatment outcomes of 37 patients with non-MDR H resistance treated from 1978-99 (Ormerod *et al*, 2001). Eighteen patients received treatment for more than 9 months, and 19 for equal to or less than 9 months. The regimen 2RZE/7RE of at least 9 months duration given daily was effective with no relapses at 1 year follow up.

To summarize: most of the regimens given in the above studies were around 9 months duration, the drugs were given daily, and some regimens had the same drugs throughout the treatment period. This varies from the current treatment in India where first-line drugs are given 3 days a week, the standard treatment duration is less than 9 months and IP and CP have different drug combinations.

A systematic review and meta-analysis of 33 trials from 1965-2008 involving about 1900 new and previously-treated patients with H-monoresistance was done (Menzies *et al*, 2009). The reviewers found that treatment failure, relapse and resistance amplification decreased when R and Z were used for longer periods, S was included in the regimen, and daily therapy was given at least in the IP. They recommend that retreatment regimens for patients with H-monoresistance should include at least 4 effective drugs in the IP including an aminoglycoside with presumed/confirmed sensitivity, and at least 3 effective drugs in the CP.

The WHO suggests treating first-line non-MDR resistance with daily regimens varying between 6-18 months, depending on the resistance pattern. Fluoroquinolones or an oral second-line drug may need to be added and the treatment duration extended for patients with widespread disease and polyresistance (WHO 2008).

6. DISCUSSION

The results of the literature review show that the problem of non-MDR first-line drug resistant TB in India is a result of inadequacies in the RNTCP as well as the private sector.

Treatment of first-line drug-sensitive TB in the RNTCP shows the following lacunae in implementation that contribute to the development of drug-resistant TB:

- wrong categorization of patients into treatment categories (Atre *et al*, 2007)
- inadequate supervision of DOT (Atre and Mistry, 2005)
- loss of patients during transfer from one part of the system to another (Kondapaka *et al*, 2012).

The reasons related to DOTS that have led to patients defaulting treatment are: distance traveled for DOT, non-availability of drugs, non-supportive behavior of staff, and low comprehension of the need to

complete the full course of treatment. These factors do not seem to have changed much between the early years of the DOTS program and now (Jaiswal *et al,* 2003; Gupta *et al*, 2011).

The program has had a positive impact in economic terms for patients treated in the program as compared to those treated in the private sector (Muniyandi *et al*, 2005). However, even now, patients bear certain expenses during RNTCP treatment (Pantoja *et al,* 2009) and poor patients spend a considerable part of their annual family income on TB-treatment related factors (Muniyandi *et al,* 2005; Pantoja *et al,* 2009).

These problems in implementation and economic factors contribute to treatment interruptions and default , which encourage the development of drug resistance (Mitchison, 1998).

The RNTCP gives thrice-weekly regimens for new and retreatment patients. However, the WHO recommends daily regimens. The WHO considers thrice-weekly regimens acceptable only if each dose is observed (WHO 2010). In the RNTCP, thrice weekly dosing in the IP is directly observed but only the first dose is observed in the CP. Thrice-weekly regimens also lead to more emergence of resistance and greater failure rates in H-resistance (WHO 2010).

In the current RNTCP guidelines, a patient must have R resistance to be eligible for any treatment other than the standard first-line regimens. Patients who do not fit this criterion are treated with the same drugs multiple times even in spite of documented resistance to first-line drugs other than R (RNTCP 2012; RNTCP 2013). The very fact of being retreated creates conditions conducive to resistance development, and length of treatment adds to the risk (Espinal *et al*, 2001). Weaker regimens increase this risk. This is compounded by the fact that DST for Z is almost never done, so unknown Z resistance may exist. This is especially likely in retreatment patients. Finally, this drug resistance is disseminated in society by PTB patients who remain infectious for long periods on suboptimal treatment (Fitzwater *et al,* 2010).

The RNTCP policy upholds the right of all TB patients irrespective of the type of TB to access appropriate diagnostic and treatment services (RNTCP 2010; RNTCP 2013). Yet, in practice, the focus has been MDR-TB and more recently XDR-TB. This is fully justified in view of the gravity of these two forms of resistance. However, other forms of resistance need attention too, in light of their large numbers and also due to the fact that large proportions of them have poor treatment outcomes (Pinto and Menzies, 2011). Selgelid and Reichman (2011) stress the necessity of appropriate anti-TB treatment from an ethical and human rights perspective. They also argue that the right to high-quality TB care in all aspects of TB care must be made effective immediately rather than gradually. This is because the gradual realization of this right harms individual patients and community health.

The private sector contributes to the creation of first-line drug resistance in various ways: use of non-standardized regimens some of which are not only different from but also therapeutically inferior to standardized ones, no treatment supervision, no or very few attempts to trace defaulters, very little advice or efforts for contact tracing, very little or no maintenance of treatment records, and little education to patients regarding necessity of treatment completion.
It is also alarming that the erratic treatment practices of doctors treated in the western system of medicine did not differ much from those trained in other systems.

RNTCP is attempting public-private mix (PPM) activities so that private practitioners also follow national guidelines for diagnosis, treatment and notification, and some such endeavors have been successful (RNTCP 2013).
However, a study on the potential acceptability of the DOT concept among patients in the private sector showed that 68% were not ready to accept the DOT method and 92% would prefer to purchase drugs than go to a DOT center (Pinto and Udwadia, 2010). Thus, even if the private practitioners co-operate with the RNTCP for PPM, their patients may not be willing for this form of treatment delivery.

It may also happen that in a PPM, private practitioners may disagree with treating patients with non-MDR first-line resistance with the same first-line drugs. They may ask patients to purchase second-line drugs in addition to what the RNTCP provides. The most commonly added single second-line drug for drug-resistant TB was a fluoroquinolone in a study on private practitioners (Udwadia *et al*, 2010). This will again limit future regimen choices in case the patient develops MDR TB. Also, patients may lose trust in the RNTCP if they feel that the RNTCP regimen they are receiving is not fully effective for them.

For PPM, the RNTCP expects private practitioners to follow its guidelines. However, doctors who follow other acceptable treatment guidelines, including daily treatment, cannot be integrated with the RNTCP because they treat patients in a different way (Udwadia *et al*, 2010).

First-line TB drugs are sold in a plethora of strengths and combinations of loose drugs and fixed dose combinations (FDC) in the private TB drug market. Only about 10% of them meet the WHO pre-qualification norms. Most drugs are of strengths that do not meet the current recommendations of the RNTCP and global drug facility (GDF). If this leads to low serum drug levels, drug resistance is likely to result. Also, there are many formulations with higher strengths. This may lead to adverse effects, causing patients to interrupt or default treatment, again predisposing to drug resistance.

Irrespective of which sector contributes to first-line drug resistance, the consequences of having first-line non-MDR TB with suboptimal treatment are: increased rates of failure, relapse, death, and further emergence of resistance; lack of improvement or worsening on treatment that leads to default; economic burden to patients as they seek multiple providers for relief outside the RNTCP and also because of income loss due to inability to work; negative impact on during-treatment and post-treatment HRQoL; long-term physical consequences in the form long-term sequelae; and spread of drug-resistant TB.
The results of the quality-of-life studies on TB patients show the negative impact of TB on all aspects of a patient's life. Also, the reactions of most patients even to a single diagnosis of TB indicate the emotional trauma they undergo. Then one can only imagine the suffering of patients who get TB repeatedly, and find that they do not respond to treatment because of progressively-increasing resistance.

India is committed to the Stop TB Strategy, which has as one of its objectives the reduction of 'suffering and socioeconomic burden associated with TB' (WHO 2006). This implies that all patients need to be treated with regimens that offer them the best possible chance of immediate treatment outcomes and freedom from the future risk of relapse. This means patients with first-line non-MDR TB also should get the regimens that offer them the best possible outcomes.
.
In treating non-MDR first-line resistance suboptimally, efforts to control MDRTB are thwarted. This is because some MDR TB is created by inadequate treatment of first-line non-MDR TB. For example, in one of the studies cited above (Santha *et al*, 2005), 15% new patients with H-monoresistance had acquired R resistance at the time of failure. Applying this figure to the estimated numbers of H-monoresistant patients among new patients, about 5000 patients with MDRTB will emerge at the end of Category I. It is reasonable to think that this risk of converting to MDR TB will be higher in those who are retreated and those who have polyresistance.

Moreover, when a patient reaches the stage of having MDR-TB, the treatment is far more expensive, prolonged and difficult than it would have been for non-MDR first line resistance. The outcomes of MDR-TB treatment in the RNTCP have shown high failure rates, attributed to high levels of fluoroquinolone resistance (RNTCP 2013). The state-wide Gujarat survey of 2005-06 showed any ofloxacin resistance at 19% and 25% respectively among new and previously-treated MDR-TB patients. Any ethionamide resistance was 41% and 25% respectively in new and previously-treated MDR-TB patients. Any kanamycin resistance was 4% in previously-treated cases (Ramachandran *et al*, 2009).

Considering this and the fact that Z DST is very rarely done though the drug has been part of a regimen that led to failure or relapse in previously-treated patients, the MDR-TB regimen may be significantly compromised in many patients of MDR-TB.

Also, a study on previously-tretaed PTB patients in a government laboratory in north India showed about 21% Ofx resistance and 8% Km resistance in patients with non-MDR first-line resistance. None of the non-MDR TB isolates showed simultaneous resistant to both Ofx and Km. Though the laboratory did not have EQA for DST of second-line drugs, these findings are not insignificant (Jain *et al*, 2012). This means that even fluoroquinolones may not be always dependable as components of regimens to treat non-MDR first-line resistant TB. However, the experiences in other settings show that modifications to first-line regimens by duration and drug combinations may produce good results at least in patients with the commonest forms of non-MDR first-line resistance (any H or S resistance). Also, WHO recommendations on treating non-MDR first-line resistance (WHO 2008) can be used. Fluoroquinolone resistance may pose a problem in treating this category of patients also, and sometimes higher-level fluoroquinolones may be needed.

It is welcome news that the RNTCP has included the following 3 topics in its operational research agenda: (i) relapse, mortality over 2.5 years and acquisition of resistance in intermittent versus daily regimens (ii) role of ethambutol in CP of regimen for new patients against the backdrop of H resistance, and (iii) a randomized controlled trial for treating non-rifampicin poly-resistant TB (RNTCP 2013). However, there is no timeframe mentioned for any of these research undertakings to be done.
Meanwhile, individual patients continue to suffer and public health is put at risk by the transmission of first-line non-MDR TB strains. It is highly desirable for the RNTCP to treat these patients with currently-recommended WHO guidelines till guidelines more aptly suited to the Indian context are established.

Rifampicin resistant, H-susceptible TB: The current RNTCP policy is to treat any R resistance with the standardized MDRTB regimen, which presumes HR resistance. This means even patients susceptible to H do not receive H in their MDRTB regimen, which denies them a valuable first-line drug (Smith *et al,* 2011).

Limitations of the Literature Review:

There was only one state-level dug resistance prevalence survey found, the one from Gujarat. The data from it was used to estimate first line non-MDR resistance in notified cases from all over India. India has large variations in health and health care levels across states (MoHFW 2012-13). Therefore, drug resistance surveys in more states would be useful to get a closer idea of the prevalence of first-line non-MDR resistant TB in India.

All studies on drug resistance prevalence cited in this thesis are from public sector patients.
It is suggested that in settings like India where almost half the TB patients are treated in the private sector, targeted surveys consisting of small numbers of patients from this sector must be done to give a more reliable estimate of drug-resistance. Drug resistance may be underestimated if based on surveys in patients in the public sector alone (Cohen *et al,* 2010).

Also, in the studies detailing treatment outcomes of patients with non-MDR first-line resistance, sometimes the resistance is not separately given for each drug. Patterns of resistance may just be classified as MDR and non-MDR. In this case, it is not possible to evaluate treatment responses by sub-types of non-MDR resistance.

There are very few studies describing treatment outcomes of first-line non-MDR TB in Indian patients. There were no studies found describing biological and quality-of-life consequences in this specific group.

Therefore, sequelae in patients with first-line susceptible or MDR TB had to be extrapolated to these patients.

7. RECOMMENDATIONS (OBJECTIVE IV) AND CONCLUSION

Recommendations:

The following recommendations are made to the Central TB Division of India in order of decreasing priority to address the issue of first-line non-MDR TB in India:

1. Treat all patients with first-line non-MDR TB with DST-based daily regimens, using the guidelines suggested by the WHO:
   The number of DOT providers may have to be increased for this. However, this issue can be addressed by increasing the participation of community-based DOT providers. Even family member-based DOT with regular supervision from the health system may need to be considered. This is because many private sector patients may not otherwise accept DOT. Based on the regimens chosen by the RNTCP, and especially as this will involve daily treatment, the cost of treating these patients may seem much more compared to treating first-line drug-susceptible TB with standard thrice-weekly regimens. However, in the long run, treating first-line non-MDR resistance at its current stage will prove to be more cost-effective than treating MDR TB or other amplified forms of resistance.

2. Include H in the treatment of rifampicin-resistant, H-susceptible TB if found to be susceptible on DST, or while awaiting DST results:
   This will entail a deviation from the standardized regimen for MDR TB, with the extra cost of daily H for these patients. However, this may lead to improved outcomes for at least a small proportion of R-resistant patients, especially considering the background of second-line drug resistance in India.

3. Regulate the private sector medical practitioners and private TB drug market strictly to reduce the creation of drug resistance.

4. Studies on treatment outcomes and long-term consequences in Indian patients with first-line non-MDR TB should be done. This will enable better understanding of any issues specific to them, thus improving their management.

5. Include Z susceptibility testing in DST for all patients otherwise eligible for DST:
   This can be initiated for at least patients suspected to have drug resistance following a retreatment regimen as they would have the greatest likelihood of having Z resistance. Till then, Z DST should be done at least in surveys representing large regions or states to give a representative estimate of Z resistance. It is important to know Z resistance as it is used to treat TB susceptible to first-line drugs, first-line non-MDR TB, as well as MDR TB.

6. Conduct drug resistance surveys in the private sector to give a better estimate of actual drug resistance situation in the country.

7. The majority of studies cited in this thesis are from the south, followed by the north of the country. Studies on all aspects of drug-resistant TB should be done in other parts of the country to find regional differences that need to be focused on to improve performance.

Conclusion:

Non-MDR first-line drug-resistant TB has multifactorial causation.

The MDR-TB crisis cannot be dealt with adequately unless other forms of first-line drug resistance are not dealt with adequately. Therefore, it is important to not only address the factors that lead to first-line drug resistance but also to treat such existing cases before they progress to MDR TB. It would be more cost-effective in the long run to treat any form of first-line drug resistance early and adequately, and thus avoid poor treatment outcomes, long-term TB sequelae and the emergence of MDR TB.

REFERENCES

Aghanwa, H. S. and Erhabor, G. E. (1998) Demographic/socioeconomic factors in mental disorders associated with tuberculosis in southwest Nigeria. *Journal of Psychosomatic Research*. Vol. 45, No. 4, pp 353-360. [Online]. Available from: *Elsevier* www.elsevier.com [Accessed 22 May 2013]

Atre, S. R. and Mistry, N. F. (2005) Multidrug-Resistant Tuberculosis (MDR-TB) in India: An Attempt to Link Biosocial Determinants. *Journal of Public Health Policy*, 26, 96-114. [Online]. Available from: *Palgrave Macmillan Ltd*. www.palgrave-journals.com/jphp. doi: 10.1057/palgrave.jphp.3200014 [Accessed 27 March 2013]

Atre, S. R., D'Souza, D. T. B., Dholakia, Y. N. and Mistry N. F. (2007) Observations on categorization of new TB cases: implications for controlling drug resistance. *Int J Tuberc Lung Dis.* October; 11(10): 1152–1153. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed Published online 2008 July 29. [Accessed 18 April 2013]

Bang, D., Andersen, P. H., Andersen, A. B. and Thomsen, V. O. (2010) Isoniazid-resistant tuberculosis in Denmark: mutations, transmission and treatment outcome. *Journal of Infection.* 60, 452-457. [Online]. Available from: *Elsevier* www.elsevierhealth.com/journals/jinf doi: 10.1016/j.jinf.2010.03.017 [Accessed 6 July 2013]

Behr, M. A., Warren, S. A., Salamon, H., Hopewell, P. C., Leon,. A. P. de, Daley, C. L. and Small, P. M. (1999) Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. *Lancet.* February 6, Vol 353:444-49 [Online]. Available from: *ScienceDirect* www.sciencedirect.com [Accessed 18 April 2013]

Cao, J. P., Zhang, L. Y., Zhu, J. Q. and Chin, D. P. (1998) Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. *Int J Tuberc Lung Dis.* 2(5):360-364. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 22 May 2013]

Charles, N., Thomas, B., Watson, B., Sakthivel, R. M., Chandrasekeran V. and Wares, F. (2010) Care Seeking Behavior of Chest Symptomatics: A Community Based Study Done in South India after the Implementation of the RNTCP. *PLoS One.* 5(9): e12379. Published online 2010 September 20. doi: 10.1371/journal.pone.0012379. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Cohen, T., Hedt, B. L. and Pagano, M. (2010) Estimating the magnitude and direction of bias in tuberculosis drug resistance surveys conducted only in the public sector: a simulation study. *BMC Public Health.* 2010; 10: 355. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed Published online 2010 June 21. doi: 10.1186/1471-2458-10-355 [Accessed 27 March 2013]

Dam, T., Isa, M. and Bose, M. (2005) Drug-sensitivity profile of clinical Mycobacterium tuberculosis isolates – a retrospective study from a chest-disease institute in India. *Journal of Medical Microbiology* (2005), 54, 269-271. [Online]. Available from: http://jmm.sgmjournals.org/content/54/3/269.full.pdf. DOI 10.1099/jmm.0.45635-0 [Accessed 27 March 2013]

Dhuria M, Sharma N, Ingle G K. Impact of tuberculosis on the quality of life. *Indian J Community Med* [serial online] 2008 [cited 2013 Aug 14];33:58-9. Available from: http://www.ijcm.org.in/text.asp?2008/33/1/58/39249 [Accessed 22 May 2013]

Escalante, P., Graviss, E. A., Griffith, D. E., Musser, J. M. and Awe, R. J. (2001) Treatment of isoniazid-resistant tuberculosis in southeastern Texas. *Chest.* 119:1730-1736. [Online]. Available from: *Chest.* http://journal.publications.chestnet.org [Accessed 6 July 2013]

Espinal, M. A., Laserson, K., Camacho, M., Fusheng, Z., Kim, S. J., Tlali, E., Smith, I., Suarez, P., Antunes, M. L., George, A. G., Martin-Casabona, N., Simelane, P., Weyer, K., Binkin, N., Raviglione, M. C. (2001) Determinants of drug-resistant tuberculosis: analysis of 11 countries. *Int J Tuberc Lung Dis.* 5(10):887-893. [Online].. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Fitzwater, S. P., Caviedes, L., Gilman, R. H., Coronel, J., LaChira, D., Salazar, C., Saravia, J. C., Reddy, K., Friedland, J. S. and Moore D. A. J. (2010) Prolonged infectiousness of tuberculosis patients in a directly observed therapy short-course program with standardized therapy. *Clinical Infectious Diseases.* 51(4):371-378. [Online]. Available from: *Oxford Journals* http://cid.oxfordjournals.org DOI: 10.1086/655127 [Accessed 22 May 2013]

Geetharamani, S., Muniyandi, M., Rajeswari, R., Balasubramanian, R., Theresa, X. and Venkatesan, P. (2001) Socio-economic impact of parental tuberculosis on children. *Ind. J Tub*. 48, 91. [Online]. Available from *medIND*: http://medind.nic.in [Accessed 22 May 2013]

Greaves, F., Ouyang, H., Pefole, M., MacCarthy, S. and Cash, R. A. (2007) Complaince with DOTS diagnosis and treatment recommendations by private practititoners in Kerala, India. *Int J Tuberc Lung Dis.* 11(1):110-112. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 18 April 2013]

Gupta, S., Gupta, S. and Behera, D. (2011) Reasons for interruption of anti-tubercular treatment as reported by patients with tuberculosis admitted in a tertiary care institute. *Indian J Tuberc*. 58: 11-17. [Online]. Available from: *National Tuberculosis Institute.* http://tbresearch.ntiindia.org.in [Accessed 18 April 2013]

Gurumurthy, P., Ramachandran, G., Kumar, A. K. H., Rajasekaran, S., . Padmapriyadarsini, C., Swaminathan, S., Venkatesan, P., Sekar, L., Kumar, S., Krishnarajasekhar, O. R. and Paramesh, P. (2004) Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis*. (2004) 38 (2): 280-283. doi: 10.1086/380795 [Online]. Available from*: Oxford Journals* http://cid.oxfordjournals.org [Accessed 27 March 2013)

Hanif, M., Malik, S. and Dhingra, V. K. (2009) Acquired drug resistance pattern in tuberculosis cases at the State Tuberculosis Centre, Delhi, India. *Int J Tuberc Lung Dis*. 13(1):74-78. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Hazarika, I. (2011) Role of Private Sector in Providing Tuberculosis Care: Evidence from a Population-based Survey in India. *J Glob Infect Dis*. Jan-Mar; 3(1): 19–24. doi: 10.4103/0974-777X.77291. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Jaggarajamma, K., Ramachandran, R., Charles, N., Chandrasekaran,V., Muniyandi, M. and Ganapathy, S. (2008) Psycho-social dysfunction: perceived and enacted stigma among tuberculosis patients registered under revised national tuberculosis control programme. *Indian J Tuberc*. 55:179-187 [Online]. Available from: *MedInd.* http://medind.nic.in [Accessed 22 May 2013]

Jain, A., Dixit, P. and Prasad, R. (2012) Pre-XDR & XDR in MDR and ofloxacin and kanamycin resistance in non-MDR Mycobacterium tuberculosis isolates. *Tuberculosis.* 92 (2012) 404-406. [Online]. Available from: *Elsevier* http://intl.elsevierhealth.com/journals/tube doi: 10.1016/j.tube.2012.05.010 [Accessed 27 March 2013]

Jaiswal, A., Singh, V., Ogden, J. A., Porter, J. D. H., Sharma, P. P., Sarin, R., Arora, V. K. and Jain, R. C. (2003) Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. *Tropical Medicine and International Health*. July, volume 8, No. 7, pp 625-633. [Online]. Available from: *Wiley Online Library*. http://onlinelibrary.wiley.com DOI: 10.1046/j.1365-3156.2003.01061.x [Accessed 18 April 2013]

Jenkins, H. E., Ciobanu. A., Plesca, V., Crudu, V., Galusca, I., Soltan, V. and Cohen, T. (2013) Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova. *Int J Tuberc Lung Dis*. 17(3):373-380. http://dx.doi. Org/10.5588/ijtld.12.0464 [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Jha, U. M., Satyanarayana, S., Dewan, P. K., Chadha, S., Wares, F., Sahu, S., Gupta, D. and Chauhan, L. S. (2010) Risk Factors for Treatment Default among Re-Treatment Tuberculosis Patients in India, 2006. *PLoS One.* 5(1): e8873. Published online 2010 January 25. doi: 10.1371/journal.pone.0008873. [Online]. Available from*: PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Johnson, J., Kagal, A. and Bharadwaj, R. (2003) Factors associated with drug resistance in pulmonary tuberculosis. *Indian J Chest Dis Allied Sci*. 45: 105-109. [Online]. Available from: *MedInd*. http://medind.nic.in [Accessed 18 April 2013]

Joseph, P., Chandrasekaran, V., Thomas, A., Gopi, P. G., Rajeswari, R., Balasubramanian, R., Subramani, R., Selvakumar, N. and Santha, T. (2006) Influence of drug susceptibility on treatment outcome and susceptibility profile of 'failures' to Category II regimen. *Indian J Tuberc*. 53:141-148. [Online]. Available from: *IMSEAR* http://imsear.hellis.org [Accessed 27 March 2013]

Joseph, M. R., Shoby, C. T., Amma, G. R., Chauhan, L. S. and Paramasivan, C. N. (2007) Surveillance of anti-tuberculosis drug resistance in Ernakulam District, Kerala State, South India. *Int J Tuberc Lung Dis*. 11(4):443-449. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Kapoor, S. K., Raman, A. V., Sachdeva, K. S. and Satyanarayana S. (2012) How did the TB patients reach DOTS services in Delhi? A study of patient treatment seeking behavior. *PLoS One.* 7(8) e:42458. Published online August 6. doi: 10.1371/journal.pone.0042458. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Kolappan, C., Subramani, R., Karunakaran, K. and Narayanan, P. R. (2006) Mortality of tuberculosis patients in Chennai, India. *Bulletin of the World Health Organization*. July, 84 (7) [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 22 May 2013]

Kolappan, C., Subramani, R., Kumaraswami, V., Santha, T. and Narayanan, P.R. (2008) Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. *Int J Tuberc Lung Dis*. 12(1): 81-86 [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 22 May 2013]

Kondapaka, K. K., Prasad, S. V., Satyanarayana, S., Kandi, S., Zachariah, R., Harries, A. D., Nagaraja, S. B., Tetali, S., Anchala, R., Kannuri, N. K., Murthy, K., Koppu, D., Vangari, L. and Rao S. (2012) Are tuberculosis patients in a tertiary care hospital in Hyderabad, India being managed according to national guidelines? *PLoS One*. 7(1):e30281. Published online January 17. doi: 10.1371/journal.pone.0030281. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Mahadev, B., Kumar, P., Agarwal, S. P., Chauhan, L. S. and Srikantaramu, N. (2005) Surveillance of drug resistance to anti-tuberculosis drugs in districts of Hoogli in West Bengal and Mayurbhanj in Orissa. *India J Tuberc*. 52: 5-10. [Online]. Available from: *IMSEAR* http://imsear.hellis.org [Accessed on 27 March 2013]

Maurya AK, Kant S, Nag VL, Kushwaha R, Dhole TN. Trends of anti-tuberculosis drug resistance pattern in new cases and previously treated cases of extrapulmonary tuberculosis cases in referral hospitals in northern India. *J Postgrad Med* [serial online] 2012 [cited 2013 Feb 9];58:185-9. Available from: http://www.jpgmonline.com/text.asp?2012/58/3/185/101379 [Accessed on 27 March 2013]

Menzies, D., Benedetti, A., Paydar, A., Royce, S., Pai, M., Burman, W., Vernon, A. and Lienhardt, C. (2009) Standardized treatment of active tuberculosis in patients with previous treatment and/or with monoresistance to isoniazid: a systematic review and meta-analysis. *PLoS Med*. 2009 September; 6(9): e1000150.
Published online 2009 September 15. doi: 10.1371/journal.pmed.1000150 [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 6 July 2013]

Ministry of Health & Family Welfare. (2012-13) *Annual Report.* New Delhi: Government of India. [Online]. Available from: http://www.mohfw.nic.in/index1.php?lang=1&level=1&sublinkid=1709&lid=1604 [Accessed 6 July 2013]

Mitchison, D. A. (1998) How drug resistance emerges as a result of poor compliance during short course chemotherapy of tuberculosis. *Int J Tuberc Lung Dis.*2(1):10-15. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Muniyandi, M., Ramachandran, R. and Balasubramanian, R. (2005) Costs to patients with tuberculosis treated under DOTS programme. *Indian J Tuberc*. 52: 188-196. [Online]. Available from: *IMSEAR* http://imsear.hellis.org [Accessed 22 May 2013]

Muniyandi, M., Rajeswari, R., Balasubramanian, R., Nirupa, C., Gopi, P. G., Jaggarajamma, K., Sheela, F., Narayanan, P. R. (2007) Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. *Int J Tuberc Lung Dis*. 11(8):887-892. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 22 May 2013]

Nagaraja C, Shashibhushan B L, Sagar C, Asif M, Manjunath P H. Resistance pattern in drug-resistant pulmonary tuberculosis. *J Postgrad Med* [serial online] 2011 [cited 2013 Mar 30];57:181-3. Available from: http://www.jpgmonline.com/text.asp?2011/57/3/181/85197[Accessed 27 March 2013]

Nagaraja, S. B., Satyanarayana, S., Chadha, S. S., Kalemane, S., Jaju, J., Achanta, S., Reddy, K., Potharaju, V., Shamrao, S. R. M., Dewan, P., Rony, Z., Tetali, S., Anchala, R., Kannuri, N. K., Harries, A.D. and Singh, S. K. (2011). How do patients who fail first-line TB treatment but who are not placed on an MDR-TB regimen fare in South India? *PLoS One*. 6(10): e25698. Published online 2011 October 11. doi: 10.1371/journal.pone.0025698 [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 27 March 2013]

Nagarathna, S., Rafi, W., Veenakumari, H. B., Mani, R., Satishchandra, P. and Chandramuki, A. (2008) Drug susceptibility profiling of tuberculous meningitis. *Int J Tuberc Lung Dis*. 12(1):105-107. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Nolan, C. M. and Goldberg, S. V. (2002) Treatment of isoniazid-resistant tuberculosis with isoniazid, rifampin, ethambutol, and pyrazinamide for 6 months. *Int J Tuberc Lung Dis.* 6(11):952-958. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 6 July 2013]

Ormerod, L. P., Horsfield, N. and Green, R. M. (2001) Can a nine-month regimen be used to treat isoniazid resistant tuberculosis diagnosed after standard treatment is started? *Journal of Infection* 42, 1-3. [Online]. Available from: *IDEAL* http://www.idealibrary.com doi: 10.1053/jinf.2000.0773. [Accessed 6 July 2013]

Pai,M., Kalantri, S., Aggarwal, A. N., Menzies, D. and Blumberg, H. M. (2006) Nosocomial Tuberculosis in India *Emerg Infect Dis.* September; 12(9): 1311–1318. doi: 10.3201/eid1209.051663. [Online] Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 27 March 2013]

Pantoja, A., Floyd, K., Unnikrishnan, K. P., Jitendra, R., Padma, M. R., Lal, S. S., Uplekar, M., Chauhan, L. S., Kumar, P., Sahu, S., Wares, F. and Lonnroth, K. (2009) Economic evaluation of public-private mix for tuberculosis care and control, India. Part I. Socio-economic profile and costs among tuberculosis patients. *Int J Tuberc Lung Dis.* 13(6):698-704. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 22 May 2013]

Paramasivan, C. N., Bhaskaraiar, K., Venkataraman, P., Chandrasekaran, V. and Narayanan, P. R. (2000) Surveillance of drug resistance in tuberculosis in the state of Tamil Nadu. *Ind. J. Tub*. 47, 27. [Online]. Available from: http://www.lrsitbrd.nic.in [Accessed 27 March 2013]

Paramasivan, C. N., Venkataraman, P., Chandrasekaran, V., Bhat, S. and Narayanan, P. R. (2002) Surveillance of drug resistance in tuberculosis in two districts of South India. *Int J Tuberc Lung Dis*. 6(6):479-484. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Paramasivan, C. N., Rehman, F., Wares, F., Sundar Mohan, N., Sundar, S., Devi, S. and Narayanan, P. R. (2010) First-and second-line drug resistance patterns among previously treated tuberculosis patients in India. *Int J Tuberc Lung Dis*. 14(2):243-246. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Paul, D., Busireddy, A., Nagaraja, S. B., Satyanarayana, S., Dewan, P. K., Nair, S. A., Sarkar, S., Quazi T. A., Sarkar, S., Shamrao, S. R. M., Harries, A. D. and Oeltmann J. E. (2012) Factors Associated with Delays in Treatment Initiation after Tuberculosis Diagnosis in Two Districts of India. *PLoS One*. 7(7) e39040. Published online July 9. doi: 10.1371/journal.pone.0039040. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013].

Pinto, L. M. and Udwadia, Z. F. (2010) Private patient perceptions about a public programme; what do private Indian tuberculosis patients really feel about directly observed treatment? *BMC Public Health.* 10: 357. Published online 2010 June 22. doi: 10.1186/1471-2458-10-357[Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013].

Pinto, L. and Menzies, D. (2011). Treatment of drug-resistant tuberculosis. *Infect Drug Resist.* 4: 129–135. Published online 2011 July 21. doi: 10.2147/IDR.S10332 [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 6 July 2013]

Prasad, R., Verma, S.K., Garg, R., Jain, A., Anand, S. C., Hosmane, G. B., Verma, R. K., Kushwaha, N. S. and Kant, S. (2012) Drug susceptibility pattern of Mycobacterium tuberculosis isolates from patients of Category-II failure of pulmonary tuberculosis under directly observed treatment short-course from north India. *BiosScience Trends*. 6(3): 110-114. [Online]. Available from: *BioScienceTrends* http://www.biosciencetrends.com/action/downloaddoc.php?docid=552
DOI: 10.5582/bst.2012.v6.3.110 [Accessed 27 March 2013]

Quazi, T. A., Sarkar, S., Borgohain, G., Sreenivas, A., Harries, A. D., Srinath, S., Khan, K., Bishnu, B., Tapadar, S., Phukan, A. C., Kabir, A., Chaddha, V., Paul, D. and Dewan, P. (2012) Are all patients diagnosed with tuberculosis in Indian medical colleges referred to the RNTCP? *Int J Tuberc Lung Dis.*16(8):1083-1085. http://dx.doi.org/10.5588/ijtld.11.0699. Epublished June 5. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 18 April 2013]

Rajeswari, R., Muniyandi, M., Balasubramanina, R. and Narayanan, P. R. (2005) Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. *Social Science & Medicine*. 60:1845-1853. [Online]. Available from: *Elsevier* www.elsevier.com/locate/socscimed [Accessed 18 April 2013]

Ramachandran, R., Nalini, S., Chandrasekar, V., Dave, P. V., Sanghvi, A. S., Wares, F., Paramasivan, C. N., Narayanan, P. R., Sahu, S., Parmar, M., Chadha, S., Dewan, P. and Chauhan, L. S. (2009) Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int J Tuberc Lung Dis.* 13(9):1154-1160. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Rawat J, Sindhwani G, Dua RJ. Five-year trend of acquired antitubercular drug resistance in patients attending a tertiary care hospital at Dehradun (Uttarakhand). *Lung India* [serial online] 2009 [cited 2013 Jul 25];26:106-8. Available from: http://www.lungindia.com/text.asp?2009/26/4/106/56342 [Accessed 27 March 2013]

Revised National Tuberculosis Control Programme, Government of India (2010) *Training Module for Medical Practitioners.* New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare. [Online]. Available from: http://www.tbcindia.nic.in/pdfs/Training%20Module%20for%20Medical%20Practitioners.pdf [Accessed 3 April 2013]

Revised National Tuberculosis Control Programme, Government of India (2012) *Guidelines on Programmatic Management of Drug Resistant Tuberculosis (PMDT) in India.* New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare. [Online] Available from: http://www.tbcindia.nic.in/pdfs/Guidelines%20for%20PMDT%20in%20India%20-%20May%202012.pdf [Accessed 9 February 2013]

Revised National Tuberculosis Control Programme, Government of India (2013) *TB India 2013.* New Delhi: Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare. [Online]. Available from: http://www.tbcindia.nic.in/pdfs/TB%20India%202013.pdf [Accessed 6 July 2013]

Sachdeva, K. S., Satyanarayana, S., Dewan, P. K., Nair, S. A., Reddy, R., Kundu, D., Chadha, S. S., Venkatachalaiah, A. K. M., Parmar, M. and Chauhan, L. S. (2011) Source of previous treatment for re-treatment tuberculosis cases registered under the National Tuberculosis Control Programme, India, 2010. *PLoS One*.6(7): e22061. Published online July 12. doi: 10.1371/journal.pone.0022061. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Sadacharam, K., Gopi, P. G., Chandrasekaran, V., Eusuff, S. I., Subramani, R., Santha, T. and Narayanan, P. R. (2007). Status of smear-positive TB patients at 2-3 years after initiation of treatment under a DOTS programme. *Indian J Tuberc*. 54:199-203[Online]. Available from: *MedInd*. http://medind.nic.in [Accessed 27 March 2013]

Santha, T., Garg, R., Freiden, T., R., Chandrasekaran, V., Subramani, R., Gopi, P. G., Selvakumar, N., Ganapathy, S., Charles, N., Rajamma, J. and Narayanan, P. R.. (2002) Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. *Int J Tuberc Lung Dis.*6(9):780-788. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Santha, T., Gopi, P. G., Rajeswari, R., Selvakumar, N., Subramani, R., Chandrasekaran, V., Rani, B., Thomas, A. and Narayanan, P. R. (2005) Is it worth treating Category I failure patients with Category II regimen? *Indian J Tuberc*. 52:203-206 [Online]. Available from: *National Tuberculosis Institute* http://tbresearch.ntiindia.org.in [Accessed 27 March 2013]

Santha, T., Thomas, A., Chandrasekaran, V., Selvakumar, N., Gopi, P. G., Subramani, R., Rajeswari, R., Rani, B., Paramasivan, C.N., Perumal, M., Wares, F. and Narayanan, P. R. (2006) Initial drug susceptibility profile of M. tuberculosis among patients under TB programme in South India. *Int J Tuberc Lung Dis.* 10(1):52-57. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013]

Satyanarayana, S., Nair, S. A., Chadha, S. S., Shivashankar, R., Sharma, G., Yadav, S., Mohanty, M., Kamineni, V., Wilson, N. C., Harries, A. D. and Dewan, P. K. (2011) From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. *PLoS One*. 6(9): e24160. Published online 2011 September 2. doi: 10.1371/journal.pone.0024160. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Selgelid, M. J. and Reichman, L . B. (2011) Ethical issues in tuberculosis diagnosis and treatment. *Int J Tuberc Lung Dis.*15(6):S9-S13. [Online]. Available from: [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 6 July 2013]

Sethi, S., Biswal, M., Chatterjee, S. S., Mewara, A., Gupta, D., Kumar, S., Singh, K. and Sharma, M. (2012) Susceptibility pattern among pulmonary and extrapulmonary isolates of Mycobacterium tuberculosis in north India. *African Journal of Microbiology Research*. April 23, Vol. 6(15), pp. 3696-3699. [Online]. Available from: *academicJournals* http://www.academicjournals.corg/AJMR DOI: 10.5897/AJMR12.195 [Accessed 27 March 2013].

Sharma, S. K., Kaushik, G., Jha, B., George, N., Arora, S. K., Gupta, D., Singh, U., Hanif, M. and Vashisht, R. P. (2011a) Prevalence of multidrug-resistant tuberculosis among newly diagnosed cases of sputum-positive pulmonary tuberculosis. *Indian J Med Res.* 2011 March; 133(3): 308–311. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 27 March 2013].

Sharma, S. K., Kumar, S., Saha, P. K., George, N., Arora, S. K., Gupta, D., Singh, U., Hanif, M. and Vashisht, R. P. (2011b) Prevalence of multidrug-resistant tuberculosis among Category II pulmonary tuberculosis patients. *Indian J Med Res*. 2011 March; 133(3): 312–315. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 27 March 2013].

Singla, N., Sharma, P. P., Singla, R. and Jain, R. C. (1998) Survey of knowledge, attitudes and practices for tuberculosis among general practitioners in Delhi, India. *Int J Tuberc Lung Dis*. 2(5):384-389. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 18 April 2013]

Singla, N., Singla, R., Fernandes, R. and Behera, D. (2009) Post treatment sequelae of multi-drug resistant tuberculosis patients. *Ind J Tuberc*. 56: 206-212 [Online]. Available from: *National Tuberculosis Institute.* http://tbresearch.ntiindia.org.in [Accessed 22 May 2013]

Singla, R., Srinath, D., Gupta, S., Visalakshi, P., Khalid, U. K., Singla, N., Gupta, U. A., Bharty, S. K. and Behera, D. (2009) Risk factors for new pulmonary tuberculosis patients failing treatment under the Revised National Tuberculosis Control Programme, India. *Int J Tuberc Lung Dis*. 13(4):521-526. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013].

Smith, S. E., Kurbatova, E. V., Cavanaugh, J. S. and Cegielski, J. P. (2011) Global isoniazid resistance patterns in rifampin-resistant and rifampin-susceptible tuberculosis. *Int J Tuberc Lung Dis*. 16(2):203-205. [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com http://dx.doi.org/10.5588/ijtld.11.0445 Published online December 2 2011 [Accessed 27 March 2013].

Srivastava, D. K., Mishra, A., Mishra, S., Chouksey, M., Jain, P., Gour, N. and Bansal, M. (2011) A comparative assessment of KAP regarding tuberculosis and RNTCP among government and private practitioners in district Gwalior, India: an operational research. *Indian J Tuberc*. 58:168-177. [Online]. Available from: http://lrsitbrd.nic.in [Accessed 18 April 2013]

Swaminathan, S., Paramasivan, C. N., Ponnuraja, C., Iliayas, S., Rajasekaran, S. and Narayanan, P. R. (2005) Anti-tuberculosis drug resistance in patients with HIV and tuberculosis in south India. *Int J Tuberc Lung Dis*. 9(8):896-900 [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013].

Thomas, A., Gopi, P. G., Santha, T., Chandrasekaran, V., Subramani, R., Selvakumar, N., Eusuff, S. I., Sadacharan, K., Narayanan, P. R. (2005) Predictors of relapse among pulmonary tuberculosis

patients treated in a DOTS programme in south India. *Int J Tuberc Lung Dis*. 9(5):556-561[Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 27 March 2013].

Udwadia, Z. F., Pinto, L. M. and Uplekar, M. W. (2010) Tuberculosis management by private practitioners in Mumbai, India: has anything changed in two decades? *PLoS One*. 2010; 5(8): e12023. Published online 2010 August 9. doi: 10.1371/journal.pone.0012023. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013].

Uplekar, M., Juvekar, S., Morankar, S., Rangan, S. and Nunn, P. (1998) Tuberculosis patients and practitioners in private clinics in India. *Int J Tuberc Lung Dis.* 2(4):324-329. [Online]. Available from: [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 18 April 2013]

Valliere, S. de and Barker, R. D. (2004) Residual lung damage after completion of treatment for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 8(6):767-771 [Online]. Available from: *IngentaConnect.* http://www.ingentaconnect.com [Accessed 22 May 2013]

Vandan, N., Ali, M., Prasad, R. and Kuroiwa, C. (2009) Assessment of doctors' knowledge regarding tuberculosis management in Lucknow, India: A public-private sector comparison. *Public Health.* 123;484-489. [Online]. Available from: *Elsevier* www.elsevierhealth.com/journals/pubh. [Accessed 18 April 2013]

Vijay, S., Balasangameshwara, V. H., Jagannatha, P. S., Saroja, V. N., Shivashankar, B. and Jagota, P. (2002) Re-treatment outcome of smear positive tuberculosis cases under DOTS in Bangalore city. *Ind. Tub* 49, 195[Online]. Available from: *National Tuberculosis Institute.* http://tbresearch.ntiindia.org.in [Accessed 27 March 2013].

Vijay, S., Balasangameshwara, V. H.., Jagannatha, P. S. and Kumar, P. (2004) Initial drug resistance among tuberculosis patients DOTS programme in Bangalore City. *Indian J Tuberc*. 51: 17-21. [Online]. Available from: *IMSEAR* http://imsear.hellis.org [Accessed on 27 March 2013]

Vijay, S., Kumar, P., Chauhan, L. S., Vollepore, B. H., Kizhakkethil, U. P. and Rao, S. G. (2010) Risk Factors Associated with Default among New Smear Positive TB Patients Treated Under DOTS in India. *PLoS One.* 5(4): e10043. Published online 2010 April 6. doi: 10.1371/journal.pone.0010043. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013]

Wells, W. A., Ge, C. F., Patel, N., Oh, T., Gardiner, E. and Kimerling, M. E.(2011) Size and usage patterns of private TB drug markets in the high burden countries. *PLoS One*. 6(5): e18964. Published online 2011 May 4. doi: 10.1371/journal.pone.0018964. [Online]. Available from: *PubMed.gov* http://www.ncbi.nlm.nih.gov/pubmed [Accessed 18 April 2013].

World Health Organization. Global Health Observatory Data Repository. India Statistics Summary (2002-present) [Online]. Available from: http://apps.who.int/gho/data/node.country.country-IND?lang=en. [Accessed 6 July 2013]

World Health Organization (2006) *The Stop TB Strategy*. Geneva: World Health Organization. [Online]. Available from: http://whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf [Accessed 26 March 2013]

World Health Organization (2008) *Guidelines for the programmatic management of drug-resistant tuberculosis.Emergency Update 2008.* Geneva: World Health Organization. [Online]. Available from: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf [Accessed 10 February 2013]

World Health Organization (2010) Treatment of tuberculosis guidelines. Fourth edition. Geneva: World Health Organization. [Online]. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf. [Accessed 12 February 2013]

World Health Organization (2012) *Global Tuberculosis Report.* Geneva: World Health Organization. [Online]. Available from: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf [Accessed 26 March 2013]

World Health Organization (2013) *Definitions and reporting framework for tuberculosis – 2013 revision.* Geneva: World Health Organization. .[Online]. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. [Accessed 2 July 2013]

Yadav, A., Garg, S. K., Chopra, H., Bajpai, S. K., Bano, T., Jain, S. and Kumar, A. (2012) Treatment practices in pulmonary tuberculosis by private sector physicians of Meerut, Uttar Pradesh. *Indian J Chest Dis Allied Sci* **.** 54: 161-163.[Online]. Available from: *MedInd*. http://medind.nic.in [Accessed 18 April 2013]

❖ ANNEX I

RNTCP organization

The RNTCP is the national public sector program for TB diagnosis, treatment and control. The RNTCP services are delivered through the general public health care system and medical colleges. The program has also formed alliances with over 2000 NGOs (non-government organizations) and about 14000 private practitioners (RNTCP 2013)

The Revised National Tuberculosis Control Program (RNTCP), adopting the directly observed treatment of short-course chemotherapy (DOTS) for first-line drug-susceptible TB, was piloted in India from 1993 and achieved coverage all over the country in 2006. There are over 13,300 designated microscopy centers (DMC) for the diagnosis of TB. They are distributed as 1/100,000 population generally and 1/50,000 population in areas with difficult access. There are over 400,000 DOT treatment centers, with decentralization as close to patients' residences as possible. Persons recognized as TB suspects in general health facilities are diagnosed as TB cases based on the RNTCP algorithms for sputum smear positive PTB, sputum smear negative PTB or EPTB, and are initiated on treatment under the program. For the diagnosis of PTB, 2 sputum samples, one on each successive day, are to be tested microscopically for TB bacilli (RNTCP 2013)

The program started 'DOTS-Plus' for the diagnosis and treatment of drug-resistant TB in 2007 and expanded these activities to all states and union territories in 2012. By February 2013, 92% of the population had geographical access to DOTS-Plus services. All districts now offer culture and DST for sputum smear positive retreatment patients at TB retreatment initiation and for sputum smear positive failures of the regimen for new patients. Some districts are also offering culture and DST to all sputum smear positive cases during monitoring of first-line regimens, and some are offering it additionally to all smear negative retreatment patients and all patients with HIV/TB coinfection.
From the initiation of DOTS-Plus services in 2007 to the end of 2012, about 145,000 patients had been tested for suspected MDR TB and about 21,000 had been started on MDR-TB treatment. XDR-TB is estimated to occur in 3% of MDR-TB patients, as per figures from the Gujarat state of India (11). XDR-TB has not been diagnosed in new patients. 131 XDR-TB patients have been initiated on treatment (Category V) from 2007 to the end of 2012 end (RNTCP 2013).

The RNTCP follows certification of labs for solid and liquid media culture and DST, and LPA as per quality assurance recommendations of the WHO and the global laboratory initiative (GLI).
TB culture and DST is done at treatment initiation for sputum smear positive patients presenting for retreatment and for sputum smear positive failures of the regimen for new patients. The program plans to provide culture and DST for all sputum smear positive patients in the RNTCP by 2015. Molecular tests [line probe assay (LPA) and cartridge-based nucleic acid amplification test (CB-NAAT)] are the preferred tests for diagnosing MDR-TB, if available. There are 45 RNTCP-accredited laboratories for culture and DST in India, including those in the public sector, private sector, and laboratories attached to medical colleges and NGOs. Of these, 35 laboratories are accredited for solid C and DST, 10 for liquid C and DST, and 35 for LPA. The RNTCP is doing a feasibility study for GenExpert at 18 sites in India (RNTCP 2013).

There are 4 NRL (National Reference Laboratory) in India, among which TRC (Tuberculosis Research Center), Chennai, is also a SNRL (supranational reference laboratory). NRLs supervise and give training for the IRL (Intermediate Reference Laboratory) under them. An IRL is responsible for TB laboratory

services for a state. IRLs carry out TB culture and DST and also supervise the DMCs at district level (RNTCP 2013).

The MDR-TB regimen has an IP (intensive phase) of 6-9 months with Km (kanamycin), Lvx (levofloxacin), Eto (ethionamide), Cs (cycloserine), Z, E and a CP (continuation phase) of 18 months with Lvx, Eto, Cs, E (RNTCP 2013).

XDR-TB is treated with an IP of 6-12 months with Cm (capreomycin), Mfx (moxifloxacin), PAS (para-amino salicylic acid), high-dose H, Lzd (linezolid), Cfz (clofazimine), Amx/Clv (amoxyclav) and a CP of 18 months with Mfx, PAS, high-dose H, Lzd, Cfz, Amx/Clv (RNTCP 2013).

Older regimens in the RNTCP: Previously, the regimen for new patients was called Category I, for previously-treated patients Category II, and there was a subclass of new patients [smear negative PTB and some forms of extrapulmonary TB] treated with a regimen called Category III [$2(HRZ)_3/4(HR)_3$] regimens. The category III regimen is abolished now (RNTCP 2010).

❖ ANNEX II: STUDIES ON PREVALENCE OF DRUG RESISTANCE

Table A: Drug resistance in new pulmonary TB patients

Year, lab for culture and DST	**Patient source**	**Sample, number of patients with MTb positive C and DST in the study**	**No. (%) pan-susceptible of all culture positive patients**	**Mono-r No. (%) of all culture positive patients**	**Poly-r (other than MDR) No. (%) of all culture positive patients**	**MDR No. (%) of all culture positive patients**
Feb-Mar 1997, TRC Chennai as national central lab with EQA by WHO SNRL Brisbane, Australia	All RNTCP diagnostic centers in the state of Tamil Nadu, south India (Paramasivan *et al*, 2000)	Sputum, 384	312/384 (81.2)	H 29 (7.6), R 2 (0.5), E 2 (0.5), S 7 (1.8)	HE 7 (1.8), HS 5 (1.3), HES 5 (1.3), RES 2 (0.5)	HR 2 (0.5), HRE 4 (1), HRES 7 (1.8)
Feb-Apr 1999, TRC Chennai (SNRL)	Patients in the RNTCP program in the district North Arcot district,Tamil Nadu state, south India (Paramasivan *et al*, 2002)	Sputum (AFB smear pos), 282	204/282 (72.3)	H: 36 (12.8), E: 1 (0.4), S: 10 (3.5)	HE: 4 (1.4), HS: 15 (5.3), HES: 3 (1.1), ES: 1 (0.4)	HRE: 2 (0.7), HRS: 4 (1.4), HRES: 2 (0.7)
Apr-Dec 1999, NTI Bangalore (NRL) with EQA by WHO	Patients in the RNTCP program of Bangalore city, Karnataka state,	Sputum (AFB smear pos), 271	196/271 (72.3)	H 10 (3.7), R 1 (0.4), E 1	HS 18 (6.6), HES 3 (1.1)	HR 2 (0.7), HRS 3 (1.1), HRES 1

SNRL Brisbane, Australia	South India (Vijay *et al*, 2004)			(0.4), S 36 (13.3)		(0.4)
May 1999-Dec 2003, TRC Chennai (SNRL)	Patients in the RNTCP program in a sub-district area, including urban and rural areas, of Thiruvallur district, Tamil Nadu state, south India (Santha *et al,* 2006)	Sputum (AFB smear pos and neg), 1603 smear pos and culture pos, 222 smear neg and culture pos ,	1358/1603 (84.7) pan-susceptible in smear pos and culture pos, 193/222 (86.9) pan-susceptible in smear neg. and culture pos	Smear Pos/C pos: H 85 (5.3), R 4 (0.2), S 74 (4.6) Smear neg/C pos: H 5 (2.3), S 15 (6.8)	Smear pos/C pos: HS 54 (3.4), RS: 1 (0.1) Smear neg/C pos: HS 8 (3.6)	Smear pos/C pos: HR: 13 (0.8), HRS 14 (0.9) Smear neg/C pos: HRS 1 (0.4)
Jul-Dec 1999, TRC Chennai (SNRL)	Patients in the RNTCP program in the district, Raichur district, Karnataka state, South India (Paramasivan *et al,* 2002)	Sputum (AFB smear pos), 278	217/278 (78.1)	H: 34 (12.2), S: 9 (3.2)	HE: 3 (1.1), HS: 6 (2.2), HES: 2 (0.7)	HR: 2 (0.7), HRE: 2 (0.7), HRS: 1 (0.4), HRES: 2 (0.7)
Aug 2000-May 2001, NTI Bangalore (NRL) with EQA by TRC, Chennai (SNRL) and Inst. Of Tropical Medicine, Belgium (SNRL).	Patients from all microscopy centers of the RNTCP in district Mayurbhanj of Orissa state, East India (Mahadev *et al,* 2005)	Sputum (AFB smear pos), 282	267/282 (94.7)	H 3 (1.1), S 8 (2.8)	HS 2 (0.7)	HR 1 (0.4), HRES 1 (0.4)
Aug 2000-July 2001, NTI Bangalore (NRL) with EQA by TRC, Chennai (SNRL) and Inst. Of Tropical Medicine, Belgium (SNRL).	Patients from all microscopy centers of the RNTCP in district Hoogli of West Bengal state, East India (Mahadev *et al,* 2005)	Sputum (AFB smear pos), 263	219/263 (83.3)	H 6 (2.3), S 17 (6.5)	HE 1 (0.38), HS 11 (4.1), HES 1 (0.38)	HR 1 (0.38), HRS 4 (1.5), HRES 3 (1.1)

May 2004-Oct 2004, local lab under supervision of SNRL of India (TRC, Chennai)	Patients in the RNTCP program from the entire district, Ernakulum district of Kerala state, south India (Joseph *et al*, 2007)	Sputum (AFB smear pos), 305	220/305 (72.1)	H 8 (2.6) R 3 (1) S 53 (17)	HS 10 (3.3) , RS 2 (0.6), HES 3 (1)	HRS 1(0.3), HRE 2 (0.6), HRES 3 (1)
Nov 2005-Oct 2006, TRC, Chennai (SNRL)	Patients from RNTCP centers, which were randomly chosen from the entire state; state-wide survey of Gujarat State (west India) (Ramachandran *et al*, 2009)	Sputum (AFB smear pos), 1571	1236/1571 (78.7)	H 84 (5.4), R 3 (0.2), E 3 (0.2), S 156 (10)	HE 3 (0.2), HS 45 (2.9), HES 4 (0.3)	MDR-TB 37 (2.4) including HRES 13 (0.8)
Feb 2008-Dec 2009; IRL for Delhi state	Patients attending a primary level chest clinic in Delhi, north India (Sharma *et al*, 2011a)	Sputum (AFB smear pos), 177	166/177 (94)	H 3 (1.7)	HE 4 (2.3), HS 1 (0.6), HES 1 (0.6)	HRS 1 (0.6), HRES 1 (0.6)

Table B: Drug resistance in previously-treated pulmonary TB patients

Year, lab for culture and DST	**Patient source**	**Sample, number of patients with MTb positive C and DST in the study**	**No. (%) pan-susceptible of all culture positive patients**	**Mono-r No. (%) of all culture positive patients**	**Poly-r (other than MDR) No. (%) of all culture positive patients**	**MDR No. (%) of all culture positive patients**
Feb-Mar 1997, TRC Chennai as national central lab with EQA by WHO SNRL Brisbane, Australia	All RNTCP diagnostic centers in the state of Tamil Nadu, south India (Paramasivan *et al*, 2000)	Sputum, 16	8/16 (50)	H 2 (12.5)	HE 1 (6.2), HES 1 (6.2)	HR 1 (6.2), HRE 2 (12.5), HRES 1 (6.2)
Feb-Apr 1999, TRC Chennai (SNRL)	Patients in the RNTCP program in the district North Arcot district,Tamil	Sputum (AFB smear pos), 16	3/16 (19)	H: 1 (6)	HS: 1 (6)	HR: 2 (12.5), HRE: 1 (6), HRS: 4 (25), HRES: 4

	Nadu state, south India (Paramasivan *et al*, 2002)					(25)
May 1999-Dec 2003, TRC Chennai (SNRL)	Patients in the RNTCP program in a sub-district area, including urban and rural areas, of Thiruvallur district, Tamil Nadu state, south India (Santha *et al*, 2006)	Sputum (AFB smear pos), 443 (relapse 146, defaulters 231, failures 66)	Relapse: 93/146 (63.7), Defaulters: 148/231 (64.1), Failures: 21/66 (31.8)	Relapse: H 26 (17.8), S 6 (4.1) Defaulters: H 35 (15.2), S 9 (3.9) Failures: H 17 (25.8), R 1 (1.5)	Relapse: HS 5 (3.4) Defaulters: HS 17 (7.4) Failures: HS 12 (18.2)	Relapse: HR 8 (5.5), HRS 8 (5.5) Defaulters: HR 14 (6.1), HRS 7 (3) Failures: HR 10 (15.2), HRS 5 (7.6)
Jul-Dec 1999, TRC Chennai (SNRL)	Patients in the RNTCP program in the district, Raichur district, Karnataka state, South India (Paramasivan *et al*, 2002)	Sputum (AFB smear pos), 11	none susceptible to all drugs	0	0	HR: 2 (18), HRE: 1 (9), HRS: 4 (36.4), HRES: 4 (36.4)
2001-2004, TRC, Chennai (SNRL)	Patients with one or more previous TB treatments from all over India, ¾ from tertiary level government institutes (Paramasivan *et al*, 2010)	Sputum, 2816	814/2816 (28.90) (total no. susceptible to HRES)	H 196 (6.96), R 21(0.74), E 1 (0.03), S 65 (2.30)	HE 32 (1.13), HS 136 (4.82), RE 3 (0.10), RS 3 (0.10), ES 2 (0.07), HES 40 (1.42), RES 5 (0.18)	HR 355 (12.6), HRE 176 (6.25), HRS 385 (13.67), HRES 582 (20.7)
Aug 2003-July 2008, IRL for the state of Uttar Pradesh	Category II failure PTB patients under RNTCP, from different districts of Uttar Pradesh state, north India (Prasad *et al*, 2012)	Sputum, 170	2/170 (1.1)	H 5 (2.9), R 2 (1.1), E 3 (1.7), S 4 (2.3), Z 1 (0.5)	HE 2 (1.1), HS 6 (3.5), RS 4 (2.3), RZ 6 (3.5), ES 1 (0.5), SZ 3 (1.7), HES 14 (8.3), HZS 5 (2.9), RES 2 (1.1), RSZ 4 (2.3), ESZ 7 (4.1), RESZ 1 (0.5)	HR 9 (4.7), HRE 14 (8.3), HRS 26 (15.4), HRZ 2 (0.5), HRES 19 (11.3), HREZ 2 (1.1), HRSZ 1 (0.5), HRESZ 16 (9.5)
Jan 2005-Nov 2010, NTI,	Cat II failures attending a tertiary level chest	Sputum (AFB smear	None	H 8 (2.57), R 2 (0.64), E 1 (0.32),	HE 7 (2.26), HS 19 (6.14), RE 2	HR 20 (6.47), HRS 39

Bangalore (NRL)	diseases institute as inpatients; Bangalore, Karnataka state, south India (Nagaraja *et al*, 2011)	pos), 309		S 2 (0.64)	(0.64), RS 2 (0.64), ES 4 (1.16), HES 35 (11.32), RES 2 (0.64)	(12.62), HRE 19 (6.14), HRSE 146 (47.24)
Mar 2005-Mar 2008; IRL for Delhi state	Cat II patients attending a primary level chest clinic and outpatient department of a tertiary care government hospital in Delhi, north India (Sharma *et al*, 2011b)	Sputum (AFB smear pos), 196	153/196 (78)	R 3(1.5)	None	HR 36 (18.4), HRS 4 (2)
Nov 2005-Oct 2006, TRC, Chennai (SNRL)	Patients from RNTCP centers, which were randomly chosen from the entire state; state-wide survey of Gujarat State (west India) (Ramachandran *et al*, 2009)	Sputum (AFB smear pos), 1047	564/1047 (53.9)	H 122 (11.7), R 10 (1), S 88 (8.4)	HE 7 (0.7), HS 66 (6), HES 10 (1)	MDR-TB 182 (17.4) including HRES 69 (6.6)
2006, IRL of the state of Delhi	Predominantly included patients treated at the New Delhi State TB center or other RNTCP centers from surrounding states; few patients referred from private sector (Hanif *et al*, 2009)	Sputum, 2880 (failures 2507, relapses 309, defaulters 64)	1382/2880 (48)	H: Failures 129 (4.47), relapses 6 (0.2)	HE: relapses 2 (0.06), HS: Relapses 4 (0.13)	HR: Failures 837 (29.06), relapses 83 (2.88), defaulters 16 (0.55); HRE: failures 22 (0.76); HRS: failures 316 (10.9); HRES: Failures 83 (2.88)

Table C: Drug resistance in Extrapulmonary TB patients

Year, Institute	Patient source	Sample, number of patients with MTb positive C and DST in the study	No. (%) pan-susceptible of all culture positive patients	Mono-r No. (%) of all culture positive patients	Poly-r (other than MDR) No. (%) of all culture positive patients	MDR No. (%) of all culture positive patients
2001-2005, National Inst for Mental Health and Neurosciences, Bangalore, Karnataka state (south India)	Patients with suspected chronic/tubercular meningitis from the neurology and neurosurgery departments of this institute (about 28% patients had past history of TB and/or contact history) (Nagarathna *et al*, 2008)	Cerebrospinal fluid, 366	301/366 (82.24)	H 46 (13), E 1 (0.2), S 1 (0.2)	8 (2.2) combinations not specified	HR +/- resistance to other drugs: 9 (2.4)
June 2002-July 2006, a tertiary care institute in Chandigarh, north India	Treatment failure extrapulmonary TB patients on a retreatment regimen (Sethi *et al*, 2012)	The 3 most common samples were: lymph node aspirate (125/338, 36.9%), cold abscess aspirates (78/338, 23.1%), and CSF (55/338, 16.27%). Total 338 extrapulmonary MTb isolates.	160/338 (47.3%)	H 15 (4.4), R 27 (8), E 7 (2.1), S 33 (9.8)	HS 14 (4.1), HE 2 (0.6), HES 6 (1.8), RS 23 (6.8), RE 2 (0.6), RES 4 (1.2)	HR 25 (7.4), HRS 7 (2.1), HRE 2 (0.6), HRES 6 (1.8)
July 2007-Dec 2010, 2 tertiary care institutes in Lucknow, Uttar Pradesh state (north India)	Patients suspected to have extrapulmonary TB attending the 2 tertiary care institutes (Maurya *et al*, 2012)	Of 756 specimens, the 3 most common were: lymph node and cold abscess aspirates (270, 35.8%),	New: 76/123 (61.8), Previously treated: 24/42 (57.2)	New: H 12 (9.7), R 1 (0.8), E 4 (3.2), S 5 (4.1) Previously-treated: H 3 (7.1),	New: HS 1 (0.8), HE 5 (4.1), RS 2 (1.6), HES 2 (1.6), RES 1 (0.8) Previously-treated: HS	New: HR 5 (4.1), HRS 3 (2.4), HRE 3 (2.4), HRES 3 (2.4)

		pleural fluid (96, 12.7%), and CSF (74, 9.8%). Total C pos for MTb and with DST: 165/756 (21%) (new 123 and previously-treated 42)		R 1 (2.3), E 1 (2.3)	1 (2.3), HE 1 (2.3), HES 3 (7.1)	Previously-treated: HR 2 (4.7), HRS 3 (7.1), HRES 3 (7.1)

❖ **ANNEX III: Studies on outcomes of patients with Non-MDR first line drug resistance**

➢ **Studies on new patients**

New sputum smear positive patients treated with Cat I regimen, April 2000-December 2001, Tiruvallur District, Tamil Nadu State (south India) (Thomas et al, 2005) , Table D:

714 patients were treated in the above period, with the following results: 534 (74.8%) cured, 6 (0.84%) treatment completed, 114 (16%) defaulted, 29 (4.1%) died, and 31 (4.3%) failed. Patients who were cured were followed up for relapse by collecting sputum samples for AFB smear and MTb culture at 6, 12 and 18 months after Cat I treatment. The DST for H and R was compared between pre-treatment sample and that at relapse. There was no pre-treatment sample with any R resistance other than MDR. (DST to H and R only done).

Of 534 cured patients, 503 (94.2%) could be contacted for follow up. The relapse rates among these 503 were as follows:

Table D: Outcomes new-smear positive patients, 2000-2001, Tiruvallur

Pre-treatment DST (no.)	**DST on relapse, no. (%)**				**Total relapse, no. (%)**
	H-res	**HR-res**	**HR-sens**	**Not available**	
H-monoresistant (30)	6 (20)	1 (3.3)	1 (3.3)	0	8 (26.67)
HR-resistant (2)	0	2 (100)	0	0	2 (100)
HR-sensitive (455)	10 (2.2)	0	39 (8.6)	2 (0.4)	51 (11.2)
Not available (16)	1 (6.3)	0	0	0	1 (6.3)
Total (503)	17	3	40	2	62

Relapse rates were almost 2.5 times higher for patients with initial H mono-resistance (26.67%) compared to those susceptible to both H and R (11.2%). The majority of relapses occurred within the first 6 months after treatment.

Study on new sputum smear positive pulmonary TB patients treated with Cat I regimen in primary and secondary government health facilities in a sub-district area of Tamil Nadu state (South India) from May 1999-December 2002 (Santha et al, 2005), Table E:

1463 patients were treated, of which 1226 had pre-treatment DST (84%), 158 (10.8%) were culture negative, and 79 (5.5%) did not have culture results. The treatment outcomes were: 1117 (76%) had treatment success, 212 (14.5%) defaulted, 74 (5%) failed, 58 (4%) died, and 2 (0.14%) were transferred out. (DST to H and R only done).

The DST patterns of failures before treatment and at failure were as follows:

Table E: Outcomes new-smear positive patients, sub-district, Tamil Nadu, 1999-2002

Pre-treatment DST (no.)	**Failure no. (%)**	**Sputum collected at failure**	**Culture, DST at failure: no. (%)**			
			HR-sens	**H-res**	**HR-res**	**C neg**
HR-sensitive (1094)	34 (3.12)	26 (76.5%)	14 (53.84)	1 (3.84)	0	11 (42.31)
H-monoresistant (111)	23 (20.7)	20 (87%)	0	16 (80)	3 (15)	1 (5)
R-monoresistant (5)	1 (20)	0	0	0	0	0
HR-resistant (16)	7 (43.8)	7 (100%)	0	0	6 (85.71)	1 (14.3)
Culture negative (158)	5 (3.2)	4 (80%)	2 (50)	1 (25)	0	1 (25)
No culture results (79)	4 (5.1)	3 (75%)	0	0	1 (33.33)	2 (66.67)
Total 1463	74	60/74	16 (26.67%)	18 (30%)	10 (16.67%)	16 (26.67%)

Thus, compared to failure rates of HR-sensitive patients (3%), patients with H and R monoresistance had 7 times higher failure rates (21%). Interestingly, failure rate with R monoresistance was the same as that with H monoresistance (20%) and both were less than half that of patients with MDR (44%). Among pre-treatment H-monoresistant patients with sputum samples available at failure, 15% acquired resistance to R at the time of failure, thus becoming MDR.

❖ **Studies on previously-treated patients**

Study in Bangalore city, Karnataka State (south India), April 1999-September 2001 (Vijay et al, 2002) Table F**:**

Sputum smear positive patients from all tuberculosis units in the RNTCP program in Bangalore city, started on the retreatment regimen from April 1999-September 2000. Of 268 such patients, 226 (84.3%) were culture positive. Of these, 136 were susceptible to HRES and 90 had some drug resistance (29/90 MDR, 61/90 non-MDR resistance).

Table F: Outcomes previously-treated smear positive patients, Karnataka, 1999-2001

DST pattern (no.)	Favorable outcome (cured + completed) (%)	Failure (%)	Death (%)	Default (%)
Sensitive to HRES (136)	61 (44.9)	7 (5.1)	5 (3.7)	63 (46.3)
MDR (29)	5 (17.2)	16 (55.2)	1 (3.45)	7 (24.14)
Non-MDR resistance (61)	24 (39.3)	7 (11.5)	1 (1.64)	29 (47.54)

Patients with non-MDR resistance had more failures and less cure and completion rates than those susceptible to HRES. (Of 61 patients with non-MDR resistance, 4 had R monoresistance and 2 had poly-resistance including to R. However, treatment outcomes were not reported for each individual resistance combination but only for HRES-sensitive, MDR and non-MDR). Pre-treatment drug resistance was identified as a factor associated with Cat II treatment failure, in the study.

Emergence of drug resistance after the re-treatment regimen could be compared in 165 patients (97 pre-treatment susceptible and 68 pre-treatment resistant) for whom pre and post-retreatment DST results were available. Additional drug resistance to H, R, E or S occurred in 1/97 (1.03%) of susceptible patients and 10/68 (14.7%) of pre-treatment resistant patients.

Study in a sub-district area (one Tuberculosis Unit) of Tiruvallur district, Tamil Nadu state (south India), May 1999-December 2004 (Joseph et al, 2006), Table G:
572 sputum smear positive PTB patients treated with the Category II regimen were included in the study. Of these, no samples were collected for culture for 50 (8.7%), 91 (15.9%) were culture negative, 254 (44.41%) were sensitive to HRES, 128 (22.4%) had non-MDR resistance, and 49 (8.6%) had MDR TB at treatment initiation. (Resistance patterns for different drug combinations are not reported separately, so it is not possible to know how many 'non-MDR' patients had rifampicin monoresistance or polyresistance).

Among 431/572 (75%) patients with DST available at treatment initiation, the outcomes of Cat II were:

Table G: Outcomes previously-treated smear positive patients, Tiruvallur, 1999-2004

DST at treatment initiation	Success, no. (%)	Default, no. (%)	Failure, no. (%)	Death, no. (%)
Sensitive to HRES (254)	105 (41)	117 (46)	14 (6)	18 (7)
Non-MDR resistance (128)	51 (40)	48 (38)	15 (12)	14 (11)
MDR (49)	13 (27)	19 (39)	13 (27)	4 (8)
Total (of 431)	169 (39)	184 (43)	42 (10)	36 (8)

Patients with non-MDR resistance had nearly 2 times higher unsuccessful outcomes (failure + death = 23%) compared to patients sensitive to HRES (failure + death = 13%).

Study at the LRSI (tertiary level national TB institute), Delhi (north India), June 2006-February 2008 (Singla et al. 2009) Tables H and I:
Patients in the RNTCP program from all peripheral centers of one district.
42 sputum AFB-smear positive patients who were failures on Cat I regimen and started on Cat II regimen were included in the study. At the time of being declared failure to Cat I, 22/42 (52.4%) had cultures positive for MTb [2/22 (9%) susceptible to HRES, 6/22 (27.3%) had MDR TB, 8/22 (36.4%) H-monoresistance, and 6/22 (27.3%) HS resistance], 17 were culture negative and 3 had contaminated cultures. (There was no R monoresistance and no R polyresistance other than MDR).
Results for 38 of 42 patients on Category II were given (3 excluded due to contaminated cultures and 1 MDR-TB lost to follow up).

Table H: Outcomes culture positive and negative patients, Delhi, 2006-2008

Culture and DST pattern (no.)	Cure (%)	Failure (%)	Died (%)	Default (%)	Transfer out (%)
Culture neg (17)	15 (88.24)	1 (5.9)	0	1 (5.9)	0
Culture pos (21) 19 had some resistance and only 2 were HRES-susceptible	6 (28.6)	5 (23.8)	1 (4.8)	8 (38)	1 (4.8)

Among 19 patients showing any drug resistance, results were as follows (from the 22 culture positive patients, 2 were susceptible to HRES and 1 MDR-TB patient was lost to follow up):

Table I: Outcomes by MDR and non-MDR resistance, Delhi, 2006-2008

DST pattern (no.)	Cure (%)	Failure (%)	Died (%)	Default (%)	Transfer out (%)
MDR (5)	2 (40)	1 (20)	0	2 (40)	0
Non-MDR (14)	2 (14.3)	4 (28.6)	1 (7.1)	6 (42.9)	1 (7.1)

Thus, even non-MDR first-line resistant patients had very poor outcomes on the Category II retreatment regimen.

Study in seven districts of Andhra Pradesh state (south India), July 2008-December 2009 (Nagaraja et al, 2011) Table J:

All Rif-susceptible patients in the RNTCP program from seven districts of Andhra Pradesh state covered by RNTCP MDR-TB program.

200 patients who had failed either a Category I, II or III regimen before and were treated with the retreatment regimen (Cat II) were evaluated for treatment outcome in the study. The treatment success was 48% (28/58 patients) in the culture-negative group, 38% (31/81 patients) in the pan-susceptible group, and only 15% (9/61 patients) in the group non-R first-line mono-and-poly resistance.

Table J: Outcomes previously-treated patients, Andhra Pradesh, 2008-2009

Culture and DST pattern (no.)	Success (%)	Failure (%)	Died (%)	Default (%)	Transfer out (%)
Culture negative (58)	28 (48.28)	21 (36.21)	7 (12)	2 (3.4)	0
Sensitive to HRES (81)	31 (38.3)	32 (39.51)	11 (13.6)	6 (7.41)	1 (1.24)
Non-rifampicin resistance (61)	9 (14.8)	30 (49)	17 (27.9)	5 (8.2)	0

❖ **Studies in new and previously-treated patients**

Study in new and previously-treated patients under the RNTCP in a primary health center, Tiruvallur district, Tamil Nadu state (south India), May 1999-April 2000 (Santha et al, 2002), Table K:
676 patients were included in the study. Drug resistance was reported for 304 sputum AFB smear positive patients. (First line drugs other than H and R for which DST was done are not mentioned separately in the study). Among 304 patients with DST results, 18 had MDR TB. Of the remaining 286 patients without MDR TB, 37/286 (13%) had any INH resistance. These patients had worse treatment outcomes than the 249 without INH resistance. (Rifampicin mono resistance and polyresistance other than MDR is not reported separately in the study. However, poor outcome is reported related to INH resistance only so Rif non-MDR resistance is not associated with it).

Table K: Outcomes by H resistance, Tiruvallur, 1999-2000

Patients without MDR TB (no.)	**Success (%)**	**Failure (%)**	**Death (%)**	**Default (%)**
No H resistance (249)	178 (71)	4 (2)	16 (6)	51 (20)
H resistance (37)	22 (59)	6 (16)	4 (11)	5 (14)

In patients without MDR-TB, H resistance was associated with an increased risk of failure.