TUBERCULOSIS IN PRIVATE INDUSTRIAL WORKERS OF PAKISTAN. WHAT COULD BE IMPROVED TO MAKE THE DOTS STRATEGY MORE EFFECTIVE?

A STUDY PROTOCOL

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DEDICATION

This work is dedicated to
my loving Mother and my Wife.

Without their prayers and support,
This work would not have been possible for me.
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Tahir Hussain Kharal

06th June, 2007
ABSTRACT

Tuberculosis (TB) is an important public health problem worldwide as one third of the world’s population is being infected by *Mycobacterium Tuberculosis*. About 95% TB cases and 98% of TB deaths are in developing countries known as 22 high-burden TB countries. The problem is further aggravated due to rapid industrialization, urbanization, increasing population density and lack of proper housing. The poverty, illiteracy, environmental pollution and poor nutritional status of individual are the principle predisposing factors in the occurrence and spread of TB. Tuberculosis has been prevalent in Pakistan and unfortunately it has been one of the neglected public health problems in the past. TB is the leading infectious disease of the younger age group within the 15-50 year age bracket. TB burden is more then 150,000 patients and deaths are more than 67,500 annually.

In 1995, directly observed treatment short course (DOTS) was launched as pilot programme and in 2001 DOTS strategy was adopted at national level to eradicate TB. By successful implementation of DOTS strategy, within six years Pakistan’s ranking as TB burden country improved from 5th to 7th high burden countries. HIV/AIDS and increasing cases of multi drug resistant tuberculosis (MDR-TB) are major threats to TB control programme.

The aim of this thesis is to review the literature on the factors contributing to treatment failure among tuberculosis patients worldwide, and to develop a study protocol to determine the risk factor of treatment failure among TB patients under TB-DOTS strategy in private industrial workers of Punjab Social Security heath care system, Pakistan.
Literature review revealed the main factors responsible for treatment failure are multi drug resistant TB, poor treatment adherence, poverty, lack of knowledge among TB patients and concomitant conditions like, HIV and diabetes. In Pakistan, treatment failure rate accounts for 10-12% and there is no specific data regarding rate of treatment failure in new smear positive and re-treatment cases. There is no study available regarding risk factors for TB treatment failure among private industrial workers in Pakistan.

A case-control study will be conducted at Punjab Social Security Hospital Islamabad. This is the main TB center in northern Punjab. Each case and control will be interviewed using a pre-defined questionnaire to collect information regarding the treatment failure. Supplementary information will be collected from secondary data sources like TB files, cards, treatment books and laboratory register.

Being the first study in Social Security, it will be an initiative for further research and the result of this proposed study would help to reduce the TB burden by improving the treatment success rate. This results in reduction of morbidity and mortality, ultimately leads to healthy nation.
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune deficiency Syndrome</td>
</tr>
<tr>
<td>ASD</td>
<td>Association of Social Development</td>
</tr>
<tr>
<td>BHU</td>
<td>Basic Health Unit</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observation treatment Short Course</td>
</tr>
<tr>
<td>EGD</td>
<td>Electronic Government Directorate</td>
</tr>
<tr>
<td>EMRO</td>
<td>Eastern Mediterranean Region Office</td>
</tr>
<tr>
<td>FBS</td>
<td>Federal Bureau of Statistics</td>
</tr>
<tr>
<td>FGD</td>
<td>Focus group discussion</td>
</tr>
<tr>
<td>GDP</td>
<td>General Domestic Product</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>IUATLD</td>
<td>International Union Against TB and Lung Disease</td>
</tr>
<tr>
<td>LFS</td>
<td>Labour Force Survey</td>
</tr>
<tr>
<td>MCHC</td>
<td>Maternity &amp; Child Health Center</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multi drug-resistant tuberculosis</td>
</tr>
<tr>
<td>NGO</td>
<td>Non Governmental Organization</td>
</tr>
<tr>
<td>NTP</td>
<td>National Tuberculosis Programme</td>
</tr>
<tr>
<td>PESSI</td>
<td>Punjab Employee’s Social Security Institution</td>
</tr>
<tr>
<td>PHCU</td>
<td>Primary Health Care Units</td>
</tr>
<tr>
<td>PMDC</td>
<td>Pakistan Medical and Dental Council</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td>PTP</td>
<td>Provincial TB Control Programme</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>UNDP</td>
<td>United Nations Development Program</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
DEFINITIONS OF TERMS

In this thesis the following terms have been used defined by the World Health Organization (WHO, 2006f).

**Compliance:**
It has been defined as ‘willingness to follow or consent to and other’s wishes’, i.e. compliance with the regulations, or the degree of adherence by a patient to prescribed regimen. ‘Action in accordance to request’. There is no single universal definition for compliance.

**Non-compliance:**
This term covers at least the following ‘irregularity of adherence or failure to attend’. ‘Refusal of treatment or complete absence of cooperation’. It may also imply ‘irregular drug intake’.

**Adherence:**
Nowadays, the word ‘adherence’ is used more frequently than compliance. The word ‘adherence’ is defined in Oxford dictionary as, ‘to stick fast, to remain firm, to continue to maintain, to give support to’.

**Treatment Outcomes:**

**Cured:** The patient, who was smear positive for TB, and who completed treatment and was smear negative one month before or at the time of completion of treatment, and on at least one previous occasion.

**Treatment completed:** The patient who, was smear negative or had non-pulmonary TB, or was smear positive and who completed treatment but whose smear examination results for at least two occasion before the completion of treatment were not available, was classified as treatment completed.

**Failure:** The patient who remained smear positive or had become so again at five months or more after treatment was counted as treatment failure.

**Died:** All deaths during treatment, irrespective of cause, were included.
**Defaulted:** The patients at anytime after registration had not collected drugs for two consecutive months or longer were labeled as defaulters. They can be further classified into:

*Early defaulters:* They are the patients who do not collect drugs in the first two months of treatment, i.e. initial phase.

*Late defaulter:* They are the patients who do not collect drugs for more than 60 days from third to eight months, i.e. the continuation phase.

**Treatment success:** It is the sum of cases cured and those who completed treatment.

**Types of Patients:**

*Sputum smear positive:* Pulmonary tuberculosis is diagnosed by examining patient’s sputum under microscope. If tuberculosis bacilli are visible, the patient is classified as sputum smear positive. These cases are most infectious.

*Sputum smear negative:* If the tuberculosis bacilli are not visible under microscope but the patient has radiological evidence of pulmonary tuberculosis, he is labeled as sputum smear negative.

*New case of Tuberculosis:* A patient who has never taken treatment for tuberculosis or has taken treatment for less than one month.

*Relapse case:* A sputum smear positive patient, who was declared cured, but now has reported back to the unit, again sputum smear positive.

*Re-treatment case:* A patient who defaulter treatment for two months (60 days) or more after registration, and has reported back again, to same unit.
I. INTRODUCTION

1.1 Tuberculosis: Basic concept

Tuberculosis is a communicable, air borne bacterial infection caused by *Mycobacterium Tuberculosis*. Mostly it infects lungs, but it can infect any part of body, such as intestine, genitourinary organs, lymph nodes, nervous system, bone and joints. Any person presenting himself with persistent cough lasting for more than three weeks, are a suspected case of pulmonary tuberculosis. Associated sign and symptoms found are nocturnal pyrexia, body aches, chest pain, anorexia, weight loss and hemoptasis. Extra pulmonary TB patient presents with specific symptom related to the organ infected.

TB spreads when untreated infected TB patient exhaled, sneeze, cough, spite or talk close to others. Infection occurs up on inhalation of these germs by a healthy non immune person. An untreated TB case can infect 10-15 persons yearly. After getting an infection of *M. Tuberculosis* only 10 % patients have lifetime risk to develop TB. The body immune system deactivates the TB bacilli and confine them in lymph nodes, and thereafter any weakening of immunity by HIV infection, malignancy, diabetes, prolong use of steroids and malnutrition can lead to reactivation of TB bacilli (WHO, 2007).

1.2 Global View of Tuberculosis

In 1993, World Health Organization declared tuberculosis as a global health emergency. Among the infectious diseases, after HIV / AIDS, it is the world second greatest cause of adult death being responsible for more the two million death per year. One third of population worldwide is estimated to be infected with *Mycobacterium Tuberculosis*. Every second some one in the world is newly infected with TB bacilli (WHO, 2006a).
Epidemiological pattern and disease burden

Worldwide more than 8 million people get active TB infection yearly, while out of these two million die. It is estimated that around 15 million are TB infected over the globe. TB is ranked 10th in the global burden of disease table. About 95% of tuberculosis cases and 98% of tuberculosis deaths are in developing countries (World bank, 1993). Tuberculosis is the leading cause of death due to a single infectious pathogen worldwide. TB is responsible for 26% of avoidable disease burden. Case fatality rate of untreated TB is below 40-60 percent. An active TB case getting no treatment can infect 10-15 people yearly (WHO, 2006a, Lee et al. 1993).

Table 1: WHO regional estimated TB incidence, prevalence and mortality data 2005 (WHO, 2007)

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Incidence</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All forms</td>
<td>Smear-positive</td>
<td>Prevalence</td>
<td>TB Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>number (1000)</td>
<td>per 100 000</td>
<td>number (1000)</td>
<td>per 100 000</td>
<td>number (1000)</td>
<td>per 100 000</td>
<td>number (1000)</td>
<td>per 100 000</td>
</tr>
<tr>
<td>Africa</td>
<td>2 529 (29)</td>
<td>343</td>
<td>1 088</td>
<td>147</td>
<td>3 773</td>
<td>511</td>
<td>544</td>
<td>74</td>
</tr>
<tr>
<td>The Americas</td>
<td>352 (4)</td>
<td>39</td>
<td>157</td>
<td>18</td>
<td>448</td>
<td>50</td>
<td>49</td>
<td>5.5</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>565 (6)</td>
<td>104</td>
<td>253</td>
<td>47</td>
<td>881</td>
<td>163</td>
<td>112</td>
<td>21</td>
</tr>
<tr>
<td>Europe</td>
<td>445 (5)</td>
<td>50</td>
<td>199</td>
<td>23</td>
<td>525</td>
<td>60</td>
<td>66</td>
<td>7.4</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>2 993 (34)</td>
<td>181</td>
<td>1 339</td>
<td>81</td>
<td>4 809</td>
<td>290</td>
<td>512</td>
<td>31</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1 927 (22)</td>
<td>110</td>
<td>866</td>
<td>49</td>
<td>3 616</td>
<td>206</td>
<td>295</td>
<td>17</td>
</tr>
<tr>
<td>Global</td>
<td>8 811 (100)</td>
<td>136</td>
<td>3 902</td>
<td>60</td>
<td>14 052</td>
<td>217</td>
<td>1 577</td>
<td>24</td>
</tr>
</tbody>
</table>

There are 22 high burden TB countries having 80% of all incident cases. The South East Asia and Western Pacific region of WHO are have 50% of the TB burden. Since 2004, in five out of six WHO regions, TB incidence estimated per capita was found stable or
falling, but growing at 0.6% annually worldwide. In the WHO region of Africa, the TB incidence is still rising due to co-infection with HIV/AIDS.

In the Eastern Mediterranean region of WHO, nine countries contribute to 94 % of the tuberculosis cases in the region: Pakistan (43%), Afghanistan (12%), Sudan (8%), Iraq (6%), Iran (6%), Somalia (6%), Morocco (5%), Egypt (4%), and Yemen (3%).

Figure 1: Contributions of countries to TB burden in The EMRO Region of WHO (WHO, 2006c).

TB and HIV

HIV alone is a known cause of human mortality and when TB combines with it becomes a lethal co-infection combination for human beings. This spreads very rapidly. HIV affects the immune system; it increases the susceptibility for infection. One of known powerful risk factor for TB epidemics is HIV. If HIV patient has latent TB infection it becomes active and there is more chances of relapse of TB in cured persons (WHO, 2006d). Compared to HIV negative persons there are 50 times more chances of TB as co-infected in HIV positive persons in a year (WHO, 2006a). Leading cause of death among HIV positive people is TB. Globally the incidence of TB has increased 5-10% annually due to reactivation or relapse in HIV positive persons. TB–HIV co-infection accounts 13% of AIDS death on the earth. Globally 8% TB cases are attributed to HIV, and Sub Saharan Africa it is 40%. Responsible for this massive increase in the incidence of TB in
Africa in last 20 years is that strong association between HIV and TB (Harries AD and Dye C, 2006). There is rapid increase in TB load up to seven fold in HIV epidemic countries, and on going strategies are no longer effective to stop TB. In combination with HIV, TB is hard to treat and now TB is the single biggest killer of HIV positive peoples. Globally about a third of the 34.3 million peoples is having co-infection of TB-HIV, and out of these 70% is living in Africa.

**TB and Drug resistance**

The global proportion of MDR-TB is around 1-2% of all TB cases. The main source and problem area for spread of MDR-TB are few countries, like, former Soviet Union known as hot spots. As observed that it is drug resistance in the local *Mycobacterium Tuberculosis* that makes TB treatment ineffective (Harries AD and Dye C, 2006). MDR-TB itself is not a disease phenomenon. It is result of mismanagement of susceptible TB cases leading to drug resistance. The problems of MDR-TB are:

1. Very toxic and expensive (100 times as compare to susceptible TB) drug therapy required.
2. Up to 2 years duration of therapy.
3. Direct supervision by hospitalization.
4. Mortality is higher as compared to susceptible TB.
5. More money and time required for diagnosis.

**TB and nation’s economic status**

In developing countries, like Pakistan, 75 percent of tuberculosis cases occur in the age group of 15-50 years, leading to economical burden as this age group constitutes the work force of country (WHO, 1997). Absence from work due to TB results in an average loss of 20-30% of house hold income and a reduction of 1% in gross domestic production per capita.

**1.3 Status of Tuberculosis in Pakistan**

Tuberculosis has been prevalent in Pakistan and unfortunately it has been one of the neglected public health problems in the past. TB is the leading infectious disease of the
younger age group (WHO, 1997). The rapid industrialization, urbanization, increasing population density and lack of proper housing, poverty, illiteracy, environmental pollution and poor nutritional status of individual are the principle predisposing factors for the occurrence and spread of TB.

Status of tuberculosis in Pakistan (NTP, 2006d):

- Pakistan is 7th on global ranking of high burden TB countries, by estimated no. of cases.
- Tuberculosis is 5.1% of total national burden of disease.
- Three out of four patients are adults – economically the most important age group.
- More than 280,000 new all forms of TB cases every year (one new person get TB in every 2 minutes).
- Almost 67,500 deaths of TB every year (one death of TB every 8 minutes).
- Estimated total number of TB patients is more than 150,000.
- There are now more than 1 million partially treated people.
- Currently one in four of TB cases are detected and treated by the public sector.
- In existing TB services only one in three patients are confirmed as cured.
- 81.6 per 100,000 populations (incidence) new smear positive TB cases per year.
- 181.3 per 100,000 population (incidence) new TB cases (all forms) per year.
- Prevalence (all cases) 329 per 100,000 population
- TB mortality (deaths) 40 per 100,000 populations per year. (WHO, 2006b)

Tuberculosis is an old disease and a serious public health issues in Pakistan, even though TB remains always on top priority of health authorities, yet the peoples are sufferers and die from this completely curable disease. This situation is due to:

- Lack of awareness in people about TB, cases is mismanaged, either undiagnosed or under dosed treated by health care staff.
- Non-adherence is the major factor leading to multi drug resistance tuberculosis (MDR-TB) which is more difficult to treat.
- There is more risk of TB among HIV infected persons.
1.4 Punjab Social Security Health Care System in Pakistan

Employee’s Social Security health care system is a public sector prepaid health coverage scheme for labour workforce in Pakistan. It is has its own health care infra structure. Industrial units having more than 10 employees getting monthly salary up to 5,000 Rupees (USD 83), have to contribute to this scheme. This scheme is providing health coverage to more than 1.4 million workers and their families, while it is only 3% of 47 million estimated total workforce in Pakistan (FBS, 2002, UNDP, 2006,)

At provincial level, Punjab Employee’s Social Security Institution (PESSI) has approximately 28,000 industrial units registered with it. The number of secured/registered workers is about 0.53 million with additional 3.2 million dependents. While in the Islamabad/Rawalpindi Region (Five Districts) the number of workers is about 44,000 with additional 156,000 dependents. PESSI has a network of 261 dispensaries and 15 hospitals in major cities of Punjab, which are mostly situated near the industrial areas.

It provides following health services:

- Medical care facilities to all the secured workers and their families including parents.
- Out-patient department & Indoor services are provided in its own Hospitals and Dispensaries.
- Also includes Dental Care, Surgeries, and Physiotherapy and blood transfusion facilities at all the Main Hospitals.
- Diagnostic facilities like Laboratory, X-ray, Ultrasound, E.C.G, and Endoscopies.
- Facilities of Cardiac Surgery, Renal Hemodialysis.
- Full Maternity care service at all the Hospitals.
- Provision of ambulance service.
- Provision of spectacles, artificial aids and dentures.
- Payment of diet charges on admission of workers and their dependents at the rate of Rs.100 per day to the all patients including TB and Cancer Patients.
• Medical care to survivors of deceased workers for one year, and to seasonal workers for six months.
• Reimbursements of expenses of Government Hospitals incurred by the workers.
• In addition to these there are cash benefits (wages) during sickness, injury and disability.
• They also provide pension to the survivor of deceased (due to employment injury).

All of these services are provided free and workers do not have to pay for any service. But still it is seen that a lot of patients come to the health care centers at a very late stage of disease. Even in infectious diseases like TB and renal failure, there is a lot of time lost before they reach and get the necessary treatment. There may be a lot of factors involved for this delay but this surely is causing an increased morbidity and mortality (Zafar, 2001).
II. OBJECTIVES

The overall objective is to strengthen the TB control strategy in Punjab Social Security health care system in Pakistan, and while doing so learning lesson that might be applicable also in other settings.

The specific objectives are

- To conduct a literature review to determine risk factors for treatment failure among tuberculosis patients under TB-DOTS strategy worldwide.
- To develop a study protocol to determine the risk factors for treatment failure of TB-DOTS strategy in TB patients among the private industrial workers in Pakistan.

Objectives of the Study Protocol

To develop a study protocol to assess,

- The non-adherence as risk factor for TB-DOTS strategy failure among TB patients taking into account.
  i.) Their socio-economic and living environmental status.
  ii.) Health facility staff behavior.
III. BACKGROUND

3.1 Pakistan Country Profile

On 14th August 1947, Pakistan emerged as an independent state on the map of the world. It lies between 23-35 to 37-05 north latitude and 60-50 to 77-50 east longitude. The neighboring countries are Iran in west, Afghanistan in the northwest, while having a long eastern border with India and Arabian Sea in the south. Pakistan shares its northern border with China.

Figure 2: Map of Pakistan (www.infoplease.com/atlas/country/pakistan.html).
The total area of the country is 796,095 square kilometer with a population of 161.37 million (estimated 2006). It has four provinces: Sindh, Punjab, North West Frontier Province and Balochistan. Geo-physically it has western offshoots of Himalayas and highest peak K-2 in the northern part. The world famous salt range lies near the Potohar plateau. The plan area of country is irrigated by the world best canal system in the Punjab and Sindh province. Pakistan is an Islamic country where 97% of population is Muslim. Christians are 2% of the population whereas rest is other religious communities.

Pakistan has four seasons. Winter begins in November and ends in February. Spring sets in March and last up to April. Hot dry summer last up to June and humid rainy season starts in July and ends up in August. The average winter temperature ranges between 8 to 20 degree centigrade and summer temperature ranges from 20 to 44 degree centigrade.

Pakistan is an agriculture country, wheat, cotton, rice, millet and sugar cane are the major corps, mangos, oranges, bananas and apples are grown in abundance in different parts of country. The natural resources are natural gas, coal, salt and iron. Industrial sector mostly textile, sugar, cement and cotton is expanding now (EGD, 2006).

Infectious diseases are most important cause of mortality and morbidity in Pakistan. Non-communicable diseases are also becoming a major burden. Access to local health care services are 100% for urban and 92% to rural population. In 2004, 90% of population was having sustainable access to improved water sources. Sanitation facilities are not good as only 54 % of the population has access. (WHO, 2006e)

The growth rate is 2.1%, birth rate is 30/1000, infant mortality rate is 71/100 and the life expectancy is 63years. The literacy rate is much better then past it is 46% (2003 est.) Economically Pakistan’s GDP is $365 billion, and PPP (purchasing power parity) per capita is $ 2,400 (2005 est.). Pakistan is facing 6.6% unemployment plus substantial underemployment. Pakistan has labor force of 47 million, exporting this labor force mostly to the Middle East, and use of child labor is in agriculture up to 42%, 20% industrial sector and 38% in services (2004 est.), (UNDP, 2006).
3.2 Existing Health Care infra-structure in Pakistan

Pakistan has a well established health system. There are four provinces and a federally administrated area. These are divided into 132 districts. In public sector, national health system is based on primary health care. The health care delivery system is as follows:

Basic health unit is an initial level of care center. It provides coverage to 5000 persons around it and at present there are 5798 in service. Rural health center, also known as primary health center, these are 581 in Pakistan and they provide coverage to the population served by basic health units around them and also act as diagnostic center for TB-DOTS. It has indoor treatment facilities. Tehsil and District headquarters hospital and teaching hospital are a part of secondary and tertiary care system, which are established in main cities to provide coverage to referred and complicated cases. These are 947 with a capacity of 99,908 beds for indoor treatment (FBS, 2006).

Besides the 48,446 registered nurses and 23,559 paramedics, a field force of 96,000 lady health workers are actively working for safe motherhood, reproductive health and for implementation of community TB-DOTS. These lady health workers are also coordinating their activities through 1,084 maternal and child health centers. National TB programme is also strengthening TB-DOTS through 357 TB centers national wide. Specialized units are providing care to cancer, psychiatric, dental, eye and leprosy patients (PMDC, 2007).

Traditional medicine is now getting popularity especially among people in the rural area suffering from chronic diseases, as they cannot avail and afford the costly allopathic treatment. Presently more than 130,000 registered practitioners of traditional medicine versus 124,313 registered doctors; it speaks somewhat about the nature of demand. Realizing this demand government provided traditional medicine care giver in secondary care hospitals (NCH, 2004).
Table 2: Health care infrastructure of Pakistan (PMDC, 2007).

<table>
<thead>
<tr>
<th>Service</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitals</td>
<td>947</td>
</tr>
<tr>
<td>Dispensaries</td>
<td>4,800</td>
</tr>
<tr>
<td>Basic Health Units (BHUs)</td>
<td>5,798</td>
</tr>
<tr>
<td>Maternity &amp; Child Health Centers</td>
<td>1084</td>
</tr>
<tr>
<td>Rural Health Centers (RHCs)</td>
<td>581</td>
</tr>
<tr>
<td>Tuberculosis (TB) Centers</td>
<td>357</td>
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<tr>
<td>Hospital Beds</td>
<td>99,908</td>
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<td>Doctors (registered)</td>
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<tr>
<td>Dentists (registered)</td>
<td>7459</td>
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<td>Nurses (registered)</td>
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<tr>
<td>Paramedics</td>
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<tr>
<td>Lady Health Workers</td>
<td>96000</td>
</tr>
</tbody>
</table>

3.3 National Tuberculosis Control Programme of Pakistan

Ministry of Health, Pakistan endorsed the Directly Observed Treatment Short course (DOTS) strategy, following the WHO declaration of TB as a global emergency. In 1995, the National TB Control Programme (NTP) Pakistan adopted DOTS to eradicate the TB by a cost-effective strategy, and launched it as a pilot programme in Balochistan Province. Since 2001, Pakistan government has declared tuberculosis as a national emergency. In May 2005, NTP got the 100% DOTS coverage in the public sector. The care of the TB patient is integrated within Primary Health Care (PHC) services, so that continuing care is provided close to the patient. TB care is now included at all levels of health facilities as well as community workers, they work as treatment supporter in community-based DOT (direct observation of treatment). NTP Pakistan is among the first few countries that have produced desk guide for improving the quality of TB care, as an easy reference in consultation room (NTP, 2006b).
Figure 3: Organogram of National TB Control Programme Pakistan (NTP, 2006c)
DOTS Strategy

Globally the DOTS (directly observed treatment, short course) strategy has been recognized as the best cost effective approach to TB control. DOTS strategy produces 95% of cure rate in the poorest countries. It prevents the new infection and prevents the development of MDR-TB by ensuring the completion of treatment course. Its cost effectiveness has been approved by the World Bank.

DOTS has five key components.

1. Commitment of government and all involved to ensure sustained TB control activities.

Figure 4: TB care services in public sector (NTP, 2006c).
2. Case detection by sputum smear microscopy through passive case finding among symptomatic pulmonary TB patients.

3. Treatment with standardized regimens of six to eight months, include direct observation of treatment (DOT) in intensive phase for all smear positive cases for two months and during the whole of treatment regimen.

4. Regular, uninterrupted supply of all essential anti-TB drugs from the nearest health facility.

5. Standardized recording and reporting system enabling outcome assessment of each patient and of overall performance of TB control programme.

Sputum smear conversion is monitor after two months to check progress and again at the end of treatment (WHO, 1999).

**Treatment Regimen (WHO, 2006b)**

**Category I:** It is given to new sputum smear positive, pulmonary TB patients and other newly diagnosed seriously ill patients with sever forms of tuberculosis. Priority is for sputum smear positive, pulmonary TB, but the treatment is also vital for other forms of tuberculosis because of associated morbidity and mortality.

Regimen: 2HRZE/6EH, initial intensive phase for two months is isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) and in continuation phase of six months ethambutol and isoniazid are given.

**Category II:** This is given to sputum smear positive relapse and failure cases. Priority is highest because theses patients are suspected of having multi-drug Tuberculosis (MDR-TB).

Regimen: 2RHZES/1RHZE/5HRZ, Two months intensive phase –rifampicin, isoniazid pyrazinamide, ethambutol and streptomycin.

One month intensive phase- rifampicin isoniazid, pyrazinamide and ethambutol and five months continuation phase- isoniazid, rifampicin and ethambutol.

**Category III:** This is given to sputum smear negative pulmonary and extra- pulmonary tuberculosis.

Regimen: Intensive phase for two months is isoniazid, rifampicin, Pyrazinamide and in continuation phase of six months- isoniazid and ethambutol.
3.4 Public Private Partnership in TB control in Pakistan

National TB control Program, Pakistan over the years has emerged as one of the largest partnership forums in the form of an inter-Agency cooperation committee (IACC) consisting of all partners. IACC was constituted to mobilize resources to augment the government efforts. NTP realizes that for effective implementation the partnership have to trickle down to the grass root levels; hence community participation has become a priority for NTP. The programme through various projects is involving local leaders, media people, private practitioners, medical colleges, volunteers and social workers. NTP is strengthened not only by the financial partners but also a wide range of implementation and technical partners. The galaxy of partners includes international/bilateral organization/NGOs and donors to the community based organizations. The commitment, evident by rapid expansion of the DOTS strategy to 132 districts of the country covering over 70% of the population have been reviewed and appreciated by a number of international agencies including WHO, the United States Agency for development (USAID), the Canadian International agency for Development (CIDA), the German Development Agency (GTZ/Kfw) and the Japan International Cooperation Agency (JICA) which are actively supporting program implementation in various parts of the country through grants. German Leprosy Rehabilitation Association (GLRA) offers technical support in TB-DOTS data and drug management. WHO Pakistan provides technical support through international consultants and 18 national program officers to provide technical support at the national, provincial and district levels. The Canadian International Development Agency (CIDA) is supporting the National TB control Programme through WHO in the areas do quality assurance of sputum microscopy and bringing about the functional integration between the tuberculosis Control and national Program for family Planning and Primary Health Care. Currently the latter has a 96,000 strong workforce of Lady Health Workers in the most rural areas of the country, who refer TB suspects to nearby diagnostic centers, act as treatment supporters for diagnoses patients, carry out counseling of patients and their
family members and help in default tracing. WHO supports training activities on surveillance, supervision and operational research in all provinces of the country. The National TB Programme (NTP) has also received two successive grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Moreover the Global Drug Facility (GDF) is supplementing ATT drugs as a grant.

For implementation support some national and international NGOs are also collaborating the NTP, like Green Star, Mercy Corp Pakistan, Agha Khan Health services Pakistan, Association of Community Development, and Pakistan Anti TB Association. Pakistan Chest Society. The Asian Foundation. (NTP, 2006b)

**Global targets for TB control**

The World Health organization has pledged to eliminate tuberculosis from the Earth by 2050. It will happen by getting 70% of new sputum smear-positive TB cases detected and 85% of them to be cured. Interim achievement shall be 50% reduction of TB prevalence and death rates by 2015 (WHO, 2007).

**National Tuberculosis Control Programme’s achievements**

Since 2001, Pakistan has declared TB as national emergency, DOTS strategy is the only programme offered by NTP and its partners. By the end of May 2005, DOTS coverage is 100%. Free diagnostic and treatment facilities are available. There is much increase in case detection for all types improved from a minimal of 4.3% in 2000 to 50% by 2005, where as case detection rate for new smear sputum positive increased from 2.8% in 2000 to 37% by 2005, but it is still below the target of 70% due to limited involvement of the private sector. The treatment success rate has also been increased from 74% in 2000 to 82% in 2004 against the target of 85% (NTP, 2006b).
IV. LITERATURE REVIEW

4.1 Methods of Literature Search

The Literature search was conducted using the Umeå University Library access to the database Medline. Literature was searched to identify the various risk factors of failure of TB-DOTS strategy among tuberculosis patient across various countries. Keywords used included TB-DOTS, adherence, treatment failure, multi drug resistance, compliance and private industrial workers. The search was restricted to articles published from 1993-2006 and articles in English, excluding case reports, editorials and newsletters. In total 105 articles were identified and among these 33 were selected for review with regards to their relevant to the study proposal. Text books and other printed journals were also used for literature search and also relevant websites on the internet were accessed.

4.2 Results of the Literature Review

The core elements of any tuberculosis control programme are the case finding, treatment and case holding. The crucial point is the treatment. Cure rate is an indicator of the success of national TB control programme. Poor adherence to the therapy is the single most important cause of the treatment failure in TB control programme, both in industrialized and developing countries (Lee et al. 1993).

As result of treatment failure, TB patients are heavy burden on the health and economic sector of country. They remain infectious and a potent source of disease transmission to surrounding peoples. Their absence and inability to work is a major direct burden over economy, apart from various other indirect burdens (Morsy et al. 2003).

Failure of the global tuberculosis control efforts is due to lack of political commitment and funding, inadequate service’s organization and case management leading to failure to cure diagnosed cases. Aim of treatment is to cure the patient, prevent death, relapse and decrease the transmission to others. Monitoring of the infections is done by bacterial
examinations. Ensuring adherence is the key factor in the treatment success (Guideline to TB treatment WHO/TB/1997).

Treatment failure rate varies from country to country. In East Mediterranean Region (EMRO) of WHO, Egypt has a treatment failure rate of 3%-5% of treatment outcome of the new smear positive cases and 13%-17% of retreated cases (Morsy et al. 2003). While Pakistan has a treatment failure rate of 10%-12% (NTP, 2006a). There is no specific data of treatment failure in case of new smear positive cases and re-treatment cases in Pakistan.

Factors Contributing to Treatment Failure

Drug Resistance

The basic principle of DOTS is to break the chain of transmission by diagnosis and curing people with infectious TB. Diagnosis is simple and treatment cures over 95% of patients in clinical trials. The problem is that in many TB programmes less than 50% of patients complete a full course of treatment. Incomplete treatment leads to an increase in the prevalence of people with infectious TB and increased drug resistance.

Drug resistance in patient with tuberculosis is the most important risk factor for treatment failure. Two forms of drug resistance are seen, primary and acquired. Primary resistance is seen due to resistant TB bacteria for anti-TB drugs. While acquired drug resistance develop due to under dose treatment given to TB patients, leading to mutants’ growth (Grange, 1999). Multi-drug Resistance TB (MDR-TB) is defined as isolates resistance to both isoniazid and rifampicin with or without resistance to other anti-tuberculosis drugs. It has a very high case mortality rate, poor treatment outcomes and is frequently associated with toxicity and intolerance to the use of second line drugs (Lee et al. 1995). Resistance to TB is dangerous as “there have been no significant new drug developed for TB for over 30 years and it seems unlikely there will be any more for several years to come” (Smith, 1999). Drug-resistance TB requires extensive chemotherapy up to two years of treatment. It is more expensive than drug-susceptible TB, and also has more toxic to patients.
The WHO/IUATLD Global Project on Drug Resistance Surveillance has found more than 4 percent prevalence of MDR-TB among new TB cases in Eastern Europe, Latin America, Africa, and Asia (WHO, 2006d). In a study in Russia upon 948 sequential culture-proven TB cases, a high proportion of new cases had tuberculosis that was resistant to isoniazid (24.9%) and rifampicin (20.3%), a known first-line drugs. There was 17.3% multi drug resistant tuberculosis (Balabanova et al. 2006).

An Indian study, revealed that most treatment failure were on account of MDR-TB, particularly 33 percent among the patients on category 2 treatment. With 3% primary resistance and 16% multi-drug resistant TB among previously treated patients, MDR-TB patients made up less than 10% of patients who remained sputum smear positive in category 1 up to 3 months, and half of them remained smear-positive in category 2 up to 4 months, labeled treatment failed. (Santha et al. 2002)

In northern Pakistan, antimicrobial susceptibility of the isolates was tested and fifteen percent resistant isolates were found for single drug, while 28 % were multi drug resistant and 7% resistant to all four first-line anti-tuberculosis drugs (rifampicin, isoniazid, streptomycin and ethambutol). Further more, resistance against individual drugs was rifampicin 32%, isoniazid 37%, streptomycin 19% and ethambutol 17%. The emergence of resistant mycobacterium strain is alarming and resulting in MDR-TB (Butt et al. 2004).

*Poverty and DOTS*

There are multiple barriers in the implementation of TB-DOTS programme in the high burden countries of the world. These are mostly low socioeconomic status of peoples, escalating number of cases, morbidity and mortality due to TB. This is a threatening situation and challenge for health care authorities. During a study in Nepal, finding was that unemployment of TB patients lead to non-compliance, unable to bear travel cost to TB treatment center. Lack of money is an important risk factor for failure of TB-DOTS in poor countries (Mishra et al. 2005). Poverty is both a cause and devastating outcome of TB. In China, TB treatment cost accounted for 55% of average annual household income, leading them to heavy debt and poverty (Jackson et al. 2006).
In Pakistan one third of the population is living below the poverty line. Poverty results in the non-adherence, leading to MDR-TB. It was observed in a study that 37% are poor large families living under one roof and are unable to bear the time and traveling cost for free treatment (Habib F and Baig L, 2006).

Treatment adherence and its determinants

To gain a better understanding of the process of treatment adherence, it is necessary to identify the determinants factors and specially those that are venerable to change. The majority of studies on TB treatment adherence lack of theoretical framework. They concentrate on socio-economic factor such as age, gender, education, occupation, traveling distance or knowledge of TB. Health seeking behavior is also known to be a dynamic characteristic therefore, it is necessary to differentiate between the factors that influence the initial acceptance of treatment and those that determine patients to persevere (Liefooghe et al. 1999). Besides all these there are significant risk factors for treatment failure were non-adherence to treatment, insufficient health education to the patient and poor patient knowledge regarding the disease (Morsy et al. 2003).

In Pakistan the problem of low treatment adherence has been observed with the drop out rates being as high as 66% in Sindh and similar situation in Rawalpindi and Sialkot. A special characteristic of defaulting in Pakistan is its very early occurrence, i.e. one- fifth of the patients default in the first month of the treatment and one-third in the second month (Liefooghe et al. 1999). As the patient start improving with the treatment, therefore they are likely to stop taking drugs and leaving the treatment incomplete. Adherence to medication is far more difficult than having the treatment recommended by the health care providers. Socio economic situation, cultural back ground, distance from the facility from where the treatment is being received, behavior of the healthcare providers with the patient, way of handling the situation by the family and a positive attitude of the patients towards cure, all having an influence on the adherence of patient to the treatment. Characteristics such as being homeless, immigrants, drug addicts, working conditions and poverty, all make a person unduly susceptible to tuberculosis infection (Comstock, 1994).
Success of DOTS programme depends upon the behavior of its providers. Health facility workers are non friendly and non responsive, while community DOTS worker are caring but they do according to their convenience (Khan et al. 2005). However, even though tuberculosis is eminently treatable, the non-adherence to medical recommendations makes it the leading cause of death attributable to a single infectious pathogen with one-third of the world’s population at risk developing the disease (Lee et al. 1995).

The most important causes of the worldwide increase in TB are non-compliance with the TB control programs, inadequate diagnosis and treatment, endemic Human Immunodeficiency Virus (HIV), migration, ambulatory and self-administered treatment. It is already 50 years since the first anti-tuberculosis drug was discovered: effective treatments capable of curing all patients in six months have been available for the last 25 years, and the results are failure plus a growing mortality curve at the beginning of 21st century (Pilheu, 1998).

**Concomitant Conditions**

There are some concomitant conditions which affect the treatment outcome. These are HIV/AIDS, diabetes, immuno-suppression, hepato-renal diseases and malabsorption syndrome. HIV / AIDS and TB co-infection may speed up the disease progress leading to poor treatment outcome. HIV infection along with poor social and health care facilities of different population groups and the lack of compliance with therapy form a group of concomitant causes that increase the number of MDR cases (Ortono and De luca, 1998). In a study in Canada it was revealed that HIV infection was found to be a dependant predictor of the failure to complete TB treatment (Wobeser et al. 1999).

Diabetes mellitus provides more favourable conditions for TB infection in human. Once infected then it is more difficult to treat as compared to non diabetics. This leads to treatment delay and failure. Diabetes as co-morbidity was identified as a risk factor for treatment failure in Egypt (Morsy et al. 2003).
**Knowledge of TB**

Health education and knowledge about disease is very important to get better cure rate. Due to lack of knowledge in TB patients, as symptoms improves within a few weeks of starting anti tuberculosis treatment, and without active intervention many patients dropout of therapy, which leads to treatment failure (Lim, 1993).

A study carried out in Ndola, Zambia, showed that 30% of TB patients stopped taking their medication within first 2 months of commencing treatment, as soon they start feeling better. Lack of knowledge in benefits of completing TB course was found among 26% (Kaona et al. 2004). In Nepal, 61 percent of non-adherent TB patients, show lack of knowledge about daily intake of medicine after they got better (Bam et al. 2006). While in a cross sectional study in Pakistan, found that 18% TB Patients would have discontinued their TB therapy following relief of symptoms (JA Khan et al. 2006).

**Role of Private Practitioners in TB cure**

Private practitioners are the main health care providers in private sector. In most of the high burden countries, like Pakistan over 80%, Egypt 26% and Yemen 25%, TB patients get initial consultation with general practitioners (GPs) nearest to their residence. During TB treatment course for drug related side effects patients often consult them as TB clinics are located far away from their residence, within 10-30 km or more (WHO, 2006c). The knowledge about TB-DOTS strategy in general practitioners is not up to-dated. In a study in Pakistan, only 3% of GPs know about the five components of DOTS and two third of prescriptions written for new sputum smear positive were not according to standard of NTP (Shehzadi et al. 2005).

**Traditional Healers as Care Providers for TB patients.**

Traditional healers are deeply rooted in a culture, mostly in rural population of developing countries. They have more social penetration and easy accessibility to society. TB-DOTS providers have lack of communication and explanation of TB therapy related side effects like red colored urine as ‘hot’ (Ito KL, 1999). These lead to patient dissatisfaction, resulting consultation with private health care providers like homeopathic,
traditional and faith healers (WHO, 2006c). It is evident from a study in rural South Africa those who consulted tradition healers got bad progress and high mortality (Barker et al. 2006).

**Stigma and TB-DOTS**

Tuberculosis is highly stigmatized in developing countries. This plays a main role in treatment success rate. In Egypt and Syrian Arab Republic it was seen that more than 30% of patients were hiding and ashamed about their TB diagnosis. They were worried about social life activities, especially marital relation, In Pakistan 85-95 percent patients felt ashamed having TB. In a study it was revealed 39% of the respondents believed in reduced chances of marriage (JA Khan et al. 2006), girl’s marriages are at risk and they hesitate to visit TB clinic (WHO, 2006c).

For implementation and follow up of DOTS strategy, the lady health workers, who act as treatment supporters, visit the diagnosed patients at their homes. It creates a social problem as they were hiding themselves to be labeled TB patients; ultimately it ends up in default. That’s why to get 100% DOTS success rate self administered DOTS is suitable then community based and facility based DOTS (MA Khan et al. 2000, NTP, 2006a).

**Default and Case Holding**

A better understanding of the various factors accounting for treatment default could help to achieve better compliance from patient, removing the most important obstacle to TB control. Various studies have shown that the consequences of non-adherent patients took longer to convert to negative sputum culture, were more likely to acquire drug resistance, required longer treatment regimens and were less likely to complete treatment (Pablos-Mendex et al. 1997). A study of urban population in Bombay found that both private and public health systems do not offer convenient, efficient, acceptable or affordable TB cure. Misdiagnosis leads to loss of time, money and high default rates. The woman dropouts were due to pressure of housework, fear of desertion, isolation and the blame for disease and men dropped out due to financial difficulties. Married men and single women had greater family support (Nair et al. 1997).
The priority should be given to case holding. The most cost-effective technique in Uganda was seen to be ambulatory treatment of patients at the nearest health unit, this improved cure rates up to 60 to 70 percent. Reasons for non-compliance are non-specified length of treatment, conflicting advice, lack of family support and stigmatization (Saunderson P, 1995).

**Smoking**

There is a close association between smoking and adherence to treatment of TB. During TB treatment smoking marijuana or mandrax was found as a risk factor for default (Holt et al. 2006). In a Turkish study, those who showed more adherences were non smokers, (Balbay et al. 2005).

**Gender**

Tuberculosis kills more women than all the causes of maternal mortality combined, leaving many children orphaned and devastating a large number of families (World Development report, 1993). Thus the socio-economic and cultural factor has greater impact on females as barriers since they are in a more economically and social precarious position (Hudelson P, 1996).

A negative impact on the health of women living in Pakistan was observed and it was expected that females would be less compliant on treatment than males. Studies in Sialkot, Pakistan, however show that there is slightly better treatment compliance for the females than males TB patients. At the TB Centre Rawalpindi, female patients attended follow-up with a greater regularity and had a higher treatment adherence rate and significantly higher cure rate than male patients. It was also seen that women in reproductive years are more prone to progress from the initial infection to clinical disease (De Muynck et al. 1999).

**4.3 Conclusion**

After reviewing all the related literature it can be concluded that risk factors for the TB treatment failure are mostly same in the high-burden countries worldwide. The detection
of patients with TB is low; treatment outcomes of the patients are also poor. Among the registered patients, compliance is alarmingly poor about one third of them complete the treatment. As a result may TB patients die because they are either not detected, detected late, in appropriately treated or they do not complete treatment. Million of people get infected and become multi drug resistant due to low case detection or poor management of TB patients.

Poor treatment outcomes are seen due to many reasons like; late seeking care behavior, less resources, untrained health care professionals, poor diagnostic facilities, poor adherence to anti-TB treatment and relatively long period of treatment (08 months) is not “short course”. Social stigmatization of the TB patients, non cooperative behavior of health care providers and lack of co-ordination between the TB treatment facilities are also included in this long list.

Multi drug resistant TB is a major problem in various countries, being a risk factor for poor treatment outcome. It is revealed by literature review that its treatment is very toxic and expensive. Its duration of therapy is up to 2 years, while most of the reasons for drug resistance are avoidable. TB patients are mostly illiterate and poor. It has been found important predictor of treatment failure in them is non adherence with treatment. It is behavioural problem, the determinants of which vary from person to person and one context to another. It is the reason for increase in multi-drug resistant TB. Less than 45% of TB cases in Pakistan are being treated under DOTS strategy in public sector, self administrated DOTS is more successful as compared to facility based DOTS, as in later patient does not bear the sole responsibility of adhering to treatment.

Community awareness and patient’s knowledge about TB has main role in the success of treatment. No doubt, medicine is being supplied regularly but the treatment providers are not informing them about drug related side effects and not removing drug related myths. Stigmatization by society, along with many other factors may prevent the patient from completing the treatment once it begun provision of intensive health education to TB patients and community should be done.
V. STUDY PROTOCOL

5.1 Justification for the study

Pakistan’s major public health challenge is the tuberculosis. Pakistan has adopted the DOTS strategy in 1995, as a pilot project. By end of May, 2005, DOTS had 100% coverage in Public sector. It is reflected by improvement in ranking from 5th to 7th among 22 high burden TB countries in the world. Every year, approximately 280,000 people in Pakistan develop TB, with a majority of economically productive adults (NTP, 2006b). Mostly they are poor and belong to the labour class, like private industrial workers.

Treatment failure is a serious problem facing national TB control programme in all the high TB burden countries. Irregularity of treatment is a factor that can lead to treatment failure. In Pakistan, treatment failure rate accounts for 10-12%. There is no specific data regarding treatment failure rate in new smear positive TB cases and re-treatment cases, specifically among the private industrial workers and their families. Their treatment failure is an economical burden for the nation. It leads them to the poverty circle and ultimately a rise in morbidity and mortality contributing to country population. There is so far no study that has addressed the factors leading to the DOTS programme being ineffective, specifically treatment failure in private industrial workers and their families in Punjab social security health care system, Pakistan.

Pakistan is in a TB emergency state facing an alarming situation. The outcome of this study can help to devise methods of decreasing the treatment failure rate and improve the effectiveness of the TB-DOTS programme, in Punjab Social Security Institution (PESSI).

5.2 Study Area

The proposed place of the study will be the Social Security Hospital in the Islamabad/Rawalpindi region. It is a teaching hospital of Islamabad Medical and Dental College. In Northern Punjab, it is the main hospital catering health care facilities for the
industrial workers from the following five districts; Rawalpindi, Islamabad, Attock, Chakwal and Jehlum. All latest diagnostic and therapeutic facilities are available. Its indoor has a capacity of 400 beds. In the region there are 2,608 industrial units having 44,000 registered workers with 156,000 dependents, who are being provided health care by 28 treatment centers in the region. This region is densely populated and having a high prevalence of tuberculosis and has an annually estimated 81.6/100,000 new smear positive TB cases. It is mostly due to poverty, malnutrition, lack of occupational hazards knowledge and protective measures provided by factories. Being the main hospital it provides an appropriate setting for investigation of risk factors of treatment failure among TB patients.

![Map of Rawalpindi Region, study area](image)

**Figure 5:** Map of Rawalpindi Region, study area (Rawalpindi, 2007).

### 5.3 Study design

Quantitative research methodology can be categorized into either observational or experimental studies. Observational studies are further grouped into descriptive and analytical studies. Case reports and case series are included in descriptive studies (Hennekens and Burning, 1987). Analysis of relationship between health status and other variables is known as analytical studies. Cross sectional, case-referent, cohort and ecological studies are different types of analytical studies (Beaglehole et al. 1993).
A case-referent design, also known as case-control design, is proposed for this study. Compared to other multiple approaches, the case-referent study is the most efficient regarding time and cost. In case-referent studies the target are selected on the basis of their outcome of interest. This design would allow identifying adequate numbers of cases and control. Thus there will be savings of time and cost.

5.4 Study population

Cases and referents will be selected from the pre-defined study population in the Rawalpindi Region. In this study a case is described as patient with treatment failure as outcome, i.e. sputum smear positive after completion of their treatment course. Referents are those patients who were declared as cured after completion of their treatment course. Further to inclusion criteria to be fulfilled are that participants both cases and referents, should be i) a private industrial worker (and their families) covered by Punjab Social Security health care system, ii) age 15 year and above, and iii) willing participants in the study.

5.5 Data collection procedure

The Punjab Social Security Hospital Islamabad is the main TB treatment hospital for the private industrial workers of five districts of Rawalpindi. There are 28 medical centers in the region serving as treatment centers, and this main hospital situated in the center act as diagnostic center, providing all the diagnostic and therapeutic facilities. There is a well established Chest & TB department where consultants treat general TB patients as well as complicated TB cases such as multi-drug resistant cases.

This study will be conducted in TB department on the reported cases of treatment failure during the period of January 2007 to December 2007. Random selection of cases will be done from the reported cases declared as treatment failure at the completion of their therapy, keeping in view also the other inclusion criteria until the required sample size is achieved. Selection of controls will be done from the patients register, next to each case, declared as cured at the end of their treatment. Particulars like name and address of cases
and controls will be traced by their social security card number from the main registration desk. Informed consent will be obtained from the study participants. Further TB treatment records will be available from TB register. Their address will be given to interviewers to conduct their interview at their houses. To reduce the risk of observational bias, interviewers have no knowledge about treatment outcome. Supervision will be carried out for securing a high quality data collection and 5% of cases and controls will be re-interviewed by the research investigator.

Cases and controls will be interviewed at home. Interviewers will be intensely trained on interview and probing techniques. They shall be supervised to apply standard techniques to questionnaire and trained also on research ethics, as error in data can be introduced by an incompetent interviewer.

5.6 Research Instruments

5.6.1 Questionnaires

To collect complete information regarding the potential predictors of treatment failure in TB patients under TB-DOTS strategy, a detailed questionnaire will be constructed. All cases and controls willing to participate will be interviewed at home according to this questionnaire. The questionnaire will be pre-tested evaluated and revised before used within the study. The questions will be designed to collect comprehensive information by using the variables like i) socio-demographic characteristics like age, and sex, ii) occupation, iii) marital status, iv) education, v) family size, vi) residence, vii) smoking, viii) previous exposure to TB. Risk factor of tuberculosis and treatment failure, patient’s knowledge and adherence behaviour regarding TB.

There will be open and close ended short questions to improve response regarding the elements that might influence their treatment adherence behaviour, such as fear of social isolation, stigma as TB patient, knowledge regarding ‘Hot’ effects of TB drugs, satisfaction with services of DOTS providers. Variables will be used to evaluate risk
factors like travel time, cost, behaviour of employers and dispensary doctors for referral to TB center.

5.6.2 Secondary sources of data information

Secondary sources of data may be an addition sources to get more information about all respondent (Hennekens and Burning, 1987). In DOTS implementation the recording and reporting system is very much developed. The laboratory register contains information of all patients who have had a smear test done, patients cards that detail the regular intake of medication and follow up sputum examination (WHO, 2006d). Information related to this study like treatment adherence and MDR-TB will be collected from these records. In addition the Patient’s TB record register, treatment files and books will be gone through to check their regularity of treatment and sputum smear record. The information collected is objective, unbiased and independent of the present study.

5.7 Sample size calculation

Sample size calculation was done by using the nQuery Advisor software (Statsol, 2007). We assumed a non-adherence to TB treatment of 12% among treatment failure cases and a non-adherence of 6% among those declared cured as their treatment outcome. Due to limited number of cases we decided to select 4 referents for each case based on 95% confidence interval and 80% power. A sample size calculated for cases is 248 and 992 controls (1:4), while total sample size is of 1240. This would allow us to detect a difference between the groups corresponding to an odd ratio of 2:1. Hence at least 1361 subjects (270 cases and 1091 controls) will be needed for study as 10% of estimated value is added to correct for those not willing to participate in the study.
5.8 Data analyses

All the data will be analyzed in the computer center of our hospital by the head of the research team. Software like, EPI info and Statistical Package for Social Sciences (SPSS-V13.0) will be used for the analyses. Data will be analyzed descriptively and started to be identified for any confounding interactions. Univariate and multivariate logistic regression analysis will be performed to find out the predictors of treatment failure by calculating crude, adjusted odds ratio and 95 percent confidence interval.

5.9 Ethical consideration

Research permission will be asked for from The Commissioner Punjab Social Security Institution, Pakistan. The study will be applied for approval by the Ethical Review Committee of Punjab Social Security Hospital, Islamabad, Pakistan. Informed consent will be asked from all study participants. During the study if some participants want to quit, they shall be allowed.

5.10 Limitation of the study

Our study population is not representative of general population but a selection of the private industrial workers. Moreover most of them have traveled from other cities of the country to get work, and they often change their employer and place of work upon completion of their contract. According to our study protocol, we shall approach their residence but some of them may not be traced, which will contribute to lower participation rate.

Our study has a retrospective design and is thus susceptible to several types of bias. This might reduce the reliability at our results. A particular problem in case-referent design is the error in information collection from subjects. Such type of bias arises for example as the respondents are interviewed about knowledge regarding TB after one year of completion of their treatment. Thus, it is not sure that they had knowledge about TB
during treatment phase but gained it after completion of treatment. Also the risk of recall bias in relation to remembering and reporting information by respondents must be considered. The interviewer will not be informed about treatment outcome status of respondents, but still there might be a chance of observation bias.

5.11 Time plan

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<td>Data entry</td>
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<td>Data analysis</td>
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<td>Report writing</td>
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43
## 5.12 Budget

<table>
<thead>
<tr>
<th>Details</th>
<th># of Persons</th>
<th>Effort</th>
<th>Duration Months</th>
<th>Monthly Rate</th>
<th>Amount USD</th>
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<tr>
<td><strong>Personnel:</strong></td>
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<tr>
<td>Research Investigator</td>
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<td>800</td>
<td>9600</td>
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<tr>
<td>Office Manager</td>
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<td>1</td>
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<td>4200</td>
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<td>Interviewers</td>
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<td><strong>Operating expenses:</strong></td>
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<td>Office and other Supplies</td>
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<td>Incidental and un-anticipated expenditures</td>
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VI. REFERENCES


Lim VKE. (1993). Drug resistant Mycobacterium tuberculosis Medical journal of Malaysia; 48(2) : 97-98.


