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Tuberculosis Control in Oman:
Challenges to Elimination

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ABSTRACT

Background: Tuberculosis (TB) is a global public health challenge. More than 1.7 million deaths worldwide in 2007 were attributed to TB. Directly Observed Therapy Short course (DOTS) is the globally recommended strategy for TB control.

Context: The Sultanate of Oman, a middle-income country that has seen substantial economic development during the last 25 years, has made remarkable progress with regard to the control of infectious diseases including TB. In 1996, TB elimination targets for the years 2005 and 2010, were set at three and one new smear positive cases per 100,000 in the Omani national population, respectively. The 2005 target was not reached, implying the need for additional TB control efforts, including research on the various factors affecting TB incidence.

Aim: The main aim of this thesis is to study TB control in Oman and to explore opportunities and challenges in relation to achieving the specified TB elimination targets in Oman. The thesis also aims to give recommendations to NTP to enhance TB control in the country.

Methods: The thesis is based on four studies. In study I, the official TB notification rates for nationals and migrant workers during the period 1981 to 2005 were analyzed. Additional data on the Gross National Income per capita during the same period and estimates of the socio-economic status of 329 TB patients notified in 2004 and 2005 were also used. Study II was a cross-sectional study. Questionnaires were used to evaluate the level of suspicion and knowledge of TB among 257 private and public general practitioners in the Muscat region. In study III, 17 qualitative interviews were carried out with health care providers, to explore their perceptions and experiences of TB control in Oman. Spoligotyping of 312 isolates of *Mycobacterium tuberculosis* from TB patients diagnosed during 2005-2007 was carried out in study IV.

Results: TB notifications declined by more than 85% from 1981 to 2005 (study I). In 2005, the highest notification rates for Omani nationals were found among persons aged 60 years and over. Approximately 95% of the 329 Omani nationals with TB diagnosed in 2004 and 2005, were living in households earning less than the gross national income per capita (Study I). Studies II and III demonstrated inadequate suspicion and knowledge of TB among general practitioners. The private health care sector providers were found to be less aware of TB than the public health care providers, and to be uninvolved in TB control (Studies II, III). Migrant workers were perceived as disadvantaged by the repatriation policy that is applied for persons diagnosed with TB (Study III). Study IV showed a predominance of strains from the Indian subcontinent. Around 50% of the migrant workers isolates were found in clusters also containing isolates from Omani patients, suggesting possible transmission between the two population groups.

Conclusion: Economic development and TB control measures have probably contributed strongly to the reduced TB burden in Oman. To further improve TB control and promote TB elimination, NTP in Oman need to: i) address high-risk individuals, ii) increase awareness and knowledge of TB among frontline health care providers, iii) involve and integrate private providers within the TB control program, iv) review the repatriation policy and consider other strategies to improve TB control among migrant workers.

LIST OF PUBLICATIONS

This thesis is based on the following articles, which will be referred to by their Roman numerals.

- I. **Al-Maniri A**, Al-Rawas O, Al-Tuhami H, Eriksson B, Diwan VK. Towards the elimination of tuberculosis in a developing country: Twenty five years of tuberculosis control in Oman. *Int J Tuberc Lung Dis*. 2007 Feb;11(2):175-80.
- II. **Al-Maniri A**, Al-Rawas O, Al-Ajmi A, Ayesha De Costa, Eriksson B, Diwan VK. Tuberculosis suspicion and knowledge among private and public general practitioners: Questionnaire Based Study in Oman. *BMC Public Health*. 2008 May 26;8:177.
- III. **Al-Maniri A**, De Costa A, Al Rawas O, Fochsen G. Immigrants and Health System Challenges to TB control in Oman. Submitted to *Qualitative Health Research Journal*.
- IV. **Al-Maniri A**, Singh JPN, Al-Rawas O, Al Busaidi S, Al Balushi L, Ahmed I, Al Mahruqi S, Haile M, Diwan VK, Hoffner S. A Snapshot on biodiversity and clustering of *Mycobacterium tuberculosis* in Oman using spoligotyping. Submitted to *International Journal of Tuberculosis and Lung Disease*.

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LIST OF ABBREVIATIONS

ARV	Anti-retroviral drugs
BCG	Bacille Calmette Guerin
CDC	Centre for Disease Control (Atlanta, USA)
CI	Confidence Interval
CMU	Condensed Meaning Units
COPD	Chronic Obstructive Pulmonary Disease
CPHL	Central Public Health Lab
DOTS	Directly Observed Therapy Short-course
DST	Drug Susceptibility Testing
GCC	Gulf Cooperation Council countries
GDP	Gross Domestic Product
GIS	Geographic Information System
GNI	Gross National Income
GP	General Practitioner
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assays
INH	Isoniazid
IOM	Institute of Medicine
IPT	Isoniazid Preventive Therapy
LTB	Latent Tuberculosis
MCQ	Multiple Choice Questions
MIRU-VNTR	Mycobacterial Interspersed Repetitive Unit-Variable-Number Tandem Repeat
MDR-TB	Multiple Drug Resistant Tuberculosis
MOH	Ministry of Health
NRL	National Reference Laboratory
NTP	National Tuberculosis Program
OR	Omani Riyal
PAL	Practical approach to Lung Health
PP	Private provider
PPM	Private Public Mix
PPP	Purchasing Power Parity
RFLP	Restriction Fragment Length Polymorphism
TB	Tuberculosis
TST	Tuberculin Skin Test
US	United States of America
USD	United States Dollar
WHO	World Health Organization
XDR-TB	Extensive Drug Resistant Tuberculosis

1 INTRODUCTION

1.1 TUBERCULOSIS (TB)

Tuberculosis (TB) is an infectious disease primarily caused by *Mycobacterium tuberculosis*. This airborne infection, through the aerosolization of droplets containing *M.tuberculosis*, affects mainly the lungs (pulmonary TB), but can also affect other parts of the body (extra-pulmonary TB) (WHO, 2009b). The World Health Organization (WHO) estimated that one third of the worldwide population has *M.tuberculosis* dormant in their lungs in the form of latent TB infection (LTB) (Dye, Scheele, Dolin, Pathania, & Raviglione, 1999). Five to 10% of individuals with LTB may develop active TB during their lifetime. The reactivation of TB may take from 3 months to decades and this depends on the existence of factors that may lower the immunity of individuals with LTB and facilitate the progression to active TB. These factors include, for example, Human Immunodeficiency Virus (HIV) infection, malnutrition and treatment with immunosuppressive drugs (Harries & Dye, 2006).

1.2 HISTORICAL LANDMARKS AND THE CURRENT GLOBAL EPIDEMIOLOGY

TB is an ancient disease that infected and killed millions of people over thousands of years (Wilbur & Buikstra, 2006). In the last 100 years, more than 100 million deaths have been attributed to TB (Frieden, Sterling, Munsiff, Watt, & Dye, 2003). The white plague, consumption and “the captain of all these men of deaths” were used to describe TB in the past (Ducati, Ruffino-Netto, Basso, & Santos, 2006). However, it is only in late 19th century that *M.tuberculosis* was discovered as the causative agent of TB by the pioneering work of Robert Koch (Schluger, 2005). Koch’s discovery of *M.tuberculosis* led to further research, which contributed to the development of the Tuberculin Skin Test (TST) and the Bacille Calmette Guerin (BCG) vaccine (Ducati et al., 2006).

During Koch’s time and for many years later, sanatoria were used as a means to prevent disease transmission, as no effective chemotherapy was available. The management of TB in sanatoria constituted of bed rest, fresh air and a healthy diet. Therefore, sanatoria played an important role in reducing the incidence of TB during the first few decades of the 20th century (Daniel, 2006). In 1944, the first anti-TB treatment, streptomycin, was discovered (Davies & Yew, 2003). In the 1960s, the current standard anti-TB treatment regimen was established (Mitchison, 2005), which diminished the role of sanatoria (Binkin et al., 1999). Following that, the incidence of TB declined rapidly, which made many public health authorities in the industrialized countries believe that TB was on the way to being eliminated (Raviglione & Pio, 2002). Thus, for some decades later, TB was neglected, although most of the developing countries were still suffering from a high burden of TB (Ogden, Walt, & Lush, 2003). In the 1980s a re-emergence of TB in the United States and in some European countries was reported (Raviglione, Sudre, Rieder, Spinaci, & Kochi, 1993). This caught the attention of the international scientific and political community and led to TB being recognized as a global public health problem (Raviglione, 2003). In the year 1993, WHO declared TB as a global public health emergency (WHO, 1993).

Today, TB is still a global public health issue. It is one of the top ten causes of deaths in the world (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). It has been estimated that every 15 seconds someone in the world dies of TB, and that every second a new person is infected with TB (Dye, Watt, Bleed, Hosseini, & Raviglione, 2005). WHO estimated over 9.2 million new TB cases and 13.7 million prevalent cases in 2007 worldwide. The overall incidence rate during the same year was 139 per 100,000 population. Smear positive cases account for 44% of the total burden of the disease (WHO, 2009a). Over 95% of TB cases and deaths are occurring in the developing world. Only 22 countries are identified as high burden countries, and they account for over 80% of the global burden of diseases (Dye, Watt, & Bleed, 2002). Fifty five percent of the total new cases were estimated to be in Asia and 30% in Africa (figure 1). However, because of HIV associated TB, out of the 15 countries with highest burden of TB 13 countries were from Africa. The highest incidence rate of TB is in Sub-Saharan countries. India has the highest number of cases with over 2 million TB cases were reported in 2007 (WHO, 2009a). Furthermore, despite the availability of highly cost-effective treatment (Dye et al., 2002), WHO estimated 1.3 million HIV-negative people died from TB in 2007, putting TB as the second cause of death from infectious diseases in the world, after HIV/AIDS, (WHO, 2009a). Around 99% of TB related deaths occur in developing countries (Dye, Maher, Weil, Espinal, & Raviglione, 2006).

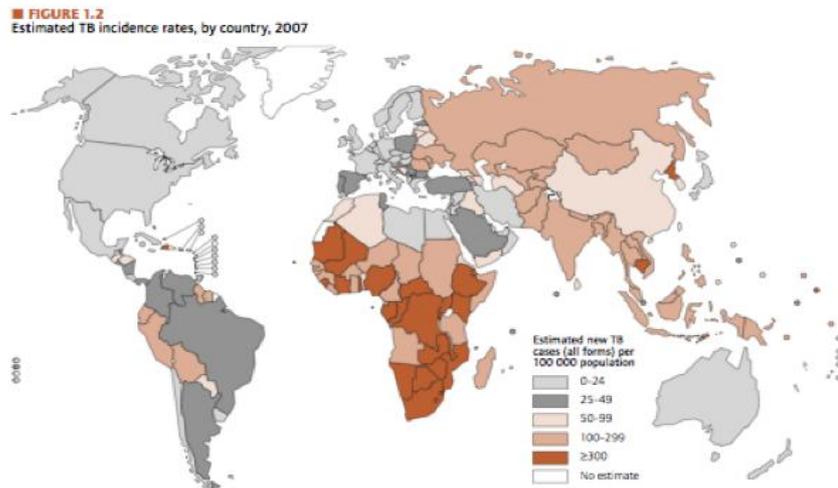


Figure (1): Estimated TB incidence rates per 100,000 by country, 2007 (Source WHO, 2009a)

1.3 HIV-ASSOCIATED TB

The association between TB and HIV was observed during the early stages of the HIV epidemic (Rieder, Cauthen, Comstock, & Snider, 1989). HIV positive patients with LTB infection are at high risk of developing active TB (Selwyn et al., 1989). In addition, HIV increases the risk of quick progress to active TB immediately after infection of *M.tuberculosis* (Hopwell & Chaisson, 2000). Re-infection and relapse of TB are also more common among HIV positive patients (Panjabi, Comstock, & Golub, 2007). HIV infected individuals may also run an increased the risk of developing primary Multiple Drug-Resistant TB (MDR-TB), as compared to HIV negative individuals (Suchindran, Brouwer, & Van Rie, 2009).

HIV associated TB has had negative consequences on TB control in regions having widespread HIV, especially Sub-Saharan Africa and South East Asia (Sharma, Mohan, & Kadiravan, 2005). According to WHO, the incidence of HIV-TB cases is estimated to have peaked in 2005 with more than 1.39 million cases expected to have TB-HIV co-infection. Around 14% of the reported TB cases in 2007 were estimated to be HIV positive. Almost 80% of these cases were in Africa and 11% in the South-East Asia Region (WHO, 2009a). It is also estimated that 12 to 14 million people have a dual infection of TB and HIV (WHO, 2004a). South Africa, the country with the highest burden of TB and HIV, alone accounted for 28% of HIV associated TB estimated in 2007 (WHO, 2009a).

Furthermore, HIV increases the risk of death among TB patients and vice versa (Lawn & Churchyard, 2009). Around 0.5 million TB deaths were estimated among HIV positive patients in 2007, and around a quarter of the deaths among the 2 million HIV deaths were attributed to TB. The major cause of death among patients with HIV-TB is found to be bacterial sepsis (Martinson et al., 2007). However, death from HIV associated TB can be reduced by the introduction of anti retroviral therapy (Akksilp et al., 2007).

In areas burdened with double infections of TB and HIV, TB control strategies alone are not sufficient (Godfrey-Faussett & Ayles, 2003). Therefore, improved TB control programs and substantial progress in delivering better HIV diagnosis and treatment can contribute to a reduction in mortality and morbidity of HIV-associated TB (Albalak et al., 2007). WHO recommends what is known as the '3I's strategy (intensified case finding, isoniazid preventive therapy and infection control) in dealing with this problem. However, to have worldwide implementation of this strategy to improve the current HIV-TB burden, resource allocations and collaborations for global actions need to be augmented (Lawn & Churchyard, 2009).

1.4 DRUG RESISTANT TB

In general, antibiotic resistance is a global threat to the control of bacterial infections (Gould, 2009). Resistance to TB treatment is no exception. The first resistance of *M.tuberculosis* to the TB treatment, streptomycin, was reported in 1947 (Miller, 1947). This has led to introduction of anti-TB regimens that have more than one drug and longer duration (Mitchison, 2005). The major causes of TB drug resistance are incomplete treatment and inadequate adherence to treatment protocols (Jain & Dixit,

2008). In addition, poorly conducted TB control programs run by inefficient health systems may contribute to the development of resistance and cause more harm than no therapy (Matteelli et al., 2007)

Multidrug-resistant TB (MDR-TB), defined as resistance to at least rifampicin and isoniazid, is currently a major challenge to TB control. MDR-TB is difficult to treat and increases the risk of death from TB (Chan & Iseman, 2008). WHO estimated 0.5 million cases of MDR-TB in 2007. Around 85% of the MDR-TB cases were in 27 countries, of which 15 were European (WHO, 2009a). In 2005, a global emergence of an even more fatal form of TB drug resistance, Extensive Drug Resistant Tuberculosis (XDR-TB), was reported (CDC, 2007). XDR-TB is MDR-TB plus resistance to any of the fluoroquinolones and at least one of the injectable second line drugs (WHO, 2009a). Currently, 55 countries have reported the incidence of at least one case of XDR-TB (WHO, 2009a). However, these estimates are limited and may underestimate the total global burden of both MDR-TB and XDR-TB (Borgdorff & Small, 2009)

2 TB CONTROL AND ELIMINATION

2.1 DEFINITIONS

Elimination or eradication of human disease is a major challenge to public health that has been the subject to discussions for over 100 years (Dowdle, 1998). The eradication initiatives in the 20th century included mostly infectious diseases for example yellow fever, malaria, poliomyelitis, and smallpox. In 1979, WHO declared the first global eradication of a human pathogen, smallpox (Henderson, 1980). Table one presents the definitions of terms referring to elimination and eradication.

Table 1: Definitions of terms referring to infectious diseases elimination and eradication (Dowdle, 1998).

Term	Definition
Control	The reduction of the disease to a locally acceptable level as a result of deliberate efforts
Elimination of the disease	Reduction to a zero incidence of the disease in a defined geographical area as a result of deliberate efforts
Elimination of infections	Reduction to a zero of the incidence of infection in a defined geographical area as a result of deliberate efforts
Eradication	Permanent reduction to zero of the worldwide incidence of the infection as a result of deliberate efforts
Extinction	The specific infectious agent no longer exists in the nature or in the laboratory

The eradication of TB was also of interest to some researchers and public health authorities during the middle of 20th century (Soper, 1962). Today, given that one third of the world's population is already infected with *M.tuberculosis*, the eradication of TB is not considered to be possible at present (Enarson, Seita, & Fujiwara, 2003). However, having the target of TB elimination is important to reduce the morbidities and mortalities associated with TB (Enarson, 2000). If the incidence of TB were to reach less than one smear positive case per 1000,000 population, TB elimination could be said to have been conventionally achieved. A low TB incidence country is defined as a country that has an overall TB incidence rate of less than 20 per 100,000. Countries achieving lower than this rate are considered to be in the TB elimination phase (Broekmans, 2000).

2.2 TARGETS TO TB CONTROL AND ELIMINATION

In 1991, the World Health Assembly formulated global targets for TB control. These were to detect 70% of all smear positive cases and to successfully treat 85% of all detected cases by the year 2000. By the year 2001, the case detection rate in high burden countries was as low as 30%. These targets were then postponed till 2005 (Dye,

Hosseini, & Watt, 2007). In 2006, a global treatment success rate of 85% had already been achieved. However, the global case detection of smear positive cases under DOTS was, and continues to be, around 63%. While the Western Pacific Region had the highest case detection rate (77%), the lowest case detection rate was in Africa (47%) and Europe (51%) (WHO, 2009a).

Furthermore, Stop TB Partnership, a network of governmental and nongovernmental organizations, countries and donors, was established in 1998 (Stop TB Partnership, 2009). Additional targets were developed by the Stop TB Partnership. These were that the incidence of and deaths caused by TB should be halved by 2015, compared to 1990 levels. In addition, global TB elimination of 1 case of all TB forms per 1,000,000 was aimed to be reached by 2050 (Dye et al., 2006). However, the current incidence rate of TB is declining by less than 1% per year (WHO, 2009a). To reach the elimination target, a global decline in TB incidence of 16% is required (Lonnroth & Raviglione, 2008).

2.3 THE GLOBAL STRATEGY TO CONTROL TB (DOTS)

During the early 1960s, research showed the importance of directly observing patients taking their medications, but the physicians were applying it selectively (Bayer & Wilkinson, 1995). The increasing global magnitude of TB in the early 1990s caused WHO to adopt a new strategy for universal TB control, in which directly observing treatment intake by the patients is central to the strategy. In 1995, WHO launched the Directly Observed Treatment Short course (DOTS) strategy, as a global strategy to control TB (WHO, 1995). DOTS strategy includes the following five components:

1. Political commitment to sustained TB control activities. This component explicitly calls for direct support from governments of TB control programs. This component mandates that governments are required to provide free or at least heavily subsidised anti-TB treatment.

2. Case detection by direct sputum smear microscopy. Among symptomatic patients seeking healthcare, direct smear microscopy should be used. Although smear microscopy is not a sensitive method, cases detected by smear microscopy are likely to be the most contagious ones, requiring prompt treatment.

3. Regular and uninterrupted supply of anti-TB treatment. This is very important to obviate the development of drug resistance, which can arise when there is an interrupted supply of drugs. This is particularly important for rifampicin and isoniazid, as resistance to both of these drugs defines MDR-TB.

4. Availability of surveillance and monitoring systems. A high quality monitoring and surveillance system is central to NTP evaluations. A monitoring and surveillance system makes it possible to estimate valid performance indicators, such as case detection rates and cure rates.

5. Use of highly efficacious regimes with direct observation of treatment for at least two months. Non-compliance hinders the treatment of TB and is a potential cause of MDR-TB. Therefore, WHO recommends that health care providers should observe the patient taking the medicines for at least the first two months.

The introduction of DOTS has led to improvements in TB control. A decline in TB incidence was observed in countries successfully implementing DOTS elements (Lonnroth, Jaramillo, Williams, Dye, & Raviglione, 2009). Case detection and treatment outcomes have improved with DOTS (Dye et al., 2002). DOTS is also a cost-effective approach to TB control, compared to self administered therapy (Moore, Chaulk, Griffiths, Cavalcante, & Chaisson, 1996). In addition, the five components of DOTS strategy for TB control offer important lessons for the control of other public health problems, including non-communicable diseases (Frieden, 2009). Currently over 187 countries are implementing DOTS (WHO, 2009a).

However, some limitations of DOTS have been reported. Detection of TB by DOTS is established by direct sputum smear microscopy, which makes DOTS a passive case finding strategy. Therefore, implementation of DOTS alone may not be effective in controlling TB in settings where there is a significant delay in TB diagnosis. DOTS is also not effective for smear negative cases and doesn't address HIV-TB co-infection (Brewer & Heymann, 2004). Furthermore, there is no confirmatory evidence from randomised clinical trials that DOTS leads to better cure rates when compared with self-administered treatment (Volmink & Garner, 2007). Another major criticism is that a TB control program under DOTS is, in principle, using a top-down approach. I.E. TB control policies are formulated at international level and implemented at local level without considering the culture and circumstances of each context within which DOTS is implemented (Fochsen, 2007). To address these limitations, WHO and the Stop TB Partnership launched a new improved strategy with six major components in 2006 (Raviglione and Uplekar 2006). These are:

1. The pursuit of high-quality DOTS expansion and enhancement.
2. Addressing TB/HIV, MDR-TB, and the needs of poor and vulnerable populations.
3. Contributions to health system strengthening based on primary health care.
4. Engagement of all care providers.
5. Empowering people with TB, and communities through partnerships.
6. Enabling and promoting research.

2.4 THE PROSPECT OF TB ELIMINATION

Achieving the elimination of infectious diseases needs political will and commitment (Henderson, 1998). The political commitment to TB elimination is central, as thinking only to control TB to a level where it is not longer a public health concern without eliminating it, may lead to a resurgence of the disease (Enarson, 2000). In addition, the scientific feasibility, medical and non-medical, of elimination is a prerequisite for elimination. The medical feasibility relates to the availability of biologically and operationally effective interventions (Dowdle, 1998). The non-medical is primarily related to improvement of socioeconomic conditions (Enarson et al., 2003).

The current medical interventions for TB diagnosis and treatment are not effective as strategies for TB elimination (Enarson et al., 2003). In addition, DOTS is a passive case finding strategy that depends on health seeking behaviours and on the health system's ability to identify suspected TB cases and promptly act on them (Thorson A, 2003). Thus, TB elimination is challenged by the presence of factors that impede the access and utilization of TB care.

2.4.1 Need for new diagnostic utilities

TB can be both one of the easiest, as well as one of the most difficult diseases to diagnose, i.e. patients with obvious symptoms and a previous history of exposure can be easily diagnosed. However, patients with vague symptoms and an inability to produce enough sputum samples can make the diagnosis of TB difficult (Davies & Pai, 2008). If a TB patient is not diagnosed within 2 months, a domestic transmission of TB is likely (Riley & Moodie, 1974). In addition; delay in diagnosis is associated with high case fatality rate (Enarson, Grzybowski, & Dorken, 1978).

The current widely used diagnostic tests have been in use for many years (Perkins, Roscigno, & Zumla, 2006). Chest X-rays are not specific, smear microscopy is not sensitive and sputum culture requires a relatively long time to yield results (Ralph, Anstey, & Kelly, 2009). In addition, the current standard Direct Susceptibility Testing (DST) tools for diagnosis of MDR-TB are difficult to use, tedious, and require experienced personal and a sophisticated laboratory infrastructure (Parsons, Somoskovi, Urbanczik, & Salfinger, 2004). Therefore, the use of these methods has been limited to resource-rich settings (Migliori, Matteelli, Cirillo, & Pai, 2008).

Keeler et al. estimated that the discovery of a newly rapid and easily accessible diagnostic test with high sensitivity and specificity could save 400,000 deaths per year (Keeler et al., 2006). Currently, there are new molecular diagnostic tests for both drug susceptible and drug resistant TB. Beside their reduced bio-safety precautions, they are important for real time point-of-care diagnosis (Cheng, Yew, & Yuen, 2005) and may be viable in limited-resource settings in the future (Bwanga, Hoffner, Haile, & Joloba, 2009). However, the implementation of these tests in remote primary care settings is difficult, and research on simpler methods is still needed (Young, Perkins, Duncan, & Barry, 2008).

2.4.2 Need for new treatment modalities

The current anti-tubercle treatment regimen used in DOTS is effective against more than 90% of TB susceptible strains, and has less than 3% post treatment relapse (Fox, Ellard, & Mitchison, 1999). The drawback of this regimen is the duration of treatment (6 months), which affects the compliance of some patients to medications (Burman et al., 1997). Some considerable side effects of the medicines among some patients, high susceptibility to drug resistance once an interruption of the treatment occurs, and interactions with anti retroviral therapy of HIV patients, are other limitations of the current anti-tubercle treatment (Guy & Mallampalli, 2008).

The development of a new and effective treatment modality for both drug resistant and drug sensitive TB is key to TB control (Chan & Iseman, 2008). Research on new drugs is being carried out, and a number of shorter duration and high efficacy drugs are under clinical evaluation and others are at the drug-discovery stage (Andries et al., 2005; Chhabria, Jani, & Patel, 2009). However, the development of new drugs faces many challenges, for while clinical trials are very costly, the commercial returns on new TB drugs are doubtful (Thangaraj & Reljic, 2009).

2.4.3 Need for new vaccine

Another important tool to reach elimination is to have a new vaccine that prevents people from getting the infection, or prevents the development of active TB. Bacille Calmette Guerin (BCG) is the only available vaccine for TB. BCG is effective in helping young children avoid developing serious forms of TB (Hussey, Hawkridge, & Hanekom, 2007). However, BCG has variable effectiveness, which makes it an unsuitable intervention to achieve TB elimination (Fine, 1995). Furthermore, BCG can be hazardous to HIV infected infants (Bannister, Bennett, Carville, & Azzopardi, 2009), with a highly increased risk of disseminated BCG disease among these infants (Hesseling et al., 2007). There is a lot of research being carried out in this area, and new vaccine trials are in the pipeline (Ly & McMurray, 2008).

2.5 HEALTH SEEKING BEHAVIOURS AND SYSTEM BARRIERS

2.5.1 Health seeking behaviour related barriers

To effectively control TB, the interval between the onset of symptoms and the first visit to a qualified health care provider should not exceed two to three weeks (Lambert & Van der Stuyft, 2005). Health seeking behaviour of TB patients is determined by many socio-cultural factors, which impact on the utilization of TB care services. A systematic review of 58 studies on delay of TB treatment and diagnosis found that age, gender, socioeconomic status, stigma, HIV, distance to health care services, alcoholism and awareness of TB were important factors contributing to delay in TB diagnosis. The economic consequences of TB diagnosis and treatment on TB patients in Thailand, for example, influenced their health seeking behaviours and lowered the case detection rate in the country (Kamolratanakul et al., 1999). Women with TB in Bangladesh are more likely to delay seeking care, when compared to men (Karim, Islam, Chowdhury, Johansson, & Diwan, 2007). In Zambia, being a woman and having low education were associated with longer delay (Needham, Foster, Tomlinson, & Godfrey-Faussett, 2001). In low incidence countries, fear of the immigration authority among immigrants is related to significant delays in diagnosis (Asch, Leake, Anderson, & Gelberg, 1998). Language barriers are also related to a delay in seeking TB care in the United States (Sherman, Fujiwara, Cook, Bazerman, & Frieden, 1999)

2.5.2 Health system related barriers

The total delay caused by the health system, i.e. from the moment a suspected TB carrier first sees a health care provider to point where a diagnosis is made, should not exceed a few days (Lambert & Van der Stuyft, 2005). Under-resourced and suboptimal

health care infrastructure and/or poor knowledge and suspicion of TB among health care providers are health system related barriers to TB control.

2.5.2.1 Knowledge and suspicion of TB among health care providers

Diagnosis of TB is not straightforward and requires knowledgeable and a competent health care providers (Lonnroth, 2000). Moreover, TB is a relatively rare disease as compared to other common respiratory diseases in many contexts (Palombini et al., 1999). Therefore, the alertness of health care providers to early detection of TB is a key to Diagnosis. General Practitioners (GP) need to be equipped with a high level of suspicion and a good knowledge of TB for them to make effective interventions at the patient level (Levin, Gums, & Grauer, 1993). The lack of well-trained health care providers is known to be a major challenge for DOTS implementation (Volmink & Garner, 2007). Health care providers may fail to use the appropriate TB diagnostic tools (Sherman et al., 1999) or to prescribe the standard TB treatment (Hoa, 2004). In a study conducted in Vietnam, for example, only 23% of patients with prolonged coughs had sputum diagnostics (Thorson, Hoa, & Long, 2000).

2.5.2.2 Private health care system

Private health care plays an essential role in the provision of health services in many low and middle-income countries (Malmborg, Mann, Thomson, & Squire, 2006). A sizeable portion of overall health expenditures are in the private health care sector (WHO, 2004c). Because of the convenience and flexibility of private care, patients from a number of different socioeconomic groups seek treatment from private practitioners (PP) (Malmborg et al., 2006). However, often PP are not involved in the control of infectious diseases, including TB, in several settings (Uplekar, 2001). Private health care establishments seem to be more ignorant when it comes to TB diagnosis and treatment (Lonnroth, 2000). Visiting private health care providers was associated with delays in TB diagnosis in many studies (Storla, Yimer, & Bjune, 2008). Integrating the private sector within the NTP in countries is important to improve case detection and treatment outcomes (Lonnroth, Uplekar, & Blanc, 2006).

2.6 TB ELIMINATION IN LOW INCIDENCE COUNTRIES: OPPERTUNITIES AND CHALLENGES

2.6.1 TB Elimination plans in some low incidence countries

2.6.1.1 TB Elimination strategies in US

“Tuberculosis can be extinguished as a public health problem...If the opportunity to end Tuberculosis is not seized now, it may be lost indefinitely.” This statement is now more than 50 years old. It first appeared in the American Lung Association conference report published in 1959 (National Coalition for Elimination of Tuberculosis, 2004). During that time the possibility of eliminating TB appeared real and appealing. However, in the US, government neglect, and the downsizing of the TB control infrastructure for TB elimination in the country led to a resurgence of TB in the 1980s (Institute of Medicine, 2000). In 1989, in response to the resurgence of TB in the US,

the Centre for Disease Control (CDC) published a strategic plan for TB elimination in the US. An elimination target of 1 per 1,000,000 population by the year 2010 was set (Dowdle, 1989). In 1992, an additional action plan was published specifically to contain MDR-TB (CDC, 1992). A decline in the incidence of TB in the US during the 1990s was then observed (Schneider, Moore, & Castro, 2005). To foster TB control, so as to reach the elimination target, the Institute of Medicine (IOM) of the National Academy of sciences published a report entitled “Ending the neglect: The elimination of Tuberculosis in the United States” in 2000 (Institute of Medicine, 2000). The report reemphasised the elimination target, and suggested aggressive action to reach it. This included accelerating the rate of decline, the development of new tools, and an increased involvement in Global TB control. Nevertheless, the decline slowed, and in 2003 the US had the smallest annual decline since 1992 (National Coalition for Elimination of Tuberculosis, 2004). Currently, there is a slow decline in the US, and TB among immigrants is a major hurdle to TB control in the US (CDC, 2009).

2.6.1.2 Elimination Framework in low incidence European countries

During the 20th century, most of the European countries experienced a dramatic decline in TB notifications. In the early 1990s, an observed leveling off of this decline was reported (Raviglione et al., 1993). This raised concerns, as it had been thought that TB had been eliminated in Europe (Schaberg, 1996). There were great disparities among the European countries in 1990s, with the Eastern and central European countries experiencing an increase in TB rates, (because of political and socio-economic crises) while the western countries continued to see a decline among their native population (Migliori & Ambrosetti, 1998). The problems of TB control in Eastern Europe, which has high rates of MDR-TB were negatively influencing TB control efforts in low incidence countries in the region (Migliori & Centis, 2002). In 2002, to foster TB elimination, the first European framework for TB control and elimination in low incidence European countries was published (Broekmans et al., 2002). Similarly to the US, immigration and immigrants poses challenges for TB elimination plans in Europe, and involvement in global TB control has been suggested as a pre-requisite for TB elimination in Europe (Borgdorff, van der Werf, de Haas, Kremer, & van Soolingen, 2005).

2.6.2 Immigrants: a challenge for TB control and elimination in low incidence countries

There are more than 200 million immigrants worldwide (International Organization for Migration, 2009). Immigrants include refugees, asylum seekers, migrant workers and students. Due to socio-economic and political factors, there is an increase in international migration from high TB incidence countries (low or middle income countries) to low incidence high-income countries (Broekmans, 2000). The majority of TB cases in low incidence countries are among immigrants (Blead, Dye, & Raviglione, 2000). In the US and New Zealand, for example, TB among immigrants has slowed down the overall TB decline, and presented a challenge to TB control programs (Cain, Benoit, Winston, & Mac Kenzie, 2008; Das, Baker, Venugopal, & McAllister, 2006)

Reactivation of LTB is the common cause of active TB cases among immigrants (Broekmans, 2000). The risk of developing active TB increases after five years of arrival, and continues up to 20 years after their arrival (Zuber, McKenna, Binkin, Onorato, & Castro, 1997). This is because in their host countries, some immigrants may live in environments favourable to TB transmission or to reactivation of latent TB infections. Malnutrition, homelessness and crowding are the known risk factors contributing to disease development among the immigrants (Carballo, Divino, & Zeric, 1998). Furthermore, factors such as poverty, language barriers, racial discrimination and lack of social support contribute to poor access and utilization of TB health care services among immigrants (Littleton, Park, Thornley, Anderson, & Lawrence, 2008).

Inefficient TB control among immigrants may result in the transmission of TB to native-born individuals and makes the elimination of TB in low incidence countries difficult for the next few decades (Wolleswinkel-van, Nagelkerke, Broekmans, & Borgdorff, 2002). In addition, TB among migrants may have an economic impact on expenditures by health authorities (Brown et al., 1995). Therefore, to control the burden of TB due to immigration, low incidence countries introduced screening strategies for permanent immigrants. These included screening for both active TB and LTB. Chest radiography is currently the main tool for screening of active TB, as well as LTB in many low incidence countries. Both tests are of limited utility, especially if the infrastructure of LTB treatment and follow up is not widely established (Dasgupta & Menzies, 2005). In Canada, for example, where immigrants are screened offshore and upon arrival, screening programs only detect 14% of TB among immigrants (Uppaluri et al., 2002). To have better TB control among its immigrant population, low incidence countries need to contribute to global TB control, especially in countries highly burdened with TB (Zumla & Grange, 1998).

2.6.3 Diagnosis and treatment of LTB: an important task for TB elimination in low incidence countries

Achieving elimination of any infectious disease requires having no new sources of the infection. The long incubation period of *M.tuberculosis* contributes to the existence of a large pool of individuals with latent TB, who are at 5 to 10% risk of developing active TB (Dye et al., 1999). This risk increases when the immunity of the patient is affected, especially among HIV patients (Antonucci, Girardi, Raviglione, & Ippolito, 1995). Therefore, detection and treatment of LTB infection is a golden opportunity to reduce the number of future TB cases (CDC, 1999). NTPs in low incidence countries aiming for TB elimination should be able to identify all individuals with LTB and treat them effectively.

The standard method for diagnosing LTB is the century old Tuberculin Skin Test (TST), which is carried out among high-risk groups e.g. contacts of patients, HIV patients and health care workers exposed to TB (Kunst, 2006). TST has many limitations. It is not sensitive and can't differentiate between active TB and latent TB. It can also easily miss LTB among HIV positive patients. TST is also not very specific, and may label individuals exposed to BCG vaccine or other environmental bacteria as being positive for LTB infection (Farhat, Greenaway, Pai, & Menzies, 2006).

In recent years, there have been major developments with regard to the diagnostics of LTB infection, with the wide commercial availability of immunological tests (Lalvani, 2007). Most of the currently available tests are based on the measurement of interferon gamma (IFN-gamma) release assays (IGRA). IFN-gamma is an antibody released by lymphocyte T cells after the stimulation by antigens, which are specific for *M. tuberculosis* (Pai, Zwerling, & Menzies, 2008). It is less cumbersome and takes less time to get the results compared to TST. However, this test, apart from being more expensive than TST, cannot distinguish LTB from active TB (Park et al., 2009). In addition, more follow up research is required to evaluate the effectiveness of these tests in certain high-risk groups (Menzies, Pai, & Comstock, 2007).

The standard practice for the treatment of LTB is to give Isoniazid (INH) for 9 months for high-risk groups. INH is proven to be effective in preventing development of active TB disease especially among HIV patients (Woldehanna & Volmink, 2004). The major challenge with the use of INH is the long duration of the treatment course and the side effect of the drug (hepato-toxicity), which would require the cessation of the treatment especially among children (Donald, 2002). INH resistance is also a risk if active TB was misdiagnosed for LTB among HIV patients (Balcells, Thomas, Godfrey-Faussett, & Grant, 2006). Abu-Raddad et al estimated that TB incidence could be reduced by 94% in 2050 if new a preventive therapy along with a short TB disease treatment course became available (Abu-Raddad et al., 2009). New treatment modalities that are currently being evaluated may have an important future role in curtailing LTB and improve progress towards elimination in low incidence countries.

2.6.4 Molecular epidemiology of *Mycobacterium tuberculosis*: a powerful tool to TB control

Preventing TB transmission between individuals and identifying factors associated with transmission are major tasks of any NTP (Hollm-Delgado, 2009). However, a major challenge to TB elimination, especially in low incidence settings, is to accurately differentiate a recent transmission of TB from reactivation of old TB. Differentiating transmission from reactivation, helps to develop evidence-based strategies for TB control, i.e. either to focus on case finding and /or treatment of LTB (Nguyen, Gilbert, & Marks, 2004). To achieve this goal, TB control programs have traditionally used a classical epidemiological tool: contacts investigations. This is a method to thoroughly explore from the patient and his / her contacts a possible source of infection, so as to identify any recent transmission. This may suffer from recall bias due to the long latency of *M.tuberculosis* (Prodinger, 2007). However, the discovery of differences in the distribution of repetitive DNA elements in the *M.tuberculosis* genome, which allowed strain differentiation, have revolutionised studies of TB transmission (van Soolingen et al., 1995). Currently, classical epidemiological investigations that incorporate DNA typing have become central for the understanding of the transmission dynamics of *M.tuberculosis* (Barnes & Cave, 2003).

The main advantages of the introduction of molecular typing, are that it: i) provides a valuable epidemiological tool to identify groups with a high-risk of transmission, ii) enables enhanced investigations' of contacts, iii) assists in the evaluation of the

effectiveness of NTP (Barnes & Cave, 2003). In addition, molecular typing methods are very useful to: i) trace transmission in TB outbreaks, ii) identify the risk factors behind the spread of a clone of TB strains in a population, iii) investigate transmission dynamics, iv) identify the occurrence of cross-contamination of TB in laboratories and infections caused by multiple strains of TB (Narayanan, 2004). These utilities make genotyping of all TB isolates a powerful tool for NTP in countries aiming to eliminate TB (McNabb et al., 2004). However, the findings of the molecular genotyping studies should be interpreted with care. Selection bias, lack of patient's clinical data and ignorance of the classical epidemiological investigations of the contacts may harm the usefulness of these methods (Glynn, 1999). The following is a short description of the common genotyping methods for DNA fingerprinting of *M.tuberculosis* used in molecular epidemiology studies.

Restriction Fragment Length Polymorphism (RFLP)

The insertion sequence IS6110 was the first genetic marker reported to be useful for strain typing of *M.tuberculosis* (Hermans et al., 1990). This discovery led to the development of one of the current standard approaches to molecular fingerprinting of *M.tuberculosis*, Restriction Fragment Length Polymorphism (RFLP) (van Embden et al., 1993). The good discriminatory power of RFLP made it the gold standard method for DNA fingerprinting of *M.tuberculosis*. However, it is very cumbersome, time consuming and needs a large amount of DNA. In addition, RFLP becomes unreliable when typing *M.tuberculosis* strains, which have no or few IS6110 copies (Barnes & Cave, 2003).

Spoligotyping

Spoligotyping or spacer oligonucleotide typing is the next to RFLP to study *M.tuberculosis* transmission. Spoligotyping is based on the detection of polymorphism in the direct repeat (DR) locus. Amplification of these DR loci using PCR and then hybridization of the denatured products to a membrane are the major steps required for spoligotyping. Therefore, being a PCR based method, spoligotyping need lesser amount of DNA and yield rapid results compared to RFLP (Kamerbeek et al., 1997). In addition, there is an international database (SpolDB4.0b) with more than 39000 spoligotyping entries, which gives a reliable picture of the global biodiversity of *M.tuberculosis* (<http://www.pasteur-guadeloupe.fr:8081/SITVITDemo/>). However, Spoligotyping has less discriminatory power than RFLP (Scott et al., 2005).

MIRU-VNTR

Mycobacterial Interspersed Repetitive Unit-Variable-Number of Tandem Repeat or MIRU-VNTR is another PCR method. MIRU-VNTR analyses multiple loci containing VNTR of different families of MIRU. MIRU-VNTR is also less cumbersome than RFLP, and at the same time has similar discriminatory powers as RFLP, when combined with spoligotyping, which makes it a new gold standard for molecular typing of *M.tuberculosis* (Oelemann et al., 2007). Its application is however limited, because of the technical and price aspects, and its lesser capacity to differentiate strains of Beijing type (Jiao et al., 2008).

3 THE SULTANATE OF OMAN

3.1 LOCATION AND GEOGRAPHY

The Sultanate of Oman is geographically positioned in the south-eastern corner of the Arabian Peninsula. The total area of Oman is around 309.5 thousand square kilometers. Oman has a coastline of over 3,000 kilometers, extending from the Strait of Hormuz in the north, to the borders of the Republic of Yemen. Oman is constituted mainly of desert, dry riverbeds and mountains. The climate differs from one area to another. While it is hot and humid in coastal areas during the summer, it is hot and dry in the interior part of Oman and cold and rainy in the south. Administratively, Oman is divided into 5 regions and 4 governorates with 61 wiliyats (small towns). The governorates are Muscat (capital), Dofhar, Al Burimi and Musandam and the regions are Ad Dahklayh, Ash Sharqiah, Al Batinah, Adh Dhairah and Al Wusta. Muscat is the political and administrative hub of Oman (Ministry of National Economy, 2008).



Map 1: Location and Map of Oman (source: www.ameinfo.com).

3.2 DEMOGRAPHY

3.2.1 Nationals (Omanis)

In 2007, the total Omani population was estimated to be approximately two million. The male to female ratio is 1.05 to 1.0. Around 12% of the Omani population is under five years and 41% of the population is under 15-years (figure 1). Only 5% of the population are 60 years and over (Ministry of National Economy 2008). The terms Nationals and Omanis will be used interchangeably in this thesis. National is defined as a person holding the Omani National passport.

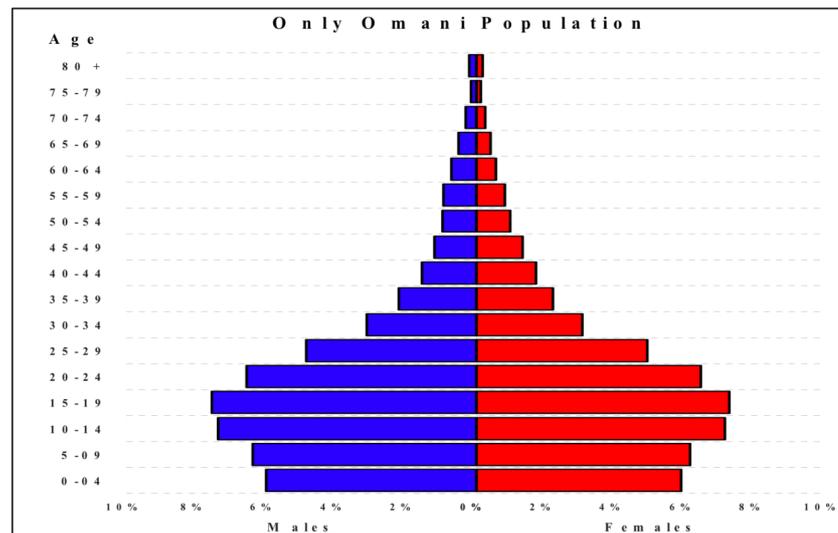


Figure (2): Population pyramid of the Omani populations in 2005 (Annual Health Report, Ministry of Health, Oman, 2005)

3.2.2 Non-Nationals (Migrant workers)

Immigrants in Oman are mainly migrant workers. There are around one million migrant workers in Oman, who constitute around 30% of the total population. Most of the migrant workers are from the Indian subcontinent. Over 70% of these migrant workers are between the ages of 20-40 years. Over 40% are living in the capital, Muscat. Around 80% of the migrant workers are males. Male migrant workers are mainly working for the private sector, with construction companies having the largest proportion. The majority of females are working in domestic services, mainly as housemaids (Ministry of National Economy, 2008). In Oman, migrant workers are referred to as expatriates or non-nationals.

3.3 ECONOMIC AND HEALTH DEVELOPMENT IN OMAN

Due to the exploitation of oil, Oman has experienced dramatic economic change over the last 40 years. In 1970, the Gross Domestic Product (GDP) per capita was 158 Omani Rial (OR) (1 OR \approx 2.7 US \$). However, the GDP per capita rose to more than

5,000 OR in 2008 (Ministry of National Economy 2008). This economic change has been accompanied by dramatic changes in the health indicators. For instance, the life expectancy at birth has increased from 49 years in 1970 to 74 years in 2008. The infant mortality rate has declined from 159 per 1,000 live births in 1970 to 9 per 1,000 live births in 2008. The crude death rate declined from 13.3 in 1980 to 3.25 per 1,000 Omani population in 2008 (Ministry of Health, 2008b). Furthermore, this socio-economic development along, with The Expanded Program of Immunization (EPI), introduced in 1981, has contributed to the reduction of some life-threatening childhood communicable diseases (Ministry of Health, 2007a).

3.4 HEALTH CARE SYSTEM IN OMAN

3.4.1 Public health care system

In Oman, both private and public health systems provide health care. The public health care system has three different levels i.e. primary, secondary and tertiary, with freely available utilization to all nationals and immigrants working in the government sector. Secondary and tertiary hospitals have subspecialties and admission facilities. They are mainly located in the major cities in each administrative region. Primary health care is the main mode of public health care delivery, delivered through health centres distributed all over Oman (Ministry of Health 2007). In the year 1970, there were two hospitals with 12 beds and 19 health centres (without beds), mostly in Muscat. In 2007, 49 hospitals and 159 health centres were offering health services all over Oman, under the umbrella of the Ministry of Health (MOH). In addition, there are five other hospitals and 45 health centres belonging to other public health institutions than the MOH (Ministry of Health, 2008).

3.4.2 Private health care system

Private health care services in Oman have been increasing over the last few years (Ministry of Health 2008). These services are delivered through private pharmacies, clinics, polyclinics and a few hospitals (table 2). In the year 2007, around 55% of the individuals seeking health care in private health services were migrant workers (Ministry of Health 2008).

	1995	2000	2007
Hospitals	1	3	5
General clinics	471	560	787
Chinese & Indian Clinics	7	20	48
Dental clinics	38	74	126
Pharmacies	254	321	350

Table 2: The development of private health services in Oman 1995-2007 (Ministry of Health Annual Report 2008)

3.5 NATIONAL TUBERCULOSIS CONTROL PROGRAM (NTP)

NTP was established in Oman in 1981. The objective of NTP is to reduce mortality, morbidity and transmission of disease through implementation of DOTS strategy, until TB is no longer a public health problem (Ministry of Health, 2007b). The DOTS strategy was adopted in 1996. The structure of NTP is vertical (figure 3). In each hospital and primary health care centre, there is a TB team. The responsibilities of the team are case finding, case holding and ensuring regular drug supply and diagnostic materials. Pulmonary tuberculosis must be notified within 24 hours to NTP. Extrapulmonary TB can be notified within a week. During the intensive phase of DOTS treatment it is mandatory to hospitalize patients for two months. The treatment is freely available to all. All HIV patients should be screened for TB and visa versa (Ministry of Health, 2007b).

Private clinics and pharmacies are prohibited from treating TB cases or prescribing anti-tubercular drugs. If a private practitioner suspects or diagnoses TB, the patient should be referred to the nearest MOH Hospital or health centre. In addition, notification should be sent to nearest regional TB focal point or NTP. Migrant workers diagnosed with TB will be treated till they are smear negative, and then will be deported from the country.

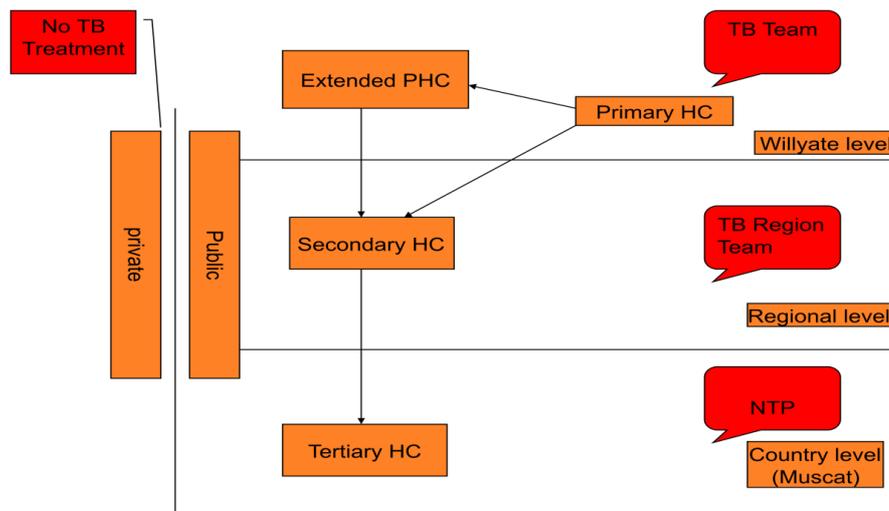


Figure 3: Health Care System and TB Control Program in Oman.

3.6 TB ELIMINATION INITIATIVE IN OMAN

Oman, along with other Gulf Cooperation Council (GCC) countries (United Arab Emirates, Saudi Arabia, Kuwait, Bahrain and Qatar), has experienced economic development as a result of the exploitation of oil. This along with good governance has contributed to a reduction in the burden of many life threatening infectious diseases including TB (Ganguly, Al-Shafae, Al-Lawati, Dutta, & Duttagupta, 2009). Some of

the Oil revenues of the GCC countries have been directed towards development of infrastructure in these countries. This has led to an increase in the demand for labour forces leading to the presence of large groups of migrant workers from South and Southeast Asia (Birks, Seccombe, & Sinclair, 1988).

In 1996, the Eastern Mediterranean Regional Office (EMRO) of the WHO and GCC countries launched “The TB Elimination Initiative in the Gulf States,” at a meeting held in Muscat. The principle elimination targets were: to achieve a national incidence rate of 3 per 100,000 per year for new smear positives by 2005, and of 1 per 100,000 per year by 2010. This was assumed to be achieved, through the implementation of WHO’s global strategy – DOTS and through strengthening the TB control programs in the region (WHO, 1996). TB elimination targets were not specified for the migrant workers.

According to the latest data from the WHO (Table 3), United Arab Emirates has a low notification rate, but with only an 18% detection rate! This indicates the need for additional efforts in order to achieve elimination targets in the GCC region, also including research on the various components and factors affecting TB control. A recent postponement of the 2010 elimination target of 1 smear positive case per 100,000 national population to 2015 was adopted in Oman (Ministry of Health, 2007). This target may still not be reached by 2015 if the current challenges to TB control are not described and analysed.

Table 3: Smear positive notification rates and case detection rates in 2007 for all GCC. (Source: WHO, 2009a)

Country	Smear Positive notification per 100,000 population	Case detection rate (%)
Bahrain	14	79
Kuwait	10	90
Oman	7	125
Qatar	14	44
Saudi Arabia	8	39
United Arab Emirates	1	18

4 ABOUT THIS THESIS:

My choice of PhD topic came after I attended a research workshop organized by the MOH. The stagnation of TB notification rates over the previous 10 years was a concern to MOH officials. At that time, no research on TB control in Oman was available. The MOH encouraged the pursuit of research on this topic. I decided to involve myself in such a research.

To study factors influencing the current TB burden and factors that influence the progress of Oman towards TB elimination, a conceptual framework was needed. I have developed the following context specific conceptual framework, which is based on public health perspectives. In relation to public health, this framework covers trans-disciplinary domains of research on TB control (figure 4). These are: 1. Socioeconomic development, 2. Access and utilization of TB care, 3. Effectiveness of the health care system and 4. Development and implementation of new technologies. Within each domain, I have listed examples of potential areas of research.

This thesis has 4 studies that illustrate some of the research areas presented within this framework. In the first study, I have addressed the domain of the role of overall socioeconomic development in TB control in Oman. In study II, the domain of the effectiveness of the health system was selected, and GPs suspicion and knowledge of TB were evaluated. Study III was within two domains, access and utilization of TB care and health system effectiveness. A qualitative study on patient and health system barriers to TB care was carried out Study IV looked at the clustering of *M.tuberculosis* between Omanis and the migrant workers using the available new molecular biology methods for TB control.

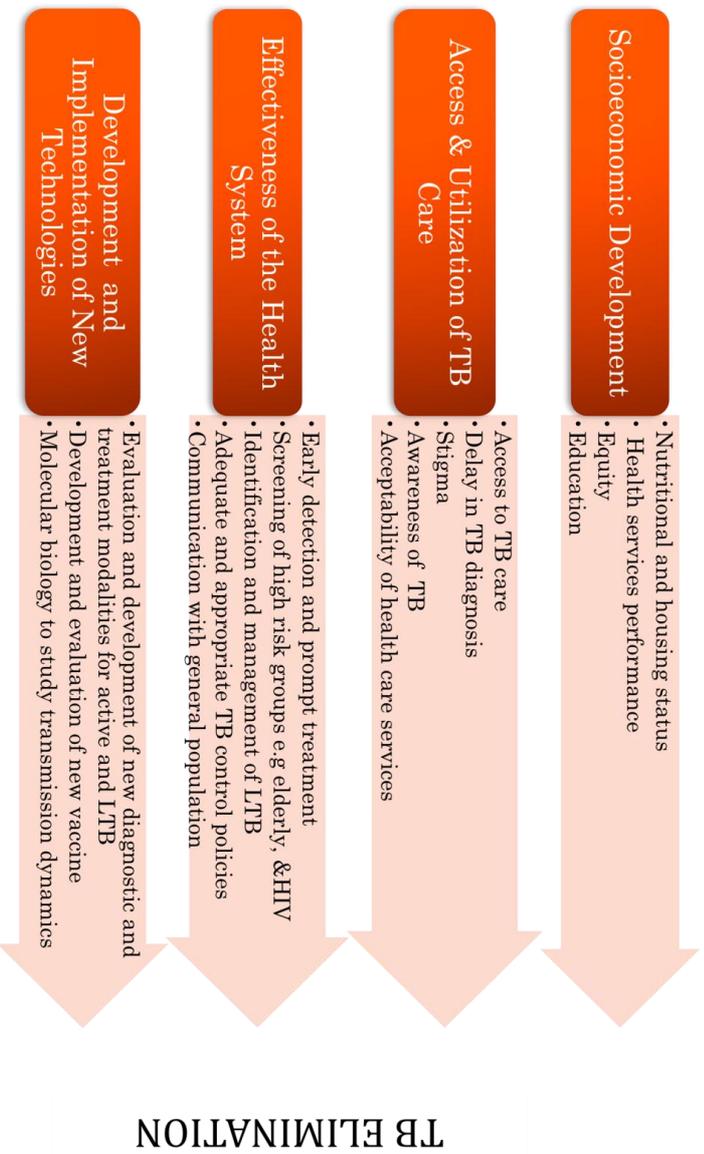


Figure 4: My conceptual framework for research on factors influencing progress towards TB Elimination in Oman.

5 AIMS:

5.1 MAIN AIM:

The main aim of this thesis is to study TB control in Oman and to explore opportunities and challenges in relation to achieving the specified TB elimination targets in Oman. The thesis also aims to give recommendations to NTP to enhance TB control in the country.

5.2 SPECIFIC AIMS:

The specific aims are

1. To describe and analyse trends of TB notification rates in Oman during the period 1981 to 2005, in relation to economic development and the migrant workers population in the country.
2. To describe and analyse the level of suspicion and knowledge of TB among private and public GPs, using written vignettes and structured questionnaires.
3. To explore and describe health care providers' (private and public) perceptions and experiences, with regard to health system and patient barriers to TB control in Oman.
4. To explore and describe the genetic population structure and clustering of *M.tuberculosis* isolates among nationals and migrant workers in Oman using spoligotyping.

6 METHODS

6.1 OVERVIEW OF STUDIES IN THE THESIS

The thesis is based on four studies. The choice of each research method was made with regard to the specific objective of each study. Table 4 summarizes the methods used in the four studies of the thesis.

Table 4: Overview of the four studies.

	I	II	III	IV
Design	Quantitative ecological study	Cross-sectional study	Qualitative study	Molecular epidemiology study
Study population/ Participants	Notified TB cases from 1981-2005	257 private and public GPs in Muscat, Oman	17 private and public health care providers	DNA of 312 <i>M.TB</i> isolates, cultured in Oman 2005-2007
Data collection method	Data from National TB Control Program (NTP) registers	Structured questionnaires	Semi structured interviews	Spoliogotyping

6.2 STUDY 1: TB NOTIFICATION RATES IN OMAN FROM 1981-2005

6.2.1 Data collection

The data was collected from the NTP databases. Information relating to Omani patients' age, sex, region and diagnosis were gathered. Information on TB patients' diagnosed from 1981 to 1991 was available via the written TB register, and data from 1992 was available from a computer database. Information on TB-HIV co-infection was also available in the same database (1992-2005). We obtained information on family income for TB patients (nationals) for the years 2004 and 2005. For non-nationals, only the year of notification and numbers of cases for each TB type were available from 1981 to 2005 in local TB reports.

Data on the size and structure of the population were obtained from Ministry of National Economy annual reports. There have been two national censuses in Oman, in 1993 and 2003. Estimates of the population of nationals before 1993 were obtained as backward projections by MOH, assuming certain fertility and mortality rates. Reliable information on the age and sex distribution of the national population was available only from 1993 onwards. Information on Gross National Income (GNI) per capita (Purchasing Power Parity -PPP) in current International Dollars (1981-2003) was obtained from World Bank data.

6.2.2 Data analysis

TB notification rates for each TB type for each year were calculated (the total number of notified TB cases in one year divided by the total population during the same year). The annual changes of TB notification rates for Omanis and non-Omanis for different years were estimated. Standard approximate tests based on the Poisson distribution were used for the comparisons of the notification rates. The 95% confidence intervals (CIs) for annual changes were estimated using standard, approximate methods. The statistical analysis was carried out using STATA version 9.

6.3 STUDY II: TB SUSPICION AND KNOWLEDGE AMONG PUBLIC AND PRIVATE GENERAL PRACTITIONERS

6.3.1 Data collection

This study is a cross-sectional survey that was conducted among the private and public GPs in the Muscat Governorate. We used two questionnaires (A & B). Questionnaire (A) had two parts. The first part assessed background demographic information. The second part had 10 short clinical vignettes. Each vignette included the age and sex of a client, who had key symptoms and signs of a respiratory illness. Some vignettes had results of diagnostic procedures. Five of the vignettes were TB cases with different presentations. The other five vignettes were typical cases of Chronic Obstructive Pulmonary Disease (COPD), pneumonia, sarcoidosis, bronchiectasis and pulmonary fibrosis. In each of the 10 vignettes, GPs were asked to provide a maximum of three possible diagnoses in order of suspicion (most likely diagnosis).

The second Questionnaire (B) had questions on background experience of TB and a typical case vignette of pulmonary TB, followed by 20 multiple choice questions (MCQs) pertinent to diagnosis, treatment, contact screening and follow up of the TB case. The questions were based on the national TB manual published by MOH. There was only one correct answer for each question. The questionnaires were thoroughly reviewed by a group of chest and infectious disease specialists and medical residents, who agreed on the diagnosis of all the clinical vignettes. The questionnaire was then piloted among five GPs.

In each public health centre, we trained the nurses' in charge to give questionnaires to all available GPs at the end of the morning hours. Questionnaire (A) was first given to the available GPs, who were requested to seal the questionnaire once they had answered it. Then, questionnaire (B) was given to the same GPs and similarly sealed.

For the private sector, we trained health inspectors who were familiar with all the private clinics in Muscat (they routinely visit them every week). The health inspectors were asked to give the questionnaire to all available private GPs. The questionnaires were distributed in a similar way to the public GPs.

6.3.2 Data analysis

The TB suspicion score in the five TB vignettes for each GP was computed. We then awarded 3, 2, 1 and 0 points for those who gave TB as a first, second, third and not-considered diagnosis, respectively. In addition, a TB general knowledge score from 20 MCQs was also computed (one point for every correct answer and none for an incorrect one). The reliability of the questionnaires was tested using Chronbach's alpha statistic and it was estimated to be 0.51 for the suspicion questionnaire and 0.64 for the knowledge questionnaire. Standard statistical measures were used to summarize the characteristics of GPs. Statistical tests were used to assess the influence of random variation in the comparisons of groups. Comparison between public and private GPs was carried out using Chi square test for categorical variables. Independent sample t-test to compare the means of age and experience in years was used. The Mann-Whitney test was applied for comparison of the distributions of the scores. A p-value of 0.05 and less was considered as indicating a statistically significant difference. Multiple linear regression analysis, with robust standard error estimation, to study a model with the two kinds of scores as dependent variables and potentially related independent variables was used.

6.4 STUDY III: EXPERIENCES AND PERCEPTIONS OF HEALTH CARE PROVIDERS

6.4.1 Data collection

The study included 17 interviews with different health care providers. The selection of these participants was purposive. The participants were selected to reflect the public and private sectors, as well as different professional backgrounds. The author of this thesis, selected the participants through his friends and colleagues working in the MOH and in the private health sector, based on a rich informant basis. Four of the interviewees were senior specialists and consultants and another four were public GPs. In addition, five private GPs were included in the study. We also interviewed four public TB focal point nurses. All health care providers had at least five years clinical experience. Three of the public senior specialists and all the private practitioners were men. All the nurses were women. Two of the GPs were women and the other two were men. Two public GPs, four private GP's and one nurse were non-Omani. Potential participants were initially contacted by telephone. Those who agreed to participate were then interviewed individually at a time and place of their own choice. Verbal consent was obtained from all the participants, who were informed of the objectives and duration of the study. They were also informed that the interviews would be digitally recorded and that the information gathered would be kept confidential.

6.4.2 Data analysis

We analyzed the transcripts using content analysis (Graneheim & Lundman, 2004). The meaning units were first identified by highlighting phrases in the transcripts. Then, they

were labeled as condensed meaning units (CMU). The CMUs were labeled with codes, and different sub-categories were created, by grouping together similar codes. Different comparable sub-categories were then assembled to make categories. Categories were analyzed and combined into three different themes.

6.5 STUDY IV: BIODIVERSITY AND CLUSTERING OF *M. TUBERCULOSIS* ISOLATES USING SPOLIGOTYPING

6.5.1 Data collection

M.tuberculosis clinical isolates were obtained from the National Tuberculosis Reference Laboratory (NRL), Central Public Health Laboratory (CPHL) in Oman. These isolates were collected between the years 2005 to 2007 and cultured on Lowenstein-Jensen medium at the NRL. The total number of positive cultures was 176, 212 and 227 for 2005, 2006 and 2007 respectively. We included all available isolates from the year 2007. For the years 2005 and 2006, we selected around 30 % of all isolates using a computer-based randomization.

Spoligotyping was performed using a commercial kit (Isogen Bioscience BV, Maarssen, The Netherlands). Detection of hybridizing DNA was done by incubation of membrane with chemiluminescent ECL (Amersham) detection liquid, followed by exposure to X-ray film (Hyperfilm ECL; Amersham) in accordance with the instructions of the manufacturer. *M.tuberculosis*, H37Rv and *M. bovis* BCG DNA were included as references.

6.5.2 Data analysis

The spoligotype patterns were analyzed, recorded and corroborated manually by two independent observers. The individual spoligotyping patterns were then compared with SpolDB4 database using spoligotype search function under the data base query tool (<http://www.pasteur-guadeloupe.fr:8081/SITVITDemo>). Major genetic lineages were assigned according to the shared-type number provided in SpolDB4. An isolate was defined as shared type if the same spoligotype was found in the database. A cluster is defined if more than one isolate had similar pattern. Clustering proportions were computed by dividing the number of isolates that were in clusters by the total number of isolates.

6.6 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the Medical Research and Ethics Committee, College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (MREC-222). In studies II and III, the participants were assured that the study was confidential, and that all the data was only to be used for research purposes. Anonymity was assured in study II, by not collecting individual details related to name, health centre or clinic. The participants in study III were informed about the objective of the study and consented verbally. The participants were allowed to decline to participate, before, during or after the interview, if he or she felt the need to withdraw.

7 MAIN FINDINGS

The main findings of the four studies are summarized in table 5.

Table 5: A summary of the main findings for each study

I	II	III	IV
TB notifications 1981-2005	Suspicion and knowledge of TB	Perceptions and experiences of health care providers	Spoligotyping of 312 <i>M.tuberculosis</i> isolates
Remarkable decline in TB notifications with improved socioeconomic status (1981-1993).	Low level of suspicion and knowledge among GPs.	Repatriation policy affects the underprivileged immigrants.	A clustering proportion of 69%.
Slower decline in TB (1994-2005).	Private GPs are less likely to suspect TB compared to public GPs.	The private health care sector is not involved in TB control.	Higher clustering proportion among Omanis compared to the migrant workers.
The elimination target of 3 per 100,000 population target was not achieved.	Private GPs have less knowledge of TB compared to public GPs.	Omani patients with TB are poor.	Around 50% of the migrant workers share their strains with Omanis.
Concentration of disease among the elderly and the poor.		Health care system needs to improve policies in TB control to reach elimination.	Predominance of Indian subcontinent TB strains.

7.1 RAPID DECLINE FOLLOWED BY SLOW DECLINE OF NOTIFICATION RATES 1981-2005 (STUDY I)

Figure (5) shows crude notification rates per 100,000 population among nationals by TB form (type) (1981-2005), and GNI per capita (PPP) (1981-2003). The notification rate of all TB forms declined by more than 85%; from 82 in 1981 to less than 12 per 100,000 population in 2005. (Average 8.4% per year (95%CI: 7.3, 9.4). The smear-negative case notification rate declined by 16% per year (95%CI: 14.4, 17.5) compared to 7.5% per year (95%CI: 6.8, 8.3) for smear positive cases during the same period, with a small non-significant decline in extra pulmonary cases of only 0.8% per year. During the same period, the GNI per capita increased from 4,680 International Dollars

in 1981 to 13,250 in 2003, corresponding to an increase of 339 International Dollars per year (95% CI: 328, 352).

The decline in notification rates varied over time. The calculated annual decline in notification rates for all TB cases was 15.8% per year (CI: 14.7, 16.8) during the period from 1981 to 1993, compared to 3.6% per year (CI: 2.3, 4.8) during the second period (1994 to 2005). The decline for smear-negative notification was 18.3% per year (95% CI: 16.6, 19.9) during 1981-1993 compared to 5.5% per year (CI: 0.9, 9.9) during 1994 – 2005. Similarly, smear-positive notification rate declined by 7.9% per year (CI: 6.4, 9.4) during 1981-1993, compared to 2.3% per year (CI: 0.7, 3.9) during 1994-2005.

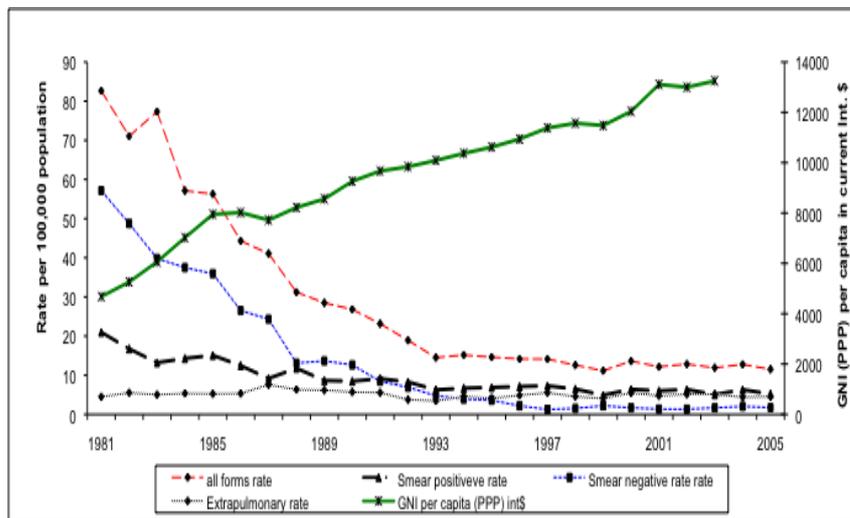


Figure (5): TB notification rate among nationals for each form (1981-2005) and Gross National Income (PPP) per capita (1981-2003)

7.2 CONCENTRATION OF TB AMONG HIGH RISK GROUPS (STUDIES I & III)

During the period from 1993 to 2004, the notification rates per 100,000 population of smear positive cases and smear negative cases were higher in the age group more than 49 years, compared to other groups with no significant decline during the same period. Figure 6 presents age specific notification rates of national smear positive cases for each age category in the year 2005.

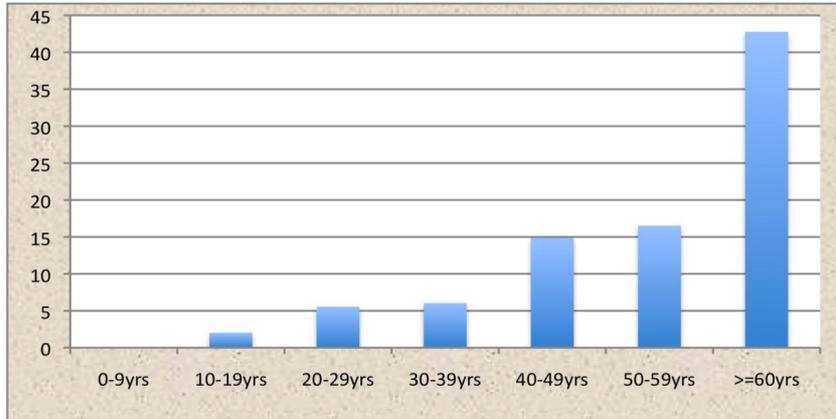


Figure 6: Age specific notification rates of smear positive case per 100,000 among Omanis during the year 2005.

The study also showed that TB is concentrated among individuals with low socioeconomic status. In study I, approximately 95% of 329 TB cases diagnosed in 2004 and 2005 lived in households with per capita income lower than the average GNI per capita of 800 USD (figure 7). In addition, in study III the health care providers referred to their patients as malnourished, living in poor, crowded conditions. They linked this to poverty and low income.

“I feel that poor housing is playing a role in this . . . I see that patients are in poor housing and they don’t have good nutrition. For example out of twenty patients fifteen of them are those who are earning for their families and they have low income ” (Public, Omani, study III)

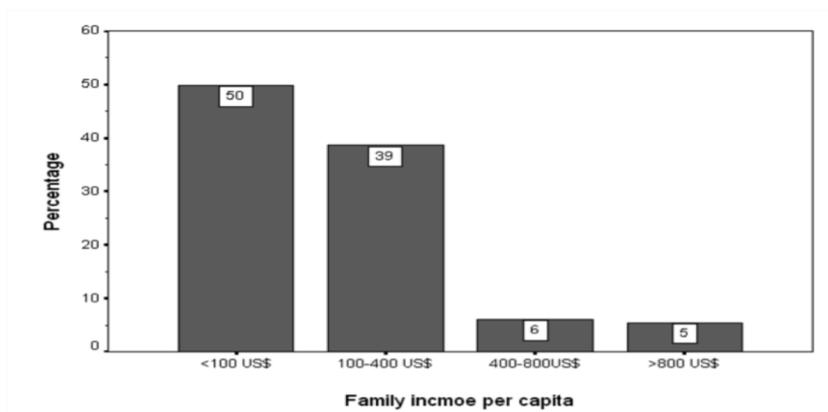


Figure (7): Percentage of national TB cases (n=329) according to family income per capita (2004-2005)

7.3 TB: A FORGOTTEN DISEASE (STUDIES II & III)

In study II, health care providers, both private and public, were having low suspicion of TB. Table 6 presents numbers and percentages of private and public GPs who considered TB as one of the three possible diagnoses in any of the five clinical vignettes describing TB-cases. In the first vignette, for example, where the patient was having 5 weeks of cough, and TB should have been the first & most likely diagnosis, 32.3% of the overall GPs didn't consider TB at all as a likely diagnosis. This finding was also supported by health care providers saying that GPs don't suspect TB and miss the diagnosis of TB (study III).

“I realized people have forgotten about TB. The physicians, the general practitioners think that TB doesn't exist in Oman” (Public, Omani)

Table 6: Numbers and percentages of GPs who considered TB as one of the three possible diagnoses in any of the 5 clinical vignettes describing TB-cases (study II)

Clinical Vignette	Private N (%)	Public N (%)	All N (%)
TB case 1 (5 weeks cough, loss of weight)	93 (60.4%)	81(78.6%)	174(67.7%)
TB case 2 (HIV with prolonged cough)	119 (77.3%)	83 (80.6%)	202(78.5%)
TB case 3 (loss of weight, night sweats)	112(72.7%)	91 (88.3%)	203(79.0)
TB case 4 (cough with haemoptysis)	109 (70.8%)	78 (75.7%)	187(72.8)
TB case 5 (Cough, crackles at the apex)	119 (77.3%)	96 (93.2%)	215(83.7%)

7.4 SUPOPTIMAL AND UNINVOLVED PRIVATE HEALTH SYSTEM (STUDIES II, III)

In study II, although all GPs had a low TB suspicion, a private GP was less likely to have diagnosed or followed up a TB case in the last year compared to a public GP (10.4% versus 64.1%; $p < 0.001$). The median scores of all GPs were 11 and 8 for suspicion and knowledge, respectively (table 5). For both scores private GPs scored significantly lower than public GPs ($p < 0.001$). Significant difference in knowledge related to diagnosis ($p = 0.037$), treatment ($p < 0.001$) and contact screening ($p = 0.041$) was observed. In addition, in the multiple analyses, sector of work was the only variable associated with TB suspicion score with private GPs scoring 1.6 points less than public GPs (95%CI; -2.9, -0.31). In the knowledge score, private GPs also scored 1.5 points less than public GPs (95%CI; -2.74, -0.28) adjusting for potential confounders (table 7).

Furthermore, in study III, the second theme was the ‘private sector: a criticized and forgotten key player’. This theme emerged from both public and private providers’ perceptions of the private health care sector’s role in TB care and control in Oman. The health care providers addressed the need to integrate the private sector into the TB control program.

“There should be some communication with MOH regarding the infectious diseases especially TB, what to do when you come across TB cases, where to send? There it should be regular communications”.
(Private, expatriate)

The private practitioners also attributed their difficulties in providing optimal TB care, to the lack of proper facilities and training for TB diagnosis and treatment.

“The private sector needs to look at the quality in their labs. I’m sure that there are cases that are being missed. They have small labs. The stains are there for years in those labs”. (Private, Omani).

Table 7: Estimated partial regression coefficients, with 95% confidence intervals in brackets, in multiple robust linear regression analyses with TB suspicion score and mean TB knowledge score as dependent variables (95% CI). For binary variables the coefficients are estimates of the difference between the means at the two levels.

Factor		TB Suspicion Score	TB Knowledge Score
Independent variable		Dependent variable	Dependent variable
Sector	Public	Ref.	Ref.
	Private	-1.61(-2.92, -0.31)	-1.51(-2.74, -0.28)
Gender	Female	Ref.	Ref.
	Male	0.63(-0.28, 1.55)	0.04(-0.82, 0.90)
Nationality	Not-Omani	Ref.	Ref.
	Omani	-0.10 (-1.86, 1.65)	0.97(-0.70, 2.63)
Duration of Practice	≤ 5 years	Ref.	Ref.
	> 5 years	0.82(-0.99, 2.65)	1.0(-0.48, 2.46)
Attended TB training course during last 5years	No	Ref.	Ref.
	Yes	-0.33(0.86, 1.65)	1.97(0.71, 3.24)
Found/followed up a TB case last year	No	Ref.	Ref.
	Yes	0.66(-0.53, 1.86)	0.86(-0.25, 1.96)
TB Knowledge score		0.10(-0.05-0.24)	Not Applicable

7.5 INADEQUATE TB CONTROL AMONG MIGRANT WORKERS (STUDIES I, III & IV)

Migrant workers contributed to around 21% of the total cases notified between 1981 and 2005 and around 40% of the total smear-positive cases notified during the same period. During the period from 1993 to 2005, the notification rate of all TB forms among non-nationals had declined by 6.0% per year (CI: 3.7, 8.2). The decline of notification rate of smear-negative cases was by 15.6% (CI: 9.4, 21.4). No significant decline in smear positive cases was observed during the same period. In addition, non-nationals have lower smear-negative case notification rates when compared to nationals ($p < 0.01$).

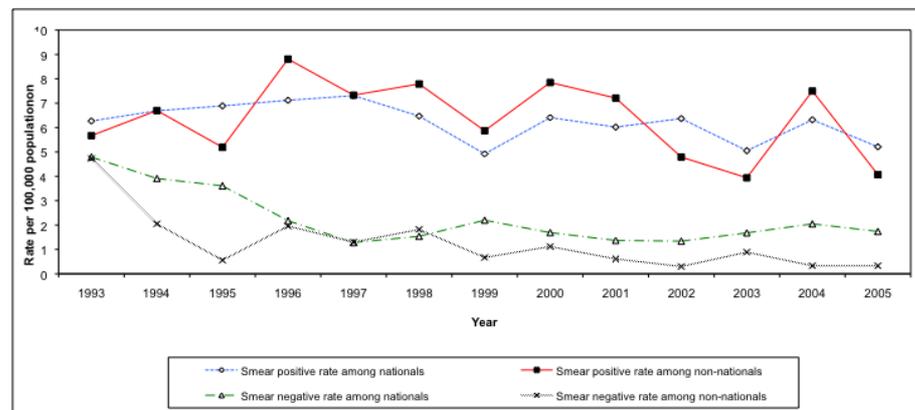


Figure 8: Smear positive and smear negative notification rates per 100,000 population among nationals and non-nationals (study I).

In study III, the first theme was ‘‘underprivileged expatriates: the threat of repatriation’’. This theme emerged from health care providers perceptions of how expatriates (migrant workers) impact on the TB burden and on TB control in Oman. They perceive TB as an imported disease, which is brought into Oman by expatriates. However, they also recognize that expatriates live on the fringes of Omani society and are disadvantaged socially and economically by the existing policy of repatriation.

‘‘I think expatriates are the most important cause of the prevalence of TB in Oman, especially expatriates coming from Asia . . . it may take three months for him to come for the check-up. So during this period he can infect persons from Oman. . . I think especially for TB, it is not enough to screen them every 2 years; they should be screened every 4 or 6 months.’’
(Public sector, expatriate)

Both public and private participants described the expatriates, mainly unskilled or semiskilled workers, as socially and economically vulnerable. The public health care providers acknowledged that there was no information available on the health status of these workers, as they mostly go to private practitioners.

“The living conditions, hygiene and crowdedness are causes of spreading TB among expatriates. If you take the upper class of the expatriates they rarely have TB, it is the lower class that have it. We have to maintain some basic standards of life for them as a policy” (Private, expatriate).

In addition, participants pointed out that the policy of repatriation is counterproductive. They pointed to the social and economic disturbances imposed on the expatriates diagnosed with TB, which results from the repatriation policy. They urged that this policy be re-evaluated, and that policies aimed at improving the health seeking behaviors of the expatriates should be adopted.

“We had a staff nurse who had small cavitations in her lungs. She told me: ‘what do you think I have’. I told her that being from India, TB should be kept in mind. Next day the patient is not on the bed. She went home on leave . . .we should treat expatriates like Omanis. Deporting them is against human rights” (Public, Omani)

Furthermore, in study IV, clustering of TB among both the migrant workers and the nationals was observed. Around 50% of the immigrants were in the same cluster as Omani patients. A total of 15 clusters included both Omanis and migrant workers, while 4 clusters had only migrant’s isolates with 2 isolates per cluster. The Beijing strain family was found in 7 Omani patients and 6 migrant workers (figure 9). Therefore, an ongoing transmission between the two groups is possible, which needs further evaluation.

In addition, study IV showed that *M.tuberculosis* Indian family lineages, i.e CAS1_Delhi, CAS and EAI5, were the predominant strains. EAI3_IND was found in 4 Omanis and 5 immigrants. CAS1_Delhi family had also mixture of both Omanis and migrant workers, but predominately Omanis. CAS1_Delhi cluster had the highest number (6 isolates) of resistant strains for INH and all were Omanis (figure 9).

8 METHODOLOGICAL CONSIDERATIONS

8.1 EPIDEMIOLOGICAL CONSIDERATIONS OF STUDY I

The validity of case reporting is essential for the results in study I. If there are cases that are not notified to the NTP, the notification rates reported in study I will lead to underestimated incidence rates. As TB care is free and accessible to all Omani patients, it is likely that TB notification rates among the Omani nationals come close to the true incidence rates. In contrast, the possibility that some migrant workers were not notified to NTP because of repatriation policy, may have led to underestimation of the incidence rates among the migrant workers. Crude TB notification rates were presented in the paper. The age structure of the population of Omani nationals has changed substantially towards a larger percentage of elderly people between the two censuses 1993 and 2003. However, for the study of TB burden, it was considered more important to describe the overall change of TB notification rates over the years than to give age and sex standardized rates. Due to data limitations, age and sex specific rates could be compared only for the years 1993-2004. The lack of data on migrant workers made the presentation of age and sex specific rates for this group unfeasible.

The decline of TB notifications may have started before the establishment of the national TB control programme, but no data was available before 1981. Information at the individual level on family income per capita for patients diagnosed between 2004 and 2005 was used for some analysis but missing data for some patients may have introduced selection bias. The relationship between income and TB is presented at the ecological level. No conclusions at the individual level can be made.

8.2 VALIDITY AND RELIABILITY OF THE QUESTIONNAIRES IN STUDY II

Vignettes or written case simulations have been widely used to assess clinical knowledge and competence, though their use is controversial when assessing practice (Peabody, Luck, Glassman, Dresselhaus, & Lee, 2000). They were, however, suitable in our study, as our intention was to assess knowledge and competence, and not clinical performance or action. Vignettes have the advantage of being easily administered, less costly and usable across different types of clinical practices. A study showed that measuring quality with vignettes consistently produced scores that were close to the standardized patient method (Peabody et al., 2004). However, the reliability of the questionnaires, based on Chronbach's alpha was suboptimal. Further validation is needed to extend the use of these questionnaires for formal evaluation of clinical practice.

Public GPs as a group of physicians (8 to 10 GPs in each health centre) share together knowledge and experiences to a greater extent than private GPs, where less practitioners in each private clinic practice together. In addition, around 20% of the GPs working in the public sector were not available during the study period. This may have introduced a selection bias. Nevertheless, it is not likely that those GPs to be different from GPs participated in the study. Non-participation was mainly because some of the GPs were on their regular leave or attending some MOH courses. Generalization of the

results to whole Oman cannot be done formally as the GPs studied were only from Muscat region.

8.3 TRUSTWORTHINESS AND TRANSFERABILITY OF THE FINDINGS OF STUDY III

Trustworthiness is the concept used to assess the validity of the findings of qualitative research (Patton, 2002). In study (III), there were few concerns that could have affected the trustworthiness of the study. Firstly, the interviews were carried out in English, which is not the mother tongue of many of the health care providers. Omani participants were encouraged to use Arabic terms, whenever they found it difficult to use the English words or expressions. The interviewer being from a public university might have made the private health participants more hesitant to express their true perceptions. Similarly, the public health participants might have been reluctant to express strong views regarding the public health system. However, the findings do reveal several critical views of the public health care sector, which suggests that the interview situation did allow for discussion of sensitive topics.

Transferability is the term used in qualitative research in parallel to the external validity or generalizability in quantitative research (Malterud, 2001). The transferability of the results of study III must be theoretical or analytical since the interviewees are purposively selected (Kvale, 1997). This means that we can generalize the results to contexts that theoretically are similar to the one studied. However, there are only 17 purposively selected interviewees that do not represent the study context well. E.g. there is an under-representation of private GPs that limit the transferability of the results.

8.4 VALIDITY AND GENERALIZABILITY OF THE FINDINGS IN STUDY IV

RFLP and MIRU-VNTR coupled with spoligotyping are the current standard methods for genotyping of *M.tuberculosis*. We have carried out only spoligotyping. An overestimation the clustering proportion is likely due to the lower discriminatory power of spoligotyping as compared to RFLP. The study was not complemented with contact tracing investigations. However, contact tracing investigation has limited value for capturing the whole transmission picture among some groups especially immigrants (Pfyffer et al., 1998). Study IV also didn't include information about risk behaviours of the patients to be related to the clustering. Such information could not be made available.

Sampling of the isolates from the years 2005 and 2006 is also a source of selection bias, which is common in some of the molecular studies on TB (Nava-Aguilera et al., 2009) (M. Murray, 2002). The selection bias in this study may have underestimated the true clustering proportion, which limits the generalizability of the findings. As this is the first TB molecular epidemiology in Oman, it shall be considered as a snapshot study with a purpose to shed light on the clustering and biodiversity of *M.tuberculosis*. Follow up, more extensive studies will provide additional characterization of TB transmission dynamics in Oman.

9 DISCUSSION

9.1 FACTORS INFLUENCING TREND OF TB NOTIFICATIONS

In the first half of the 20th century, most of the industrialised countries were experiencing a steady decline in TB incidence (Lonnroth et al., 2009). Because this took place before the discovery of the anti-TB treatments, a debate started about whether it was socioeconomic developments, (including improved living conditions) or medical interventions, or sanatoria, or mass screening, that had played the major role for this decline (Wilson, 2005). More recently, in China a significant decline in the burden of TB between 1990 and 2000 can be attributed to DOTS, as well as to the positive economic growth in the country (Squire & Tang, 2004). Another example of this comes from Russia. The deterioration in the 20th century followed by the recent improvements in TB control in Russia, can both be explained by the vitality of the TB control program there, as well as by socioeconomic changes (Dye, 2005).

In a recent analysis of TB data from 134 countries, the contribution of TB control programs was seen as important to the prevention of deaths caused by TB, but their role in reducing the incidence of TB was not clear. Factors such as high income, high expenditure on health and low child mortality were seen to be more important predictors of TB incidence in those countries than TB control programme measures (Dye, Lonnroth, Jaramillo, Williams, & Raviglione, 2009). Another analysis also found that countries with improvements in overall population health and health services had a lower incidence of TB (Oxlade et al., 2009).

In Oman, during the last 4 decades, substantial achievements in infectious disease control, including TB, was reported (Hill, Muyeed et al. 2000; Ganguly, Al-Shafae et al. 2009). Study I showed that Oman was able to reduce the burden of TB by more than 85% during the period 1981 to 2005. NTP activities, which started in 1981, may have played an important role in this success. Implementation of DOTS may have contributed to the decline of smear positive notification rates, especially among the 15 to 49 years age group, in the last 10 years. In addition, since 1996, the treatment success rate was on average more than 90%. Only 12 patients defaulted from treatment since implementation of DOTS. On the other hand, the increase in GNI per capita may have increased access to health care, including more resources to the NTP, improved health services, and the general health of the population, which directly reduced the burden of the disease. Therefore, it is viable to consider the process of positive economic growth in the country, as another factor to have played an important role in the declining trend of TB during the last 25 years in Oman.

Currently, both high and low-income countries are experiencing a slow decline in the incidence of TB (WHO, 2009a). Oman is no exception, in the last 15 years, despite DOTS implementation, a slower decline of TB notifications has been observed. The target of 3 per 100,000 was not achieved and the target of 1 per 100,000 by 2015 (previously set for 2010) might not be achieved either. This slow decline is not

explained by MDR-TB or HIV-TB co-infection, which are related to the increased number of TB cases worldwide (WHO, 2009a). In Oman, only 13 MDR-TB national cases were reported in the last five years, with no new MDR-TB cases in the last two years (Mohammadi, Nassor et al. 2008). Furthermore, being a country with a low HIV prevalence, having less than 0.5% of the adult population estimated to be infected with HIV (WHO, 2009c), TB-HIV also doesn't explain the current slow decline of TB notification rate.

9.2 THE ELDERLY AND THE POOR: NEED FOR ADDITIONAL CONTROL EFFORTS

Another explanation of the slow decline is the concentration of TB cases among the high-risk populations. Individuals at high-risk of active TB, in low incidence countries such as Oman, may include the elderly, the poor and immigrants from high prevalence countries (Tocque et al., 1998). While the notification rates were declining at the rate of 4% per year for the age group 15-49 years, notification rates among the elderly didn't show significant change. In 2005, notification rates were three times higher among the elderly (more than 60 years), as compared to younger age groups. This picture could be explained by the epidemiological concepts of cohort and age effects. In countries with socio-economic development, the longevity of its individuals increases. Because these countries experienced higher TB rates in the past, their current elderly population has a higher probability of having LTB (cohort effect) (Davies, 1999). However, since immunity is also lowered by the aging process, the elderly are at a higher risk of reactivation of LTB (age effect) (Lesourd & Mazari, 1999). In addition, elderly people with chronic diseases, e.g. diabetes, are at high risk of developing active TB (Jeon & Murray, 2008). In Oman, as the life expectancy at birth has increased, and chronic diseases are a major public health problem (Al-Lawati, Mabry, & Mohammed, 2008), the institution of screening guidelines for the elderly, especially those at high risk of TB could be of importance for TB control in the country.

Another and more important TB risk factor is poverty. At the ecological level, countries with a high Gross Domestic Product (GDP) per capita have a lower incidence of TB (Janssens & Rieder, 2008). The relationship can also be seen within regions in a country. In the US, poverty and income inequality at the state-level has been seen to be associated with variations of TB notification rates (Holtgrave & Crosby, 2004). It was also seen that poor neighbourhoods had higher TB incidence rates as compared to neighbourhoods with higher socioeconomic status (Acevedo-Garcia, 2001).

In study I, most of the reported TB cases were living in households earning below the national GNI per capita of 8,800 USD per month. More than 50% of them were living in households earning less than 100 USD per month. In addition, study III found that health care providers perceived Omani TB patients as being mostly poor, indicating that TB is concentrated among the poor in Oman. An association between TB and social deprivation was found in some studies. But it is not yet fully understood how socioeconomic factors influence the risk of TB (Lonroth et al., 2009). In a recent study, with a social epidemiology framework carried out in South Africa, socioeconomic factors at both individual and community level, influenced the odds of having TB (Harling, Ehrlich, & Myer, 2008). This suggests that poverty and social

inequality increase the risk of TB, through some causal pathways. Conversely however, in a cross-sectional study carried out in Zambia, a high socioeconomic position was associated with higher odds of TB infection (Boccia et al., 2009). This calls for more research on TB and poverty, so as to understand the causal links and mechanisms of interactions between socioeconomic factors and TB.

In short, studies I and III found that TB is common among the poor and the elderly in Oman. This may partly explain why TB notification rates are not declining further, and why the elimination target of 3 per 100,000 population was not achieved. More research is needed to ascertain both the proximal and distal risk factors of TB disease and LTB among nationals and migrant workers in Oman. This would help to identify other high-risk groups for targeted interventions, which could include screening for active and latent TB, and provision of treatment. In addition, primary prevention strategies, e.g. improving the socioeconomic status of the poor and of their neighbourhood, should also be the focus of an intervention. However, identifying high-risk groups for TB should be done cautiously, and ethical issues, e.g. the stigma of such interventions, need to be considered.

9.3 INADEQUATE SUSPICION OF TB AMONG FRONTLINE HEALTH CARE PROVIDERS: A HEALTH SYSTEM CHALLENGE

To stop the transmission of TB there is a need to accurately identify contagious patients, and to treat them immediately and effectively (Lienhardt & Ogden, 2004). Therefore, prompt diagnosis of TB is fundamental to TB control in any setting, and has positive impacts on both clinical and public health outcomes (Sreeramareddy, Panduru, Menten, & Van den Ende, 2009). However, delay in diagnosis of TB, both patient delay and health system delay, is a challenge to TB control, and it is common in both low and high-income countries (Storla et al., 2008). As longer delays cause the patient to be more contagious, an early diagnosis of TB will reduce the number of future morbidities and mortalities associated with active TB disease (Enarson et al., 1978). Treatment of active pulmonary TB has positive externalities; each case diagnosed and then adequately treated will prevent other future TB cases.

In study II, some of the GPs, didn't suspect TB in the written vignettes. In addition, in study III, health care providers acknowledged that they miss TB diagnosis and that TB is being forgotten in their practices. A possible explanation of this could be, that as Oman is already a low incidence country, the probability of encountering TB patients in such settings is small. Such trivial exposure to TB cases reduces the clinical experiences of TB. Less awareness of TB among health care providers may lead to diagnostic delays (Sarmiento, Hirsch-Moverman, Colson, & El-Sadr, 2006). Study II found that there is a lack of training courses related to TB. Less than 15% of the GPs attended any TB training courses during the last 5 years.

NTP in Oman needs to address the health care providers awareness of TB as a key issue to improve TB control, so as to avoid health system related delays in diagnosis. A recent randomized controlled trial showed that educational interventions aimed at promoting TB screening are effective in increasing TB detection (Griffiths C et al., 2007). Similar contextualised interventions in Oman may improve the ability of GPs

to promptly diagnose and act upon TB cases. In addition, WHO recommends that the Practical Approach to Lung Health (PAL) strategy be implanted in the primary care settings, to improve TB detection and improve the management of other respiratory conditions (WHO, 2004b). Most of the literature of PAL comes from the WHO literature, and there is limited research on the effectiveness of this strategy (Murray, Pio, & Ottmani, 2006). In a pragmatic randomized trial, which measures the effectiveness of interventions, carried out in South Africa, PAL has increased the TB case detection rate (Fairall et al., 2005). Despite the difficulties involved with implementation of PAL (WHO, 2007), its integration within primary health care centres in Oman may serve as a good tool for improving TB case detection among GPs.

9.4 PRIVATE HEALTH SECTOR: NEED FOR EVALUATION AND INTEGRATION WITHIN NTP

Due to economic development, and in response to an increasing number of migrant workers, the number of private practices has increased significantly over the last few years in Oman (Ministry of Health, 2008). However, Oman has a classical view of TB diagnosis and treatment, in which only the public health institutions are considered suitable for TB management (Lonnroth, 2000). Private health care establishments are not allowed to treat TB, and may only refer suspected cases where they will be re-evaluated in a public health institution.

In settings with a highly privatised health system, such as India for example, patients with chronic cough prefer to seek care from a private practitioner (Fochsen, 2007). Private practitioners inability to diagnose TB, and the effect this has of delaying the diagnosis of TB patients, has been reported in high as well as low incidence countries (Golub et al., 2005; Lonnroth, 2000). In study II, private general practitioners were less suspicious of TB in a written clinical vignette and also had lower knowledge of TB than their counterparts in the public health system. A large number of private practitioners in Oman have received their education in countries with a high incidence of TB, so it is surprising that suspicion of TB is low among private practitioners.

Health care providers, including those working in the private sector, acknowledged that private clinics have difficulties in TB diagnosis (study III). This may indicate a lack of competence to make early diagnosis in the private health system. Furthermore, participants in study III pointed out that there is a lack of integration and collaboration between the private and public health systems, and that the private health care system is being overlooked, as it is not directly involved in TB control.

WHO suggested Private-Public Mix (PPM) strategies as means of enhancing TB care in the private sector and of involving private providers in TB control (Uplekar, 2001). A package of different tools was developed to increase collaboration between the private and public sector. These include different forms (for example, notification forms, laboratory forms and feedback forms), guidelines for TB treatment and diagnosis and contracts between private and public health sector (WHO, 2003). The implementation of PPM was found to improve the TB detection rate by 25-30% (Lonnroth et al., 2006). In addition, other advantages are gained from PPM. These include: improved access to care and quality of diagnosis, decreased delays in

diagnosis, standardization of treatments, improvements in surveillance, and lower costs for patients (WHO, 2004c). PPM also has the potential to increase case detection among the poor and the most vulnerable TB patients (Malmborg et al., 2006)

The new stop TB strategy demands engagement of all health care providers in TB care (Raviglione & Uplekar, 2006). To improve TB care delivery in Oman, strategies and policies to regulate and integrate the private sector are needed. For example, NTP may allow some private health care providers to have access to the sputum microscopy services in the primary health care centres, and to sputum culture services in the central public health lab (Needham et al., 2001). Treatment can also be provided by some certified private health establishments under the supervision of the public health authorities.

However, involving the private health care system in TB care is not that simple and straightforward. Public practitioners in study III expressed concerns about the priorities of the private sector, and perceived private practitioners as being overly influenced by economic imperatives. On the other hand, private practitioners consider the public health practitioners to be inefficient in the care process. This conflict of values between the two sectors makes it difficult to have a PPM strategy. (De Costa, Johansson, & Diwan, 2008). In addition, as the private health sector is heavily loaded with patients, both nationals and migrant workers, it becomes necessary to evaluate its general performance and competencies and the services provided.

9.5 TB CONTROL AMONG MIGRANT WORKERS: A CHALLENGING TASK TO TB ELIMINATION

In many high-income countries with a low incidence of TB, the number of migrants from high incidence countries has been increasing (Frothingham, Stout, & Hamilton, 2005). As a consequence, TB associated migration has become an important public health issue in such countries (MacPherson & Gushulak, 2006). Many of these countries have legislation in place with regard to temporary migrants such as visitors, foreign students, and skilled and unskilled labour. Although the expected individual and public health benefits of these legislations have been questioned (Dasgupta & Menzies, 2005), many of the legal migrants are either screened offshore before departure, e.g immigrants to Canada, or are screened on arrival, as in Europe (MacPherson & Gushulak, 2006).

In Oman, migrant workers from high incidence countries are screened for active TB in their home country before being granted their work permit. Only certified clinics are allowed to carry out the clinical evaluations and chest x-rays, of immigrants in their home countries. Repeat screenings are carried out within one month of arrival and then every two years. If active TB cases are confirmed, or individuals are suspected of having TB, based on abnormal chest x-rays, they are normally not granted a visa. Such measures have been effective in reducing the burden of TB in the US (Liu, Weinberg, Ortega, Painter, & Maloney, 2009), for example, and may have contributed to better TB control in Oman as well. However, as an extra measure to prevent TB transmission, migrant workers developing TB during their stay in the country are deported (after conversion to smear negative). This deportation is commonly referred to as “the

repatriation policy". The overall perceptions of the health care providers who participated in study III, was that repatriation of migrant workers presents a major challenge to TB care and control in Oman, and that it needs to be removed.

Fear of repatriation prevents immigrants from accessing health care services, especially when they know or suspect they may have TB (Littleton et al., 2008). Similar concerns have also been expressed by many of the participants in study III. Examples of migrant workers with TB going unreported were given, based on the experiences of participants. The delay in seeking care by the migrant workers may result in increased transmissions in the community. These transmissions may occur among the migrant workers themselves, or also between migrants and Omanis. Furthermore, poorly and inadequately treated TB patients may result in the development of drug resistant TB. Transmission and the treatment of drug resistant TB have several economic and public health implications. Therefore, such potential outcomes of the repatriation policy make it counterproductive, and may have future unprecedented implications. The ethical concerns of this repatriation also need to be considered by the NTP.

Furthermore, in study III, health care providers perceived the majority of migrant workers as living on the fringes of society and as having many socioeconomic difficulties. Migrant workers are therefore more likely to fall outside the overall health care system, where their access to and utilization of the health care system is largely unknown. Research on the health seeking behaviors of migrant patients, especially those with low wages, is important. National disease control authorities should also give more attention to improving the socioeconomic environment of the migrant workers, and their access to affordable and appropriate health care services.

Immigrants from high incidence countries to low incidence countries tend to have their own *M.tuberculosis* strains, and it is unlikely that transmission from immigrants to natives occur (Dahle, Eldholm, Winje, Mannsaker, & Haldal, 2007; Lillebaek et al., 2001). In contrast, around 50% of the migrant worker's isolates spoligotyped in study IV were reported to be in clusters with Omani isolates. As one third of the total population consists of migrant workers, the interpretation of the observed clustering as possible ongoing transmission between the two groups should be considered. However, this needs to be further evaluated and studied, with stringent molecular characterization of clusters that contain both Omanis and migrant workers. In addition, the use of a multi-disciplinary approach to study the transmission of TB is important. For example, coupling molecular epidemiology with investigations on social networks (Hollm-Delgado, 2009) and also a Geography Information System (GIS) (Moonan et al., 2004) could give a better picture of the transmission dynamics of TB.

Furthermore, in study IV, the clusters identified were from clades predominately found in India (Singh et al., 2007). There is a predominance of CAS sublineages (Central Asia Strain), especially CAS1_Delhi. Other important Asian clades, which show clustering among our isolates, are EAI family lineages, which are also common in India and Southeast Asia (Singh et al., 2004). Such findings can be explained by the geographical proximity and the historical relationship between Oman and India, which has existed for centuries because of the coastal trade between the two countries.

The current TB elimination targets take account of eliminating TB among Omanis only. But, TB elimination is not feasible, if TB control among migrant workers is not adequately addressed. Specific TB elimination targets should also include elimination among migrant workers. To improve TB control among migrant workers in Oman, the repatriation policy needs to be revised, and alternative policies and strategies need to be developed. These could include short-term interventions, focusing on early detection and treatment of active TB and latent TB, rather than on post treatment deportation. A long-term strategy to increase efforts towards global control of TB, especially in high incidence countries is recommended. These could include technical and financial support for TB control programs in these countries, as well as funding for further research, which could result in more cost-effective and sustainable outcomes (Menzies, 2001). Interventions to improve housing plus overall living circumstances, as well as institution of compulsory health insurance system for the migrant workers are also needed.

10 CONCLUSION

This is the first study of TB control in Oman looking at the possibilities and challenges to TB elimination. The main conclusions from this study are:

- The notification of TB in Oman decreased by 85% during the period from 1981 to 2005.
- The GNI per capita increased from 4,680 International Dollars in 1981 to 13,250 in 2003, corresponding to an increase of 339 International Dollars per year.
- Economic development and National Tuberculosis Control Programme activities may have contributed to the significant reduction of the TB burden over the last 25 years in Oman.
- Despite the implementation of DOTS program though, a slower decline is observed in TB notification rates during the last 15 years.
- Many challenges might hinder the country from achieving the specified TB elimination target of 1 per 100,000 Omani national population by the year 2015. These may include;
 - High burden of TB among high-risk groups, especially the poor and the elderly.
 - Low suspicion of TB among the general practitioners.
 - Suboptimal and un-involved private health care system.
 - Repatriation policy may be an obstacle for TB control among migrant workers and it needs to be reviewed.
- High proportion of the migrant workers *M.tuberculosis* strains were within the same clusters as the Omani strains, which suggest possible transmission between the two groups.

11 RECOMMENDATIONS

Based on the findings of this thesis, the following recommendations are given for the National TB control Programme to consider. The aim is to improve TB control, and to accelerate the decline of TB notification rates and promote early TB elimination:

- The National Control Programme needs to explicitly address high-risk individuals in Oman with a particular emphasis on the elderly and the poor
- Access to high quality and complete data on TB patients was limited in this study. For further research, improved notification, registration and data management is necessary.
- Conduct educational interventions that can increase the suspicion and knowledge about TB among private and public health care providers.
- The integration of the private sector into the NTP program is very important and can increase case detection among patients attending private clinics. A Private Public Mix (PPM) strategy needs to be drawn up. The involvement of private practitioners in setting the objectives and the process of any PPM strategy is indispensable.
- Cancellation of the current repatriation policy along with development of strategies for early identification of TB among the migrant workers to avoid transmission. In addition, Oman may contribute to global TB control, especially in high incidence countries through bilateral or multilateral co-operation.
- Public health authorities should give more attention to optimizing the socioeconomic environment of migrant workers and to improving their access to affordable and appropriate health care services.
- Support routine nationwide genotyping of all strains, and couple it with high quality data on contact investigations, to have a clear picture of transmission dynamics of TB and identify factors associated with recent transmission.
- Invest in research in the field of tuberculosis to overcome scientific difficulties with regard to TB elimination, which include vaccine development, rapid and reliable diagnostic tests and effective and short duration treatment.

12 FUTURE RESEARCH

This thesis represents the first study of TB epidemiology and TB control in Oman. More research in the area of TB is still needed and essential for NTP to draw evidence-based policies. More research is likely to give more insight into the epidemiology of TB and challenges to elimination, not only for Oman, but also for the entire GCC region. The following research areas could be pursued in the future:

- Research is needed to understand health-seeking behaviour of TB patients and patients with chronic cough among both nationals and migrant workers.
- Qualitative research to explore the perceptions and experiences of the patients especially migrant workers when seeking health care from both private and public sectors.
- Qualitative and quantitative studies evaluating the services, performance, accessibility and utilization of the private health sector.
- Analytical studies on risk factors for TB development among both nationals and migrant workers are also required. These would help to identify and quantify the risk of TB among patients diagnosed with TB or suspected of having TB.
- Research on the influence of gender on TB diagnosis and treatment is also needed.
- Evaluation of the effectiveness and feasibility of using Interferon Gamma Release Assays (IGRA) tests for the diagnosis of LTB.
- Evaluation of the introduction of Practical Approach to Lung Health (PAL) strategy at the primary care settings to improve TB case detection.
- Interventional studies to evaluate effective intervention tools for increasing awareness and suspicion of TB among general practitioners.
- Molecular epidemiological studies that use stringent genotyping tools, a high quality social network, a Geography Information System and contact tracing information are also needed, so as to gain a better understanding of transmission dynamics.

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15 APPENDICES

Appendix 1: Clinical Vignettes in the same order as presented in Questionnaire A.

	Clinical Vignette	Details
1	Sarcoidosis	Khalid, a 46-year-old man, complained of breathlessness on exercise for 6 months. He also had mild chest tightness and stiff joints but no skin or eye problems. There was no previous history of chest disease and he had never been abroad. On examination, he was afebrile and had bilateral basal inspiratory crackles. Rest of examination was unremarkable. His chest X-ray showed fine, diffuse shadows, predominantly in the mid zones, and bilateral hilar lymphadenopathy.
2	TB case 1	Abdullah, 40 year old, works as a security guard in an industrial company in Muscat. He presents to the clinic with non-productive cough for 5 weeks associated with fever and loss of appetite for 2 weeks. On examination, his weight was 54 Kg and his temperature was 37.2 C. Remainder of examination was unremarkable except for mild pallor.
3	Fibrosis	Khadejah, a 59-year-old woman, complained of increasing exertional breathlessness for 2 years which rapidly worsened over the last 2 months. On examination she had finger clubbing and widespread crackles in her chest but no cyanosis or skin lesions. Her chest X-ray showed diffuse fine shadowing throughout both lung fields, especially in the lower zones
4	Pneumonia	Saeed, 32- year old man, presented with five-day history of acute shivering, cough, and pleuritic chest pain. He has no previous chest disease and never smoked. On examination, he looked ill with high grade fever (39.2°C), tachycardia (110/minute) and tachypnoea 28/minutes) and had coarse crackle in the left lower zone of his chest.
5	TB case 2	Ali is 45-year old taxi driver was diagnosed as HIV positive 2 years ago. He presented with a 3-week history of cough and night sweats and one-week of a general feeling of malaise, but no haemoptysis, breathlessness or chest pain. On examination, he had features of anemia and was underweight, but his chest was clear.
6	TB case 3	Fatma is 47-year old widow and living with her son presented with 3-month history of loss of appetite and general feeling of weakness. She has noticed that she is slightly febrile in the evenings for the last 2 weeks with occasional night sweats, and mild right chest pain with no other chest symptoms. On examination, she was febrile (37.8 C), with dullness and reduced breath sounds in the left lowers zone. Others systems were normal
7	Bronchiectasis	Zakiah is a 22-year old lady with history of productive cough since childhood, presented with one week history of fever, worsening productive cough and increasing breathlessness. Her younger brother has the same condition. On examination she was febrile, cyanosed with finger clubbing and had bilateral wheeze and crackles in her chest
8	TB case 4	Moosa is a 31-year old from Muttrah. He has been unemployed for 2 years and been smoking cigarette and drinking alcohol since then. He presented with 3-week history of cough with heamoptysis in the last 2 days. He lost weight of 5 kgs over the last three months. On examination, he was malnourished and under-weight, but had no finger clubbing or cyanosis. His chest revealed coarse crackles in the right mid zone.
9	COPD	Salim is a 52-year old man with 7-year history of productive cough which worsens in winters, presented with 3 days history of increasing cough, sputum production and breathlessness. He stopped smoking 6 years ago. On examination, he was afebrile with no cyanosis or finger clubbing, but his chest was full of wheeze.
10	TB case 5	Fahad is a 23-year-old man presented with a 4-week history of cough, breathlessness and general malaise. He had lost 4kg in weight, but had no history of night sweats or haemoptysis. On examination, he was mildly febrile (37.8°C) but had no evidence of anaemia or clubbing. Coarse crackles were audible over the apex of the left lung, with no other abnormalities.

Appendix 2: The 20 multiple choice questions questionnaire used to assess the knowledge.

Below are short case scenarios for Pulmonary TB patient. Each is followed by an MCQ with ***only one answer is right***. When you write in some of the questions, it is not necessary to write in full sentences. Key words are enough.

Salim is a 40 years old male from Muscat. He is married with 5 children. He presented with history of chronic cough. The general practitioner suspected pulmonary TB. On clinical examination, patient was normal. Then, the general practitioner asked for chest x-ray and AFB specimens to make diagnosis of pulmonary TB.

According to Ministry of Health policy,

1. What is the minimum duration of cough required to suspect TB in this patient?

- 1. One week
- 2. Two weeks
- 3. Three weeks
- 4. One month
- 5. Others: Specify
- 6. Don't Know

2. How should AFB specimens be requested from the patient?

- 1. One specimen on the spot.
- 2. Two specimens, one on the spot and one in the morning next day.
- 3. Three specimens one on the spot and two early in the morning for tow consecutive days.
- 4 Three specimens all should be early in the morning for 3 consecutive days.
- 5. Others: Specify.....
- 6. Don't Know

3. What is the definition of Smear Positive?

- 1. Patient with at least two sputum specimens positive
- 2. Patient with one sputum specimen positive and x-ray is suggestive
- 3. Patient with at least one sputum specimen positive and culture positive
- 4. Any of the above
- 5. Others specify
- 6. Don't Know

4. What other underlying infection should this patient is routinely screened for?

- 1. Pneumonia
- 2. Atypical mycobacterium
- 3. HIV
- 4. Others: specify.....
- 5. Don't Know

The case was notified and then referred to a hospital for Anti-TB treatment. The patient was told that he will be admitted in the hospital and he will be put on standard DOTS regimen.

According to Ministry of Health Policy,

5. When should Pulmonary TB case notified? (Select from below)

- 1. Within 24 hours
- 2. Within one week
- 3. Within two weeks
- 4. Within one month
- 5. Others. Specify.....
- 6. Don't Know

6. How long should this patient be admitted?

- 1. One week
- 2. Two week
- 3. One month
- 4. Two months
- 5. Others: specify.....
- 6. Don't Know

7. What is the main purpose of patient admission?

- 1. Insure that patient take medications
- 2. Isolate the patient
- 3. Monitor sputum smear
- 4. Monitor the side effects of the drugs
- 5. Other: specify.....
- 6. Don't Know

The patient was admitted at the hospital and started the initial phase of the treatment.

8. How long is the initial phase?

- 1. Two weeks
- 2. One month
- 3. Two months
- 4. Others: specify.....
- 5. Don't Know

9. What are the **four** standard drugs used in the initial phase in Oman? (Please select from the following list)

- | | | | |
|------------------|--------------------------|-----------------|--------------------------|
| 1. Caperomycin | <input type="checkbox"/> | 5. Pyrazinamide | <input type="checkbox"/> |
| 2. Ethambutol | <input type="checkbox"/> | 6. Prothinamide | <input type="checkbox"/> |
| 3. D-cycloserine | <input type="checkbox"/> | 7. Rifampicin | <input type="checkbox"/> |
| 4. Isoniazaid | <input type="checkbox"/> | 8. Streptomycin | <input type="checkbox"/> |

10. Which blood test is essential before starting the drugs?

- 1. CBC
- 2. Thyroid function test
- 3. Renal Function Test
- 4. Liver Function Test
- 5. Others: specify.....
- 6. Don't Know

After completion of initial phase, he was referred to the local health centre for the continuation phase.

11. How long is the continuation phase?

- 1. Two weeks
- 2. One month
- 3. Two months
- 4. Others: specify.....
- 5. Don't Know

12. What are the **two** standard drugs used in the continuation phase? (Please select from the following list)

- | | | | |
|------------------|--------------------------|-----------------|--------------------------|
| 1. Caperomycin | <input type="checkbox"/> | 5. Pyrazinamide | <input type="checkbox"/> |
| 2. Ethambutol | <input type="checkbox"/> | 6. Prothinamide | <input type="checkbox"/> |
| 3. D-cycloserine | <input type="checkbox"/> | 7. Rifampicin | <input type="checkbox"/> |
| 4. Isoniazaid | <input type="checkbox"/> | 8. Streptomycin | <input type="checkbox"/> |

13. To assess the treatment outcome, what would be the single most important investigation performed during continuation phase?

- 1. ESR
- 1. Chest x-ray
- 2. Mantoux
- 3. Sputum culture
- 5. Others: specify.....
- 6. Don't Know

14. How often will you do the above investigation?

- 1. Every week
- 2. Every two weeks
- 3. Every Three weeks
- 4. Every Month
- 5. Others: Specify.....
- 6. Don't Know

As part of contact tracing, the wife of the above patient was reported to be asymptomatic and had a normal chest x-ray. She was reassured and asked to report back if she became unwell in anyway.

According to Ministry of Health Policy,

15. Of patient contacts, who should be investigated to rule out TB?

- 1. All household contacts
- 2. Only living with patient in the same room
- 3. Only symptomatic contacts
- 4. Only Children contacts with no BCG scar
- 5. Others: Specify.....
- 6. Don't Know

16. Who are the contacts eligible for TB prophylaxis among adults?

- 1. All adult contacts
- 2. Adults with cough
- 3. Adults more than 50 years old
- 4. Not indicated
- 5. Others specify.....
- 6. Don't Know

17. Who are the contacts eligible for TB prophylaxis among children?

- | | |
|-------------------------------|--------------------------|
| 1. All children | <input type="checkbox"/> |
| 2. Children less than 3 years | <input type="checkbox"/> |
| 3. Children more than 6 years | <input type="checkbox"/> |
| 4. Not indicated | <input type="checkbox"/> |
| 5. Others. Specify..... | <input type="checkbox"/> |
| 6. Don't Know | <input type="checkbox"/> |

18. What is the standard drug used for prophylaxis?

- | | | | |
|------------------|--------------------------|------------------|--------------------------|
| 1. Capromycin | <input type="checkbox"/> | 5. Pyrazinamide | <input type="checkbox"/> |
| 2. Ethambutol | <input type="checkbox"/> | 6. Prothionamide | <input type="checkbox"/> |
| 3. D-cycloserine | <input type="checkbox"/> | 7. Rifampicin | <input type="checkbox"/> |
| 4. Isoniazid | <input type="checkbox"/> | 8. Streptomycin | <input type="checkbox"/> |

19. After how long do patients with smear positive treated with standard anti-TB drugs become non-infectious, in general?

- | | |
|-------------------------|--------------------------|
| 1. One week | <input type="checkbox"/> |
| 2. Two weeks | <input type="checkbox"/> |
| 3. One month | <input type="checkbox"/> |
| 4. Two months | <input type="checkbox"/> |
| 5. Others: specify..... | <input type="checkbox"/> |
| 6. Don't Know | <input type="checkbox"/> |

20. When should the patient be labeled as cured?

- | | |
|---|--------------------------|
| 1. Patient completed the treatment. | <input type="checkbox"/> |
| 2. Patient completed the treatment and had the last smear as sputum negative prior stopping treatment. | <input type="checkbox"/> |
| 3. Patient completed the treatment and had at least two negative smear results during the treatment. | <input type="checkbox"/> |
| 4. Patient completed the treatment and had at least two negative smear results during the continuation phase prior stopping the treatment | <input type="checkbox"/> |
| 5. Others specify..... | <input type="checkbox"/> |
| 6. Don't Know | <input type="checkbox"/> |