Determinants of household costs and access to care for tuberculosis in Tajikistan

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Abbreviations and acronyms

AFB	Acid-fast bacilli
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CP	Continuation phase (of anti-TB chemotherapy)
CXR	Chest x-ray (chest radiograph)
DOT	Direct observation of treatment
DOTS	The internationally recommended strategy for tuberculosis control
EPTB	Extra-pulmonary TB
EQA	External Quality Assessment
FGD	Focus group discussion
FSU	Former Soviet Union
GDP	Gross domestic product
HIV	Human Immunodeficiency Virus
IP	Intensive phase (of anti-TB chemotherapy)
LR	Likelihood ratio
MDR-TB	Multi-drug resistant TB
MTB	*Mycobacterium tuberculosis*
NRL	National Reference Laboratory
NTP	National TB program
OR	Odds ratio
PPP	Purchasing power parity
PTB	Pulmonary TB
PTB-	Sputum-smear negative pulmonary TB
PTB+	Sputum-smear positive pulmonary TB
RCT	Randomised controlled trial
SES	Socio-economic status
SRS	Simple random sampling
SSM	Sputum smear microscopy using the Ziehl-Neelsen technique
SS-	Sputum-smear negative
SS+	Sputum-smear positive
TB	Tuberculosis
US	United States of America
USD	United States Dollar
USSR	Union of Socialist Soviet Republics
WFP	World Food Program of the United Nations
WHO	World Health Organisation

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Summary

This thesis investigated access to medical care for tuberculosis (TB), with a focus on the economic component of access. TB is among the worst infectious diseases globally, causing about 2 million deaths per year. TB control will not be possible, if the most vulnerable and poorest sections of society do not have access to appropriate treatment. Studies for the present thesis were carried out in Tajikistan, one of the poorest countries of the world. The health system of Tajikistan is firmly rooted in its Soviet history with a dense network of facilities and allegiances to separate vertical programs for different tasks of the health system. Low expenditure for the health system and inefficiencies severely affect its performance. Several post-Soviet countries share at least some of the above characteristics and our studies may serve as a showcase for access to TB care in other countries of the former Soviet Union.

The thesis used a previously described analytical framework for access to care in contexts of livelihood insecurity. Within this framework it focussed on access more than on livelihoods. For the categorisation of costs of illness, the thesis used a conceptual framework of the economic burden of illness for households.

The seven studies in this thesis used qualitative and quantitative methods to investigate access to care and specific aspects of it. The first study took advantage of the explorative nature of focus group discussions to comprehensively investigate any factors that community members, TB patients and health care providers considered important for access to care. Factors that were reported to be important were discussed in depth. At the end of the discussion, the relative importance of the mentioned factors was rated. The results showed that community members associated cough with TB disease and that they were aware of facilities providing care for TB in their districts. The main finding of the study was that all respondent groups (community members, patients and providers) considered economic factors the most important barriers to medical care.

A subsequent study investigated health care seeking and the relationship between organisational aspects of health care delivery and delay to TB treatment. Data for this study, two studies on illness-related costs and one study on food supplements were collected jointly, in a questionnaire survey among registered TB patients. Generally moderate delays (median 52 days) until start of TB treatment were found. However,

two subgroups of patients had high hazard ratios for long health system delays. These were the patients who first presented to peripheral primary care facilities and especially those who developed active disease while working in Russia and who presented to health care in Russia. The long delays of the former are related to the vertical structure of TB control inherited from Soviet times: primary care providers were reluctant to diagnose TB and chest radiography, which is not available at primary care facilities, was over-used for diagnosis. Diagnosis at the primary care level based on sputum smear microscopy should be promoted to shorten the delays of these patients. For labour migrants developing active TB in Russia, an international referral system is needed, including availability of treatment until sputum conversion for Tajik citizens in Russia.

The third study investigated extent and timing of illness-related costs at the level of the patients' households. It attempted to measure all material and monetary costs related to the TB disease, but not psychological pain or costs in terms of missed education. Mean self-reported total costs of an episode of TB were USD1'053, or c. USD4'900 purchasing power parity. Of these costs, USD396 were incurred in the form of expenditure (direct costs) and USD657 in the form of lost income due to the inability to pursue usual income-generating activities. Almost three fourths of the total costs were incurred during anti-TB treatment, despite the availability of free TB drugs. The costs peaked before starting TB treatment and in the intensive phase of TB treatment. It was concluded that the costs of an episode of TB are catastrophic and that both strategies to reduce costs and strategies to help patients cope with costs are urgently needed. These strategies should be timed early in treatment in order to correspond with the highest cost peak.

The fourth study identified factors associated with higher direct costs of TB, including factors relating to case management. It further investigated coping strategies that may lead to impoverishment: selling productive assets and borrowing money. The final mixed-effects regression model showed that receiving 'additional medication' was the most important predictor of higher direct costs. 'Additional medication' refers to drugs received in addition to the anti-TB therapy, mainly for symptomatic treatment and for iatrogenic problems. Further significant predictors were the delay until start of TB treatment and hospitalisation. TB patients raised on average USD182 through selling productive assets and through borrowing. Based on the results, it was suggested that

changes in the management of TB, namely reducing additional treatment and hospitalisation, should be considered in order to avoid the high costs for patients. The rationality of both additional treatment and hospitalisation is questionable in many cases and there is room for improvement. The potentially detrimental coping strategies employed confirm the severe economic burden that TB patients carry.

The fifth study used data from the TB registry to identify predictors of hospitalisation. It investigated eight independent variables as predictors of hospitalisation. Treatment result was studied as a secondary outcome, using the same eight variables plus hospitalisation as potential predictors. Sputum smear result was the most important predictor of hospitalisation, with age and sex being further significant factors. Treatment success was significantly lower for sputum-smear positive patients and there was a tendency for lower treatment success among hospitalised patients. The finding that sputum smear positive patients were much more likely to be hospitalised is consistent with national guidelines, but not necessarily with international recommendations that focus more on outpatient care. It is recommended that national guidelines be adapted to emphasise outpatient treatment.

A survey among patients found that a considerable proportion of TB patients had already received the three food supplements that they are entitled to – before the end of the treatment. The number of food supplements received was significantly associated with the time elapsed since start of treatment and with residing in four out of the six districts with a food distribution program. Food supplements made a contribution of about USD225 to the household economy.

Bayesian modelling of the sensitivity of routine sputum smear microscopy in peripheral laboratories in Tajikistan yielded an estimate of sensitivity of 53% for the examination of a single slide. The contribution of the third slide to total case finding through sputum microscopy was estimated at 13%. These results are important from a global and from a national perspective. On the global level they contribute to the surprisingly scarce evidence about the sensitivity of sputum microscopy in peripheral routine settings. This scarcity of evidence is probably linked to the difficulty of conducting the gold standard test, culture, in such settings. Our evidence suggests that the third serial sputum specimen could make a substantial contribution to case finding, if it were carried out with equal quality as previous examinations – a conclusion that is highly relevant to an ongoing policy discussion. From the national perspective, these findings highlight that

the sensitivity of routine sputum microscopy is reasonably good and that its use should be promoted. Concurrently, strengthening of the quality assurance should continue.

The present thesis found that an analytical framework for access to care, developed in the context of a malaria control program, is useful also in the area of TB. Adaptations to make the analytical framework fit better to the context of access to TB care are suggested. The theoretical framework used for the classification of illness-related costs also proved useful. The studies conducted in the frame of this thesis identified economic factors as the main barriers to access medical care for TB. Several characteristics of health care delivery that are rooted in the Soviet health system contributed to the high costs faced by patients and to the long delays until treatment experienced by certain subgroups of patients. The importance of factors related to the Soviet history of health care suggests that many of our findings may also apply to other post-Soviet countries.

In order to improve access to TB care and hence TB control in Tajikistan and possibly other countries of the former Soviet Union, the economic burden for the patients must be reduced as a matter of priority. Further, the long delays of certain subgroups of patients need to be shortened. The latter can be achieved more easily than the former, among others by improving referral systems, by further integrating TB services with general health care and by promoting the use of sputum smear microscopy. Reducing the economic burden for TB patients requires measures on both sides: reducing the costs faced by patients and increasing their ability to cope with these costs. Collaboration between the health system, implementing partners like non-governmental organisations and funding agencies as well as between different programs within the health system, like the TB control program and primary care, will be necessary. Several measures that can be implemented and that will contribute to the much-needed reduction of the economic burden have been identified in the studies conducted in the frame of the present thesis.

Zusammenfassung

Diese Doktorarbeit untersuchte Zugang zu medizinischer Pflege für Tuberkulose (TB), mit einem Fokus auf den ökonomischen Komponenten dieses Zugangs. TB gehört zu den schlimmsten Infektionskrankheiten weltweit und verursacht etwa 2 Millionen Todesfälle pro Jahr. Die Kontrolle dieser Krankheit wird nicht möglich sein, wenn die Randgruppen der Gesellschaft und die Ärmsten keinen Zugang zu wirkungsvoller Behandlung haben. Die Studien für die vorliegende Dissertation wurden in Tadschikistan ausgeführt, einem der ärmsten Länder der Welt. Das tadschikische Gesundheitswesen ist stark in seiner sowjetischen Geschichte verwurzelt, weist ein dichtes Netzwerk von Gesundheitseinrichtungen wie Praxen und Kliniken auf und Loyalitäten zu jenem System, welches aus getrennten vertikalen Programmen für verschiedene Aufgaben des Gesundheitswesens bestand. Tiefe Staatsausgaben für das Gesundheitswesen und Ineffizienzen haben einen starken negativen Einfluss auf das seine Leistung. Mehrere post-sowjetische Länder teilen wenigstens einen Teil der obgenannten Eigenschaften und unsere Studien könnten Zugang zu Pflege exemplarisch auch für andere Länder der ehemaligen Sowjetunion abbilden.

Diese Dissertation verwendete einen analytischen Rahmen für "Zugang zu Pflege im Kontext unsicherer Lebensgrundlagen", der bereits beschrieben war. Innerhalb dieses analytischen Rahmens konzentrierte sie sich mehr auf den "Zugang" als auf die Lebensgrundlagen der Menschen. Für die Einteilung von Krankheitskosten verwendete die vorliegende Doktorarbeit ein Rahmenkonzept für die "ökonomische Last von Krankheiten für Haushalte".

Die sieben Studien in dieser Dissertation verwendeten sowohl qualitative als auch quantitative Methoden um Zugang zu Pflege und spezifische Aspekte hiervon zu untersuchen. Die erste Studie nutzte den Vorteil der explorativen Eigenschaften von Fokusgruppendiskussionen um umfassend jegliche Faktoren zu untersuchen, welche von Vertretern der Allgemeinbevölkerung, von TB-Patienten und von Pflegepersonal als ausschlaggebend erachtet wurden für den Zugang zu Pflege. Faktoren, welche als wichtig erachtet wurden, wurden eingehend diskutiert. Am Ende der Diskussion wurde die relative Stärke des Einflusses diskutierter Faktoren bewertet. Die Studienergebnisse zeigen, dass Vertreter der Bevölkerung Husten mit TB assoziierten und über Gesundheitseinrichtungen in ihren Distrikten, welche TB behandeln, Bescheid wussten. Das Hauptergebnis der Studie war, dass alle Gruppen von Informanten (Vertreter der

Allgemeinbevölkerung, Patienten und Pflegepersonal) die ökonomischen Komponenten des Zugangs zu medizinischer Pflege als die einflussreichsten erachteten.

Eine nachfolgende Studie untersuchte das Verhalten von betroffenen Personen im Falle von Krankheit und den Zusammenhang zwischen organisatorischen Eigenschaften der Gesundheitsdienste und dem Ausmass von verspätetem Behandlungsbeginn. Die Daten für diese Studien, zwei Studien über Krankheitskosten und eine Studie über Nahrunsmittel-Ergänzungsleistungen wurden gemeinsam gesammelt, in einer Umfrage unter registrierten TB-Patienten. Über Alles gesehen wurden moderate Verspätungen bis Behandlungsbeginn gefunden (Median von 52 Tagen). Allerdings gab es zwei Gruppen von Patienten, die eine hohe statistische "Hazard Ratio" für lange Verspätungen aufwiesen. Dies waren Patienten, die sich zuerst an einen Grundversorger in peripheren Gebieten wandten, und insbesondere diejenigen Patienten, die eine aktive TB entwickelten, während sie in Russland am Arbeiten waren und dort einen Gesundheitsversorger aufsuchten. Die langen Verspätungen der ersteren hängen mit der von Sowjetzeiten geerbten vertikalen Struktur der TB-Kontrolle zusammen: es widerstrebt den Grundversorgern, eine TB-Diagnose zu erstellen, und Röntgenbilder, welche bei Grundversorgen nicht vorhanden sind, wurden für die Diagnose von TB übermässig verwendet. Die Diagnose bei den Grundversorgern und abgestützt auf mikroskopische Untersuchung eines Ausstrichs von Auswurf sollte gefördert werden um die Verspätungen dieser Patienten zu verkürzen. Für die Migranten, die in Russland eine aktive TB entwickeln, wird ein internationales Überweisungssystem benötigt, inklusive der Verfügbarkeit der Behandlung für tadschikische Bürger in Russland bis zur sogenannten Konversion des Auswurfs.

Die dritte Studie untersuchte das Ausmass und das zeitliche Auftreten von Krankheitskosten für den Patienten und seinen Haushalt. Sie zielte darauf ab, alle materiellen und finanziellen Kosten in Zusammenhang mit einer TB-Erkrankung zu messen, aber nicht den psychischen Schmerz oder Kosten wie verpasste Ausbildungsmöglichkeiten. Durchschnittliche Gesamtkosten einer TB-Erkrankung waren 1'053.- $ oder etwa 4'900.- $ gemessen in Kaufkraftparität. Von diesen Kosten wurden 396.- $ als Ausgaben getätigt und 657.- $ waren Einkommensverluste, die durch die krankheitsbedingte Arbeitsunfähigkeit zustande kamen. Beinahe drei Viertel der Gesamtkosten traten während der TB-Behandlung auf, obwohl die TB-Medikamente gratis verfügbar waren. Die höchsten Kosten traten vor dem Beginn der TB-

Behandlung und während der sogenannten Intensiven Phase der Behandlung auf. Es wurde geschlussfolgert, dass die Krankheitskosten von TB katastrophal sind und dass Massnahmen sowohl zur Reduktion der entstehenden Kosten als auch zur Befähigung der Patienten, entstandene Kosten zu bewältigen, notwendig sind. Diese Strategien müssten frühzeitig während der Behandlung greifen, um mit den höchsten Kosten überein zu stimmen.

Die vierte Studie identifizierte Faktoren, welche mit höheren Ausgaben für TB zusammen hängen, einschliesslich Faktoren, die den Behandlungsmethoden zugehören. Weiter untersuchte sie Bewältigungsstrategien der Patienten, die zu weiterer Verarmung führen können: das Verkaufen von Produktionsgütern und das Borgen von Geld. Das resultierende statistische Model ("mixed-effects") zeigte, dass "zusätzliche Medikamente" der wichtigste Prediktor höherer Ausgaben war. "Zusätzliche Medikamente" bezieht sich auf Medikamente, die zusätzlich zur TB-Chemotherapie genommen werden, mehrheitlich für die Behandlung von Symptomen und von Nebenwirkungen. Weitere signifikante Prediktoren waren die Verspätung bis Behandlungsbeginn und Hospitalisierung. TB-Patienten trieben durchschnittlich 182.- $ durch den Verkauf von Produktionsgütern und durch Borgen auf. Aufgrund dieser Ergebnisse sollten Veränderungen der Behandlungsmethoden für TB in Betracht gezogen werden, nämlich den verminderten Gebraucht von zusätzlicher Medikation und von Hospitalisierung. Die medizinische Notwendigkeit dieser beiden Methoden ist in vielen Fällen fragwürdig und Verbesserungen sind möglich. Die verwendeten potenziell schädlichen Bewältigungsstrategien bestätigen die schwere ökonomische Last, welche TB-Patienten tragen.

Die fünfte Studie verwendete Daten aus dem TB-Verzeichnis um Prediktoren der Hospitalisierung zu untersuchen. Acht unabhängige Variablen wurden als Prediktoren der Hospitalisierung untersucht. Als sekundäres Studienergebnis wurde das Behandlungsergebnis untersucht, wobei die gleichen acht unabhängigen Variablen und zusätzlich Hospitalisierung als potenzielle Prediktoren in Betracht gezogen wurden. Das Resultat der Auswurfuntersuchung war der wichtigste Prediktor der Hospitalisierung, während Alter und Geschlecht ebenfalls signifikant waren. Der Behandlungserfolg war signifikant tiefer für Patienten mit positivem Auswurf und eine statistische Tendenz für tieferen Erfolg bei hospitalisierten Patienten wurde gefunden. Das Ergebnis, dass Patienten mit positivem Auswurf eher hospitalisiert wurden, stimmt mit den nationalen Richtlinien überein, aber nicht unbedingt mit internationalen Empfehlungen, die mehr auf

ambulatorische Behandlung abzielen. Es ist empfehlenswert, die nationalen Richtlinien anzupassen und stärker auf ambulatorische Behandlung auszurichten.

Eine Umfrage unter Patienten ergab, dass ein beachtlicher Anteil der TB-Patienten die drei Nahrungsmittel-Ergänzungsleistungen, auf welche sie Anspruch hatten, bereits vor dem Ende der Behandlung erhalten hatten. Die Anzahl der erhaltenen Ergänzungsleistungen war signifikant mit der Zeit korreliert, die seit Behandlungsbeginn verstrichen war, sowie damit in vier der sechs Distrikte mit Nahrungsmittelergänzungen zu leben. Die Ergänzungsleistungen trugen etwa 225.- $ zum Haushaltsbudget bei.

Bayes'sche Modellierung der Sensitivität der routinemässigen mikroskopischen Auswurfuntersuchung in peripheren Laboratorien Tadschikistans ergab eine Schätzung von 53% für die Sensitivität der Untersuchung eines einzigen Auswurfes. Der Beitrag der dritten von drei aufeinanderfolgenden Auswurfuntersuchungen zur Gesamtzahl der identifizierten Fälle wurde auf 13% geschätzt. Diese Ergebnisse sind sowohl aus globaler als auch aus nationaler Perspektive wichtig. Global tragen sie zur erstaunlich mageren wissenschaftlichen Faktenlage über die Sensitivität der Auswurfuntersuchung unter Routinebedingungen bei. Die knappe Faktenlage hängt wahrscheinlich zusammen mit der Schwierigkeit, den Goldstandardtest, Kultur, unter solchen Bedingungen durchzuführen. Unsere Fakten suggerieren, dass die dritte Folgeuntersuchung von Auswurf einen substanziellen Beitrag zur Gesamtzahl der gefundenen Fälle beitragen könnte, wenn sie mit der gleichen Qualität ausgeführt würde wie vorhergehende Untersuchungen – eine Schlussfolgerung, die für eine laufende Debatte sehr relevant ist. Vom nationalen Blickwinkel zeigen diese Ergebnisse, dass die Routineuntersuchung von Auswurf gut funktioniert und gefördert werden sollte. Gleichzeitig müssen die Anstrengungen zur Qualitätssicherung weitergehen.

Die vorliegende Doktorarbeit zeigte, dass ein analytischer Rahmen für "Zugang zu Pflege", der innerhalb eines Programmes zur Malariakontrolle entwickelt worden war, auch im Bereich der TB-Kontrolle nützlich ist. Es werden Änderungen vorgeschlagen, um den analytischen Rahmen besser an den Kontext von Zugang zu Pflege für TB anzupassen. Das Rahmenkonzept für die Einteilung von Krankheitskosten erwies sich ebenfalls als nützlich. Die Untersuchungen, die im Rahme dieser Dissertation durchgeführt wurden, identifizierten wirtschaftliche Faktoren als die Haupthindernisse zum Zugang zu medizinischer Pflege für TB. Mehrere Eigenschaften der Gesundheitsdienste, die ihren Ursprung im sowjetischen Gesundheitswesen haben,

trugen zu den hohen Kosten für Patienten und zu den langen Verspätungen bis Behandlungsbeginn für gewisse Gruppen von Patienten bei. Die Bedeutung der Faktoren, die mit der sowjetischen Geschichte des Gesundheitswesens zusammenhängen, weisen darauf hin, dass unsere Ergebnisse auch in anderen post-sowjetischen Ländern Gültigkeit haben könnten.

Um den Zugang zu TB-Pflege und dadurch TB-Kontrolle in Tadschikistan und möglicherweise anderen Ländern der ehemaligen Sowjetunion zu verbessern, muss prioritär die wirtschaftliche Last für die Patienten vermindert werden. Weiter müssen die langen Verzögerungen bis Behandlungsbeginn für gewisse Patientengruppen verkürzt werden. Letzteres ist einfacher zu erreichen als Ersteres, unter Anderem durch eine Verbesserung der Überweisungsmechanismen, durch eine weitergeführte Integration der TB-Pflege mit allgemeiner Gesundheitspflege und durch eine geförderte Verwendung der Auswurfuntersuchung. Um die wirtschaftliche Last für TB-Patienten zu vermindern, sind Massnahmen beiden Seiten notwendig: Verminderung der auftretenden Kosten, und Befähigung der Patienten, die auftretenden Kosten besser zu bewältigen. Dies wird Zusammenarbeit zwischen dem Gesundheitswesen, Partnern wie Nichtre-gierungsorganisationen und Entwicklungsorganisationen erfordern. Mehrere Massnahmen, die eingeleitet werden können und zur dringend benötigten Verminderung der ökonomischen Last beitragen werden, sind in den Untersuchungen im Rahmen dieser Doktorarbeit bestimmt worden.

1. Introduction

1.1. Overview

The main subject of this thesis – as the title suggests – is the ability of affected people to make use of medical care for tuberculosis (TB), summarised under the term 'access to care'. Particular attention is given to illness-related costs at the level of patients' households, i.e. the economic aspects of access to care. The introduction will first give a general overview of etiology, epidemiology and clinical features of TB, then introduce the concept of access to care and subsequently present some of the difficulties patients face in relation to TB and TB treatment.

1.2. Etiology and basic epidemiologic features

TB is caused by the gram-positive bacterium *Mycobacterium tuberculosis* (MTB). About one third of the world population, i.e. about 2 billion people, are infected with MTB (Dye et al 1999). However, only about 10% of people infected with MTB will develop the disease during their whole lifetime, 90% of infections will remain latent or be cleared (Hopewell & Jasmer 2005). Latency can last for years or even decades. The exact site and physiologic state of MTB during latency are debated, but clearly protect it from the fast effect of drugs that are rapidly bactericidal in vitro (Gomez & McKinney 2004). The risk of active disease is higher among HIV-positive people, where annual rates of progression from latent infection to disease of 2%-8% have been reported. A variety of organs can be affected, but most commonly the lungs are and then the disease is referred to as pulmonary TB (PTB). In the absence of HIV around 85% of reported TB cases are PTB (Hopewell & Jasmer 2005). In areas with high rates of HIV, the proportion of extra-pulmonary TB (EPTB) is much higher.

1.3. Burden of Disease

The high and rising numbers of TB incidence from the mid 1980ies onwards prompted the World Health Organisation to declare TB a global public health emergency in 1993 (World Health Organisation 1994). In the year 2007, an estimated 9.3 million people worldwide newly fell ill with TB and about 1.8 million people died from it (World Health Organisation 2009). An overwhelming proportion of the burden of disease is experienced by low- and middle-income countries (Figure 1.1). The highest incidence rates occur in Africa and Asia (Corbett 2003, World Health Organisation 2009). In the

former Soviet countries of Central Asia, TB burden was relatively low in 1990 at an incidence of about 66 cases per 100 000 of population per year (own calculations from data in World Health Organisation 2005). After the breakdown of the Soviet Union, there was a severe rise in TB incidence in the five post-Soviet countries of Central Asia. By the year 2003, the incidence rate had almost doubled to about 126 and approximately remained constant with 127 in 2005 (data source: World Health Organisation 2005, 2009). Within former Soviet Central Asia, Tajikistan has been and still is the country with the highest burden of disease. Moreover, Tajikistan was the only Central Asian country, for which the estimate of incidence increased substantially over the last years – reaching a new peak at 231 cases per 100 000 population in the year 2007 (World Health Organisation 2009). For another Central Asian country, Afghanistan, the World Health Organisation (2006) estimated an incidence rate of 333 as well in 1990 as in 2004. This is one of the highest rates outside Africa and migration between Afghanistan and Tajikistan might affect the incidence rates in the two countries.

Globally 1.74 times as many men are notified with TB than women (World Health Organisation 2004). The sex bias is in the opposite direction for the age group of 0 to 14 years and less-than-average for the age groups of 15 to 24 and 25 to 34. In the older age groups, the rate is even more strongly male-biased. Borgdorff et al (2000) reviewed prevalence survey and notification data from 14 countries and concluded, that the higher number of men notified with TB "may be largely due to epidemiological differences and not to differential access to health care". In a study in Vietnam, 1.5% of women and 1.3% of men reported symptoms consistent with TB (Thorson 2000). Among these, 14% of women and 36% of men indicated having given a sputum sample – a finding which suggests women have more difficulties accessing health care. Balasubramanian et al (2004) screened a study community in southern India by CXR and confirmed cases by sputum smear microscopy. They compared prevalence of symptoms and sputum-positivity in the community with notification rates, and concluded, that in their study site men had significantly less access to TB diagnosis and treatment than women. In a study in the Philippines, Tupasi et al (2000) found that 21% of men and 15% of women had symptoms consistent with TB. Unfortunately, the results of diagnosis by means of CXR and sputum microscopy are not given for the sexes separately. These results show that there is major variation among different settings in regard to gender disparities.

TB strains that are resistant at least against isoniazid and rifampicin are referred to as multi-drug resistant TB (MDR-TB). Their treatment is more complex and much more expensive than that of drug-susceptible TB. The post-Soviet countries of Eastern Europe and Central Asia are among the countries with the highest proportions of MDR-TB cases (World Health Organisation 2003a). Specifically, Kazakhstan and the Qaraqalpoqston region of Uzbekistan are two of the settings with the highest rates of MDR-TB with estimates of 56% and 40%, respectively, among re-treatment cases. The corresponding rates for new cases are 14.2% and 13.2%. For Tajikistan an MDR-TB rate of 8.6% among new cases was estimated by means of a mathematical model, suggesting that there is also a large problem of MDR-TB (Zignol et al 2006).

As mentioned above, HIV dramatically increases the risk of developing active TB (Hopewell & Jasmer 2005). It is therefore noteworthy, that the prevalence of HIV in Tajikistan is low, estimated at 0.3% among adults in the year 2008 (UNAIDS 2008). Mainly injecting drug users are known to be affected in Tajikistan.
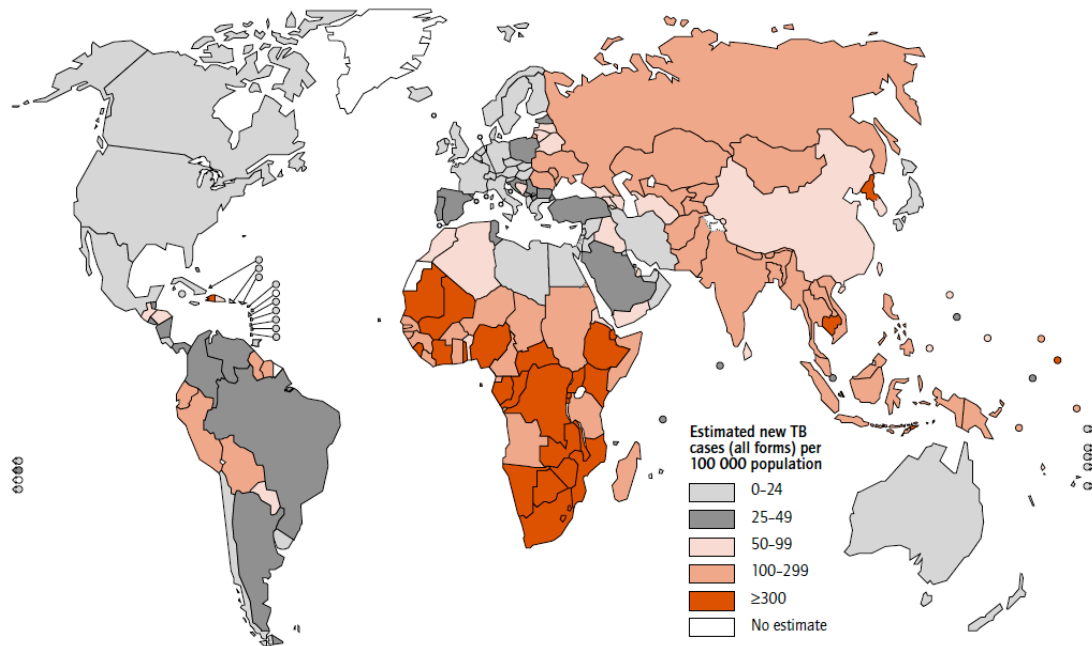
Figure 1.1. Estimated incidence rates of tuberculosis globally – in 2007. Reproduced with the kind permission of the World Health Organisation, Geneva, Switzerland.

1.4. The DOTS strategy

Adherence to the long-lasting traditional TB treatments – often associated with extended hospital stays – was low and the burden of TB increasing in the 1990ies. As a response, the World Health Organisation developed a new TB control strategy: the

Directly Observed Treatment, Short Course (DOTS) strategy, made available to national health authorities in 1993 (World Health Organisation 1993). The DOTS strategy is based on five components: i) political commitment, ii) access to quality-assured sputum microscopy, iii) standardized short-course chemotherapy for all cases of TB under proper case management conditions (including direct observation of treatment), iv) uninterrupted supply of quality-assured drugs, and v) a recording and reporting system enabling outcome assessment of all patients and assessment of overall program performance (World Health Organisation 2003b). Based on the DOTS guidelines, each country defines its national guidelines for the treatment of TB. Implementing these guidelines should allow reaching the official DOTS objectives of detecting 70% of estimated PTB+ cases and of successfully treating 85% of them.

DOTS relies on passive case finding, which means that screening of the population is not foreseen – not by sputum microscopy and even less by means of CXR (World Health Organisation 2003b). Rather, patients presenting to a health care facility with symptoms consistent with TB (especially cough lasting more than two or three weeks) should be referred to and actively motivated for sputum smear testing. This requires that patients actually do access the health care system if they have these symptoms, and that the health care system delivers diagnostic services according to guidelines for all patients. After diagnosis, patients are put on treatment according to three treatment categories. Treatment consists of two parts, the intensive and continuation phases (IP and CP). The exact duration of these two phases depends on the drug regimens used and on the patient's history of previous TB treatment. In the IP, which lasts at least two months, treatment should take place daily or thrice weekly and invariably under direct observation (DOT). In the CP, which lasts four to six months, exemptions from DOT are more widely accepted. While DOT gave the DOTS strategy its name, the importance of direct observation has been questioned and is intensively debated (Volmink & Garner 2007, Frieden & Sbarbaro 2007, Maher et al 2007). There is a consensus, however, that assuring treatment adherence requires strong leadership and a multi-faceted and locally adapted approach that takes the patients' needs into account.

The regimens recommended by the World Health Organisation consist of a combination of four to five anti-tuberculous agents during the IP and of two to three during the CP. All standard regimens include isoniazid and rifampicin. Recommended regimens for cases with drug-resistant strains are more complicated. Guidelines for the

treatment of MDR-TB have been issued under the name of DOTS-plus (World Health Organisation 2000).

The DOTS strategy was found to have improved access to diagnosis and treatment of TB for example in India (Khatri & Frieden 2002). However, a more general evaluation of the progress of DOTS showed, that global case detection had remained relatively constant from 1996 till 2003 at around 56%, i.e. substantially below the target of 70%, which DOTS designers hoped to reach by 2005 (World Health Organisation 2005). Dye et al (2002) made similar findings reviewing the numbers of detected cases in DOTS programs and summarised their findings as "low access to a highly effective therapy".

1.5.   Health care delivery and DOTS in Tajikistan

Tajikistan is a relatively small, very mountainous and land-locked country situated in Central Asia (Figure 1.2). It borders China to the east, Afghanistan to the south, Uzbekistan to the west and Kyrghyzstan to the north. After independence, Tajikistan fell into civil war and experienced a dramatic drop in economic output (Central Intelligence Agency 2009). Its gross domestic product per capita is estimated at USD 2'100 purchasing power parity for the year 2008.

Figure 1.2. Map of Asia showing Tajikistan (in black). Available from http://commons.wikimedia.org.

At independence, Tajikistan inherited the Soviet health care system based on the

Semashko model, comprising a dense network of facilities (compare also table 5.1) and high in-patient capacity (Atun & Coker 2008, Falkingham 2004). Health care focussed on curative and specialist services, was universally available and free of charge at the point of delivery. Control of epidemic diseases and hygiene were the responsibility of the Sanitary-Epidemiological Services, a separate vertical system. Currently, health sector reform is ongoing in Tajikistan (Tediosi et al 2008). One of the main objectives of health sector reform is the strengthening of primary care, whereby primary care also takes over preventive and public health services that were organised vertically before.

In the Semashko model, TB control was usually organised in four vertical structures: screening of the population by means of fluorography, the penitentiary TB program, hospital-based TB services, and primary care-based TB services (Atun & Coker 2008). In 2002 a DOTS program was started in Tajikistan – in Dushanbe and Rudaki districts, covering 13% of the country's population. By the end of 2005 the program expanded to 24 districts covering 44% of the population and by the end of 2007 it reached 100% (World Health Organisation 2006, World Health Organisation 2009). The program is steered by the National TB Program (NTP) (National Coordination Committee on malaria prophylactic and control in Republic of Tajikistan 2003). Generally there is one laboratory performing sputum smear microscopy per rayon (district), in the district centre. At the same site, the TB laboratory and treatment registries are kept. Primary care services refer TB suspects to the TB laboratory for diagnosis and provide treatment supervision. Case detection in the Tajik DOTS program has so far remained below international targets – at 39% in 2007 instead of 70%. Official data suggest that the rate of treatment success is close to international targets at 84% for the 2006 cohort (World Health Organisation 2009).

1.6. Clinical manifestation and diagnosis

1.6.1. Clinical diagnosis

Clinical symptoms of TB are unspecific. They include night sweats, general weakness, lack of appetite, and weight loss. The most important symptom of PTB is prolonged cough; typically accompanied by expectoration after the initial period. Most TB control programs consider any patient with cough for at least two weeks (in some programs at least three weeks) to be a TB suspect and require that she or he be evaluated for TB diagnosis. Diagnostic tests include direct microscopy of sputum, fluorescence

microscopy, culture (including assessment with or without microscopy), a variety of rapid diagnostic tests, methods based on nucleic acid amplification, chest radiography and computed as well as positron emission tomography. However, in most parts of the world, only direct sputum microscopy is available – maybe complemented by a chest x-ray (CXR) if the patient can afford to pay for such (Davies & Pai 2008). Some of the advantages and disadvantages of the most important diagnostic tests for TB are presented in table 1.1.

1.6.2. *Direct sputum microscopy*

For direct microscopy, sputa are collected from the patient, prepared as a smear, stained using the Ziehl-Neelsen technique and then analysed under the microscope. Ziehl-Neelsen microscopy is an inexpensive and relatively quick test identifying acid-fast bacilli (AFB), which include MTB. AFB are visible in red against a background of light blue (Figure 1.3). With the Ziehl-Neelsen sputum smear examination, patients excreting a significant number of bacilli can be identified. These patients are obviously the most infectious ones and are called sputum smear positive PTB (PTB+) cases. Hence, the priority for the control of the TB epidemic is to detect and successfully treat PTB+ cases (World Health Organisation 2003b). However, the sensitivity of sputum smear microscopy is rather low. In part to compensate for low sensitivity, current diagnostic guidelines specify that three sputum samples should be obtained from each patient, usually an on-the-spot sample when the patient presents at the health facility, an early morning sample that the patient collects at home, and a second on-the-spot sample when the early morning sample is brought to the health facility. As a consequence of this schedule, the diagnosis of TB by means of sputum smear microscopy requires at least two days.

1.6.3. *Sensitivity of sputum smear microscopy*

Estimates of the sensitivity of sputum smear microscopy against the gold standard of culture vary enormously, from 8.8% to 94% (Aber et al 1980, World Health Organisation 1998, Steingart et al 2006). Part of this variation may be accounted for by the quality achieved by a particular laboratory. Another important factor is the bacillary load – the sensitivity of sputum smear microscopy in detecting the most infectious cases in the community has been postulated to be as high as 90% (World Health Organisation 1998, Grzybowski et al 1975). Chan et al (1971) have performed both,

microscopic (fluorescence microscope) and culture examination, on two sputum samples from each patient in their study population in Singapore. The numbers presented in their paper suggest, that microscopic examination of a single sputum sample on average could identify 58% to 65% of all cases that would be positive on repeated culture examination (own analysis of data in Chan et al 1971). Heifets & Desmond (2004) postulate that 60-70% of all culture-positive cases could be identified by high-quality direct microscopy.
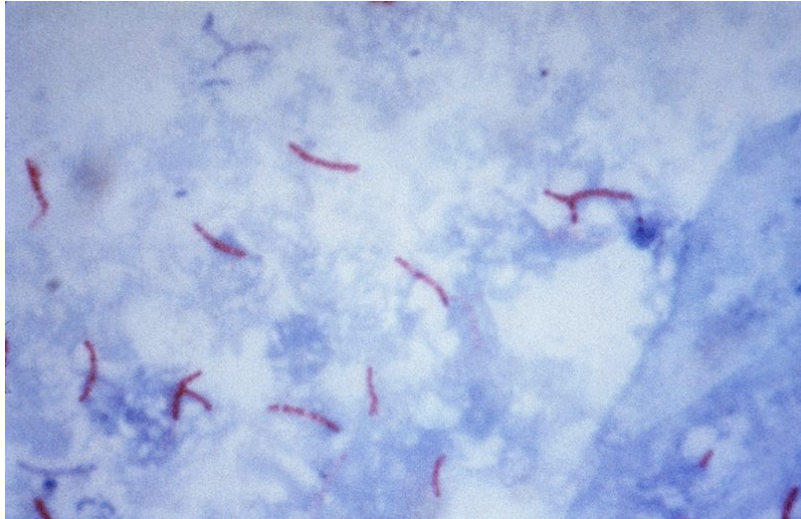
Figure 1.3. Mycobacterium tuberculosis. Ziehl-Neelsen stain.
Image released into the public domain by CDC, Atlanta.

It has repeatedly been found that the third diagnostic and the second follow-up sputum smear examinations contribute few cases and detect few failures of conversion (Ipuge et al 1996, Harries et al 2000, Rieder et al 2005, Mabaera et al 2006). The third sputum contributed only a very small proportion of total cases detected in a four-country-study (Rieder et al 2005). The authors conclude that: "under prevailing settings in some of these countries, it makes little sense to require a third serial diagnostic smear [...]". However, before implementing such a fundamental change in different countries across the world, it would be favourable to have more and independent estimates of the fraction of cases that would be missed if only two serial sputum smears were required. If the sensitivity of examining a single sputum smear were known, this could provide an independent estimate of cases missed by dropping the requirement for a third serial sputum.

DANTB (2002) in a study in Orissa, India, report cultural factors inhibiting women to cough and to produce sputum. Many women reported feeling embarrassed when producing sputum. Unfortunately, these findings are not quantified. Good quality

sputum is essential for diagnosis, because saliva and nasopharyngeal discharge do not contain suitable numbers of bacilli (American Thoracic Society 2000). Whether sputum smear microscopy does diagnose one sex preferentially is unknown. Rieder et al (1997) analysed the number of slides from suspects that had to be analysed to find one case in four different countries. In all four countries, they found that a higher proportion of male than female suspects were diagnosed as cases, which they interpreted as true difference in prevalence among suspects.

Table 1.1. Comparison of the most important diagnostic tests for tuberculosis†

Test	Advantages	Disadvantages
Conventional sputum smear microscopy	Cheap, basic equipment, simple to learn, relatively quick, high specificity.	Low sensitivity, considerable workload.
Fluorescence microscopy	Relatively cheap, quick, high throughput, better sensitivity than conventional microscopy, high specificity.	Uninterrupted supply of electricity needed, training and maintenance more demanding than conventional microscopy, acceptability to laboratory staff is an issue.
Culture	Gold standard, sensitive and very specific, basis for species identification (to exclude other acid-fast bacilli).	Obtaining results often takes 4 weeks or more in low-resource settings, proficiency needed to avoid contamination and to assure quality.
Chest x-ray	Quick.	Intra- and inter-rater variability high, sensitivity and specificity depend on rater, but neither is very good.
Fluorography	Quick.	Similar to chest x-ray, but even less accurate.
Rapid diagnostic tests	Quick, no equipment needed, very simple to administer.	Diagnose infection including latent infection, consequently limited utility in high-incidence settings. Sensitivity and specificity may be issues.
Tests based on nucleic acid amplification	Species identification is possible (to exclude other acid-fast bacilli), highly specific and fairly sensitive.	Advanced equipment and expertise needed.

† References: Davies & Pai (2008), Koppaka & Bock (2004), Steingart et al (2006), Steingart et al (2007), Van Deun (2008), World Health Organisation (1998).

In several TB programs in Central Asia, including the Tajik NTP, unusually high rates of PTB- cases are noted (World Health Organisation 2009). Neher (2005) wrote about the high rate of PTB- cases in Tajikistan: "it has to be assumed that a high percentage

of sputum smear negative and extra-pulmonary TB-cases are inactive cases and therefore over-treated". So far there have been no studies investigating the sensitivity of sputum smear microscopy and its potential link to the high proportion of sputum smear negative cases in Central Asia. Understanding the possible role of the quality of microscopy examination in the high proportion of PTB- cases would be crucial. A study on the diagnostic accuracy of sputum smear examination in the routine program setting of Tajikistan is presented in chapter 10 of the present thesis. The quality of microscopy examination will also influence the choice of diagnostic test, which may determine access to diagnostic services. The result of microscopy examination may play a role in the decision about in- or outpatient treatment, which may strongly influence access to medical care, mainly but not exclusively through affordability of services. Chapters 5 and 7 elaborate on the links between accurate sputum smear examination and access to care for TB.

1.6.4. *Fluorescence microscopy*

The preparation of slides for fluorescence microscopy is generally similar to the procedure for sputum smear microscopy according to Ziehl-Neelsen. However, different dyes are used and consequently the requirements differ in some details. The slides are viewed in a darkroom under a fluorescence microscope and AFB appear as bright green rods against a dark, partly red background. Fluorescence microscopy is conducted at a magnification that is ten times lower than the magnification in conventional microscopy, but the bright green AFB are still well visible. Due to the lower magnification a larger area of the slide can be viewed and consequently the sensitivity of fluorescence microscopy is higher – especially in the case of scanty-positive cases (Steingart et al 2006). However, fluorescence microscopy requires higher initial investment, the ability to assure maintenance of the more sophisticated microscopes, uninterrupted supply of electricity and that darkrooms be acceptable to the laboratory staff (Van Deun et al 2008). So far, no laboratory in Tajikistan is equipped for fluorescence microscopy.

1.6.5. *Culture of Mycobacterium tuberculosis*

Culture of MTB is conducted on egg-based or agar media and is considered the gold standard of TB diagnosis. Due to the slow doubling time (15-20 hours) of MTB compared to other bacteria, culture of MTB is time-consuming and results are not

available before two weeks even in the most advanced laboratories and may take up to eight weeks (Heifets & Desmond 2004). Consequently, culture plays only a limited role in the diagnosis of tuberculosis in high-incidence settings. However, culture capacity has been built up in recent years in the order to improve the possibilities of diagnosis of MDR-TB.

1.6.6.   *Chest radiography for diagnosis of tuberculosis*

Chest radiography, or chest x-ray (CXR), is another very widely used means for the diagnosis of tuberculosis. At the initial site of infection in the lungs, the so-called Ghon complex will usually form, consisting of a calcified focus of infection and associated lymphatic lesions. The Ghon complex is usually visible on a quality CXR, even in people who do not develop active disease. During active disease, the lesions are more extended. However, the lesions caused by TB can take almost any form on CXR and diseases other than TB can cause patterns that have often been thought typical of TB (American Thoracic Society 2000, Koppaka & Bock 2004). Similarly, a recent study in Russia found considerable inter-observer variation in the interpretation of CXR in a sample consisting of tuberculosis specialists, radiologists and respiratory specialists (Balabanova et al 2005). CXR should not be confounded with fluorography, which has been used extensively and sometimes is still used for TB diagnosis. The World Health Organisation (2003b) explicitly discourages the use of fluorography in the diagnostic procedure for tuberculosis.

While CXR is not required for the diagnosis of a PTB+ case, the diagnosis of sputum smear negative cases (PTB-) relies heavily on CXR in low-resource settings. The guidelines for national TB control programs recommend that PTB- be diagnosed only in patients of whom at least three negative sputum smears have been obtained, whose CXR shows abnormalities consistent with active TB, whose disease did not improve upon a full course of broad-spectrum non-TB antibiotics and who will be put on a full treatment course of anti-TB chemotherapy by a clinician (World Health Organisation 2003b).

1.6.7.   *Rapid diagnostic tests*

A large number of rapid diagnostic tests have been developed and are commercially available. All of these diagnose infection of TB – including latent infection – rather than exclusively active disease (World Health Organisation 2008, Davies & Pai 2008).

Advantages of rapid tests include the simplicity of their handling, which is expected to lead to more consistent results, as well as the availability of the result at the point-of-care and within minutes. In comparison, obtaining a final result by means of sputum smear microscopy requires at least two days. Further, rapid tests could reduce problems of work overload in many TB laboratories in high-incidence countries.

Several studies have investigated the accuracy of rapid diagnostic tests for the diagnosis of active TB disease and found that none of the currently available tests has the potential to play an important role in the diagnosis of either pulmonary or extra-pulmonary TB (Steingart et al 2007a, Steingart et al 2007b, World Health Organisation 2008).

1.6.8.   Other diagnostic tools

Other diagnostic tools including nucleic acid amplification and tomography require advanced equipment and are currently hardly available in low-resource settings. Due to the very limited role that these techniques currently play in countries with medium to high incidence, they are not further explored here.

1.7.   Health care seeking

Options for health seeking include self-treatment, informal providers (traditional healers), private doctors, and public medical facilities of any kind (Auer et al 2000, Hoa et al 2003, Storla et al 2008). The question of adequacy of choice of care for a particular health condition arises. Inadequate choice of the care provider may cause a health condition to progress or to spread to other people. Given that TB control relies mostly on passive case finding, i.e. on TB patients presenting to health services, adequate health care seeking of TB patients is important not only for the individual patient, but also from a societal perspective. Perception of causes and remedies for TB varies in different contexts and may differ from biomedical concepts to a varying degree. The patient's perception of the causes and remedies for TB will shape the health care seeking behaviour and misperceptions of TB may lead to patients not accessing medical care. Even when patients access medical care, the choice of the provider can still strongly influence the time required to obtain a correct diagnosis and whether patients receive appropriate treatment. Moreover, the patient's choice is influenced and often limited by the access to a particular kind of care.

1.8. Access to care

1.8.1. Global perspective and theory of access

The Universal Declaration of Human Rights (United Nations General Assembly 1948) is unequivocal: "Everybody has the right to [...] medical care [...]". Contrary to this normative statement, many health systems do not provide health services in a way that all people can exert their right to medical care: access to medical care is not a matter of course, rather it is a key goal that health system are striving to achieve (Murray & Evans 2003). On a global scale, Victora et al (2003) have found that for a multitude of reasons, poor people lack access to medical care even though they are exposed to disease more often than wealthier people and consequently are more in need of medical care. Children in low-income countries face a risk of dying before their fifth birthday that is about 20 times higher than that of children in high-income countries. Gross inequalities are also found within many countries between the poorest and the wealthiest parts of societies. In addition to income, many other reasons – often correlated with poverty – can contribute to the lack of access to health care. These include among others education, cultural factors, or the location of health care facilities and are further discussed below. While poverty is not the only reason for lack of access to medical care and good health, it has a tremendous effect. Ill-health affects people's ability to sustain their livelihoods and often forces them to make out-of-pocket expenditures for health care – two factors that often lead to further impoverishment and make affected households more susceptible to future disease. This vicious circle is known as the 'medical poverty trap' (Whitehead et al 2002).

Access entails several components, namely availability, accessibility, affordability, adequacy and acceptability (Aday & Andersen 1974, Obrist et al 2007). These are sometimes referred to as 'the five A's'. No precise and universally accepted definitions of the five A's exist, but a few of the main components will be presented in the following. Availability depends on the existence of diagnostic services, drugs, vaccines, trained health providers, and health care infrastructure in the wider area or the country of question. Accessibility depends on factors like geographical distance to the care provider, available infrastructure (roads, transport, etc.), and the patient's ability to use the latter and to move. Affordability depends on direct and indirect costs as well as on the patient's ability to pay. Adequacy describes the match between patients' needs and expectations on the one side and the organisational characteristics of health

services on the other, including opening hours. Acceptability of health care services includes socio-cultural concepts of a disease, questions around confidentiality, as well as the perception of staff friendliness. Some authors have used utilisation as a measure of access to care (see also Obrist et al 2007, Andersen 1995), but here, utilisation is seen as the product of need and access.

1.8.2. Access to tuberculosis services

For various reasons access to care is of particular importance in the field of TB control. Maher & Nunn (1998) identified access as "the most important determinant of the outcome of treatment of TB". All the components of access to care described above may affect access to TB treatment. One of the reasons exacerbating the issue of access in the area of TB treatment is that DOT requires daily or thrice weekly meetings with the DOT provider. Consequently any barriers to access have to be overcome on a daily or at least regular basis. So far, the analytical framework presented in the previous section has never been used to analyse access to care for tuberculosis – nor have any other comparably comprehensive theories of access to care.

Some studies on adherence have examined several of the factors that are important barriers to access. Given that adherence is influenced by a multitude of factors, it is often easier to document, that a particular factor has *some* influence on adherence, than to assess the relative importance of different factors. Greene (2004) formulated this in a very eloquent way: "just because a culture-specific barrier [is present and therefore] *might affect* adherence to tuberculosis therapy does not mean it is the *determining factor* behind nonadherence" [emphasis by Greene]. From his studies in urban Bolivia, he concluded that structural barriers to TB care were much more important than patient-side factors. However, there is no consensus on the factors that are included on the demand- or patient-side. Contrary to Greene (2004), Ensor & Cooper (2004) included financial costs incurred outside the health facility (including among others transport costs) among demand-side factors.

Despite the global burden of TB and the pivotal role that access to TB services plays in the fight against TB, surprisingly few studies exist on access to TB treatment – and even fewer from post-Soviet countries. No systematic study about access to care for TB in a former Soviet country is found in the scientific literature. A relatively recent article by Keshavjee & Becerra (2000) describes anecdotal evidence from Tajikistan of

serious problems of availability of TB services, which is one component of access to care. Patients were unable to access TB care due to drug shortages in the hospital of a regional capital. However, this relates to the pre-DOTS era and it is likely that the situation has considerably improved since. The distance between the patient and the health worker providing DOT was a serious obstacle to TB control based on the field experience of a program implemented in Uzbekistan (Shafer et al 2001). Understanding the determinants of access to TB treatment would be crucial to better tailor TB programs to the needs of patients.

1.8.3. Delay

Access is often not a binary trait that can either be present or absent. Rather patients can reach health care services and obtain treatment more or less readily, depending on how difficult access is for them and on the severity of their condition. The period from onset of symptoms to first consultation at a health care facility is referred to as patient delay. The period from first consultation to diagnosis is referred to as health system (or provider) delay. It may be followed by a treatment delay designing the time span from diagnosis up to onset of treatment. Seen from this point of view, patients who never reach the health care facility have an infinite patient delay. Many studies have shown, that people sick with TB may delay obtaining health care for long periods of time, which constitutes a serious problem for the control of the epidemic. Several studies tried to quantify the influence of delay on the TB epidemic. Asch et al (1998) found that during a mean delay of 74 days, TB patients in Los Angeles county infected an average of eight contacts. A commonly cited estimate is that an untreated case of TB will infect over 20 contacts during the natural history of the disease until death (Styblo 1991, Grzybowski et al 1975, Lawn et al 1998).

In a study in Brazil, the median delay found was three months and about 60% of patients had a delay longer than two months (dos Santos et al 2005). In Ghana, a median delay of four months was reported by patients (Lawn et al 1998). It can be assumed that there is a lot of overlap between factors hampering access to health care and factors leading to longer delay. Commonly, urban residence was associated with shorter delays than rural residence, which might reflect the better accessibility of health care in these areas (Lawn et al 1998; Lienhardt et al 2001). In general, however, health system delay tends to be longer than reported patient delay. A review identified several characteristics of health systems and their interaction with the patient as risk factors for

delay, including the type of the facility where the first contact with the patient took place (Storla et al 2008). Making the first contact at a low-level government health facility or with a private provider was often associated with longer delays. These findings show that there are links between the organisation of health care delivery, health care seeking and delay, which again is linked to the control of TB. How long patient and health system delays are and which patients experience the longest delays in Tajikistan or other former Soviet republics is all but unknown. Especially in view of the low estimated case detection rate in Tajikistan, a better understanding of factors influencing delay and access to care is urgently required. It will help policy makers and program managers to better tailor TB services to the needs of patients and thus to improve TB control.

1.8.4. *Affordability of tuberculosis services*

Studies comparing the health system costs of the DOTS strategy to more traditional ways of organising TB services, have shown that the relatively shorter duration of chemotherapy and the predominantly ambulatory provision of treatment foreseen by the DOTS strategy allows health systems to deliver TB services at lower costs (Jacobs et al 2002, MacIntyre et al 2001, World Health Organisation 2003b, Wurtz & White 1999). Several studies tried to quantify the household costs of TB in different settings (Croft & Croft 1998, Kamolratanakul et al 1999, Needham et al 1998, Rajeswari et al 1999, Wyss et al 2001). Russell (2004), in a review of household costs of different diseases, found that TB often has catastrophic effects on household economy and linked this to the long duration of the disease. Costs of disease are usually classified into direct and indirect costs (Russell 2004, Wyss et al 2001), where the former are all expenses incurred and the latter comprise missed income and intangible costs. Direct costs are further divided into medical (for consultation, diagnostic tests, medication, etc.) and nonmedical costs (for transport, special food items, etc.). Nonmedical and indirect costs often make up significant shares of the total cost of illness. Total costs of a TB episode may be as high as nine tenths of annual household income (Wyss et al 2001). However, the total costs as well as the contribution of different kinds of costs are not fully understood. Availability of free medical services, need for transport, and need (perceived or actual) for special diets are just a few of the factors that may influence household costs and their breakdown (Russell 2004). As seen above, ambulatory as compared to inpatient treatment may lead to substantial savings for the

provider side. For the patient side, the picture is more complicated. Russell (2004) noted that hospitalisation for different diseases caused very high costs in some countries, where fees were charged, in contrast to other countries providing inpatient health care for free. Benefits of hospitalisation in Russia, for example, are not restricted to free care, but include a kind of substitute for social services (Atun et al 2005a, Floyd et al 2006). Very little is known about factors that potentially determine the illness-related costs faced by TB patients. Male sex, longer delay until start of treatment and most importantly clinic-based DOT (versus self-administered treatment) were the determinants of higher costs in an urban setting in Zambia (Aspler et al 2008). The determinants of costs in settings where self-administered treatment is not foreseen by the program are unknown.

1.8.5. *Affordability of care in Tajikistan*

As seen above, affordability is one of the components of access to care. Falkingham (2004) investigated the influence of out-of-pocket payments on access to medical care in Tajikistan based on the data of the Tajik Livings Standard Survey. Almost half of the respondents who had consulted a doctor in the last two weeks preceding the interview indicated they had paid for the consultation. Among those who felt they had needed medical care, a significant proportion did not obtain it. Exact figures for the total population are not given, but for women of age 65 or above, almost two thirds who felt they needed care did not seek such. Of those who did not seek care, about one third indicated they couldn't afford to do so. Among the wealthiest quintile, this proportion was at about 24%, while it was around 42% among the poorest quintile. Falkingham (2003) studied changes in the access to maternal health care services. She found a significant decline in the utilisation of these services since independence of Tajikistan from the Soviet Union. Whether the decrease in utilisation of non-sex-specific health services has decreased similarly remained unstudied. It is conceivable that women suffered particularly from deteriorating access to health care. Studies on sex-differences in access to TB care in Central Asia are so far missing. The decade-long Soviet area, when gender equity was relatively high on the political agenda, has been followed by a period of nation-building and cultural return to more conservative values. To what extent access to medical care for women was affected, is poorly known.

The distinction between formal and informal payments is not clear to many patients (Falkingham 2004). Moreover, there is a tradition in Central Asia and the Caucasus to

thank caregivers with gifts that may be in-kind or cash. More detailed investigations are needed to document the purpose of payments and gifts as well as the degree to which these are made voluntarily. The case of TB is special in terms of informal payments because the health system and the patients receive considerable external support targeted specifically to TB control. This includes free TB-drugs provided to the health system and food supplies for patients' families. Information on household costs of a TB episode is lacking, and it is unclear, how these relate to the support patients receive and to funds available at the household level. Evidence on household costs is needed to better understand the financial barriers to access to health care.

1.8.6. *Acceptability of tuberculosis services*

Acceptability of services comprises several domains, including perceived competency of providers, aspects of interpersonal communication, and confidentiality of services (Obrist et al 2007, Aday & Andersen 1974). In different contexts, TB was linked to a strong stigma. Stigma often translates into the patients' unwillingness to disclose their disease to others. In a study in Pakistan, Khan et al (2000) found that patients were very unwilling to disclose their TB to anyone outside the immediate family. The reasons given were fear from seclusion and social boycott. Especially young women were afraid they would face difficulties marrying or would be sent away by their husbands. The researchers hypothesised that the observed stigma is closely linked with the community's belief that TB is incurable and go on saying: "which in the current circumstances of Pakistan is probably a reasonable perception." The problem that a stigma poses for the success of detection and cure of TB cases is accentuated in Pakistan by a lack of patient confidentiality. In Orissa, India, 2% of all TB patients expressed anxiety of social isolation (DANTB 2002). Only 2% of men and 9% of women expressed concerns about disclosing their disease to their families and to other people in the village. This is low in relation to a high proportion of more than 60% of patients who were sceptical about the curability of TB. In a study in southern India, at least three quarters of people in the study community stated that TB patients would hide their disease (Atre et al 2004). Almost 50% of respondents in this study thought that heredity played a role in TB. Such misperceptions of the causes of TB may mean, that patients do not perceive a need for conventional medical care. Furthermore the perceived necessity to hide the disease may hamper the acceptability of medical facilities, subject to the confidentiality of services.

Even if not connected to a stigma, knowledge about TB may influence the decision to seek care and the choice of services. Studies in Peru and Brazil have found that typically patients consulted TB diagnostic facilities if they noticed weight loss, rather than chronic cough (Baldwin et al 2004, dos Santos et al 2005). Another symptom found to prompt earlier care seeking was haemoptysis (Lienhardt et al 2001), whereas similar studies did not find a link between level of education or literacy status and the delay in treatment (Lienhardt et al 2001, Dhingra 2002).

1.8.7. Adherence to TB treatment

Greene (2004) identified five general approaches to non-adherence in the literature. Greene summarises them with the terms (i) "decontextualised blaming of the patient", (ii) discussion of "the intrapersonal psychologic structures" in certain types of patients, (iii) prediction of non-adherence based on demographic factors, (iv) "targeting cultural difference as the chief determinant of non-adherence", and (v) "structural violence". His own study from Bolivia shows that structural constraints do play a determining role in non-adherence. In the literature blaming the patient or discussing intrapersonal psychological structures of the patient, her or his ability to rationally assess and prioritise need for medical care relative to other perceived needs, took a prominent position (Greene 2004, Sumartojo 1993). Demographic variables of course are not proximate causes of adherence or access. The cultural identity of the patient again may influence the acceptability of medical services but cultural identity may also be an ultimate factor and correlate with socio-economic characteristics of the patient, which then determine another component of access to care, e.g. affordability of services. 'Structural violence' comprises many aspects of the health system. These may include components of access to medical care like availability, accessibility, affordability, adequacy and acceptability.

Khan et al (2000) also investigated determinants of treatment adherence. They concluded that their results showed no clear pattern to allow distinguishing between patients who completed or defaulted treatment. However, they also observed that patients often stopped working after TB had been diagnosed, and the data they present indicate that this was more common in non-adherers than in adherers. Stopping to work comprises high indirect costs and it can therefore be hypothesised, that patients who have to stop working because of direct consequences of the disease and factors associated to treatment delivery, have a higher probability of defaulting.

1.9. Hospitalisation for tuberculosis treatment

The strong variation in hospitalisation rates for TB and in reasons for hospitalisation are probably linked to the lack of detailed recommendations on hospitalisation in the guidelines for NTPs (World Health Organisation 2003b), which leaves room for national programs to handle hospitalisation according to the national context. Perelman (2000) emphasised the tradition of hospitalising TB patients in Russia. He linked the need for hospitalisation to overcrowding at the patient's home and to patient-side problems like alcoholism and antisocial behaviour (cf. section adherence). Much of this tradition of hospitalisation and its reasons supposedly apply also for other parts of the former Soviet Union, because these shared the same health system over decades and have inherited its structure at independence. However, there have been no systematic studies of the reasons for hospitalisation in other parts of the Soviet Union.

A study in the Samara region of the Russian Federation found that the system of service remuneration gives perverse incentives to the providers (Atun et al 2005b). There was no performance-related element. Providers benefited from maximising the time patients were under supervision, from repeatedly admitting the same patients to hospital, and from increasing the number of investigations or surgical activities performed. Such inefficient use of resources can negatively affect access to care. On the other hand, hospitalisation of TB patients in Russia also fulfilled the role of social services (Atun et al 2005a). In Tajikistan, the lack of resources likely means that the health system cannot fulfil the same role of social services for TB patients as in Russia.

1.10. References

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2. Objectives

The overall goal of this thesis was to make a scientific contribution to the understanding of access to medical care for TB in Tajikistan. This was not seen in isolation but as a showcase for other medical services in Tajikistan and for TB services in other countries. A comprehensive set of factors was considered as potential determinants of access to medical care, including availability, accessibility, affordability, adequacy and acceptability of care. Based on the results of the first study, special attention was given to household costs of TB and their determinants and timing.

The general and specific objectives of the individual studies presented in chapters 4 to 10 were:

1. **To identify key factors for access to care for TB.**
   1.1. To identify factors impeding or contributing to access to medical care for TB as perceived by community members, TB patients and health care providers.
   1.2. To determine the relative importance of factors pertinent to availability, accessibility, affordability, adequacy and acceptability for access to TB care.
   1.3. To assess the general population's knowledge and awareness of TB and its symptoms.

2. **To investigate delay to TB treatment.**
   2.1. To estimate the patient and health system delays experienced by patients in the TB program of Tajikistan.
   2.2. To describe typical health care seeking patterns including the quantification of the use of different diagnostic tests.
   2.3. To analyse statistical relationships between the extent of delay and different predictors related to the patient and to the organisation of health care delivery.

3. **To quantify the cost burden faced by TB patients.**
   3.1. To quantify all direct and indirect material costs incurred by TB patients and their households in relation to TB disease.
   3.2. To compare the total costs of a TB episode with measures of income in Tajikistan.
   3.3. To identify the time periods when patients face peaks of high costs.
   3.4. To quantify the contribution of different line items to total direct costs.

4. **To identify quantitative determinants of affordability of TB care.**

   4.1. To identify patient and system factors associated with higher direct costs.

   4.2. To quantify the use of selected economic coping strategies.

   4.3. To identify patient and system factors associated with coping strategies that can potentially lead to impoverishment.

5. **To analyse factors associated with hospitalisation of TB patients.**

   5.1. To identify factors associated with hospitalisation.

   5.2. To assess predictors of treatment success.

6. **To assess the performance and potential impact of a food distribution program for TB patients.**

   6.1. To assess whether patients are aware of their entitlement to food supplements and receive them.

   6.2. To quantify the local market value of food supplements and any costs associated with them.

7. **To model the sensitivity of routine sputum smear microscopy.**

   7.1. To model the sensitivity and specificity of sputum smear microscopy as carried out in peripheral laboratories under routine program conditions.

   7.2. To inform the policy discussion on reducing the requirement for TB diagnosis from three to two serial sputum smears.

   7.3. To provide evidence to program managers and providers about the performance of sputum smear examination in Tajikistan.

3. Study framework and overview

3.1. Theoretical framework of access to care

The present thesis investigated access to medical care on the example of tuberculosis in Tajikistan. This chapter presents the theoretical framework that guided our studies conceptually. The ethos behind our framework is the conviction that people who need medical care should be able to use it, i.e. should have access to care. We define access to care as the ability of people with an objectivistic need for medical care to utilise such. We make use of a conceptual framework of access that was developed in the frame of a program for malaria control, but with the goal of providing a theory of access to care more generally (Obrist et al 2007). This framework emphasises the link between access and livelihood insecurity and relates these to the wider context of health systems and the vulnerability context (Figure 3.1). According to this concept, access consists of five components: availability, accessibility, affordability, adequacy and acceptability, called the five A's. The key factors comprised in each of the five A's are summarised in table 3.1. While the concept includes the wider context of livelihoods, our analyses were concentrated around the access itself.
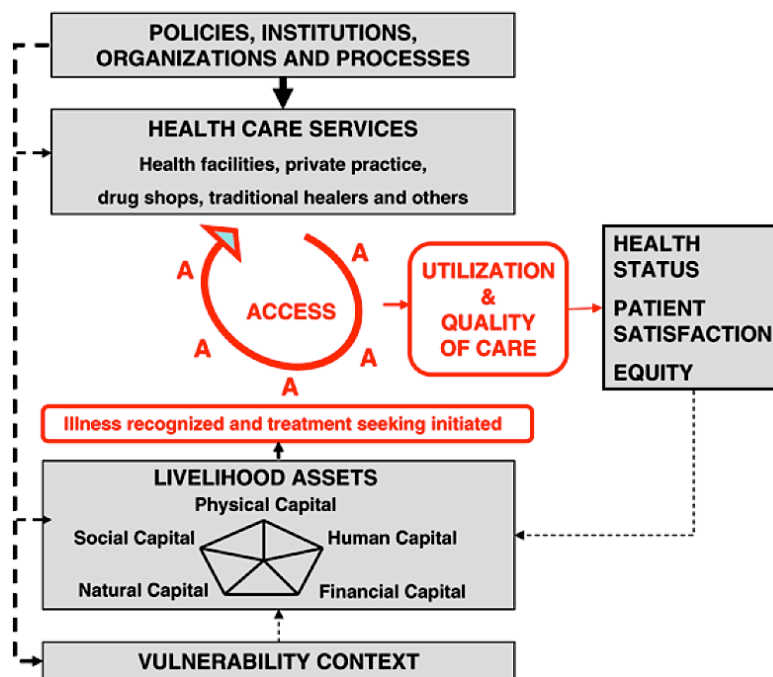
Figure 3.1. Framework of access. Figure from Obrist et al (2007), adapted.

3.2.   Concepts and types of illness-related costs

We used a framework for the analysis of the economic costs of illness at the level of the household that was given by Russell (2004, Figure 3.2). Studies of costs of illness at the level of the patients' households differ in terms of the types of costs they included (Russell 2004, McIntyre et al 2006). In our studies we have been guided by the rationale that all material and financial costs that are incurred due to the disease should be included. In other words, a causal relationship between disease and the incurred costs was the criterion to include a specific cost. This causal relationship could be indirect or only perceived. An example for a perceived causality could be special disease-related diets (termed 'special foods' by some authors, Attanayake et al 2000, Needham et al 2004), which are not necessarily evidence-based but for which patients spend money. Costs related to co-morbidities (e.g. medication for diabetes) were not included.

Table 3.1. Theoretical framework for access to care: its five components and some of the factors entailed§

Component	Factors* (and examples)
Availability	Presence of health care facilities in near or not-too-far region
	Presence of health care staff (doctors, specialists, nurses, etc)
	Presence of consumables in facility/pharmacy (drugs, vaccines, test kits, etc)
Accessibility	Geographical distance to facility
	Available transport infrastructure (road, means of transport)
Affordability	Patient's ability to pay
	Medical direct costs (consultation fee, drug costs, cost of surgery, informal payments, etc)
	Non-medical direct costs (cost of transport, special diets, etc)
	Missed opportunities (lost income due to inability to work)
Adequacy	Convenient opening hours
	Appropriateness of organisation of health services
	Physical state and cleanliness of infrastructure
Acceptability	Match between local health beliefs and health services
	Match between socio-cultural values and health services
	Expected quality of care (perceived competency, friendliness of staff)
	Confidentiality of services
	Side-effects of treatment

§ Following Obrist et al (2007), adapted.
* Access to care is a very comprehensive concept and the factors listed here are not meant to be exhaustive.

Illness-related costs are classified into direct and indirect costs (Wyss et al 2001, Russell 2004, McIntyre et al 2006). Direct costs denote expenditure, also called out-of-pocket payments, and indirect costs denote opportunity costs, like income that was foregone due to the patient's inability to work (Table 3.2). Other household members may also forego income because they accompany the patient to the facility or spend time on patient care at home (Russell 2004, Wyss et al 2001); their lost income was also included. Where income was in-kind, like often in subsistence agriculture, we estimated its monetary value based on the local market value reported by the patient. However, immaterial indirect costs like the psychological distress or foregone education opportunities when children were unable to attend school were not included.
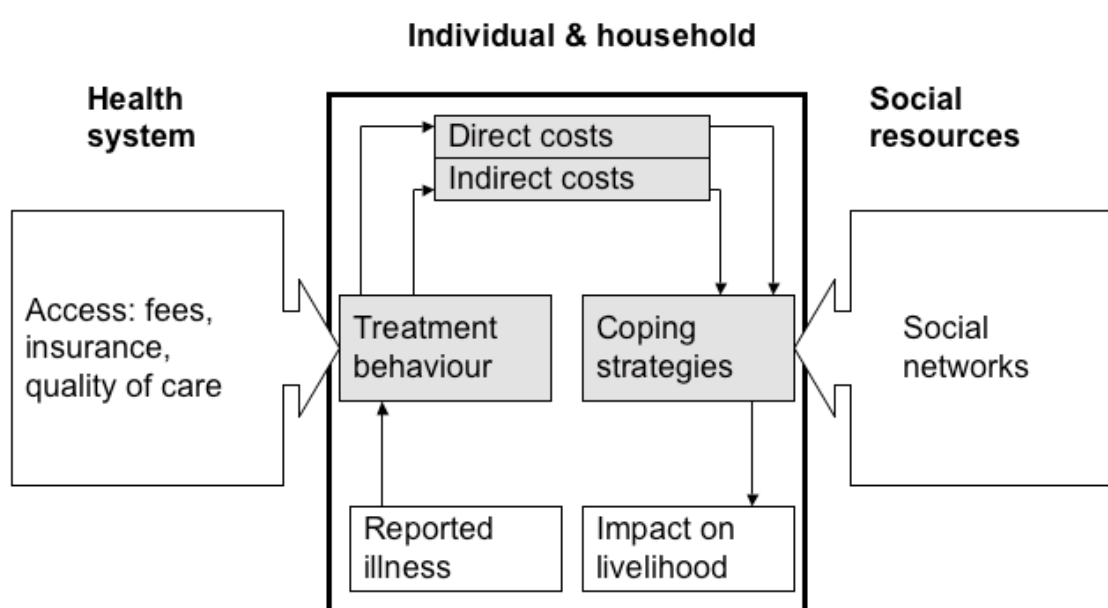
Figure 3.2. Analytical framework for economic costs of illness. Boxes with grey background designate the areas covered in chapters 5 to 7 of this thesis.

Direct costs are further broken down into medical and non-medical direct costs (Russell 2004, McIntyre et al 2006). For the line items included in medical and non-medical costs, we generally followed Russell (2004). We completed single line items found in other studies (e.g. Wyss et al 2004) and adapted the apportioning of certain items. Medical costs included costs of diagnostic tests, consultation fees, drug costs, cost of surgery, hospitalisation fees and other services delivered by the formal health system (Table 3.2). Some studies included costs for traditional healers in medical costs. We adapted this approach in order to increase the focus of medical costs on allopathic medicine. Consequently, we included costs of traditional healers in non-medical costs. Non-medical costs also include 'additional food costs', which is sometimes termed 'special foods' and comprises the costs for special food items that contribute to cure

according to local health beliefs (Russell 2004). These are food items that are not usually part of people's diets during times of good health (or only in smaller amounts) and that may be expensive. In Tajikistan, these may be expected to correspond to concepts of 'warm' and 'cold' foods also found in South Asia (Khan et al 2000, Attanayake et al 2000, Pool 1987). The distinction between special foods and traditional home-remedies may sometimes be gradual only. The last item among non-medical costs that requires explanation is 'changes in housing'. This term summarises expenditures for furniture or amendments in the housing that are made to better accommodate the patient.

Table 3.2. Classification of illness-related costs at the household level

Type of cost	Examples
1. Direct costs	
1.1 Medical costs	
Diagnostic examination	Radiography, blood count, sputum smear examination, any laboratory test
Consultation fees	Medical doctor fee, prescription fee
Drugs	Anti-TB drugs, vitamins, medication for cough
Hospitalisation	Admission fees, cleaning of ward, washing sheets
Surgery	Consumables and fees for surgical procedures
Other medical services	Any medical service or good that has to be paid for
1.2 Non-medical costs	
Transport costs	Transport to pharmacy, to traditional healer, to family doctor, etc.
Additional food costs	Illness-related diets
Home-remedies	Herbs or special kinds of meat (marmot, dog, etc)
Traditional healer fees	Monetary or in-kind fees paid to a traditional healer (tabib)
Modifications to housing	Changes aimed at better accommodating the patient
2. Indirect costs	
Patient loss of income	Cash or in-kind income foregone due to the inability to continue usual income-generating activities
Caregiver loss of income	Income foregone while taking care of patient or substituting his labour

3.3.   Overview over studies conducted for the present thesis

In the following, an overview of the studies conducted in the framework of this thesis is given. We present brief information on the main subject, the methodology and the study area. The studies are presented in the same sequence in more detail in the chapters 4 to 10. The format of these chapters varies to a certain extent because most of these chapters are manuscripts that have been submitted or already published and the manuscripts are presented in the format of the respective scientific journal.

We had a close collaboration with Project Sino for this thesis and many of our results have also been summarised in project reports in order to provide an evidence-base for certain aspects of project implementation. Project Sino has been supporting the Ministry of Health of the Republic of Tajikistan since 2003 in the implementation of health sector reform strengthening primary care. Among many other activities, the project was providing support to introduce DOTS in its pilot districts by 2005 and to integrate DOTS services with primary care services.

The first study conducted for this thesis used focus group discussions to explore access to medical care for TB. A comprehensive range of factors were considered and two methods were used to determine their relative importance as determinants of access to care. The study was conducted in the four pilot district of Project Sino (Figure 3.3). The results of this qualitative study guided the focus of subsequent studies.

The second study was a questionnaire survey among registered TB patients concentrating on health care seeking and delay to start of anti-TB chemotherapy. It was conducted in twelve study districts purposefully chosen among districts with an established DOTS program to represent the typical range of conditions found in Tajikistan. A map showing these twelve districts can be found in the corresponding chapter (Figure 5.1) and is not duplicated here. Data collection for this study was conducted together with the data collection for the two studies on illness-related costs at the level of the patients' households and for the study on food supplements. Consequently, the study area and the study sample of those studies were the same. The study on health care seeking and delay investigated common referral patterns and the use of diagnostic tests in order to identify aspects of the organisation of health services that influence access to care and consequently delay until the start of TB treatment.
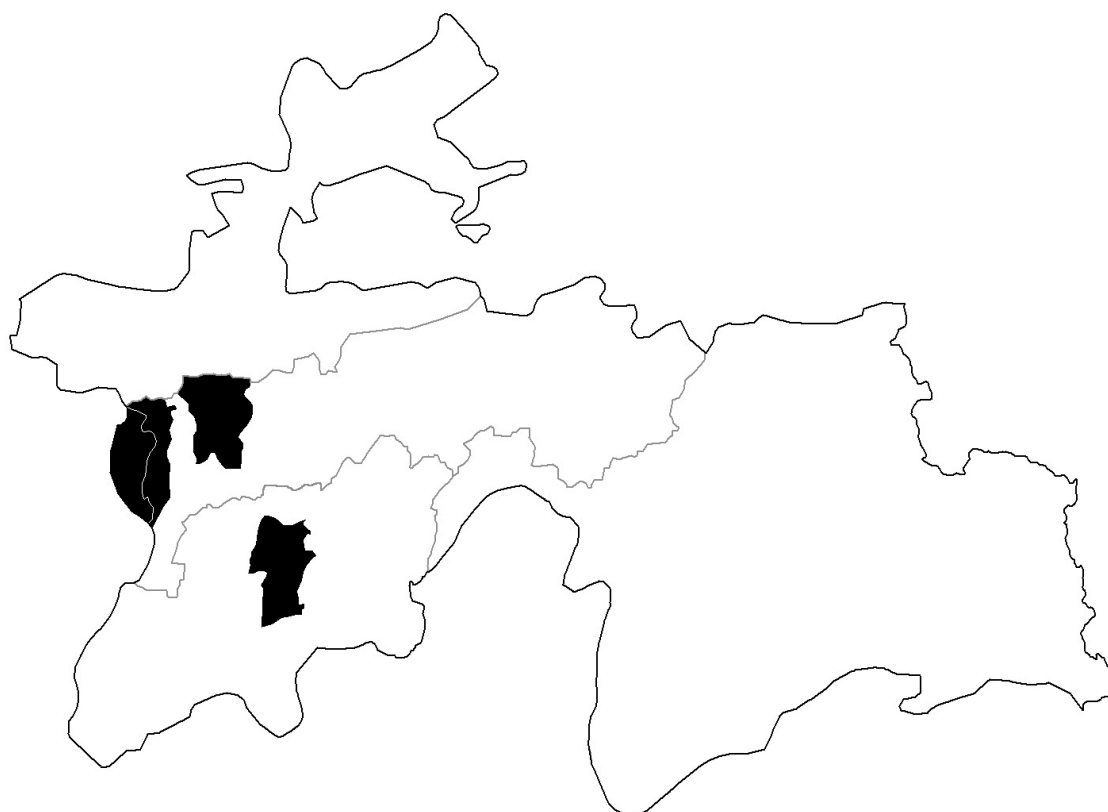
Figure 3.3. Map of Tajikistan showing the four districts, where Project Sino is supporting health sector reform to strengthen primary care (black).

The qualitative study had found that affordability was the most important component of access to TB services and guided the focus of the third and the fourth study. They quantified illness-related costs at the level of patients' households ('household costs'), their repartition over different time periods of TB treatment, and statistical predictors of higher household costs. The fourth study additionally looked into a selection of coping strategies that are most likely to incorporate risks for impoverishment.

The fifth study looked at hospitalisation as a management measure for pulmonary TB. It used registry data from ten TB centres to analyse predictors of hospitalisation out of a set of eight independent variables. As a secondary outcome, treatment success was analysed using the same independent variables and additionally the binary factor hospitalisation.

The sixth study assessed the performance and potential impact of a food distribution program for TB patients. Data collection for this study was conducted alongside the studies on delay and household costs. Only six of the twelve study districts of these studies had a food distribution program and hence this study encompassed six study districts. We looked at the patients' awareness early in treatment about their eligibility for food supplements, at the number of food supplements patients had received towards

the end of treatment, at the monetary costs involved in receiving and picking up food supplements and at their local market value and thus contribution to the household economy.

The seventh and last study of this thesis mathematically modelled the sensitivity and specificity of sputum smear examination based on registry data. Only limited data is available about the accuracy of this test under routine conditions – even though it is the most widely used diagnostic test for TB, one of the most devastating diseases in the world. This study was important not only in terms of a global perspective and the information on the internationally recommended first test for TB, but also from a local perspective: the previous studies had shown a link between under-use of sputum smear microscopy and access to care.

3.4. References

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4. Illness costs to households are a key barrier to access diagnostic and treatment services for tuberculosis in Tajikistan

In memoriam Alisher Jamolovich Rahmonberdiev, who was a great, thoughtful and sensitive person – and acted as moderator for this study.

Running head: Costs to households and access in Tajikistan

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Abstract

Background: Tuberculosis control is based on early detection and complete treatment of infectious cases. Consequently, it is important that tuberculosis suspects and patients can readily access medical care. The present study investigated determinants of access to DOTS services as identified by patients, health providers and community members in four districts in Tajikistan.

Methods: Thirteen focus group discussions involving a total of 97 informants were conducted. Content analysis of discussions and a rating to quantify the relative importance of discussed factors were carried out. A conceptual framework for access to care guided the analysis.

Results: Financial factors were considered the most important determinants of access to diagnosis and treatment of tuberculosis. Expenditure for drugs and consultations, for transport, and for special foods as well as lost income were identified as major barriers to treatment. Notably, out-of-pocket expenditures were emphasized more than lost income. Stigma, doubts about curability and low perceived quality of care were not seen to be significant determinants of access to care for tuberculosis. Community members were well aware of symptoms of tuberculosis and of medical services.

Conclusions: Illness costs to households formed the main barrier to tuberculosis diagnosis and treatment. Medication and the provision of food to hospitalised patients are thought to cause high costs. Patients and community members attributed less importance to lost income than found in other studies. To improve access and ultimately adherence to tuberculosis treatment, effective mitigation strategies, e.g. food contributions or financial stimuli, need to be explored and implemented.

Background

The difficulty in controlling the global tuberculosis (TB) epidemic has been attributed to "low access to a highly effective therapy"[1]. The factors determining access of TB cases to treatment remain poorly understood. This qualitative study was conducted to identify factors influencing access to diagnosis and treatment of TB in Tajikistan and to investigate their relative importance. Thereby it used a framework of 'access to care' developed in a malaria control program[2].

Even when TB control programmes offer chemotherapy free of charge, suspected cases often considerably delay seeking care[3] and defaulting from treatment is frequent. Irregular drug intake and default can lead to relapse which causes further transmission of TB and increases the risk of drug-resistance[4]. Some of the countries with the highest rates of drug-resistant TB are in Central Asia, making treatment adherence even more important in this region[5]. Jones et al[6] identified a list of requirements for treatment adherence, including that patients understand the implications of their illness, regard their health to be a high priority issue, can afford and access treatment and be able to tolerate the inconvenience of clinic visits, medication regimens, and possible side effects of drugs. These requirements show wide overlap with affordability, accessibility, acceptability and adequacy of services, which are core components of access to care[2]. The fifth component of access is availability.

In many contexts, TB is linked to stigma[7-10]. Many communities perceive TB to be incurable[9-11]. For those patients believing their illness be the result of supernatural causes, common sense dictates that they would not utilise biomedical health care. However, in rural Haiti, providing home visits, incentive payments and food complements in addition to free treatment had a strong positive influence on adherence, whereas no influence of sorcery beliefs was found[12]. In urban Bolivia, Greene found that structural barriers including costs of treatment such as transport and radiography were more important determinants of adherence than socio-cultural factors[13]. Saunderson[14] was among the first to emphasize the literature's neglect of costs to patients' households. At large, there are many factors that potentially influence access to care for TB – which ones are the actual determinants is debated.

Tajikistan has seen the breakdown of the previously comprehensive health system. Health care workers are badly paid and poorly motivated. Often patients have to pay for

health services that are stipulated to be free of charge. Since independence from the former Soviet Union in 1991, utilisation rates of services have decreased and incidence of TB has increased by about 80%[15]. A recent study in Tajikistan suggested costs of care to influence access to medical care[16]. Among people who reported not seeking care for their health problem, one third – 24% among the wealthiest quintile and 42% among the poorest – stated that lack of money was the reason for not doing so.

The National TB Programme of Tajikistan adopted the DOTS strategy in 2002 assisted by several international NGOs, including Project Sino funded by the Swiss Agency for Development and Cooperation, which supports the ongoing integration of TB services into primary care in the study districts. Hospitalisation rates are typically above 50%. Official data for 2006 indicated 79% DOTS coverage, 33% case detection and 84% treatment success in Tajikistan[15,17]. In most areas, DOTS was introduced during 2005 and 2006.

Methods

Setting and study population

The present study received ethical approval from the Ministry of Health of Tajikistan. It was conducted in the four pilot districts of Project Sino, which include two of the districts of Tajikistan where DOTS was introduced earliest. The four districts lie within two hours road travel from the capital Dushanbe in the west of this extremely poor country that has a per capita gross domestic product of $1'300 purchasing power parity[18]. Varzob district lies immediately north of the capital in the rocky Hissor mountains. Most people in Varzob district rely on livestock farming, others work in different sectors in the nearby capital. Danghara, Shahrinaw and Tursunzoda are partly mountainous, mostly rural districts with semi-urban centres. In the lowlands there is extensive cotton farming. DOTS implementation in these districts started in 2004 (Danghara and Varzob) and October 2005 (Shahrinaw and Tursunzoda). TB laboratory services and treatment are available at DOTS facility in each district centre. Primary care facilities collect sputa or refer patients for diagnosis and provide treatment supervision.

Thirteen focus group discussions (FGDs) were conducted in early 2006 to investigate a comprehensive range of factors influencing access to care for tuberculosis. Five FGDs

were conducted with community members, four with TB patients and four with health services providers to cover opinions and experiences of stakeholders involved in TB treatment. Respondents with different backgrounds were selected and stratification along different criteria were used in order to obtain more valid results (Table 4.1). Patients were identified through the TB patient registry. Information on treatment adherence was incomplete. At the time of invitation, patients were asked whether they had been forced to interrupt treatment at any time. Patients reporting irregular treatment intake were included in the same FGD as defaulters. The language of the FGDs was Tajik. Participants who preferred to speak in Uzbek or Russian were free to do so. The research team consisted of a moderator, a transcriber and two observers. FGDs with patients took place in the offices of Project Sino in Dushanbe in order to assure the confidentiality of their health status within their communities and to provide patients with an additional sense of independence and thus improve the veracity of their responses.

Table 4.1. Eligibility criteria for the 13 focus group discussions, by respondent category

Community members	Patients	Providers
1) Women from small rural town	1) Women in treatment	1) Family doctors from Danghara
2) Men from remote rural village	2) Men in treatment	2) Nurses from Varzob
3) Women from rural village	3) Women and men after treatment success	3) Family doctors from Shahrinaw and Tursunzoda
4) Men from rural village	4) Defaulters and patients indicating irregular drug intake	4) TB specialists from all four districts
5) Women from semi-urban centre		

Focus Group Discussions

The FGDs covered the following topics: (i) symptoms and causes of TB, (ii) perceived appropriateness of treatment, and (iii) factors determining the communities' ability to receive diagnosis and (iv) to complete treatment for TB. At the beginning of the FGDs with community members, participants were asked about diseases causing cough, without hint to TB. Then subsequently participants were asked about symptoms like sputum production, slight fever, fatigue, weight loss, night sweats and chills. After the discussion on diseases causing cough and the other named symptoms, the focus on TB was disclosed to the participants. In FGDs with patients and providers, the focus on TB was known from the beginning.

After the discussion, participants of community and patient FGDs were asked to rank the factors preventing "people from receiving full medical treatment" by importance in a participatory approach ('rating'), using chickpeas to rank the perceived importance of different factors. No rating was conducted among providers, because it was felt to interfere with local concepts of professionalism. For the rating, all factors named during the discussion on access to care were listed. The following factors were suggested as potential relevant factors by the research team in case they were not spontaneously mentioned: attitude of providers, insufficient confidentiality of medical services, stigma of TB, attitude of other community members towards TB patients and lost income. Each participant was asked to allocate six, three and one chickpea to the three most important factors. This was done one by one without other participants being present during the ballot.

Table 4.2. Analytical framework used in this study for factors influencing access to care†

Main categories	Affordability	Acceptability	Accessibility*	Adequacy*
Sub-categories (and examples)	▪ Missed opportunities (lost income due to inability to work) ▪ Medical costs (costs for diagnostic tests, drugs, etc.) ▪ Non-medical costs (transportation costs, expenditure for disease-related diets, etc.)	▪ Side effects of treatment ▪ Perceived quality of care (technical specialisation of providers) ▪ Attitude of providers (friendliness of doctors) ▪ Lack of confidentiality (other community members find out about TB patient) ▪ Health beliefs (lack of belief in curability)	▪ Distance to facility (effort to cover distance, time needed)	▪ Organisational appropriateness of services ▪ Physical state and cleanliness of facilities ▪ Convenient opening hours

†Adapted from reference 2.
*In the participatory approach, factors relating to accessibility and adequacy were not regarded as important (no chickpeas allocated) and the results are presented without these factors.

All FGDs were recorded on audio tape and transcribed to English. The principal researcher listened to the whole recording double-checking the transcription. Then transcriptions were read repeatedly and codes added in TAMS Analyzer (version 3.31b2pt, Matthew Weinstein, 2005).

Analytical framework

We used a previously described analytical framework of access to care in contexts of livelihood insecurity[2]. Our analysis focussed on access and did no go into details of livelihoods. Further, availability was not covered specifically, as TB services were known to be available (see above). The resulting adapted analytical framework is presented in table 4.2. Statements were grouped into three categories: factors relating to accessibility, affordability, acceptability (including stigma, perceived appropriateness of care, perceived quality of care) and adequacy. The number of statements for the four categories were summed up and expressed as a percentage along the three respondent groups. There were hardly any statements relating to adequacy and therefore only the other three categories are presented in the results.

Results of the rating were analysed by calculating the proportion of chickpeas allocated to each factor, whereby each FGD was equally weighted, independent of the number of participants. The four categories from the content analysis were further divided into twelve sub-categories (Table 4.2). 'Poor living conditions' and 'late presentation to the doctor', each mentioned in one FGD, were excluded from the analysis as no meaningful relation to the topic of investigation could be established for the first and as the second is rather a consequence of barriers to access than a barrier by itself.

Results

FGDs consisted of five to 12 participants. 43 community members participated in the community FGDs, 21 women and 22 men with a mean age of 42 years. Among providers, 15 doctors, nine nurses and seven TB specialists participated. Their mean age was 45 years. Of 23 patients, eight were women and 15 were men. Participants were mainly from rural areas with about one fourth coming from semi-urban areas.

First the results from the discussion on basic characteristics of TB and on barriers to treatment are presented, second the relative importance of identified factors from the rating and third the composition of illness costs to households from the rating. The topics that came up in the discussion on access to diagnosis and on access to treatment were very much the same. Participants also explicitly stated that the same factors were important at both times. Consequently the results are presented jointly. Further, the composition of illness costs was discussed and these results are presented at the end.

Upon presentation of symptoms of TB, community members mentioned a number of respiratory diseases, most prominently asthma, influenza and bronchitis. Community members also mentioned TB soon in all FGDs. Overall, knowledge of symptoms was accurate. Community members were able to identify medical facilities providing TB treatment in their surroundings.

Knowledge about causes of TB was limited. In particular the belief that TB was inherited and normally incurable was found commonly among community members and also expressed by one patient and one provider. These beliefs were closely linked to the stigmatisation of the illness. The stigma was magnified by the fact that TB services are offered in separate facilities. Despite the misunderstandings on causes of TB and prospects of care, all respondent groups deemed medical treatment necessary and community members stated that they would seek medical care in case of illness. Community members showed themselves well aware of the availability of TB services at the DOTS centres. Overall it was revealed that due to the difficulties associated with accessing medical care, patients tended to delay presenting until their health status had become severe – despite community members being aware of better prospects of cure at earlier presentation to care.

Respondents in all FGDs agreed that financial factors were the strongest determinants of access to care and the patient's ability to take the full treatment, i.e. adherence. On the question, why people with TB do not get treatment, a woman (teacher, 47 years old) from Varzob town said: "No money, no treatment – money plays a great role." A general practitioner (40 years) from Danghara answered: "First, because of the financial situation, because of the funds." Other possible reasons were not perceived to be equally important. Although stigma of TB was acknowledged, most participants emphasized it would not prevent patients visiting medical facilities. Side-effects of treatment were experienced by some participating patients, but were not mentioned very often and were considered important by a small minority only.

The perceived higher importance of economic factors relative to acceptability and accessibility of services was reflected in the number of statements among all respondent groups (Figure 4.1). Factors relating to adequacy of services were mentioned even less often and are not presented here. Notably, factors relating to acceptability of services were mentioned least often among patients. Financial factors included all direct costs and lost income. Geographical factors included the effort for

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the patient to travel and time spent travelling. It did not include transport costs and statements linking travel time to money.

Community members allocated 12%, 62% and 20% of chickpeas to the categories 'missed opportunities', 'medical expenditure' and 'non-medical expenditure' respectively (Figure 4.2). Patients allocated 21%, 21% and 37% of chickpeas to the same factors. Thus a total of 94% and 78% of chickpeas respectively were allocated to financial factors. Factors related to acceptability unified only 11% and 6% of chickpeas in patient and community FGDs respectively, despite the moderator carefully probing for and explaining rational ways of action of these factors.
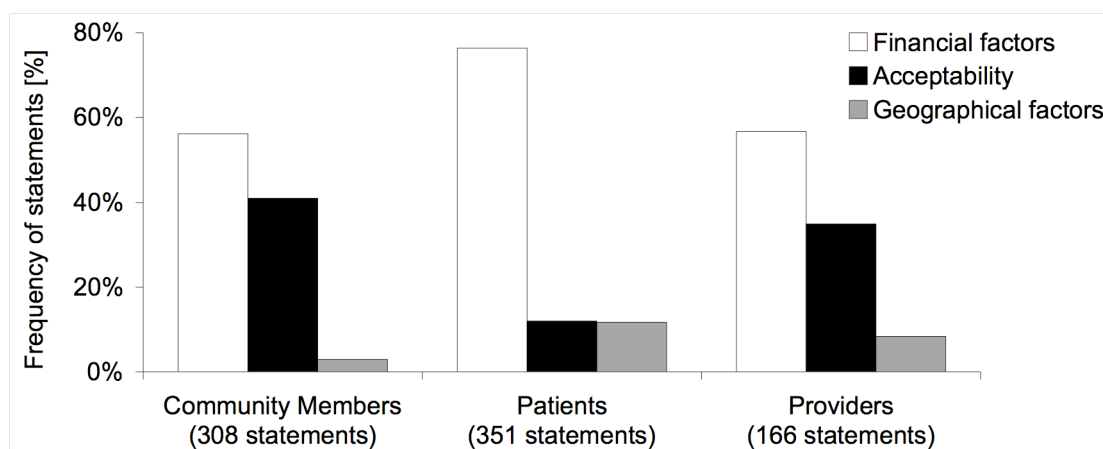
Figure 4.1. Frequency of statements referring to three components of access to care.
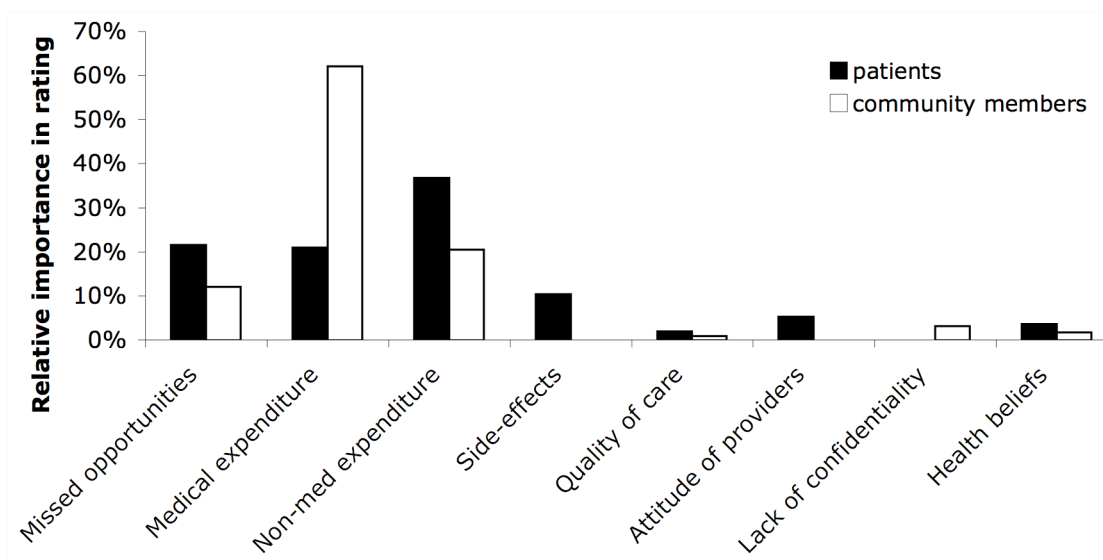
Figure 4.2. Relative importance of different barriers to tuberculosis treatment, measured by the proportion of chickpeas allocated by participants of FGDs.

Costs mentioned in the FGDs can be grouped into six categories: diagnosis, drugs and consultation, hospitalisation, transport, increased expenditure for food and lost income.

Diagnostic expenditure was seen by patients as well as community members to be less important with the exception of radiography, which was considered expensive by patients and community members. Cost of drugs and consultation were identified as important barriers by patients and especially by community members (Figure 4.3). Three patients reported they were asked to pay for the TB drugs. For the majority of patients, 'cost of drugs' stands for symptomatic treatment, like vitamin injections or intravenous rehydration. Admission to hospital has received little attention, probably because there is no admission fee. Admission is however linked to a range of services that have to be paid for, including cleaning and disinfection with UV light. Expenditure for transport and increased expenditure for food were also closely associated with hospitalisation. Food for hospitalised patients has to be provided by caregivers such as family members leading to higher food-related expenditure during hospitalisation. Participants of the FGDs did not always conceptually separate the costs of travel for food provision from the cost of the food itself. Patients and community members mentioned increased expenditure for food mainly in connection with hospitalisation.
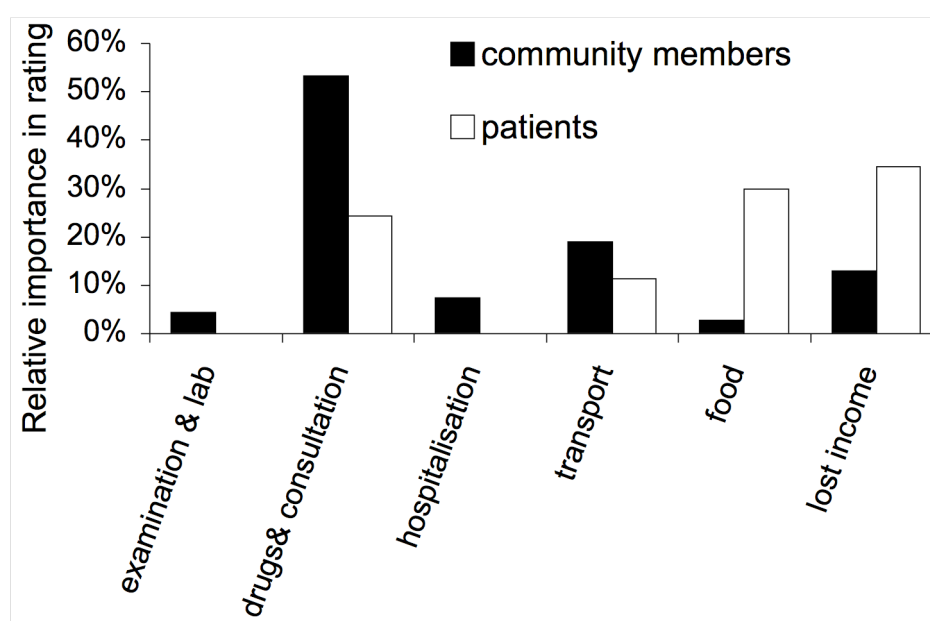
Figure 4.3. Relative importance of financial factors regarding access to TB services, measured by the proportion of chickpeas allocated by participants of FGDs.

Participants regarded time constraints and missed opportunities as less important than direct costs: "It's not about time, but she needs to spend money. She cannot find enough funds to buy drugs", a rural woman (farmer, 47 years) stated. Missed opportunities, although defined broadly (including 'household expenditure', a factor expressing difficulties to cover the usual expenditures of the household and the concurrent illness-

related costs), received only 18% of chickpeas on average (Figure 4.4). The higher importance attributed to lost income by patients relative to community members was explained with the long duration of TB treatment, of which community members were only partially aware.
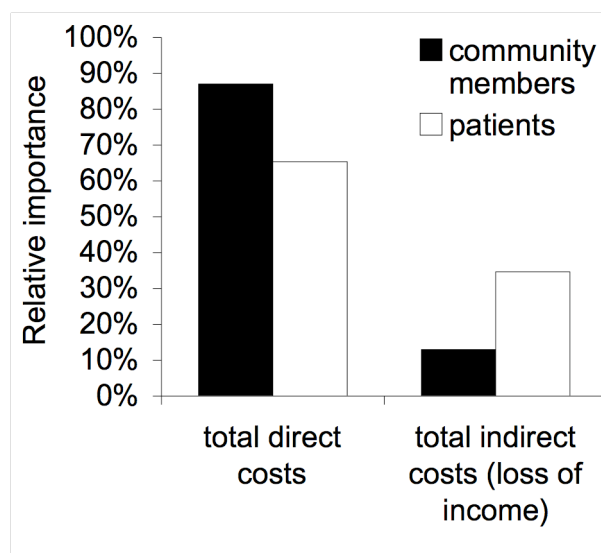
Figure 4.4. Relative importance of direct versus indirect costs, measured by the proportion of chickpeas allocated by participants of FGDs.

Discussion

While several studies showed that patients face costs even where TB drugs are stipulated to be free of charge[19-21], few previous studies have investigated the relative importance of financial versus other barriers to TB care. We investigated the influence of various health system and household-related factors on access to care for TB in Tajikistan. Community members, patients and providers agreed that illness costs to households determine access to diagnosis and treatment to a large extent and deemed quality of care, stigma and other factors less important.

The importance of financial factors is amplified for community members by their lack of awareness about anti-mycobacterial therapy being offered free of charge. This is likely to influence their health care seeking. The predominance of financial factors corresponds well to the results of the small number of previous studies investigating the importance of financial and a wide range of other factors[12-13]. To our knowledge, this is the first study to demonstrate that illness-related costs are experienced by a broad range of stakeholders including health care providers as the major determinant of access to TB treatment.

Limitations of this study include the small sample size, possible reporting bias and the lack of quantification of illness-related costs. Reporting bias, however, should be

reduced in the confidential participatory approach. The high consistency between the open discussion and the participatory approach lead us to believe that reporting bias was limited. At the time of study implementation, DOTS was still new to two of the study districts. Further improvements may have happened since then. For the analysis of the participatory approach, the factors 'poor living conditions' and 'late presentation to a doctor' were excluded. Retaining these factors would not have changed the results and conclusions. 'Poor living conditions' relates to economic difficulties and would have reinforced the result that affordability is the key aspect of access to TB treatment – if anything. It should be kept in mind, that components of access to care are interrelated. For example, improvements in the quality and reliability of food provided at the hospital would reduce the need for patients' relatives to travel on a daily basis to bring meals to hospitalised patients.

Among different cost items, expenditure for drugs and consultation was deemed most important, especially by community members. The high importance of expenditure for drugs and consultation corresponds well with a study from Thailand, which also found that drugs caused the highest expenditures during TB treatment[21]. The lower importance attributed to cost of drugs by patients relative to community members may indicate that most patients received treatment for free – contrary to the experience of community members with other treatments. However, almost all patients receive and pay for additional, symptomatic medication (like vitamin injections, intravenous rehydration). Missed opportunities including lost income were perceived as important but far less important than suggested in the literature, where estimates reach from 69% to 95% of total costs[14,22-24]. This result may be linked to the qualitative method insofar as health care users see very directly when they spend money, but less directly that they forego income. The dominance of direct costs was more striking in FGDs amongst community members than amongst patients. Many patients are hospitalised for a long time and providers often advise them to abandon their current job. Nonetheless, patients perceived direct costs (the sum of expenditures) to be a more important barrier to TB treatment than lost income.

Conclusions

For TB control to be successful and Millenium Development Goals to be reached in Tajikistan and many other countries, financial barriers to TB treatment have to be considered by TB control programs. As long as people's immediate concerns are not

addressed it is difficult to increase case detection, adherence and treatment success rates. Possible ways to ease the financial hardship of TB to affected households include refunding travel costs, financial stimuli and – as is already being done in Tajikistan – food complements[5,12,25-27].

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA was the main responsible researcher for all parts of the study. KW contributed to designing the study and to writing the manuscript. HA and SS participated in design of the study and data collection. All authors read and approved the final manuscript.

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5. Patient's site of first access to health system influences length of delay for tuberculosis treatment in Tajikistan

Running head: Health care seeking for tuberculosis

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Abstract

Background: Tajikistan has the highest incidence rate of tuberculosis (TB) in Central Asia. Its health system still bears many features from Soviet times and is under-funded. Affordability is a major barrier to health care. Little is known about health care seeking of TB patients in post-Soviet countries and their delay until the start of TB therapy. The low estimated case detection rate in Tajikistan suggests major problems with access to care and consequently long delays are likely.

Methods: The study investigated extent and determinants of patient and health system delays for TB. A questionnaire was administered to a cohort of TB patients in twelve study districts representing a wide range of conditions found in Tajikistan. Common patterns of health care seeking were analysed. Cox proportional hazards models using eight predictor variables, including characteristics of health services delivery, were built to identify determinants of patient and health system delays.

Results: Two-hundred-and-four TB patients were interviewed. A common pattern in treatment-seeking was visiting a specialised TB facility at some stage. Typical delays until start of TB therapy were moderate and did not confirm the expectation of long delays. Median patient, health system and total delays to TB treatment were 21.5, 16 and 52 days, respectively. None of the investigated predictors was significantly associated with patient delay. The type of facility, where patients made their first contact with the health system, was the main determinant of health system delay (p<0.00005). We show for the first time that patients who had fallen ill and first presented to health care in Russia had the longest delays. Those who first presented to peripheral primary care facilities also had relatively long delays.

Conclusions: While overall delays were moderate, further improvement is needed for different subgroups. An international referral system between Russia and Tajikistan to reduce delays of Tajik migrants who develop active TB in Russia is urgently needed and would benefit both countries. Within Tajikistan, diagnostic pathways for patients in the periphery should be shortened. To achieve this, strengthening of sputum smear examination possibly including collection of sputa at peripheral primary care facilities may be needed.

Background

The tuberculosis (TB) incidence rate in Tajikistan is estimated at 231 cases per 100'000 population in 2007[1]. The case detection rate ranges from 32% for sputum smear positive cases to 39% for all cases. While the incidence estimate from the national TB control program is slightly lower (160 – 180 cases per 100'000), it is clear that the TB epidemic is ravaging. Integration of the vertical TB program rooted in the Soviet tradition with primary care is not yet complete. Historically, TB diagnosis and treatment was the exclusive task of specialised TB facilities and providers. The DOTS strategy was introduced in two pilot districts in 2002 and by the end of 2007 has reached 100% coverage of Tajikistan. Under DOTS, primary care providers also have the task of diagnosing and treating TB. Despite insufficient funding, the health system has been latching onto a dense network of facilities with different levels of specialisation inherited from Soviet times (Table 5.1). Real government expenditure for health was less than US$2 per capita in Tajikistan in 2003[2]. Health care workers are poorly paid and informal payments are common[2-3]. Out-of-pocket payments are an important barrier to access health care services[4]. The policy in Tajikistan is to provide anti-TB chemotherapy free of charge. Currently, health reform is ongoing in order to strengthen primary care under the name of Family Medicine[3].

It is estimated that up to a fifth of the population of Tajikistan is working abroad, mainly in Russia, where Tajik migrant workers are very vulnerable[5]. Albeit labour migration has recently decreased due to the current economic crisis and the loss of job opportunities in Russia, remittances from labour migration are likely to remain an important component of the Tajik economy.

TB control in low-income countries relies primarily on treatment of active cases. A dose-response relationship has been found between the delay to TB treatment and the transmission to household members[6]. Consequently, prompt start of treatment is of utmost importance. Passive case finding requires that patients present to a health care facility and that health providers take appropriate measures. Repeated referrals that do not result in a diagnosis and effective treatment can frustrate patients, leading to delayed or missed diagnoses. Storla et al[7] reviewed studies on delay to tuberculosis treatment–defined as the period from onset of symptoms until the start of treatment. They found that many factors can influence delay and that the same factor could lead to shorter or longer delays in different settings. The type of the first health care provider

chosen often influenced delay with findings relatively consistent among studies: patients who first visited a traditional healer, private provider, or a low-level government health facility had longer delays[8-16]. Poverty and rural residence were almost invariably associated with longer delays[7]. Factors that often led to longer but sometimes also to shorter delays were female sex and old age[7]. Despite the specific traditions of TB control in the former Soviet Union (FSU), no studies on the relationship between health services delivery and delay in a post-Soviet country were found in the scientific literature. The only study on delay from the FSU concentrated on stigma and patient delay in Russia[17]. Investigating delay to TB treatment in the FSU may contribute to the understanding of the devastating TB epidemic in this region.

Table 5.1. Characteristics of facilities in the Tajik health system§

Facility type	Specialisation of health worker†	Hospital beds	Description
Medical House	Nurse	No	Facility serving villages without a Rural Health Centre. Together with the latter forms the peripheral primary care. Basic services from a nurse or a trained health worker.
Rural Health Centre	Generalist/ family doctor	No*	Facility serving mid-sized and larger villages. Stands at the centre of Family Medicine and thus primary care. One or more family doctors and a number of nurses.
Polyclinic	Specialist doctor	No	Facility found in district centres and larger towns. Specialist doctors provide ambulatory services.
Central District Hospital	Specialist doctor	Yes	Found in district centres. Specialist doctors provide in- and out-patient services. Usually contains an ambulatory functioning like a Rural Health Centre.
District TB facility (including TB hospitals)	TB specialist	Partially	Usually in the district centre. Often more than one in large districts. Part of the historical vertical structure providing care for TB exclusively.
Republican Hospital	Specialist doctor	Yes	Tertiary referral centres providing the most specialised services available.
Private clinic	Varying	Varying	Exist only in large towns, mainly in the capital.

§This list is by no means complete, but contains the facilities of relevance to this study.
†This column shows the highest professional specialisation that is usually found at facilities of the respective type.
*Some Rural Health Centres are historically derived from rural hospitals with beds and in a transitional period may have hospital beds.

The objective of the present study was to describe common health care seeking behaviours of new pulmonary TB patients in Tajikistan and to identify determinants of delay based on the following explanatory variables: sex, age, rural versus urban residence, district, durable assets, labour migration to Russia, belief in curability of TB, use of self-treatment, sputum smear result, and the type of facility first visited.

Methods

Study population

As DOTS expansion was under way in Tajikistan and in order to produce meaningful evidence for the future, we included only districts with an established DOTS program (started in July 2006 at the latest) in the study. Two regions were excluded because they were accessible only by air at the time of the study, Badakhshan and Sughd. Among the 24 remaining districts ('rayons'), twelve were purposefully selected to represent urban, rural, lowland and mountainous settings (Figure 5.1).

Table 5.2. Reasons for drop-out

Reason	Number of cases (% of drop-outs)
Wrong or insufficient address	18 (23)
Not found at home or in hospital when visited	17 (22)
Died	5 (6)
Initial defaulter	3 (4)
Already in continuation phase when visited	25 (32)
Did not consent	10 (13)
Total	**78 (100)**

Questionnaire and Interviews

All patients who fulfilled the inclusion criteria and who were registered in the twelve study districts were recruited into the study. Our inclusion criteria were: enrolled for TB treatment in the period 1 December 2006 to 31 March 2007, new pulmonary tuberculosis case (sputum smear positive or negative) and at least 15 years old. Data for this study were collected alongside a study on household costs of an episode of TB[18]. The latter study included two interviews with each patient. For the present study, only data from the first interview were analysed. Patients were visited in hospital or at their homes during the intensive phase of treatment, written informed consent was obtained and a trained interviewer administered a questionnaire. The questionnaire included detailed questions about the onset of symptoms, health care seeking behaviour

(including traditional healers and self-treatment), the timing of health care seeking steps, diagnostic investigations that were conducted and household assets. Onset of symptoms was self-reported and concerned any symptoms likely to be due to TB, most importantly cough. Patient delay was defined as the period from onset of symptoms until the first visit to a formal health care provider. Formal health care providers included all the facilities listed in table 5.1, but not traditional healers nor pharmacies, as they are not allowed to diagnose and treat patients in the Tajik health system. Health system delay was defined as the time from the first visit to a formal health care provider to the start of treatment.

Interviewers were trained during a fortnight before conducting interviews on their own and were supervised at least twice per month through joint interviews with the main researcher. Specific emphasis was given to support the patients in their recall efforts, including the use of a calendar of locally important events. Data were entered in FileMaker (version 8.0v1, FileMaker Inc, USA, 1984-2005).

Data Analysis

All analyses were conducted in Stata IC/10.1 for Macintosh (Stata Corporation, USA, 1985-2008). We carried out a principal component analysis on 15 household asset variables and three housing characteristics variables to construct a wealth index using a well established and validated method[19-20]. The wealth index was used to assign patients to quintiles of socio-economic status (SES).

For each patient, we listed every health care seeking step and identified common patterns in the history of health care seeking up to the start of anti-TB chemotherapy. Particular attention was given to the timing and the place of the sputum smear examination.

In order to investigate delay, we built Cox proportional hazards models with delay as time-to-event. Two separate models were built for patient and system delay, because predictor variables are likely to differ. Sex, age (categorised into four groups), residence, SES quintiles, district, and labour migration were included in both models. Belief in curability of TB and use of self-treatment were included only in the model on patient delay. Sputum smear status and the type of facility visited in first instance were included only in the model for system delay. Knowledge of symptoms was not included, as the encounters with health care professionals could change this variable

between the times when it acts (before the first visit to a formal provider) and when it is measured (during treatment). We selected the best model by subsequently excluding factors with p>0.2 in the likelihood-ratio test from the full model, until no more factors could be excluded. The respective univariate models were also built and the hazards ratios of factors were compared between univariate and multivariate models in order to investigate potential confounding. The present study has received approval from the Ministry of Health of the Republic of Tajikistan in a memorandum of understanding signed 18th October 2006.
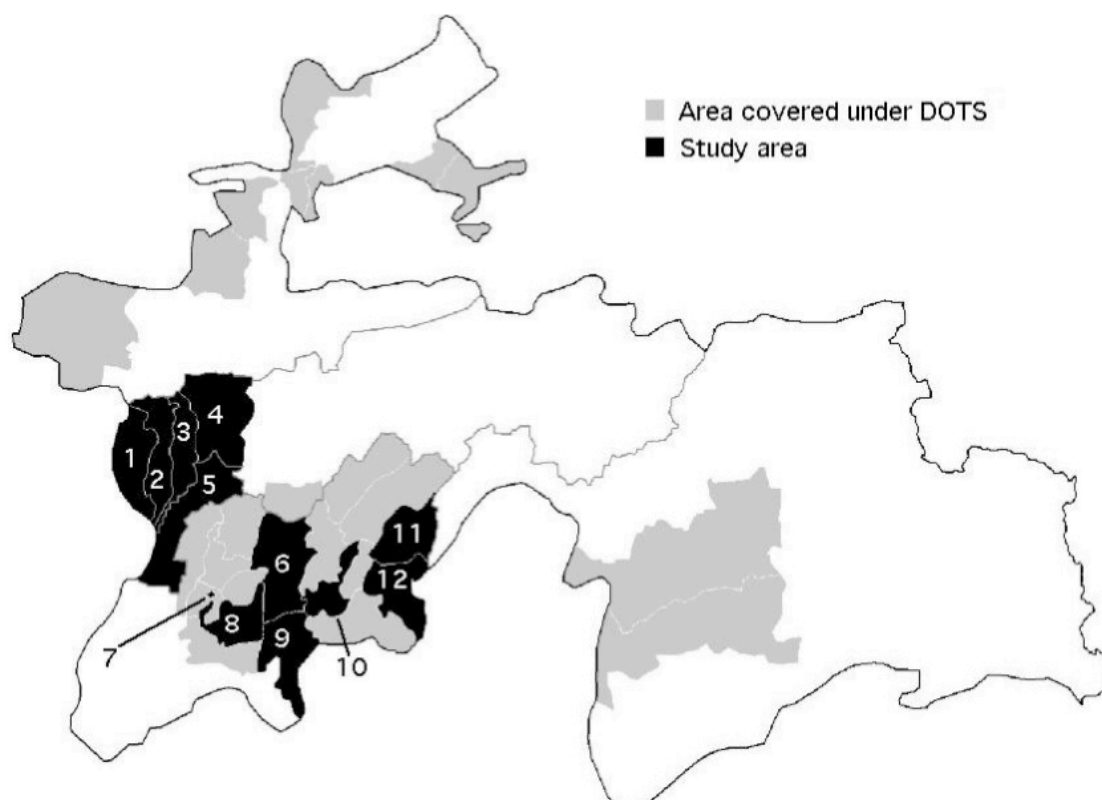
Figure 5.1. Location of study districts among all districts with a DOTS program in July 2006 in Tajikistan. District codes: 1=Tursunzoda, 2=Shahrinaw, 3=Hissor, 4=Varzob, 5=Rudaki, 6=Danghara, 7=Qurghonteppa, 8=Vakhsh, 9=Farkhor, 10=Vose, 11=Muminobod, 12=Shurobod.

Results

Study population and health care seeking

The study identified 282 eligible patients, of whom 78 dropped out (Table 5.2) and 204 were interviewed (Table 5.3). The patients who dropped out were virtually identical to included patients in terms of the proportions of smear-positive (60%in both cases) and male patients (54% versus 56%), but differed somewhat in their age-distribution and in terms of residence. The proportion of patients who were at least 45 years old was 36%

among dropouts versus 16% amongst the study sample. The proportion of rural patients was 79% versus 90%.

Self-treatment was used by 64 patients (31%) before the start of anti-TB chemotherapy. A large variety of self-treatments were used, ranging from honey and different herbs over meat and fat of boar or dog to opium and allopathic medicines. Self-treatment was used both before and after the first visit to a formal health care provider. Only one patient (0.5%) reported having visited a traditional healer before the first visit to a formal health care provider and four more patients did so after such visit.

Table 5.3. Demographic characteristics of study sample

	Women	**Men**	**Total**
Profession	**n (%)**	**n (%)**	**n (%)**
Unemployed	9 (10)	20 (18)	29 (14)
Student	4 (4)	12 (11)	16 (8)
Housewife	52 (58)	0 (0)	52 (25)
Retiree	5 (6)	2 (2)	7 (3)
Employee in industry	1 (1)	7 (6)	8 (4)
Employee in private service	0 (0)	2 (2)	2 (1)
Owner of business	0 (0)	0 (0)	0 (0)
Police	0 (0)	3 (3)	3 (1)
Health Care Worker	1 (1)	1 (1)	2 (1)
Civil service (other than police and health)	3 (3)	5 (4)	8 (4)
Petty Trader	3 (3)	19 (17)	22 (11)
Labour Migration to Russia	1 (1)	30 (26)	30 (15)
Farmer	11 (12)	13 (11)	24 (12)
Total	**90 (100)**	**114 (100)**	**204 (100)**
Age			
15-24y	34 (38)	44 (39)	78 (38)
25-34y	23 (26)	40 (35)	63 (31)
35-44y	16 (18)	14 (12)	30 (15)
45y and older (max 72y)	17 (19)	16 (14)	33 (16)
Total	**90 (100)**	**114 (100)**	**204 (100)**
Residence			
Rural	79 (88)	105 (92)	184 (90)
Semi- or Peri-urban	3 (3)	8 (7)	11 (5)
Urban	8 (9)	1 (1)	9 (4)
Total	**90 (100)**	**114 (100)**	**204 (100)**

The first formal health care facility approached was a Rural Health Centre for 36 patients (18%), a central district hospital for 39 patients (19%) and the district TB facility for 41 (20%) patients (Table 5.4). None of the study subjects visited a private clinic. Each facility that was visited was visited approximately twice on average (Table

5.4, right-hand column). Patients made 4.8 (±s.e. 0.17) visits to formal health care facilities on average before anti-TB chemotherapy was started. It is noteworthy that the district TB facilities were visited at some stage before initiation of anti-TB chemotherapy by a large majority (86%) of patients. Of the 28 patients who had not visited their district TB facility, 15 lived in Danghara district and all 15 had visited the Central District Hospital. In Danghara there was no separate TB facility as it had already been integrated in the Central District Hospital.

Table 5.4. Health care facility visited by TB patients

	#patients visiting facility in first instance	mean #visits (all patients)	#visits among patients who visited†
Medical house	22 (10.8%)	0.23	1.88
Rural Health Centre	36 (17.7%)	0.45	2.04
Polyclinic	17 (8.3%)	0.28	2.19
Private clinic	0 (0.0%)	0.00	0.00
Central District Hospital	39 (19.1%)	0.83	1.77
Republican Hospital	41 (20.1%)	0.53	1.96
District TB facility	15 (7.4%)	1.86	2.16
Health facility in Russia	20 (9.8%)	0.25	2.60
Other facility*	14 (6.9%)	0.39	1.65
Sum	**204 (100%)**	**4.83**	**N/A**

†Mean number of visits among those patients who visited the respective facility.
*Including a health care facility reserved to staff of a large industrial company and Ministry of Defence facilities.

Table 5.5. Results of the multivariate Cox proportional hazards model on patient delay (n=168)

Factor	Hazards Ratio§	Lb95%CI†	Ub95%CI°	p-value
Male sex*	1.000	NA/	NA/	NA/
Female sex	0.745	0.523	1.061	0.103
SES quintile	**NA**	**NA**	**NA**	**0.132¶**
SES quintile 1*	1.000	NA	NA	NA
SES quintile 2	0.661	0.409	1.067	0.090
SES quintile 3	1.045	0.645	1.694	0.859
SES quintile 4	0.614	0.365	1.032	0.065
SES quintile 5	0.712	0.432	1.174	0.183

§A hazards ratio >1 means a shorter delay, a hazards ratio <1 points to a longer delay relative to the comparison group.
†Lb95%CI=Lower boundary of 95%-confidence interval
°Ub95%CI=Upper boundary of 95%-confidence interval
*Comparison group
¶Based on log-likelihood ratio test

Delay

The median patient delay was 21.5 days (range: 0 to 410 days; mean: 45.7 days). Thirty-six patients were excluded from the analysis of patient delay, because they reported either no symptoms, a chronic pulmonary condition, or because they were unable to assign at least an approximate date to both the onset of cough and the first visit to a health care provider. The median reported system delay was 16.0 days (0 to 339; 42.2). One patient was excluded from the analysis of system delay because he could not assign a date to the first visit to a formal provider. The median total delay from onset of cough until start of anti-TB chemotherapy was 53 days (2 to 542; 81.8). Note that mean delays are not additive because of the 36 patients excluded from analysis of patient delay, but not system delay.

Determinants of Delay

None of the factors included in the model on patient delay proved significant. Sex (hazards ratio women to men 0.745, p=0.103) and SES quintile (p=0.132) were retained in the final model (Table 5.5). The final model on system delay included the factors 'first facility' and 'district' (In order to check for potential confounding, the 16 univariate models that are relevant to the above two multivariate models were also computed. The univariate models on patient delay showed consistent results with all hazards ratios in the same direction and in a similar range (Table 5.7). Among the univariate models on health system delay (Table 5.8), the factor 'labour migration' showed a strong association in the univariate model (hazards ratio 0.563, p=0.006) but showed no significant relationship (at the p=0.2 level) in the multivariate model and was consequently excluded.

Table 5.6). The proportional hazards assumption was not violated (based on Schoenfeld residuals, p=0.91). There was a striking relationship between first visiting a district TB specialist and system delay: the median was six days versus 23 days for all other facilities combined. Also, visiting first a Central District Hospital was associated with a short system delay. Visiting first a Medical House, Rural Health Centre, Polyclinic or a facility in Russia was associated with longer system delays. Patients who had first visited a health facility in Russia had the longest system delays of all. It was found that most patients were advised at the health facility in Russia to travel to Tajikistan for treatment – often already with a diagnosis or at least suspicion of TB. Several patients

reported that the Russian health system made no treatment available to them.

In order to check for potential confounding, the 16 univariate models that are relevant to the above two multivariate models were also computed. The univariate models on patient delay showed consistent results with all hazards ratios in the same direction and in a similar range (Table 5.7). Among the univariate models on health system delay (Table 5.8), the factor 'labour migration' showed a strong association in the univariate model (hazards ratio 0.563, p=0.006) but showed no significant relationship (at the p=0.2 level) in the multivariate model and was consequently excluded.

Table 5.6. Results of the multivariate Cox proportional hazards model on health system delay (n=203)

Factor	Hazards Ratio§	Lb95%CI†	Ub95%CI°	p-value
District	NA	NA	NA	0.0191¶
Danghara*	1.000	NA	NA	N/A
Farkhor	0.917	0.490	1.716	0.786
Hissor	1.243	0.639	2.417	0.522
Muminobod	0.412	0.208	0.817	0.011
Qurghonteppa	1.502	0.623	3.623	0.365
Rudaki	1.516	0.837	2.744	0.170
Shahrinaw	1.293	0.291	5.738	0.735
Shurobod	1.335	0.600	2.968	0.479
Tursunzoda	0.966	0.509	1.835	0.916
Vakhsh	1.462	0.769	2.781	0.247
Varzob	0.953	0.334	2.720	0.928
Vose	0.879	0.488	1.584	0.669
First facility	NA	NA	NA	<0.00005¶
District TB facility*	1.000	NA	NA	NA
Medical House	0.325	0.183	0.580	<0.0005
Rural Health Centre	0.418	0.255	0.688	0.001
Polyclinic	0.409	0.216	0.773	0.006
Central District Hospital	0.704	0.435	1.136	0.151
Republican Hospital	0.646	0.341	1.226	0.181
Health facility in Russia	0.212	0.117	0.383	<0.0005
Other facility‡	0.365	0.185	0.721	0.004

§A hazards ratio >1 means a shorter delay, a hazards ratio <1 points to a longer delay relative to the comparison group.
†Lb95%CI=Lower boundary of 95%-confidence interval
°Ub95%CI=Upper boundary of 95%-confidence interval
¶Based on log-likelihood ratio test
*Comparison group
‡Including health care facilities reserved to staff of a large industrial company or the Ministry of Defence, respectively.

Table 5.7. Results of univariate Cox proportional hazards model on patient delay (n=168)

Factor	Hazards Ratio§	Lb95%CI†	Ub95%CI°	p-value
Male sex*	1.000	NA/	NA/	NA/
Female sex	0.834	0.613	1.136	0.250
Age	**NA/**	**NA/**	**NA/**	**0.562**
15-24y*	1.000	NA/	NA/	NA/
25-34y	0.870	0.598	1.265	0.466
35-44y	0.827	0.527	1.299	0.409
45y and older	0.728	0.458	1.157	0.179
Residence	**NA/**	**NA/**	**NA/**	**0.831**
Semi- or peri-urban*	1.000	NA/	NA/	NA/
Rural	0.903	0.459	1.777	0.767
Urban	0.751	0.288	1.961	0.559
SES quintile	**NA/**	**NA/**	**NA/**	**0.221**
SES quintile 1*	1.000	NA/	NA/	NA/
SES quintile 2	0.669	0.414	1.080	0.100
SES quintile 3	1.116	0.693	1.798	0.651
SES quintile 4	0.730	0.454	1.175	0.195
SES quintile 5	0.828	0.520	1.319	0.428
District	**NA/**	**NA/**	**NA/**	**0.755**
Danghara*	1.000	NA/	NA/	NA/
Farkhor	0.898	0.468	1.724	0.747
Hissor	0.639	0.315	1.297	0.215
Muminobod	1.023	0.496	2.111	0.95
Qurghonteppa	0.833	0.334	2.079	0.696
Rudaki	0.717	0.393	1.307	0.277
Shahrinaw	4.935	0.643	37.845	0.125
Shurobod	1.507	0.636	3.573	0.351
Tursunzoda	0.859	0.449	1.645	0.647
Vakhsh	0.751	0.390	1.446	0.392
Varzob	0.544	0.184	1.607	0.271
Vose	0.873	0.492	1.549	0.642
No migration*	1.000	NA/	NA/	NA/
Labour migration	0.889	0.565	1.400	0.612
Lack of belief in curability*	1.000	NA/	NA/	NA/
Belief in curability	1.121	0.827	1.518	0.462
No self-treatment*	1.000	NA/	NA/	NA/
Self-treatment	1.011	0.727	1.406	0.949

§A hazards ratio >1 means a shorter delay, a hazards ratio <1 points to a longer delay relative to the comparison group.
†Lb95%CI=Lower boundary of 95%-confidence interval
°Ub95%CI=Upper boundary of 95%-confidence interval
*Comparison group

Table 5.8. Results of univariate Cox proportional hazards models on health system delay (n=203)

Variable	Hazards Ratio§	Lb95%CI†	Ub95%CI°	p-value
Male sex*	1.000	NA/	NA/	NA/
Female sex	1.201	0.908	1.589	0.200
Age	**NA/**	**NA/**	**NA/**	**0.270**
15-24y*	1.00	NA/	NA/	NA/
25-34y	0.777	0.556	1.087	0.141
35-44y	1.126	0.736	1.721	0.584
45y and older	0.810	0.535	1.226	0.319
Residence	**NA/**	**NA/**	**NA/**	**0.682**
Semi- or periurban*	1.000	NA/	NA/	NA/
Rural	1.066	0.579	1.965	0.836
Urban	1.441	0.594	3.494	0.419
SES quintile	**NA/**	**NA/**	**NA/**	**0.442**
SES quintile 1*	1.000	NA/	NA/	NA/
SES quintile 2	0.946	0.608	1.471	0.804
SES quintile 3	1.004	0.646	1.558	0.987
SES quintile 4	0.781	0.501	1.219	0.277
SES quintile 5	1.205	0.779	1.865	0.402
District	**NA/**	**NA/**	**NA/**	**0.368**
Danghara*	1.000	NA/	NA/	NA/
Farkhor	1.043	0.564	1.930	0.892
Hissor	1.189	0.631	2.240	0.593
Muminobod	0.680	0.362	1.279	0.232
Qurghonteppa	1.725	0.734	4.052	0.211
Rudaki	1.553	0.895	2.694	0.118
Shahrinaw	0.857	0.201	3.653	0.835
Shurobod	1.418	0.650	3.092	0.380
Tursunzoda	1.284	0.696	2.368	0.423
Vakhsh	1.526	0.822	2.831	0.180
Varzob	1.311	0.495	3.472	0.586
Vose	1.180	0.684	2.038	0.551
No migration*	1.000	NA/	NA/	NA/
Labour migration	0.563	0.375	0.846	0.006
Sputum smear negative*	1.000	NA/	NA/	NA/
Sputum smear positive	1.153	0.870	1.530	0.322
First facility	**NA/**	**NA/**	**NA/**	**0.0003**
TB facility*	1.000	NA/	NA/	NA/
Medical House	0.425	0.249	0.724	0.002
Family Doctor	0.442	0.281	0.697	<0.0005
Central District Hospital	0.768	0.492	1.196	0.243
Policlinic	0.562	0.317	0.996	0.049
Republican Hospital	0.613	0.338	1.111	0.107
Russia	0.302	0.175	0.524	<0.0005
Other‡	0.478	0.259	0.882	0.018

§A hazards ratio >1 means a shorter delay, a hazards ratio <1 points to a longer delay

relative to the comparison group.
†Lb95%CI=Lower boundary of 95%-confidence interval
°Ub95%CI=Upper boundary of 95%-confidence interval
*Comparison group
‡Including health care facilities reserved to staff of a large industrial company or the
Ministry of Defence, respectively.

Discussion

This study investigated the influence of health services delivery rooted in the Soviet
tradition of vertical TB control programs on delay to TB treatment. To our knowledge
there have been no similar studies previously. We found generally moderate delays in
our study sample. Much longer delays for certain subgroups of patients highlight the
need for improvements in the organisation of health services delivery. These
improvements include the implementation of an international referral system between
Russia and Tajikistan.

Limitations

As in any study on self-reported delay, there is potential recall and reporting bias:
patients might not remember exactly (or even realise) when the first symptoms started,
thus they might report delay incorrectly. We have tried to minimise recall and reporting
bias by supporting the interviewees in their recall work–among others using a calendar
of local events–and by carefully training interviewers to be non-judgmental in the
inquiries about delay.

Residence broken up into the three levels rural, semi- or peri-urban and urban, is a very
approximate measure of geographical accessibility. However, during the pilot study
patients could not give estimates of the distance in kilometres from their place of
residence to the nearest health care facility. We therefore included residence in our
models on patient and system delays–a factor which may include other information in
addition to geographical accessibility. The small number of patients from urban and
peri-urban areas made it difficult to detect statistical differences by residence. Medical
Houses and Rural Health Centres exist in very remote places and it is likely that
remoteness contributed to the long delays found in patients who first visited one of
these two facility types. Residence, which was included in the analysis, could only
partly account for this because many district centres (where a TB facility and a hospital
are situated) were also classified as rural.

The sample of patients for our study did not span a full year. Consequently, we cannot exclude that delays differ during other seasons.

It is possible that some patients went by without ever being registered in the TB registry–for instance if patients relied on self-treatment or informal providers exclusively. The present study might consequently underestimate some aspects of difficulty in access and delay to TB treatment. This could affect our secondary finding that this study did not find evidence of the very strong barriers to access that might explain the low case detection rate in Tajikistan. However, such underestimation of difficulties in access is most likely for Tajik TB patients in Russia, which would reinforce our findings if anything.

Health care seeking

Patients in our study group made on average 4.8 visits to a formal health care provider up to anti-TB chemotherapy. This is more than the two to three visits that the diagnostic pathway requires, namely two visits to conduct sputum smear examination (usually at the district TB facility) and possibly one additional visit at the peripheral level, from where patients are referred. However, it is less than what was found for example in urban Zambia, where TB patients made 6.7 health care visits on average[21].

In this study there was a lot of variability in the facility type, where the first contact with the health system took place: eight of the nine facility types accounted for a considerable proportion (6.9% or more) of first contacts each. This is a broader variety than found by Mfinanga et al[22] in Tanzania. Strikingly, almost all patients visited the district TB facility at some time during health care seeking. Especially primary care providers tend to refer patients to TB specialists rather than diagnosing TB themselves. At the district TB facility, usually both chest x-ray (CXR) and sputum smear examination were conducted. Similar to a study in the Philippines[23], we found that almost all patients had had a CXR – despite national and international guidelines not requiring CXR for sputum smear positive patients.

Eighty-six percent of patients reported a visit to the TB specialist. Fifteen patients who did not report such visit came from Danghara and had visited the Central District Hospital there, which includes a TB ward. Hence, the proportion of patients who have been seen by a TB specialist is likely even higher than 86%.

The patients in our study sample reported very limited use of informal providers. Social desirability bias could be suspected. However, interviewees freely reported their experiences in other areas where social desirability bias could be suspected such as in the area of informal payments. We therefore believe that social desirability bias is not the reason for the low use of informal providers reported, but that TB patients in Tajikistan really preferred formal health care providers.

Delay

Given the heavily resource-constrained setting, the total delay found in this study is moderate. It is longer than those reported in the Philippines and in China (median delay of one month in both cases[15,23]), but much shorter than found in studies in high-incidence settings, where the median delay ranged from 80 to 120 days[7,11-13,24]. This result is encouraging and to a certain extent surprising. The estimated case detection rate according to data of the World Health Organisation is very low[1] and suggests that TB patients face major barriers to care and many of them remain undetected. The reasonable median delay found in this study does not necessarily support this view.

Determinants of delay

District and type of first facility visited were significant determinants of health system delay. Muminobod is a mountainous district and this may be one of the reasons why treatment delays were longest there (cf. figure 5.1). On the other hand, the similarly mountainous neighbouring district of Shurobod was among the districts with relatively short delays. Differences between districts may account for a multitude of factors including differences in socio-economic conditions, accessibility, or practices in the health centres in the district. The type of the facility where the first formal health care contact took place was the strongest predictor of system delay. Visiting first a tertiary hospital or TB specialist is associated with shorter delays. This is consistent with findings from other settings, although there is considerable variation[11-16,25]. Making the first visit to a Central District Hospital was also significantly associated with shorter delay. While a history of immigration has been shown to influence delay in western countries[25-26], this study shows for the first time that developing active TB while being a temporary migrant worker abroad leads to long system delays: patients who first visited a facility in Russia had the longest delays of all. This is not

surprising given that these patients fell ill in Russia and had to travel back to Tajikistan to start anti-TB chemotherapy. About 10% of all TB patients receiving treatment in the study area had developed active TB in Russia. This may also be relevant for citizens of several other Central Asian and Caucasian countries who migrate to Russia to find work. The moderate delays of many patients are encouraging, but improvements are needed for patients first presenting to Medical Houses, Rural Health Centres and especially facilities in Russia.

The consistent results of the univariate analyses compared to the multivariate analysis support the view that these results are not due to confounding. The factor 'labour migration' is an exception in the sense that it shows a significant impact on health system delay in the univariate but not in the multivariate analysis. There is strong correlation between 'labour migration' and having visited a facility in Russia. This does, however, not affect our conclusions.

In order to reduce delays for Tajiks who develop active TB while working in Russia, an international referral system should be developed. The Russian TB program and international organisations involved in TB control in Russia should investigate the options of foreigners who develop TB while in Russia. If the situation is as described by the patients in our study sample, there are disincentives to early presentation to the Russian health system, because the patient cannot expect treatment. Rather, presenting to the Russian health system will mean that patients will have to spend money to return to their home country. Such a disincentive is likely to lead to delayed diagnosis and consequently to extended periods of infectiousness in the community.

As mentioned above, most providers other than TB specialists are reluctant of diagnosing TB and would rather refer the patient. This is related to the vertical TB control program inherited from the Soviet Union and the resulting notion that TB patients should be diagnosed and treated outside the general health services. The large difference in the hazards ratios from the peripheral facilities to the TB facility point at a need to shorten referral pathways and referral times for TB patients from the periphery. This needs to be achieved without jeopardizing the short delays that patients experience at the TB facilities. A good possibility would be the diagnosis of TB in the peripheral facilities without referral. At least for part of the districts, a sputum collection plan exists, whereby peripheral facilities are required to collect three sputa from a TB suspect and then organise transport to the district TB facility, where microscopic

examination is conducted. Due to the Soviet tradition of over-reliance on CXR and to doubts about accuracy of sputum smear microscopy, sputum collection at the periphery hardly ever takes place.

Lönnroth et al[27] have pointed out that the perceived financial consequences of seeking health care affect the decision of whether and when to initiate health care seeking. Community members, TB patients and health care providers in four districts of Tajikistan identified financial costs of health care seeking as the main obstacle to obtaining a diagnosis and treatment[28]. Consequently, a better understanding of illness-related costs and resulting mitigation strategies may also contribute to shorter delays.

Conclusions

Before being diagnosed, TB patients visit a broad range of different health facilities. While the median total delay until start of treatment is moderate for most patients, improvements are needed for certain subgroups. Those patients who develop TB while working in Russia have the longest health system delays. Those who first present to peripheral primary care facilities or polyclinics have long system delays, too. Improvements for both subgroups are possible through better organisation of health care delivery. An international referral system for migrant workers developing active TB in Russia is urgently needed and is in the interest of both countries. Primary care providers should be enabled and encouraged to diagnose TB and start patients on treatment. Strengthening of sputum smear examination and collection of specimens at primary care facilities should be considered.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA led the study from planning to writing up. KW contributed to designing the study and to writing the manuscript. HA and SS participated in design of the study and data collection. All authors read and approved the final manuscript.

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6. Household costs of illness during different phases of tuberculosis treatment in Central Asia: a patient survey in Tajikistan

Running head: Costs during different phases of treatment

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Abstract

Background: Illness-related costs incurred by patients constitute a severe economic burden for households especially in low-income countries. High household costs of illness lead to impoverishment; they impair affordability and equitable access to health care and consequently hamper tuberculosis (TB) control. So far, no study has investigated patient costs of TB in the former Soviet Union.

Methods: All adult new pulmonary TB cases enrolled into the DOTS program in 12 study districts during the study period were enrolled. Medical and non-medical expenditure as well as loss of income were quantified in two interviews covering separate time periods. Costs of different items were summed up to calculate total costs. For missing values, multiple imputation was applied.

Results: A cohort of 204 patients under DOTS, 114 men and 90 women, participated in the questionnaire survey. Total illness costs of a TB episode averaged $1053 (c. $4900 purchasing power parity, PPP), of which $292, $338 and $422 were encountered before the start of treatment, during intensive phase and in continuation phase, respectively. Costs per month were highest before the start of treatment ($145) and during intensive phase ($153) and lower during continuation phase ($95). These differences were highly significant (paired t-test, $p < 0.0005$ for both comparisons).

Conclusions: The illness-related costs of an episode of TB exceed the per capita GDP of $1600 PPP about two-and-a-half times. Hence, these costs are catastrophic for concerned households and suggest a high risk for impoverishment. Costs are not equally spread over time, but peak in early stages of treatment, exacerbating the problem of affordability. Mitigation strategies are needed in order to control TB in Tajikistan and may include social support to the patients as well as changes in the management of TB cases. These mitigation strategies should be timed early in treatment when the cost burden is highest.

Background

Illness often leads to substantial economic burden for the patients and their households, especially in resource-poor settings and in the absence of social support mechanisms [1, 2]. Economic costs of illness at the household level–below referred to as household costs–have strong implications for issues of poverty and equitable access to health care. A review found that ill-health, especially long-lasting disease including tuberculosis (TB), puts households at high risk of impoverishment [1]. Poor households are deterred from the use of health care due to household costs, preventing the health services from reaching those most in need [3]. In the case of TB, where the main control and prevention measure consists of treating active disease [4], it must therefore be expected, that high household costs have a negative impact on TB control.

There have been many studies on cost-effectiveness of different TB control strategies, mainly investigating the costs to the health system. Important findings of these studies include the feasibility and cost-effectiveness of short-course TB chemotherapy on a predominantly ambulatory basis [5-10]. Far fewer studies measured the costs to households [11-13]. One of the first studies to comprehensively measure household costs found that the costs of an episode of TB in Thailand amounted to 20% of annual household income in the poorest third of patients and thus were devastating [12]. Other studies also found that household costs of an episode of TB were considerable–ranging from $186 to $1457 in Tanzania depending on treatment duration and around $920 in China [13-14]. A number of studies investigated reasons for delay to treatment and consequently measured only the costs up to diagnosis and registration with the TB control program [15-17]. Also when studying the economic impact on households, this strategy may be tempting, based on the rationale that TB treatment should be free of charge afterwards. However, those studies that measured costs after enrolment in TB control programs invariably found considerable costs during treatment [1, 12-14]. In his review, Russell [1] found that "health expenditures tended to be lumpy, coming in peaks that intensified cost burdens over a few days or weeks". However, to our knowledge so far no study looked at the distribution of household costs of TB over time other than differentiating before diagnosis and after diagnosis.

Tajikistan is the poorest republic of the former Soviet Union with a per capita gross domestic product (GDP) of $1600 purchasing power parity (PPP, 2007 estimate) [18]. The country's infrastructure was severely damaged during the civil war from 1992 to

1998. Many villages and even whole districts are cut off in winter from electricity supply and transportation axes in this mountainous country. The economy of Tajikistan is highly informal and it has been observed that the grey economy is more important in several respects than the official economy [19]. Corruption is widespread and Transparency International ranks Tajikistan number 151 out of 180 countries in their perceived corruption index [20]. Temporary labour migration to Russia is very common, especially among young men. The health system is still very specialised, hierarchical and at least nominally comprehensive as in the Soviet Union [21]. Profound health sector and health financing reform is ongoing. Patients have to pay predefined fees for specific services above the primary care level, with different fee rates depending on referral or non-referral of the patient from primary care level. Informal payments are widespread also in the health system and out-of-pocket payments may constitute as much as 80% of total health funding [22]. In a recent survey in two districts piloting a new primary care model, almost half of the patients who had visited a family doctor reported that they had made an informal payment [23]. Involvement of the private sector in health care is very limited and virtually nonexistent outside the capital. The WHO estimate of TB incidence was 204 cases per 100,000 per year in 2006 [24], while the national TB control program estimated incidence between 160 and 180 cases per 100,000 per year. The country began DOTS implementation in 2002 and DOTS coverage reached 100% by the end of 2007. A study in ten districts of Tajikistan showed that the hospitalisation rate of TB patients was high (58%) and that a positive sputum smear result was the main predictor of hospitalisation [25]. For patients who are not hospitalised, the program foresees facility-based observation of treatment.

In most settings in the former Soviet Union anti-TB drugs are provided for free, but patients have to pay for other services including additional medicines, x-rays and laboratory services and potentially face major financial barriers [26]. In urban Ukraine, total illness-related costs of TB varied from $57 to $450 depending on the TB control strategy and on the locality [27]. These costs were often outweighed by the social benefits provided to TB patients. Overall, very little is known about illness-related costs of TB in the former Soviet Union. This study aimed at quantifying household costs of an episode of TB in Tajikistan, with special attention to the time period, when costs were incurred.

Methods

Study population

Only districts with an established DOTS program were considered for inclusion in the study. Two regions were excluded because they were accessible only by air at the time of the study, Badakhshan and Sughd. In close collaboration with the Republican Centre for TB control of Tajikistan, 12 districts were purposefully selected to represent different urban, rural, lowland and mountainous settings. All pulmonary TB patients at least 15 years of age who were registered for the first time (i.e. "new" patients according to WHO definition) in the 12 study districts in the period from 1st December 2006 until 31st March 2007 were eligible for study participation. Patients who had defaulted from treatment before the first interview were excluded. Patients who defaulted during or at the end of the intensive phase were excluded from the second interview, as they could not possibly give information on the continuation phase.

Questionnaire and Interviews

Patients were visited in hospital or at home during the intensive phase of treatment, written informed consent was obtained and the first interview conducted. Three to four months later, the same patients were visited for a follow-up interview. The first interview covered the period before diagnosis, starting from the time point, when the patients experienced the first symptoms, and the intensive phase. The follow-up interview covered the continuation phase. The costs from the day of interview until the end of the respective phase were extrapolated, assuming a duration of four months for the continuation phase. The questionnaires were adapted from a questionnaire used for the quantification of costs of HIV/AIDS [28]. They were piloted and finalised prior to the start of data collection. They are available from the authors upon request. Completing an interview took about one hour on average. The questionnaires included detailed questions about health care seeking, about the costs incurred by patients and their households and about household assets. Household costs included medical expenditure (for drugs, medical fees and laboratory tests), non-medical expenditure (for transport, special food items, modification of housing, traditional healers, self-treatment and any other reported expenditures), and loss of income due to the inability to work. To quantify loss of income, patients were asked about the actual reduction of income that they themselves and caretakers had experienced due to absence from their

usual income-generating activities for a day. This daily income reduction was then multiplied with the number of days away from work. If patients did not know the income reduction for one day, but could give an estimate for the total income reduction until the day of interview, the total estimate was registered and divided by the number of days away from work during data entry. Where income was in-kind, like sometimes in agriculture, the monetary value was estimated. Information on treatment outcome could not be obtained, as treatment was not completed at the time of the interview.

Interviewers were trained for two weeks before conducting real interviews and supervised at least twice per month through interviews conducted together with the main researcher. Specific emphasis was given to support the patients in their recall work, including the use of a calendar of locally important events, to motivate the patient to provide accurate information on costs and to ask back if reported costs were unexpectedly high or low for local context. Data were entered by the main researcher in FileMaker (version 8.0v1, FileMaker Inc, USA, 1984-2005).

Data Analysis

All analyses were conducted in Stata IC/10.1 for Macintosh (Stata Corporation, USA, 1985-2008). Individual cost items were summed up to the categories of medical costs, non-medical costs, and lost income–for each of the three phases of treatment separately (before start of treatment, intensive phase, and continuation phase). For conversion of Tajik Somonis to international US$ PPP, we used data provided by the World Bank [29].

Table 6.1. Characteristics of study participants

Age	Mean	31years
	Range	15-72years
Form of TB	Pulmonary	204 (100%)
	Sputum smear positive	122 (60%)
History of TB disease	New cases	204 (100%)
Delay until start of treatment	Median patient delay	21.5days
	Median health system delay	16days
	Median total delay	52days
Hospitalisation	Hospitalised patients	153 (75%)
	Median duration of hospitalisation	39days
Direct observation of treatment	Median number of visits for treatment observation	53 visits

In order to avoid the problems associated with complete case analysis and as recommended by Manca and Palmer [30] for similar problems, we used multiple imputation to deal with missing observations, implemented in the function "ice" in Stata [31-32]. The algorithm in "ice" assumes normally distributed variables; this was assured through transformation to normal scores. The statistical comparisons of costs during the different phases were done with a paired t-test because we were mainly interested in the pair wise comparisons (n=204 for all comparisons). To correct for the fact that we conducted three t-tests, we decreased our significance level to 1.67%. We plotted the residuals and checked visually whether the distributions were normal. In order to normalise the distribution of residuals, we used log-transformation.

We conducted a principal component analysis on 18 variables to construct a wealth index following the methodology described by Filmer and Pritchett [33]. The 18 variables included 15 household assets and three housing characteristics. To improve validity of the wealth measure, we used continuous variables, where this was possible, and we did not recode any categorical variables as dummies [34]. Subjects were allocated to five quintiles by their wealth index. To investigate the internal consistency of our measure of socio-economic status (SES), we plotted the mean of each asset variable against SES quintile and found that the asset variables were highly consistent with expectations. The study has received ethical approval from the Ministry of Health of the Republic of Tajikistan.

Results

In the 12 study districts, 282 eligible patients were registered for treatment during the recruitment time. Seventy-eight (28%) of them were not interviewed, because they did not consent (10 patients; 3.5%), were not at home or in hospital when visited (17; 6.0%), had died (5; 1.8%), were initial defaulters (3; 1.1%), were already in the continuation phase at the time point when visited by the research team (25; 8.9%), or the address in the registry was wrong or insufficient (18; 6.4%). The remaining 204 (72%) patients, 114 (56%) men and 90 (44%) women, were found, provided informed written consent and were interviewed. Their mean age was 31 years and they reported a median delay of 52 days until start of treatment; 122 (60%) were sputum-smear positive patients and 153 (75%) were hospitalised at some stage during the disease (Table 6.1). Among women, most identified themselves as housewives (58%) or farmers (12%). Among men, most reported temporary labour migration to Russia

(26%) or unemployment (18%).

The mean total household costs of an episode of TB were $1053 (±standard deviation $1601; median $378). Patients reported household costs of $292 (±620; 54) before the start of DOTS treatment, costs of $338 (±575; 139) during the intensive phase, and $422 (±705; 95) during the continuation phase (Figure 6.1). Thus about ¾ of costs were encountered after the patients were enrolled in the DOTS program. Direct costs amounted to $152 (±219; 47), $147 (±213; 108), and $97 (±111; 53) for the period up to start of DOTS treatment, intensive phase, and continuation phase, respectively. Thus direct costs amounted to $396 (±357; 282) in total over all periods and constituted 38% of total costs, the rest being lost income. Table 6.2 shows that direct costs most notably included costs for drugs (27% of total direct costs), transportation (25%), and special foods (29%). Drugs that were paid for mainly included vitamins and IV rehydration. The mean expenditure for the anti-TB drugs (which are officially provided for free) was very small: $0.35. Special foods included among others different kinds of meats and animal fats that were not consumed during times of good health or only in smaller amounts. Indirect costs were mainly incurred by patients themselves: 93 (79%) out of 117 patients with complete information spent some time away from usual income-generating activities. The median amount of time away from work was 135 working days. For those who worked seven days a week this would correspond to 4.5 months, for those who worked five days a week to 6.3 months. Among caretakers, 44 (36%) out of 122 cases with complete information spent a median of 24 working days away from work.

Household costs were not evenly spread over time. Costs incurred during one month were $145 (±296, median 37) before start of DOTS treatment, $153 (±256, 62) during the intensive phase, and $95 (±159, 21) during the continuation phase (Figure 6.2). Thus costs incurred during one month were significantly higher before start of treatment (paired t-test, $p<0.0005$, n=204) and during the intensive phase ($p<0.0005$), both compared to the continuation phase. The residual plot suggested that a few observations might violate the assumption of normality. We therefore conducted a sensitivity analysis excluding these observations. Both differences were still highly significant (and in the same direction). The difference in monthly costs before start of treatment compared to the intensive phase was also significant ($p=0.001$), but much smaller. While lost income was relatively constant across the three periods, direct costs
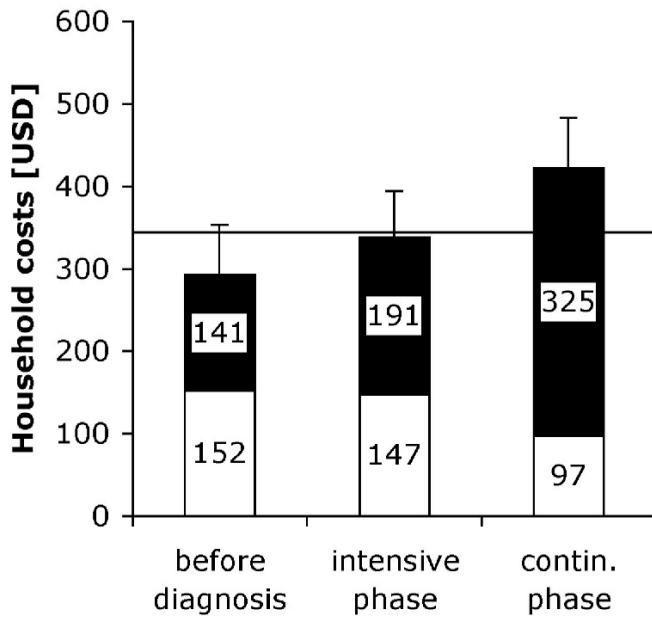
Figure 6.1. Household costs of an episode of tuberculos in three separate periods of treatment. Direct costs (white), lost income (black) and standard errors of total costs are shown. The horizontal line denotes the annual per capita income [18].
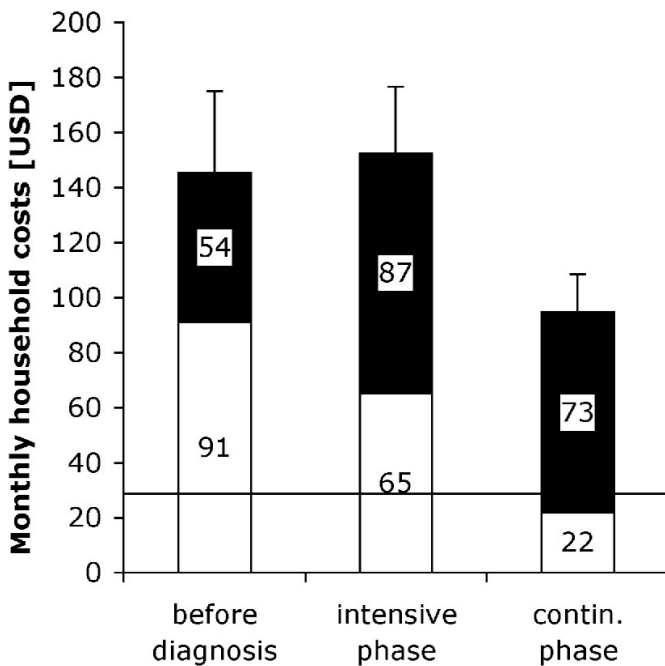
Figure 6.2. Household costs incurred during one month during three separate periods. Direct costs (white), lost income (black), and standard errors of the total are shown. The horizontal line denotes the monthly per capita income [18].

per month were about 4.2 times higher before start of DOTS treatment than during the continuation phase and about three times higher during the intensive phase than during the continuation phase (p<0.0005 for both comparisons). The difference between the period before the start of treatment and the intensive phase was not significant (p=0.089). Thus costs were most acute during early stages of treatment. This was particularly the case for direct costs. However, patterns varied considerably for individual line items (Table 6.3). Costs of drugs were highest during the intensive phase and lowest before start of treatment. Costs of diagnostic and laboratory tests, and

Table 6.2. Composition of household costs

Cost item	Mean in US $	Standard Deviation	Percentage of direct costs
Indirect costs	**657**	**1391**	**N/A**
Direct costs	**396**	**357**	**100%**
Medical costs	**154**	**148**	**39%**
Drug costs	107	105	27%
Costs of diagnostics and lab tests	18	19	4.5%
Costs of medical fees	29	64	7.3%
Non-medical costs	**242**	**286**	**61%**
Transportation	100	162	25%
Special foods	113	202	29%
Self-treatment & traditional medicine	16	41	4.0%
Other expenses	13	26	3.3%

Table 6.3. Variation of selected costs items over time [in US $]

Cost item	Before start of treatment		Intensive phase		Continuation phase	
	Mean	SD§	Mean	SD§	Mean	SD§
Drug costs	21.3	39.9	51.7	74.7	34.3	56.1
Costs of diagnostic and lab tests	7.8	16.2	7.4	8.7	2.5	3.9
Costs of medical fees	15.2	60.8	9.2	15.8	4.8	14.4
Transportation	71.2	139	8.2	12.9	20.4	26.4
Special foods	31.4	68.7	67.5	173	14.5	66.3

§SD=Standard deviation.
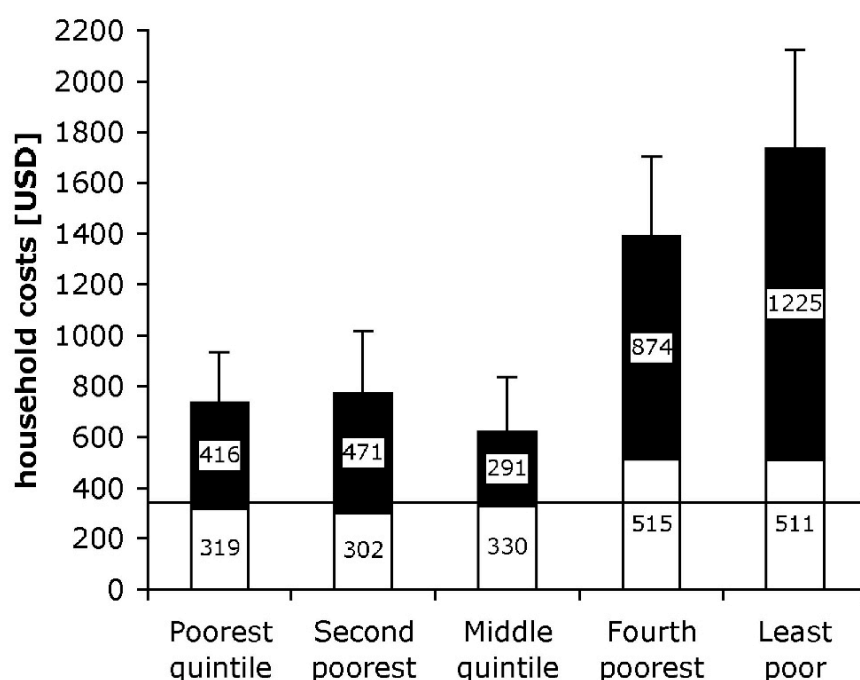
Figure 6.3. Household costs by socio-economic quintiles. Direct costs (white), lost income (black), and standard errors of the total are shown. The horizontal line denotes the annual per capita income [18].

similarly costs of medical fees, were highest before start of treatment and lowest during the continuation phase. Costs of transportation were by far highest before start of treatment.

Costs varied considerably by SES. Those in the lower three SES quintiles incurred less than half of the costs of the highest SES quintile on average–$735, $773 and $621 respectively versus $1735 (Figure 6.3). This difference was mainly due to higher income loss in the higher SES quintiles, the mean income loss in the wealthiest quintile being almost three times that of the poorest. Medical direct costs were similar across all SES quintiles; non-medical costs of the wealthiest quintile were double those of the poorest ($351 versus $168).

Discussion

The mean total household costs of a TB episode amounted to $1053, corresponding to $4894 PPP. While a considerable part of the scientific discussion on household costs has concentrated on the period before diagnosis [15-17], this study found that costs during treatment account for three quarters of total costs–in a setting with free TB drugs. Monthly costs were most acute before treatment and during the intensive phase. The total costs presented here do not yet take into account that patients may incur costs after the end of treatment; especially further loss of income for those who have lost their jobs.

The study may seem only partly representative of Tajikistan, as two regions had to be excluded. One of the regions (Badakhshan) is remote and very sparsely populated. The other one (Sughd) had only eight districts with an established DOTS program at the time of the study (versus 34 districts with DOTS in the whole country) and was only accessible by air in winter. The study is representative of an area of Tajikistan, from where 80% of all cases under DOTS came in the year up to the study.

As other studies on household costs, this study also relied on self-reported costs–it is thus not excluded that patients forgot or overestimated some of the costs [7]. By using two interviews for separate periods of treatment, this study limited recall time and recall bias. Further we tried to limit the potential problem of overestimation by training the interviewers for this situation.

The mean total household costs found in this study were even higher in terms of PPP

than those found in other studies [12-14]. There may be several reasons for the high costs found in this study and these are discussed in the following. One reason may be our methodology that reduced recall bias. Further, there is a habit among TB specialists in Tajikistan to hospitalise many TB patients and to prescribe many drugs for perceived iatrogenic problems and symptomatic treatment (own data, unpubl.). Hospitalisation itself does not usually have to be paid for, and this is consistent with the fact that costs of medical fees, which include hospitalisation fees, are relatively low (cf. table 6.2). However, hospitalisation may be linked to other services like the provision of additional medication. Additional drugs, including those for symptomatic treatment, have to be paid for and it seems likely that these have led to the very high costs of drugs during the intensive phase (cf. table 6.3). Only a small minority of patients reported payments for anti-TB drugs. Costs of transportation were very high before the start of treatment and this may point to another reason for high costs. Thirty-one patients (15%) had developed active TB while being migrant workers in Russia. These patients encountered high transportation costs for their return to Tajikistan. An analysis of the difficulties faced by migrant workers who develop active TB in Russia is presented in a separate publication [35]. Informal payments that occur in the health system are a further potential reason for high costs. Disaggregating formal and informal payments was not possible in our study, among others because a health financing reform was ongoing during the time of the study–including formalisation of some informal payments. However, as reported above, the mean payments for anti-TB drugs were very small.

Household costs were approximately three times higher than the per capita GDP and thus must be considered catastrophic for affected households. As TB disproportionately affects poorer segments of society this burden may be even more catastrophic in the typical TB-affected household than average GDP values indicate. Direct costs were relatively similar for all SES quintiles, while indirect costs, which depend on income, were three times higher in the wealthiest compared to the poorest quintile. This is suggestive of a regressive cost burden at least for direct costs.

Monthly costs were especially high before enrolment in DOTS treatment and during the intensive phase. Monthly costs were significantly higher during these two periods than during the continuation phase. This pattern was very clear for direct and total costs, but less so for lost income, which was more constant over the different phases of

treatment. Patients who stopped working often did so for the duration of four months and more. This suggests that they did not only stop working during the time of acute illness, but for the whole treatment. Tajik doctors often recommend them not to work during treatment and for up to two years afterwards. Seasonality of income may have led to underestimation of lost income especially before the start of treatment, because patients were enrolled into the study in the winter months, which is the season when least work is available. Consequently, the observed pattern of higher costs during early stages of treatment may even be stronger in reality. The spread of costs over time affects the ability of households to cope with these costs [1], and our findings suggest that the problem of affordability of services is most acute in early stages of treatment.

The high costs found in this study suggest that sheer poverty and inability to cope with the economic burden of treatment negatively affect treatment adherence and treatment outcomes, as has been suspected in other contexts [12, 36]. Farmer et al [37] have shown that mitigation strategies including incentives for adherence can improve treatment adherence among TB patients. Donors and program managers need to implement effective mitigation strategies to enable patients to adhere to DOTS and to avoid severe impoverishment. The present study shows that these mitigation strategies must be timed early in treatment, when most of the costs are incurred. A recent study from Russia has identified types of incentives that are preferred by TB patients [38]. Additional strategies to reduce the economic burden of TB disease on households might target the high costs for drugs, which are related to the prescription patterns including common use of symptomatic treatment. Studies from Russia have shown features in the management of TB that are also found in Tajikistan, including high hospitalisation rates and widespread use of symptomatic treatment [39-40]. Furthermore similar factors influence hospitalisation in Russia and Tajikistan [25, 41]. These parallels suggest that some of our results may also apply to Russia and other post-Soviet countries.

Conclusions

During an episode of TB, patients and their households face costs of approximately $4900 PPP. Comparison with the per capita GDP of $1600 PPP shows that these costs are catastrophic for the households concerned and suggest a high risk for impoverishment. Costs are not equally spread over time, but are highest in early stages of treatment, exacerbating the problem of affordability. Free TB drugs do not lead to

free treatment and non-TB drugs, transport, and loss of income are very important cost drivers for patients. Mitigation strategies are needed in order to control TB in Tajikistan and may include social support to the patients as well as changes in the management of TB cases. Mitigation strategies need to be timed early in treatment when the cost burden is highest. The provision of food supplements to TB patients may contribute to somewhat alleviate the economic burden. However, our results suggest that these should be delivered soon after a TB diagnosis. Reducing the use of non-TB drugs should be considered.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA led the study from planning to writing up. KW contributed to designing the study and to writing the manuscript. HA and SS participated in design of the study and data collection. All authors read and approved the final manuscript.

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7. Factors determining household expenditure for tuberculosis and related coping strategies: a patient survey in Tajikistan

Running head: Determinants of household expenditure of tuberculosis

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Abstract

Objective: To investigate factors influencing expenditure levels and the use of potentially detrimental coping strategies among tuberculosis (TB) patients. For the purpose of the present study, potentially detrimental coping strategies included borrowing money and selling assets.

Design: Questionnaire survey with an initial and a follow-up interview of each adult new pulmonary TB case registered over a period of four months. Conducted in twelve districts with DOTS in central, western and southern Tajikistan, one of the poorest countries in the world.

Results: Patients and their households faced mean expenditures of US$396 related to a TB episode. In a multivariate mixed-effect regression, the main determinant of out-of-pocket payments–either over the whole course of the disease or after enrolment in DOTS treatment–was receiving complementary treatment besides the anti-TB drugs. Hereby, complementary treatment refers mainly to vitamins and rehydrating infusions. Further important factors were duration of hospitalization and treatment delay. Sex showed no association with expenditure. To cope with the costs of illness, two thirds of patients employed a potentially detrimental coping strategy. TB patients raised on average US$23 through credits, US$57 through borrowing money without interest and US$102 through selling assets.

Conclusion: The catastrophic out-of-pocket payments faced by TB patients and their households are correlated with i) receiving complementary treatment, ii) delay to treatment and iii) duration of hospitalisation. More parsimonious use of complementary treatment and hospitalisation could reduce illness-related costs for patients. Consequently, the use and rationality of complementary treatment and hospitalisation should be reassessed and adapted correspondingly.

Introduction

Tuberculosis (TB) patients encounter substantial costs during the course of their disease–despite anti-TB chemotherapy offered for free in most settings (Saunderson 1995, Habib & Baig 2006, Kamolratanakul *et al.* 1999, Wyss *et al.* 2001, Aspler *et al.* 2008, Jackson *et al.* 2006). In most countries of the former Soviet Union anti-TB drugs are provided for free, but patients have to pay for other services including additional medicines, x-rays and laboratory services (Mosneaga *et al.* 2008). In Tajikistan, household costs of an episode of TB amounted to almost US$5000 purchasing power parity (Ayé *et al.* 2010a). Expenditure and loss of income associated with TB put poor households at risk of impoverishment (Russell 2004) and have been identified as a major barrier to TB services (Wei *et al.* 2009). Several studies observed differing costs depending on socio-economic status and hospitalization (Russell 2004, Kamolratanakul *et al.* 1999, Saunderson 1995); others have shown that the provision of treatment observation influences costs to the patients (Saunderson 1995, Floyd *et al.* 1997). The only study so far that statistically tested such observed differences, found clinic-based observation of treatment, longer patient-delay and male sex to be the main determinants of higher household costs in urban Zambia (Aspler *et al.* 2008). At the time of the study, there was no alternative to clinic-based treatment observation in Tajikistan.

Several authors have pointed out that the investigation of household costs of disease is incomplete if coping strategies employed by households are ignored (Russell 2004, McIntyre *et al.* 2006). The most immediate response to illness-related costs is to use cash income and savings, but this option is not available to all households (McIntyre *et al.* 2006, Russell 1996). Further common coping strategies are borrowing and selling assets. Borrowing can increase the level of debt; sale of assets decreases the resilience to future economic shocks (Russell 2004). This is particularly true for the sale of productive assets, because this reduces future household income. While there are many more coping strategies (cf. Sauerborn *et al.* 1996, Obrist *et al.* 2007), available studies emphasize that selling productive assets and taking out loans often negatively affect future income and can lead to impoverishment (Russell 2004, Leive & Xu 2008, McIntyre *et al.* 2006, Russell 1996). For the purpose of this article, the term "detrimental coping strategies" refers to selling assets and taking out loans. The present study aimed at identifying determinants of TB-related out-of-pocket payments and the use of detrimental coping strategies in Tajikistan.

Methods

Study setting

WHO (2009) estimated tuberculosis (TB) incidence for the year 2007 at 231 cases per 100'000, while the national TB control program's estimate is 160 to180 cases per 100'000. The internationally recommended strategy for TB control, DOTS, was introduced in Tajikistan starting 2002 and coverage reached 100% by the end of 2007. However, hospitalization rates remain high: 58% in a study in ten districts (Thierfelder *et al*. 2008). Data for this study were collected alongside two studies investigating i) delay to TB treatment and ii) the timing of costs of illness (Ayé *et al*. 2010b, Ayé *et al*. 2010a). Out of all districts with an established DOTS program in the Khatlon and Republican Subordination regions of Tajikistan, twelve districts were selected– representing urban, rural, lowland and mountainous settings. All adult (≥15 years) new pulmonary TB patients who were registered in the twelve study districts in the period from 1st December 2006 until 31st March 2007 were eligible for the study. The study participants received TB treatment according to the national guidelines of Tajikistan. This involved an intensive phase of treatment lasting two months and a continuation phase lasting four months. If sputum smear conversion was not achieved after two months, the intensive phase was prolonged by one month.

The research team visited patients in hospital or at home during the intensive phase of treatment, obtained written informed consent and administered the first questionnaire. Three to four months later, a follow-up questionnaire was applied to the same patients. The first questionnaire asked about costs encountered from first symptoms to onset of treatment and during the intensive phase. The follow-up questionnaire asked about costs encountered during the continuation phase. For analysis, we extrapolated costs from the day of the interview until the end of the respective phase. The questionnaires included detailed questions about the costs incurred by patients and about household assets. Household costs included medical and non-medical expenditure.

Statistical analysis

Three statistical models were built in order to achieve the objectives of the present study and are described below. The three outcome variables were: i) total TB-related expenditure, ii) TB-related expenditure after onset of treatment and iii) TB-related detrimental coping strategies.

All analyses were conducted in Stata IC/10.1 (Stata Corporation, USA, 1985-2008). We applied multiple imputation to our dataset to deal with missing observations as recommended by Manca & Palmer (2005) for similar problems and in order to avoid the problems of complete-case analysis (Schafer 1997). We built a wealth index based on 18 asset variables (Filmer & Prichett 2001). Details on these two steps have been presented elsewhere (Ayé *et al.* 2010a).

The factors influencing direct costs to households were identified through a mixed-effects linear regression. We reduced the number of repeated significance tests by identifying a basic model at the outset and by considering only a limited number of predictor variables (Grafen & Hails 2002). We built our basic model around five variables. A variable identifying individual DOTS centres had to be included in the model based on the design of the survey and was included as a random effect. Three variables that had previously been shown to influence household costs were identified from the literature, namely sex (Aspler *et al.* 2008), socio-economic status (Russell 2004, Kamolratanakul *et al.* 1999) and hospitalization (Saunderson 1995, Russell 2004). Socio-economic status was included as a continuous variable, the wealth index described above. Hospitalization, one of the case management factors of main interest, was also included as a continuous variable, namely the log-transformed duration of the hospital stay in days. The fifth variable, the second of the main variables of interest relating to TB case management, was a binary denoting patients that had received complementary treatment, including medication for perceived iatrogenic problems. Two further variables were considered in addition to the basic model: the sputum smear result and the total delay from onset of symptoms to treatment–both as proxies for the severity of disease and as continuous variables. Both the length of hospital stay and the delay until onset of treatment were log-transformed because the relationship was expected to have the shape of a saturation curve rather than a linear increase. The full model was run, its validity was checked by visually examining the residual errors and then the model was simplified by excluding factors with $p > 0.2$. However, the five factors included from the outset were retained even if their p-values were above the threshold (Grafen & Hails 2002).

In order to test more specifically the influence of a case management decision on the costs incurred subsequent to this decision, a similar mixed-effects regression model was built, but the outcome variable included only those expenditures that were incurred

after the onset of anti-TB chemotherapy (referred to as "during treatment" below). Explanatory variables and criteria for model simplification were identical to the previous model.

Further, we built a mixed-effects model on the amount of funds mobilized through detrimental coping strategies. Taking out loans (with or without interest) and selling assets were considered detrimental coping strategies, but not the use of household income and savings. The explanatory variables were the same as in the models on expenditure, but an additional variable was considered, a binary identifying patients who had worked in Russia until falling ill. This was included because it was thought that it could have a major influence on the amount of cash available at the household level.

For all three models, we plotted the residuals and checked visually whether they were approximately normally distributed. Residuals were close to normally distributed when expenditure data (first two models) were log-transformed and when funds mobilized through detrimental coping strategies (third model) were root-transformed.

The study has received ethical approval from the Ministry of Health of Tajikistan.

Results

The study identified 282 eligible patients. Reasons for drop-out and demographic characteristics of the 204 patients who consented and were interviewed are listed in Tables 7.1 and 7.2, respectively.

Expenditure over the whole course of disease

As reported previously (Ayé *et al.* 2010a), mean total costs of an episode of TB amounted to US$1053 (US$4900 PPP) in the twelve study districts. This study concentrated on direct costs, i.e. expenditures. Of the total amount, on average US$396 (±standard deviation US$357; median US$282) were direct costs, the rest being lost income due to the inability to work. Mean expenditure for drugs was US$107 (±105; 72), including mean reported expenditure of US$0.35 for the anti-TB drugs. The full multivariate linear regression model for total expenditure was run and simplified as described in the methods section (sputum smear result was excluded). The final multivariate regression model showed that the delay until onset of treatment and

Table 7.1. Reasons for drop-out

Reason	Number of cases (% of drop-outs)
Wrong or insufficient address	18 (23)
Not found at home or in hospital when visited	17 (22)
Died	5 (6)
Initial defaulter	3 (4)
Already in continuation phase when visited	25 (32)
Did not consent	10 (13)
Total	**78 (100)**

Table 7.2. Characteristics of the 204 study participants

Age [years]	15 to 24	25 to 34	35 to 44	≥45
Women	34	23	15	17
Men	44	40	15	16
Total	78	63	30	33

Profession	House-wife	Migrant worker†	Farmer	Petty trade	Un-employed	Other
Women	52	1	11	3	9	14
Men	0	30	13	19	20	32
Total	52	31	24	22	29	46

Setting	Urban	Peri- and semi-urban	Rural
Women	8	3	78
Men	1	8	106
Total	9	11	184

†These patients had returned after labour migration to Russia.

Table 7.3. Results of the mixed-effects linear regression on total expenditure (in US$, log-transformed); n=204

Factor	Coefficient/ slope	S.E.§	p-value	fmi†
sex	0.147	0.132	0.263	0.160
wealth index	0.0449	0.0347	0.196	0.130
days in hospital (log-transformed)	0.0163	0.00910	0.073	0.131
delay in days (log-transformed)	0.231	0.604	*** <0.0005	0.151
complementary treatment	0.744	0.280	** 0.008	0.128
intercept	3.91	0.392	*** <0.0005	0.139
DOTS centre (estimate for variance-covariance matrix)	-1.17	0.420	N/A	0.178

§S.E.=standard error
†fmi=fraction of missing information. The fmi is a measure of the information contained in the missing data in a multiply imputed dataset (Schafer 1997).
*denotes significance levels

complementary treatment were the main determinants of expenditure (Table 7.3). On average, a doubling of the delay led to an increase in total expenditure by 17%. Receiving complementary treatment led to an increase in total expenditure by a factor

of 2.10. Complementary treatment most commonly included Aloe Vera 1% 1ml, glucose 5% infusion, vitamin C 1% 1ml, vitamin B1, B6 and B12 (in single and compound formulation), calcium gluconate 10% 10ml, and Polyvinylpyrrolidone 6% infusion. There was a statistical tendency for increased costs with longer hospital stay (p=0.073). A slight departure from linearity was observed in the influence of the sputum smear result on total expenditure. A sensitivity analysis with sputum smear result as a categorical variable showed fully consistent results.

Expenditure during anti-TB therapy

The regression model on expenditure during treatment could not be simplified. The delay was not significantly associated with direct costs during treatment. However, receiving complementary treatment and duration of hospital stay during treatment significantly increased expenditure (Table 7.4). Receiving complementary treatment led to 2.12 times higher expenditure. Patients hospitalized for one week had 50% higher expenditure compared to patients who were not hospitalized. Patients hospitalized for two months had 5.6% higher expenditure than patients who were hospitalized for one week only.

There was no statistical relationship between sex and expenditures during treatment. Also the factor sputum smear result showed no statistical relationship with expenditure in either of the two models.

Coping strategies

Two thirds (65.7%) of patients relied on a detrimental coping strategy to handle the costs of tuberculosis. The mean credit taken up by patients' households over the course of the whole treatment amounted to US$22.7, the mean amount of borrowing (without interest) was US$56.9, and the mean amount of money raised through sale of assets was US$102. The mean total amount for all detrimental coping strategies was US$182.

The mixed-effects linear regression did not show any statistically significant relationships (Table 7.5). There was a weak statistical tendency (p=0.096) for patients with higher wealth indices to raise less money through detrimental coping strategies. Patients who had returned from Russia due to their TB showed a statistical tendency (p=0.069) for raising more funds through detrimental coping strategies than patients who had not been to Russia.

Discussion

Limitations

Like other studies investigating household costs of illness, we also had to rely on self-reported costs. Consequently, recall and reporting bias cannot be excluded (e.g. Saunderson 1995). We limited recall bias by means of conducting two interviews, which reduced recall time. Interviewers were trained to recognize unusually high costs for specific items and to ask back comparing the reported costs to local prices for comparable items. Another limitation is that we have only analyzed two coping strategies, while many more exist (Obrist *et al.* 2007). We have focused on those financial coping strategies that bear risks for future impoverishment.

Expenditure

The main factor leading to higher expenditure related to tuberculosis was receiving complementary treatment; further important factors were longer hospital stay and longer treatment delay. The latter two factors were each significantly associated with higher costs in one of the two time periods investigated, but only showed a tendency ($p<0.1$) in the other time period. A similar finding was made in Lusaka, Zambia, where longer patient delay led to higher costs (Aspler *et al.* 2008). The present study looked at total delay rather than patient delay only. Including two proxies for severity of disease had very little influence on the estimated coefficients or significance levels of different factors–with the exception of the factor hospitalization in the model on costs during the whole episode. Thus, it seems unlikely that these findings be confounded by severity of disease. The strong influence of complementary treatment is most likely related to a tradition among Tajik (and other post-Soviet–Mosneaga *et al.* 2008) TB doctors to frequently prescribe additional medication, often several types of drugs (see above). An additional reason could be that doctors supplement their meager incomes through prescribing and/or selling additional drugs. It has been described for other post-Soviet countries, that doctors practice in public premises but for private revenue (Mosneaga *et al.* 2008). The use of additional medication in our study population exceeds international standards by far (WHO 2003) and its rationality is doubtful. For the patients, additional medication is associated with the costs of the drugs themselves, and with traveling to the health facility for a prescription and to the pharmacy. Reducing the use of complementary treatment and of hospitalization could be simple measures to

decrease the costs to TB patients in Tajikistan. Expenditure was not associated with sex in either of the two models. In fact, the p-values were high and the two estimated coefficients in the opposite direction. In Zambia male TB patients spent more money for diagnosis and treatment (Aspler *et al*. 2008). In our study, men and women have incurred similar expenditure over the course of disease.

Table 7.4. Results of the mixed-effects linear regression on expenditure during anti-TB chemotherapy (in US$, log-transformed); n=204

Factor	Coefficient/ slope	S.E.§	p-value	fmi†
sex	-0.0586	0.128	0.646	0.141
wealth index	0.0344	0.0357	0.335	0.204
sputum smear result	0.0796	0.0613	0.196	0.260
days in hospital during treatment (log-transformed)	0.0256	0.00945	** 0.007	0.192
delay in days (log-transformed)	0.0994	0.0601	0.099	0.178
complementary treatment	0.752	0.299	* 0.012	0.261
intercept	3.98	0.419	*** <0.0005	0.236
DOTS centre (estimate for variance-covariance matrix)	-0.947	0.332	N/A	0.123

§S.E.=standard error
†fmi=fraction of missing information. The fmi is a measure of the information contained in the missing data in a multiply imputed dataset (Schafer 1997).
*denotes significance levels

Table 7.5. Results of the mixed-effects linear regression on detrimental economic coping strategies (in US$, root-transformed); n=204

Factor	Coefficient/ slope	S.E.§	p-value	fmi†
sex	-4.82	3.09	0.120	0.286
wealth index	-1.22	0.733	0.096	0.200
sputum smear result	8.19	4.49	0.069	0.365
days in hospital during treatment (log-transformed)	0.269	0.196	0.170	0.273
complementary treatment	3.31	5.67	0.559	0.135
intercept	16.5	5.91	0.005	0.143
DOTS centre (estimate for variance-covariance matrix)	2.83	0.048	N/A	0.427

§S.E.=standard error
†fmi=fraction of missing information. The fmi is a measure of the information contained in the missing data in a multiply imputed dataset (Schafer 1997).

Coping strategies

About two thirds of households employed at least one detrimental coping strategy. The mean amount raised was US$182. This high amount suggests that costs associated with

an episode of TB push affected households deeper into poverty. The proportion of households employing detrimental coping strategies is higher than found in 15 African countries, where among hospitalized patients (independent of diagnosis), about 50% reported borrowing and/or selling assets (Leive & Xu 2008). Most commonly, the assets sold were cattle, sheep or goats. These are productive assets and confirm our choice to treat sale of assets as a potentially detrimental coping strategy.

While none of the investigated factors was significantly associated with detrimental coping strategies, some aspects are worth discussing. The factor "migration to Russia" showed a tendency towards higher use of detrimental coping strategies–rather contrary to expectation. It was assumed that patients who recently returned from Russia would on average have more cash available, because wages are several times higher in Russia than in Tajikistan. However, the data showed a tendency only and should be interpreted with care. The long treatment delays experienced by migrants developing TB in Russia could have contributed to higher costs (Ayé *et al.* 2010b).

In conclusion, patients and their households face major expenditure during an episode of TB and two thirds of affected households employ detrimental coping strategies that potentially impair future income. Hence household costs of TB are catastrophic. Both sexes experience similar expenditure in this setting. The main factors associated with higher expenditure are receiving complementary treatment in addition to anti-TB chemotherapy, longer treatment delay and longer stay in hospital. Complementary treatment, which is probably questionable on medical grounds, had the strongest effect–more than doubling expenditure. Reduction of additional medication and limited hospitalization are simple interventions at the level of case management that could lead to lower expenditure for patients. In view of the high costs, such mitigation strategies are urgently needed. Similar health system characteristics and the common use of complementary treatment for TB patients suggest that this factor would also play a role for TB patients in other post-Soviet countries (Mosneaga *et al.* 2008). Studies on the impact of these measures on treatment outcomes in the local context would be highly informative.

Acknowledgements

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8. Management of Pulmonary Tuberculosis in Tajikistan: Which factors determine hospitalisation?

Running head: Factors determining hospitalisation

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Abstract

Objectives

In Tajikistan the prevalence of tuberculosis has tripled since the collapse of the Soviet Union and political independence in 1991. TB control relies increasingly on the Directly Observed Short Course Strategy favouring outpatient care for patients, but there are 2000 TB hospital beds available. An analytical cross-sectional study was carried out to assess predictors for hospitalisation and treatment-outcome.

Methods

Stratified, single stage cluster sampling was used to include 1495 adult patients with pulmonary TB during 2 calendar years (2005-06) from the registries of 10 TB-centres chosen by simple random sampling. The primary outcome was referral to hospital. Logistic regression was conducted to test associations with the study-outcome using linearization and a variance formula.

Results

Prevalence of hospitalisation for tuberculosis was 58%. The odds of patients with smear-positive tuberculosis being referred were three times those of smear-negative patients (OR 2.99 [95% CI 1.81-4.96]). Other predictors for hospitalisation were the availability of TB hospital-beds within the same district (OR 2.15 [95% CI 1.22 to 3.76]) and male gender (OR 1.46 [95% CI 1.07-2.48]). The overall treatment success was 80%.

Conclusions

Hospitalisation of patients with pulmonary tuberculosis was determined by positive sputum smear, supply of hospital beds, and gender. Reducing hospitalisation with support of national guidelines is not expected to have a negative impact on treatment outcome and spread of disease, but could lead to improved efficiency and effectiveness of health service delivery for pulmonary tuberculosis in Tajikistan.

Introduction

Following the breakdown of the Soviet Union, there has been a significant increase in the incidence of tuberculosis (TB) in the five countries of former Soviet Central Asia. Tajikistan with an estimated annual prevalence rate of 298 per 100,000 in 2006 has the highest burden of TB in the region (1). In a country where 64% of the people are living below the poverty line (2) re-emerging TB has been attributed to poverty, a damaged health infrastructure as consequence of the collapse of the Soviet health care system and a devastating civil war. In contrast to Sub-Saharan Africa, TB is not driven by a generalised HIV/AIDS-epidemic, which is still at an early, concentrated stage in Tajikistan (3).

Tajikistan inherited a health care system from the Soviet Union. Its main features were an emphasis on hospital based- rather than primary care with a vertical organisation of infectious disease control and vaccination services. With the loss of the subsidies of Soviet times and the economic decline over the last years, the country increasingly faces problems in maintaining the state-run health infrastructure (4).

Particularly in TB-care, the former Soviet Union maintained European traditions from the 19th century: frequent and long-term inpatient-stays in specialised TB-sanatoriums, often in isolated places on the edge of the towns. Recent data from Samara, Russia, showed that supply driven factors, social factors (5) and seasonal factors (6) influence referral to hospital.

For Tajikistan there is no conclusive data on hospitalisation for TB, but previous evaluations suggest persistently high hospitalisation rates (7). Officially, potential infectiousness in patients with sputum smear positive tuberculosis is regarded as a sufficient single factor to justify hospitalisation according to national regulations by the Ministry of Health (prikazes 78 & 192). The American College of Chest Physicians however clearly focuses on ambulatory care, stating that "Infectiousness alone is not an indication for hospitalisation" (8). Also the DOTS strategy by the WHO favours outpatient care (9).

For individual patients in Tajikistan, high costs, loss of work and disruption of family structures are negative consequences of the hospital stay. Moreover, inpatient conditions for TB care are particularly poor, involving renovation need of facilities, frequent lack of heating in the winter due to electricity cut-offs and food-shortage for

patients (7).

In spite of a rising burden of tuberculosis in Tajikistan, little research has been carried out. A database-search on the MESH-terms "tuberculosis" and "Tajikistan" showed only 10 publications, mostly from the era of the Soviet Union. Seven publications were in Russian; only three of them dated from after 1990; none of them related to hospitalisation for tuberculosis. This study aimed to identify predictors for hospitalisation and treatment-outcome of patients with pulmonary TB in Tajikistan.

Methods

Sampling strategy

A stratified sampling approach was chosen including three regions of Tajikistan, covering 70% of the country's population, considering probable differences in demographic composition, disease pattern and hospitalisation rates between urban and periurban/rural TB-centres. The urban stratum comprised the towns of Dushanbe and Qurghonteppa, and the periurban/rural stratum included all districts within a 50 km radius around each of the two towns. Because they were better accessible to the research team it was decided to include proportionally more urban centres, to maximise the efficiency of data collection. The sampling frame comprised 8 urban and 23 periurban/rural TB-centres. A single-stage cluster sampling scheme was used, with TB centres as clusters. In each cluster all adults (aged ≥ 18 years) registered with pulmonary TB during 2005-06 were included. Four urban centres and six periurban/rural centres were selected using simple random sampling (SRS) representing a 50% and 26.1% probability of inclusion in the sample for patients living within the catchment population of the periurban/rural centres respectively.

Data collection

Data on hospitalisations were collected from the TB registry-books of the National TB control program, available in the TB-centres. Hospitalisation was defined as referral to the hospital which is documented for each patient in the 2003 version of the WHO TB-registry form. Treatment success was the combined outcome of patients who had recovered according to smear result or had completed the treatment. Data about the centres were collected separately using a questionnaire completed by each centre head.

Analysis strategy

Data were weighted during analysis to allow for sampling design. Analyses were conducted with and without the design-setting in order to compare adjusted with unadjusted results (10).

Weighted proportions estimates with 95% confidence intervals (CI) were computed by Pearson's chi squared test and included a second order Rao or Scott correction to account for the survey design (11). Univariable analyses of associations between all potential predictors and the study outcomes were performed using logistic regression. Tests for trend were computed using logistic regression for the design adjusted approach. A likelihood ratio (LR) test was used to investigate interaction between confounding factors in the final model. Variables were included in multivariable logistic regression models using a forward stepwise approach. To assess the association between smear-status and referral to hospital the centre-variables (distance, availability of electricity, availability of TB-beds) were not included as these are health-services variables and have no association with the exposure of mycobacteria in the sputum of a patient. All analyses were conducted in Stata Release 9.0 (STATA Corp., College Station, Tx, USA).

Results

The study sample comprised 1495 adult patients, 45% of them women. Ages ranged from 18 to 84 years (median age 32 years). An estimated 65% of patients were for the first time notified with tuberculosis and 58% had positive sputum-smear status. The degree of smear-positivity according to AFB-classification varied (Table 8.1). 58% of patients attended TB centres between April and September with 33% presenting between April and June. The overall prevalence of hospitalisations was 58% percent. Two thirds of patients with positive smear results were referred to hospital compared with 39% with negative results (Figure 8.1). Hospitalisation increased with increasing sputum smear results from 60% in smear degree 1 to 76% in smear degree 3 (p<0.001). Among all patients for whom treatment was available, 80% had successful treatment and 6% of patients died. In patients with repeated treatment 75% were successfully treated.

The prevalence of hospitalisation ranged from 27% in Varzob to 73% in Tursunzade. Centres with TB-hospitals in the rayon (district) referred on average 62% of patients to

Table 8.1. Characteristics of patients enrolled in the study

N=1495		n	%
Agegroup (years)	18-27	564	37.73
	28-37	372	24.88
	38-47	284	19.00
	47-max	275	18.39
	missing	0	0.00
Gender	male	818	54.72
	female	676	45.22
	missing	1	0.07
Disease classification	new notification	987	66.02
	re-treatment	443	29.63
	missing	65	4.35
Smear Status	negative	521	34.85
	positive	884	59.13
	+	457	30.57
	++	152	10.17
	+++	275	18.39
	not carried out	60	4.01
	missing	30	2.01
Seasonality of Presentation	winter (oct-mar)	613	41.22
	quartal (oct-dec)	280	18.73
	quartal (jan-mar)	333	22.27
	summer (apr-sep)	874	58.46
	quartal (apr-jun)	486	32.51
	quartal (jul-sep)	388	25.95
	missing	8	0.54
Hospitalisation	no	680	45.55
	yes	812	54.39
	missing	1	0.07
Treatment Outcome	failure	204	13.70 (20.46)*
	bad outcome	62	4.15
	non-compliance	60	4.01
	died	82	5.48
	success	793	53.00 (79.54)*
	recovered	418	27.96
	completed	375	25.08
	not available	385	25.75
	missing	113	7.50

* proportion among available treatment-outcome

hospital, whereas centres without TB-hospitals within the rayon referred 45% to hospital (p<0.001) (Figure 8.2). Treatment success ranged between centres from 62% to 94%. The odds of treatment-success in patients referred to hospital compared to outpatients ranged from 0.36 (95% CI: 0.16-0.82) to 1.39 (95% CI 0.61-3.15).

Prevalence of hospitalisation in the rural/periurban stratum was higher than in the urban stratum (60% vs. 46%; p<0.001). Overall treatment success was similar in both strata (80% vs. 79%). The odds of treatment success among patients referred to hospital was 0.69 (95% CI: 0.43-1.09) in the urban centres and 0.42 (95% CI: 0.26-0.66) in periurban/rural centres.

Predictors for Hospitalisation

Patients with a positive sputum smear status were almost three times more likely to be referred to hospital compared with patients with negative sputum-smear (OR 2.99, 95%
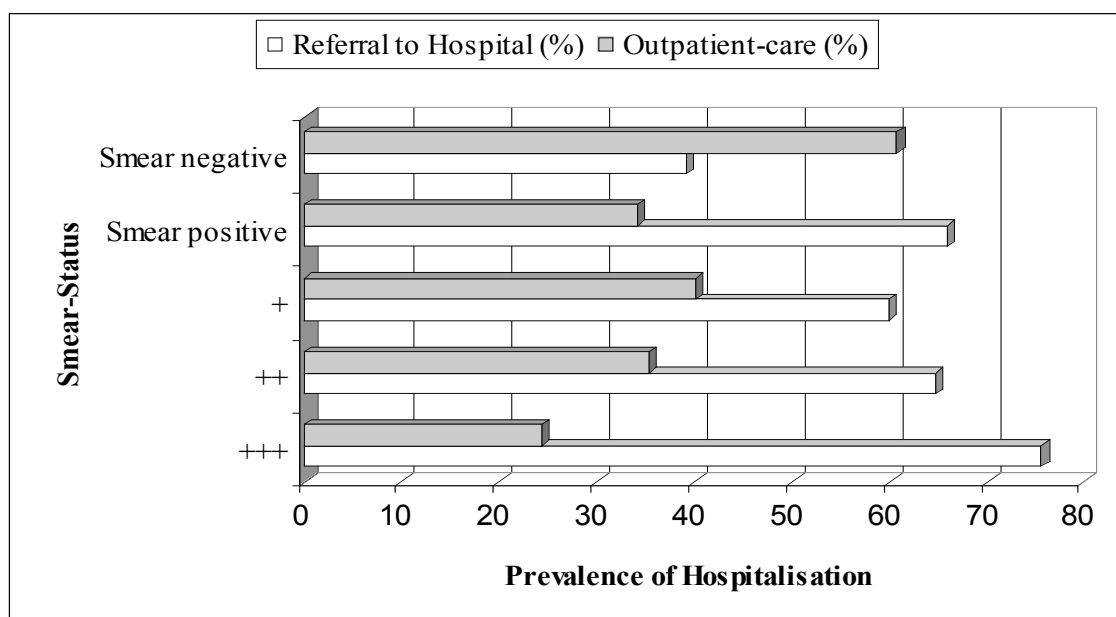
Figure 8.1. Prevalence of Hospitalisation by Sputum Smear-Status.
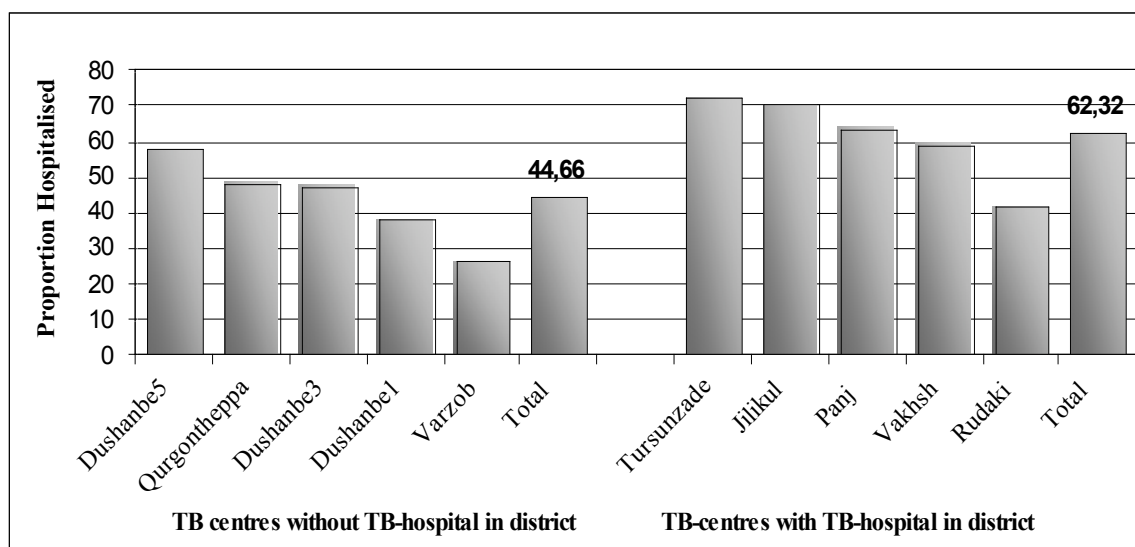
Figure 8.2. Prevalence of Hospitalisation per TB-centre by Availability of TB-hospitals.

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Table 8.2. Predictors for Hospitalisation (design-adjusted findings)

Variable	Univariate Analysis			Multivariate Analysis†		
	OR	95% CI	p-value	OR	95% CI	p-value
				D		
Smear Status						
positive	2.99	1.81-4.96	0.001	2.93	1.91-4.49	<0.001
+	2.31	1.62-3.29	0.001	2.25	1.69-3.00	<0.001
++	2.84	1.53-5.25	0.004	2.78	1.57-4.92	0.003
+++	4.81	2.41-9.57	0.001	4.74	2.55-8.79	<0.001
negative	1			1		
Agegroup (years)			<0.001*			0.036*
18-27	1.90	1.18-3.07	0.014	1.60	1.06-2.44	0.031
28-37	1.89	1.41-2.55	0.001	1.87	1.32-2.65	0.003
38-47	1.45	1.05-1.99	0.027	1.49	1.06-2.10	0.027
48-max	1			1		
Gender						
male	1.46	1.07-2.00	0.023	1.49	1.08-2.05	0.02
female	1			1		
Disease classification						
re-treatment	0.90	0.71-1.14	0.354			
first notification	1					
Seasonality of Presentation						
winter (oct-mar)	1.11	0.69-1.80	0.607			
summer (apr-sep)	1					
quartal (oct-dec)	0.75	0.52-1.08	0.116			
quartal (jul-sep)	0.91	0.63-1.31	0.587			
quartal (apr-jun)	0.70	0.41-1.19	0.166			
quartal (jan-mar)	1					
TB-beds in rayon						
yes	2.15	1.22-3.76	0.014			
no	1					
Distance TB-centre & Hospital			<0.001*			
< 10 km	4.43	2.84-6.92	<0.001			
10-20 km	2.03	1.18-3.49	0.016			
> 20 km	1					
Electricity available						
no	1.18	0.51-2.73	0.654			
yes	1					

*p-value for test for trend
†Results of Multivariate Analysis, adjusted for Age and Gender

CI 1.81 to 4.96; table 8.2). Patients with the most severe degree of sputum-smear positive results (+++) were almost five times as likely to be referred to hospital compared with patients without tubercle-bacteria in their sputum (OR 4.81, 95% CI 2.41 to 9.57). There was evidence for a trend in the odds of hospitalisation per unit

Table 8.3. Predictors for Treatment-Success (design-adjusted findings)

Variable	OR	95% CI	p-value	OR	95% CI	p-value
	Univariate Analysis			Multivariate Analysis†		
Smear Status						
positive	0.46	0.32-0.65	0.001	0.53	0.35-0.79	0.007
+	0.46	0.29-0.77	0.008	0.51	0.30-0.86	0.019
++	0.51	0.33-0.81	0.01	0.59	0.35-0.99	0.04
+++	0.43	0.26-0.69	0.004	0.52	0.30-0.87	0.02
negative	1			1		
Hospitalisation						
yes	0.49	0.32-0.77	0.006	0.62	0.35-1.06	0.075
no	1			1		
Agegroup (years)						
18-27	1.49	0.95-2.36	0.074			
28-37	0.97	0.75-1.26	0.842			
38-47	1.3	0.93-1.81	0.099			
48-max	1					
Gender						
male	0.63	0.39-1.01	0.055			
female	1					
Disease classification						
re-treatment	0.8	0.65-1.00	0.051			
first notification	1					
Seasonality of Presentation						
winter (oct-mar)	1.07	0.72-1.60	0.672			
summer (apr-sep)	1					
quartal (oct-dec)	0.7	0.42-1.17	0.154			
quartal (jul-sep)	0.81	0.42-1.55	0.489			
quartal (apr-jun)	0.79	0.58-1.07	0.116			
quartal (jan-mar)	1					
TB-beds in rayon						
yes	0.755	0.30-1.88	0.5			
no	1					
Distance TB-centre & hospital			<0.001*			
< 10 km	0.1	0.06-0.15	<0.001			
10-20 km	0.28	0.20-3.84	<0.001			
> 20 km	1					
Electricity available						
no	1.29	0.54-3.09	0.515			
yes	1					

*p-value for test for trend
†Results of Multivariate Analysis, adjusted for Smear-Status

increase in sputum-smear (p-value for trend p=0.001). The youngest patients were more likely to be sent to hospital compared with the oldest patients: OR 1.9 (95% CI 1.18 to 3.17). There was evidence for a trend in the odds of hospitalisation per unit

decrease in age-category (p<0.001). Men were more likely to receive treatment in hospital than women (OR 1.46, 95% CI 1.07 to 2.48). Patients were more than twice as likely to be referred to hospital if an associated TB hospital was located within the same rayon as the TB centre (OR 2.15, 95% CI 1.22 to 3.76). Patients from centres <10km from the associated TB hospital were more likely to be referred to hospital compared with patients from centres >20 km away (OR 4.43, 95% CI 2.84 to 6.92). There was evidence for a trend with decreasing distance (p<0.001). Season was not associated with the outcome, comparing winter or summer (OR 1.11, 95% CI 0.69 to 1.80) and comparing four quarters of the year (Table 8.3). There was no evidence that patients re-treated for tuberculosis were any more likely to be referred to hospital (OR 0.9, 95% CI 0.71 to 1.14). Referral to hospital was not found to be associated with availability of electricity (OR 1.18, 95% CI 0.51 to 2.73).

Predictors for Treatment Success

Patients referred to hospital were half as likely to have a successful treatment compared with patients treated as outpatients (OR 0.49, 95% CI 0.32 to 0.77; table 8.3). Patients with positive sputum-smear status were also half as likely to have a successful treatment outcome compared with those with negative smear-status (OR 0.46, 95%CI 0.32 to 0.65). There was suggestion that younger patients (aged 18-27 years) were more likely to have treatment-success (OR 1.49, 95% CI 0.95 to 2.36) compared with the oldest (aged ≥48 years). There was no good evidence that men were any more likely to have treatment success than women (OR 0.63, 95% CI 0.39 to 1.01). Patients who were treated repeatedly for TB had less treatment success than those treated for the first time (OR 0.8, 95% CI 0.65 to 1.0). Patients treated in a centre <10 km of the associated TB-hospital had reduced chances of treatment success (OR 0.1, 95% CI 0.06 to 0.15) compared with those treated by centres >20km away. No evidence was found for associations between seasonality of presentation, availability of TB beds within the rayon, and availability of electricity.

Adjusted Analyses

In a multivariate model the association between sputum-smear and hospitalisation was reduced from OR 2.99 to 2.93 adjusting for age and gender (Table 8.2). In the adjusted model, the strength of association between age and gender and referral to hospital did not change considerably in comparison to the crude analysis and is unlikely to be due

to chance. Adding further variables (i.e. disease-classification, seasonality) did not improve the model. The distance variable was not included because residual confounding was considered likely to cause the observed difference in the treatment outcome.

Hospitalisation was found to be associated with decreased treatment success, but could have been due to chance after adjusting for smear-status (OR 0.62, 95% CI 0.35 to 1.06) in the design-based analysis. The association between sputum-smear and treatment-success remained unchanged and is unlikely to be due to chance (Table 8.3). In the model of sputum smear and hospital referral no evidence was found for an interaction between gender and age (p=0.56). In the design-adjusted model, tabulations and logistic regression carried out separately for the two gender subgroups did not find evidence that the effect of age on hospitalisation differed between men and women.

Discussion

This cross-sectional study showed that hospitalisation was determined by smear-positive TB, age, gender and supply of TB-beds. Having adjusted for potential confounding factors, a positive smear result remained the main predictor for referral to hospital. In-patient management of smear positive patients is in accordance with Tajik National Recommendations (Prikazes 192 & 78). One reason often cited for initial hospitalisation is concern that the patient is infectious and must therefore be isolated from family and community. However, patients with drug-susceptible organisms become non-infectious within 2 weeks (14). Moreover, it could be shown that tuberculosis developed no more frequently in contacts of home-treated patients than in contacts of patients treated in a sanatorium, suggesting that infection occurred before the start of the treatment (15).

Also a sizeable proportion of patients with smear negative results (40%) was sent to hospital. Concern of increased infectivity of an open tuberculosis does not apply to these patients and there is no evidence that inpatient treatment for TB is more effective than outpatient treatment (16). US-guidelines (8) and the WHO-developed DOTS-strategy (9) focus much more on outpatient care for tuberculosis.

More young patients were referred than older age groups. This is remarkable because commonly older patients develop more severe and complicated disease, leading to increased hospital-admission in the older age-groups (17). Thus, findings from our

sample suggest that smear results were of more relevance for hospitalisation than older age and associated severity of disease. More young people presenting with a positive smear-result in this study might be linked to the fact that they are better able to expectorate sputum.

In accordance with findings from Russia, men were more likely to be referred (5). This association remained after adjusting for all other predictors for hospitalisation. There is no evidence from the literature and from clinical practice that tuberculosis is more severe in men. This suggests that there are social reasons inclining health care providers to hospitalize men: men are less self-sustained when they are sick at home in the Tajik culture. It is also known that drugs and excessive alcohol consumption, which are risk factors for hospitalisation in patients with TB (17), are more common in males (18). Men had significantly more smear positive results than did women, which supports findings from other developing countries where women were less likely to test smear-positive than men (19). Cultural inhibitions about producing deep sputum in public places and lack of knowledge about TB diagnosis in women have been suggested as possible causes.

One explanation for a great variability in hospitalisation prevalence among centres might be a difference in supply of TB beds among participating rayons. Centres with TB-hospitals within the rayon were more likely to refer patients to hospital. This supply-driven hospitalisation for tuberculosis in Tajikistan presents an analogy to findings from Russia (5) and Ukraine (20).

The overall treatment success of 80% confirms previous findings in Tajikistan (7). Successful TB treatment outcomes were below the 85% threshold of the WHO-target, but showed better performance than the 74.4% estimate of treatment success for 13 European countries, including the former USSR (21). There was considerable variation in treatment success among centres, with periurban/rural centres being inferior to urban centres. This might be due to less favourable conditions in periurban/rural centres than in urban centres. Two centres had not yet adopted the DOTS strategy and were therefore without a standardised registry including any information on treatment-outcome. As the global treatment success rate under DOTS has been high since the first observed cohort (12), bias towards a more favourable treatment outcome overall might therefore have been introduced. This study utilised routinely collected registry data. The reliability of smear results depends on the sensitivity of the AFB sputum

diagnostic technique used to diagnose TB. Judgements about the quality of the smear microscopy cannot be made in this study. Given that health-workers are responding to performance targets of the national programme, the possibility of overestimating cure rates cannot be excluded (12).

Patients referred to hospital were less likely to have a successful therapy outcome compared with patients treated with ambulatory care. Reduced treatment success in patients with positive smear results has been reported elsewhere (22). However, the inferiority in outcome of hospitalised patients still remains surprising since compliance with TB-therapy (DOT) should lead to improved clearance of TB-bacteria. The reduction in favourable outcomes among in-patients may be due to sicker patients being admitted. A predictor of clinical severity of disease would have been valuable to have included in the multivariable analysis.

Centres were chosen by means of simple random to ensure generalisability of the study-findings. Because all adults with pulmonary TB registered during the two year period were included, selection bias is unlikely. Therefore, study findings can be generalised to the general population of Tajikistan in three of five regions of the country, covering about 70% of the population. We recommend that smear-positive pulmonary TB should not be imperative for hospitalisation. Hospitalisations in smear negative-patients should be evaluated in more detail. In each of these cases it should be questioned if hospitalisation is necessary. Instructing women in a gender-sensitive way could improve smear-positive case detection as has been shown in a recent pragmatic RCT in Pakistan (19). Hospitalisation for tuberculosis should not be based on TB-bed supply only. Rather, the number of tuberculosis-beds should be evaluated and adapted to the needs of a post-soviet health care system in the process of reforms and TB control measures should progressively be integrated into primary care services. Further research in form of a prospective study is needed to analyse conditions and duration of hospital stay as well as TB infection in household-contacts of hospitalized patients.

In Tajikistan, the DOTS-strategy has reached 100% coverage at the end of 2007. Accordingly, treatment for tuberculosis has to be shifted increasingly to outpatient services. However, hospitalisation prevalence in this study showed to be still high with great differences between included TB-centres. Existing recommendations by the Ministry of Health and the National TB-Programme should be modified in focussing on outpatient care leaving hospitalisation to defined conditions. This approach

disseminated to TB health care personnel in the frame of the DOTS-training, is expected lead to a harmonization between rayons and a more effective and efficient-control of pulmonary TB in Tajikistan.

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9. Food Supplements for Tuberculosis Patients in Tajikistan – do they reach the target group?

Running head: Food supplements for tuberculosis patients

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Abstract

Background: In order to enable tuberculosis patients to adhere to treatment, they receive food supplements in several districts within the DOTS program of Tajikistan.

Objective: To study awareness about food supplements among tuberculosis patients. Further, to investigate whether tuberculosis patients receive the foreseen food supplements and to estimate monetary benefits and potential payments related to food supplements.

Methods: Questionnaire survey with initial and follow-up interview among new pulmonary tuberculosis patients in twelve study districts in Tajikistan, complemented by information from the organisations implementing food distributions.

Results: Eighty out of 116 eligible patients knew about the food supplements, eleven knew the exact number (three). At the time of the follow-up interview, patients had on average received 1.7 food supplements and this number was significantly higher for those patients who were interviewed later in treatment. In two districts, the number of food supplements received was significantly lower due to considerable delay in the food distributions. Patients estimated the total value of three food supplements at 244USD and reported payments of 18USD.

Conclusions: The patients' awareness about their eligibility for food supplements and the regularity of food distributions need further improvement. Overall, the food supplements constitute a big contribution (225USD on average) for the household budget of each tuberculosis patient.

Introduction

The health system of Tajikistan has inherited its basic structure from the Soviet Union. It is focused on the specialist level and at least nominally is very comprehensive (World Bank 2004). The Ministry of Health of the Republic of Tajikistan is leading health sector reform in Tajikistan, whereby among others primary health care is being strengthened and a system of co-payments is introduced for selected services. The introduction of co-payments aims at the formalisation of informal payments, which are widespread and make up a considerable part of total health spending (Cashin 2004, Falkingham 2004). A recent study in Tajikistan found that about 45% of patients at the primary care level had made an informal payment to the provider (Tediosi et al 2008). It is clear that in this context, disease exerts a heavy economic burden on vulnerable households and this is particularly true for a long-lasting illness like tuberculosis (TB). The economic burden is an important reason for patients to interrupt treatment (Greene 2004, Dodor & Afenyadu 2005, Hill et al 2005, Mishra et al 2005, O'Boyle et al 2002). A focus group study on access and adherence to TB treatment identified costs of illness at the household level as the key barrier in the context of the Tajik DOTS program (Ayé 2006). A questionnaire survey found that total household costs of an episode of TB amounted to 1050USD (4900USD purchasing power parity) on average (Ayé et al. 2010). More than a third of households sold assets and almost half of households took out loans to cope with the financial demands of treatment. Such a catastrophic economic burden may prevent patients from adhering to treatment and make other household members more vulnerable to disease. The TB incidence in Tajikistan was recently estimated at 231 cases per 100'000 population per year (World Health Organisation 2009) and 8.6% of new TB cases were estimated to be multidrug-resistant (Zignol et al 2006). These high rates show an urgent need to enable TB patients in Tajikistan to access and adhere to treatment.

TB control programmes have used different strategies to improve treatment adherence. Among these strategies is the requirement for direct observation of treatment (DOT) at least in the intensive phase included in the DOTS strategy. However, a review of randomised controlled trials could not show a positive effect of DOT on TB treatment outcomes (Volmink & Garner 2007). In order to improve treatment outcomes, additional or other measures are needed to ease the economic hardship that the disease and its treatment exert on households, including cash payments to patients, meals

alongside TB treatment, travel vouchers and provision of food supplements to patients' households. Such measures have been shown to effectively reduce defaulter rates and to improve treatment outcomes (Farmer et al 1991). However, it remains difficult to disentangle the influence of the single components of such interventions on treatment outcomes and diverse approaches have been employed (Macq et al 2003).

Five months after the start of the DOTS programme in the first two pilot districts (rayons) of Tajikistan, a scheme of food supplements was started by Project HOPE and the World Food Program (WFP) of the United Nations Organisation (Mohr et al 2005). Initially, TB patients who were vulnerable according to WFP definition were eligible. Food supplements have since been given in several districts and about 300 TB patients and their family members have received food supplements each year in the four Project Sino pilot districts.

Food supplement distribution programmes commonly encounter problems of accountability. Therefore, we studied the following research questions:

1) Are TB patients aware about their entitlement to food supplements and do adherent patients receive food supplements as they should?

2) What is the estimated local market value of the food supplements that patients receive?

3) Do patients report formal and/or informal payments in relation to the food supplements and what is their extent?

Methods

Food supplements in the DOTS program in Tajikistan consist of wheat flour, vegetable oil, peas and salt, the exact amount depending on the family size. The food supplements are brought to distribution centres, from where the patients organise transport to their homes themselves. In districts with food supplement provision, all TB patients are eligible for food supplements as long as they adhere to the treatment regimen. Six districts in the study area had a program of food supplements. The latter are distributed three times to each patient, the first food supplement usually being provided after the completion of the intensive phase of treatment. Food distributions were organised quarterly. Correspondingly, the third food supplement would variably be received two to five months after the end of treatment. Information on how often food distributions took place was collected from Project Sino and Project Hope, who

carry out the food distributions together with WFP.

The patient-level data for the present study was gathered in the framework of the study on costs of illness at the household level mentioned above (Ayé et al 2010). We collected information on the reception of food supplements and on expenses associated with food supplements. The study was conducted in twelve districts of Tajikistan, six of which had a programme of food supplements. In the other six districts, no food supplements were provided at the time of the study. We conducted two interviews with each patient who was enrolled – the first one in the intensive phase of TB treatment and the second one two to four months later in the continuation phase. In the first interview, patients were asked whether they would be eligible for food supplements during their TB treatment. In the second interview, patients were asked whether and how many times they had received food supplements, what the approximate value of these food supplements on the local market was, and how much they had spent to receive the food supplements and for the transport to bring them home from the point of delivery. Thus, most information about food supplements is self-reported by the patients. The date when the patient had started treatment and the date when the continuation phase was started, were recorded, too.

For the analysis, the proportion of patients who had received zero, one, two and three food supplements respectively were computed. A linear regression model was built including the time since start of treatment (in days) as a continuous variable and a categorical variable for the district as independent variables and the number of food supplements received as the dependent variable. Further, the mean amount of money spent to be eligible for food supplements (informal payments) and for transportation to pick them up and bring them home were calculated. The mean was used rather than the median, because the distributions of the paid amounts were not particularly skewed and therefore the mean was an appropriate measure.

Results

Number of food supplements received by patients

The study spanned the period from December 2006 to August 2007. During this period, four food distributions took place in each of the districts with the exception of two districts. Only three distributions took place in the latter two districts. All the food distributions took place between 26th March and 27th June 2007. Consequently, there

were gaps in food distribution from December 2006 to March 2007 and from June 2007 to August 2007. These gaps were due to characteristics of the contracting process between the organisations involved.

For the main study, 282 eligible patients were registered. The number of patients involved and drop-outs are shown in figure 9.1. In the districts, where there are no food supplements, 54 out of 88 patients (61%) knew that they were not entitled (Table 9.1). On the other side, 116 patients (57%) lived in districts, where food supplements are provided and thus were entitled to food supplements. Eighty (69%) of the 116 patients were aware about their entitlement. Eleven patients (9%) knew that they were entitled to three food supplements.
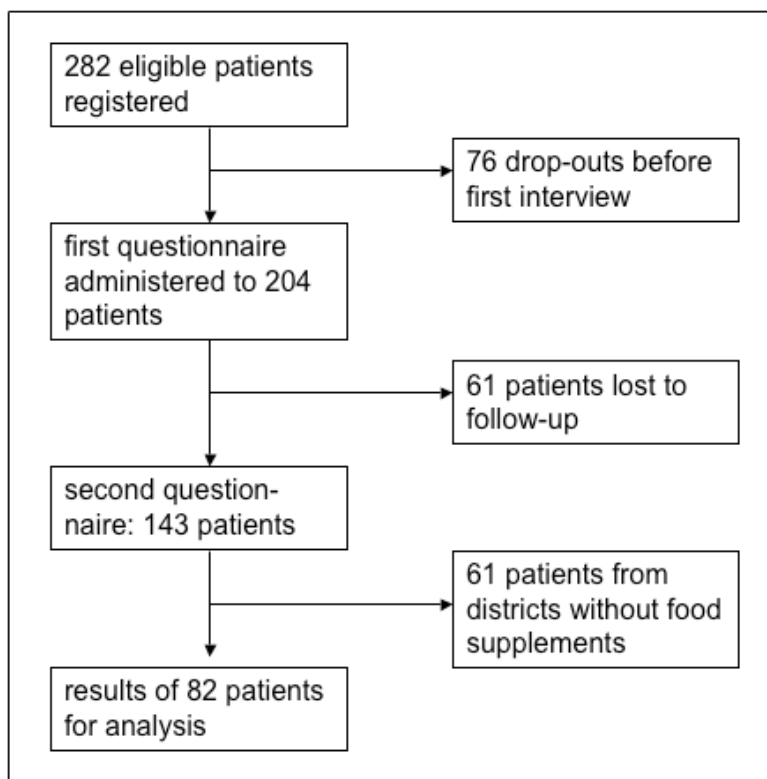
Figure 9.1. Flow-chart of the number of eligible patients, drop-outs and number of patients providing data for the analysis.

At the time of the second interview, on average 167 days into treatment, 143 patients could be found and interviewed again. On average, eligible patients had received 1.7 food supplements by this time. Twenty-four patients indicated they had already received all three food supplements (30% of the eligible patients). Sixteen patients (20%) indicated they had received two food supplements, 34 patients (42%) one, and seven patients (8.6%) none (Figure 9.2). All patients who had received either no or only one food supplement were residents of the same two districts.

The regression analysis including the factors district and time since start of treatment, showed a significant increase in the number of food supplements received over time

Table 9.1. Awareness of tuberculosis patients about their entitlement to food supplements at the time of the first interview

Awareness of food supplements	#patients interviewed	#patients who knew whether they were entitled or not	#patients who knew correct number of food supplements
Districts with food supplements (6 districts)	116	80 (69%)	11 (9%)
Districts without food supplements (6 districts)	88	54 (61%)	n/a
Total (12 districts)	204	121 (59%)	n/a
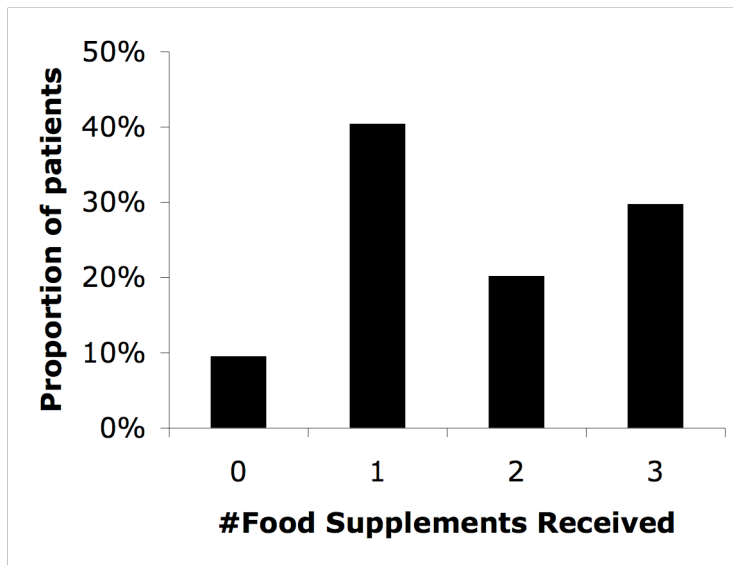
Figure 9.2. Percentage of patient who had received 0, 1, 2 and 3 food supplements.
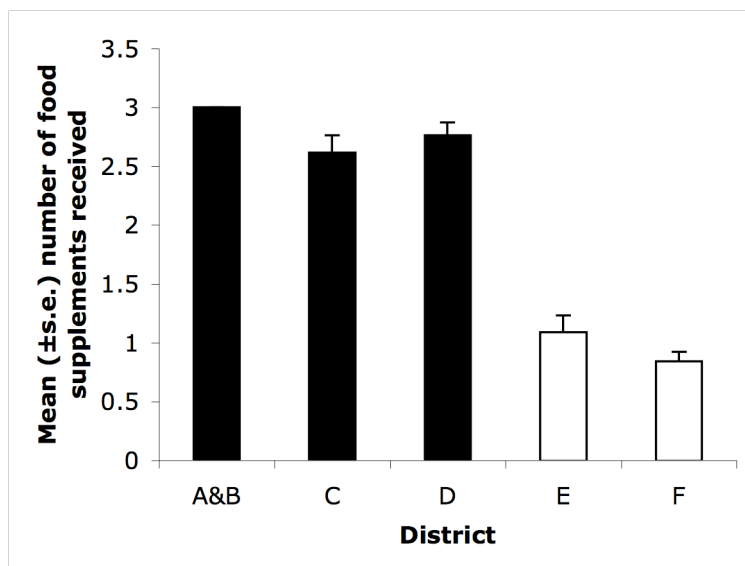
Figure 9.3. Number of food supplements received by patients in the six study districts (A-F). Note that districts A and B contributed only four patients combined, all of whom had received three food supplements.

(Table 9.2). In two districts, the number of food supplements received was significantly lower than in the other four districts (Figure 9.3), and the factor district was highly significant (log-likelihood ratio test; $p < 0.0001$). The residuals were checked visually

and did not show a major departure from normality. The result that fewer food supplements were received in two districts corresponds with the information of the implementing organisations indicating that in these two districts three instead of four food distributions had taken place during the study period.

Table 9.2. Results of the linear regression on number of food supplements received (n=81)

	Coefficient/slope	S.E.	p-value
Time since start of treatment [days]	0.00452	0.00169	0.009
District2	-1.67	0.164	<0.0005
District3	0.472	0.518	0.366
District4	-0.178	0.186	0.342
District5	0.330	0.314	0.296
District6	-1.69	0.162	<0.0005
Factor District	n/a	n/a	<0.0001
Intercept	1.95	0.322	<0.0005

Patients from districts without food supplement provision expressed bitter grieve about the inequity that they were not entitled to the same benefits as patients from other districts. For example, Hissor district does not have food supplements, but is encircled by three districts, all of which have food supplements (Dushanbe, Rudaki and Shahrinaw). There were also episodes of patients who accused TB doctors of theft. They had witnessed that food supplements were given to TB patients in other districts, but never received any themselves, because they lived in a district without food supplements. They had wrongly concluded that the doctor had taken possession of their food supplements.

Monetary Value and Expenditures

Patients were also asked to estimate the value of the food they had received. The mean value (the median value was almost identical) of one food donation was estimated at 81USD (±s.e.=4.0USD). The most valuable items in the food donations were the bags of flour. Patients mostly estimated that the local market price of one bag of flour (50kg) lay between 16.0 to 18.9USD. Depending on family size, patients often received three to five bags of flour. The estimated local market value of three food supplements, associated expenditure and the household costs of an episode of TB are shown in figure 9.4.

On the question, whether they had paid anything (or made any in-kind gifts) in order to

be eligible for food supplements, 13 out of 68 patients (19%) reported having paid to be eligible for food supplements. The mean self-reported payment of those who did pay was 1.1USD (±0.61) per food supplement.

On average, patients paid 4.9USD (±0.43) each time for the transport to pick up and bring home the food donations. These were mostly made to hire a car to bring the heavy food supplements from the distribution points (up to three per district) to the patients' homes.
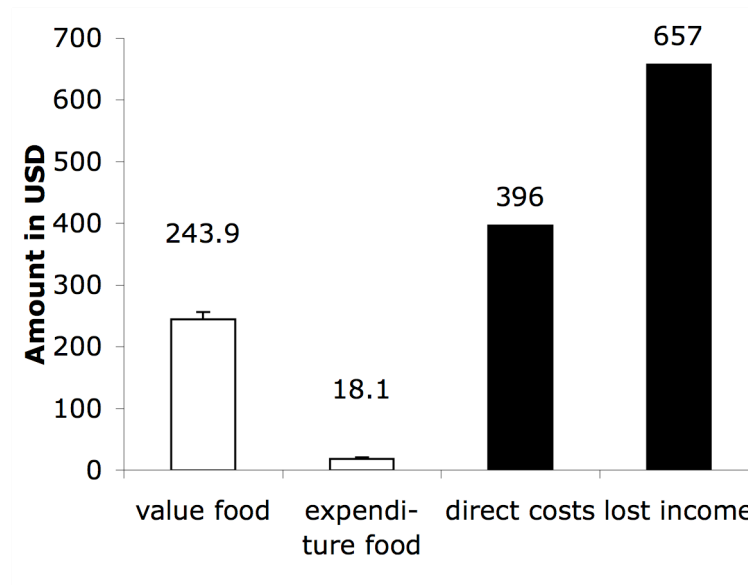
Figure 9.4. Value of and expenditures made for three food supplements in comparison with direct and indirect household costs of illness (source: Ayé et al. 2010).

Discussion

Study results indicate that almost all the scheduled food supplement distribution cycles have taken place, although in some cases delayed by several months. Patients were not well aware of their entitlement to food supplements at the beginning of the TB treatment. At the time of the second interview patients had on average received 1.7 food supplements, with a clear trend for more food supplements for those who had been on treatment for a longer time period. The total benefit received through food distributions amounted to about 225USD and informal payments were limited.

Limitations of this study include the relatively early time point, when the second and last interview with the enrolled patients was conducted. Given the long and often irregular intervals between food distributions, we were consequently not able to make final conclusions about the proportion of patients who had received food supplements and all food supplements. A regression model was used to test the increase of food supplements received over time. Linear regression is not theoretically appropriate,

among others because the number of food distributions is censored at three. However, the deviations from these assumptions were minor in this case, where a majority of patients were below the maximum number of three food supplements – provided the model is only used for interpolation but not for extrapolation. This study did not investigate the exact amount of food that was received. Informal discussions with beneficiaries showed that many patients were aware that food supplements were given based on the number of household members up to a threshold of seven household members. Patients also reported the use of scales during food distributions as foreseen by the programmes.

The awareness of patients about their entitlement to food supplements was low at the time of the first interview. Being uncertain, whether they will receive food supplements, may make patients believe that they should pay informally in order to increase their chances of receiving these benefits. More detailed discussions with patients revealed that most of them have heard about or even witnessed the distribution of food supplements. However, they were not very confident that they themselves would also receive food supplements. The irregular intervals at which food supplements are distributed probably contribute to the patients' uncertainty.

The extent of the patients' uncertainty, whether they will receive food supplements or not, does not seem justified in the light of the study findings: almost a third of patients in the study had already received all three food supplements before the end of the treatment. It seems likely that a majority of those who had received only a part of their food supplements at the time of the interview have received the remaining ones after the interview. The fact that there was a clear statistical relation between the number of food supplements received and time in treatment also points in this direction. However, the latter relation was weaker than expected. The regression slope estimated in the statistical model suggests that it would take patients about 1.8years to receive all the three food supplements rather than nine to eleven months as would be expected if food distributions were on time. This clearly shows that further efforts are needed to ensure the timeliness of the food distributions. The seven patients who reported not having received any food supplements by the time of the interview warrant discussion. They point towards the possibility that a small proportion of patients might be denied food distributions altogether. Alternative explanations include that these patients would have been non-adherent and therefore not eligible for food distributions. However, this was

not investigated in this study. After patients have received food supplements once, the likelihood of not receiving the other food supplements is assumed to decrease, because they meet fellow patients and representatives of the health system and at least two involved organisations there – consequently they will be better aware of their entitlement afterwards.

Assuming that all patients did receive three food donations in the end, the programme contributed 244USD on average to each patient's household budget, according to the patients' estimates. Subtracting the mean payments reported in direct relation to the food supplements, this amount comes to 225USD. In order to put this amount into context, we compared it to the costs of an episode of TB at the household level. Hereby it must be born in mind that the methods to measure these costs differed somewhat and that direct comparison should be interpreted with caution. The total illness-related costs at the level of TB patients' households were found in the main study to be around 1050USD (Ayé et al. 2010). Correspondingly, the food supplements made a substantial contribution to the household budgets of patients during times of economical hardship. The contribution to the household budget fell, however, well short of balancing the total household costs.

Reducing and mitigating economic and structural barriers to treatment has been suggested to improve treatment outcomes (Greene 2004). An operational study on food supplements for TB patients in Tajikistan using a plausibility-design concluded that food supplements have likely led to improved treatment outcomes (Mohr et al 2005). Financial or in-kind incentives with or without food supplements have been shown to improve treatment outcomes (Bock et al 2001, Davidson et al 2000, Farmer et al 1991). In a different context and program, conditional cash transfers and food fortification have led to improved physical and cognitive development (Fernald et al 2008). Furthermore, good nutrition is important both in the prevention of adverse reactions to the treatment regimen and in the interaction of TB and the immune system (World Health Organisation 2003, Schwenk & Macallan 2000). Historically, nutritious food has been the only "treatment" of TB and cholesterol-rich diet has been shown to contribute to bacteriologic sterilisation in TB (Pérez-Guzmán et al 2005).

While this study did not investigate the influence of food supplements on the treatment outcomes, we have shown that food contributions contribute to mitigating the impoverishment associated with an episode of TB. The dire need and economic

hardship of TB patients that have been documented (Ayé et al. 2010) are clearly alleviated by the contribution of food supplements. It is very likely that food supplements enable patients to better adhere to the treatment. Hence, food supplements are a valid option to contribute to the reduction of impoverishment and the improvement of treatment outcomes including adherence in TB control programmes in Tajikistan and elsewhere.

From the study results it can be concluded, that a large majority of TB patients have received food supplements as foreseen by the programme, albeit sometimes with delays of several months. The study showed no indication of large proportions of food supplements failing to reach the patient. However, monitoring should be further strengthened especially in two districts. Three food supplements make a contribution to the patients' household budgets of about 225USD and contribute to the mitigation of TB-related impoverishment. It seems likely that this has contributed to better treatment outcomes and nutritional status. The absence of food supplements in certain districts constitutes an inequity and is bitterly felt by the affected patients. In some instances, it also negatively affects the relationship of trust between patients and TB doctors. In order to improve TB control in Tajikistan it would be advisable to expand food supplements to those districts where they do not exist currently.

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10. Modelling the sensitivity of routine Ziehl-Neelsen sputum microscopy in the absence of a gold standard

Running head: Sensitivity of routine sputum examination

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Working paper

Abstract

Objectives: We wanted to model the sensitivity of sputum smear microscopy in the absence of a gold standard using a rigorous statistical modelling approach and data from the External Quality Assessment (EQA). The results should provide evidence for the international policy debate on diagnostic standards and for the Tajik program.

Methods: Registry data from EQA were collected from the national reference laboratory and from 38 district laboratories in Tajikistan. Data were extracted and used to estimate sensitivity and specificity of sputum microscopy by means of a Bayesian formulation of the latent class model fitted via Markov chain Monte Carlo simulation.

Results: Data from 21'627 individual slide examinations were obtained. The sensitivity of examining a single sputum specimen was estimated at 0.53 (95% credibility interval 0.43-0.68). Consequently, the sensitivity of examining three specimens amounts to 0.90 if all examinations are carried out with equal quality. The third serial specimen contributes 13% of all detected cases.

Conclusions: Routine sputum microscopy is performing reasonably well in Tajikistan and its use should be promoted. From a global perspective, the third serial smear could make a major contribution to case finding if all three examinations were carried out with equal quality. Requiring only two serial smears for diagnosis has a potentially serious negative impact on case finding. Consequently, the third smear should not be dropped. Measures to strengthen laboratory services and specifically the quality of the second and third serial smears should be evaluated and could include blinding of the laboratory technician.

Introduction

Sputum smear microscopy (SSM) using Ziehl-Neelsen staining is one of the five cornerstones of the DOTS strategy. It is *the* component of DOTS that most directly relates to the detection of tuberculosis (TB) cases. It is a simple and inexpensive technique that can be implemented even in settings with limited infrastructure and unreliable supply of electricity. However, its low sensitivity is an impediment to TB control (Keeler et al 2006). Current guidelines stipulate that three specimens should be examined before excluding sputum-smear positive (SS+) TB (Enarson et al 2000). On the global level, detection of TB patients is at 57% of estimated incident cases – clearly below the target of 70% (World Health Organisation 2009). Even though rapid diagnostic tests are commercially available, currently none of these has the potential to replace SSM and the latter will remain the mainstay of TB diagnosis in most settings (Steingart et al 2007, World Health Organisation 2008, Tuberculosis Division International Union Against Tuberculosis and Lung Disease 2005).

The sensitivity of SSM against the gold standard of culture has been reported to be 20-65% in settings with well-functioning laboratories (World Health Organisation 1998, Urbanczik 1985). In a review of the performance of fluorescence microscopy versus SSM, the sensitivity of SSM against culture was 32% to 97% in different research settings (Steingart et al 2006a). Under field conditions, sensitivity of SSM against culture was found to vary from 8.8% to 46.6% in African laboratories (Aber et al 1980). Measuring sensitivity and specificity of SSM under routine conditions is difficult because culture cannot be conducted at most sputum microscopy points. Moreover, an imperfect gold standard affects measures of diagnostic accuracy (Ochola et al 2006).

Several studies pointed out that the yield of the third sputum examination in terms of additional identified TB cases is very low (Ipuge et al 1996, Harries et al 2000, Yassin & Cuevas 2003, Rieder et al 2005, Mabaera et al 2006). In view of the high average workload of TB laboratories it was hypothesized that eliminating the need for the third sputum examination could lead to higher quality on the first two sputum examinations and would not have significant costs in terms of missed TB cases.

In view of the low case detection globally, changes in the requirements for diagnostic procedures that might potentially reduce case detection should be investigated carefully

before implementation. An option that previous scientific studies have not taken into account is the improvement of the quality of SSM on the third specimen. It would be very important to know how many cases would theoretically be found with the third serial smear if all smears were conducted with equal diligence. This proportion could be computed if the sensitivity of SSM under routine conditions were known.

The DOTS program of Tajikistan reached 100% coverage in 2007 (World Health Organisation 2009). The treatment success rate among 2006 new SS+ cases was 84%. The official estimate for case detection of new SS+ cases was 30% in 2007 – far below the global target of 70%. The proportion of SS+ among new pulmonary TB cases was 51%. Providers and program managers have doubts about sensitivity of SSM as carried out in Tajikistan. An External Quality Assessment (EQA) collects data on the reliability of SSM, but it does not constitute a gold standard and analysis of the data has so far been limited.

We wanted to model the sensitivity of sputum smear microscopy in the absence of a gold standard using a rigorous statistical modelling approach and data from the External Quality Assessment (EQA). Based on the results we aimed at providing evidence for the policy on diagnostic standards and for the Tajik program.

Methods

Study Area and Data Collection

According to the national guidelines for TB control in Tajikistan, every patient presenting to health services with cough for more than two weeks has to be referred for sputum smear examination. Three sputa are collected (spot-morning-spot) and examined at one of the 96 DOTS laboratories. Within the monitoring activities for the DOTS program EQA of SSM is conducted. The main component of EQA is blinded re-checking of slides from all DOTS laboratories at the national reference laboratory (NRL). A NRL technician takes a predefined number of slides from the district to the NRL, the number being determined according to a standard (Association of Public Health Laboratories & Centers for Disease Control and Prevention 2003). The slides are selected by starting at an arbitrary number and then taking additional slides at regular interval, the interval being defined by dividing the total number of slides examined by the number of sample slides needed. The result of the original reading of the slides does not play a role in slide selection. The selected slides are re-checked by a

NRL laboratory technician who is blinded to the result of the original reading. In case of disagreeing results, a senior NRL technician will conduct a second check, knowing that the first two results differed. The second reading was not used for the present analysis, because it was only available for a specific subset of slides.

We retrospectively collected all forms of the EQA of sputum examination that were available at the level of the NRL covering the period 2004 to 2007 inclusive. The study included all districts, from which at least 100 individual results were available at the level of the NRL, and collected the laboratory journals of the original examinations on a field visit (from each laboratory if there were several laboratories in the district).

Data Entry

All data were entered in EpiData Entry 3.1 (Epidata Association 2008) using a data entry mask with quality and consistency checks. Three research assistants conducted double-entry of the data from EQA. The two datasets were then compared and reconciled by the main researcher using the hard copy of the data. For each examinee, year, quarter, code of the laboratory, registration number, result of reading in periphery, result of reading at NRL, and remarks were entered. For the district laboratory journal data, double-entry was conducted for a random sample of nine laboratories (1045 records) to validate the data. The error rate was 1.30%. The laboratory journals include additional data compared to the NRL forms, including sex, age, date of each examination and the results of other slides from the same examinee. After data entry, data were imported into Stata IC/10.1 for Macintosh (Stata Corporation, USA, 1985-2008) and the results of all sputum examinations were recoded to a binary variable, whereby scanty positive slides were included in positive.

Case definition and analysis

We have pointed out in the introduction that microscopy is less efficient than culture in detecting TB. It is not only less efficient overall, but tends to detect only a subset of TB cases detected by culture. Therefore the case definition, for which we model sensitivity, is "pulmonary TB with a bacillary load above the detectability threshold". The detectability threshold has been estimated at 5'000–10'000 bacilli/ml (Toman 2004a).

Statistical analysis was conducted in WinBUGS (version 1.4, Imperial College & Medical Research Council, UK, 1996-2003). We modelled the sensitivity of SSM by

means of a Bayesian formulation of the latent class model, which allows for estimation of sensitivities and specificities in the absence of a gold standard if at least two tests are applied to the same individuals (Hui & Walter 1981, Ochola et al 2006). The model assumes an unobserved true prevalence of TB with a detectable bacillary load for each population, common sensitivity and specificity across the populations for each test and conditional independence of test results given the true disease status. Missing values, for instance if a patient did not submit all sputum samples, do not constitute a major

A separate true prevalence was modelled for each district. Note that the modelled true prevalence refers to the population of examinees whose slides were sampled for EQA, not to the general population. Separate sensitivity and specificity parameters were estimated for first, second and third serial examinations and for the examination at the reference laboratory, because the literature suggests that these differ. The second serial smear is almost invariably an early morning specimen and early morning specimens have been reported to have higher yield (Toman 2004b). It is commonly thought that the third serial smear may be carried out with less care and motivation and consequently its accuracy may be lower (Yassin & Cuevas 2003, Rieder et al 2005). Consequently, a total of 46 parameters were estimated: 38 prevalences, four sensitivities and four specificities.

The model was fitted using Markov chain Monte Carlo simulation. Details on the model are available upon request from the corresponding author. To investigate the sensitivity of our results to the priors, we ran the model with four different sets of priors. This is referred to as the four 'runs' below.

Results

The 55 laboratories in the 40 study districts had submitted 7'079 sputum smear slides to the NRL for EQA in total. We were able to obtain journals of 51 of the above 55 laboratories, and to match 5'884 individual records (83% of 7'079) from the laboratory journals with their EQA results (Figure 10.1). The mean number of examinees from one district was 155. Demographic data was available for 5'856 examinees. The mean age was 39 years (standard error 0.27) and there were 46% women. The 5'884 examinees yielded results of 21'627 slides. The positivity rate among the 21'627 slides was 16.7%.

The estimates for all the 46 parameters estimated by the model were extremely similar

for the four different runs of the model. The confidence intervals for the same parameter across different runs showed almost complete overlap. The modelled true prevalences of positive slides in the EQA samples from the 38 districts were between 0.06 and 0.53 with the exception of two extreme values of 0.013 (range among the four runs: 0.0128-0.0132) and 0.72 (0.71-0.73).
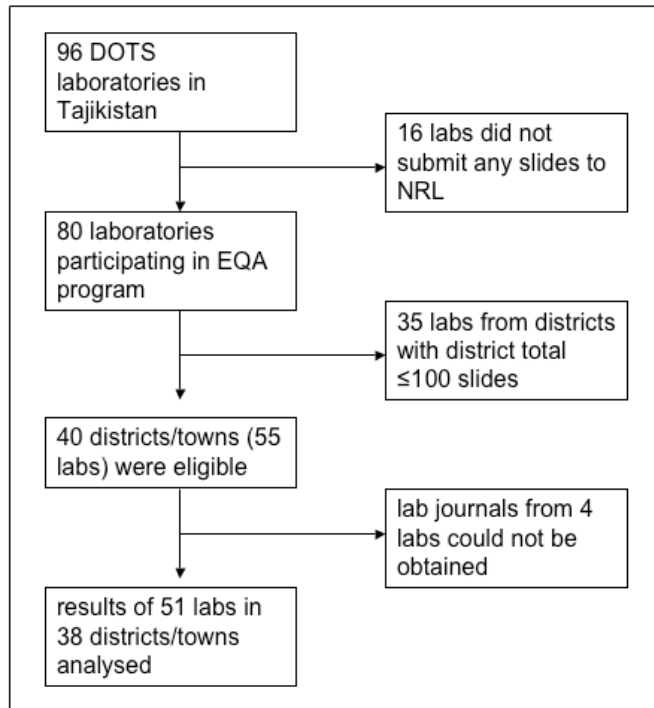
Figure 10.1. Flow-chart showing number of laboratories in Tajikistan and in the study.

The estimates for the specificities ranged from 0.985 to 0.998. The ranking was consistent among the four runs with the highest specificity on the third serial examination, the second highest on the first serial examination and the second-lowest specificity on the second serial examination. The estimate for the specificity of the examination at the NRL was consistently the lowest. The sensitivities were estimated between 0.501 and 0.585. Again the ranking was absolutely consistent among the four runs with the first serial examination having the lowest sensitivity, then the examination at the NRL, then the second serial examination and the third serial examination having the highest sensitivity. These results are counterintuitive, as the highest accuracy might have been expected at the NRL because the laboratory technicians there have considerably more experience than the technicians at the district level. Also the fact that the third serial examination fares better in both specificity and sensitivity than the first and the second serial examination is a surprise. However, while these differences were consistent between the four runs, the credibility intervals showed very wide overlap. Given that the differences between the runs were negligible, results are presented as the combined credibility intervals for the sensitivities and

specificities.

Using the model results and the assumption of independence, the combined sensitivities of two and three serial smears were 0.78 and 0.90, respectively. The relative difference between the two sensitivities is 13%. Hence, reducing the requirement for the diagnostic procedure from three serial smears to only two serial smears is therefore expected to lead to a decrease of smear-positive case finding by about 13%.

Discussion

The present study estimated sensitivity and specificity of sputum smear examination by the Ziehl-Neelsen technique using a novel rigorous statistical approach. We used a Bayesian formulation of the latent class model to compute data that are routinely collected in many TB control programs around the world. This approach had been used to assess other diagnostic tests, e.g. for malaria (Ochola et al 2006), but not so far in the area of TB. Consequently our approach could readily be applied to other settings, too. The study contributes to the surprisingly limited knowledge about the routine performance of the most important diagnostic test for TB globally.

Limitations

Our study has several limitations, which are discussed in the following. The slides sampled for EQA are not a perfect random sample of the slides examined in our study districts. However, as the interval for sampling is defined only at the moment of sampling and as the starting point is arbitrarily chosen by the monitoring team, i.e. an outsider, we believe that the influence of non-random sampling can safely be neglected for the purpose of our analysis.

The assumption of the model that sensitivity and specificity are the same in all settings is of course not perfectly true, as there may be variation in the performance of different laboratories. However, there are several factors contributing to the homogeneity of the study laboratories. The TB program is very vertically organised and all districts were directly supervised directly by the national level at the time of the study – without an intermediate regional level. All lab technicians have undergone the same training course and are similarly equipped. As a result, the studied laboratories have comparable standards, which improves the validity of the model. Computing separate sensitivities and specificities for each laboratory is impossible in the absence of a gold standard, as

the model would be over-parameterised.

The model assumed that the examination at the NRL was an independent examination. Strictly, this would require that a separate specimen be collected from the patient, rather than using a slide that was already viewed at the district laboratory. This deviation from the model assumptions is expected to lead to an overestimation of the sensitivities and specificities. The exact extent of this overestimation is unknown. Validation using a prospective design where actually a separate specimen is collected from the patient could clarify this issue. Irrespective of validation, our conclusions regarding the need of a third serial specimen would only be reinforced if the sensitivity of a single smear were lower.

The final significant limitation is linked to the way sputum smear examination is implemented in most routine programs. In most laboratories performing sputum smear examination, the laboratory technician is not blinded towards the previous results from the same suspect. This could lead to a bias when examining the second or the third serial smear. Our finding that the estimated accuracy of second and third serial smears was consistently better than that of first smears and of the examination at the NRL could point to such a bias. While the differences were far from significant in our model, it has to be kept in mind that the model is not designed to detect a directional bias in the original data. Validation using a prospective design and blinding of the laboratory technician would provide crucial information on this aspect.

Implications for national and international policy

Based on the results of 21'627 individual slides, our parameter estimates for the sensitivity of a single sputum smear examination were around 0.53. The combined estimate for three serial examinations was 0.90. Sensitivities reported in international guidelines are 0.35 for a single slide and between 0.6 for pauci-bacillary cases and 0.90 for patients with a high bacillary load for three slides combined (Toman 2004b). Hence our estimate for a single slide was considerably above the previously reported values. As laboratories see a mixture of pauci-bacillary cases and patients with high bacillary load, the expectation for three slides combined is actually a weighted mean of the above-mentioned values. Our finding of 0.90 does not indicate major problems with the quality of sputum smear examination in our study setting. This is contrary to ideas revealed in discussions with health care providers, TB program managers and in some

reports (Neher 2005, Vrakking & Talevski 2008).

It has been suggested to reduce the requirement for the diagnostic procedure using Ziehl-Neelsen examination from three to two serial slides in international guidelines (Yassin & Cuevas 2003, Rieder et al 2005). Reducing the requirements from three to two sputum specimens would contribute to relaxing the heavy strains on often under-funded and under-staffed laboratory services in high-incidence countries. However, access to diagnosis would not be improved *per se* as patients would still need to travel twice to the health facility to submit two sputum samples. Moreover, our results suggest that such a change might lead to a decrease in case finding of 13% compared to three serial smears implemented with equal quality. Given that TB programs worldwide are struggling to achieve the target of 70% case detection, a decrease of 13% is unacceptable. While our findings will need to be confirmed by research in other settings and possibly also using prospective study designs, we recommend not to proceed with a reduction from three to two slides for TB diagnosis. Other measures will need to be taken to solve the problematic issue of overloaded laboratories in some settings (Harries et al 2000, Rieder et al 2005). These may involve increased funding, staffing and recognition for the laboratory, an often underestimated component of functioning TB control. Fluorescence microscopy and different sputum processing methods have shown promising results at least in some settings (Torrea et al 2008, Van Deun et al 2008, Steingart et al 2006b). Measures for retention and motivation of laboratory staff, including appropriate salaries, have to be considered and put in place.

As to the perspective of the Tajik DOTS program, our results suggest that sputum smear examination is working reasonably well. As argued in the limitations section, we cannot exclude a slight overestimation of the sensitivity. Consequently, further efforts to improve the quality of sputum smear examination are useful. Interestingly, the modelled accuracy of the NRL examination is lower than the accuracy of examinations in the periphery. Potential bias in the examination of second and third specimens in the periphery could lead to this pattern. Laboratory specialists need to be made aware of the importance of unbiased examination of the second and the third serial specimens. Moreover, clerical errors when sampling slides and registering original results for EQA are a possibility. It is therefore important, that the monitoring team sampling slides for EQA pay attention to avoiding any clerical errors.

Conclusions

We have modelled for the first time sensitivity and specificity of sputum smear examination in the absence of a gold standard. Modelling of sensitivity and specificity using a Bayesian approach and routinely collected data from the EQA is feasible and provides valuable insight. Sensitivity of sputum smear examination under routine program conditions in 38 predominantly peripheral laboratories in Tajikistan was estimated at 0.53 for a single slide. None of the possible combinations of the three serial examinations at the periphery and the NRL examination showed statistically significant differences in terms of significance. If all examinations were carried out with the same quality, the third specimen would yield an incremental gain of 13% of all cases. Consequently we do not recommend changing international requirements of three serial specimens for diagnosis.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA led the study from conception through data collection and analysis to writing up. KW participated in conception, planning and writing-up. CB, MB and ZH participated in the design of study tools, conducted data collection, data cleaning and provided local information for analysis. SS participated in conception and planning as well as in data collection. PV contributed to the conception, analysis and the writing-up.

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11. General Discussion and Conclusions

11.1. Outline of the chapter and summary of findings

This thesis investigated factors influencing access to care for TB in Tajikistan. Seven studies were conducted and their results are briefly summarised below. In the following sections, the methods employed and the relevance of the findings are discussed in more detail. The findings are discussed from the viewpoint of academic research as well as from the stance of program implementers and policy makers.

The initial qualitative study (chapter 4) found a striking agreement among community members, TB patients and health care providers, that the main determinants of access to TB care are factors relating to affordability, the economic component of access. Factors relating to the other four main components of access to care – availability, accessibility, acceptability and adequacy – were not considered equally important, neither in the open discussion, nor in a confidential participatory approach. While there was agreement on affordability being the main barrier to care, a diverse range of opinions was found about the actual items that caused problematic costs to TB patients.

A subsequent study on health care seeking found that delays until start of anti-TB chemotherapy were reasonable given the resource constraints (chapter 5). However, patients who first presented to a peripheral primary care facility or to a facility in Russia experienced unacceptably long system delays. Further findings were that sputa were hardly ever collected at primary care facilities and that CXR was over-used for diagnosis. Effective referral systems from peripheral primary care and from Russian facilities are needed to reduce the above-mentioned long delays. Repeated visits to peripheral facilities, the distance to the specialised TB facility and paying for CXR are features of the health care seeking that may contribute to the economic burden of disease.

Taking into account the results of the qualitative study, two subsequent studies in the framework of this thesis concentrated on household costs. The first of these two studies (chapter 6) showed that TB patients and their households face illness-related costs of USD 1'053 on average, of which USD 396 were direct costs and the rest lost income due to the inability to work. In terms of PPP, this corresponds to approximately USD 4'900. These costs exceed the per capita GDP by a factor of three and must therefore be

considered catastrophic. The cost burden was most acute during early stages of treatment, namely before anti-TB chemotherapy was started and during the IP.

The second study on costs of an episode of TB investigated predictors of higher illness-related costs at the patient level (chapter 7). This study looked at direct costs (expenditure) of TB (see also section 11.2.2 for a discussion of this approach). A regression analysis identified medication that is received in addition to the anti-TB drugs as the main predictor of expenditure. Further influential factors were hospitalisation and the delay until anti-TB treatment had been started. Three coping strategies were identified as being potentially detrimental and increasing the risk of impoverishment. Two thirds of the patients in the study employed at least one of these three coping strategies. On average, USD 182 were raised using these three coping strategies – illustrating major risks for impoverishment.

Hospitalisation was mainly determined by sputum smear status; to a lesser extent, older age and male sex also predicted hospitalisation (chapter 8). This finding is in keeping with national guidelines that emphasise the need for isolation of sputum smear positive patients. International recommendations, however, do not consider infectiousness alone a sufficient indication for hospitalisation. Negative sputum smear was the only significant predictor of successful treatment in the multivariate analysis. There was a tendency for lower treatment success in hospitalised patients.

A survey among patients found that a considerable proportion of TB patients had already received the three food supplements that they were entitled to – before the end of the treatment. The number of food supplements received was significantly associated with the time elapsed since start of treatment and with residing in four out of the six districts with a food distribution program. Food supplements made a contribution of about USD 225 to the household economy.

Sensitivity of routine sputum smear microscopy in peripheral laboratories in Tajikistan was estimated at 53% for a single specimen and at 90% for three serial specimens in our Bayesian model. Consequently, it is estimated that the third serial smear would contribute 13% of all detected cases, if the three smears were carried out with equal quality. These results suggest that sputum microscopy is working reasonably well in Tajikistan and that its use can be promoted. Our findings are relevant to the global policy discussion on requiring two or three sputum specimens for TB diagnosis. The

proportion of cases that are expected to be found with the third specimen only is considerable and keeping the requirement for three specimens seems appropriate. Other measures to strengthen sputum smear microscopy including increased funding, staffing and staff retention programs should be considered. Fluorescence microscopy and sputum processing also have potential to improve case finding at least in some settings.

11.2. Methodology: limitations and strengths

The studies of the present thesis were based on three main methods: focus group discussions (FGDs), a survey with interviewer-administered questionnaires and registry analyses. In the following section, the most important limitations and advantages of the employed methods as well as the generalisability of the obtained results to the whole of Tajikistan and to other countries of the former Soviet Union (FSU) will be discussed.

11.2.1. Focus Group Discussions

The initial study used FGDs to study access to TB services. This qualitative method has important strengths. It capitalises on the interaction between study subjects and on a free discussion among them to enable researchers to explore beliefs and concepts about a specific topic (for example TB) and to gain in-depth understanding without conducting a full anthropologic study (Kitzinger 1995, International Nutrition Foundation for Developing Countries 1994). Studying communities' or patients' views about an issue as complex as treatment adherence or access to care, may exactly require this in-depth understanding (Dick 1999). The FGDs allowed us to explore beliefs about TB, awareness about TB services and a comprehensive set of factors potentially influencing access to care for TB, including potentially sensitive topics like beliefs about TB and its social consequences (cf. Liefooghe et al 1995). We were able to recruit a moderator with extensive previous experience in FGDs who contributed enormously to the success of the study through his considerate and sensitive manner. The open questions used in qualitative research and the environment of trust created were conducive of an open discussion where also questions that the research team did not directly think of were discussed and answered. This contributes to the exploratory nature of FGDs. Limitations of the method include the fact that no quantification of the different factors and their associations with the outcomes are possible (Kitzinger 1995). Most importantly, the total economic costs – while found to be the most important component of access to care in our setting – could not be quantified. Several items were

reported by participants of FGDs to play a role in the high costs, but their contributions could not be quantified with this qualitative method. As any method relying on self-reporting, FGDs potentially suffer from reporting bias. Reporting bias is expected to be less of a problem for questions relating to knowledge about the disease, but may be an issue for aspects of the respondent's attitudes and especially practices. The so-called 'Hawthorne effect' may occur, whereby study participants behave differently because they are aware of being studied. Furthermore, respondents may give responses that correspond to the researcher's views (or what the respondents believe to be the researcher's view) rather than their real attitude and practices (Last 2001). Among the topics investigated in our FGDs, the use of traditional home-remedies and healers (rather than allopathic medicine) was especially prone to biased reporting. We tried to limit such bias by explaining that we were interested in participant's personal views and were not going to assess these as either right or wrong. The fact that the moderator was not working in health care but was studying the health care system from an external view was a further plus and was openly communicated to the respondents. Furthermore, reporting bias is typically reduced when questions are answered confidentially. The results of the confidential participatory approach conducted during the FGDs, however, were highly consistent with the results from the open discussion.

Results from other studies support this view. The study on health care seeking and delay (chapter 5) also showed the low importance of informal providers. At the same time, interviewees freely reported the use of non-medical self-treatments. The free reporting – sometimes even of illegal practices like consuming opium – shows that the interviewees were able to express themselves freely. In conclusion, we believe that reporting bias is not the reason for the low importance of informal providers found, but that TB patients in Tajikistan really prefer formal health care providers.

A further important aspect is the language in which research is conducted. This is also true for the interviewer-administered questionnaires discussed below, but the issue is particularly important in FGDs and therefore it is discussed in more detail here. As explained above, FGDs capitalise on the discussion that happens naturally among participants and on their interactions. Simultaneous translation would interrupt the flow of discussions considerably (International Nutrition Foundation for Developing Countries 1994). Tajikistan is multilingual, Tajik, Uzbek and Russian being the three most common languages. The moderator and the transcriber of the FGDs were fluent in

all the three languages, which permitted participants to express their ideas in their preferred language and contributed to the validity of our results.

The FGD study was conducted in the four pilot districts where the health sector reform is implemented with support from Project Sino. In generalising the results of these studies to the rest of Tajikistan, caution is required because it cannot be excluded that the study districts differ from other districts. On the other hand, the four study districts incorporated a range of very rural, mountainous and semi-urban settings, including areas with Uzbek majorities and other areas with almost exclusively Tajik populations. There are no reasons to believe that our study districts would be fundamentally different from most other parts of Tajikistan. For a few topics, there was an overlap with later studies conducted in a larger study area. The results from overlapping subjects suggest important findings – including low utilisation of traditional healers and the fact that TB patients encounter high costs acting as a barrier to access care – to be true for other areas of Tajikistan, too.

11.2.2. Questionnaire survey

Descriptive studies, including questionnaire surveys, have several strengths and are often the first foray of scientific research on a specific subject that may trigger more studies later (Grimes & Schulz 2002a). Their strengths include being relatively inexpensive, simple and often quicker to conduct than more rigorous studies. They may consequently be more resource-efficient (Grimes & Schulz 2002a). Descriptive studies may suffer from three main types of bias: selection bias, information bias or confounding (Grimes & Schulz 2002b). In our study, selection bias could have occurred because not all eligible patients were found and interviewed. We attempted to limit selection bias by including a consecutive sample of TB patients and by making considerable efforts to find all patients. Consequently, the drop-out rate was reasonably low at 26%. Other studies using complete or probability sampling have had drop-out rates of 9%, 30% and 76% (Aspler et al 2008, Lambert et al 2005, Khan et al 2000). Two kinds of information bias could have occurred in the study: interviewer bias and reporting bias. Our interviewers had not previously worked in the health sector and thus were less likely to have strong preconceptions about appropriate health care seeking and payments in the health sector. Interviewees of Uzbek and Russian ethnicity were interviewed by an ethnic Uzbek who was bilingual Uzbek-Tajik and fluent in Russian. Reporting bias related to social desirability has been discussed in the previous section.

Another form of reporting bias is recall bias. Aspects of recall bias are probably more important in most topics covered in the questionnaires than aspects of the Hawthorn effect. Interviewees may have forgotten part of their symptoms, treatment seeking steps or incurred costs.

Recall bias is most likely for small expenditures, for the onset of the first, potentially mild, symptoms and for actions that lie a long time back. Recall bias can lead to both, under- or overestimation of costs. Underestimation occurs if costs are forgotten completely; overestimation may occur if the amount is forgotten and over-estimated at the time of the interview (Saunderson 1995). Our survey used several strategies to reduce recall bias: among others conducting two interviews, using a calendar of local events and asking many precise questions about health care seeking and different line items (Lu et al 2009, Lambert et al 2005). The use of two separate interviews – to our knowledge unique among studies of illness-related costs – considerably reduced recall times. In the first interview, recall times were four months or less for a majority of study participants, in the second interview recall times were usually three to four months. Recall periods of 6 months or less were found to be "an optimal recall period for self-report surveys" in a review of recall bias in regard to health care service utilisation (Bhandari & Wagner 2006). The review pointed out that short recall periods may lead to overestimation of utilisation because interviewees tend to include utilisation that was outside the specified period in reality. For health care expenditure it was also found that shorter recall periods yielded significantly higher estimates than longer recall periods (Lu et al 2009), but it was not clear which of the two was more accurate. Recall periods from two weeks up to one year are commonly used (Saunderson 1995, Kamolratanakul et al 1999, Wyss et al 2001, Russell 2004, Lambert et al 2005, Lu et al 2009). It is clear that rarer events and bigger expenditures will be remembered for a longer time. In our study, we included only new cases in order to avoid stronger recall bias and to improve data quality – experience during a pilot study had shown that re-treatment cases mixed up episodes from earlier health care seeking with their most recent health care seeking experience.

The last type of bias listed by Grimes & Schulz (2002b), was confounding. Confounding could possibly have occurred for the factors 'additional medication' and 'hospitalisation' in the statistical model on costs of illness (chapter 7). A likely confounding variable for both factors would have been severity of disease. As

discussed in the respective chapter, the statistical estimates for the two factors were not sensitive to including two proxies for severity of disease in the model. Therefore confounding does not appear likely.

In the paper on delay to TB treatment and its association with health services delivery (chapter 5) we argued that including knowledge of symptoms in an explanatory model for patient delay until presentation to allopathic medical services was at a risk of being flawed. The argument was that the patient's knowledge is likely to change between the moment when this factor acts (at the time when the decision to initiate health care seeking is taken) and the moment, when the factor is measured (during the interview, i.e. during IP). The encounters between patient and health care provider that take place in the meantime are likely to influence the patient's knowledge about the disease. A similar argument could be made for belief in curability, because the health care provider is supposed to inform the patient about the curability of TB in the frame of patient counselling to foster adherence. We anyway included belief in curability, because we felt that people's beliefs about curability were often very deep-rooted and – contrary to knowledge – were more likely to change only gradually or not at all.

Even when all reasonable practical measures are taken to improve reporting, measuring costs remains a difficult task. This is especially true for indirect costs, which have been measured using a range of different methods (Russell 2004). One of the main problems for measuring indirect costs is that income is mostly informal, often irregular and sometimes in kind. Several studies have therefore measured time costs and converted these using the ratio of estimates of income (for example national average) and working hours (Saunderson 1995, Russell 2004, Wyss et al 2001). This approach has been criticised for different reasons, including the uncertainty of national average incomes and the fact that average incomes tend to be not representative of the subpopulations most at risk of developing TB. Most importantly, however, this approach neglects coping strategies like intra-household labour substitution (Sauerborn et al 1996, Russell 2004). Intra-household labour substitution can considerably reduce indirect costs. A further aspect is that Tajik law requires employers to pay employees during sick leave. The long Soviet tradition still has its influence and this often actually happens in practice. We therefore decided to ask study participants about the actual reduction of income that they have incurred. This led to high variation at the individual level (many patients reporting zero lost income because they still received their full

wage or because of intra-household labour substitution – other patients reporting high income losses, for instance because they had been migrant workers in Russia where wages are often 10-20 times higher than in Tajikistan). However, we think that this approach gives a more realistic picture of the average costs encountered by patients.

In our dataset on costs of illness, there was a considerable amount of missing data (around 15%). This likely reflects among others the problem of recall bias discussed above. Rather than excluding patients with missing data (which could introduce selection bias) or replacing missing values with mean values (which could introduce selection bias and additionally leads to underestimation of the variance), we chose a rigorous statistical technique known as multiple imputation (Schafer 1997, Royston 2005). Multiple imputation makes use of correlations between different variables in a dataset. Based on all available data, it estimates a predicted mean and variance for each missing value. The method makes an assumption called 'missing at random', which is non-testable, but more relaxed than the implicit assumption called 'missing completely at random' made by complete-case analysis (Schafer 1997). The interested reader is referred to the statistical literature for details. Strengths of this method include that all available information is used efficiently (by not deleting incomplete cases) and that the uncertainty about the true value at the place of a missing value is taken into account (Schafer 1997). Multiple imputation method has been recommended for similar problems of missing cost data in studies in the health sector (Manca & Palmer 2005). Further, the robustness of our statistical findings with p-values often considerably below 1% make us confident that the missing data, had we been able to collect it, would not have altered our conclusions significantly.

The question whether the study sample is representative of the whole of Tajikistan has already been discussed in single chapters and is not elaborated in detail here. Given the time requirements of travelling to patients' homes (including their location with imprecise 'addresses'), expanding the study area even more would have negatively affected our ability to participate in data collection as well as to monitor and support the interviewers. Participation in data collection, monitoring and support contributed to data quality. We therefore excluded two regions but for the reasons stipulated in the discussion sections of the different papers (chapters 5 to 7) think that our findings and conclusions are valid in most areas of Tajikistan. An exception might be the thinly populated Badakhshan region, where the majority of people are Pamiri, speaking one of

several Pamiri languages and adhering to the Ismaili branch of Shiite Islam rather than Sunnite Islam as in the rest of Tajikistan.

Generalising from new pulmonary TB patients to all TB patients requires caution. It is likely that re-treatment patients have even higher costs than new patients, because they receive more drugs, they may have more complications and their treatment lasts two months longer. The extent of the increase of costs for re-treatment compared to new patients is unknown and based on the experience from our pilot study (see above) may be very difficult to measure. We also did not attempt to measure costs of extra-pulmonary TB patients. As pulmonary TB is the only commonly infectious form of TB and therefore the driver of the TB epidemic, concentrating on pulmonary TB seemed appropriate. The only previous study investigating determinants of household costs included both pulmonary and extra-pulmonary patients, but did not find a difference between the two in terms of costs (Aspler et al 2008).

For the regression analysis of determinants of illness-related costs, we included only direct costs – even though indirect costs were higher. The main reason were the very high individual variation (see above), which could have introduced spurious relationships. It was expected that a regression including indirect costs would mainly identify factors associated with migrant workers in Russia. In other words, indirect costs are higher in those with higher income – so direct costs are not only easier to measure but may also be a better indicator of costs exceeding the patient's ability to pay.

11.2.3. Registry analyses

Among the strengths of registry analyses is the possibility to collect a large amount of data in short time and with limited efforts. One of the main limitations is that obviously only those variables that are routinely recorded in the registries – usually variables that are simple to measure like sex or age – can be used in the analysis. Registry studies are, like the two previous types of studies used and discussed in this thesis, observational studies. Inference from statistical association to causality cannot be made because registry analysis also constitute a form of descriptive studies (Grimes & Schulz 2002b). This is true even more so as researchers cannot freely choose the variables that seem most sensible, but the choice is restricted to the variables already present in the registry. Meaningful analysis also depends on the registries being reasonably complete and

accurate. Accuracy thereby also includes data quality. In the FSU, data quality may be a very important issue, as hypothesized by Coker et al (2008). As already discussed in the discussion section of chapter 8, a variable measuring the severity of disease would have been a desirable indicator for the analysis on predictors of both, hospitalisation and treatment success. However, severity was not noted in the registry. The registry analysis on sensitivity of sputum smear microscopy could have analysed sensitivity and specificity of the whole diagnostic procedure even more stringently if the repetitions of the test would have been independent and complete replicates. They were not, because the EQA does not rely on a new specimen from the patient, but on a slide from the laboratory. In order to investigate the sensitivity and specificity of the whole diagnostic procedure more stringently, we would have had to experimentally manipulate the setup of conducting a sputum smear examination. This would at the same time have compromised the routine of the setting and a Hawthorn effect would have been possible. Concluding, the registry analyses have their inherent limitations, but overall are a valid, parsimonious and efficient approach to gain general insight.

Both registry analyses presented in this thesis covered relatively large parts of Tajikistan. The registry analysis on hospitalisation used a stratified random sample of DOTS centres in three areas centred around the cities of Dushanbe, Qurghonteppa and Kulob, respectively. It is therefore representative of a considerable part of Tajikistan. The registry analysis on repeatability of the microscopy reading of sputum smear slides used a complete sample of all the laboratories in Tajikistan that fulfilled the inclusion criteria (a limited number of small DOTS centres were not eligible). The study is thus representative of all medium-sized and large DOTS centres of the country.

11.3. Contributions to the understanding of the concept of access to care

This thesis investigated determinants of access to medical care for tuberculosis in Tajikistan with a focus on household costs. The theoretical concept of access to care has been developed among others by Aday & Andersen (1974), Andersen (1995) and Obrist et al (2007). Our analytical framework, presented in chapter 3, followed mainly the latter reference, differentiating five components of access, called the five A's: availability, accessibility, affordability, adequacy and acceptability. To our knowledge, the present thesis reports the first application of this framework to TB care. The framework proved useful in fostering a deeper understanding of the factors influencing access to medical care for TB. Similar to studies on access to malaria treatment in the

Kilombero valley in Tanzania, the setting where the concept was developed, we also found that health system factors played a pivotal role.

The main adaptation that we suggest in order to make the model fit the context of a TB program is to view treatment adherence as a form of continued utilisation. Like utilisation, treatment adherence would then be an outcome of access to care rather than of quality of care. This is despite the fact that good quality of care including interpersonal skills of providers and appropriate counselling contribute to adherence. This adaptation is warranted on theoretical grounds, because DOT requires patients to go to the health care facility and to interact with providers much in the same way as for a consultation, but also on the grounds of our findings. Our FGDs showed that community members, patients and providers perceived the same factors to be important for diagnosis as for treatment adherence. The studies on costs of illness showed that the problem of affordability occurs throughout treatment – despite an exemption mechanism that was well functioning. This view of treatment adherence is shown in figure 11.1.

The perception of need for care is closely interlinked with socio-cultural concepts of a disease, beliefs and knowledge about the disease. These again are important factors of acceptability. We therefore suggest that the perceived (as opposed to the objectivistic) need for care be understood as a part of acceptability and thus access. Adherence requires a continued perception of the patient that she or he needs care. This is in keeping with the requirements for adherence listed by Jones et al (2000).

A further factor that is necessary for people to be able to utilise medical care is awareness about health care services, a factor that was not made explicit in the original concept (Obrist et al 2007). People need to have at least a basic knowledge about where health care facilities are located and what kind of services these facilities offer. This basic knowledge has been termed 'Awareness about health care' in our theoretical framework (Figure 11.1). In our FGDs, participants showed generally good and often surprisingly detailed knowledge about different health care services in their district.

It is important to realise that the five A's cannot be completely separated from one another, but are closely interlinked. For example, for patients who are able to pay for different means of transport accessibility is expected to be less of an issue than for those who are unable to pay – so that affordability and accessibility can be traded off

against each other. Patients who are able to pay may even travel from a rural area to the capital, where more services are available than in rural locations. For instance the credibility of health services in the sense of the perceived technical quality of care is linked to availability of essential drugs at the facility (Mamdani & Bangser 2004). And the availability of drugs is also not always clear-cut. Drugs that were initially unavailable at a facility could later be organised if the patient was willing and able to pay (Mamdani & Bangser 2004).
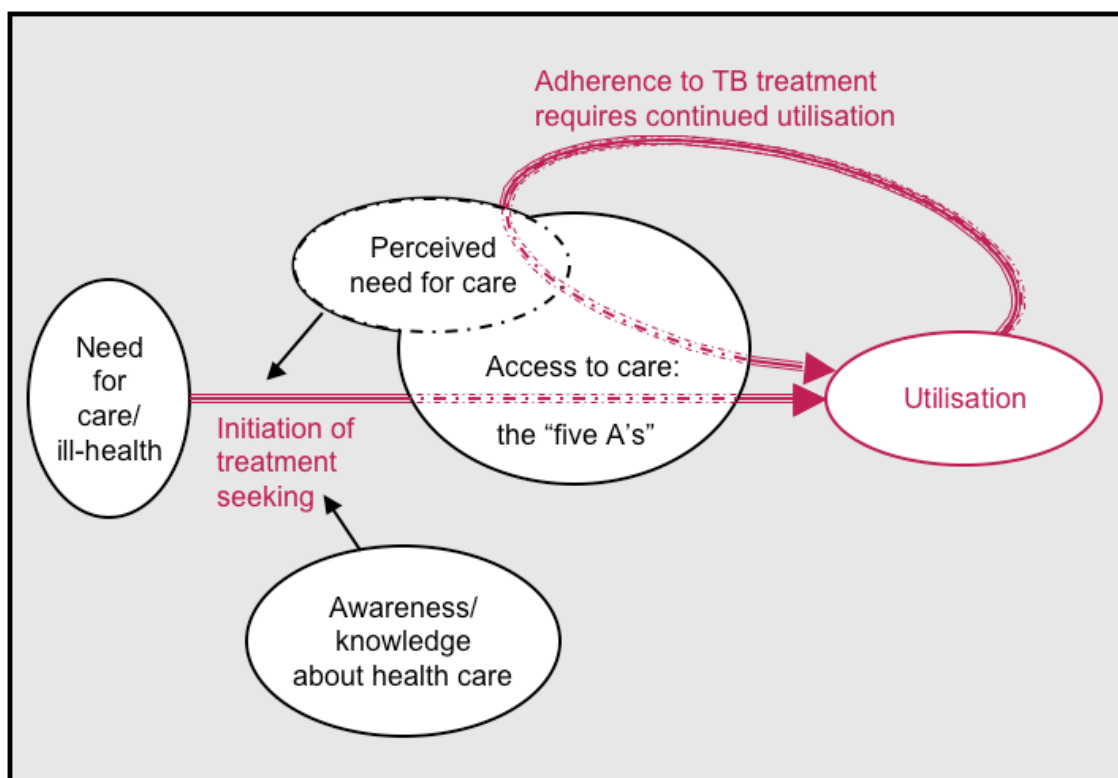
Figure 11.1. Representation of the position of 'access' between need for medical care and its utilisation.

11.3.1. Determinants of access to care

The FGD study showed that community members spontaneously associated cough with a number of diseases, including TB. They were also aware of the two means of diagnosis used in Tajikistan, sputum examination and CXR, and of the district TB facilities, where TB services are available. Community members emphasised that TB requires (allopathic) medical treatment. Economic barriers to TB services were the most important barriers in accessing TB care identified in the FGD study. The participants of all three respondent groups agreed on this. The finding is further supported by the high absolute costs found in the subsequent questionnaire survey among TB patients. This is not to say, that further improvements in patient education

and in the interpersonal skills of health care providers were not possible or unnecessary – rather it illustrates the urgent need to reduce the economic burden to TB patients.

Against a background of reviving religious feelings and traditions after independence in this predominantly Muslim country, most outside observers would probably have expected that women face more barriers to health care than men. Interestingly, we did not find any significant differences between women and men in the variables that are linked to access in our studies. The case of patient delay is somewhat ambiguous. The p-value is just above 0.1 and thus is close to a statistical tendency, even if not significance. The estimate of the hazards ratio suggests that women might have somewhat longer delays. But then again this comparison is only valid if both sexes experience and report symptoms in a similar way. Direct costs of an episode of TB were similar for women and men and in the two models the estimates for the influence of sex were in the opposite direction. Our sample was large enough for other factors to be highly significant, suggesting that there is no considerable difference between the sexes.

While very few previous studies have investigated access to TB care using a comprehensive theoretical framework rooted in the concept of access to care, there are many studies on delay to TB treatment and on adherence. It was argued in section 1.8.3 that access to care strongly influences delay until start of TB treatment and literature on delay was briefly reviewed there. Important factors commonly associated with longer delays included low knowledge or awareness of TB, rural residence, poverty and presenting first to a private provider or a low-level government facility (Storla et al 2008). Based on our studies and theoretical considerations, we have discussed in section 11.3 that access to care is a key determinant of adherence to TB treatment. The importance of adherence for TB control is widely recognised and many studies investigated predictors of adherence. Studies of adherence differ in their definition of the outcome and even more strongly in the set of factors that were investigated. These differences make comparisons challenging, but some factors have commonly been found to be influential. Alcoholism, homelessness, lack of social or family support, the interaction between patient and health care worker, and adverse effects of the treatment regimen have repeatedly been associated with non-adherence (Wares et al 2003, Baum & Lafair 2003, Salles et al 2003, Dodor & Afenyadu 2005, Jakubowiak et al 2007, Mateus-Solarte & Carvajal-Barona 2008). Traditional cultural beliefs may influence

adherence and access to TB treatment, too (Liefooghe et al 1997, Martins et al 2008). Numerous studies have found that one or several variables linked to affordability of services (low income or poverty of the patient, being unemployed or working as unskilled labourer, crowding, inability to afford additional medicine, facing costs to access the clinic, not receiving financial or in-kind support) were associated with non-adherence (Dodor & Afenyadu 2005, Jakubowiak et al 2007, Mateus-Solarte & Carvajal-Barona 2008, Mishra et al 2005, Martins et al 2008). Our finding that economic barriers are even more important than any other barriers to access TB services may also be true in other countries and settings.

The co-existence of catastrophically high patient-side costs and reasonably good treatment adherence are further evidence, that patients are aware of the importance of treatment and treatment adherence.

11.3.2. Costs and the influence of health system factors

Several of the findings related to household costs of an episode of TB are worth discussing in regard to academic research, mainly the high absolute level of these costs, their timing, and the factors that predicted higher costs.

Costs of USD 4'900 PPP are far higher than the costs found in any other study on patient-side costs of a TB episode. As briefly discussed in chapter 6, the shorter recall period (which was about half as long than in many other studies because two interviews were conducted with each patient), Soviet traditions persisting in the management of TB patients in Tajikistan and the pervasiveness of informal payments in the Tajik health sector (Cashin 2004, Falkingham 2004, Tediosi et al 2008) are likely factors to have contributed to this finding. Our strategy of conducting two interviews with each patient considerably shortened recall periods and makes us confident that our results give a reasonably accurate picture of the economic burden faced by TB patients.

The more important reasons are likely rooted in the Soviet tradition of TB care. Like in other post-Soviet countries there is a continued allegiance to the Soviet system in Tajikistan (Atun & Coker 2008). This includes the virtually exclusive reliance on TB specialists for TB diagnosis, the over-use of CXR, widespread hospitalisation during IP (sometimes also during CP) and the prescription of usually several types of additional drugs to the large majority of patients. As reported in chapter 5, primary care doctors in Tajikistan are reluctant to diagnose TB themselves. After decades of separation of TB

control in a separate vertical structure, many primary care providers do not yet consider diagnosing TB to be part of their responsibilities. Consequently patients are referred to the TB specialist, usually meaning that they have to pay for transport to the district centre. Both, diagnosis and follow-up of treatment success often rely on CXR, for which the patients usually have to pay, because there is not enough CXR film available. The last two factors mentioned above, hospitalisation and additional medication, have been shown in chapter 7 to be significantly associated with higher costs of illness. Hospitalisation has been shown in chapter 8 to be mainly due to the perceived need for isolation of the patient, which is not in accordance with international guidelines. Drugs commonly involved in additional medication are listed in chapter 7. Among others they commonly include vitamin B6. According to the World Health Organisation (2003), vitamin B6 should be given routinely to all patients if the general health status of the population is low – which is probably the case in Tajikistan. The rationality of other drugs commonly prescribed is more doubtful and in view of the high costs should be reviewed carefully. It seems likely that a considerable reduction will be possible. A further potential reason for the high costs is the pervasiveness of informal payments in the Tajik health system. The present thesis did not focus on the distinction between formal and informal payments. The distinction is difficult because health financing reform was ongoing. Until 2005, all health care was stipulated to be free of charge (Mahon & Tediosi 2007). In 2005 a co-payment system was introduced but soon withdrawn. The second version of the co-payment program was introduced during the time of our data collection in several pilot districts. At the time of writing this thesis, a move to user fees is under discussion (Ministry of Health of the Republic of Tajikistan 2009). Due to these ongoing changes, a rigorous distinction between formal and informal payments was not possible and was not attempted. However, patients were asked about the part of drug expenditure that was made in connection with the anti-TB drugs: only a small minority reported payments and these were usually small. Summarising, the high costs are related mainly to the additional services provided, which are rooted in the Soviet tradition of TB management. It seems likely that TB patients in many parts of the FSU would face the same problem, mainly because these countries still have similar health systems and the delivery of TB services follows the same tradition (Atun & Coker 2008, Atun & Olynik 2008). A further similarity is the widespread occurrence of informal payments in the health sector of many countries of the FSU (Ensor & Savelyeva 1998, Thompson et al 2003, Thompson 2004).

Patients with other long-lasting diseases or chronic conditions are likely to face similar problems as TB patients. If their condition requires regular visits to a physician and/or to a pharmacy to buy drugs they are likely to face both, direct and indirect costs, to a considerable extent. Additionally, other conditions are usually not eligible for free treatment, which may lead to even higher costs for drugs. As an example, cancer patients conceivably face an equally high or even higher economic burden. Affordability is also likely to be an issue for milder conditions. In a population survey, roughly half of those who self-reported need for medical care in the preceding two weeks, did not obtain it – mainly because they could not afford it or felt that self-medication was sufficient (Falkingham 2004). Patients in primary care spent about USD 12.5 for a visit to the doctor and for obtaining prescription medicines from the pharmacy (Tediosi et al 2008). Most of this amount was spent for the medicines. Even if patients with milder diseases are less likely to incur costs as high as those of TB patients, their costs may still have considerable implications for affordability of medical care and deter them from using health care altogether.

A second important aspect is the timing of the costs of a TB episode. More than 70% of costs were faced during anti-TB treatment. This is more than in other studies, where half or less than half of the total costs were encountered during anti-TB treatment (Saunderson 1995, Kamolratanakul et al 1999). Regular trips to the facility for DOT, to pick-up drugs, or to visit the patient in hospital, additional medication and loss of income are some of the most important items that lead to high costs despite free anti-TB chemotherapy. Monthly costs were highest during IP, which was unexpected in view of the free anti-TB chemotherapy. The large differences in monthly costs between the three periods investigated in the present thesis reinforce the insight that costs of ill-health tend to come in peaks (Russell 2004). Peaks of costs affect the affordability over-proportionately and the distribution of costs of TB over time deserves more attention in the research on affordability of TB services. Understanding the timing of costs is also important in order to target mitigation strategies. The food supplements provided to TB patients in Tajikistan are a valid and important mitigation strategy (see also chapter 9). As will be argued in the next section, the food supplements are designed as an incentive, rewarding the patient after she or he has completed several months of treatment. This is based on the logic that the patient needs to be convinced and motivated to complete treatment. An alternative view focussing on the sheer inability of the patient to afford and thus to adhere to treatment has been proposed for

example by Greene (2004). If this alternative view is taken, mitigation strategies should preferably be aimed at *enabling* the patient rather than motivating the patient and should consequently be targeted to early stages of treatment, when the highest cost peak occurs, rather than after. The timing maximising the effect of mitigation strategies is a subject for future research.

A further, not directly related, question for future research concerns the penitentiary sector. In the framework of the present thesis, we were not able to include the penitentiary sector in any of our studies. The provision of medical services in the penitentiary sector was a separate vertical program run by the Ministry of Justice rather than the Ministry of Health during Soviet times. Virtually nothing has been published about access to medical care in the penitentiary sector of Tajikistan.

11.3.3. Improving TB diagnosis in low-resource settings globally

Diagnostic tools to measure the humoral immune response (serological tests) have been reviewed repeatedly (Steingart et al 2007, WHO 2008) and it was consistently found that none of the available tests has the potential to replace sputum smear microscopy. Consequently, the latter will remain at the centre of TB case detection for several years at least. This underlines the importance of information on its performance in routine application.

Many efforts in external quality assessment of sputum smear microscopy, but also in research, have concentrated on the reading part of the examination. Our results suggest that the reading part is functioning reasonably well in Tajikistan. Obtaining a good quality sputum specimen from the patient is likely the higher hurdle. The importance of a good quality sample has been pointed out in guidelines repeatedly (World Health Organisation 2003, Toman 2004). The reason that it has received less attention in research may lie in the difficulty of measuring the quality of a sample. A pragmatic randomised-controlled trial in Pakistan, however, found a positive influence of instructions to produce better samples on case detection (Khan et al 2007).

11.4. Findings relevant to programs and policy – and possible implications

11.4.1. General situation of TB control in Tajikistan

The Tajik health system and TB control program have delivered treatment to 8081 TB patients in 2007 (World Health Organisation 2009). The treatment success rate was 84% among new sputum smear positive cases. The case detection rate for new sputum smear positive cases was estimated at 30%. Both rates have been disputed. The former, because biased reporting in order to receive rewards was claimed (Vrakking & Talevski 2009), the latter because it is based on incidence estimates, which are inherently difficult to achieve. The present thesis did not investigate either of the two. However, data from the patients who dropped out from the patient survey (compare table 7.1) provide a basis for a speculative assessment of mortality and defaulter rates in our sample. Out of 292 patients, five had died and three had defaulted approximately one month into treatment. Both numbers are below the official statistics, but are likely to increase until the end of treatment. The final defaulter and mortality rates in our study sample may have been approximately in the range of official statistics. It was pointed out in chapter 5 that the moderate delays do not point towards a major problem with access, as the staggeringly low case detection rate of 30% suggests. On the other hand, moderate median delays do not exclude that there are some subpopulations that lack access to the services. Overall, the situation of access to care is likely not as dramatic as the low case detection rate suggests and the treatment outcomes may be reasonably good. However, in light of the high MDR-TB rates suspected for Tajikistan (Zignol et al 2006, see also section 1.3), the program needs to achieve particularly good treatment adherence rates to control TB. In any case, considerable further improvements in terms of access to care are possible and necessary.

Table 11.1. TB control statistics in the countries of Central Asia°

Country	Total population	TB incidence§	Case detection rate∂	Proportion of SS+†	Treatment success rate*
Afghanistan	27.1 million	168	64	62	84
Kazakhstan	15.4 million	129	70	34	72
Kyrghyzstan	5.3 million	121	60	44	82
Tajikistan	6.7 million	231	32	51	84
Uzbekistan	27.4 million	113	46	47	81

° Source: World Health Organisation 2009.
§ Estimated incidence of TB (cases per 100'000 population per year).
∂ Ratio of notified new sputum smear positive cases (SS+) to total estimated SS+ cases.
† Proportion of sputum smear positive cases among pulmonary cases.
* Among new sputum smear positive cases.

11.4.2. Measures to improve access to medical care for TB

To improve the population's access to medical care for TB and probably other conditions, a range of issues have to be addressed. A priority aspect is affordability of services. The focus on economic barriers is not to say that other factors play no role at all: inter-personal skills of the health care workers, good counselling of TB patients at the time of diagnosis and again later, management of adverse effects of anti-TB chemotherapy and other factors likely also play a role. Furthermore, as has been argued above, different components of access to care are interlinked. Access to care is also intimately linked to the way health care services are organised and delivered. Examples of such links from this thesis are 1) the long health system delays experienced by TB patients first presenting to facilities without well-functioning referral systems to a TB facility, 2a) the high costs faced by patients who receive additional medication or 2b) are hospitalised, and 3) the under-use of sputum smear examination for diagnosis.

To decrease costs for the patients, delays should be shortened through better referral systems for certain subgroups, the use of additional medication and hospitalisation should be reduced, and other measures like reduction of the use of CXR and provision of food at the hospital should be considered. Where the use of additional medication is based on a firm evidence-base and cannot be reduced, additional medication should be provided free of care. Measures in this direction have already been taken and the Global Fund will provide 25 types of additional drugs for the TB program, including some of those mentioned in chapter 7 of this thesis (Z. Maksumova, *in litt.*). Shortening delays will additionally make a significant contribution to TB control by reducing transmission directly. Most of the above-mentioned measures can only be implemented if the health system is strengthened and in collaboration with implementing partners and funding agencies. Primary care providers need to be further trained and involved in TB care in order to play a more efficient role in the diagnosis of TB and in order to conduct supervision of the treatment of patients that would otherwise have been hospitalised. If primary care providers are enabled and feel comfortable to diagnose TB based on the results of sputum smear microscopy and to initiate treatment, the referral pathway will be considerably shortened for remote rural patients – who were among the subgroups with the longest delays. This may include many measures that are beyond the scope of this thesis, including among others financial reform: despite a recent increase in salaries, primary care providers are still underpaid and unable to

subsist on their salaries. While the strengthening of primary care is ongoing, hospitalisation rates for TB should be further reduced. As has been shown in chapter 8, hospitalisation is mainly based on infectiousness in Tajikistan. Infectiousness is not considered a sufficient reason for hospitalisation in international guidelines and a reduction of hospitalisation rates can be started without major concerns. In chapter 8 it was also shown that hospitalised patients did not have higher treatment success rates – if anything, the rates were somewhat lower. Reducing hospitalisation rates may free up resources for the ambulatory supervision of TB treatment, but the details of the financing have not been studied in the framework of this thesis.

Organising an international referral system for Tajik citizens who develop active TB in Russia is a further measure to decrease delays to treatment. Such a referral system is not equally dependent on health system strengthening as other measures. Ideally, the patients should start treatment in Russia (where DOTS programs have been implemented with external support, too). A transfer to Tajikistan should be considered only after smear conversion.

11.4.3. Provision of food and other material support to TB patients

Also if the above-mentioned measures are implemented, TB patients will still face considerable costs and strategies to mitigate the high household costs of TB will continue to be necessary. They include the provision of food supplements to TB patients and their household members. The delivery of food supplements was investigated in chapter 9 and they were found to be a substantial contribution to the patients' household economies. Recommendations made in chapter 9 include more timely distribution of the food items, improved monitoring generally but especially for two of the six study districts and expansion of the program of food supplementation to districts that currently do not have them. In the meanwhile food distributions have already been implemented in an additional two of the twelve districts covered by the household survey on private costs of TB. Consequently, food supplements are currently provided in eight of the twelve districts covered in the household survey. Countrywide, food supplements are provided in 33 of the 64 districts and towns covered under DOTS. Hence, expansion has started. Donors and program managers should work together to expand the food supplements to the whole country. An earlier timing of the food supplements should be considered to *enable* patients for treatment adherence rather than incentivising them.

11.4.4. Sputum smear examination and external quality assessment

As has been illustrated in chapter 5, sputum smear examination is not yet being used in primary care facilities, leading to long delays for patients presenting at these peripheral facilities. The under-use of sputum smear examination and concurrent over-use of CXR is one aspect of the 'Soviet flavour' of the DOTS program in Tajikistan. Managers at the level of the NTP and doctors at all levels often have doubts about the accuracy of sputum smear examination. Doctors further suspect patients to bring sputum of healthy people instead of own sputum collected at home (a behaviour that was observed also in Western Europe a few decades ago – R. Galeazzi *in litt*). Our study did not show evidence of this. The positivity rate was higher for second slides than for first slides, which is not consistent with patients commonly bringing sputum of healthy people. The repeatability of the re-reading was relatively high. This suggests that the reading at the microscopy is not a major problem. In fact, quality of sputum smear examination is possibly higher than previously thought. Piloting interventions to improve the instructions for patients to produce high quality sputum should be considered. Most importantly, sputum smear examination should be prioritised in order to find infectious cases with a cost-efficient measure. The access of the poor and of those living in remote places far away from a TB laboratory could be improved by organising sputum collection at primary care facilities. In Georgia, former TB laboratories with low workload were transformed into sputum collection points and a sputum collection system was put in place. This measure resulted in a substantial rise in the case detection rate. Tajikistan could possibly improve its case detection considerably by similar, simple measures.

Funding agencies and international consultants have often used the coarse rule of thumb that 10% of diagnostic examinations should yield a TB diagnosis as the main or only indicator of the quality of sputum smear examination – irrespective of the setting, globally (Toman 2004, World Health Organisation 2003, Auer 2008). While many have been aware of the limitations of such an approach, there was often no alternative in the absence of the capacity to conduct culture for quality control. The novel approach presented in this study could become such an alternative, whereby the diagnostic accuracy of routine sputum smear examination can be measured in the absence of a gold standard. Advantages of our approach include the reliance on data that are routinely collected and recorded in programs that have a system for EQA.

Moreover, our approach avoids the doubtful assumption that the examination by the NRL would constitute a gold standard for comparison (cf. chapter 10). The additional effort needed to conduct an analysis as presented here is moderate even in places where data of the EQA are not routinely entered in digital format. Where data of the EQA are available in digital format, the efforts are minimal.

11.5. Conclusions

The analytical framework for access to care in contexts of livelihood insecurity, developed in the context of a malaria control program, has proven useful for our studies in the area of TB. Adaptations to make the analytical framework fit better to the context of access to TB care have been suggested. Most importantly, this concerns the way in which we look upon treatment adherence. Adherence was looked upon in the access framework as an outcome of the quality of care. In the area of TB control it seems more appropriate to regard adherence as continued utilisation and thus an outcome of access to care. The theoretical framework used for the study of illness-related costs also proved valuable. The studies conducted in the frame of this thesis identified economic factors as the main barriers to access medical care for TB. Other components of access to care were not found to be equally important. The timing of illness-related costs may further have jeopardised affordability: a high cost peak was encountered by most patients in the intensive phase of treatment.

Several characteristics of health care delivery that are rooted in the Soviet health system contributed to the high costs faced by patients and to the long delays experienced by certain subgroups. The importance of factors related to the Soviet history of health care suggests that many of our findings may also apply to other post-Soviet countries. In order to improve access to TB care and hence TB control in Tajikistan and possibly other countries of the former Soviet Union, the economic burden for the patients must be reduced as a matter of priority. This will require measures on both sides: reducing the costs incurred by patients and increasing their ability to cope with these costs. In order to reduce the costs incurred, reducing the use of additional medication for the treatment of symptoms and (perceived) iatrogenic problems and more strongly advocating and using ambulatory care are the most promising measures. Delays to TB treatment were also associated with higher costs and shortening delays is likely to contribute to reduced costs, too. For those patients for whom additional medication or hospitalisation are medically warranted, medication

should be provided for free and free food of good quality should be provided at the hospital in order to reduce costs. In order to improve the patients' ability to cope with the costs of illness, the distribution of food supplements should be continued and its expansion to other districts should be swiftly completed. The partial implementation of some of these measures has already started at the time of writing.

One aspect of access that contributes to the high costs of illness, but is likely not a direct consequence of problems of affordability is the long delays until treatment that certain subgroups of patients experience. The delays of patients who first present to peripheral primary care facilities or to health care in Russia need to be shortened. This can be achieved by improving the referral systems. An international referral system for Tajik temporary migrant workers who develop active TB in Russia should be implemented to enable them to promptly start treatment. In order to shorten delays for patients presenting first to primary care, a further integration of TB services with general health care is recommended, whereby general practitioners are supported and encouraged to make a diagnosis of TB (based of sputum microscopy) and to start TB themselves. The analysis of the sensitivity of routine sputum microscopy in peripheral laboratories in Tajikistan showed that its sensitivity is reasonably good and that prioritisation of sputum microscopy can be more vigorously pursued.

The analysis of the sensitivity of routine sputum microscopy also suggested that on theoretical grounds a considerable proportion of cases are expected to be found only with the third serial smear. While TB programs globally are struggling to achieve their detection targets, it is therefore not recommended that the debated policy change from three to two serial smears for diagnosis be implemented now. Rather, measures to enable laboratories to carry out three smear examinations with high quality should be developed and tested. This could increase the yield from third serial smears closer to the theoretical maximum and could improve case detection in many settings worldwide.

This thesis investigated determinants of access to care and household costs and it is very much hoped that its results will contribute to improved TB control and to a reduction of the risk of impoverishment associated with it – in Tajikistan and elsewhere. While several areas of priority for action were identified and while it was attempted to formulate these clearly, we should not forget that access to care is a complex issue and that its components are interlinked. Making TB control work will

require many more efforts, strong leadership, commitment and certainly also many measures that go beyond the ones studied in this thesis!

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12. Appendix

12.1. Discussion Guidelines for Focus Group Discussions

12.1.1. Discussion Guidelines – Population

CULTURAL ASPECTS OF TB AND APPROPRIATE CARE FOR TB

1 WELCOME AND INTRODUCTION

For the moment, on no account mention the word tuberculosis!
Pass the following information
• very happy that you came here and give us your time
• we want you to feel comfortable here, please feel free to tell us if you do not feel at ease
• research team from project Sino, independent from MoH, independent from Republican health institutions
• project Sino works in four rayons V, D, Sh, T, on strengthening of PHC, on all levels: from policy-making, together with general practitioners, on access to care for the population, and also in health promotion
• would like to learn from you, your personal opinions and experience
• what you say here is confidential, we will not tell anybody, who said what
• we would like to talk with you about respiratory diseases
• happy about any input, there is no "right" or "wrong" statements, there are no stupid answers
• your personal opinion counts and we would like to reconfirm that we are going to treat it confidentially
• before we start introducing ourselves personally, if you have suggestions, remarks or questions you are welcome to tell us now
Ask permission to record on tape. If participants unsure, discuss issues. Switch on tape.
"Let's get acquainted to one another." Introduce yourself.
"I have been talking very much, now I don't want to monopolize the speech any longer".
Invite participants to introduce themselves one by one.

2 PARTICIPANTS' PERCEPTIONS OF TB
• Please name diseases that have symptoms like the following: strong cough, fever. (Make list of all the diseases and of the respective symptoms, ask for differences in symptoms)

Introduce the word for tuberculosis. Which of the named diseases is tuberculosis?
• Are there other names for this disease in your area? Do these names denote exactly the same or are there small differences?
• Are there diseases in your area that are similar to TB in terms of symptoms?

We would like to concentrate on TB now, and mainly on the pulmonary form.

- What are the causes that make women and men have TB? (List causes named spontaneously. Afterwards: Probe for beliefs that TB were
    - o inherited,
    - o due to misbehaviour [if yes, dwell on issue and find out what kind of misbehaviours],
    - o dependent on sex differences,
    - o due to bad water,
    - o due to wrong food.

Find out whether factors are considered essential or contributing factors.)

- Do people who have it disclose it to others in the village? (Possibly probe for following: "would you want your child to get married to somebody who has had TB previously? Are there people in your area who would not want this?)
- Do you act differently towards somebody who has TB? Do you take precaution measures?
- What should somebody who has TB do about her or his condition? And why should she or he do so?

3 HOW DO PARTICIPANTS PERCEIVE CARE FOR TB? DIAGNOSIS

- What you suggested before, what people with (symptoms of) TB should do: is this what the people in your village actually do?
- Maybe you have heard that the doctors at the RHC ask people with these symptoms (see above) to give one sputum sample each on three different days. Are people able to give that?
- Is there a problem for any particular subgroup (f. i. women)?
- Do some of them rather go to a tabib or a person delivering care other than a doctor or a mid-level health worker? Do you think this will help?
- If we consider somebody who has TB and if we consider that this person should go to the doctor at the RHC: what are the factors preventing that this person actually does go to the RHC?
- Will other people in the village know, if somebody receives care for tuberculosis from the doctor? Is this a problem for them? Would it be a problem for you?

4 HOW DO PARTICIPANTS PERCEIVE CARE FOR TB? TREATMENT

- The doctors suggest that people with TB make a treatment for six months – Are the patients in your area very convinced to do so?
- If people do the six-month treatment, do you think they will get cured?
- Can people in your village do this?
- Are there some people who are not able to take this six-month treatment? Who are these people and why are they unable to take this treatment?
- Which of these factors are the most important ones? (Participatory Approach)

12.1.2. Discussion Guidelines – Patients

BARRIERS AND ENABLERS TO ACCESS CARE FOR TB

1 WELCOME AND INTRODUCTION

Pass the following information
- very happy that you came here and give us your time
- we want you to feel comfortable here, please feel free to tell us if you do not feel at ease
- research team from project Sino, independent from MoH, independent from Republican health institutions
- project Sino works in four rayons V, D, Sh (TB only), T (TB only), on strengthening of PHC, on all levels: from policy-making, together with general practitioners, on access to care for the population, and also in health promotion; it includes a TB component
- would like to learn from you, your personal opinions and experience
- talk about TB
- happy about any input, there is no "right" or "wrong" statements, there are no stupid answers
- your personal opinion counts and we would like to reconfirm that we are going to treat it confidentially
- before we start introducing ourselves personally, if you have suggestions, remarks or questions you are welcome to tell us now

Ask permission to record on tape. If participants unsure, discuss issues. Switch on tape.

"Let's get acquainted to one another." Introduce yourself.

"I have been talking very much, now I don't want to monopolize the speech any longer".

Invite participants to introduce themselves one by one.

2 INITIAL CONTACT WITH HEALTH SYSTEM AND EXPERIENCE WITH DIAGNOSTIC PROCEDURE

- Please tell us, which symptoms you had. Which of these symptoms was the most important one that made you decide to go and seek health care?
- Please try to remember in detail the sequence of events until you were diagnosed with TB:
  - whom you asked for help to improve your health (family members, tabib, MedDom, RHC [SUB/SVA], etc.),
  - when and how your diagnosis was made,
  - where you had to travel,
  - whether you had to provide a sputum sample,
  - whether an x-ray was made,
  - when and by whom you were told your diagnosis.
- Was it difficult for you to receive diagnosis for TB? What were the factors that made it difficult for you to go to the doctor/to diagnostic services? (Make a list of factors named spontaneously. Afterwards: Probe for
  - lack of confidentiality of services,
  - neighbours potentially finding out about their disease,
  - unfriendly attitude of health workers,
  - low quality of services,
  - distance to services)

For those who underwent sputum smear microscopy:
- Did you have difficulties providing a sputum sample? Did it hurt in your throat? Did you feel uneasy to produce sputum? Would there be a difference between men

and women in this respect?
- Did you believe that microscopy examination of your sputum would give a good diagnosis?
- Did you have to travel for the sputum delivery? Did you have to pay for transport? How much?
- As you may know, due to their very low salary, doctors have started asking money from patients. Although most people know that this happens, we have very little knowledge about the amounts paid. It is very important that we understand, for which services how much money is paid to find solutions for this problem. In here, we can talk about everything and we will never tell anybody who has made which statement within this FGD. I would therefore like to invite you to tell, whether you had to pay money for the sputum test (encourage each participant to comment on this question)
- How much did you pay? Or did you make any gifts?
- Did you want to give something, or did you feel that you had to?
- Did you pay for the X-ray if you had any (encourage each participant with X-ray to comment). How much was paid for X-ray? Compare this to the sputum smear examination.
- Let us consider the time from the onset of your symptoms until you knew your diagnosis from a doctor. Can we make a complete list of all the expenditures that you had, including transport costs, gifts you have given in return for something, etc. etc.? (create a table with line-items and amount of money spent on, encourage discussion and consolidation of indicated amount)
- Have you been working at the time when your symptoms started? Did you continue working or have you had to reduce or to stop? How did this affect your income?
- We have now been talking about your expenditures for a while. Now, please think back and consider all other factors as well. What were the most important factors?
(Let the discussion run for a while. Then use the list of factors hindering access to health care, add time constraints, missed income, transportation costs, and payment for health services. In confidential participatory approach, rank them by importance).

3 HOW DO PARTICIPANTS PERCEIVE CARE FOR TB?
You are now on treatment. We would be very interested to learn about your experience with the treatment, about your personal view of the treatment. "Wrong" or "right" answers do not exist here. Your personal opinion counts and differences between personal opinions can be accepted.
- How convinced are you to do this treatment for such a long time? Do you sometimes think that you are already cured and you do not need it anymore? Or are you afraid that it anyway wouldn't help?
- Except for the conviction with which you do this treatment, are there any factors that make it difficult for you to continue treatment? Please also mention factors that made it difficult at some stage of the treatment or that you feel may make it difficult for you to continue treatment in the future. (Make list of factors mentioned spontaneously. Afterwards: Probe for
    o lack of confidentiality of services,
    o neighbours potentially finding out about their disease,
    o unfriendly attitude of health workers,
    o low quality of services,

> o distance to travel to take treatment,
> o being obliged to stay in hospital,
> o side effects of drugs).

- Can we again try to make a list of all the expenditures that you had during your treatment until now? (Make table with line-items and amounts indicated by participants for each line-item, encourage participants to discuss and consolidate the amount listed)
- We have now been talking about your expenditures for a while. Now, please think back and consider all other factors as well. What were the factors that mostly affected your ability to receive treatment? (Let the discussion run for a while. Then use the list of factors hindering access to health care, add time constraints, missed income, transportation costs, and payment for health services. In confidential participatory approach, rank them by importance).
- How do the food contributions affect your ability to receive treatment?

12.1.3. Discussion Guidelines – Providers

ASPECTS OF DOTS PROGRAMME AS BARRIERS AND ENABLERS TO ADHERE TO CARE FOR TB

1 WELCOME AND INTRODUCTION

Pass the following information
- very happy that you came here and give us your time
- we want you to feel comfortable here, please feel free to tell us if you do not feel at ease
- research team from project Sino, independent from MoH, independent from Republican health institutions
- project Sino works in four rayons V, D, Sh (TB only), T (TB only), on strengthening of PHC, on all levels: from policy-making, together with general practitioners, on access to care for the population, and also in health promotion; it includes a TB component
- would like to learn from you, your personal opinions and experience
- talk about TB, factors that influence the way you are able to provide services for patients
- happy about any input, there is no "right" or "wrong" statements, there are no stupid answers
- your personal opinion counts and we would like to reconfirm that we are going to treat it confidentially
- before we start introducing ourselves personally, if you have suggestions, remarks or questions you are welcome to tell us now

Ask permission to record on tape. If participants unsure, discuss issues. Switch on tape.
"Let's get acquainted to one another." Introduce yourself.
"I have been talking very much, now I don't want to monopolize the speech any longer".
Invite participants to introduce themselves one by one.

2 HOW DO PARTICIPANTS PERCEIVE THE DIAGNOSTIC PROCEDURE

• Please tell us about the symptoms that trigger patients to come to you and about the symptoms that make you suspect TB.

• How do you proceed with TB suspects? What are all the measures that you take?

• How do you feel about this procedure? Are you convinced? Does it work? Are there difficulties?

• How does the communication between PHC and the TB services work?

• Do you prefer sputum smear or Chest X-Ray?

• Once the test is made (sputum smear or CXR), how does the information come back from the TB services to PHC?

• Do patients experience difficulties with this procedure? Do you have any ideas, what the reasons are that patients do not come to seek health care and do not get diagnosed? (Make a list of factors named spontaneously. Afterwards: Probe for
  o lack of confidentiality of services,
  o neighbours potentially finding out about their disease,
  o distance to services)

3 HOW DO PARTICIPANTS PERCEIVE TREATMENT FOR TB?

• How is treatment usually given to TB patients in your area? (in-patient or out-patient, do all DOTS patients have to be under DOT, where does DOT take place, which drugs are given)

• Does this procedure work well? Do you think it should be adapted?

• How do you feel about the workload it puts on you?

• Can you think about aspects of the programme that make it difficult for the patients to receive treatment? (Make a list of factors named spontaneously. Afterwards: Probe for
  o lack of confidentiality of services,
  o neighbours potentially finding out about their disease,
  o distance to services)

The MoH had started the implementation of the Basic Benefit Package. The implementation has been stopped, but the most important change was that some services would have to be paid for. It is clear, that resources are lacking in the health sector. Some services simply cannot be offered for free anymore. How is that with services that TB patients consume?