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**Strategies to detect and treat concurrent tuberculosis and
diabetes mellitus in Indonesia, Peru and Romania:
Costs, operational feasibility and impact on health-
related quality of life**

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Abstract

There is an established link between tuberculosis (TB) and diabetes mellitus (DM); active TB is two to three times more likely to develop in people with DM and TB outcomes are worsened in people with concurrent disease. The aim of this PhD thesis is to assess the costs, operational feasibility and health-related quality of life impact of alternative screening and management strategies for patients with concurrent TB and DM (TB-DM) in Indonesia, Peru and Romania. In these three countries with an increasing prevalence of DM and high country burdens of TB, this evidence is essential for establishing cost-effective and feasible diagnostic guidelines and treatment protocols.

Primary data were obtained from a cross-sectional study where patients underwent bi-directional screening for TB-DM in Indonesia, Peru and Romania. However, since the overall study evolved differently in the three countries, analyses in the thesis are not always for all three countries. Indonesia is for instance the only country where patients with TB-DM were recruited to a randomised controlled trial (RCT) that compared standard DM care to intensive DM monitoring with education and counselling over six months. All patients in the RCT were monitored for TB and DM outcomes over the subsequent 12 months.

In Indonesia and Romania, the cost per accurate diagnosis for various algorithms was lower when screening people with TB for DM compared to screening people with DM for TB. The testing algorithm with the lowest cost per accurate diagnosis was age and point of care random plasma glucose in Indonesia (US\$ 1.49) and Romania (US\$ 5.64). From the perspective of health care workers, the barriers, opportunities and the most favourable test characteristics for implementing each test into routine practice were identified in Indonesia and Peru, with POC HbA_{1c} being the most operationally feasible. Preliminary findings from the RCT in Indonesia illustrate that patients with TB-DM in the intensive monitoring arm reported a better HRQoL, but incurred 2.5 times more costs (out of pocket payments and productivity losses) than those in the standard care arm.

This comparative analysis is the first to assess and combine the costs, accuracy and feasibility of implementing bi-directional diagnostic testing, as well as patient treatment costs and health-related quality of life of concurrent TB-DM across several countries. It provides novel information needed for the cost-effective delivery of services for TB-DM, an emerging syndemic with an increasing burden in low- and middle-income countries.

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
CE	Cost-effectiveness
CHOICE	CHO osing Interventions that are Cost-Effective
CI	Confidence interval
CXR	Chest radiography or chest x-ray
CVD	Cardiovascular disease
DM	Diabetes mellitus
DOTS	Directly observed treatment, short-course
DS-TB	Drug-susceptible tuberculosis
EE	Economic evaluation
EURO	WHO European Regional Office
FBG	Fasting blood glucose
FN	False negative
FP	False positive
GDP	Gross domestic product
GNI	Gross national income
HbA _{1c}	Glycated haemoglobin
HCW	Health care worker
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IGRA	Interferon gamma release assay
IDF	International Diabetes Federation
LMIC	Low- and middle-income countries
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
MoH	Ministry of Health
NCD	Non-communicable disease

NTP	National Tuberculosis Programme
PAHO	Pan American Health Organization, Regional Office for the Americas of the World Health Organization
PCA	Principal component analysis
POC	Point of care
Puskesmas	Community Health Centre (Pusat Kesehatan Masyarakat) in Indonesia
RCT	Randomised controlled trial
RPG	Random plasma glucose
SES	Socio-economic status
TANDEM	Concurrent T uberculosis and D iabetes M ellitus
TB	Tuberculosis
TB-DM	Concurrent TB-DM
The Union	The Union Against Tuberculosis and Lung Disease
TN	True negative
TP	True positive
TST	Tuberculin skin test
UHC	Universal health coverage
WDF	World Diabetes Foundation
WHO	World Health Organization

Useful terminology

Active tuberculosis	The disease that occurs when infected with <i>Mycobacterium tuberculosis</i> , characterised by signs or symptoms of active disease. Distinct from latent tuberculosis infection, which occurs without signs or symptoms of active disease. It is curable and preventable.
Clinician	Staff member with medical training (doctor or nurse), working in health facility clinics, hospital wards or other area where they interact directly with patients
Diagnostic accuracy	An assessment of the association between the test result and the disease status of the patient, using sensitivity and specificity measures in this thesis, to create an estimation of the post-test probability of a disease (prediction) (Eusebi, 2013).
Diabetes management	For type 2 DM, this is a comprehensive approach to correcting, as far as possible, insulin resistance through modifications in diet and exercise. In the long-term, oral antidiabetic drugs and/or insulin may also be required. DM management also aims to prevent or treat complications from the disease or prevent the need for treatment of the disease.
High burden country	Within the context of TB, there are three lists of high burden countries (HBCs), each comprising 30 countries: TB, TB/HIV and MDR-TB. These were redefined in 2015 by a WHO document and are meant to be used from 2016 to 2020.

	<p>HBCs are defined as the countries with the top 20 absolute number of cases plus 10 additional countries, not already in the top 20 list, with the most severe burden (cases per capita) that meet the minimum threshold of absolute number of cases (i.e. 10,000 per year for TB and 1,000 per year for TB/HIV and MDR-TB) (WHO, 2015f).</p>
Hyperglycaemia	<p>Occurs when the blood glucose levels are elevated (IDF, 2011).</p>
Latent tuberculosis	<p>Also called latent tuberculosis infection; defines when a person is infected with the <i>Mycobacterium tuberculosis</i> but does not have any clinical manifestations of active tuberculosis.</p>
DOTS TB treatment	<p>World Health Organization recommended tuberculosis (TB) control strategy for TB cases with a positive sputum smear. DOTS ensures that patients can be cured of active TB and stop being infectious. It entails six months of chemotherapy (anti-TB drugs) administered under direct and supportive observation. It is split into:</p> <ol style="list-style-type: none">1. Intensive phase: months 1 to 2, and2. Continuation phase: months 3 to 6
Sensitivity	<p>Proportion of true positive samples with the disease in a total group of samples reported to have the disease: $TP/(TP+FN)$. Probability of getting a positive test result in a person with the disease (Eusebi, 2013).</p>
Specificity	<p>Proportion of samples without the disease with a negative test result in a total group of samples without the disease:</p>

TN/(TN+FP). Probability of getting a negative test result in a healthy person (Eusebi, 2013).

Type 1 DM

Type 1 diabetes mellitus is usually caused by an auto-immune reaction where the body's defence system attacks the cells that produce insulin in the pancreas (IDF, 2011). Previously called juvenile-onset diabetes.

Type 2 DM

Type 2 diabetes mellitus is characterised by insulin resistance and relative insulin deficiency (IDF, 2011). Previously known as non-insulin dependent or adult-onset diabetes.

Preface

This 'paper-style' thesis has one systematic literature review and three results chapters that are written as independent manuscripts but they are related to the common theme of assessing diagnostics and treatment for TB and DM. I have included preambles and linking material where necessary to make the thesis flow as well as possible. Given this format there is an avoidable degree of repetition between the research papers and the traditional thesis chapters, particularly with respect to the content of the background, some methods sections and acronym definitions.

Additionally, because there are four research papers which have been prepared to conform with the style of different journals, the heading and section styles vary within the thesis. I tried to merge the styles as smoothly as possible but apologise for any incongruity.

PART I - INTRODUCTION

This PhD aims to assess the strategies used to detect and treat people with concurrent Tuberculosis (TB) and Diabetes Mellitus (DM) in Indonesia, Peru and Romania. Since the two diseases are traditionally managed in separate vertical programmes, co-management requires integration of one into the other or some other health system collaboration. The thesis explores several aspects of this process from the perspectives of health care providers and patients, including costs, operational feasibility of implementation and patient quality of life.

Structure of the thesis

This thesis consists of 13 chapters divided into four parts: introduction, methods, results and discussion. The introduction contains a background chapter, which provides the context for the PhD by providing epidemiological information on the two diseases and how they relate. The PhD aims, objectives and conceptual framework were also presented here. Chapter 2 contains literature reviews of costs and cost-effectiveness studies of diagnosis and treatment of TB.

Part 2, the methods, describes the study settings and the health systems in Indonesia, Peru and Romania in chapter 3. The TANDEM study protocols and sampling for screening and treatment of concurrent TB and DM are explained in chapter 4. Chapter 5 presents an overview of all of the data collection and analysis methods used in the PhD, which are described in further detail in the results chapters or research papers that contribute to this thesis.

Part 3 contains the results of the various analyses performed, which are presented as three traditional chapters and three research papers. Though the poverty indices were not a PhD objective, the results of that analysis are included in chapter 6, as they were not fully explained in any of the research papers. Chapter 7 is the paper outlining How to do (or not to do) a micro-costing study, which was the methods used to obtain unit costs for

the TB and DM diagnostic tests. Chapter 8 presents the results of the micro-costing studies performed and assesses the costs of accurate diagnosis for TB and DM screening and diagnostic tests included in the TANDEM project. The operational feasibility of implementing the DM and TB screening and diagnostic tests from the perspective of the health care workers are presented in Chapter 9. Health-related quality of life of TB and DM patients at baseline and 6 months is the focus of Chapter 10, with the patient costs of diagnosis and treatment of concurrent disease in Chapter 11.

The discussion in part 4 includes the thesis discussion in Chapter 12. The discussion includes a summary of the research findings presented in the chapters and papers of part 3, as well as a reflection on the analyses and how the cost, feasibility and health-related quality of life results relate to those of similar interventions for TB and DM. This chapter also reflects on how this PhD has contributed to the field of research and explores the implications of the findings for policy formation and how these can inform future research. Limitations are acknowledged in this chapter. The final chapter (13) is the conclusion of the thesis.

Chapter 1 Background

This chapter provides the context in which the research was performed for the diseases and the settings, in addition to highlighting my specific contributions to the limited body of evidence on the understanding of concurrent TB and DM and informs an integrated approach for TB and DM services.

1.1 Prevalence, diagnosis and treatment of tuberculosis (TB)

It is estimated that between a quarter and a third of the world's seven billion people are infected with the tuberculosis (TB) bacterium, called *Mycobacterium tuberculosis (Mtb)*, and therefore have latent TB infection (LTBI) (Houben and Dodd, 2016, WHO, 2016a). An individual infected with *Mtb* has a 10% lifetime risk of becoming ill with TB disease (WHO, 2013d). In 2015, 6.1 million of the 10.4 million estimated cases of active TB were notified to National TB Programmes (NTPs), which reported these to the World Health Organization (WHO). In the same year, there were 1.4 million TB deaths, making TB one of the top ten leading causes of death globally, surpassing the human immunodeficiency virus (HIV) (WHO, 2016a). As one of the main co-morbidities of TB, HIV has prolonged the TB pandemic (WHO, 2012).

Three revised lists of high burden countries for TB, TB/HIV and MDR-TB, each containing 30 countries, were published by the WHO in 2015 (WHO, 2015f). The TB list is defined as the top 20 countries with the highest absolute number of TB cases and 10 additional countries with the highest rate per capita that were not already included in the top 20 countries, provided they have a minimum threshold of at least 10,000 cases per year.

TB most commonly affects the lungs, which is called pulmonary tuberculosis (PTB). TB can in fact affect all parts of the human body and TB in any part of the body other than the lungs is called extrapulmonary TB. PTB spreads through the air when people who have TB disease exhale *Mtb*. This typically occurs when coughing. There is less evidence on the

veracity of infectiousness when sneezing, singing or speaking (Turner and Bothamley, 2014). The focus in this thesis will be LTBI and PTB.

LTBI is diagnosed by the tuberculin skin test and more recently by the interferon gamma release assay (IGRA) blood test. The IGRA test can detect both LTBI and TB disease, but cannot distinguish between them and is therefore only recommended for the diagnosis of LTBI. PTB is most often diagnosed by sputum smear microscopy (in resource constrained settings) or sputum culture (in settings with fully developed laboratory capacity), which is the gold standard. Chest x-ray (CXR) is also a commonly used tool for identifying PTB, but has limitations due to reliance on film quality and interpretation by the reader, which often results in low specificity where non-TB abnormalities on lungs are difficult to distinguish from TB (van Cleeff et al., 2005). Since 2011 the WHO has endorsed the Xpert® MTB/RIF assay for national adoption as the initial diagnostic test for adults and children in settings with a high drug-resistant or HIV-associated TB burden (WHO, 2013a). A sputum sample is used to test for TB disease and drug-susceptibility for rifampicin only (the key first-line anti-TB drug); the test does not need to be performed by trained laboratory personnel, it does not require advanced biosafety equipment and results are available within two hours (Lawn et al., 2013). However, Xpert® MTB/RIF requires sophisticated equipment that needs frequent calibration and maintenance, a connection to a computer, a continuous electricity supply and air conditioning.

In order to achieve the WHO Strategy of ending the global TB epidemic by 2035, new or improved, rapid, accurate and affordable diagnostic tools need to be more accessible, particularly for universal drug-susceptibility testing, high-risk groups, including people with HIV or diabetes and vulnerable populations, such as children (WHO, 2015a, Abubakar et al., 2016, Lienhardt et al., 2016). Another obstacle to the elimination of TB is drug-resistance, which occurs due to either poor adherence to the six month, first-line anti-tuberculosis medication regimen or contracting a drug-resistant *Mtb* strain.

Drug susceptible (DS) TB is relatively cheap to treat, particularly in comparison to multidrug-resistant tuberculosis (MDR-TB). However, the global incidence (1990: 149 per

100,000; 2014: 133 per 100,000) is not decreasing as quickly as had been predicted with the introduction of the directly observed treatment, short-course (DOTS) by the World Health Organization (WHO) in 1993 (Dye et al., 2011, WHO, 2015b). DOTS for DS-TB traditionally lasts six months and comprises two phases: intensive and continuation. The intensive phase lasts two months, where patients take daily dosages of four first line anti-TB drugs (Isoniazid (I), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E)). The continuation phase lasts four months with a reduced drug regimen of two anti-TB drugs (I and R). Both phases need a consistent level of support and supervision by health care workers as well as family, friends and/or members of the patient's community. Of the 9.6 million cases of TB in 2014, 5% (480,000) were estimated to have had MDR-TB, which is defined as resistance to at least rifampicin and isoniazid, the two core first-line anti-TB drugs (WHO, 2015c). There is variability in the format of observed treatment for MDR-TB. The average length is approximately 20 months, with the first eight months constituting the intensive phase, and diversity in the combination of first-, second- and third-line anti-TB drugs that are prescribed (WHO, 2014a).

There is currently no vaccine available to prevent active TB in adults, but there are several in the development stages, with one candidate having completed phase III (Mendez-Samperio, 2016). The focus of TB vaccine development is either prevention of infection or halting progression of the disease in people already infected. Options for alternative immunological approaches are also being discussed (Lienhardt et al., 2016, Abubakar et al., 2016).

In 2015, 94% of all TB cases occurred in low- and middle-income countries (LMICs) and Asia had the greatest proportion (61%) of incident TB cases globally. (WHO, 2016a, WHO, 2012).

The budgeted cost to control TB in LMICs for 2015 was US\$ 8 billion, of which DS-TB detection and treatment accounted for 67% (US\$ 5.3 billion). The 2014 cost per patient to detect and treat DS-TB was estimated to be between US\$100 and US\$500, but there is large variation in costs between countries in different income groups (WHO, 2015b). The

majority (approximately 75%) of TB cases are in people between the ages of 15 and 54, which are the most productive years of life and this further impacts the economic and social burden that the disease places on a society (The Union and WDF, 2014).

1.2 Prevalence, diagnosis and treatment of diabetes mellitus (DM)

The prevalence of diabetes mellitus (DM) has doubled over the last 30 years in both high-income countries (HICs) and LMICs (Basu et al., 2013). It is estimated that there are currently 415 million people with DM (9% of all adults) and three out of four live in LMICs (IDF, 2015, Kapur et al., 2016). DM is estimated to directly cause 1.5 million deaths annually, but this rises to 5.0 million when complications due to DM are included (IDF, 2015).

DM is a chronic, metabolic disease that weakens the immune system. There are three main types of diabetes: type 1, type 2 and gestational, which are all characterised by elevated blood glucose levels, called hyperglycaemia. While there are several other types of diabetes due to factors such as genetic mutations, damage to the pancreas or complications from other diseases, these are estimated to constitute less than 1% of all diabetes (IDF, 2015).

Type 1 DM (T1DM) occurs if the body cannot produce the insulin hormone it requires for transporting glucose from the blood to body cells where it is turned into energy. T1DM most often presents in children and young adults who must then go on lifelong insulin injections and it is not preventable.

Type 2 DM (T2DM) occurs due to a combination of factors: increased insulin demands when the body becomes resistant to the insulin it produces, which ultimately leads to insufficient insulin levels in the blood, and inability of the pancreas to produce enough insulin to meet the increased metabolic demands (relative beta cell failure) (Kasuga, 2006). Traditionally, T2DM was considered a disease of adulthood, but more sedentary lifestyles and poorer diet compositions in populations across the world have caused a noticeable increase in the diagnosis of T2DM in children and adolescents. The main risk

factors for T2DM are obesity and being overweight. The risk of developing T2DM can be substantially reduced by regular physical activity and a healthy diet. T2DM can also be reversed, partially by loss of body weight.

Gestational DM is any hyperglycaemia detected for the first time during pregnancy. The symptoms of increased thirst and frequent urination can present as normal pregnancy symptoms and a laboratory test is therefore needed to diagnose gestational DM.

There are common symptoms for T1 and T2 DM, but they often present more suddenly in T1DM. Upon diagnosis, the type of DM is often not reported, so the exact burden of each type is not clear. However, prevalence studies in high-income countries (HIC) estimate that approximately 87-91% of all DM is T2, 7-12% are T1 and the remaining types of DM account for 1-3% (IDF, 2015). This thesis will deal solely with T2DM.

The 2006 World Health Organization (WHO) and International Diabetes Federation (IDF) diagnostic criteria for DM is the reference point used globally, and are based on two tests: the fasting plasma glucose (≥ 7.0 mmol/l) and 2-hour plasma glucose (≥ 11.1 mmol/l) (WHO, 2006). Updated recommendations to complement the diagnostic criteria for DM have been made and include the use of the laboratory glycated haemoglobin (HbA_{1c}) test ($\geq 6.5\%$), but context specific factors, such as structural capacity (for quality assurance and compliance with international standardisation criteria for assays) and demographic profile (particularly ethnicity and age) must be considered when using this test (WHO, 2011b, Shepard et al., 2015).

The prescribed method of managing DM is behavioural change, including healthy diet, regular physical activity, maintaining body weight and avoiding tobacco use. The structural changes needed to facilitate this on a societal level are challenging but oral drugs and injectable insulin are second and third line measures that are instrumental in patients with DM living productive lives

A major concern with DM is the wide range of co-morbidities, classified as macrovascular or microvascular. Macrovascular diseases affect the heart and large blood vessels,

including angina, myocardial infarction, heart failure, stroke and others, while microvascular complications arise from damage to smaller blood vessels and are more localised, including retinopathy, nephropathy, neuropathy, foot ulcers and many more (Williams et al., 2002).

In 2015, treating DM and preventing complications were estimated to cost between US\$ 673 billion and US\$ 1,197 billion globally. The average annual cost per patient to treat and manage DM are estimated to range between US\$ 1,622 and US\$ 2,886 in various settings (IDF, 2015). This mean cost per patient again varies by GNI per capita. Out-of-pocket costs for people with DM are substantial and often impact the entire household, as management of DM is not episodic, but lifelong.

1.3 Concurrent TB and DM

The understanding of the link between TB and DM has a long history, documented as early as 800 AD, when TB was known as “consumption” (phthisis in Greek), and thought to complicate DM (Morton, 1694). TB has interactions with several infectious and non-infectious diseases, but TB-DM is of particular concern because the interaction between the two diseases increases the vulnerability of individuals and can also maintain the TB epidemic within a population (Lin et al., 2012). The risk of TB infection is increased approximately three-fold if an individual has DM, due to depressed immunity and greater susceptibility to infection. Moreover, they may have worsened TB treatment outcomes. Patients with TB have also been shown to be at increased risk of DM because they have chronic stimulation of the inflammatory system, which ultimately decreases insulin production, thus increasing the risk of DM (Young et al., 2009).

The immunological, genetic, pharmacokinetic and economic interactions between TB and DM are not yet well understood, and comprehensive treatment protocols and policies for the double burden of disease have therefore not yet been developed. There are currently no international guidelines for management and care of concurrent TB-DM. In 2011 the International Union Against Tuberculosis and Lung Disease (The Union) and the WHO

produced a Collaborative Framework that identified gaps in current knowledge and sought to guide countries and communities in the process of developing treatment protocols (The Union and WHO, 2011).

In order to increase efficiency of the management and control of TB, it is important to recognise that the disease in many ways has more in common with non-communicable diseases (NCDs) than acute infectious diseases. This is because patients with TB are often dealing with long-term treatment adherence issues, they are monitored within primary health care settings, and lifestyle changes during treatment are needed for it to be successful (Marais et al., 2013). The best approach to address concurrent TB-DM is thus to more creatively manage these infectious and non-infectious diseases together (Marais et al., 2013). TB and DM share similar challenges and they collectively accounted for over 6.5 million deaths in 2014 (WHO, 2015b, IDF, 2015). This is especially important in LMICs where the increasing burden of NCDs and a higher incidence of TB means that one disease increases the risk of the other disease (Marais et al., 2013).

Many countries still have vertical, disease specific approaches (such as National TB Programmes (NTPs)), which are unable to exploit the similarities and potentially merge the already established, but distinct infectious disease and NCD control programmes (Marais et al., 2013). However, there is consensus about the need to integrate health services in order to improve service delivery (WHO, 2008).

1.3.1 Epidemiology of concurrent TB-DM

Despite Avicenna's very early recognition around the 11th century that there must be a relationship between TB and DM (Morton, 1694), the association was not fully documented until 1934 when Root reviewed autopsy studies from the late 1800s onwards that looked at people with DM who also had TB. Root (1934) established a link between TB and DM, but without fully understanding the nature of it. In the second half of the 20th century, recognition of the TB-DM association faded due to the successful treatment of DM in the 1920s with insulin and sulfonylureas in the 1950s, and later of TB when effective antibiotics became easily accessible (Restrepo, 2007, White, 1997). In the 21st century

there has however been a resurgence of the recognition of the link between the two diseases due to a global increase in the prevalence of both TB and DM, which are now both classified as pandemics (Restrepo, 2007).

Since the initial analysis by Root (1934) there has been a clear understanding that people with DM are at least two to three times more likely to develop active TB than people without DM. This is driven by demographic factors, namely age (younger) and ethnicity (Jeon and Murray, 2008), but further investigation is needed to understand how ethnic differences modify the association between TB and DM. The susceptibility of patients with DM to TB has only been clearly documented in the last 20 to 30 years. One of the other major challenges within the physiology of concurrent TB-DM is understanding which condition was contracted first (Littleton and Park, 2009).

The prevalence of DM in patients with TB varies according to setting (Marais et al., 2013). Rural China, Peru and Indonesia have recorded an adult prevalence of 10.6%, 11.1% and 14.8%, respectively, while Iran, India and Mexico have reported as high as 23.1%, 25.3% and 35.2%, respectively (Lin et al., 2012, Magee et al., 2013, Alisjahbana et al., 2007, Golsha et al., 2009, Viswanathan et al., 2012, Ponce-de-Leon et al., 2004). This wide variation is thought to be partly attributed to timing of the DM diagnosis, which is more accurate when performed after TB treatment has begun, as untreated TB disease can prompt hyperglycaemia that may be misclassified as DM and result in an over-diagnosis of DM (Jeon et al., 2010).

There is limited data on the prevalence of TB in people with DM, but this is being investigated more and more, particularly in countries that are experiencing an increase in the incidence of TB in the general population. In recent studies, the prevalence of pulmonary TB in people with DM ranges from 1.3% in Tanzania (Mtwangambate et al., 2014) to 6.2% in Ethiopia (Amare et al., 2013), both of which are classified as TB high-burden countries.

The possible physiological mechanisms that drive the TB-DM association are that people with DM are more easily infected with TB than people without DM, and therefore are at higher risk of LTBI. DM also facilitates reactivation of LTBI due to the faster immune system impairment than in people without DM. Moreover, TB contributes to DM through chronic inflammatory effects that predispose people to DM. There are also mutual underlying causations (e.g. renal insufficiency and vitamin A, C and D deficiencies) and certain contributing factors (e.g. smoke exposure). Finally, complications arising due to inappropriate treatment of either disease can result in longer TB infectivity and poorer glucose control (Jeon and Murray, 2008, Stevenson et al., 2007a).

A systematic review on the prevalence TB-DM based on bi-directional screening was published in 2010 by Jeon et al. (2010). They reported that active screening for TB in people with DM was justified due to the high prevalences of TB, which met the established criteria (WHO, 2013c) for implementation of active case finding for TB in high-risk populations such as HIV positive individuals, gold miners and prisoners in LMICs. The prevalence of DM in people with TB had a wide range, with high values found in countries with a high prevalence of DM (Jeon et al., 2010).

1.3.2 Screening, diagnostics, treatment and prevention

Identifying people with concurrent TB-DM is essential. While the absolute numbers of TB cases identified when screening people with DM are often low, this can still be valuable since the case notification rate of TB per screened DM population is often higher than found in the general population (Lin et al., 2012). A potential challenge of TB screening in DM programmes is improperly conducted screens where clinical staff are not accustomed to reading CXRs or assisting patients to produce quality sputum samples for smear and culture tests for TB. Moreover, DM clinicians may be unaware of increased risk of active TB in patients with DM. Additional challenges of screening for TB in DM programmes are under-reporting of positive TB symptom screens due to test imprecisions in people with DM, poor referral and tracing systems, and limited follow-up of people with DM due to health system inadequacies in recording and reporting people with DM (Lin et al., 2012).

Reducing the risk of infection to staff and other patients during sputum collection can be a barrier to implementation, as many DM clinics do not have suitable sputum collection sites (Bantubani et al., 2014).

Screening for DM in people with TB gives a substantially higher yield due to higher DM prevalence in the general population. However, the best screening protocol and diagnosis cut-off values for laboratory and point of care glucose tests are not yet known and is complicated by the fact that DM diagnosis is not binary like for instance HIV (Harries et al., 2011). A limitation found in studies that have screened patients with TB for DM is that TB can cause stress hyperglycaemia, therefore impacting the accurate diagnosis of DM (Faurholt-Jepsen et al., 2013), which can be refined once timing of DM diagnosis is better understood in people with TB.

In people with active TB, DM may negatively affect TB treatment outcomes by delaying the time to microbiological response and thereby increasing the risk of relapse or death (Jiménez-Corona et al., 2013). DM may also interfere with the effectiveness of certain anti-TB medications (Dooley and Chaisson, 2009). Increased risk of treatment failure suggests that DM may also accelerate drug-resistant TB, but the results on this are still inconclusive (Stevenson et al., 2007b). TB may trigger the onset of DM in pre-diabetics and worsen glycaemic control in people with existing DM. Moreover, TB medications may also worsen glycaemic control.

No clear prevention strategies for concurrent TB-DM have yet been proposed and experts in the field stress the importance of further research to inform such guidelines. Given the current knowledge gaps, recommendations are that efforts should continue for preventing the two diseases through their usual mechanisms: isoniazid preventive therapy (IPT) for TB prevention in susceptible people (such as people with HIV or poorly controlled DM) (Harries et al., 2011) and lifestyle modifications for prevention or delay in progression to type 2 diabetes (Alberti et al., 2007).

1.3.3 Collaborative TB-DM Framework and the Bali Declaration

The Collaborative Framework for Care and Control of Tuberculosis and Diabetes (“The Framework”) published by the Union and WHO in 2011 (The Union and WHO, 2011) was the first international guideline for TB and DM that sought to inform decision-makers and clinicians about the disease interactions and how to decrease the joint burden. For The Framework, systematic literature reviews were commissioned to answer key questions surrounding the management and control of TB-DM. This was followed by expert consultations that assessed the review findings and developed the provisional framework and recommendations. The nine recommendations focus on establishing mechanisms for collaboration, improving the detection and management of TB in patients with DM, and improving the detection and management of DM in patients with TB (Table 1-1).

Table 1-1: Recommended collaborative activities in the TB-DM Framework

A. Establish mechanisms for collaboration
A.1. Set up means of coordinating DM and TB activities
A.2. Conduct surveillance of TB disease prevalence among people with DM in medium- and high-TB burden settings
A.3. Conduct surveillance of DM prevalence in TB patients in all countries
A.4. Conduct monitoring and evaluation of collaborative DM and TB activities
B. Detect and manage TB in patients with DM
B.1. Intensify detection of TB among people with DM
B.2. Ensure TB infection control in health-care settings where DM is managed
B.3. Ensure high quality TB treatment and management in people with DM
C. Detect and manage DM in patients with TB
C.1. Screen patients with TB for DM
C.2. Ensure high quality DM management among TB patients

In The Framework it is proposed that process and outcome indicators are developed alongside the activities to facilitate monitoring and operational research on feasibility, effectiveness and cost-effectiveness of all proposed models of collaboration that seek to prevent, diagnose and treat concurrent TB-DM.

The systematic literature reviews conducted for The Framework identified gaps in knowledge that were converted into 11 key research questions with priority rankings of high (n=5), medium (n=5) and low (n=1). The high priority research areas were concerned with (i) screening patients with DM for TB; (ii) screening patients with TB for DM; (iii) TB treatment outcomes in patients with DM; (iv) implementing and evaluating the DOTS model for standardised case management of DM; and (v) development and evaluation of a point of care (POC) glycated haemoglobin (HbA_{1c}) test for TB patients. One of the medium priority research questions was to determine the additional medical costs associated with diagnosis and management of dual disease; this will be assessed in this PhD dissertation.

According to The Framework, the implications of the TB-DM link can be addressed in four key areas: TB prevention, TB screening, TB treatment and post exposure prophylactic TB treatment in people with DM. Since there is linked susceptibility between the two diseases, preventing TB at the population level requires primary and secondary prevention of DM. Additionally, if people with DM are at a higher risk of TB than people without DM, screening for TB in patients with DM may be justified, particularly in populations with a high TB prevalence. Since it is also thought that DM increases the risk of unfavourable TB treatment outcomes, specialised and high-quality TB treatment in people with DM is essential, similar to the management of HIV associated TB. Finally, prophylactic TB treatment may be indicated in people with DM who have recently been exposed to TB.

The Framework highlights that due to lower than expected TB treatment rates and a slower than expected decline in TB prevalence, the ability of health systems to successfully prevent, diagnose and treat concurrent disease is compromised, especially in countries with high or rapidly increasing DM prevalence. Therefore, collaborative activities between TB and DM programmes could not only address the complications of the concurrent diseases, but also strengthen the efforts to address the separate challenges of each disease. A particularly appealing collaborative effort is to use the successes of the TB DOTS model to improve the management of DM by standardising the protocols, which would

require support and supervision of patients during treatment, medication that is supplied through a regulated and consistent mechanism, and political commitment that demands transparent management, monitoring and evaluation of all programmes and activities.

The Bali Declaration came out of the first world summit on TB-DM in Bali, Indonesia in November 2015. The declaration is a signed commitment by world leaders in public health, research, business and technology to advocate for both diseases and to ensure international implementation of The Framework. This is a first step in political commitment and the key solution was to focus on bi-directional screening:

“...where people diagnosed with TB are screened for diabetes, and, in certain contexts, people with diabetes are screened for TB. Getting this done will require closer and more thoughtful collaboration between stakeholders in infectious diseases and non-communicable diseases.” (The Union, 2015b)

1.4 TANDEM project

The project, of which this PhD is part, is called TANDEM: ‘Concurrent **T**uberculosis **a**nd **D**iabetes **M**ellitus; unravelling the causal link and improving care’. TANDEM is funded by the European Commission under the Seventh Framework Programme of the European Union (EU FP7). The study originated as a response to a call for proposals from the EU to research the interaction between an infectious and a non-infectious disease. The TANDEM consortium consists of a multi-disciplinary team of individuals and sites that are investigating the immunological, epidemiological, genetic, pharmacokinetic, operational and health economic components of screening for TB-DM and treating patients with concurrent diseases. The objectives of TANDEM directly address the nine recommended activities in the collaborative TB-DM Framework (Table 1-1).

The study sites are in four TB endemic countries that are experiencing increases in DM prevalence: Indonesia, Peru, Romania and South Africa. These sites are linked to and supported by leading laboratories in four European countries: United Kingdom, Germany, Netherlands and Romania. The project is comprised of 11 organisations and one project management partner based in Germany.

The aims of TANDEM are to generate evidence that will guide future management of concurrent TB-DM and provide insights into the biological nature of the interaction, which could enhance clinical care (van Crevel and Dockrell, 2014a).

The project objectives are divided into four scientific and two administrative “work packages” (WP):

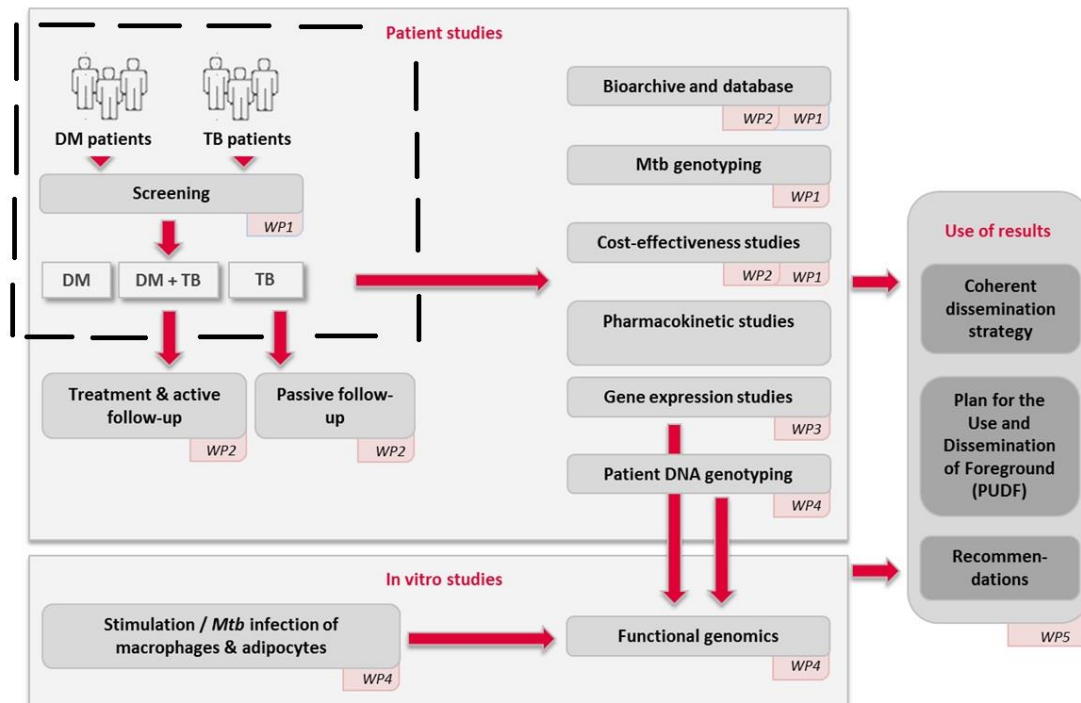
- WP1. To identify feasible, accurate and cost-effective ways of screening patients with TB for DM, and determine the prevalence of DM among patients with TB and of TB in patients with DM in different geographic regions.
- WP2. To determine the level of DM management required during and after TB treatment, and the effect of glucose control on TB treatment outcome.
- WP3. To identify key pathways which may account for enhanced susceptibility to, and poorer treatment outcomes of, TB-DM by comparing gene expression and biomarker profiles in TB patients with, compared to those without, DM.
- WP4. To establish the cellular and molecular basis responsible for the causal link between DM and TB, and in particular to determine the effect of hyperglycaemia and genetic variation on the host protective response to *Mycobacterium tuberculosis (Mtb)*.
- WP5. To ensure coherent dissemination and timely exploitation of project results.
- WP6. To enable a smooth project workflow and provide the necessary support mechanisms to ensure that all contractual commitments are met according to the timeline.

TANDEM was officially launched in February 2013. Recruitment of patients with existing or newly diagnosed DM and patients with newly diagnosed TB (WP1) began in December 2013 and January 2014, respectively (Figure 1-1). Patients were screened for concurrent disease until November 2015 and June 2016, respectively. In order to increase the sample size of the RCT, “targeted” recruitment of patients with TB and DM was initiated in Indonesia in February 2016 and ended in February 2017. Targeted recruitment included enrolling all patients with TB or suspected TB who have any history of DM as well as any patient with TB or suspected TB without a history of DM but 35 years or older and a random capillary blood glucose of more than 110 mg/dL.

Due to capacity issues, only patients in Indonesia and Romania progressed to the intervention in WP2. In WP2 patients with TB who were screened for DM and diagnosed with TB-DM were randomised to two arms of DM management and actively followed-up for 18 months. A practical decision was made to not include people with DM who were screened for TB in WP2 in order to ensure that patients were not double counted and to avoid the data management challenges that would be entailed in correcting this.

The randomised controlled trial (RCT) began in March 2014 in Romania and in April 2014 in Indonesia. The Romania RCT was however discontinued in December 2015 due to discordance between the TANDEM DM management protocol and regulated DM management in Romania, as well as operational obstacles at the participating hospitals and low patient follow-up rates. The RCT in Indonesia is expected to end in July 2017 and follow-up of patients in the RCT 12 months later in July 2018. The RCT is registered at ClinicalTrials.gov (NCT02106039).

Figure 1-1: TANDEM studies and patient flow



Source: TANDEM EU FP7 Proposal
 WP – work package
 DM – diabetes mellitus
 TB – tuberculosis
 Mtb – *Mycobacterium tuberculosis*

1.4.1 Published studies related to TANDEM objectives

Over the last few years, results of several pilot studies with similar objectives to various parts of the TANDEM project have been published. One study from China with results published in two separate papers prospectively assessed the feasibility and disease prevalence from screening people with DM for TB (Lin et al., 2012) and screening patients with TB for DM (Li et al., 2012) during routine service at five DM clinics and six TB clinics/hospitals across China. Newly diagnosed DM was found in 2.9% of patients registered with TB. RCG screening followed by FBG if RBG \geq 6.1 mmol/L and referral to DM clinics for management, if concurrent TB-DM disease was confirmed, was considered to be feasible in routine services. However, improved services could be achieved by offering free diagnostic blood tests and if TB and DM services were integrated. TB was detected in 0.5% of people with DM after TB symptom screen at the DM clinic, followed by sputum smear microscopy and chest radiography at a TB facility. TB screening in DM settings was also considered to be feasible (without stating how this was assessed), but to achieve better performance recommendations were made to add staff to assist with the increased workload and utilise the electronic medical record system to assist with reporting (Lin et al., 2012).

In India, Jali et al. (2013) also reported on the feasibility and results of bi-directional screening for TB and DM in a prospective observational study in routine services. There were 49 (16.0%) newly diagnosed cases of DM in patients with TB and 111 (2.7%) cases of TB in people with DM. The study found that bi-directional screening was feasible (again, without indicating the criteria for determining feasibility) and resulted in high rates of TB detection, earlier and better detection of DM and TB, as well as improved clinical outcomes for anti-TB treatment and DM management.

Lastly, in Mexico, bi-directional screening and joint management of concurrent disease was deemed to be feasible and to improve clinical outcomes in an observational cohort study where people with TB and DM were followed-up for at least 12 months (Castellanos-Joya et al., 2014). The prevalence of TB in people with DM was highest in this setting at

4.9%. DM in patients with TB was 19.4%. Screening and management were demonstrated as feasible, but the recommendation was to implement DM screening in patients with TB rather than the converse since the yield was higher in this scenario. Most impressive was the higher treatment completion rate for joint treatment than for individual treatment programmes. The higher TB prevalence among people with DM than in the general population, suggests that TB transmission may be occurring in the health care setting, which may be due to poor compliance to international guidelines for the prevention of TB transmission in primary healthcare centres and specialised units (Castellanos-Joya et al., 2014).

The studies in China and India only assessed the bi-directional screening, whereas the study in Mexico was most similar to TANDEM in terms of a cross-sectional bi-directional screening and six months of concurrent TB treatment and DM management followed by several months of follow-up. The additional advantage of TANDEM is the randomised comparison of intensive DM management versus standard care.

1.5 Indonesian context

Indonesia is a lower-middle income country in Southeast Asia with a 2015 gross national income (GNI) per capita of US\$ 3,440 and population of 258 million (WB, 2016a). Indonesia is a state comprising approximately 6,000 inhabited (17,504 registered) islands lying between the Indian and Pacific oceans on a total area of 1.9 million square kilometres (Central Bureau of Statistics (Indonesia), 2015) (Figure 1-2).

Figure 1-2: Map of Southeast Asia with Indonesia highlighted



Just over half (54%) of the population live in urban areas of this fourth most populated country in the world (141 people per square kilometre) (WB, 2016b, WHO, 2015g). The official language is *Bahasa Indonesia* and is used in formal settings but many Indonesians speak one or more of the 600 languages, including Javanese and Sundanese (Paauw, 2009).

It is a high burden country for TB, with 395 cases per 100,000 population in 2015, resulting in an estimated 1 million (95% uncertainty interval: 0.7 million – 1.5 million) new cases. Only 330,729 (32%) of these 1 million new PTB cases were notified, 64% of whom were bacteriologically confirmed (WHO, 2016a).

Indonesia had the seventh largest number of adults, aged 20-79 years, with DM in 2015, with an estimate of 10 million (95% uncertainty interval: 8.7 – 10.8 million) cases, representing 6.2% of the adult population, and almost 185,000 deaths (IDF, 2015).

The fourth highest number of adult TB cases associated with DM (48,000) is in Indonesia (Harries et al., 2015), but very little else is known about the TB-DM syndemic in the country.

1.6 Peruvian context

Peru spans a total of 1,285,216 square kilometres on the western coast of South America (Figure 1-3).

Figure 1-3: Map of South America with Peru highlighted



It is bordered by Ecuador and Colombia to the north, the Amazon region of Brazil to the east and Bolivia and a sliver of Chile to the south. The country reported a population of 31 million people in 2015, of which the capital city of Lima, kissed by the South Pacific Ocean mid-way between Ecuador and Chile, is home to 31% (9.9 million) (WB, 2016b). The GNI per capita for that year was US\$ 6,130, classifying it as an upper-middle income country (WB, 2016a).

Spanish is the most commonly spoken language but many Peruvians speak one or more native languages, such as Quechua. The 2015 population density was 25 people per square kilometre, with 79% living in urban areas (UNSD, 2016). The peak elevation is 6,768 metres above sea level at Huascarán. Due to its tropical latitude, topography and ocean currents, Peru has diverse climates along the coast, in the mountainous regions and in the Andean peaks (Weiss, 1954).

Peru had 37,000 (95% uncertainty interval: 29,000 – 47,000) new cases of TB in 2015 at a rate of 119 per 100,000 (WHO, 2016a). WHO reported that 30,988 (84%) of these cases were notified, 81% of whom were PTB, and 82% of PTB were bacteriologically confirmed. The mortality rate for all TB cases was 7.8 per 100,000 population (2,500 deaths) in 2015.

There were an estimated 1.2 million (95% uncertainty interval: 0.9 – 1.9 million) Peruvian aged 20-79 with DM in 2014, producing an adult prevalence of 6.4% (IDF, 2011). DM related deaths were recorded as 7,769; partially due to a high proportion of patients having poor glycaemic control. This has been reported to be around 70% (Huayanay-Espinoza et al., 2016).

1.7 Romanian context

The final country included in this thesis is Romania, an upper-middle income country in southeast Europe with a 2015 GNI per capita of US\$ 9,500 (WB, 2016a). The country covers 238,000 square kilometres and is land locked by five countries except for a 225 km coastline that lies on the Black Sea (Figure 1-4).

Figure 1-4: Map of Europe with Romania highlighted



The population density is 86 people per square kilometre (WB, 2016b). The climate is temperate, with average temperatures ranging from 11 degrees Celsius in the south of the country to -2.5 degrees Celsius in the mountain peaks. The population was 20 million in 2015, of which 55% were estimated to live in urban areas (WB, 2016b). The official and most widely spoken language is Romanian (European Commission, 2009). There was a revolution in 1989 that led to the transformation of Romania from a communist country into a republic that has partially introduced capitalism and market systems, but also continues to maintain platforms for social democracy (Vlădescu et al., 2005). Romania became a member of the European Union in 2007, joining a community of approximately 500 million citizens (European Union, 2016).

There were an estimated 16,000 (95% uncertainty interval: 14,000 – 19,000) new cases of TB in 2015 and a TB incidence rate of 84 per 100,000 (WHO, 2016a). There were a total of 15,195 notified cases, of which 83% were PTB and 81% of PTB were bacteriologically confirmed.

Romania was estimated to have 1.5 million (95% uncertainty interval: 0.9 – 2.3 million) adults with DM in 2014, which accounted for 7% of the population and 10.6% of the adult population; this resulted in approximately 18,900 deaths (IDF, 2015). A study from 2011 reported that 93% of people with DM in Bucharest had T2DM and 7% had T1DM (Donicova et al., 2011). The prevalence of DM complications in new cases is estimated to be 50%, but details about the most common complications are limited (Donicova et al., 2011).

1.8 How this PhD fits into the TANDEM project

Two of the six TANDEM work packages have objectives that are part of this PhD. The PhD addressed the “cost-effectiveness studies” part of WP2 in Figure 1-1. This PhD also assessed the operational feasibility, WP1, of the TB and DM screening tools from the perspective of the health care workers.

The cost per accurate diagnosis and feasibility of bi-directional screening of TB and DM was assessed alongside the cross-sectional study component of the TANDEM project, and

the cost and health-related quality of life comparisons of two different DM management strategies was estimated alongside the longitudinal intervention.

1.9 Aims and objectives

The aim of this PhD is to assess the costs, operational feasibility and health-related quality of life impact of alternative screening and management strategies for patients with concurrent TB and DM in Indonesia, Peru and Romania.

Research question: What are the costs and health-related quality of life outcomes of various screening algorithms and management strategies for TB-DM?

There are five PhD objectives:

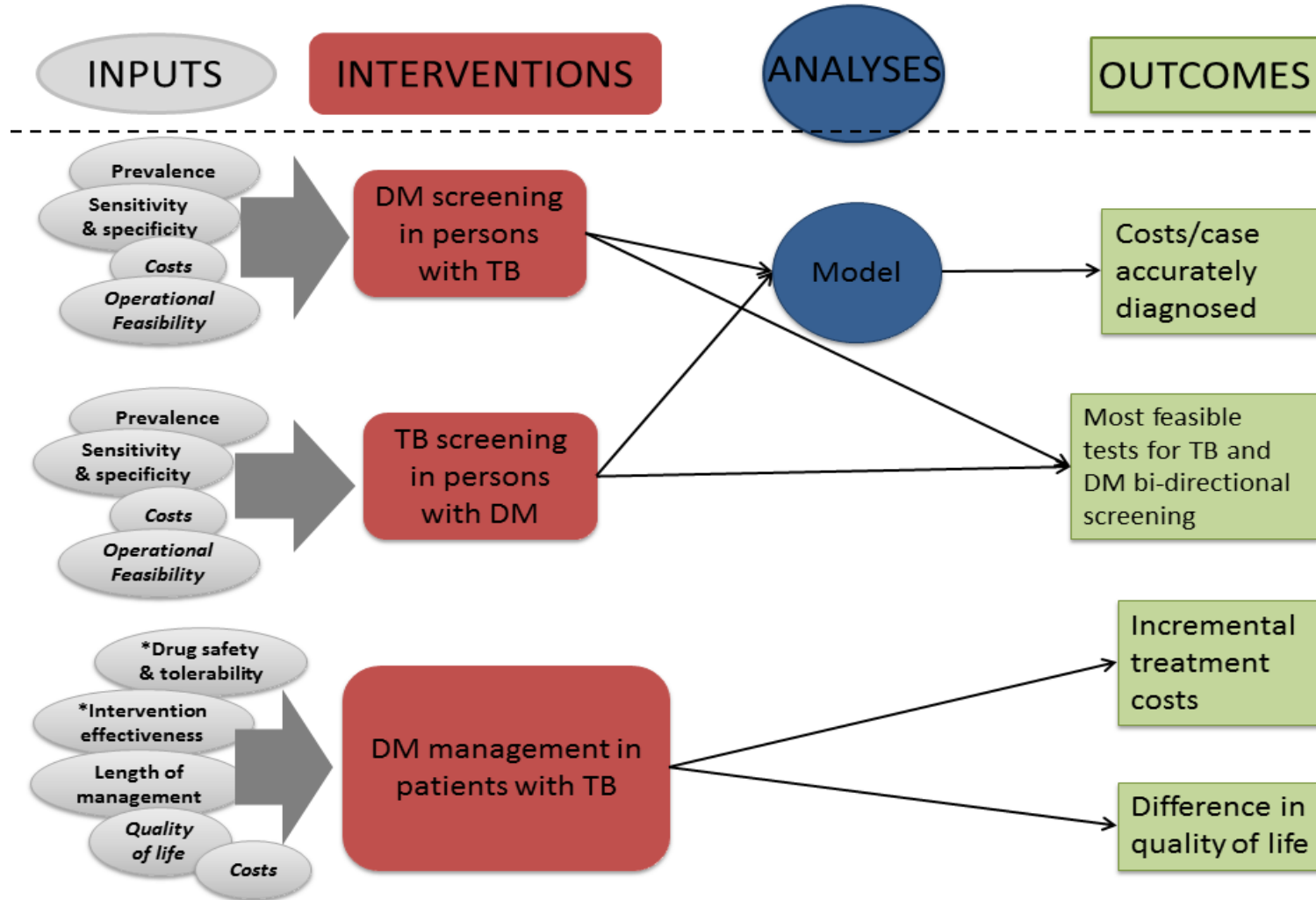
1. To compare the mean cost per accurate diagnosis of DM for four screening and one diagnostic tests in newly diagnosed TB patients when used alone, in various combinations and when used with the gold standard of laboratory glycated haemoglobin (HbA_{1c}) test:
 - i. DM risk score
 - ii. Point of care (POC) Random plasma glucose (RPG) test
 - iii. Urine dipstick
 - iv. POC HbA_{1c} test
 - v. Fasting blood glucose (FBG) test
2. To compare the mean cost per accurate diagnosis of two TB screening methods in existing cohorts of patients with type 2 DM, which will be followed by sputum examination (smear and culture) if irregular results are found:
 - i. TB symptom screen
 - ii. Chest X-ray
3. To evaluate and compare the operational feasibility of various DM screening strategies in people with TB; and various TB screening strategies in people with DM
4. To compare the health-related quality of life of patients with concurrent TB-DM receiving two different clinical management strategies for DM:

- i. Standard care: standard practice at each study site
 - ii. Enhanced intensive monitoring: FBG and clinical review at baseline, 2 weeks, 4 weeks and then monthly until 12 months after TB treatment completion
5. To compare the incremental cost (above TB treatment costs) of patients with concurrent TB-DM receiving two different clinical management strategies for DM:
- i. Standard care: standard practice at each study site
 - ii. Enhanced intensive monitoring: FBG and clinical review at baseline, 2 weeks, 4 weeks and then monthly until 12 months after TB treatment completion

1.10 Conceptual framework

The conceptual framework, Figure 1-5, illustrates the relationship between the various components of the PhD and how the inputs are utilized.

Figure 1-5: Conceptual framework for strategies to detect and treat people with concurrent tuberculosis and diabetes



*Not being considered in thesis because randomised controlled trial is ongoing

1.11 Contribution of the candidate

This PhD was conducted alongside the cross-sectional and longitudinal RCT studies of the TANDEM project. The health economics components of the TANDEM grant application were conceived by Dr Ulla Griffiths. I joined the project after the grant had been awarded by the European Commission, which is when I began to develop the health economics components for implementation under the guidance of Dr Griffiths. Prior to health economic data collection, I secured two additional grants that allowed me to work full-time on the project to co-ordinate the health economics activities and which funded my field work.

For the cross-sectional studies to assess bi-directional screening, I designed and analysed the cost data and undertook the cost data collection of the screening and diagnostic strategies, with some follow-up support for missing bits of data given by TANDEM team members in Indonesia and Romania. I designed and analysed the operational feasibility questionnaires. After piloting in Indonesia and Peru, the questionnaires were refined with additional input from TANDEM members in both countries. I administered the questionnaires in Indonesia, with an interpreter when needed. In Peru, the questionnaires were administered by TANDEM members.

For the RCT data, I again designed and performed the cost analyses. I collected the provider treatment cost data for the intensive monitoring arm, but required substantial help in accessing resource and unit cost data from primary health centres in the standard care arm in Indonesia, for which I designed the data collection tools and then guided the data collection. This was done by a health economics collaborator from Universitas Padjadjaran, Bandung. With input from Dr Griffiths, I designed the patient costs questionnaire. I assessed various options for the quality of life outcome tools and selected the EuroQol EQ-5D-5L questionnaire and visual analogue scale. I analysed the quality of life data for Indonesia, Peru and Romania. I also designed the socio-economic status data collection tools based on the World Bank questionnaires for low- and middle-income countries. I analysed the socio-economic status indices for each country. The patient

costs, quality of life and socio-economic status questionnaires were included in the electronic case report forms and collected by health professionals in each country.

I wrote all of the health economics sections of TANDEM reports and study manuscripts, under the supervision of Dr Griffiths.

Chapter 2 Literature reviews

Two systematic literature reviews were conducted that provided information for this PhD. The objective of this literature review chapter is to assess current research related to costing studies of screening for and treatment of TB. The first systematic literature review on TB treatment costs has already been published (Laurence et al., 2015). The second systematic literature review is on costs of TB diagnostics. I undertook these two reviews as part of projects other than TANDEM, but they are directly related to my thesis objectives. The purpose of the TB treatment cost review was to provide cost inputs for a cost-effectiveness analysis of new TB vaccines (Knight et al., 2014). The systematic review of TB diagnostic costs was part of a modelling exercise to assess the cost-effectiveness and feasibility of implementing the WHO's framework on the global strategy and targets for TB control after 2015 (WHO, 2013b, Menzies et al., 2016). Though I initially planned to publish the diagnostic costs review, a systematic review of TB and HIV prevention, diagnosis, treatment and care is currently being updated by the Bill and Melinda Gates Foundation funded Global Health Cost Consortium (GHCC), with plans to publish the results and make the extracted data freely available in a unit cost repository (GHCC, 2017). As such, I have given my extracted data to GHCC, as well as advise on the selection, extraction and analysis processes and will be included in the publication of the TB diagnostic costs.

Published costs for TB diagnosis and treatment in Indonesia and Romania are extracted and discussed in this chapter. No cost data for Peru are discussed here since no costings were performed in Peru during the TANDEM project.

2.1 TB treatment costs – a global systematic review

Costs to health services and the patient of treating tuberculosis: a systematic literature review

Preamble to Research Paper 1

This aim of Research Paper 1 was to assess the cost of treating drug-susceptible (DS) and multidrug-resistant (MDR) TB, from the perspective of the provider, patient or both. The review identified 71 papers for DS, ten for MDR and nine for DS and MDR-TB. This represented 50 countries with DS-TB costs and 16 with MDR-TB costs.

In addition to providing insight into the treatment cost data available for Indonesia and Romania, conducting the literature review also highlighted the structure of different TB treatment programmes, the methods being used to cost TB services, and approaches to reporting the cost and cost-effectiveness results.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Yoko Laurence
Principal Supervisor	Ulla Griffiths
Thesis Title	Strategies to detect and treat concurrent tuberculosis and diabetes in Indonesia, Peru and Romania: costs, operational feasibility and impact on health-related quality of life

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	Pharmacoeconomics		
When was the work published?	September 2016		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	NA		
Have you retained the copyright for the work?*	Yes	Was the work subject to academic peer review?	Yes

**If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order.	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	See details of author contribution on the next page
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Student Signature: _____ Date: 15/1/2018
 Supervisor Signature: _____ Date: 16/02/2017

Research Paper 1

Costs to health services and the patient of treating tuberculosis: a systematic literature review

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Status: Published in *Pharmacoeconomics*; 2015

Author contribution: I conducted the search, extracted, analysed and interpreted the data. UKG independently extracted some data in order to verify my data extraction. I also produced the first draft of the manuscript, on which the co-authors provided feedback.

Abstract

Background

Novel tuberculosis (TB) drugs and the need to treat drug resistant tuberculosis (DR-TB) are likely to bring about substantial transformations in TB treatment in coming years. An evidence base for cost and cost-effectiveness analyses of these developments is needed.

Objective

To perform a review of papers assessing provider as well as patient incurred costs of treating both drug susceptible (DS) and multidrug-resistant (MDR)-TB.

Methods

Five databases (EMBASE, Medline, National Health Service Economic Evaluation Database, Cost-Effectiveness Analysis Registry, and Latin American and Caribbean Health Services Literature) were searched for cost and economic evaluation full-text papers containing primary DS-TB and MDR-TB treatment cost data published in peer-reviewed journals between January 1990 and February 2015. There were no language restrictions. The search terms were a combination of “tuberculosis”, “multidrug-resistant tuberculosis”, “cost”, and “treatment”. In the selected papers, study methods and characteristics, quality indicators and costs were extracted into summary tables according to pre-defined criteria. Results were analysed according to country income groups and for provider costs, patient costs and productivity losses. All values were converted to 2014 US\$, so that studies could be compared.

Results

We selected 71 treatment cost papers on DS-TB only, 10 papers on MDR-TB only and nine papers that included both DS- and MDR-TB. These papers provided evidence on the costs of treating DS-TB and MDR-TB in 50 and 16 countries, respectively. In 31% of the papers only provider costs were included, in 26% only patient incurred costs, and in the remaining 43% costs incurred by both were estimated. From the provider perspective, mean DS-TB treatment costs per patient were US\$ 14,659 in high-income countries, US\$ 840 in upper

middle-income, US\$ 273 in lower middle-income, and US\$ 258 in low-income countries, showing a strong positive correlation. The respective costs for treating MDR-TB were US\$ 83,365, US\$ 5,284, US\$ 6,313 and US\$ 1,218. Costs incurred by patients when seeking treatment for DS-TB accounted for an additional 3% of the provider costs in HICs. A greater burden was seen in the other income groups, increasing the costs of DS-TB treatment by 72% in UMICs, 60% in LICs and 31% in LMICs. When provider costs, patient costs and productivity losses were combined, productivity losses accounted for 16% in HICs, 29% in UMICs, 40% in LMICs and 38% in LICs.

Conclusion

There is limited cost data for MDR-TB treatment and the variation in delivery mechanisms as well as the rapidly evolving diagnosis and treatment regimens means that it is essential to increase the number of studies assessing the cost from both provider and patient perspectives. There is substantial evidence available on the costs of DS-TB treatment from all regions of the world. The patient incurred costs illustrate that the financial burden of illness is relatively greater for patients in poorer countries without universal health care coverage.

Key Points for Decision Makers

1. Drug-susceptible tuberculosis treatment cost data are available from the perspective of both providers and patients from various settings around the world.
2. Multidrug-resistant tuberculosis treatment costs are not widely available, particularly not for middle- and low-income countries.
3. Productivity losses were presented in 57% of the papers, for both drug susceptible and multidrug-resistant tuberculosis. There was however, wide variability in methods used, reflecting the lack of clear guidelines on the best instrument and methods for this estimation.

Introduction

The post-2015 World Health Organisation (WHO) 'End TB strategy 2016-2035' has a vision of a 'world free of TB (zero deaths, disease or suffering due to TB)' and a goal of 'ending the global TB epidemic' by 2035, defined as an annual incidence of <10 cases per 100,000 of population [1]. These targets are likely to require scaling-up of high quality drug sensitive (DS) TB and drug-resistant (DR) TB treatment, but may stretch the resource capacity of national TB programmes far beyond any previous efforts. Country and context specific economic evaluations and budget impact analyses are essential for decision-making, but it can be expensive and labour intensive to obtain timely cost data. Assembling a repository of quality assessed DS-TB and multidrug-resistant (MDR)-TB treatment costs can facilitate these processes, and identify gaps for future targeted cost data collection.

There have been earlier reviews of TB treatment costs, but these are either incomplete or no longer up to date. We identified eight previous reviews on TB treatment costs. In 1997, Fryatt reviewed cost-effectiveness papers of TB treatment programmes [2], in 2004 Russell reviewed the economic burden of households due to TB [3], and in 2011 Verdier et al. reviewed economic evaluations of TB control in high-income countries [4]. Three reviews were published in 2012; two on patient incurred TB treatment costs in sub-Saharan Africa [5, 6] and one on MDR-TB treatment costs [7]. In 2013, Diel published a review for determining the costs of TB in the European Union [8], and in 2014 Tanimura and colleagues reviewed papers on patient costs in low- and middle-income countries [9]. This present review complements and synthesises the evidence provided in these previous reviews by including papers from all countries, assessing both DS-TB and MDR-TB costs, and evaluating both provider and patient incurred costs.

Methods

Search strategy and data extraction

Peer reviewed papers were eligible for inclusion if mean treatment cost estimates of DS-TB or MDR-TB in adults were reported and based on primary data that originated from

1990 or later. Five databases were searched: EMBASE, Medline, National Health Service Economic Evaluation Database, Cost-effectiveness analysis Registry, and Latin American and Caribbean Health Sciences Literature. An initial search was done in April 2013 and then updated in February 2015. Therefore, the search period was from January 1990 until February 2015. Search terms were a combination of “tuberculosis”, “multidrug-resistant tuberculosis”, “cost”, and “treatment”. The full search strategies are included in Appendix A. No language restrictions were applied in the search. To assess relevance, abstracts or papers in Spanish were translated by the authors, and abstracts obtained in French, Hungarian and Russian were translated using electronic translation software (Google Translate) [10]. Reference lists of identified reviews were checked for papers that may have been missed by the database search and references cited in retrieved papers were also examined.

Data extraction was independently conducted by two authors. Any discrepancies were resolved by re-evaluation of the paper in question. A data extraction sheet was used, whose composition was informed by the data extraction guidelines for economic evaluations in the Centre for Reviews and Dissemination’s guidance for undertaking reviews in health care [11] and the Cochrane Handbook for Systematic Reviews of Interventions [12]. Variables included were on the characteristics of the study, as well as provider and patient incurred costs. The outcome measure was mean treatment costs per patient. For each paper, all cost items reported, such as drugs, hospitalisation, diagnostic tests and productivity loss, were extracted separately and, where relevant, divided into patient incurred and provider costs. Patient incurred costs were further divided into direct costs and productivity losses. Direct patient costs were defined as expenses paid by patients for receiving treatment, such as user fees for health facilities or monitoring or diagnostic tests, drug expenditures, transportation and other costs, which included food, non-TB drugs, traditional medicine, room and board for patients not resident near the TB treatment facility. Moreover, if costs were aggregated, this total was included in the ‘Other’ category. Productivity losses were defined as the value of paid and unpaid production loss due to time seeking treatment, being ill, or because of premature mortality [13].

Given that our aim was to provide a dataset that best informs the estimation of current TB treatment costs, in papers that compared the costs of more than one treatment delivery strategy, for instance directly-observed treatment (DOT) versus self-administered treatment (SAT) [14], we selected the intervention we considered to best reflect the current standard practice in the respective country. This was determined from the paper or, if not stated, by consulting with TB experts familiar with the respective countries.

Data analysis

Costs were converted to 2014 values in the local currency and then to US\$ using the International Monetary Fund's average consumer price indices and OANDA's average annual exchange rates [15, 16]. For papers where the year of cost data was not given, we used the year prior to the publication date.

Results were presented according to 2013 World Bank country income groups. High-income countries (HICs) were classified as those with per capita Gross National Income (GNI) above US\$ 12,746, upper middle-income countries (UMICs) between US\$ 4,125 and US\$ 12,746, lower middle-income countries (LMICs) between US\$ 1,045 and US\$ 4,125, and low-income countries (LICs) were those with GNI per capita less than US\$ 1,045 [17].

The relationship between provider costs and country GNI per capita was assessed using Pearson's correlation coefficient.

Study quality assessment

Quality assessment focused on methods for estimating and reporting costs; methods used for determining health effects as part of cost-effectiveness studies were not evaluated. Quality appraisal was based on two guidelines; the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [18] and The Tool to Estimate Patient's Costs published by the TB Coalition for Technical Assistance (TBCTA) [19]. Four requirements of the CHEERS statement were used: (i) sources used for resource quantities and unit costs clearly described, (ii) dates of estimated resource quantities and unit costs reported, (iii) methods for adjusting unit costs to the reporting year and performing

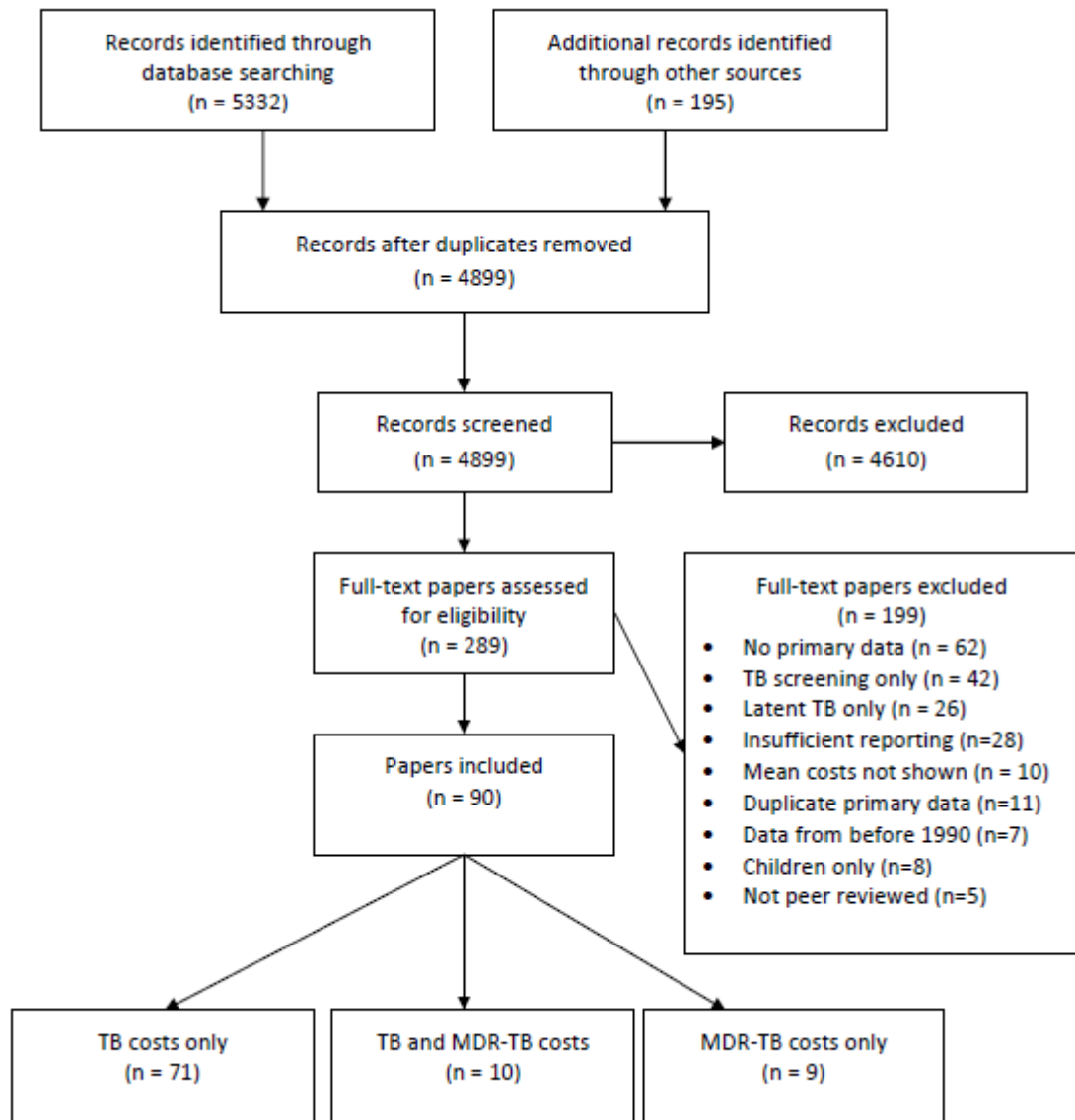
currency conversion explained, and (iv) mean values for main categories of estimated costs reported [18]. For papers that included patient costs, quality was further evaluated using two requirements of the TBCTA tool: (i) clear description of patient interview procedures given and (ii) methods used for valuing productivity losses explained and justified [19]. Additional quality indicators abstracted from all papers were the number of patients included in the study sample in order to provide some indications of representativeness [20, 21]. We also extracted whether any measures of dispersion, such as standard deviation (SD), around the mean cost values were given or not [22]. The review protocol was not registered in any systematic review database or registry. Two authors independently assessed paper quality, with disagreements resolved through discussion.

Results

Paper selection

The search identified a total of 4,899 papers and 289 papers were included for full text review, after which 199 papers were excluded (Figure 1). Forty-two of the excluded papers presented costs of TB screening in schools or in high-risk individuals, such as immigrants, health care workers, people with HIV or the elderly. Twenty-eight papers had insufficient reporting, including only presenting selected cost items or providing costs of a national TB programme without mean treatment costs per patient. Eleven papers were excluded because the same primary data were used in an already included paper. Ninety papers were included in the analysis; 71 were on DS-TB treatment costs only, nine on MDR-TB only and 10 included the costs of both.

Figure 2-1: Literature review flow chart



Study characteristics

For DS-TB and MDR-TB, 50 and 16 countries were represented, respectively (Table 1). In this review we distinguished between paper and study to illustrate where a paper included cost values for two or more countries, which would thereby represent two or more studies in one paper. Therefore, a total of 95 studies were represented in this review. The oldest paper was from 1995; there were six papers from 2014 and one from 2015, as of the February 2015 search. Country income groups were relatively evenly represented; 28% of the papers were from HICs, 32% from UMICs, 19% from LMICs, and 21% from LICs.

In 51 papers, only one type of TB treatment management was evaluated (for example ambulatory DOT), while in the remaining 39 papers two or more strategies were compared in either a cost-comparison or a cost-effectiveness analysis.

In 31% of the papers only provider costs were included, in 26% only costs incurred by patients, and in the remaining 43% both provider and patient costs were evaluated (Table 1). This varied according to country income group. While a provider only perspective was taken in 15 and 11 of the HIC and UMIC papers (60% and 38%, respectively), only one LMIC paper (6%) and one LIC paper (5%) included provider costs only. Productivity losses were included in 81% of the papers that measured patient incurred costs.

Table 2-1: Summary of treatment cost papers included in review

First author	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
HICs (n=25)						
Burman (Burman et al., 1997)**	1997	USA	DOT vs. self-administered therapy	X		X
Palmer (Palmer et al., 1998)	1998	USA	Universal vs. partial DOT	X		
Migliori (Migliori et al., 1998)	1998	Russia	New vs. old treatment strategies	X		
Migliori (Migliori et al., 1999)	1998	Italy	DOT vs. DOT with staff incentives	X		X
Marchand (Marchand et al., 1999)	1999	Canada	Hospitalised treatment of elderly	X		
Weis (Weis et al., 1999)	1999	USA	DOT vs. traditional therapy	X		
Wurtz (Wurtz and White, 1999)	1999	USA	Traditional therapy	X		
White (White and Moore-Gillon, 2000)**	2000	UK	Hospitalised treatment	X		
MacIntyre (MacIntyre et al., 2001)	2001	Australia	In-patient vs. out-patient therapy	X		
Jacobs (Jacobs et al., 2002)	2002	Russia	DOTS vs. traditional treatment	X	X	X
Rajbhandary (Rajbhandary et al., 2004)*	2004	USA	MDR-TB	X		X
Atun (Atun et al., 2006)	2006	Russia	TB control system	X		
Kang (Kang et al., 2006)*	2006	South Korea	MDR-TB	X	X	X
Bocchino (Bocchino et al., 2006)	2006	Italy	Integrated in- and outpatient	X		
Burns (Burns and Harrison, 2007)	2007	New Zealand	DOT in non-resident population	X		
Kik (Kik et al., 2009)	2009	Netherlands	Household costs of immigrants		X	X
Miller (Miller et al., 2010)	2010	USA	Total TB costs in a Texas county	X		X
Montes-Santiago (Montes-Santiago et al., 2010)	2010	Spain	Hospitalisation only	X		

First author	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Tu (Tu et al., 2011a)	2011	Taiwan	Comparison of diagnostic methods	X		
Eralp (Eralp et al., 2012)	2012	UK	Screening, diagnosis and treatment	X		
Diel (Diel et al., 2012)**	2012	Germany	Hospital and outpatient	X		X
Floyd (Floyd et al., 2012)*	2012	Estonia, Russia	Traditional vs. WHO approach	X		
Miller (Miller et al., 2013)**	2013	Latvia	DOTS and MDR-TB	X		
Marks (Marks et al., 2014)*	2014	USA	Hospitalisation	X		X
Diel (Diel et al., 2014)*	2014	Germany	WHO guidelines	X		X
UMICs (n=29)						
Masobe (Masobe et al., 1995)	1995	South Africa	Isoniazid prophylactic therapy	X		
Wilkinson (Wilkinson et al., 1997)	1997	South Africa	DOT vs. traditional treatment	X	X	X
Sawert (Sawert et al., 1997)	1997	Thailand	TB programme improvements	X		X
Dick (Dick and Henchie, 1998)	1998	South Africa	TB programme in Cape Town	X		
Xu (Xu et al., 2000)**	2000	China	DOTS vs. traditional treatment	X		
Suarez (Suarez et al., 2002)*	2002	Peru	MDR-TB 2 nd line drug treatment	X		
Kamolratanakul (Kamolratanakul et al., 2002)**	2002	Thailand	Comparison of delivery centres	X		
Moalosi (Moalosi et al., 2003)	2003	Botswana	Home-based vs. hospital DOT	X	X	X
Ruiz (Ruiz, 2003)	2003	Mexico	National costs	X		
Costa (Costa et al., 2005)**	2005	Brazil	Treatment in Salvador state	X	X	X
Sinanovic (Sinanovic and Kumaranayake, 2006)	2006	South Africa	Public-private partnership model	X		
Peralta Perez (Peralta Perez et al., 2006)	2006	Cuba	DOTS	X		
Jackson (Jackson et al., 2006b)	2006	China	Household costs		X	X

First author	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Liu (Liu et al., 2007)	2007	China	Household costs		X	
Elamin (Elamin et al., 2008)	2008	Malaysia	Costs in Penang state	X	X	X
Cusmano (Cusmano et al., 2009)	2009	Argentina	DOTS	X	X	X
Guzman-Montes (Guzman-Montes, 2009)	2009	Mexico	Household costs		X	X
Fairall (Fairall et al., 2010)	2010	South Africa	Educational outreach services	X	X	
Rouzier (Rouzier et al., 2010)**	2010	Ecuador	Household costs		X	X
Steffen (Steffen et al., 2010)	2010	Brazil	DOTS vs. non-DOTS	X	X	X
Prado (Prado et al., 2011)	2011	Brazil	Guardians vs. health workers	X	X	X
Samandari (Samandari et al., 2011)**	2011	Botswana	DOTS for DS-TB and MDR-TB	X		
Nieto (Nieto et al., 2012a)	2012	Colombia	Increased guardian supervision	X	X	
Schnippel (Schnippel et al., 2013b)*	2013	South Africa	Hospitalised management	X		
Pooran (Pooran et al., 2013)*	2013	South Africa	MDR-TB	X		
Zou (Zou et al., 2013)	2013	China	DOTS incentives vs. no incentive	X	X	X
Pan (Pan et al., 2013)	2013	China	DOTS		X	X
Wei (Wei et al., 2014)	2014	China	DOTS		X	
Foster (Foster et al., 2015)	2015	South Africa	DOTS		X	X
LMICs (n=17)						
Rajeswari (Rajeswari et al., 1999)	1999	India	Household costs		X	X
Khan (Khan et al., 2002)	2002	Pakistan	Health worker vs. family	X	X	X
Vassall (Vassall et al., 2002)	2002	Egypt, Syria	DOTS vs. previous strategies	X	X	X
Nganda (Nganda et al., 2003)	2003	Kenya	Increased community involvement	X	X	X

First author	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Peabody (Peabody et al., 2005a)	2005	Philippines	Economic burden of TB	X	X	
Tupasi (Tupasi et al., 2006)*	2006	Philippines	DOTS-Plus MDR-TB	X	X	
Floyd (Floyd et al., 2006)	2006	India	Public-private mix DOTS	X	X	X
El-Sony (El-Sony, 2006)	2006	Sudan	Comparison of HIV+ and HIV-	X		
Aspler (Aspler et al., 2008)	2008	Zambia	Household costs		X	X
Muniyandi (Muniyandi et al., 2008)	2008	India	DOTS vs. non-DOTS		X	X
Pantoja (Pantoja et al., 2009a)	2009	India	Public-private mix DOTS	X	X	X
John (John et al., 2009b)	2009	India	DOTS		X	X
Vassall (Vassall et al., 2009)	2009	Ukraine	DOTS implementation	X	X	
Mahendradhata (Mahendradhata et al., 2010)	2010	Indonesia	Private practitioner referral	X	X	X
Mauch (Mauch et al., 2011)	2011	Kenya	Household costs		X	X
Umar (Umar et al., 2012)	2012	Nigeria	Household costs		X	
Mauch (Mauch et al., 2013)	2013	Dom. Republic [§] , Ghana, Vietnam	Household costs		X	X
LICs (n=19)						
Saunderson (Saunderson, 1995)	1995	Uganda	Hospital vs. ambulatory care	X	X	X
Maponga (Maponga, 1996)	1996	Zimbabwe	TB/HIV co-epidemic	X		
Gibson (Gibson et al., 1998a)	1998	Sierra Leone	Household costs		X	
Wyss (Wyss et al., 2001)	2001	Tanzania	Household costs		X	X
Islam (Islam et al., 2002)	2001	Bangladesh	CHW vs. no CHW	X	X	X
Floyd (Floyd et al., 2003)	2003	Malawi	Increased community involvement	X	X	X

First author	Year	Country	Interventions evaluated in study	Provider costs included	Direct patient costs included	Productivity losses included
Okello (Okello et al., 2003)	2003	Uganda	Increased community involvement	X	X	X
Wandwalo (Wandwalo et al., 2005)	2005	Tanzania	Community vs. health facility	X	X	X
Jacquet (Jacquet et al., 2006)	2006	Haiti	DOTS expansion	X	X	X
Karki (Karki et al., 2007)	2007	Nepal	Public-private partnership	X	X	X
Mirzoev (Mirzoev et al., 2008a)	2008	Nepal	Community vs. family observation	X	X	X
Aye (Aye et al., 2010)	2010	Tajikistan	Household costs		X	X
Datiko (Datiko and Lindtjorn, 2010)	2010	Ethiopia	Health extension workers	X	X	X
Vassall (Vassall et al., 2010)	2010	Ethiopia	Collaborative TB-HIV		X	X
Pichenda (Pichenda et al., 2012)**	2012	Cambodia	Early diagnosis and non-hospital	X	X	X
Laokri (Laokri et al., 2013)	2013	Burkina Faso	Household costs		X	
Yitayal (Yitayal et al., 2014)	2014	Ethiopia	DOTS		X	X
Laokri (Laokri et al., 2014)	2014	Benin	DOTS		X	
Gospodarevskaya (Gospodarevskaya et al., 2014)	2014	Bangladesh, Tanzania	DOT female community worker; DOT family		X	X

* MDR-TB costs only, **Both DS-TB and MDR-TB costs

[§] Dominican Republic is an upper-middle income country

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, DOT: Directly Observed Treatment, DOTS: Directly Observed Treatment, short course, UK: United Kingdom, CHW: Community health worker

Quality assessment

Quality assessment of individual papers is included in Appendix B and Appendix C. A summary according to country income group is seen in Table 2-2.

Data collection methods

The year of cost data and the main cost categories were adequately reported in 77% of papers (Table 2-2). In 79 of the 90 papers, cost data were collected from a sample of patients. The mean sample size across these studies were 324 patients (SD = 532), ranging from nine in a MDR-TB study from the United Kingdom to 3,510 patients in a German cost of illness study [23, 24]. However, in spite of relatively large sample sizes in many studies, only 30% presented descriptive statistics showing the spread around the mean cost values.

In 10 of the remaining 11 studies, costs were determined by making assumptions about resources needed to treat TB according to national guidelines. In a South African study by Pooran et al., it was for instance assumed that all DS-TB patients received drugs for six months and MDR-TB patients for 24 months, as this was the length of a full recommended treatment course [25]. In the one study of the 12 that did not follow this approach, annual costs of primary health clinics in a specific area of South Africa were estimated and costs of TB treatment were determined by weighing total costs by the proportion of patients presenting due to TB [26].

Provider costs

The ingredient approach, which entails determining resource quantities and unit costs separately, is generally viewed as the most robust and transparent method for provider cost estimation [27]. This approach was transparently used in 54 of the 67 studies that included provider costs. While the method may also have been partly used in the remaining 13 studies, techniques were not clearly described and resource quantities and unit costs were not separately presented in these papers.

Table 2-2: Quality assessment: Percent of papers*

	Mean number of patients in study sample**	Ingredient approach used for provider costs	Resource use and unit costs clearly described	Year of cost data reported	Main cost categories clearly separated	Descriptive statistics presented	Patient interviews	Methods for valuing productivity loss clearly explained	Sources for productivity losses assumptions justified
<i>Papers with provider costs only (n=28)</i>									
HIC (n=15)	307	73%	60%	80%	73%	20%	NA	NA	NA
UMIC (n=11)	384	100%	73%	91%	82%	9%	NA	NA	NA
LMIC (n=1)	1,797	0%	0%	0%	100%	0%	NA	NA	NA
LIC (n=1)	300	100%	0%	100%	0%	0%	NA	NA	NA
<i>Papers with patient costs included (n=62)</i>									
HIC (n=10)	475	89%	82%	82%	82%	45%	18%	82%	64%
UMIC (n=18)	305	91%	78%	61%	83%	22%	94%	61%	56%
LMIC (n=16)	345	63%	94%	88%	81%	50%	94%	69%	50%
LIC (n=18)	154	73%	78%	78%	89%	33%	100%	56%	44%
<i>All papers</i>	324	81%	76%	77%	80%	30%	83%	65%	52%

*These results are shown for each study in Appendix B and Appendix C

**Among the studies with patient-level data

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, NA: not applicable

Patient incurred costs

Patient interviews were conducted in 52 of the 62 studies that included a patient perspective. The mean sample size was 298 (SD = 527) patient interviews, ranging from 13 patients in a US study to 3,510 in the German cost of illness study [24, 28]. Patient interviews were more common in low- and middle-income countries than in HICs. While 10 studies from HICs included patient incurred costs, interviews were only conducted in two of these, which were a study from Holland assessing costs among immigrant TB patients and an economic evaluation of the Russian TB treatment scheme and short-course chemotherapy [29, 30]. In the other eight studies, productivity losses (and transport costs in a study from South Korea [31]) were the only type of patient costs included and these were estimated without data from interviews.

Methods used for estimating productivity losses varied in six different ways in the 51 papers that included these: (i) Patients were interviewed about their loss of income (n=15). (ii) Patients were interviewed about productive time lost and on their income before falling ill. Productivity losses were then calculated by multiplying mean income across the patient sample with reported time loss (n=12). (iii) Patients were interviewed about productive time lost, which was multiplied by an official wage rate (n=11). (iv) Assumptions were made about the length of time patients were not able to work, which was valued using an official wage rate (n=7), (v) A value was placed on death based on average life time income or GNI per capita, which was multiplied by estimated life years lost (n=4) and (vi) methods were not clear (n=2). Across the 51 studies, only 65% clearly explained the methods used for productivity losses and 52% justified the sources used for these estimates.

Mean costs per patient

Mean provider and patient incurred costs per patient are summarised in Table 2-3 and Table 2-4 according to country income groups. These data are presented for each study in Appendix D-Appendix G.

Table 2-3: Mean drug-sensitive and multidrug-resistant TB provider treatment costs according to country income group, 2014 US\$ (n)*

Income group	Hospitalisation	Outpatient visits	Drugs	Diagnostic and monitoring tests	Other**	Total***	SD ⁶
DS-TB							
HIC (n=19)	11,283 (8)	1,471 (5)	1,392 (6)	961 (7)	3,413 (5)	14,659 (19)	13,594
UMIC (n=19)	380 (5)	218 (10)	107 (14)	69 (11)	386 (9)	840 (19)	1,105
LMIC (n=10)	215 (4)	75 (6)	39 (6)	48 (8)	25 (5)	273 (10)	212
LIC (n=11)	128 (2)	61 (5)	49 (8)	19 (3)	50 (8)	258 (11)	352
All income groups (papers = 58 ^a)	4,909 (19)	396 (26)	329 (32)	453 (26)	744 (27)	6,667 (59)	10,105
Proportion, %	73.6	5.9	4.6	4.1	11.7	99.9	
MDR-TB							
HIC (n=10)	53,078 (10)	18,720 (7)	19,887 (8)	1,201 (6)	1,841 (3)	83,365 (10)	64,825
UMIC (n=7)	6,056 (2)	622 (3)	2,052 (6)	350 (5)	823 (5)	5,284 (7)	3,420
LMIC (n=1)	207 (1)	218 (1)	2,930 (1)	397 (1)	2,567 (1)	6,313 (1)	NA
LIC (n=1)	---	---	---	---	---	1,218 (1)	NA
All income groups (papers = 18 ^b)	41,776 (13)	12,102 (11)	11,623 (15)	779 (12)	1,356 (9)	46,219 (19)	61,027
Proportion, %	61.8	17.9	17.2	1.2	2.0	100.1	

(n): Number of studies

*These are shown for each study in Appendix D - Appendix G

**Other provider costs include start-up costs, treatment supervision, staff salary and training, advocacy, adverse effects, contact tracing, supplies and transportation; or in some papers, where costs were not disaggregated, the total treatment costs to the provider, including supervision, training, supplies and drugs

***Total ≠ sum of categories because some papers did not itemise costs and only reported total costs

^aVassall (2002) presented two LMIC studies (Egypt and Syria) in one paper^bFloyd (2012) presented two HIC studies (Estonia and Russia) in one paper⁶SD: Standard deviation for total mean provider treatment costs

---: Cost not itemised

NA: Not applicable

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries

TB: Tuberculosis, DS: Drug susceptible, MDR: Multidrug-resistant

Table 2-4: Mean drug-sensitive and multidrug-resistant TB direct patient costs and productivity losses according to country income group, 2014 US\$ (n)*

Income group	Clinic visits and clinical tests user fees	Drugs	Transport	Other**	Total direct costs ***	SD ^δ	Productivity losses	SD ^ε
DS-TB								
HIC (n=6)	107 (1)	---	260 (1)	379 (1)	373 (2)	106	2,801 (6)	2,018
UMIC (n=19)	221 (9)	62 (4)	120 (13)	491 (12)	603 (18)	868	600 (12)	847
LMIC (n=17)	55 (9)	21 (7)	9 (4)	47 (10)	84 (17)	90	238 (11)	320
LIC (n=19)	49 (13)	38 (5)	45 (10)	96 (16)	155 (19)	164	248 (14)	266
All income groups (papers = 53^{α β γ})	101 (32)	36 (16)	82 (28)	212 (39)	432 (36)	544	700 (43)	1,229
Proportion, %	23.3	8.5	19.1	49.1	100.0			
MDR-TB								
HIC (n=5)	NI	NI	21 (1)	NI	21 (1)	NA	49,204 (5)	51,216
UMIC (n=2)	12 (2)	---	178 (2)	470 (2)	660 (2)	394	3,532 (2)	4,578
LMIC (n=1)	909 (1)	---	---	707 (1)	1,616 (1)	NA	NI	NA
LIC (n=1)	103 (1)	---	18 (1)	285 (1)	406 (1)	NA	1,256 (1)	NA
All income groups (papers = 9)	259 (4)	---	99 (4)	483 (4)	672 (5)	621	28,260 (8)	45,605
Proportion, %	30.8	0.0	11.7	57.4	99.9			

(n): Number of studies

*These are shown for each paper in Appendix D - Appendix G

**Other patient costs typically include direct medical costs (non-TB drugs, hospitalisation) and direct non-medical costs (food, drink, vitamins, traditional medicine, and accommodation); or in some papers, where costs were not disaggregated, the total costs during pre-diagnosis, diagnosis, intensive treatment and continuation treatment phases

***Total ≠ sum of categories because some papers did not itemise costs and only reported total costs

^α Mauch (2013) presented one UMIC study (Dominican Republic) and two LMIC studies (Ghana and Vietnam) in one paper^β Vassall (2002) presented two LMIC studies (Egypt and Syria) in one paper^γ Gospodarevskya (2014) presented two LIC studies (Bangladesh and Tanzania) in one paper^δSD: Standard deviation for total mean patient costs^εSD: Standard deviation for mean productivity losses

---: Cost not itemised

NI: Cost not included; NA: Not applicable

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, TB: Tuberculosis, DS: Drug susceptible, MDR: Multidrug-resistant

DS-TB provider costs

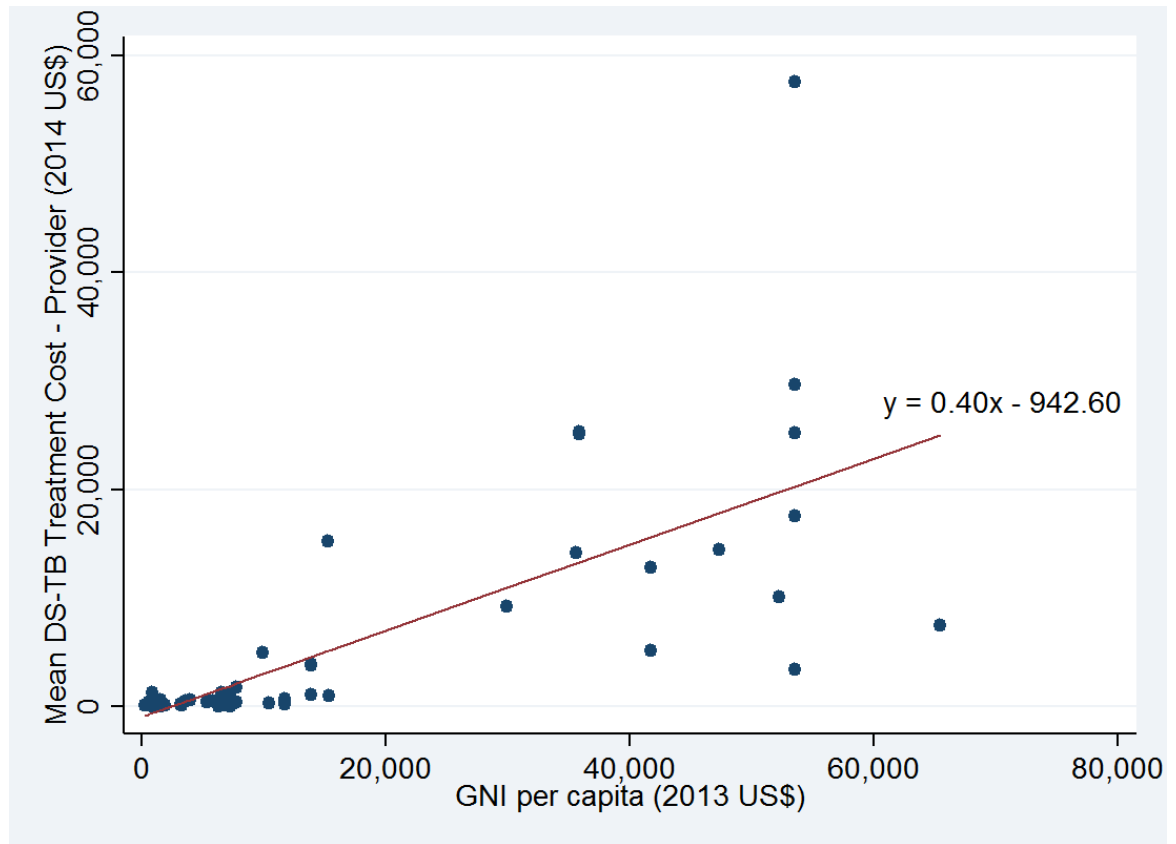
DS-TB provider costs were positively correlated with GNI per capita ($r=0.73$, $p<0.001$). A scatterplot illustrates the relationship (Figure 2-2). Mean DS-TB treatment costs per patient were 57 times higher in HICs (US\$ 14,659 [SD = US\$ 13,594]) than in LICs (US\$ 258 [SD = US\$ 352]). There is a high degree of variability of income group cost values, with the SD being almost as large as the mean provider costs in HICs and larger for LICs.

Hospitalisation and outpatient care

Across all 59 studies, hospitalisation accounted for 74% of all DS-TB provider costs (Table 3). Hospitalisation accounted for 63% in HICs (US\$ 11,283), 51% in LMICs (US\$ 215) and LICs (US\$ 128), but only 12% in UMICs (US\$ 380). However, within the income groups, the proportion of hospitalisation costs varied widely between studies, with 2% for an unreported number of hospital days in a public-private sector implementation scenario in India to 81% in a study on DOT in Texas, USA with 23 hospital days [32, 33]. Among LMICs, India consistently had the lowest costs for hospitalisation, as well as the other cost categories [32, 34]. In LMIC costs, Ukraine had the highest hospitalisation and outpatient costs, at approximately twice the average income group costs [35]. Only two of the 11 LIC studies reported hospitalisation costs, with US\$ 75 (60%) in Malawi [36], and US\$ 181 (50%) in Uganda [37].

Mean outpatient treatment costs were 12 times less than hospitalisation costs and comprised only 6% of total costs. However, the importance of outpatient costs varied substantially among country income groups. In HICs, only five out of 19 studies reported any outpatient costs [24, 38-41]. Of the 10 UMIC studies that reported these costs, Argentina and South Africa had the lowest values of around US\$ 20 per patient [42-44] and Botswana the highest of US\$ 658 per patient [45]. Egypt was an outlier among the LMICs, reporting outpatient costs of US\$ 187 [46], which was 15 to 25 times more than in Pakistan (US\$ 11) and India (US\$ 6) [32, 47]. In LICs, five studies reported outpatient costs, with a mean of US\$ 61.

Figure 2-2: Mean TB provider treatment costs per patient (2014 US\$) according to GNI per capita (2013 US\$)



Drugs

Costs of DS-TB drugs were on average 5% of total costs, but varied widely between settings, from a mean of US\$ 49 across LICs to US\$ 1,392 in HICs. Within the HICs, drug costs were US\$ 311 in a US study [38], US\$ 654 in another US study [33], and as much as US\$ 4,055 for an unstated combination of DS-TB and MDR-TB drugs in Italy [48]. Within this group of countries it is difficult to discern whether drug costs have decreased or increased over time as only six of the 19 studies presented disaggregated drug costs. In upper middle-income South Africa, drug costs appear to have decreased from US\$ 46 in 1994 [49] to US\$ 3 in 2003 [42]. In LMICs and LICs, drug costs were lowest in India at approximately US\$ 15 between 2002 and 2005 and highest at US\$ 166 in Uganda in 1992 [32, 34, 50]. Without these outliers, mean drugs costs in LMICs and LICs were US\$ 51 and US\$ 33, respectively, with data from between 1992 and 2007.

Diagnostics and monitoring tests

Unlike the costs of drugs and hospitalisation, mean costs per patient for diagnostics and monitoring tests were relatively similar across income groups. In the UK, costs of TB tests in a population of healthcare workers were US\$ 157 [51]. In three US studies on urban DOT programmes by Miller et al., Burman et al. and Weis et al., costs per patient were reported as US\$ 124, US\$ 635 and US\$ 1,505, respectively [33, 38, 52]. In the Miller et al. study only one acid-fast bacilli (AFB) smear and culture was included, while the other studies typically included at least two CXRs, four sputum cultures and one TST. Burman et al. additionally included five serum bilirubin tests and five aspartate aminotransferase tests [38]. Interferon-Gamma Release Assay was used instead of sputum culture in the UK study by Eralp et al. [51]. Although this review excluded latent TB, some studies presented aggregated costs for diagnosis of latent TB together with tests for diagnosis and monitoring of active TB, in which case the cost of the latent TB tests could not be excluded.

Mean diagnostics and monitoring costs in UMICs were US\$ 69, with Cuba being the only outlier at US\$ 289 in 2002 [53]. A Sudanese study that compared the costs of managing HIV-positive and HIV-negative TB patients reported the largest monitoring costs within this income group at US\$ 135 per patient [54].

MDR-TB provider costs

Mean provider costs for MDR-TB treatment were US\$ 83,365 (SD = US\$ 64,835) for the ten included studies and far less for the seven UMICs, US\$ 5,284 (SD = US\$ 3,420). There was a large variation in costs for both groups; measures of spread were not available for the LMIC and LIC groups as there was only one study included in each of these categories.

Hospitalisation and outpatient care

MDR-TB hospitalisation represented the highest proportion of provider costs in HICs, contributing to 64% (Table 2-3). Even though patients were hospitalised for an average of 192 days in Estonia, hospitalisation represented only 50% of total costs at US\$ 8,007 [55]. In the US, Burman et al. reported hospitalisation costs four times higher than Rajbhandary et al. because the length of stay decreased from an average of 90 days in 1994 to 28 days

in 2000 (US\$ 181,909 versus US\$ 41,612) [28, 38]. The mean length of MDR-TB hospitalisation in the US in 2010, as reported by (Marks et al.), remained 28 days but the cost, US\$ 87,619, more than doubled Rajbhandary et al.'s 2000 value [56].

In Russia, hospitalisation and outpatient care comprised 37% and 3%, respectively, if treatment is delivered according to WHO guidelines [55]. This Russian study reported an average of 321 days in hospital, costing US\$ 6,493, which was the second lowest value in the HIC group. In South Korea, hospitalisation costs the least per patient (US\$ 3,521) but the length of stay was only eight days, by far the shortest stay for any HIC or UMIC [31].

In South Africa, Schnippel et al. reported a mean hospitalisation period of 105 days, contrasting greatly with Pooran et al. who estimated costs according to prevailing guidelines, which recommended complete outpatient care for smear negative MDR-TB patients [25, 57]. Pooran et al. estimated that surgery, which we presented as a hospital cost, amounted to US\$ 97 (2%) per patient, while outpatient visits totalled US\$ 712 (17%). Schnippel et al. reported no outpatient costs, but hospitalisation accounted for 95% of total MDR-TB costs (US\$ 12,666). Both treatment scenarios are present in South Africa, but only 10% of MDR-TB patients are thought to require hospitalisation [25].

Only the Philippines were represented in the LMIC group. In a DOT short-course plus pilot programme, hospitalisation for seven days amounted to 3% and outpatient visits to 4% of total costs [58]. In the LIC group there was no disaggregated data for the one country represented, Cambodia, but the total MDR-TB cost was the lowest value of any country at US\$ 1,218 [59].

Drugs

In Estonia, 18 months of first- and second-line drugs amounted to half of hospitalisation costs (192 hospital days) [55] (Annex 5). In the 2004 US study by Rajbhandary et al., costs of drugs, tests and personnel were not separately reported, but in the 1997 US study by Burman et al. MDR-TB drug costs amounted to approximately US\$ 12,000 per patient (6%) [28, 38].

Diagnostic and monitoring tests

Mean costs per MDR-TB patient for diagnostics and monitoring tests were US\$ 779 (1%) across the 12 studies reporting this data. This accounted for less than 1% of total treatment costs in both the US and the UK [23, 38]. In the South Korea study, diagnostics and monitoring test amounted to 24% of total costs [31]. The costs reported in the UK was for drug monitoring only, while Estonia, Germany, South Korea and the US (Burman et al.) each included at least one drug susceptibility test, 13 sputum culture tests and a combination of audiograms (US), sputum smear tests (Estonia), x-rays, liver function and blood count tests.

The mean costs of diagnostics and monitoring tests were US\$ 350 in UMICs, ranging from US\$ 82 in China to US\$ 1,013 in South Africa [25, 60]. With the exception of the South African study by Schnippel et al., all studies reported at least eight sputum smear tests. Costs of sputum culture tests were included in all studies, with for instance three tests per patient during 24 months in Thailand and 18 tests per patient during 18 months in Peru [61, 62]. Costs of at least four CXRs per patient were included in all UMIC studies, except in South Africa where only one CXR was included and all patients were hospitalised during the intensive phase of treatment [57]. Drug-susceptibility tests were reported in Thailand and in the two studies from South Africa [25, 57, 61]. In the only LMIC, the Philippines, costs of 34 smear tests, 27 culture tests, two drug-susceptibility tests and three x-rays were estimated at US\$ 397 per patient, equivalent to 6% of total costs [58].

DS-TB patient costs

Across all 61 studies, in 57 papers, mean direct costs incurred by patients was US\$ 432 (SD = US\$ 544), ranging from US\$ 4 in Egypt to US\$ 3,525 in China (Table 2-4) [46, 63]. Approximately half of patient costs, the highest proportion, was recorded in the “other” category, which mainly consisted of non-TB drugs and food while hospitalised, or aggregated direct (medical and/or non-medical) patient costs. User fees comprised 23%, drugs 9%, and transportation 19% of total costs. In contrast to provider costs, there was no clear relationship between patient incurred costs and GNI per capita. UMIC studies

reported the highest mean patient costs (US\$ 603), followed by two HIC studies (US\$ 373), LICs (US\$ 155), and LMICs (US\$ 84).

User fees

The user fees category comprised cost incurred by patients for medical consultations or examinations when attending clinics or other health facilities during treatment, or to obtain diagnostic or monitoring tests. Mean user fees payments were similar in high-income Netherlands and upper-middle income Botswana at around US\$ 105. In the Netherlands user fees accounted for 22% of patient payments, but only 11% in Botswana [29, 45].

Patients in upper-middle income Mexico and low-income Haiti paid the highest user fees of US\$ 344 and US\$ 299, respectively [64, 65]. The greatest proportion of total direct costs spent on user fees were in India (80%), Kenya (69%), South Africa (68%) and Tanzania (66%) [34, 42, 66, 67]. In general, user fees appeared to constitute the greatest proportion of patient costs in LMICs and smallest in UMICs.

Drugs

No out-of-pocket payments were paid for drugs in HICs. Patients in Vietnam paid the least for drugs (US\$ 1), followed by the Dominican Republic (US\$ 5) [68]. Studies in Tajikistan and China reported the highest payments of US\$ 126 and US\$ 118, respectively [69, 70]. In most LMICs drug expenses were around US\$ 20, ranging between US\$ 1 and US\$ 63. Only five studies reported payments for drugs in LICs, ranging from US\$ 4 in Ethiopia to US\$ 126 in Tajikistan [69, 71].

Transportation

The only HIC study that reported transportation costs was Russia, with US\$ 260 [30]. Transportation costs in UMICs comprised 1% of direct costs in the Dominican Republic and as much as 85% in Malaysia [68, 72]. In LMICs, patients paid on average US\$ 9, comprising between 2% and 28% of total direct costs. Ten of the 19 LIC studies reported

transportation costs, comprising 80% of direct costs in Bangladesh and between 22% and 44% in Ethiopia, Tajikistan and Tanzania [67, 69, 71, 73-75].

Productivity losses

Time lost due to seeking treatment and being ill with DS-TB was reported as 81 days in the Netherlands, 60 days in Thailand, 30 days in Italy, 25 days in the US, 14 days in Malaysia, and 50% disabled for two months in Haiti [29, 64, 72, 76, 77].

DS-TB productivity losses increased with increasing GNI per capita, but amounts varied widely within country income groups (SD = US\$ 1,229) with a mean loss of US\$ 700 per patient for 43 studies. In HICs, values varied from US\$ 450 in Russia to US\$ 6,246 in Italy [30, 78]. In UMICs, the range was between US\$ 46 in Argentina and US\$ 3,048 in China [44, 63]. In LMICs, an Indonesian study reported productivity losses of US\$ 12 per patient compared to US\$ 996 in Vietnam [68, 79]. In LICs, costs were US\$ 11 in Bangladesh versus US\$ 775 Tajikistan [69, 73]. Studies from similar countries also showed quite different productivity loss estimates, such as US\$ 11 and US\$ 332 in Brazil [80, 81], US\$ 52 and US\$ 636 in India [82, 83], US\$ 9 and US\$ 200 in Ethiopia [71, 84], and US\$ 18 and US\$ 825 in Tanzania [67, 85].

MDR-TB patient costs

Mean direct costs incurred by MDR-TB patients were US\$ 672 (SD = US\$ 621) across five studies (Table 4). The “other” category constituted 57% of total costs, which included food, non-TB medication, follow-up tests and ventilation improvements to family homes. No patient costs were reported for MDR-TB drugs in any studies.

User fees

Similar to DS-TB user fees, MDR-TB user fees incurred by patients were for medical consultations or examinations at health facilities or to obtain diagnostic or monitoring tests. The mean MDR-TB user fees were US\$ 259, which were almost three times higher than for DS-TB. The Philippines reported the highest user fees at US\$ 909, comprising 56% of all direct MDR-TB patient costs [58]. The user fees in low-income Cambodia (US\$ 103)

were around eight times more than in UMICs (US\$ 4 – US\$ 20) [59]. No user fees were reported in HICs.

Transportation

Mean transport costs incurred from receiving DS-TB treatment were US\$ 99 across the four studies. The highest costs were reported in the two UMICs, Brazil and Ecuador, at US\$ 90 and US\$ 266, respectively [81, 86]. Studies from high-income South Korea and low-income Cambodia each reported around US\$ 20 per patient [31, 59].

Productivity losses

Productivity loss amounted to US\$ 28,260 per patient across the eight studies that included these values. As with DS-TB, productivity losses increased with income group, ranging from US\$ 295 in Brazil to US\$ 136,802 in the US and an overall SD of US\$45,605 [56, 81]. Only three studies, two from the US and one from Germany, clearly stated productive time lost for MDR-TB, which was six, 24 and eight months respectively [38, 56, 87].

Discussion

There is substantial variation in the cost of TB treatment globally, with lower income countries adopting comparatively low cost ambulatory methods of treatment delivery and benefitting from lower drug regimen prices than HICs. Provider costs are strongly correlated with GNI per capita. The cost of treating DS-TB from the provider perspective ranged from US\$ 45 in Zimbabwe to US\$ 57,559 in one of the US studies [88, 89]. Provider costs of MDR-TB treatment are substantially higher than those for DS-TB and varied from US\$ 1,218 in Cambodia to US\$ 204,876 in the US [38, 59]. It should be noted, that many MDR-TB patients are primarily infected with transmitted MDR-TB strains, and do not acquire the disease through misuse of their first line regimen, so on the individual level these are not always alternative treatments. At a population level however, the origins of MDR-TB lie in the misuse of TB drugs, and the improved delivery of first line treatment can potentially reduce the level of comparative high MDR-TB treatment costs [90, 91].

We also observed substantial cost variation within country income level groups. In the case of DS-TB, very low comparative costs were observed in LIC and LMIC countries using community based models of care. While this suggests devolvement of TB treatment at the community level may be efficient, the cost of community provision of TB treatment is highly dependent on whether community workers are paid, and the valuation of their time. In the case of MDR-TB treatment, the variation in costs within country income level groups was also substantial. Lower cost treatment within groups was observed where primarily ambulatory models of care are adopted, with hospitalisation being a major driver of total cost. Across DS-TB treatment, there is a clear reduction in costs over time due to the extent of hospitalisation decreasing as countries moved towards ambulatory DOTS, although in countries such as Germany, Spain, the US and Latvia high hospitalisation costs were still reported between 2010 and 2013 [24, 41, 52, 65] (DS-TB patients were hospitalised for an average of 115 and 72 days in Latvia and the US, respectively). Care should therefore be taken when using costs from this review to estimate current costs for any one setting to ensure that the cost applied reflects the current mix of hospitalisation and ambulatory treatment. In particular, while the majority of MDR-TB treatment is currently provided in hospital, several countries are now piloting ambulatory models of care so these costs may fall in coming years.

The costs of DS-TB drugs were reported in 34 studies. When compared with DS-TB treatment, drug costs remain a substantial component of MDR-TB treatment, and are particularly high in countries using individualised MDR-TB regimens and/or with high levels of extensively drug-resistant (XDR)-TB, or not accessing concessionary prices. In the Philippines, MDR-TB drugs comprised 46% of total provider costs in 2006 [58].

While there has been substantial research on direct costs incurred by TB patients in low- and middle-income countries, these were only included in two HIC studies, possibly highlighting a lesser interest in the poverty impact of TB in countries with higher income levels and more comprehensive social protection and health insurance systems. Nevertheless, some patient costs were found. Kik et al. reported that immigrant DS-TB patients in Holland on average paid US\$ 486 for receiving treatment [29]. In contrast, in

poorer countries there has been substantial attention to patient incurred costs. Although in many settings TB treatment is provided free, it incurs a high economic burden, either through out-of-pocket/direct payments (in some settings 'under the counter' payments), but also through substantial productivity loss. DS-TB direct patient costs were on average US\$ 603 in UMICs, US\$ 84 in LMICs and US\$ 155 in LICs. The high values in LICs were noted by many studies to be catastrophic, and are primarily driven by costs captured in the 'Other' category, which included out-of-pocket payments made by patients and their social networks for non-TB drugs, food and specialised diets, traditional healers, accommodation, among other costs. The respective direct patient costs for MDR-TB patients were US\$ 660, US\$ 1,616 and US\$ 406. There was substantially less evidence on the patient cost of MDR-TB. The few studies found highlight the potential of MDR-TB to have a substantially higher catastrophic impact than DS-TB. More research is required in this area, in particular to better understand how these costs are incurred over time, and how patient cost is affected by different levels of hospitalisation.

Well defined estimates of productivity losses were included in 81% of DS-TB papers and 75% of MDR-TB papers. As a proportion of DS-TB patient costs, productivity losses comprised 96% in HICs, 68% in UMICs, 98% in LMICs and 74% in LICs. The methods used to estimate productivity loss vary widely, nevertheless it can be seen that this is an important component of the economic impact. Therefore, by excluding this cost, the majority of reported TB patient costs are under-estimating the impact of TB on patients substantially. The difference in methodological approaches taken also makes it challenging to draw general conclusions about the key drivers of patient incurred costs; and for analysts to use this review to extrapolate patient costs across settings or over time. It is therefore recommended that although the costs presented in this review provide some guidance, the measurement of setting specific costs that are comprehensive may still be required in economic analyses of TB control interventions for some time to come.

We captured 90 papers in all income groups. The review of economic evaluations in TB control published by Verdier et al. in 2011 included 118 papers from high-income

countries only. This large volume was due to the inclusion of mathematical modelling papers and multiple papers using the same primary data [4]. For MDR-TB, 16 countries were included in our review, compared to only four countries captured by Fitzpatrick and Floyd in 2012 [7]. Quality assessment is crucial for systematic reviews, but only three of the previous reviews completed this [2, 4, 5]. Using the CHEERS and TBCTA guidelines, we identified several key methodological issues that suggest further standardisation is required in order to further develop a set of costs that can be used globally. First, even when the ingredient approach to costing was used, cost items were insufficiently separated in several studies, hindering the ability to observe cost drivers and analyse trends over time, such as drug costs. The lack of reporting of disaggregated costs was also an issue for patient incurred costs. Secondly, methods for calculating productivity losses were not clearly explained in more than a third of the studies that included these costs and disparate approaches were used between studies, which lead to widely different estimates within the same country. The lack of standard methods for identification, measurement and valuation of productivity losses have frequently been acknowledged in the wider literature on the measurement of costs, and minimum standardised approaches are urgently required to enable comparisons across settings, particularly in the light of the increased global attention on social protection [13]. Thirdly, even though cost data were collected from a relatively large number of patients, insufficient statistical analyses were undertaken in most studies. In addition to mean values, descriptive statistics, such as SD, minimum and maximum values must be presented and any outliers in the patient sample should be highlighted.

Conclusion

In summary, there is extensive literature on the costs of DS-TB treatment to both providers and patients. However, evidence is still scarce on the costs of treating MDR-TB, and how these costs may vary by mode of delivery and setting. MDR-TB treatment is rapidly evolving; a recent global guideline change recommends Xpert® MTB/RIF diagnostics, which is more sensitive and also detects rifampicin resistance, therefore identifying more cases. In addition, there has recently been substantial global investment

in further testing of existing MDR-TB drugs as well as development of new drugs. More data are urgently required to estimate the budgetary impact of these changes and to support economic evaluations of new MDR-TB control approaches.

Acknowledgements

UKG and AV planned the study. YVL conducted the search, extracted, analysed and interpreted the data, as well as produced a draft of the manuscript. UKG also extracted, analysed and interpreted the data, and wrote components of the manuscript. AV oversaw the progression of the review, provided guidance and contributed to various versions of the manuscript. All authors read and approved the final manuscript. YVL is the overall guarantor of this work.

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End of Research Paper 1

2.2 TB diagnostic costs

The costs of TB diagnostic tests are an important component in assessing the cost of TB control. A systematic literature review was conducted to provide background information for assessing the cost-effectiveness and feasibility of the WHO post-2015 TB control strategy and targets, using China, India and South Africa as case studies. This review was also instrumental in providing an understanding of the economic context of the bi-directional screening in the TANDEM study and the issues associated with the various tests used to diagnose TB. The objective of this review was to obtain the costs related to the screening and diagnosis of TB.

2.2.1 Methods

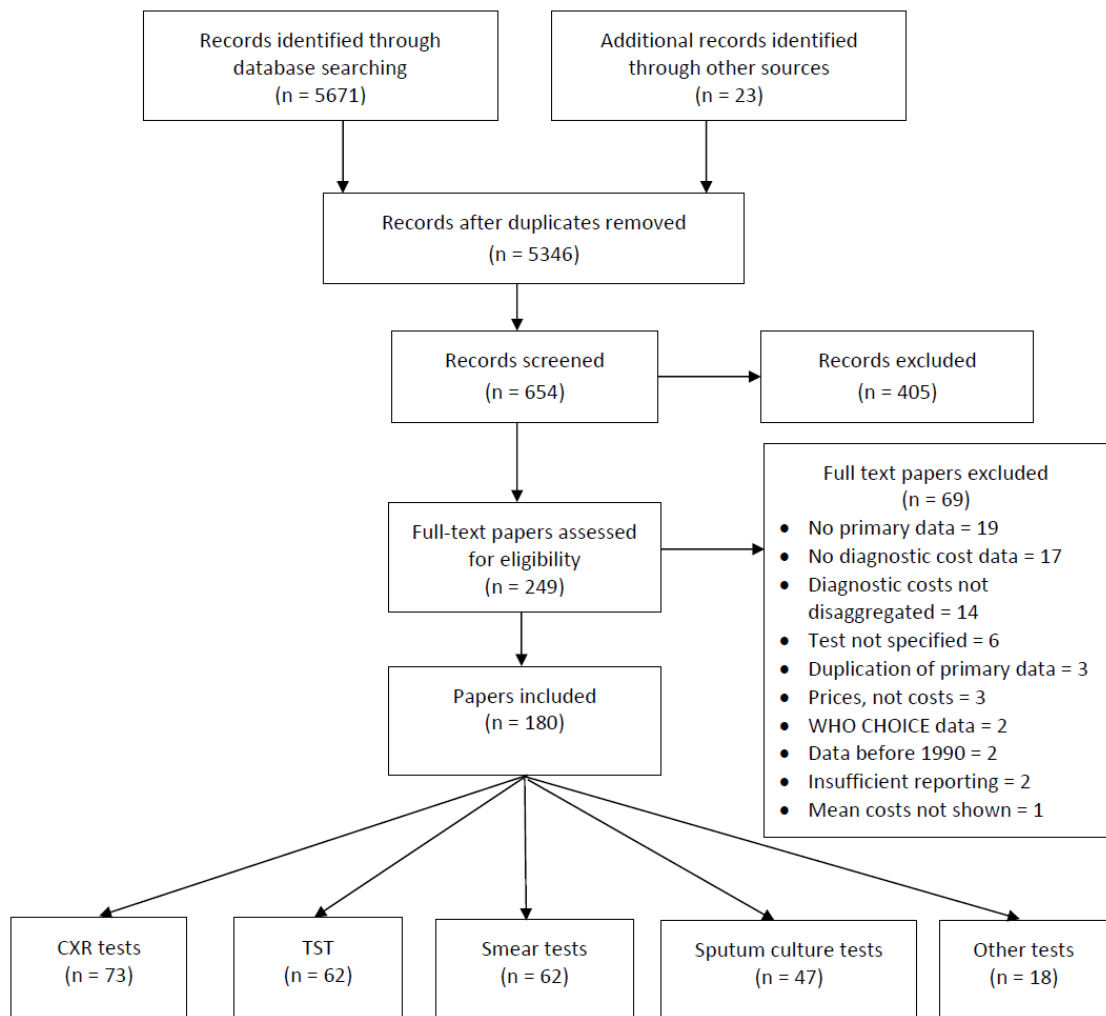
Search strategy

I conducted a systematic literature review of peer-reviewed papers with TB diagnostic costs for the period January 1990 to September 2015. The six databases searched were Pubmed, Embase, EconLit, Centre for Reviews and Dissemination (CRD), Cost-Effectiveness Analysis Registry (CEA) and Latin American and Caribbean Health Sciences Literature (LILACS). The search criteria were adapted to each of the databases by using combinations of three categories of keywords, such as “cost/economics/finance/expenditure”, “TB/tuberculosis” and “diagnostics/diagnosis/screening/test/chest x-ray/smear/culture/Xpert/skin test/IGRA”. The detailed search strategy used for each database can be found in Appendix H. The inclusion criteria were primary costs of TB diagnostic tests across the world, in all income groups; active and latent; pulmonary and extrapulmonary; and adult and paediatric. No language was excluded. The search was initially conducted between 22 January 2014 and 18 April 2014 and updated between 18 August 2015 and 2 September 2015. Citations were collected and managed using EndNote X6 (Philadelphia, PA, USA).

A total of 5,671 citations were obtained from the six databases and an additional 23 from colleagues and references of papers (Figure 2-3). After removing 348 duplicate citations, 5,346 remained. These titles were screened for relevance to the review objective and this

resulted in 654 citations. Further screening was performed on the abstracts of the 654 citations and 405 were excluded. The full text of the remaining 249 papers were then assessed for eligibility and 69 were removed because they did not have diagnostic cost data. This yielded 180 papers that were included in the review, which equated to 183 studies, representing 53 countries. The United States had the most studies (n=29), followed by South Africa (n=23) and Canada (n=9). The most commonly assessed test was CXR, which was included in 73 studies. Sputum smear and tuberculin skin test (TST) were evaluated in 62 studies each and sputum culture in 47 studies (Figure 2-3).

Figure 2-3: Flow chart for systematic literature review for tuberculosis diagnostic test costs



Data extraction

In order to meet the objectives of the project to assess the cost-effectiveness and feasibility of the WHO's global strategy and targets for TB control after 2015, a decision was made to focus on three key countries: China, India and South Africa. Therefore, I prioritised data extraction of these three countries in addition to the countries included in this PhD: Indonesia and Romania. The data for the five countries were extracted between 20 November 2015 and 18 December 2015. Data from additional papers were later extracted but not analysed and are therefore not included in this thesis. I extracted data using a single, standardised form in Excel (Microsoft Corporation, Redmond, WA, USA, 2013). The data were checked for accuracy by my line-manager for the project.

The outcome measure of interest was cost per test but any additional outcomes reported in a paper was extracted, for example cost per negative or positive test result, cost per TB case detected, cost per disability adjusted life years (DALYs) averted, etc. Both mean and median values were extracted whenever presented. When the costs of several tests combined (a testing algorithm) was reported instead of or in addition to the individual test, this algorithm cost was also extracted.

Analysis

All cost data were converted to 2015 local currency values using the International Monetary Fund's average consumer price indices (IMF, 2016), then to a common currency, US\$, using OANDA's average annual exchange rates (OANDA, 2016).

2.2.2 Main findings

Data were extracted for 12 types of TB tests from the 35 papers based in China, India, South Africa, Indonesia and Romania (Table 2-5). Of the 35 papers, five presented costs from the patient perspective only (John et al., 2009a, Ray et al., 2005, Muniyandi et al., 2008, Pantoja et al., 2009b, Liu et al., 2007), one provided costs from the perspective of both the provider and the patient (Van Rie et al., 2013), and the remaining 29 papers presented provider costs only.

Table 2-5: Journal articles with TB diagnostic tests unit costs for China, India, South Africa, Indonesia and Romania (as of March 2015)

Test	China	India	South Africa	Indonesia	Romania
CXR		(Muniyandi et al., 2006)	(Sinanovic et al., 2015, Theron et al., 2012, Pooran et al., 2013, Hausler et al., 2006)		
Sputum collection	(Li et al., 1999)		(Peter et al., 2013)		
Smear	(Xia et al., 2013)	(Muniyandi et al., 2006, Muniyandi et al., 2008, Vassall et al., 2011)	(Hudson et al., 2000, Dorman et al., 2012, Shah et al., 2013, Sinanovic et al., 2015, TB Diagnostics Market Analysis Consortium et al., 2015, Theron et al., 2012, Vassall et al., 2011, Whitelaw et al., 2011, Hausler et al., 2006)	(Chaidir et al., 2013, Mahendradhata et al., 2010)	(Olaru-Peter et al., 2014)
Culture		(Lazarus et al., 2012, Michael et al., 2010, Vassall et al., 2011)	(Hudson et al., 2000, Chihota et al., 2010, Dorman et al., 2012, Shah et al., 2013, Sinanovic et al., 2015, TB Diagnostics Market Analysis Consortium et al., 2015, Vassall et al., 2011, Hausler et al., 2006)		
TST	(Chen et al., 2011)		(Mandalakas et al., 2013, TB Diagnostics Market Analysis Consortium et al., 2015, Masobe et al., 1995, Hausler et al., 2006)		
IGRA	(Chen et al., 2011)		(Mandalakas et al., 2013, TB Diagnostics Market Analysis Consortium et al., 2015)		
Xpert		(Vassall et al., 2011)	(Andrews et al., 2012, Dorman et al., 2012, du Toit et al., 2015, Meyer-Rath et al., 2012, Pooran et al., 2013, Schnippel et al., 2013a, Shah et al., 2013, TB Diagnostics Market Analysis Consortium et al., 2015, Theron et al., 2012, Van Rie et al., 2013, Vassall et al., 2011, Schnippel et al., 2012)		

Test	China	India	South Africa	Indonesia	Romania
DST	(Pang et al., 2013)	(Lazarus et al., 2012, Vassall et al., 2011)	(Shah et al., 2013, Sinanovic et al., 2015, TB Diagnostics Market Analysis Consortium et al., 2015, Vassall et al., 2011)		
Genechip	(Pang et al., 2013)				
LPA			(du Toit et al., 2015, TB Diagnostics Market Analysis Consortium et al., 2015)		
MTBDR-plus			(Shah et al., 2013)		
NAAT			(TB Diagnostics Market Analysis Consortium et al., 2015)		

NA: not applicable; CXR: chest radiography; TST: tuberculin skin test; IGRA: interferon gamma release assay; DST: drug susceptibility testing; LPA: line probe assay; MTBDR-plus: Assay for Molecular Detection of Rifampin and Isoniazid Resistance in *Mycobacterium tuberculosis*; NAAT: nucleic acid amplification test

In the 30 papers with provider costs for diagnosis of TB, 25 presented provider costs for CXR, sputum collection, smear, culture, TST or IGRA, which were the tests included in the TANDEM study and therefore the focus of this review.

The 2015 US\$ mean provider costs of the CXR, sputum smear and culture, TST and IGRA tests in the five countries were assessed and the findings are presented in Table 2-6. Unit costs were available in 14 papers, with one paper (Vassall et al., 2011) presenting costs for both India and South Africa. The remaining 16 papers with provider costs either had data non-TANDEM tests or combined costs for various TB diagnostic tests and are not presented here.

Table 2-6: Mean provider costs for TB diagnostic tests, 2015 US\$

Country	Author (year)	CXR	Smear	Culture	TST	IGRA	
China	Pang et al. (2013)			58.19 L-J			
				61.22 L-J			
India	Muniyandi et al. (2006)	0.97	0.39				
	Vassall et al. (2011)		1.25 AFB	15.02 L-J			
South Africa	Hausler et al. (2006)	24.36	3.71	8.64	1.23		
	Sinanovic et al. (2015)	24.01	6.30	12.90			
	Van Rie et al. (2013)			2.93 LED-FM	11.08 liquid		
				1.69 ZN			
	Pooran et al. (2013)	24.19	2.81 Auramine	10.63 MGIT			
	Shah et al. (2013)			2.95 LED-FM	10.55 MGIT		
				1.94 ZN			
	Chihota et al. (2010)				12.41 L-J		
					16.70 MGIT		
	Whitelaw et al. (2011)			1.48 Auramine			
				1.91 ZN			
	Vassall et al. (2011)		1.20 AFB	11.55 MGIT			
	Andrews et al. (2012)		3.49	11.29 liquid			
Indonesia	Chaidir et al. (2013)		1.70 LED-FM				
			1.60 ZN				

Country	Author (year)	CXR	Smear	Culture	TST	IGRA
	Mahendradhata et al. (2010)		2.50			
Romania	Olaru-Peter et al. (2014)			4.84	MODS	
				4.81	L-J	
				11.34	MB/BacT®	

TB: tuberculosis; CXR: chest radiograph; TST: tuberculin skin test; IGRA: interferon gamma release assay; AFB: acid fast bacilli; LED-FM: light emitting diode-fluorescence microscopy; ZN: Ziehl-Neelsen; L-J: Lowenstein-Jensen; MGIT: Mycobacteria Growth Indicator Tube; MODS: microscopic observation drug susceptibility

Only one paper presented the costs of a TST (US\$ 1.23 in South Africa) while no relevant studies had the cost of an IGRA (Hausler et al., 2006). The cost of a CXR was reported in four studies, three of which were in South Africa. The reported cost of a smear test, either light-emitting diodes by Fluorescence microscope (LED-FM) or Ziehl-Neelsen (ZN) ranged from US\$ 0.39 in India to US\$ 3.49 in South Africa (Muniyandi et al., 2006, Andrews et al., 2012). The range was much larger for sputum culture tests, costing as little as US\$ 4.81 in Romania to as much as US\$ 61.22 in China, for a solid medium Lowenstein-Jensen (L-J) test (Olaru-Peter et al., 2014).

For Indonesia, two papers presented disaggregated diagnostic costs for sputum smear tests. The first reported US\$ 1.51 for diagnosis consultation and US\$ 0.99 (one slide) for smear microscopy in 2009 (Mahendradhata et al., 2010). The second study reported the average running costs per slide for a LED-FM and a ZN smear as \$ 1.70 and \$ 1.60, respectively (Chaidir et al., 2013). The latter study was unclear in describing how the costs were obtained and what was included in the 'running costs' of the tests. The authors also omitted the year of data and the currency of the costs.

The only TB diagnostic costs identified in Romania was from a study that sought to compare various forms of culture tests: microscopic-observation drug-susceptibility (MODS) assay, solid L-J medium and MB/BacT[®] in terms of sensitivity, contamination rate, speed and costs (Olaru-Peter et al., 2014). The method used to determine the costs was not described, but simply referred to as 'sample processing' and 'specific cost per sample'. These combined values resulted in costs of € 4.4 (US\$ 4.84) for MODS, € 4.37 (US\$ 4.81) for L-J and € 13.3 (US\$ 11.34) for MB/BacT[®].

2.3 Summary

TB treatment costs in Indonesia, for six months of DOTS, from the provider perspective was similar at public and private health facilities, but increased by 2.5 times from public to private for direct medical costs from the patient perspective. This then meant that total out-of-pocket payments and productivity losses for patients increased by an astounding ten-fold increase (1042%), from US\$ 33.74 in the public sector to US\$ 351.66 in the private sector, placing a heavy burden on patients without private health insurance to reimburse them for these costs. No TB treatment costs were identified for Romania in the published literature.

The two studies reporting the costs of different types of smear analysis for TB diagnosis in Indonesia are not reliable since key reporting data (year and currency of costs) were omitted (Husereau et al., 2013). Similarly, for the cost of TB diagnostics in Romania, a study compared costs of three types of culture tests but the costing method was not clearly described.

The cost data obtained for TB in Indonesia and Romania is a useful reference point but all of these studies assessed TB interventions in silos, with some findings poorly reported. The work in this PhD aims to assess the costs of integrated TB-DM services and therefore provide evidence needed for planning the continuum of care for people with concurrent disease.

Systematic literature reviews were not conducted for DM diagnostics or treatment but the relevant literature are discussed in Chapters 8 and 11, respectively.

PART II - METHODS

This section describes the general and specific health contexts of the three countries included in this PhD, Indonesia, Peru and Romania. It also describes the study protocols, sampling and workflow of TANDEM's cross-sectional study and randomised controlled trial. Finally, an overview is included of the quantitative and qualitative methods utilised to provide an economic and feasibility assessment of bi-directional screening for TB and DM as well as management of these concurrent diseases. The methods used are described in more detail in the respective research papers.

Chapter 3 Study settings

In this chapter an overview is provided of the health systems in Indonesia, Peru and Romania. There is a description of how services are delivered for TB and DM separately, which will provide the context for recommendations on how to integrate services for the two diseases. The sites at which TANDEM participants were enrolled, monitored and treated are also described.

Indonesia, Peru and Romania are not only geographically and culturally disparate but there is also quite a contrast in the social and economic indicators (Table 3-1), with a population contraction in Romania (-0.8%) and growth in Indonesia and Peru (1.3% both) between 2010 and 2015. As Indonesia and Peru's populations grow, their maternal mortality ratios and infant mortality rates fare worse than Romania. Despite performing so poorly, Peru spent almost twice as much of its gross domestic product (GDP) on health compared to Indonesia. Indonesia has a population that is 8 times that of Peru and 13 times that of Romania, but a GDP that is only 4.5 times as large as that of either country.

Table 3-1: Social, health and economic indicators, Indonesia and Romania

Indicator	Indonesia	Peru	Romania	Year
Population (projected, 000) ^α	260,581	31,774	19,373	2016
Population density (per sq. km) ^α	143.8	24.8	84.2	2016
Population growth rate (average annual %) ^α	1.3	1.3	-0.8	2010-2015
Urban population (%) ^α	53.7	78.6	54.6	2015
Fertility rate, total (live births per woman) ^α	2.5	2.5	1.5	2010-2015
Life expectancy at birth (female/male, years) ^β	71/67	78/73	79 /71	2015
Under-5 mortality rate (per 1000 live births) ^β	27	17	11	2015
Maternal mortality ratio (per 100,000 live births) ^β	126	68	31	2015
Total health expenditure (% of GDP) ^α	2.9	5.5	5.6	2014
Physicians (per 10,000 population) ^β	2.0	11.3	23.9	2013
Nurses (per 10,000 population) ^β	13.8	15.1	55.1	2013
Beds (per 10,000 population)	9.0	15.0	61.0	2012
GDP (million current US\$) ^α	888,538	201,809	199,045	2014
GDP growth rate (annual %, constant 2005 prices) ^α	5.0	2.4	2.8	2014
GDP per capita (current US\$) ^α	3,492	6,516	10,129	2014
GDP-gross domestic product				

Sources: ^aWorld Statistics Pocketbook 2016, United Nations Statistics Division; ^bWorld Health Statistics Report 2016: Monitoring health for the SDGs, WHO

3.1 Indonesia

3.1.1 Health system and service provision

The life expectancy in Indonesia for 2015 was 73 years for females and 69 years for males (Table 3-1) (UNData, 2016). In 2014 the main causes of death were cardiovascular disease (37%), followed by communicable diseases (including TB) (22%), cancers (13%) and other NCDs (10%) (WHO, 2014c). For the same year, diagnosed and undiagnosed DM was estimated to directly account for 6% (90,000) of the 1.5 million deaths (WHO, 2014c), but as many as 184,985 deaths (12%) were considered to be DM-related, including some due to cardiovascular disease (IDF, 2011).

The most recent data available indicated that 3% of the total 2014 gross domestic product (GDP) was spent on health, which is well below the target of 15% (WHO, 2009, UNSD, 2016). Indonesia has a public-private mix for health care provision with private health care accounting for approximately 40% of services provided (WB, 2013). The government provided 40% of the expenditure, but the majority (60.4%) was private expenditure (mostly out-of-pocket payments and a much smaller component for private prepaid plans) (WHO, 2015g). This resulted in a health expenditure of US\$ 108 per person in 2012 (WHO, 2015g). The Ministry of Finance provides the funds for health for the entire year to the Ministry of Health, who then acts as financier and provider for most public health services (WB, 2009). The Ministry of Health receives funds according to a budget based on the previous year rather than actual expenditure or estimated need.

Within the Indonesian public health care delivery system there are centralised MoH hospitals (teaching and specialised hospitals), provincial hospitals, district hospitals, sub-district primary health centres (Puskesmas), and village mobile clinics (Puskesmas Keliling – four wheeled vehicles or boats) (WB, 2009, WHO, 2009). There is a three-tier referral system, but many patients can access services directly at the secondary or tertiary levels. As of 2013, 2.0 physicians and 13.8 nurses were available per 10,000 population (WHO,

2015g). There are 9.0 beds per 10,000 persons through 3.5 primary health care centres (Puskesmas) and 5.6 hospitals per 1,000,000 persons (WB, 2008), resulting in a total of 1,632 secondary care hospitals and over 9,000 Puskesmases (WB, 2013).

Health services and salaries are funded by central government as well as community-based resources (MOH, 2014). Traditionally, a point of care payment is required at public health facilities if individuals do not have some form of health insurance. Jamkesmas, a national health insurance program for the poor and near-poor, is central government financed by general taxation and administered through the Ministry of Health. Jamkesmas coverage has gradually increased to cover more near-poor and vulnerable individuals, and on 1st January 2014 it was merged with other social insurance programmes in an effort to fully move towards universal health care (UHC) by 2019 (WB, 2013, Lancet, 2014). The other social insurance programmes included Jamkesda, which also provided coverage to the poor and near-poor, but was funded by districts with some out-of-pocket payment. Secondly, Askes administered by the Ministry of Health, which covers civil servants and military retirees who contribute through their salary, which is matched by the government. Thirdly, free health services to military personnel through the Ministry of Defense (WB, 2009). Fourthly, the Jamsostek health insurance provides coverage through the Ministry of Labor to private sector employees and their dependents in companies with ten or more employees. Civil servants and military personnel are also covered by Jamsostek, contributing through their salary. Fifth, private health insurances are administered and regulated by the Ministry of Finance, but financed through premiums by private, formal sector employees and dependents. The National Health Insurance Agency (*Badan Penyelenggara Jaminan Sosial - BPJS*) coordinates all the social health insurance programmes that have been merged to provide UHC, under a scheme called Jaminan Kesehatan Nasional (JKN) (Lancet, 2014). Despite all these mechanisms to finance health care in Indonesia, as much as 50% of the population remained uninsured in 2014 (WHO, 2016b). A high proportion of people in informal work sectors, self-employed and unemployed not being eligible for coverage, and others being unaware that they are eligible for insurance coverage from the government. In addition to this inequitable

access, the JKN has been plagued by insufficiently trained personnel to administer the plan and ineffective management (Reich et al., 2016).

The Ministry of Health manages and operates the teaching and specialised hospitals as well as recruits and allocates public sector health professionals. Health policies are produced and regulated by the Ministry of Health, including disease specific programmes, such as those for TB or HIV/AIDS (WB, 2009). In the 1980s the Health Sector Development Plan produced a health system in Indonesia that focused on primary health care and included health professionals with modest training. Political decentralisation began in 1999 and districts became more involved in decision making for the provision of health care and other social services. Decentralisation was expanded to administrative and financial functions within the health sector in 2006. However, funding of TB programme activities remains centralised, with money coming directly from the Ministry of Health or external donors, such as the Global Fund (WHO, 2009).

The National TB Programme (NTP):

The National TB Programme (NTP) was established in 1970. Prior to 1972, TB treatment occurred exclusively in hospitals. From 1972 to the early 1990s TB treatment was focused on diagnosis and treatment at the Puskesmas. The directly observed therapy, short-course (DOTS) strategy was piloted in Indonesia in 1993 and integrated into national policy in 1995, but DOTS uptake was slow and only became widespread around 2000, with technical support from the WHO and the Royal Netherlands Association (KNCV) Tuberculosis Foundation (WHO, 2009).

The NTP has released four National Strategic Plans (NSPs) since 2002. The latest plan covers 2015 to 2019 (WHO, 2015d). The goal of the plan is to “end the tuberculosis epidemic in Indonesia”, but also incorporates the goal of moving towards universal access for all people exposed to TB (WHO, 2016b). The activities are similar to those of the 2010-2014 NSP, but with more ambitious targets (WHO, 2015d). The main activities of the 2015-2019 Strategic Plan include (WHO, 2015d):

- scaling-up public-public and public-private partnerships to support quality DOTS expansion and ensuring their compliance to International Standards for TB care
- implementing Xpert[®] MTB/RIF machines for faster diagnosis of DS-TB and Rifampicin resistant (RR) TB
- active DR-TB surveillance
- scaling-up of isoniazid preventative therapy (IPT) in people living with HIV and children as part of the drive to address MDR-TB, TB/HIV, paediatric TB, the needs of the poor and other vulnerable groups
- empowering TB patients and affected communities through scale-up of advocacy, communication and mobilisation activities
- contributing to health system strengthening, particularly capacity building of TB staff, a drug management plan to prevent stock-outs and the national laboratory network to increase the capacity for sputum smear and culture testing
- strengthening policy and the central-local government commitment in the TB control programme
- promoting research, development and utilisation of strategic information.

While none of these activities directly address the challenges of comorbidity with DM, the efforts to improve the hospital-DOTS linkages and the laboratory network can provide opportunities to integrate DM services with those of TB. People with diabetes are recognised as a high-risk group for TB in the strategic plan.

In 2014 the total government budget for the TB control programme was US\$133 million, of which the government contributed 13% (WHO, 2015d). The remainder was covered by international donors, such as The Global Fund to Fight AIDS, Tuberculosis and Malaria (The Global Fund) and the United States Agency for International Development (USAID). This heavy dependence on donor funding is a key area of concern for the NTP. Efforts are being made to increase financial contributions from the government at the district level with the ultimate goal of phasing out all donor funding by 2018 (WHO, 2016b). The cost of implementing the new TB control strategy for 2015-2019 was estimated at US\$ 926 million, with annual costs increasing from US\$ 128 million in 2015 to US\$ 250 million in 2019. The majority (38%) of the budget is earmarked for successful DOTS treatment in the public and private sectors as well as infrastructure and human resource strengthening (19%) (WHO, 2016b). The average expenditure per notified TB patient in 2014 was just over US\$ 100 (WHO, 2015e).

The MOH administratively manages TB control under three directorates (Medical Service, Community Health and Center for Disease Control), which oversee the National TB Control Programme and TB services in Puskesmas and Hospitals (MOH, 2010). TB services are also performed by private providers, prisons, military services and employers. A core DOTS team operates at the provincial level under the NTP. This team consists of a Provincial Project Officer (PPO) and head office staff, who are responsible for oversight of the health services at the district level as well as improving the quality of DOTS services in hospitals. The Head of the District Health Office is responsible for planning, budgeting, implementing and monitoring health programmes. A TB supervisor (wasor) operates within the District Health Office to monitor and advise on all TB activities in the district, as well as maintaining treatment registers and ensure drug availability.

There is high staff turnover and an inappropriate distribution of staff in the health workforce, which has been blamed on the poor implementation of the decentralisation policy, and resulted in a shortage of trained TB staff, particularly in hospitals (MOH, 2010). There is an effort to scale up DOTS training and improve the human resource capacity, with improvements being most notable at Puskesmas, where 98% of TB staff have been DOTS trained, compared to only 24% of TB staff in hospitals.

Since the implementation of UHC in 2014, all medication on the drug formulary list are available free of charge, including anti-TB drugs, which are available from DOTS clinics at Puskesmas or hospitals. Fees for hospital visits and laboratory tests (TB monitoring, adverse events and monitoring for co-morbidities) are sometimes charged to patients with TB, but according to the National TB Strategy, all public and private health care services should be free of charge to people with TB through linkages with the NTP (MOH, 2010, Collins and Parihatin, 2011). Therefore, the expectation is that the expansion of the Jamkesmas insurance coverage has improved access to TB treatment and reduced the financial burden of some people with TB. However, many people with TB are in the informal work sectors (such as farming, fishing, et cetera) or not regularly employed and therefore have not yet benefited from the improved access offered under Jamkesmas.

In both the public and private sectors sputum smear is underused despite being the recommended minimum for TB diagnosis. Regional reference laboratories have been tasked with building capacity for culture tests. The most commonly used diagnostic is chest radiography (WHO, 2009).

The treatment of TB is focused in Puskesmases, with complex cases being referred to hospitals or lung health facilities. By 2009 the six month, drug-susceptible DOTS regimen had been implemented in 98% (n=7,200) of Puskesmases, all of the chest clinics (n=26) and lung hospitals (n=9), and 30% (n=494) of the public, government, military, police and private hospitals (MOH, 2010). Regulation of private practitioners is not strong and the level of DOTS implementation in that sector is unclear.

First line anti-TB drugs in Indonesia follows the Fixed Drug Combination (FDC) regimen, which provides a standardised package of isoniazid, rifampicin, pyrazinamide and ethambutol to people being treated for TB for the first time and without any drug resistance. Individual packages (CombiPak) are also available to treat the side effects of the anti-TB drugs. These drug packages, along with buffer supplies to prevent stock outs, are distributed by the central government to district level facilities and are cheaper than the individual drugs, but only 13 out of the 32 provinces have access to the FDCs (MOH, 2010).

Diabetes Services:

DM health care services in Indonesia are meant to be provided by endocrinologists, but as there is an insufficient supply of these, primary care physicians and nurses with DM training also provide care at DM clinics. However, most DM care occurs through outpatient services in hospitals (Wibowo et al., 2016, Soewondo et al., 2013). Clinical practice guidelines, which are the responsibility of the Indonesian Society of Endocrinology (“Perkeni”), were initially established in 1993 and are regularly updated (Soewondo et al., 2013). The Perkeni guidelines focus on screening and diagnosis (Rudianto et al., 2011). The recommended protocol for DM diagnosis is two-tiered: if a person has classic symptoms (including polyuria, polyphagia, polydipsia and unintentional

weight loss or gain), either a random blood glucose (RBG) or a fasting plasma glucose (FPG) test should be performed. If a person has no classic symptoms, the oral glucose tolerance test (OGTT) should be performed as per WHO guidelines (WHO, 2006). If the result is negative for a person in a high-risk group, such as people with a poor diet, sedentary lifestyle, family history of DM or other related comorbidities, the recommendation is further annual screening to monitor the individual.

The management of DM in Indonesia is an adaptation of the International Diabetes Federation's and the American Diabetes Association's guidelines for T2DM (Widyahening et al., 2014). The initial treatment protocol for people with elevated blood glucose is two to four weeks of lifestyle modification (diet and exercise) (Soewondo, 2011). If that is unsuccessful in achieving a lowered blood glucose level, pharmacologic interventions can be prescribed, including oral antidiabetic drug (OAD) monotherapy, insulin monotherapy, or combined OAD and insulin (Soewondo et al., 2013).

There are several challenges within the health system that hamper the care of DM (Soewondo et al., 2013). First, some of the essential OADs for DM and related comorbidities and complications are not available free of charge as part of the national drug formulary. Secondly, health care services in rural and remote inland or small island parts of Indonesia are limited; and thirdly, the clinical guidelines are not evidence informed, as illustrated by renal care guidelines, which did not include the renal registry or regular health survey in its development.

In late 2015, through coordination by the Union and the Ministry of Health in the Republic of Indonesia, seven Indonesian professional health organisations committed to addressing concurrent TB-DM (The Union, 2015b). The first step will be to develop guidelines and a manual that allows accelerated implementation of bi-directional screening to ensure no opportunity to detect concurrent disease is missed. This will be followed by management of the diseases at primary, secondary and tertiary level health facilities.

3.1.2 Study sites

In Bandung 48 health facilities were involved in the TANDEM study (Figure 3-1). The Balai Laboratorium Kesehatan (BLK) is a provincial, government owned referral laboratory serving a catchment population of 43 million. Sputum samples for TB screening were collected and analysed at this facility.

BLK is across the street from the Hasan Sadikin Hospital (RSHS), a teaching and referral hospital serving the same population with a bed capacity of 935. There were approximately 614,000 hospital visits during 2014. In the TANDEM study, people with DM were diagnosed and managed in the Endocrinology Clinic within RSHS. CXRs for TB screening in patients with DM were performed in the Radiology Department of RSHS and laboratory analysis on blood samples were done in the Clinical Pathology Laboratory at RSHS. Patients identified to have both TB and DM were managed for both diseases in the DOTS clinic in RSHS.

The Universitas Padjadjaran (UNPAD) Teaching Hospital completes the triangle of large health facilities in the west of Bandung city. Here, health professionals were trained for TANDEM patient recruitment and management. Patients involved in any of the numerous research studies being conducted are seen at this hospital. For TANDEM, patients with suspected TB were initially referred from 30 Puskesmas to a multi-study TB clinic at UNPAD. Here, patients received confirmation of active TB, they were screened for DM, and if DM was confirmed, they were randomised to either the standard DM care or intensive DM monitoring arms of the TANDEM RCT. Management of both diseases, including collection of anti-TB drugs, oral anti-diabetic drugs or insulin, occurred at the DOTS clinic for patients in the intensive DM monitoring arm and at various Puskesmas within Bandung for patients in the standard DM care arm.

To augment recruitment of patients with TB, an additional district hospital in east Bandung city, Ujung Berung Hospital (RSUB), was included in the study in March 2015, along with 14 satellite Puskesmas, which were associated with the original 30. Patients with suspected TB at Puskesmas in the east of Bandung city were referred to RSUB,

where they were confirmed for TB and then screened for DM by TANDEM staff, consisting of two doctors and one nurse.

Figure 3-1: Map of Indonesia and the city of Bandung indicating the TANDEM study sites



3.2 Peru

3.2.1 Health system and service provision

Peru's female and male life expectancies were 78 years and 73 years, respectively (Table 3-1). The main causes of death in adults (30-70 years) in Peru in 2014 were communicable (including TB), maternal, perinatal and nutritional conditions (24%), cardiovascular diseases (22%), cancers (20%), chronic respiratory diseases (4%) and other NCDs (18%) (WHO, 2014c). DM was directly accountable for 2% of deaths, but almost 6% of adult deaths were DM-related and included diagnosed and undiagnosed DM (WHO, 2014c, IDF, 2015).

Health expenditure has consistently remained between 4% and 5% over the last two decades, but peaked at just under 6% in 2014 (Table 3-1). In that year, Ministry of Health (MINSa) expenditure was 61% (funded by general taxation), patient out of pocket expenditure was 29%, and the remaining 10% was from private health insurance and non-governmental organisations (WHO, 2014b). Government per capita expenditure on health was US\$ 396, out of pocket payments was US\$ 221. Private health insurance usage was low at 3%.

EsSalud, in existence since the 1940s, is the social health insurance system in Peru that covers employed individuals and their families (approximately 24% of the population), through contributions of 9% of earnings (Alcalde-Rabanal et al., 2011, Villena, 2015). Comprehensive Health Insurance (Seguro Integral de Salud - SIS) was introduced in 2002 to provide fully subsidised health insurance coverage to the poor and extremely poor. SIS was expanded in 2007 to offer partial subsidisation of coverage for self-employed and people in informal work sectors or small businesses. The coverage by SIS was 31% of the population in 2013 (Villena, 2015). Health insurance coverage for the military, police and their families is provided through two systems: Armed Forces (Sanidades de las Fuerzas Armadas - FFAA) and National Police (Policía Nacional de Perú - PNP). The FFAA, PNP and private sector provide health services for approximately 10% of the population. More than a third of the population were reported to have no health insurance in 2013 (Villena,

2015). UHC was introduced in 2010 in order to reform the health system by improving accountability mechanisms and providing minimum benefit requirements for all (Alcalde-Rabanal et al., 2011).

The National TB Programme (NTP)

The Peruvian government established the National Anti-Tuberculosis Service (NATS) in 1940, which introduced mandatory BCG vaccinations for children, followed by various drugs and treatment programmes from 1960s to 1980s (2011). Daily supervision of anti-TB drugs began in 1980 as part of a 12-month treatment regimen, which was soon replaced by an 8-month regimen.

In 1990, the government identified TB as a priority and provided support and funding to establish the National TB Control Programme (NTP) (Harvard Medical School, 2011). A charismatic and driven young doctor was appointed the director and the first TB guidelines were published in 1991. It included an early version of the current DOTS strategy: six months of treatment split into a 2-month intensive phase and a 4-month continuation phase. The efforts in Peru saw the NTP become a global model of efficiency; between 2002 and 2003 the country was on target for achieving the Millennium Development Goals, but this halted in 2004 due to decreased case detection driven by the decade long health reform process that began in earnest in 1993 under President Alberto Fujimori (Peru Stop TB Committee, 2009).

The average budget allocated to the NTP was US\$ 10 million in 2008 (Peru Stop TB Committee, 2009). The Ministry of Finance provided 70% of these funds and the remainder came from International funders, including The Global Fund, USAID, Centers for Disease Control and Prevention, and Partners in Health. In 2007, 91% of the NTP budget was spent on treatment, 4% on diagnostics and less than 1% on preventative activities.

The 2009-2018 Multisectoral Strategic Plan for the National Response to Tuberculosis in Peru includes instruction on free and rapid diagnostic tests, as well as free treatment for

TB and MDR-TB. Diagnosis protocols include smear microscopy, culture and drug sensitivity testing.

Diabetes Services

A national health strategy for the prevention of NCDs (2005) and legislation outlining the legal framework for preventing, treating and tracking DM in the Peruvian population (2006) do exist, but there is no WHO recognised national policy or action plan to guide the response to the increasing burden of DM in Peru (Villena, 2015). Additionally, there is no protocol or guideline for primary care DM management; despite a draft of one approved by MINSA in 2014, it is yet to be published and distributed (IDF, 2014, Villena, 2015).

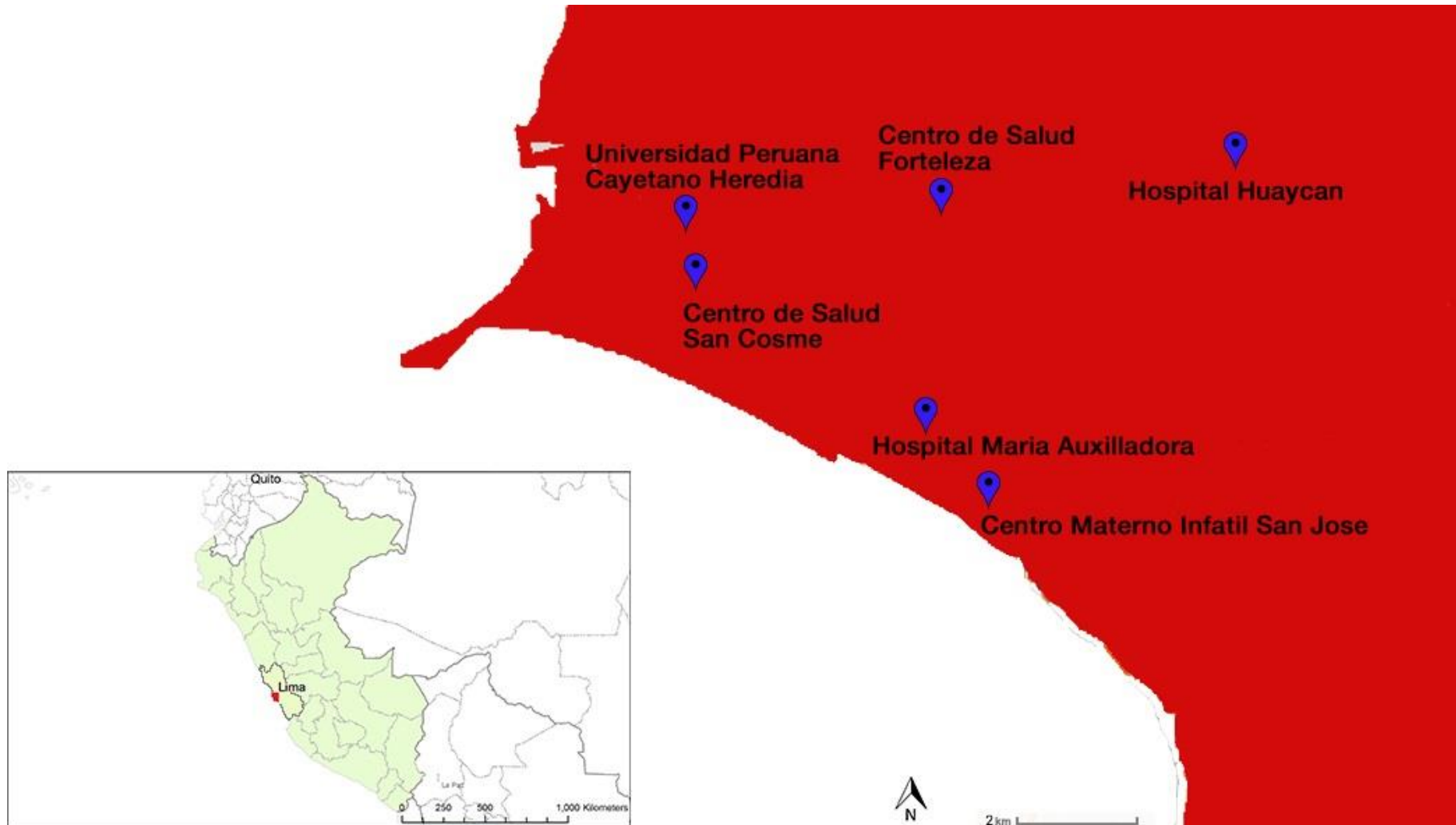
There are 300 registered endocrinologists providing care for the 1.23 million [95% CI: 0.87 – 1.93 million] people with DM in Peru (Villena, 2015, IDF, 2011). Given the lack of national guidelines, most endocrinologists follow the American Diabetes Association's guidelines for DM management, with a target of HbA_{1c} <7% (Villena, 2015). Despite the presence of a wide range of DM drugs on the Peruvian market, only insulin, metformin and glyburide are available on the national drug formulary for access at public health facilities. Continuous glucose monitoring devices and insulin pumps are not covered by any health insurance scheme and are therefore not widely used in Peru.

While there is an acknowledgement of the TB-DM burden in Peru, there is a delayed government response to and stewardship in addressing the increasing prevalence of DM in patients with TB. It is therefore not surprising that no position has been identified that guides how the health system should respond to TB-DM in Peru (Harries et al., 2016), despite published prevalence values between 11% and 19% DM in patients with TB (Magee et al., 2013, PAHO and WHO, 2013). DM services, including drugs and tests, for patients with TB are free at the point of care while patients are in the care of the more established NTP network (Riza et al., 2014). Once TB treatment has ended, all costs associated with DM care must be borne by the patient.

3.2.2 Study sites

There were one general hospital, one community hospital and three health centres included in the TANDEM study, which are located in various parts of the 2,800 square kilometres of the Lima Metropolitan Area, Peru (Figure 3-2). The population of this city is almost ten million. Patients with DM were recruited from the endocrinology clinic at the Hospital General Maria Auxiliadora (HAMA) in San Juan de Miraflores, south Lima, which is affiliated with the Universidad Científica del Sur. Patients with suspected TB were confirmed and recruited for DM screening at four health facilities: Hospital Huaycan, in Ate-Vitarte (east Lima); Centro de Salud Forteleza, also in Ate-Vitarte; Centro de Salud San Cosme, La Victoria (near the city centre); and Centro Materno Infantil San Jose in south Lima. These sites were coordinated by TANDEM staff based at the collaborating facility, Universidad Peruana Cayetano Heredia (UPCH) in the low-income district of San Martin de Porres in the north of the Lima Metropolitan Area.

Figure 3-2: Map of Peru and the metropolitan area of Lima indicating the TANDEM study sites



3.3 Romania

3.3.1 Health system and service provision

In Romania, 2015 life expectancy at birth was 78 years for females and 71 years for males (Table 3-1). A total of 254,000 people died in 2014, of which cardiovascular disease was accountable for more than half (58%), cancers responsible for 20%, other NCDs 10% and communicable, maternal, perinatal and nutritional conditions (including TB) and injuries accounted for 4% each (WHO, 2014c). DM (diagnosed and undiagnosed) was directly responsible for 1% of adult (30-70 years) deaths in 2014, but 7% of deaths were considered DM-related (WHO, 2014c, IDF, 2015).

Health expenditure accounted for 6% of 2014 GDP (Table 3-1) (US\$ 1172.0 billion (WB, 2012)); the government was responsible for 80.3% of this expenditure, with the remainder coming from private sources. These private payments are used to pay for services in the private health sector, as well as co-payments and informal payments in the public sector (WHO and ECDC, 2015). Expenditure on health resulted in US\$ 468 per person in 2012, which was a 641% increase from 2000 when only US\$ 73 was spent per person.

The National Health Insurance House (NHIH), through the Ministry of Finance, collects compulsory health insurance payments from the salary of formal sector workers. People with disabilities, pregnant women and people with TB and HIV are exempt, among others. In 2004, this social health insurance contribution accounted for approximately 83% and general taxation approximately 16% of the revenue provided to the NHIH for health care provision (Vlădescu et al., 2008). This insurance body ensures that all Romanians have health care coverage for primary, secondary and tertiary health care, but with co-payments for hospital admission as well as 50-100% point of care payments for tests and medicines.

The National TB Programme (NTP)

The NTP budget for 2014 was US\$ 7.4 million, with an average of just over US\$ 400 spent per notified TB patient (WHO, 2015b, WHO, 2015e). The NHIH is also responsible for distribution and regulation of funds to national programmes, such as the NTP or directly to pulmonology hospitals. These procure medical equipment, drugs and laboratory consumables from pre-approved suppliers that have been vetted by the Unit of Central Procurement in the Ministry of Health (WHO and ECDC, 2015).

The Tuberculosis National Strategic Plan 2013-2017 includes advice from the National Commission of Pulmonology, Allergology and Clinical Immunology, which is comprised of members that are nominated by the Ministry of Health (WHO and ECDC, 2015). Governance of the NTP falls directly under the Ministry of Health. The central unit of the NTP contains 10 people, including eight part-time clinicians, one full-time finance officer and one full-time secretary, but is not functioning at full capacity. The NTP also employs 42 TB coordinators, one for each county and one for Bucharest. These coordinators are responsible for local management and coordination of staff, laboratory commodities and drugs provided by the NTP. There are 80 pulmonology departments in general hospitals, 33 pulmonary hospitals and four sanatoria, with a total capacity of 5,625 TB beds. There are a total of 105 laboratories in the national TB laboratory network. The laboratories range from level 1 (for smear microscopy testing only) to level 3 (for smear microscopy, culture and drug susceptibility testing). Two level 3 laboratories operate as National TB Reference Laboratories, one in Bucharest in the south east and the other in Cluj in the north west (WHO and ECDC, 2015).

Family doctors are required to identify potential TB cases and refer those patients to a specialist for diagnosis and treatment. However, this rarely occurs. Most suspected TB cases initially present at hospital emergency departments. Any suspected cases that present in the private sector must be referred to the public sector where all TB treatment occurs.

TB treatment, including anti-TB drugs, diagnostic and monitoring tests, any hospitalisations and medication for adverse events, are free at the point of care for all people diagnosed with the disease (Marica, 2009). However, prior to being identified as having presumptive TB, people experiencing symptoms are required to make co-payments for any investigative tests or medicines required. Patients with presumptive TB may also be required to pay co-payments for additional tests if diagnosis is difficult and for medication for some clinical complications of TB (WHO and ECDC, 2015). It has been estimated that informal payments are paid by more than 60% of patients in order to receive inpatient hospital care (Lewis, 2007).

The national guidelines for TB require three sputum samples for people with presumptive TB, while only two sputum samples are required for patients in TB treatment. Although radiological investigations are not a diagnostic requirement in the national guidelines, CXRs are often taken for people with presumptive TB, along with a clinical examination for symptoms and the sputum samples used for smear microscopy as well as bacteriological culture (WHO and ECDC, 2015).

Despite the adoption of the WHO DOTS strategy in 1998, people with new cases of PTB are treated as in-patients for at least 37 days out of the six-month DS-TB treatment regimen. Hospitalisation occurs even if the patient is not infectious or does not have severe TB disease. Hospitals are reimbursed by the NHIH a fixed amount (€45 per day for hospitals and €36 per day for sanatoria) for each patient with TB as they are considered to have ‘a condition of public health relevance’; a legacy from past policy that has remained, where the intention was to isolate patients with TB from the community (WHO and ECDC, 2015). This has created an economic incentive to hospitalise patients, even if the clinical severity of their condition does not warrant it.

Subsequent outpatient TB treatment, which typically occurs between the second and sixth months, is administered through TB dispensaries (WHO and ECDC, 2015). Standard treatment for new patients with DS-TB consists of two phases. Phase 1 or the intensive phase consists of two months of daily doses of isoniazid, rifampicin, pyrazinamide and

ethambutol (WHO, 2010b). This is followed by the continuation or maintenance phase, where isoniazid and rifampicin are taken every other day for four months. This standard TB treatment regimen may be adapted based on the needs of the patient. People with DR-TB or patients who previously started TB treatment receive a different TB treatment regimen based on their personal situation.

There are 184 TB dispensaries staffed by pulmonologists, TB nurses and TB pharmacists who manage the care of people with TB until the end of the continuation phase (WHO and ECDC, 2015). The infrastructure of the individual dispensary determines whether the care is self-administered every other day (based on a weekly or monthly supply of anti-TB drugs) or daily clinician administered DOT. Family doctors or community nurse-based DOT programmes are rare due to the discontinuation of the NHIH funded incentives for family doctors to perform TB related activities and a lack of funding for home visits by nurses.

Through a national tender process conducted by the NHIH, the price of anti-TB drugs was renegotiated in 2013. Using state funds supplemented by international donors, hospitals are able to procure anti-TB drugs monthly, but unfortunately without a buffer to prevent stock outs, which is not uncommon. First and second line TB drugs (with the exception of capreomycin and para-aminosalicylic acid) are obtained free of charge by patients from hospitals or TB dispensary pharmacies.

People diagnosed with TB are required to stay away from work for the entire duration (six months) of the treatment. Employed patients will receive sick pay from the government (NHIH), but the benefit may not extend to the entire period of TB treatment. Patients who are self-employed, unemployed or perform casual work are not eligible for sick pay and there is no social protection system to provide a safety net when income is lost (WHO and ECDC, 2015).

Diabetes Services

A national diabetes registry for Romania was established in 1941 (Donicova et al., 2011). Care for DM is provided by specialists diabetologists in both the public and private sector.

They are contracted and paid by the NHIH, but can only work in one sector. DM consultations, glucometers with strips and prescriptions are accessed free of charge in both sectors. However, additional services, such as blood and urine tests, administrative fees and some inpatient care in private clinics are largely out-of-pocket payments for patients. DM care can also be provided by family doctors or internal medicine specialists, which is needed to compensate for the shortage of diabetologists.

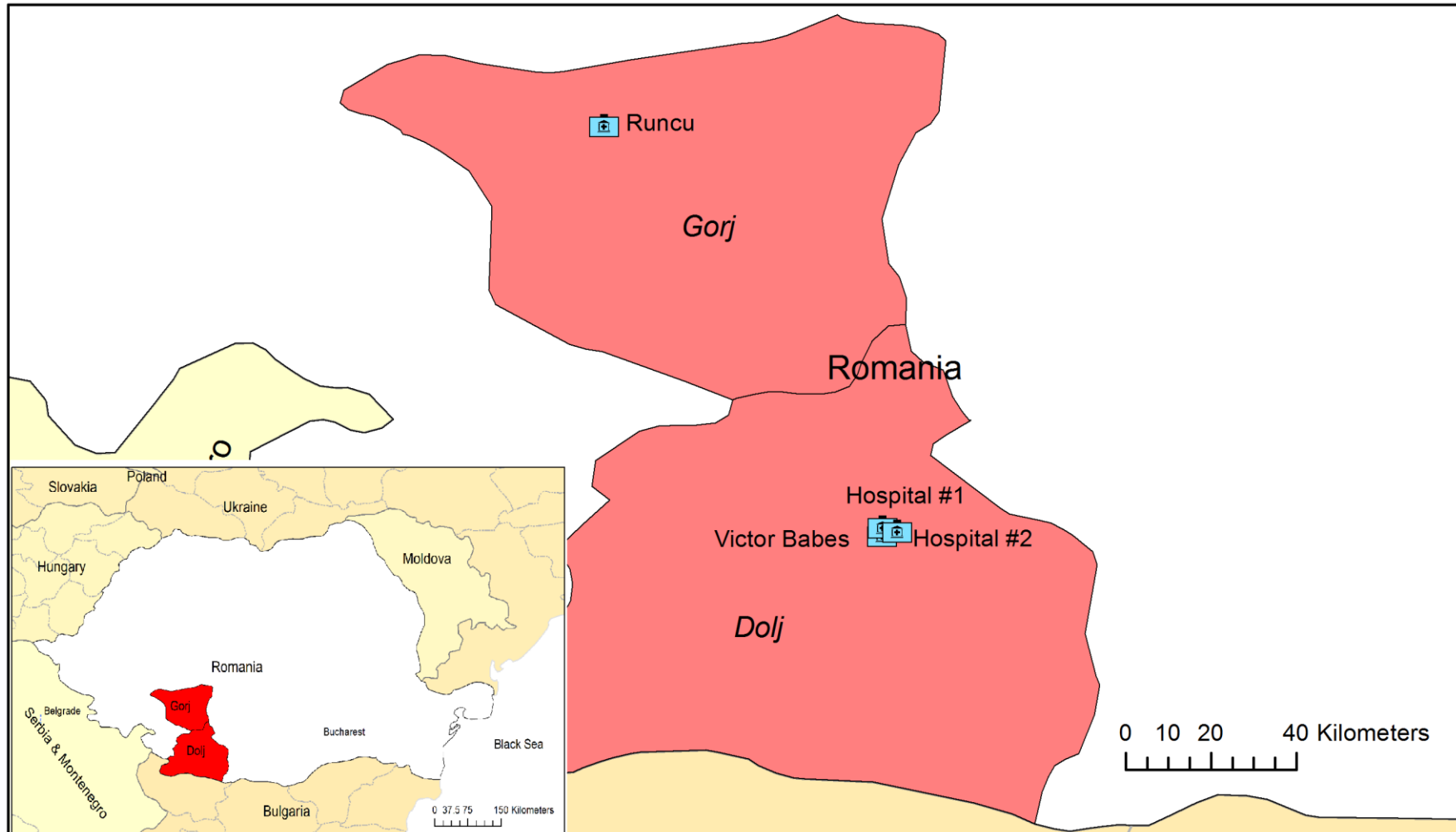
Dieticians are not part of the management team for people with DM. Nurses provide most of the dietary guidance for patients in hospitals, but they are not available in outpatient DM clinics. Podiatry care often occurs in the university hospital of major cities. The podiatry team consists of a doctor specialized in dermatology and a nurse.

NHIH guidelines state that patients with concurrent diseases must be treated for the diseases separately. Hence, people with TB and DM would need to be treated for TB as described above, but then also require that their DM be managed at a hospital with an endocrinology department (WHO and ECDC, 2015).

3.3.2 Study sites

Patients were recruited, screened and treated at four hospitals in the southwest region of Romania, called Oltenia (Figure 3-3).

Figure 3-3: Map of Romania and the counties of Dolj and Gorj indicating the TANDEM study sites



Within this region, there are two general hospitals in Dolj county where patients with DM are treated as inpatients in the Diabetes Department for an average of seven days; the Emergency County Hospital Craiova (Hospital #1) and Craiova Philanthropic Municipal Hospital (Hospital #2). Additionally, there is a TB hospital (also called sanatorium) and an infectious diseases hospital with a TB ward. These are the Hospital for Lung Diseases “Tudor Vladimirescu” (Runcu TB Hospital) in Gorj; and the “Dr. Victor Babes” Clinical Hospital for Infectious Diseases and Pneumology (Victor Babes Hospital) in Dolj, respectively. All patients with TB, whether or not they also had DM were treated as inpatients for at least 37 days or until their sputum smear became negative in either Runcu or Victor Babes.

After smear negative TB-DM patients were discharged, they were monitored for DM as outpatients by local diabetologists or family doctors as per standard DM care (standard DM care arm of RCT) or followed-up by field workers and three diabetologists, with remote guidance from a senior diabetologist in Bucharest (intensive DM monitoring arm of RCT). TB treatment continued on an outpatient basis at a TB dispensary close to the patient’s home or by ambulatory pulmonologists for patients from the Runcu TB Hospital. The intention was to follow patients in both arms, but as explained in Chapter 1, the RCT was discontinued after the first 40 patients were recruited and before any patients with TB-DM reached the six-month mark, largely due to discordance between the TANDEM DM management protocol and regulated DM management in Romania.

3.4 Country and site selection

For the TANDEM study, it was important to select countries from different geographic regions so that diverse cultural, health system structures and population demographics could be represented. The burden of TB and DM also needed to be sufficiently high so that there would be sufficient TB-DM burden within the populations to be able to detect a causal effect. The countries also needed to be typical of settings where economic improvement and changes in lifestyles would be likely to increase the risk of DM substantially. During the TANDEM proposal development in 2011, current data indicated

that Peru and Romania had some of the highest TB incidence rates in the South American and European regions respectively (106 and 159 per 100,000 population respectively) and an expected increase of DM between 90% and 160% (WHO, 2010a). With a TB incidence of 189 per 100,000 population (WHO, 2010a), Indonesia's burden was well above the recommended screening threshold for TB in people with DM of 100 per 100,000, as recommended by the WHO/Union Framework (The Union and WHO, 2011), even though it was not one of the highest in the South-East Asia region at that time.

The feasibility of conducting the studies was also an important criterion in the country selection and this was largely informed by long-term pre-existing research relationships between the TANDEM project principal investigators and research institutions within the countries as well as the collaborators' capacity to recruit, test and treat patients for TB and DM and their access to potential participants. Given these considerations, Indonesia, Peru and Romania, each with a high burden of TB and an increasing prevalence of DM, were selected.

The UNPAD Teaching Hospital research team in west Bandung, Indonesia (Figure 3-1) has a pre-existing research relationship with RSHS, thus the DOTS and Endocrinology clinics at RSHS were selected for recruitment of people with TB and DM, respectively. The Puskesmas' with the greatest number of patients with TB in Bandung were contacted and asked to participate in the TANDEM study, with the permission and endorsement of the City Health Office. Additional patients with TB were recruited from those facilities along with the 14 additional satellite Puskesmases. Recruitment of patients with TB was lower than expected, particularly from Puskesmases in the east. Therefore, the second hospital, Ujung Berung Hospital, was later added so that patients with suspected TB at Puskesmases in east Bandung could be sent to the district hospital for confirmation and enrolment in TANDEM.

In Peru, TANDEM made a request to the Ministry of Health to get permission and access to health facilities in Lima to conduct the studies in WP1 and WP2. The Ministry of Health then provided a list of facilities with sufficient patient volume to meet the Peru

recruitment targets and that were not already involved in another research project, conducted by any other local or international institution. HAMA, the reference hospital for almost one million people in South Lima (Figure 3-2), was chosen for recruitment of people with DM since the Endocrinology Department and the daily DM clinic are the most accessed DM services in the area, particularly by uninsured people with DM. To recruit people with TB, four health facilities with a high or medium prevalence of TB in the Metropolitan area of Lima were chosen.

In Romania, sites were also purposively selected based on pre-existing research collaborations with the country principal investigator in Dolj and Gorj counties (Figure 3-3) as well as a high volume of patients with TB at the Victor Babes Hospital and the Runcu Hospital, and patients with DM at the two general hospitals.

Chapter 4 TANDEM study protocols and workflow

TANDEM's work package 1 (WP1) (Figure 1-1) comprised four studies, of which two were pertinent to this PhD; these were two cross-sectional studies where people with DM were recruited and screened for TB (Pathway A of Figure 4-1) and people with TB were recruited and screened for DM (Pathway B of Figure 4-1) (bi-directional screening). In work package 2 (WP2), people with TB also diagnosed as having DM were enrolled in a nested randomised controlled trial (RCT) and cohort study (Figure 4-1). In this study, intensive DM monitoring versus standard DM management was delivered during six months of TB treatment followed by 12 additional months of follow-up for TB and DM outcomes.

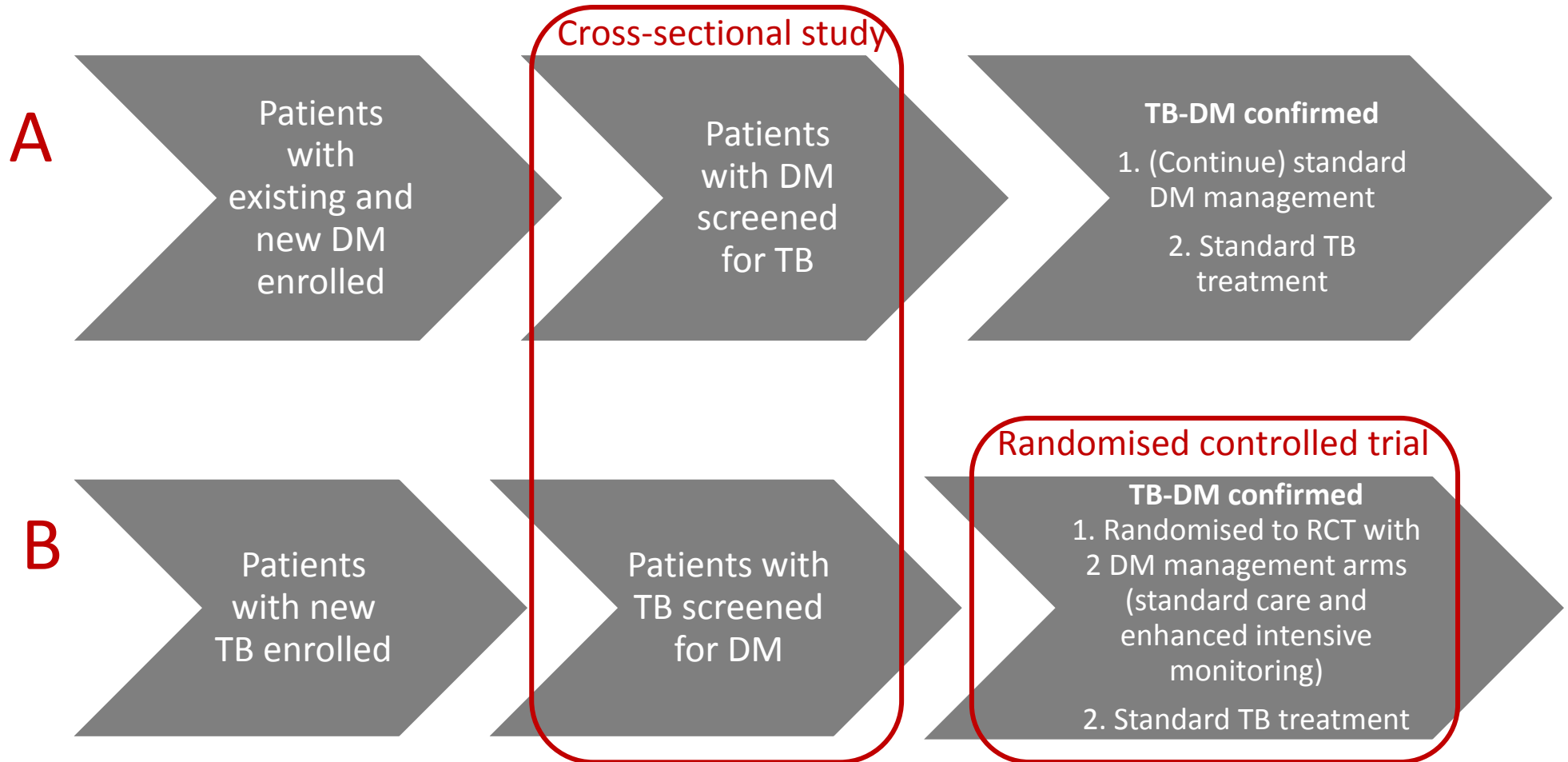
The TANDEM objectives of the bi-directional screening (two cross-sectional studies) in WP1 were:

1. To compare the screening tests for DM, when used alone and when combined, with the laboratory glycated haemoglobin (HbA_{1c}), which was used as the gold standard for diagnosing DM in patients with TB. This was performed in the four locations in TANDEM: Indonesia, Peru, Romania and South Africa. The aim was to determine the sensitivity, specificity, predictive values and cost-effectiveness of the screening tests
2. To determine the prevalence of DM in patients with newly diagnosed TB in the four countries
3. To determine yield and cost-effectiveness of the computer-assisted chest x-ray (CXR) reading and/or TB symptom screen, followed by sputum smear and culture, for TB screening among people with DM
4. To establish the proportions of DM-associated TB that were attributed to reactivation or to recently acquired infection
5. To determine the prevalence of active TB in people with DM in the four countries

6. To determine the operational feasibility from the perspective of the health care worker of performing the DM tests in TB clinics and the TB tests in chronic disease or DM clinics

Ethical approval was obtained from the Research Ethics Committee of the London School of Hygiene & Tropical medicine for the entire TANDEM study (Appendix I). This included the data collection and analysis of the costs, operational feasibility, health-related quality of life and any later cost-effectiveness analysis for this PhD. Ethical approval was also collected from the review boards in the respective countries: the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia (Appendix J); the Institutional Committee on Research Ethics, Universidad Peruana Cayetano Heredia, Lima, Peru (Appendix K); and the University of Medicine and Pharmacy of Craiova Committee of Ethics and Academic and Scientific Deontology, Romania (Appendix L).

Figure 4-1: Overall TANDEM patient workflow



The primary objective of the RCT in WP2 was to assess the effect of enhanced intensive monitoring of DM upon diabetes glycaemic control during TB treatment. In Indonesia, people with TB and DM were randomised at TB treatment initiation to one of two strategies for clinical monitoring of DM:

- i. predefined standard practice at the study site (standard DM care), or
- ii. enhanced, intensive monitoring of fasting blood glucose and clinical review at baseline, after two weeks, after four weeks and monthly until TB treatment completion, with adjustments of anti-diabetes medication according to standardised protocols (intensive DM monitoring).

For the DM outcomes, glycaemic control was compared and DM phenotypes were defined. For TB outcomes, two-month culture conversion, six-month bacteriological outcome and 12-month recurrence were compared between TB-DM patients and people with TB but without DM.

The sampling frame for pathway A (Figure 4-1) was all patients with DM attending DM clinics at the selected facilities in Indonesia and Peru or admitted to the DM or Internal Medicine Departments of the general hospitals in Romania. Patients meeting the selection criteria (newly or previously diagnosed DM, 18 years and over and no gestational or steroid-dependant DM) were consecutively asked to enrol in the TANDEM study.

The sampling frame for pathway B (Figure 4-1) was all patients with suspected TB referred to or attending TB clinics at the selected facilities in Indonesia and Peru or admitted to the TB sanatorium or infectious disease hospital in Romania. Patients meeting the inclusion criteria (newly diagnosed new or previously treated pulmonary TB, 18 years and over and within 72 hours of treatment initiation) were consecutively asked to enrol in the TANDEM study.

Recruitment for pathways A and B in each facility continued until the predetermined sample size was obtained in each country.

To obtain a 90% sensitivity of the combined DM testing approach (DM risk score then POC RPG), assuming a 95% confidence interval with a precision of +/- 0.15 at each site, the exact mid-P method was used to calculate the sample size of approximately 2000 patients with newly diagnosed TB in Indonesia, Peru and Romania (Table 4-1).

A priori, the sample size and power for the RCT was assessed, assuming an estimated DM prevalence of 20% (Alisjahbana et al., 2007). As we planned to recruit 2000 patients with TB across the TANDEM sites, we expected 400 to have DM, and allowing for patient attrition and exclusions, about 350 could be randomised to the trial (Table 4-1).

The primary outcome for the RCT was to detect a 1% difference in laboratory HbA_{1c} between the two arms of the RCT at three months (primary endpoint) and at six months (secondary endpoint) after starting DM management.

We assumed a difference of 1.0% in HbA_{1c} would be important to detect clinically, and the standard deviation of this difference would be around 2.2% (estimated from data from Indonesia). In a single site trial, the required sample size would be approximately 206 (with 90% power, at the 5% significance level). This estimate is highly dependent on the standard deviation, for which only have limited empirical data available. If the standard deviation is greater than this estimate (for example, 2.8) then we would require approximately 332 patients.

There is debate amongst clinicians about the minimum difference in HbA_{1c} which might be “clinically important” to detect but most recent trials have set this at between 0.5% – 1.0%, so our sample size estimates fall within this reasonable range.

Table 4-1: TANDEM sample sizes for Indonesia, Peru and Romania

			Indonesia	Peru	Romania	Total
Initial sample size	Study 1 (Pathway A)	Patients with DM	800	600	600	2,000
	Study 2 (Pathway B)	Patients with TB	800	600	600	2,000
	Randomised controlled trial	Patients with TB-DM				350
Interim analysis	Randomised controlled trial – Indonesia ONLY		150	NA	NA	150

TB-tuberculosis; DM-diabetes mellitus; NA-not applicable

Patient recruitment and RCT participation as of October 2016 are presented in Table 4-2.

Table 4-2: TANDEM patient recruitment in Indonesia, Peru and Romania as of October 2016

		Indonesia	Romania	Peru
Study 1 (Pathway A)	Patients with DM	809	603	600
Study 2 (Pathway B)	Patients with TB	862	509	601
TB-DM	From DM screening in study 2	177	88	52
Randomised controlled trial	Standard DM care	60	NA	NA
	Intensive DM monitoring	60	NA	NA

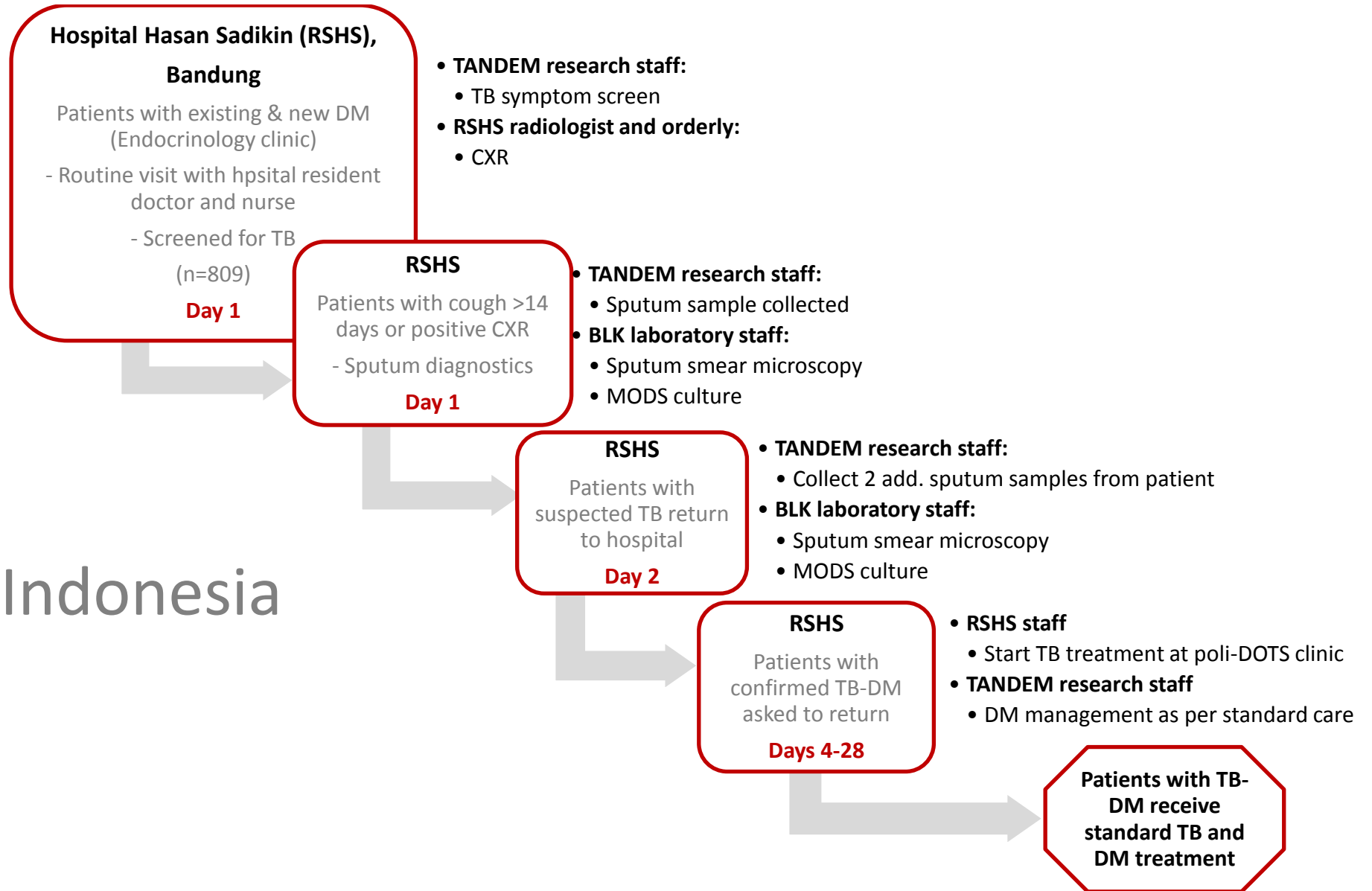
TB-tuberculosis; DM-diabetes mellitus; NA-not applicable

The patient and sample workflows for WPs 1 and 2 were different in Indonesia, Peru and Romania due to the variation in health systems of the three countries.

In Indonesia, 809 people with existing DM attending their routine appointment at the Endocrinology Clinic at the RSHS were enrolled in the TANDEM screening study and screened for TB at the Clinic (Figure 4-2). The TB symptom screen was administered and irrespective of the presence of any symptoms, patients were escorted to the Radiology Department at RSHS for a CXR. All patients in Indonesia were also screened for latent TB infection using the IGRA test. Any patient with a productive cough for longer than 14 days or any abnormalities on the CXR were asked to produce a sputum sample in the toilets of

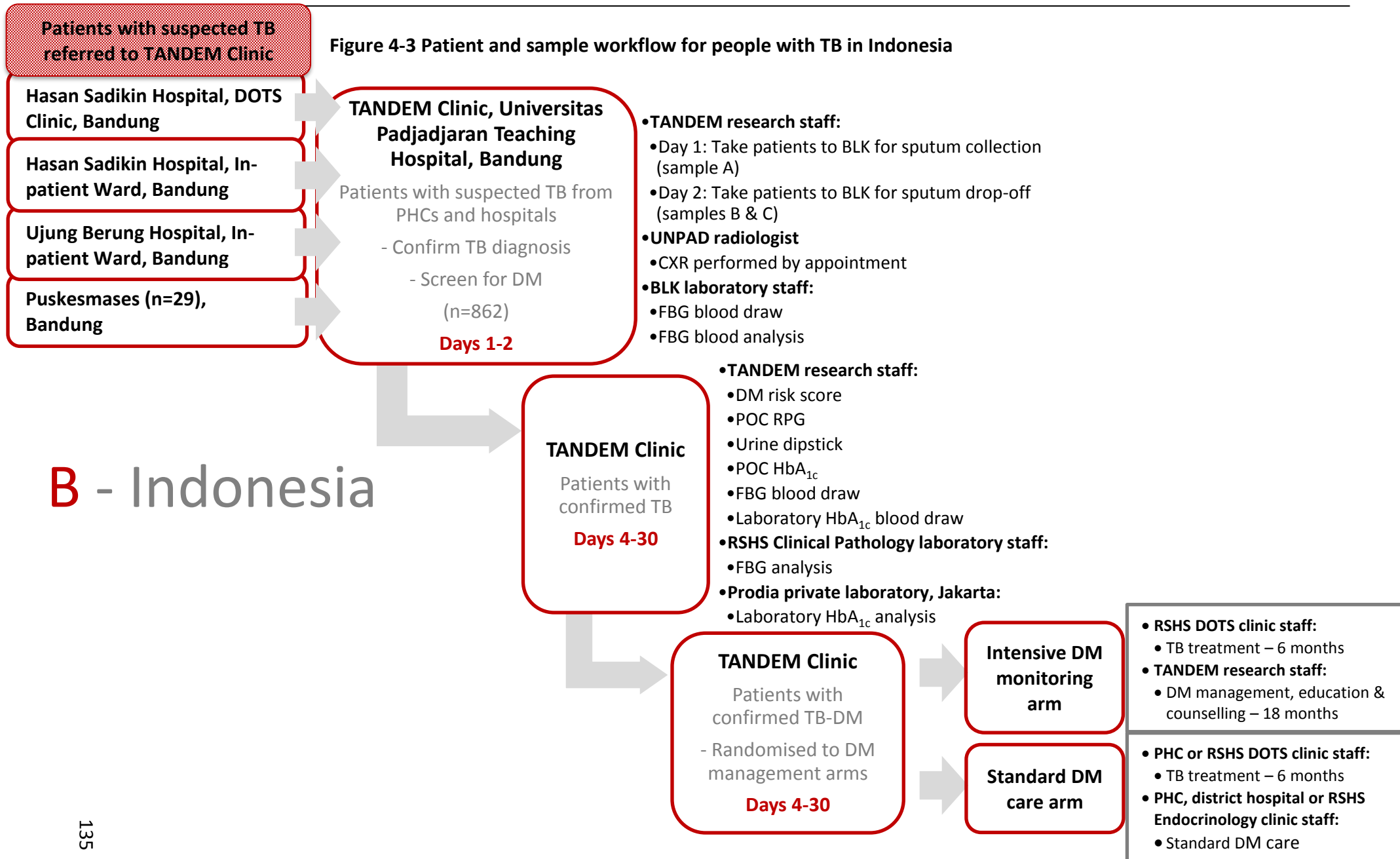
the Endocrinology Clinic. The patients were asked to return to the Clinic the following day having produced two additional sputum samples at home: late night and early morning samples. All sputum samples were taken daily to the BLK by a TANDEM nurse and tested for active TB using Ziehl-Neelsen (Z-N) sputum smear microscopy and sputum MODS culture. Any patient diagnosed with TB started TB treatment at the RSHS DOTS clinic and DM management continued as per standard care at the RSHS Endocrinology Clinic. The patients were not enrolled in the TANDEM RCT for people with TB-DM, as described in Chapter 1, to avoid potential double counting of RCT patients.

Figure 4-2: Patient and sample workflow for people with DM in Indonesia



A - Indonesia

Figure 4-3 Patient and sample workflow for people with TB in Indonesia



B - Indonesia

People with suspected TB were identified in several locations: RSHS DOTS clinic, RSHS TB inpatient ward, Ujung Berung Hospital inpatient TB ward and the 29 Puskesmas participating in the TANDEM study (Figure 4-3). These patients were asked to visit the TANDEM recruitment clinic at the UNPAD Teaching Hospital. There, suspected TB was confirmed using two sputum samples for smear microscopy and a CXR, which were conducted at the BLK and UNPAD Teaching Hospital, respectively.

Between June 2014 and October 2016, a total of 862 people were confirmed to have active TB and then screened for DM at the UNPAD TANDEM Clinic (between four and 30 days of first presenting at the UNPAD TANDEM Clinic) (Figure 4-3). DM screening consisted of a DM risk score performed by nurses recruited for the TANDEM study and the following tests:

1. Point of care (POC) RPG
2. POC HbA_{1c}
3. POC urine dipstick
4. Blood draw for FBG and laboratory HbA_{1c}

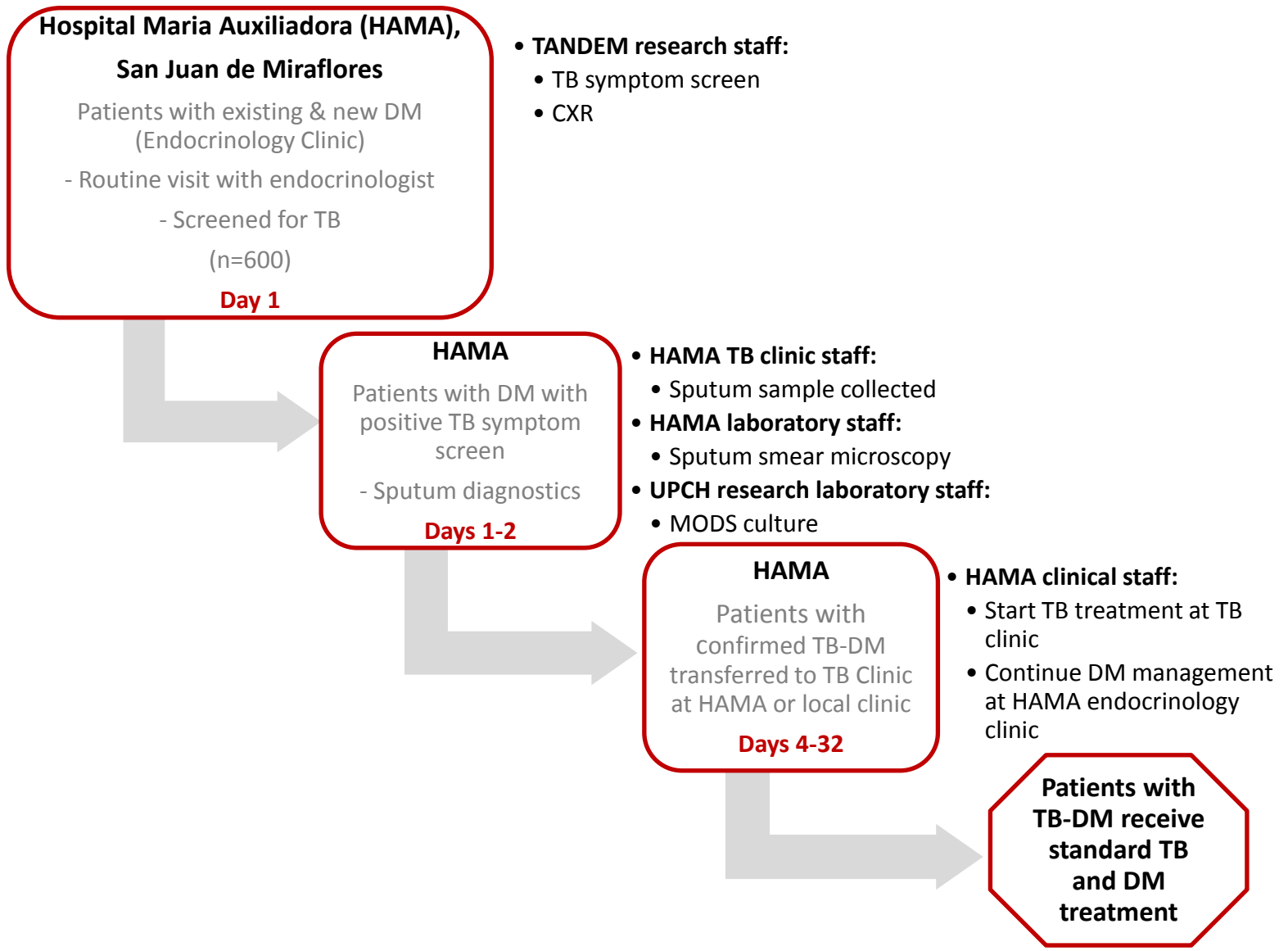
The FBG was sent for analysis at the Clinical Pathology Laboratory at the RSHS. The HbA_{1c} blood was analysed by a private laboratory, Prodia. People with concurrent TB and DM were asked to participate in the RCT and those agreeing were randomised into one of the two RCT DM treatment arms. TB-DM patients in the intensive monitoring arm were treated at the RSHS DOTS clinic for TB for six months by DOTS clinic staff. DM was managed by a TANDEM research resident doctor trained in DM management, with oversight from a consultant endocrinologist based in the RSHS Endocrinology Department. The TANDEM doctor monitored glycaemia levels, and provided education and counselling for DM self-care during patient visits to the RSHS DOTS clinic at two weeks, one, two, three, four, five, six, 12 and 18 months. Additional visits were required only if patients had adverse events related to either TB or DM treatment leading to the medication dosage needing adjustment. The TB-DM patients in the control arm followed the standard care in their setting by following up with their family doctor or attending a local endocrinology clinic, but were required to return to the TANDEM clinic for RCT follow-up at two weeks, two, three, six, 12 and 18 months. Patients in the standard care

arm were required to follow the TB treatment regimen for six months at their local DOTS clinic (at a Puskesmas or hospital).

In Peru, 600 people who attended the out-patient Endocrinology clinic at the Maria Auxiliadora Hospital (HAMA) for DM services were recruited to the TANDEM study (Figure 4-4). After people with confirmed DM were asked to participate in TANDEM by the clinic endocrinologist, they were enrolled and screened for TB by TANDEM research staff using the TB symptom screen and escorted to the Radiology Department at HAMA for a CXR. Patients with a positive TB symptom screen, i.e. cough for more than 14 days, were taken to the TB Clinic at HAMA and asked to produce a sputum sample. They were also asked to produce a second sample at home the following morning and bring it to the TB Clinic, where it was collected by TANDEM staff daily or as needed. The two samples were split: half of each sample stayed at the bacteriology laboratory at HAMA and was tested by Z-N smear microscopy, and the other half was taken by TANDEM staff to the research laboratory at UPCH where MODS culture was performed. If the sputum smear or the MODS culture was positive, the patient with confirmed TB-DM was transferred to the TB Clinic at HAMA or a local TB Clinic for at least six months of DOTS TB treatment. The patient's DM management continued at the HAMA Endocrinology Clinic.

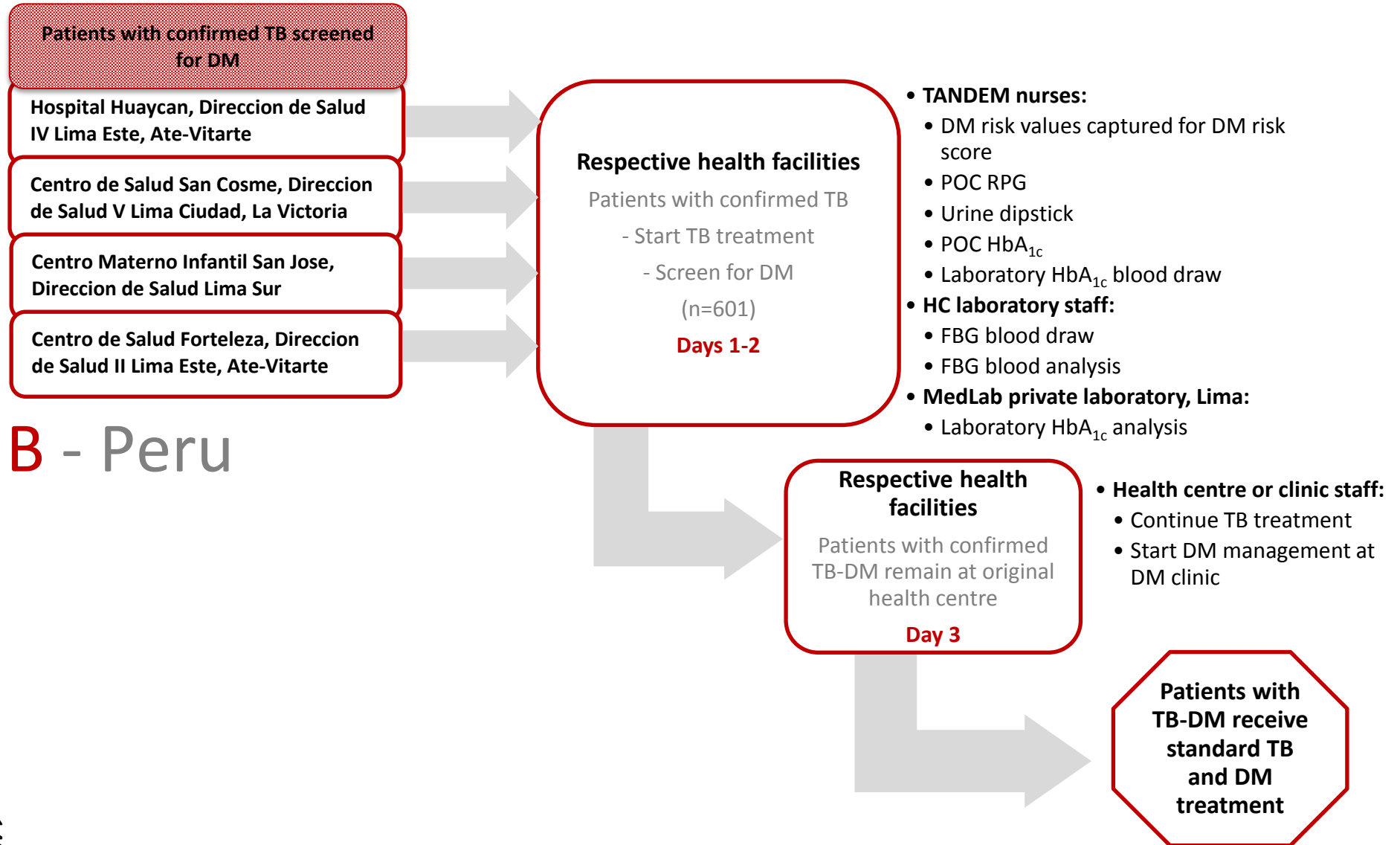
Figure 4-4: Patient and sample workflow for people with DM in Peru

A - Peru



A TANDEM research nurse was based at each of the four health facilities in Lima with DOTS Clinics: Hospital Huaycan, Centro de Salud San Cosme, Centro Materno Infantil San José and Centro de Salud Fortaleza. People with newly diagnosed TB who had started TB treatment within 72 hours were approached by the nurse and asked to join the TANDEM cross-sectional study. Enrolled patients (n=601) were screened for DM by the TANDEM nurse. DM risk values were captured so that a DM risk score could be assessed at a later date. POC tests were performed by collecting a urine sample for the urine dipstick test and finger pricks for the RPG and HbA_{1c} tests. Blood was also drawn for the laboratory HbA_{1c} test. The patient was then taken to the laboratory at the health facility, where an additional vial of blood was taken, and later analysed at the health facility laboratory. The blood sample for the laboratory HbA_{1c} test was delivered to a private laboratory, MedLab, by a TANDEM driver. Patients with confirmed TB-DM remained at the respective health facilities, where TB treatment continued at the DOTS Clinic and they were managed for DM at the DM Clinic within the same facility.

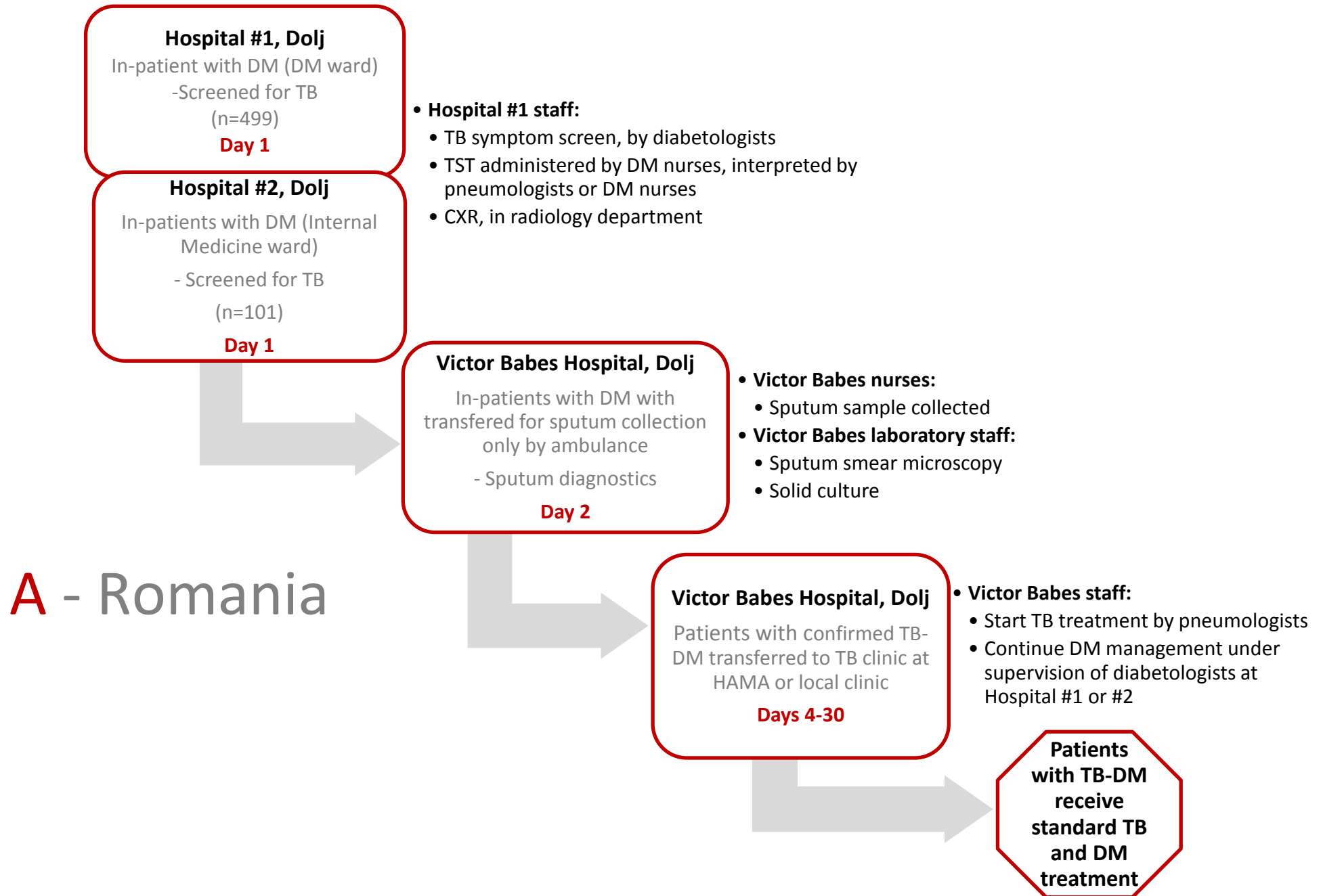
Figure 4-5: Patient and sample workflow for people with TB in Peru



B - Peru

In Romania, people with existing or newly diagnosed DM were recruited for TANDEM (n=603) at two county hospitals in Craiova (Figure 4-6). At Hospital #1 the enrolled patients were all being treated as in-patients in the DM ward and at Hospital #2 as DM in-patients in one of the two internal medicine wards. They were screened for TB by the TB symptom screen and CXR, in addition to being screened for latent TB infection using the TST. If any TB symptoms were identified or any abnormalities seen on the CXR, the patient was discharged from the DM or internal medicine wards and sent by ambulance or asked to use their own transportation to go to the Victor Babes Infectious Disease Hospital, also in Craiova (Figure 3-3). There, each patient was asked to produce two sputum samples, which were then tested by smear microscopy and solid culture, as per NTP guidelines. If TB was confirmed, the patient would be admitted to the Victor Babes hospital where they would remain as inpatients for at least 30 days or until their sputum smear converted to negative. Similar to Indonesia, these TB-DM patients were not enrolled in the TANDEM RCT, but followed up in order to measure their TB and DM outcomes. If TB was not confirmed, the patient was asked to return to Hospital #1 or Hospital #2 for readmission for DM treatment.

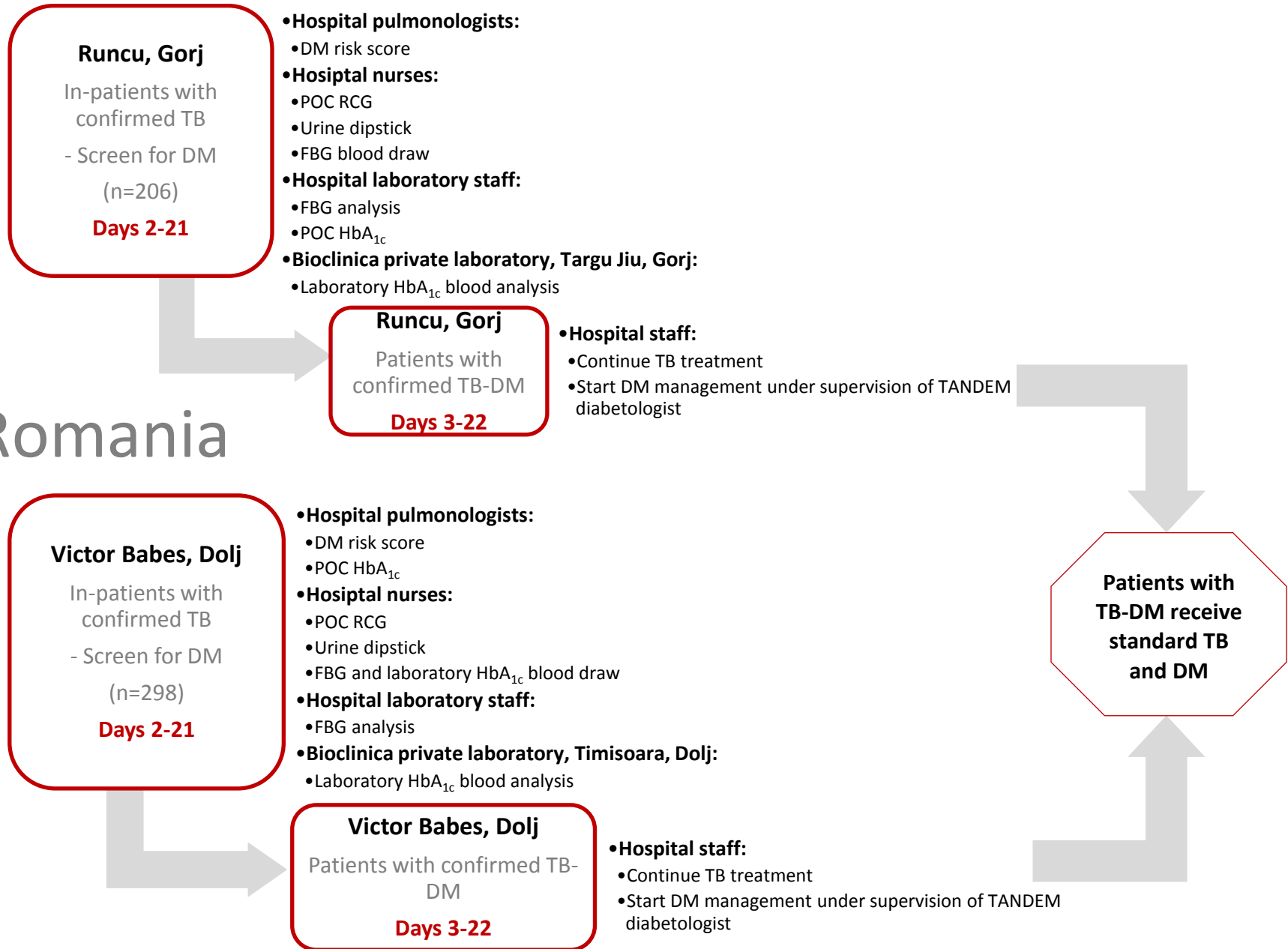
Figure 4-6: Patient and sample workflow for people with DM in Romania



At the Infectious Disease hospital in Craiova (Victor Babes) and the TB sanatorium in the Dolj mountainside (Runcu), 509 patients admitted for DS-TB treatment for the first time were screened for DM using the DM risk score by the pulmonologist responsible for their care (Figure 4-7). Personnel from the Medical Laboratory at these hospitals performed POC tests (RCG, HbA_{1c} and urine dipstick) and drew blood for the FBG (analysed in the hospital laboratory) and laboratory HbA_{1c} (which was analysed at a private laboratory, Bioclinica). If patients were confirmed to have newly diagnosed DM or existing DM that had been untreated, they were randomised to either the standard care or intensive monitoring arm of the RCT. In Romania, patients with TB must be treated as in-patients for at least 30 days or until sputum smear conversion. During this period, TB treatment was performed as per NTP guidelines and DM treatment for patients in the intensive monitoring arm was overseen by a senior TANDEM diabetologist. Patients were also monitored and visited by a junior diabetologist affiliated with the TANDEM study. Patients in the standard care arm of the RCT received standard DM care. Once patients became smear negative, they were discharged and TB treatment continued at TB Dispensaries that were convenient to the patient until the end of the six-month regimen. This could be any location in the region of Oltenia or even throughout Romania (Figure 3-3). This vast spread of patients meant it was difficult to monitor patients in either arm of the RCT and often patients did not return to agreed dispensaries for their TANDEM scheduled DM management visits. For this reason, in June 2016, a decision was made to discontinue the RCT in Romania.

Figure 4-7: Patient and sample workflow for people with TB in Romania

B - Romania



Chapter 5 Methods framework and overview

This section provides an overview of the methods used in this PhD and where they are presented in the results chapters. While most methods were quantitative, a semi-qualitative assessment of the operational feasibility of integrating the tests was also undertaken. The methodological description of each approach is provided in greater detail in the respective results papers or chapters in Part III.

Chapters 6 to 9 focus on data collected during the cross-sectional screening studies in the TANDEM project. These baseline data include patient assets that were collected in electronic case report forms and used to create socio-economic quintiles in Chapter 6 through principal component analysis. The quintiles are later used to investigate the relationship between socio-economic status and change in health-related quality of life over six months of treatment for TB and DM (Chapter 10).

A methodology paper for micro-costing diagnostic tests is presented in Chapter 7. This paper highlights some of the challenges experienced, with some practical remedies for obtaining comprehensive and accurate unit costs from the perspective of the health service provider, with some degree of consistency between the two countries and at the various sites. The results of the micro-costing were combined with the diagnostic accuracy (sensitivity and specificity) of each test to produce the cost per accurate diagnosis of bi-directional screening in Indonesia and Romania in Chapter 8. The information in this paper is intended to inform the decision-making around implementation of integrated screening strategies for concurrent TB-DM. To complement this discourse, operational feasibility of screening people with TB for DM and vice versa are assessed from the perspective of the health care workers performing the application and analysis of these tests. This paper, presented in Chapter 9, uses a combination of the quantitative and qualitative data derived from interviewer administered questionnaires.

Health-related quality of life (Chapter 10) and patient costs (Chapter 11) data were collected during the RCT and patients in the standard care and intensive DM management

arms were compared in both chapters. Here the analyses and results are presented as chapters rather than as manuscripts because patient recruitment is ongoing, at the time of writing, for these data and the results are therefore preliminary.

Additional data collection for provider treatment costs is also ongoing and this data, along with the patient treatment costs, health-related quality of life and trial effect (percent change in laboratory HbA_{1c} between baseline and after 18 months of treatment), is expected to be finalised in July 2018. At that time, these data, along with the diagnostic costs, will be combined to assess the costs per Quality Adjusted Life Years over the lifetime of the patient using a Markov model.

PART III – RESULTS CHAPTERS

Preamble to papers

The three results papers included in this thesis are concerned with collecting and analysing the cost, accuracy and operational feasibility data for bi-directional screening of people with concurrent TB and DM in the TANDEM study.

Research paper 2 is a methodological paper on micro-costing of laboratory tests, which was derived out of the field work done to obtain the costs of the TB and DM screening tests. In performing the micro-costing, it was apparent that there were no practical guidelines for researchers wishing to conduct a micro-costing of laboratory tests and therefore creating one was deemed useful for ensuring that data collected in the three countries went as efficiently and consistently as possible. It was decided that it should be published as it would be helpful to others performing micro-costings in similar settings. This is presented in Chapter 7. Research papers 3 and 4 relate solely to the bi-directional screening activities in the study. Research paper 3 reports the 2014 costs of all the screening strategies employed for both TB and DM along with the diagnostic accuracy of the tests (Chapter 8). Research paper 4 is presented in Chapter 9 where the operational feasibility of implementing these screening strategies from the perspective of the health care workers performing them is assessed.

The titles of the three papers which will be submitted to journals are:

1. How to do (and not to do): Planning and conducting micro-costing – an application to laboratory tests (*to be submitted to Health Policy and Planning*)
2. Costs of accurate diagnosis for bi-directional screening in Indonesia and Romania: integrating TB and diabetes services (*to be submitted to Lancet Global Health*)
3. Operational feasibility of bi-directional screening for TB and diabetes – lessons from Indonesia and Peru (*to be submitted to PLoSOne*)

The remaining data are presented as traditional chapters in narrative form. This includes analysis of the socio-economic status of all patients recruited for bi-directional screening in Indonesia, Peru and Romania in Chapter 6. The health-related quality of life of people with TB, with and without concurrent DM, recruited at baseline in Indonesia, Peru and Romania are compared along with the change in HRQoL of people with TB-DM from enrollment, through treatment and follow-up at 18 months in Indonesia only (Chapter 10). Lastly, the costs incurred by patients with concurrent TB-DM who are in the standard DM care and intensive DM monitoring arms of the RCT are assessed in Indonesia only in Chapter 11.

Chapter 6 Socio-economic status

6.1 Introduction

The asset index method was used to develop socio-economic status (SES) quintiles. This method was chosen in order to compare the long-term wealth of people with TB or TB-DM across different settings. This is in contrast to using short-term monetary values of household income, consumption or expenditure (Gwatkin et al., 2007). It was important to select a method for determining SES where the data were not excessively labour or time intensive to collect, but that would be more reliable than simply asking patients to report their income earned (Howe et al., 2008).

The objective of this analysis was to obtain a socio-economic index for patients in Indonesia, Peru and Romania using assets by combining patients with TB and patients with DM for the analysis within each country. The asset index was used to assess the differential effects of SES on health outcomes for the patients in Indonesia, Peru and Romania.

6.2 Methods

Using the exact mid-P method, it was estimated that a sample of 2,000 people with TB should be screened for DM (and 2,000 with DM screened for TB) in Indonesia, Peru and Romania. These sample sizes were needed in order to obtain a sensitivity of approximately 90% for the combined DM testing approach, with an estimated undiagnosed DM prevalence of 8% and a precision (95%) of +/- 0.15 at each site.

6.2.1 Data collection

A Principal Component Analysis (PCA) was performed in order to build a socio-economic status (SES) index based on asset ownership by patients. SES was determined by creating an asset index based on information on non-sellable and sellable (durable) asset ownership. Non-sellable assets included possession of a bank account; presence and type

of sanitation facility (flush toilet connected to sewage system, traditional toilet, septic tank or pit [ventilated improved pit (VIP) latrine, latrine with or without slab]; and household water source (private sources piped to house or yard, communal well or tap, from neighbour's source, spring, river, pond, water vendor, bottled water or public network) (Appendix M). Sellable assets included ownership of a stove, refrigerator, microwave, washing machine, air conditioner, fan, computer, television, DVD player, radio/CD player, camera, mobile phone, bicycle, motorcycle/scooter, car or truck. The choice of assets to include was informed by the World Bank's Household Survey Questionnaires for Developing Countries (WB, 2000).

The TANDEM health care workers captured the data along with clinical data at baseline only, when screening patients. Data were collected electronically on tablets or laptop computers between April 2013 and November 2016. The data were then transferred into a centralised database that was adapted for the TANDEM study via a web-based application called Research Electronic Data Capture (REDCap) Version 6.9.1 (Vanderbilt University, Nashville, TN, USA).

6.2.2 Data analysis

Descriptive analysis (frequency, mean and standard deviation) of the assets was performed to inform decisions on which assets to include in the analysis and highlight any issues with the data. Only patients with complete asset information were included in the analysis.

PCA allows aggregation over a range of different assets to derive a uni-dimensional measure of SES. The first step was to recode the categories of each variable into a separate binary variable. For example, the "house" variable with seven categories (renting a room, renting a house/flat, own house/flat, live with family, not usual place to live, live in shelter and other), was turned into seven corresponding variables, whose categories then became yes and no. Secondly, similar variables with low frequencies were combined (for example the people without a usual place to live and people living in a shelter were combined into a single variable: no fixed abode (that is, having no fixed or permanent

address)) and variables with no observations were dropped (Vyas and Kumaranayake, 2006).

From the initial set of statistically correlated variables, PCA was used to create uncorrelated indices, or components, where each component was a linear weighted combination of the initial variables (Filmer and Pritchett, 2001). The first (that is, principal) component was selected and the factor scores, or standardised weights, on that component were divided into quintiles to reflect the poorest to richest households. These scores reveal the importance of having each item in order to be considered richer (or poorer, for items with a negative score) than other people in the sample.

In Indonesia, the analysis was carried out on the combined sample of 1,678 people, where there were 869 people with TB and 809 people with DM across five sites (Table 6-1). In Peru, the sample was 1,200 people with 600 of each type of patient and in Romania the sample was 1,103 people with 504 with TB and 599 with DM across four sites. These sample sizes were based on the data extracted on 25th November 2016.

Table 6-1: TANDEM patient enrolment for bi-directional screening in Indonesia and Romania, by site

Site name	Patients with TB	Patients with DM	Total
Indonesia	869	809	1,678
Puskesmas	649	106	
RSHS DOTS Clinic	120	---	
RSHS Endocrinology Clinic	---	701	
RSHS inpatient wards	26	---	
Ujung Berung Hospital	74	---	
Unknown	0	2	
Peru	600	600	1,200
San Jose Health Centre	67	---	
Fortaleza Health Centre	64	---	
Huaycan Hospital	366	---	
San Cosme Health Centre	103	---	
Maria Auxiliadora Hospital	---	600	
Romania	504	599	1,103
Victor Babes	298	---	
Runcu	206	---	
Hospital #1	---	499	
Hospital #2	---	100	
TOTAL	1,973	2,008	3,981

The analysis was not performed separately for urban and rural residents because all patients in Indonesia and Peru lived in urban residences and urban/rural stratification in Romania was only available for people with DM being screened for TB. The PCA was performed on the combined datasets of people with TB and people with DM in each country.

All analyses were done in STATA version 14.1 (StataCorp LP, College Station, TX, USA).

6.3 Results

6.3.1 Useful assets and categories

Some assets were excluded from the index analysis due to a low standard deviation of less than 0.25, which was a pragmatic threshold. A low standard deviation indicates a low

weight in the PCA if the asset was either very common or nearly absent in all respondents (for example, an asset that all or no respondents owned). These assets would be assigned a weight equal to zero in PCA and therefore would not contribute to differentiating the SES. The variables that were merged and those that were excluded because of a low standard deviation are identified for each country in Table 6-2.

In all countries, for the variable asking “where you live, do you...”, new asset categories were created. ‘Renting’ was created by merging renting a room in a house and renting a house or self-contained flat and ‘no fixed abode’ by merging no usual place to live and live in a shelter. For the variable “what toilet facility do you have in your house?”, a category called ‘pit or bowl’ was created by merging the VIP latrine, bowl or bucket and other toilet type categories. Four new “water source” categories were created in the three countries except Romania where water vendor and bottled water remained separate while two additional categories were included and merged into a category called ‘public network’.

Table 6-2: Merged and dropped variable categories before principal component analysis in Indonesia, Peru and Romania

Country	Variable	Question	Merged categories		Dropped categories
			Categories with low frequencies	New category	
Indonesia	house	Where you live, do you...	rent a room in a house?	Renting	No fixed abode Other living arrangement
			rent a house/self-contained flat?		
			have no usual place to live?	No fixed abode	
			live in a shelter (homeless)?		
	water_main	What is your main source of water for drinking and cooking?	Private connection to pipeline	Private sources	Public well/standpipe Neighbours Nature Other water source
			Private well		
			Public taps/standpipe	Public well/standpipe	
			Public well		
			Water vendor	Bottle or water vendor	
			Bottled water		
Spring					
River/stream/lake/pond		Rainwater	Nature		
toilet	What toilet facility do you have in your house?	Ventilated improved pit (VIP) latrine	Pit or bowl	Traditional toilet Pit or bowl No toilet	
		Bowl/bucket			
possessions	Do you own any of the following items? (check all that apply)			Stove Air conditioner Television	
Peru	house	Where you live, do you...	rent a room in a house?	Renting	No fixed abode Other living arrangement
			rent a house/self-contained flat?		
			have no usual place to live?	No fixed abode	
			live in a shelter (homeless)?		
	water_main	What is your main source of water for drinking and cooking?	Private connection to pipeline	Private sources	Public well/standpipe Neighbours Bottle or water vendor Nature Other water source
			Private well		
			Public taps/standpipe	Public well/standpipe	
			Public well		
			Water vendor	Bottle or water vendor	
			Bottled water		
Spring					
River/stream/lake/pond		Rainwater	Nature		

Country	Variable	Question	Merged categories		Dropped categories	
			Categories with low frequencies	New category		
Romania	toilet	What toilet facility do you have in your house?	Ventilated improved pit (VIP) latrine Bowl/bucket	Pit or bowl	Traditional toilet Pit or bowl No toilet	
	possessions	Do you own any of the following items? (check all that apply)			Air conditioner Bicycle Motorbicycle Car/truck	
	house	Where you live, do you...	rent a room in a house?	rent a house/self-contained flat?	Renting	Renting
			have no usual place to live? live in a shelter (homeless)?		No fixed abode	No fixed abode
						Other living arrangement
	water_main	What is your main source of water for drinking and cooking?	Private connection to pipeline	Private well	Private sources	Public well/standpipe Neighbours
			Public taps/standpipe			
			Public well	Public well/standpipe	Water vendor Nature	
			Spring	Nature	Bottled	
			River/stream/lake/pond Rainwater		Public network	
toilet	What toilet facility do you have in your house?	Ventilated improved pit (VIP) latrine Bowl/bucket Other	Pit or bowl	Pit or bowl No toilet		
possessions	Do you own any of the following items? (check all that apply)			Stove Refrigerator Television Motorbicycle		

6.3.2 The asset weights

Descriptive analysis (frequencies, means and standard deviations) of the socio-economic variables and the standardised weights of each variable from the PCA are presented in Table 6-3, Table 6-4 and Table 6-5. Since only participants with complete information were included, the sample size for the PCA was reduced to 1,650, 1,189 and 1,084 in Indonesia, Peru and Romania, respectively. This resulted in 2%, 1% and 2% patients missing from the analysis in the three countries, respectively.

In all three countries the PCA indicates that people who own their home are more likely to be in wealthier SES quintiles and those who live with extended family are more likely to be in poorer quintiles. Having a flush toilet at home was the sole indicator of SES within the sanitation facility grouping in Indonesia (Table 6-3) and Peru (Table 6-4), with a higher proportion of patients with this facility being in the wealthier quintiles in all countries. There was some variation amongst countries in terms of the durable assets that were included in the PCA, as well as those representative of patient SES. Having a computer had the highest and second highest factor scores in Romania and Indonesia, respectively (Table 6-5, Table 6-3), but in Peru having a computer was surpassed by six other assets, including stove and television (Table 6-4). The latter two assets were dropped in both Indonesia and Romania, since they were selected as a personal asset by almost all patients in these countries.

The lowest factor score, or weight, in Indonesia and Peru was ascribed to renting a home, and to having a traditional toilet in Romania.

Table 6-3: Standardised weights (factor scores) of principal component analysis for patients with TB and patients with DM recruited to the TANDEM study in Indonesia

Variable category	Frequency	Mean	SD	Factor score [^]
Bank account	605	0.3645	0.4814	0.2533
Housing status				
Renting	254	0.1514	0.3585	-0.1650
Owns home	908	0.5411	0.4985	0.2161
Live with family	464	0.2765	0.4474	-0.1053
No fixed abode	5	0.0030	0.0545	
Other living arrangement	45	0.0268	0.1616	
Water source				
Private sources	968	0.5769	0.4942	-0.0013
Public well/standpipe	41	0.0244	0.1544	
Neighbours	7	0.0042	0.0645	
Water vendor/bottled	636	0.3790	0.4853	0.0218
Nature	22	0.0131	0.1138	
Other sources	4	0.0024	0.0488	
Sanitation facility				
Flush toilet	1,540	0.9178	0.2748	0.1315
Traditional toilet	85	0.0507	0.2194	
Pit or bowl	17	0.0101	0.1002	
No toilet	31	0.0185	0.1347	
Durable assets				
Stove	1599	0.9529	0.2119	
Refrigerator	1167	0.6955	0.4603	0.2996
Microwave	220	0.1311	0.3376	0.2569
Washing machine	705	0.4201	0.4937	0.3320
Air conditioner	79	0.0471	0.2119	
Fan	799	0.4762	0.4996	0.2239
Computer	570	0.3397	0.4737	0.3241
Television	1596	0.9511	0.2157	
DVD player	903	0.5381	0.4987	0.2303
Radio/CD player	784	0.4672	0.4991	0.2444
Camera	329	0.1961	0.3971	0.3052
Mobile phone	1466	0.8737	0.3323	0.1531
Bicycle	653	0.3892	0.4877	0.2005
Motorcycle/scooter	1106	0.6591	0.4741	0.2190
Car or truck	266	0.1585	0.3653	0.3074

SD-standard deviation

Variables in red were excluded from PCA due to a low standard deviation (<0.25)

[^]Variables with a positive factor score are associated with a higher socio-economic status and variables with a negative factor scores are associated with a lower socio-economic status

Table 6-4: Standardised weights (factor scores) of principal component analysis for patients with TB and patients with DM recruited to the TANDEM study in Peru

Variable category	Frequency	Mean	SD	Factor score [^]
Bank account	104	0.0875	0.2826	0.1800
Housing status				
Renting	186	0.1550	0.3621	-0.1032
Owns home	604	0.5033	0.5002	0.1547
Live with family	385	0.3208	0.4670	-0.0638
No fixed abode	8	0.0067	0.0814	
Other living arrangement	17	0.0142	0.1182	
Water source				
Private sources	1,118	0.9317	0.2524	0.1033
Public well/standpipe	22	0.0183	0.1342	
Neighbours	22	0.0183	0.1342	
Water vendor/bottled	35	0.0292	0.1683	
Nature	2	0.0017	0.0408	
Other sources	1	0.0008	0.0289	
Sanitation facility				
Flush toilet	1,121	0.9342	0.2481	0.1035
Traditional toilet	42	0.0350	0.1839	
Pit or bowl	36	0.0300	0.1707	
No toilet	1	0.0008	0.0289	
Durable assets				
Stove	1,003	0.8358	0.3706	0.2921
Refrigerator	672	0.5600	0.4966	0.3658
Microwave	234	0.1950	0.3964	0.3505
Washing machine	257	0.2142	0.4104	0.3253
Air conditioner	4	0.0033	0.0577	
Fan	141	0.1175	0.3221	0.2465
Computer	191	0.1592	0.3660	0.2755
Television	1,016	0.8467	0.3605	0.3034
DVD player	473	0.3942	0.4889	0.2844
Radio/CD player	723	0.6025	0.4896	0.2523
Camera	145	0.1208	0.3261	0.2652
Mobile phone	854	0.7117	0.4532	0.1271
Bicycle	63	0.0525	0.2231	
Motorcycle/scooter	41	0.0342	0.1817	
Car or truck	34	0.0283	0.1660	

SD-standard deviation

Variables in red were excluded from PCA due to a low standard deviation (<0.25)

[^]Variables with a positive factor score are associated with a higher socio-economic status and variables with a negative factor scores are associated with a lower socio-economic status

Table 6-5: Standardised weights (factor scores) of principal component analysis for patients with TB and patients with DM recruited to the TANDEM study in Romania

Variable category	Frequency	Mean	SD	Factor score [^]
Bank account	328	0.3026	0.4596	0.1707
Housing status				
Renting	24	0.0218	0.1460	
Owns home	630	0.5712	0.4951	0.1574
Live with family	438	0.3971	0.4895	-0.1621
No fixed abode	0	0.0000	0.0000	
Other living arrangement	4	0.0036	0.0601	
Water source				
Private sources	944	0.8558	0.3514	-0.2368
Public well/standpipe	65	0.0589	0.2356	
Neighbours	2	0.0018	0.0426	
Water vendor	1	0.0009	0.0301	
Nature	28	0.0254	0.1574	
Bottled	56	0.0508	0.2196	
Public network	0	0.0000	0.0000	
Sanitation facility				
Flush toilet	563	0.5104	0.5001	0.2606
Traditional toilet	532	0.4823	0.4999	-0.2583
Pit or bowl	0	0.0000	0.0000	
No toilet	0	0.0000	0.0000	
Durable assets				
Stove	1089	0.9873	0.1120	
Refrigerator	1075	0.9746	0.1574	
Microwave	363	0.3291	0.4701	0.2910
Washing machine	720	0.6528	0.4763	0.2916
Air conditioner	103	0.0934	0.2911	0.2386
Fan	252	0.2285	0.4200	0.2180
Computer	428	0.3880	0.4875	0.3064
Television	1054	0.9556	0.2061	
DVD player	159	0.1442	0.3514	0.2820
Radio/CD player	564	0.5113	0.5001	0.1613
Camera	215	0.1949	0.3963	0.2915
Mobile phone	891	0.8078	0.3942	0.1760
Bicycle	390	0.3536	0.4783	0.0285
Motorcycle/scooter	62	0.0562	0.2304	
Car or truck	349	0.3164	0.4653	0.2840

SD-standard deviation

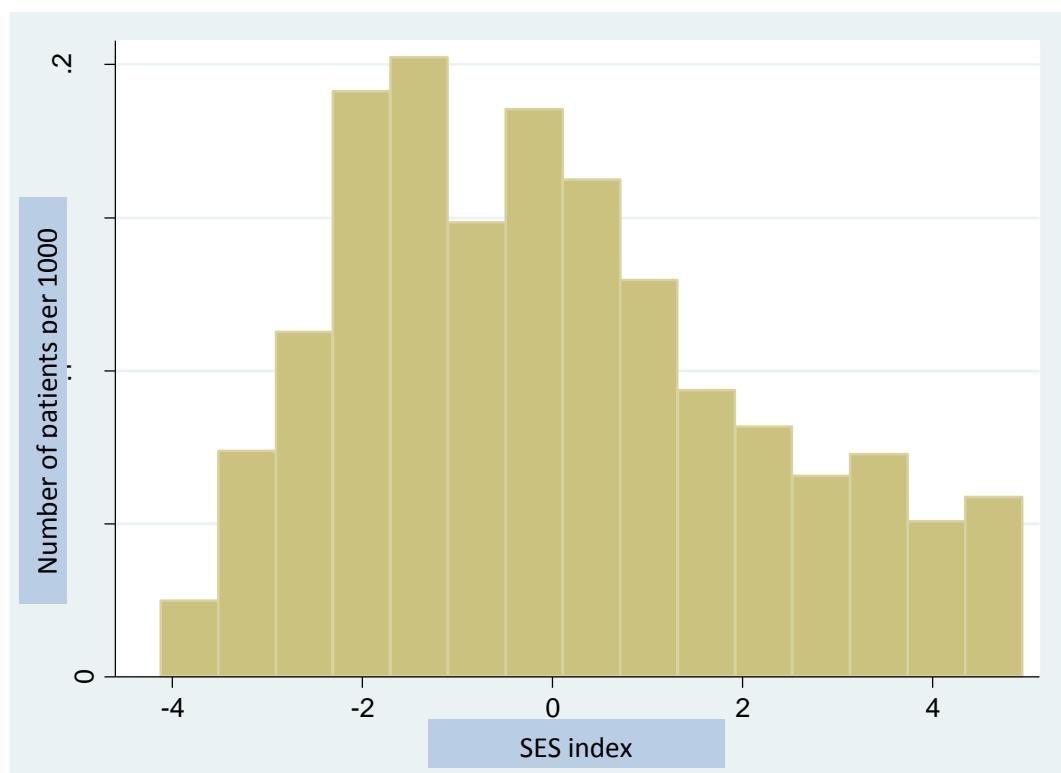
Variables in red were excluded from PCA due to a low standard deviation (<0.25)

[^]Variables with a positive factor score are associated with a higher socio-economic status and variables with a negative factor scores are associated with a lower socio-economic status

6.3.3 Distribution of asset ownership

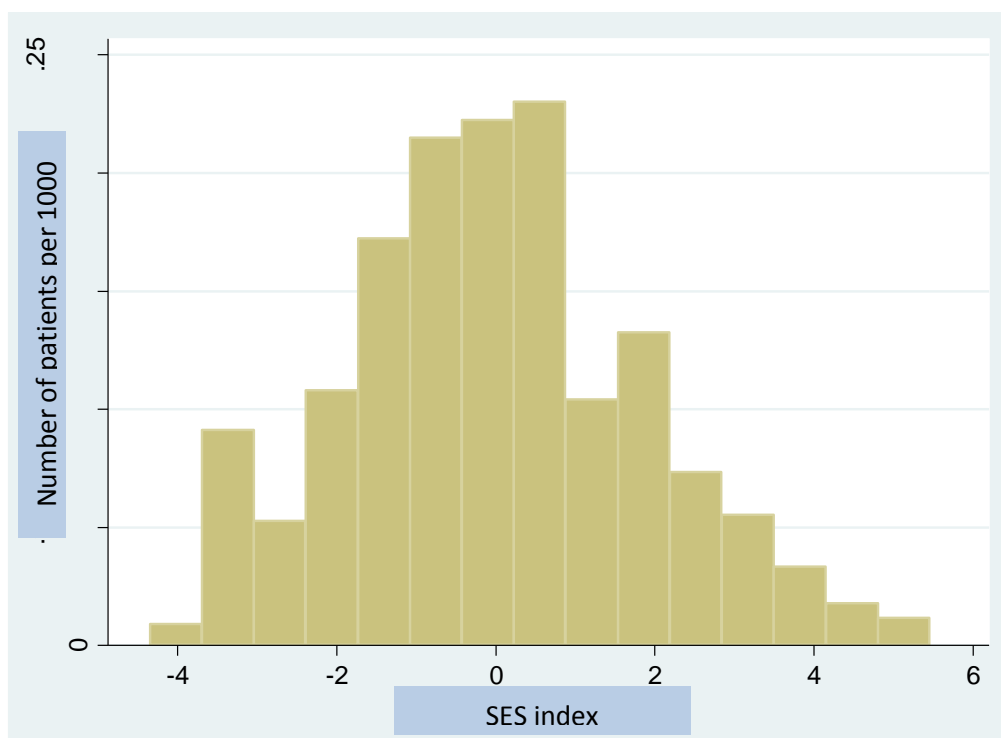
Patients in each country sample were split into quintiles, that is 20% of patients in each SES category. The distributions of the overall SES index for each country are shown in Figure 6-1, Figure 6-2 and Figure 6-3. All countries were positively (right) skewed, which could be due to some wealthier families who are outliers in the right tail. This could indicate that households are somewhat homogenous in terms of assets that they possess, so that there are small differences by which SES quintiles can be distinguished (Amek et al., 2015). Additional variables may be needed to better discriminate between the poorest households (Vyas and Kumaranayake, 2006).

Figure 6-1: Distribution of socio-economic status index for patients with tuberculosis and patients with diabetes, Indonesia



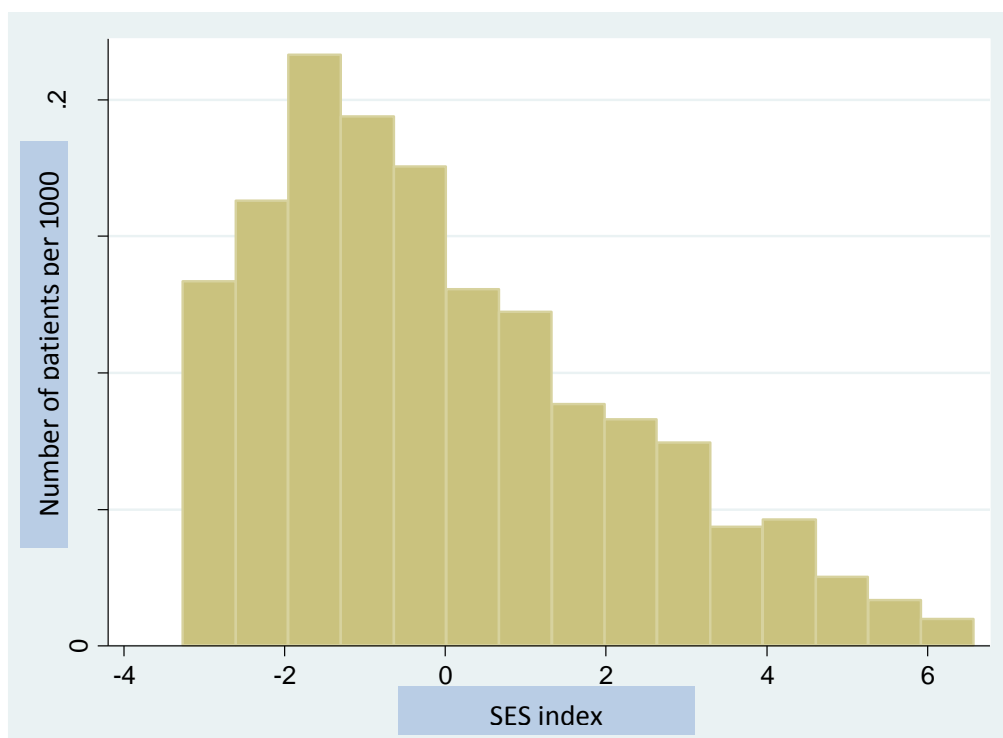
SES: socioeconomic status

Figure 6-2: Distribution of socio-economic status index for patients with tuberculosis and patients with diabetes, Peru



SES: socioeconomic status

Figure 6-3: Distribution of socio-economic status index for patients with tuberculosis and patients with diabetes, Romania



SES: socioeconomic status

In Indonesia, Peru and Romania the proportion of the wealthiest patients (96%, 70% and 99.5%, respectively) owning a washing machine is much higher than the proportion owned by the poorest patients in all countries (1%, 0.4% and 9%, respectively) (see Table 6-6, Table 6-7 and Table 6-8). This trend was seen for other durable assets, but was not consistent for all countries for those assets.

The majority (86%, 62% and 79%) of people in the wealthiest quintile in Indonesia, Peru and Romania, respectively, own their own home, while 68% to 77% of those in the poorest quintile in all countries either rent or live with family. The proportion of people in the wealthiest quintile with a flush toilet was above 90% in all countries, but the proportion of people in the poorest quintiles with a flush toilet varied from 84% in Peru to 4% in Romania. Further differences in the regional infrastructure is evident in the water sources, where over 80% of patients in all quintiles in Peru got drinking and cooking water from private sources, but in Indonesia approximately a third of all quintiles got their water from a water vendor or bottled water and 50-60% of all quintiles got their water from private sources.

The financial infrastructure or regulation also appears to be different in the three countries. While only 1% of the poorest quintile in Peru had a bank account in their name, this proportion rose to 8% and 11% in Indonesia and Romania, respectively. Only 27% of the patients in the wealthiest quintile had a bank account in Peru, but 57% and 78% of the wealthiest quintile in Romania and Indonesia had one.

Table 6-6: Proportional ownership of bank account, housing characteristics and durable assets by socio-economic quintile, Indonesia

Label	Poorest	Second	Middle	Fourth	Richest
Bank account	8.38%	15.15%	33.13%	47.59%	78.01%
Housing status					
Renting	39.52%	22.12%	7.23%	5.12%	1.51%
Owns home	17.96%	44.24%	51.51%	70.78%	85.54%
Live with family	38.02%	32.42%	36.75%	21.69%	9.94%
Water source					
Private sources	51.80%	61.21%	57.23%	65.66%	52.71%
Water vendor/bottled	41.62%	32.42%	37.95%	31.33%	45.78%
Sanitation facility					
Flush toilet	77.25%	89.70%	96.08%	98.19%	98.80%
Durable assets					
Refrigerator	11.98%	53.94%	84.34%	97.89%	100.00%
Microwave	0.00%	1.21%	3.61%	13.25%	47.59%
Washing machine	0.90%	13.94%	30.12%	68.37%	96.39%
Fan	15.57%	31.21%	46.69%	62.65%	81.63%
Computer	2.40%	6.67%	21.39%	47.29%	91.27%
DVD player	18.56%	39.09%	56.93%	66.87%	88.55%
Radio/CD player	12.28%	26.97%	47.89%	62.65%	83.73%
Camera	0.00%	0.30%	6.63%	19.88%	70.78%
Mobile phone	65.87%	85.15%	92.47%	94.58%	99.10%
Bicycle	11.98%	26.97%	37.35%	47.29%	70.78%
Motorcycle/scooter	21.56%	56.67%	77.41%	85.24%	89.16%
Car or truck	0.00%	0.00%	1.51%	10.84%	66.57%
Mean socio-economic status index	-2.65	-1.40	-0.27	1.00	3.33

Table 6-7: Proportional ownership of bank account, housing characteristics and durable assets by socio-economic quintile, Peru

Label	Poorest	Second	Middle	Fourth	Wealthiest
Bank account	1.23%	3.25%	5.17%	6.93%	27.43%
Housing status					
Renting	23.05%	21.95%	15.09%	9.52%	6.75%
Owns home	18.93%	51.63%	60.34%	59.31%	62.03%
Live with family	51.85%	24.39%	24.14%	29.44%	31.22%
Water source					
Private sources	83.54%	92.68%	96.12%	96.54%	97.47%
Sanitation facility					
Flush toilet	83.95%	92.28%	97.41%	95.24%	98.73%
Durable assets					
Stove	38.27%	86.99%	97.41%	97.84%	98.31%
Refrigerator	3.70%	23.58%	72.84%	87.88%	95.36%
Microwave	0.00%	1.22%	1.72%	22.51%	73.84%
Washing machine	0.41%	2.85%	6.90%	27.71%	70.04%
Fan	0.00%	1.22%	3.02%	17.75%	37.13%
Computer	2.88%	1.22%	5.17%	20.35%	49.79%
Television	39.92%	89.02%	97.84%	98.27%	99.58%
DVD player	3.70%	23.98%	34.05%	60.61%	76.79%
Radio/CD player	18.11%	56.10%	70.69%	68.40%	89.03%
Camera	0.82%	1.63%	2.59%	12.55%	43.88%
Mobile phone	60.91%	63.01%	69.40%	76.19%	86.92%
Mean socio-economic status index	-2.46	-0.94	-0.08	0.86	2.74

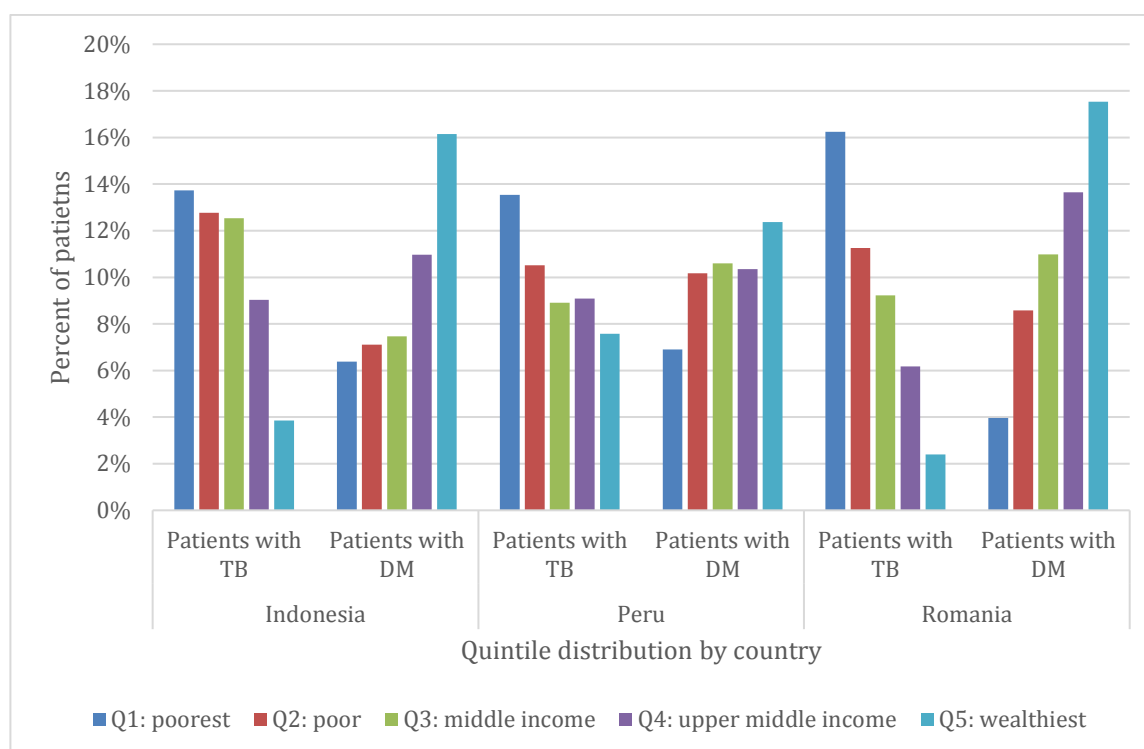
Table 6-8: Proportional ownership of bank account, housing characteristics and durable assets by socio-economic quintile, Romania

Label	Poorest	Second	Middle	Fourth	Richest
Bank account	10.50%	17.21%	28.77%	37.67%	57.41%
Housing status					
Owns home	30.59%	49.77%	60.27%	69.30%	78.70%
Live with family	68.04%	47.44%	36.07%	27.91%	18.06%
Water source					
Private sources	99.09%	98.14%	94.52%	84.65%	52.31%
Sanitation facility					
Flush toilet	4.11%	40.47%	52.05%	69.30%	91.67%
Traditional toilet	94.98%	59.07%	47.95%	30.70%	8.33%
Durable assets					
Microwave	0.91%	9.77%	25.11%	46.98%	85.19%
Washing machine	8.68%	43.26%	83.56%	95.81%	99.54%
Air conditioner	0.00%	0.00%	0.46%	10.23%	37.04%
Fan	4.11%	6.98%	14.61%	35.35%	55.09%
Computer	2.28%	8.84%	33.33%	62.33%	89.35%
DVD player	0.46%	1.86%	1.83%	11.16%	58.33%
Radio/CD player	26.48%	42.33%	50.68%	57.21%	79.63%
Camera	0.00%	0.93%	7.31%	26.05%	65.28%
Mobile phone	52.05%	74.88%	86.76%	94.88%	97.69%
Bicycle	31.96%	34.42%	34.25%	35.35%	40.28%
Car or truck	0.46%	8.84%	21.92%	51.16%	78.24%
Mean socio-economic status index	-2.53	-1.45	-0.43	0.98	3.48

6.3.4 SES differences between patients with TB and patients with DM

There was a greater proportion of patients with DM in the wealthier quintiles in all countries and a greater proportion of people with TB in the poorer quintiles (Figure 6-4).

Figure 6-4: Proportion of patients by quintile for TB and DM in Indonesia, Peru and Romania



6.4 Discussion

Housing status and ownership of durable assets are the best variables for assessing socio-economic status in TANDEM participants. Transportation assets were not useful in determining SES in Peru because ownership was low for the bicycle, motorcycle/scooter and car/truck, possibly because the majority of patients in that setting are already in the lower SES. Motorcycle/scooter ownership was only useful in differentiating SES in Indonesia. Patients with DM are wealthier than patients with TB.

Deriving asset indices using PCA avoids the weaknesses associated with the traditional methods of assessing wealth, including analysis of income, expenditure or consumption

data. These measurement limitations include recall bias and lengthy data collection for expenditure and consumption reporting, and variability in consumption and income data due to seasonality, particularly for people in informal or agricultural sectors or those who are self-employed (Vyas and Kumaranayake, 2006).

These socio-economic position quintiles are relative measures of SES and compare the status between patients in the study, but does not provide absolute values of poverty or income group within the population.

There are challenges in knowing which assets or variables to include in the PCA as certain infrastructure variables can result in geographic bias when classifying socio-economic groups (Lindelow, 2002). It is important to understand the potential bias created by the choice of variables, such as what are valued as assets of wealth in different settings – for example household *conveniences* versus communication, when making an assessment of the study population.

Validity and reliability of the asset variables were not tested in this thesis, but have been assessed in previous studies. There is a consensus that while asset index reliability is not high, income data is also not reliable unless accompanied by detailed expenditure data. A study by Filmer and Pritchett (2001) compared asset and income data in India, Indonesia, Pakistan and Nepal and found that the asset index is a plausible proxy for the measure of wealth and is less error prone than in-depth patient and household expenditure interviews.

The SES quintiles were used in later analysis (Chapter 10) to assess the relationship between wealth and health-related quality of life during TB-DM treatment.

Chapter 7 How to do (or not to do) ... a micro-costing of laboratory tests

Preamble to Research Paper 2

The costing of the screening and diagnostic tests presented in Research Paper 2 was particularly challenging to conduct in the study settings (Indonesia and Romania). I spent an average of three weeks in each country, on two separate occasions in Indonesia and three occasions in Romania. Within this time period, it was difficult to explain my objectives and get the support needed to access and interview people involved in performing the tests as well as those responsible for resource utilisation and cost information. It was challenging to perform all the steps in the micro-costing during the time I had. Moreover, following up with individuals to obtain missing information was difficult to do remotely. This led me to think that a 'how to...' on micro-costing would have been useful to me in the planning stages, before starting the micro-costing. It then became clear that since none seemed to exist at the time, it could be useful to others hoping to obtain the economic costs of tests or other health technologies in the future to learn from my experiences. This is the intended purpose of this research paper.

After giving a detailed description of how to perform a micro-costing, the results of the micro-costings performed for the TANDEM study are presented in Research Paper 3.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	Yoko Laurence
Principal Supervisor	Ulla Griffiths
Thesis Title	Strategies to detect and treat concurrent tuberculosis and Schistosomiasis in Indonesia, Peru and Romania: costs, operational feasibility and impact on health-related quality of life

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	
When was the work published?	
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Health Policy and Planning
Please list the paper's authors in the intended authorship order.	Yoko Laurence, Adrien Cheorghu, Ulla Griffiths
Stage of publication	Not yet submitted - journal editors contacted and interest expressed

SECTION D – Multi-authored work

For multi-authored work give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	See details on the next page
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Student Signature: _____ Date: 17/11/2016

Supervisor Signature: _____ Date: 16/02/2017

Research Paper 2

How to do (or not to do) ... a micro-costing of laboratory tests

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Status: Target journal: *Health Policy and Planning* – journal editors have been approached and there is conditional interest

Author contribution: The idea for the paper was suggested by Ulla Griffiths after my complaints about the lack of guidelines for and difficulties of performing micro-costing studies for laboratory tests included in this thesis (Indonesia and Romania). I collected the data in the case study, drafted the paper and the case study and made revisions based on comments from Ulla Griffiths and Adrian Gheorghe.

Abstract

Micro-costing has long been advocated as a methodologically robust, but resource intensive approach to accurately estimate the cost of health services. However, only few practical guidelines support researchers in planning and conducting such studies, particularly within limited research budgets. This paper proposes a practical process for planning and conducting a micro-costing study and demonstrates it with an application to costing laboratory tests. Using an example from a laboratory in Indonesia, a step-by-step method for completing a micro-costing laboratory study is outlined together with required informational, organizational, financial and time resources. In practice, the extent to which the micro-costing study can fit into the health facilities' routine operations will ultimately dictate the applicability of each step of the process and its associated caveats. Common challenges in collecting and analysing cost data for laboratory tests are discussed, including obtaining equipment utilisation data; determining the optimal method for allocating shared costs; costing all alternative test pathways; and the importance of including overhead costs. The suggested framework is meant to be adapted and used as a guide by anyone undertaking costing in settings with limited routine accounting systems.

Running head: How to do a micro-costing

Manuscript word count: 3,506

Keywords: micro-costing, ingredients approach, laboratory tests, Indonesia

Introduction

Costing methods

Determining the cost-effectiveness of any health service is best done using cost values that are rigorously derived by a common methodology in order to make valid comparisons of alternative strategies (Drummond et al., 2005). The costs of a laboratory test estimated using different methods, even in the same setting, can vary substantially (Cunnamá et al., 2016). Approaches used to derive the costs of laboratory tests include micro-costing (Chihota et al., 2010), activity-based cost allocation systems (Barletta et al., 2013, Cao et al., 2006), and the analysis of administrative databases (using the ratio of costs to charges within a health facility or the reimbursement values) (de Oliveira et al., 2012). Although the costs to charges ratio method is convenient and easy, it is an inaccurate estimate, particularly if applying ratios from a different country.

Why micro-costing?

Micro-costing of health services is thought to be the most accurate method and is the preferred method where costs are not already available from routine systems in a given setting (Xu et al., 2014, Marks et al., 2014). Given the increasing interest in economic evaluations in LMICs (NICE and BMGF, 2014), methodologically sound costing in resource-constrained settings is a necessity.

What is micro-costing?

Micro-costing, also referred to as the 'ingredients approach', entails collecting information on the quantity and value of each resource used. It requires allocation of cost categories, e.g. overhead costs, staff time, equipment and consumables, to the activity that is being costed. Micro-costing is also called a bottom-up approach (Mogyorósy and Smith, 2005), but often includes top-down activities, particularly for assessing the overhead costs. Therefore, in this paper we consider micro-costing to be a mixed bottom-up and top-down approach (Cunnamá et al., 2016).

Micro-costing of any health service can be challenging because data collection can be time-consuming or data may be inaccessible (Alvin et al., 2014). This is especially the

case in low- and middle-income countries (LMICs), which may not have comprehensive computerised routine cost accounting systems. In the costing of laboratory tests a large number of reagents, supplies and equipment usage require proportional allocation, which can be challenging to determine. Additionally, laboratories are commonly situated within a health facility, meaning that a considerable proportion of overhead costs are for the functioning of the entire health facility and not just the laboratory.

Methodological guidance for micro-costing studies is already available, with varying degrees of detail and instruction. Some guidelines describe various costing methods and include micro-costing examples (Ozaltin and Cashin, 2014, Creese and Parker, 1994); others are disease specific and address the specific nuances of costing TB, HIV and other diseases (Sohn et al., 2009a, UNAIDS, 2000, WHO, 1988); and another addresses the collection of good quality resource data for a micro-costing (Frick, 2009). There is however a lack of guidance on the practical aspects of designing and implementing a micro-costing exercise, particularly for laboratory tests.

Objective of this paper

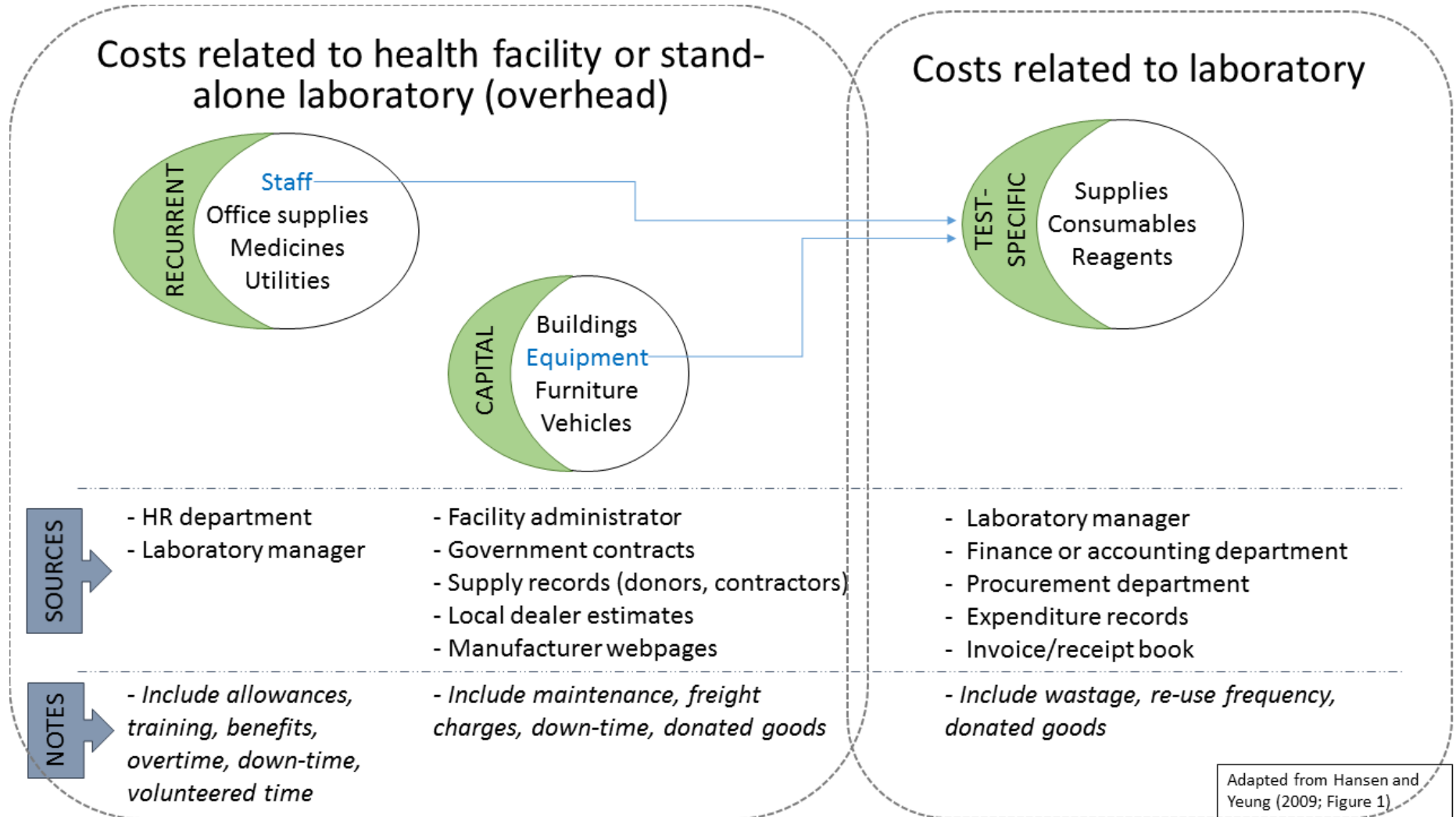
The objective of this paper is to present a practical process for micro-costing of laboratory tests in LMICs that is manageable and can be standardised. The method proposed is for economic costing, which values resources in terms of their opportunity cost. This is in contrast to financial costs used for budgeting purposes. This paper focuses on LMICs where laboratory costs require more resources and time to obtain compared to high-income countries (HICs) where cost accounting systems are generally in place (Ghaffari et al., 2009, Raulinajtys-Grzybek, 2014). Additionally, there are often insufficient staff in LMIC settings that are trained to conduct costing exercises (Conteh and Walker, 2004) and hence this guide could be beneficial to those undertaking costing work in LMICs.

Cost components

Recurrent overhead, capital overhead and test-specific costs are the key cost components in micro-costing. Although staff and equipment costs are overhead

expenses, only the personnel and machines directly involved in the test are included in the mean cost of the test and therefore are categorised as test-specific costs (see Figure 7-1).

Figure 7-1: Cost categories for calculating mean costs of a laboratory test



Adapted from Hansen and Yeung (2009; Figure 1)

Conducting a micro-costing of laboratory tests

Micro-costing can be performed on a range of activities within the health sector, including clinic or other consultations with medical professionals, preparation and dispensing of pharmaceutical products, radiological examinations, surgeries, or counselling. The facility level can also range from primary health centres to specialised, tertiary level hospitals. Laboratory tests were chosen to demonstrate the micro-costing process since it requires a combination of different cost allocation approaches. Laboratory testing can include commonly performed tests in basic laboratories, such as complete blood counts or urinalysis, or specialised diagnostic tests requiring more sophisticated laboratories, for example Plaque Reduction Neutralisation Tests. In order to more clearly illustrate the steps, we will use the example of micro-costing a Ziehl-Neelsen (Z-N) sputum smear microscopy test for tuberculosis (TB) followed by a microscopic observation drug susceptibility (MODS) culture test, also for TB, in a provincially run referral laboratory in Bandung, Indonesia.

During the initial planning, all costing options must be considered. An assessment of whether standardised cost estimates already exist for the intervention or technology (which would not be the case for newly developed or non-market goods) or if precision is required (as it would be for use in individual level cost-effectiveness analyses) will inform which method is suitable for the given context (Frick, 2009, Mogyorosy and Smith, 2005). Once the micro-costing approach has been chosen, the amount of time and effort required to conduct it can be overwhelming, but a well thought out and organised protocol can make the process manageable. A practical micro-costing framework is presented here to achieve this (Box 7-1).

Box 7-1: Micro-costing framework

1. Plan, plan, plan! What, why, how, who, where, how long? **(2 weeks)**
2. Conduct interviews **(1 week)**
3. Produce validated laboratory workflow **(2-3 weeks)**
4. Create inventory of capital items (equipment) **(1 day)**
5. Create lists (by time-motion study or observation)
 - a. Consumables and reagents **(2-3 days)**
 - b. Staff **(2-3 days)**
 - c. Unit costs **(3 weeks)**
 - d. Recurrent overhead costs **(1 week)**
6. Complete spreadsheet, including missing data follow-up **(3-8 weeks)**
7. Calculate mean cost per test **(2 days)**

Step 1. Plan it out!

The first step in determining the cost of a health service activity is to carefully plan what information is needed, from whom, how you will gather the information, and where and when the study will be performed so that there is minimal disruption of health services.

A preliminary visit to the site(s) of the costing should be made in order to prepare for data collection. This ensures that the laboratory practices are fully understood and that the data collection tool can be modified to the specific setting. However, in practice a preliminary visit may not be possible, which makes it even more essential that detailed preparation are guided by a clear process.

A spreadsheet for data collection should be created or adapted before the data collection begins. Costing spreadsheet templates for data collection and analysis are available in Appendix N ([HYPERLINK TO EXCEL FILE](#)). They are based on the example in this paper of Z-N sputum smear microscopy and MODS culture for the diagnosis of tuberculosis and is separated into test-specific, staff and overhead costs, with a 'Total' tab to combine the values.

The practical steps for conducting a micro-costing in a laboratory are presented in Box 7-1. These steps are further illustrated in a case study of micro-costing in Indonesia.

Table 7-1: Activities and resources for micro-costing of a laboratory diagnostic test

Activity (what to do and why)	Method (how to achieve the step)	Resources (list of staff, hospital ledger, equipment inventory, etc.)	Time frame
Produce a laboratory workflow (sample collection, preparation, analysis and result reporting)	Interview staff in all components of test	Laboratory manager Laboratory analysts Porters/couriers (samples and results) Nurses, doctors, other staff involved in sample collection Administrative laboratory staff	Interviewing all staff can take up to two to three weeks as scheduling interviews can be challenging
Perform an inventory (capital equipment, furniture and section(s) of the health facility used for the test, including manufacturer, model and square footage)	Walk through the laboratory and/or facility	Patient charts Equipment list Standard operating procedures Peer reviewed literature Note book or sketch pad Camera (pictures of equipment manufacturer information) Tape measure (for square footage)	Within one day
Create a list (all consumables and reagents used in the test, with quantity per test)	In-depth interviews, verified by direct observation of process for each step in test	Patient charts Standard operating procedures Peer reviewed literature Camera (pictures of product specifications)	Additional interviews in two to three days , and list produced whilst all interviews being conducted
Create a list (all staff required to conduct each step in the test and amount of time each staff member spends on each step)	Time-motion studies Item-by-item database Direct observation* <i>*If time-motion study not possible, alternatively ask each staff member for an estimate of time for each step in test</i>	Note book or sketch pad Stop watch	Two or three days* <i>*Two or more rounds of observation or time-motion study per process is a good way to obtain a mean time value</i>
Create a list (potential unit cost sources; then provide these sources with a list of unit and overhead costs needed from them)	Draft list created after initial interviews for lab workflow Contact persons on draft list for in-depth interviews with list of unit costs needed to fill out Request permission to access databases or reports on draft list	Expert panel Clinical coordinators with managerial oversight Facility administrative database Procurement personnel	Three weeks* <i>*Going through the list or spreadsheet with the sources is useful in helping them understand exactly what you require</i>
Produce a spreadsheet (data collected and output calculations)		Excel or other software for data entry and analysis	The time taken ranges from a few weeks to several months , depending on how much missing data need to be collected after leaving the facility

Step 2. Conduct initial interviews

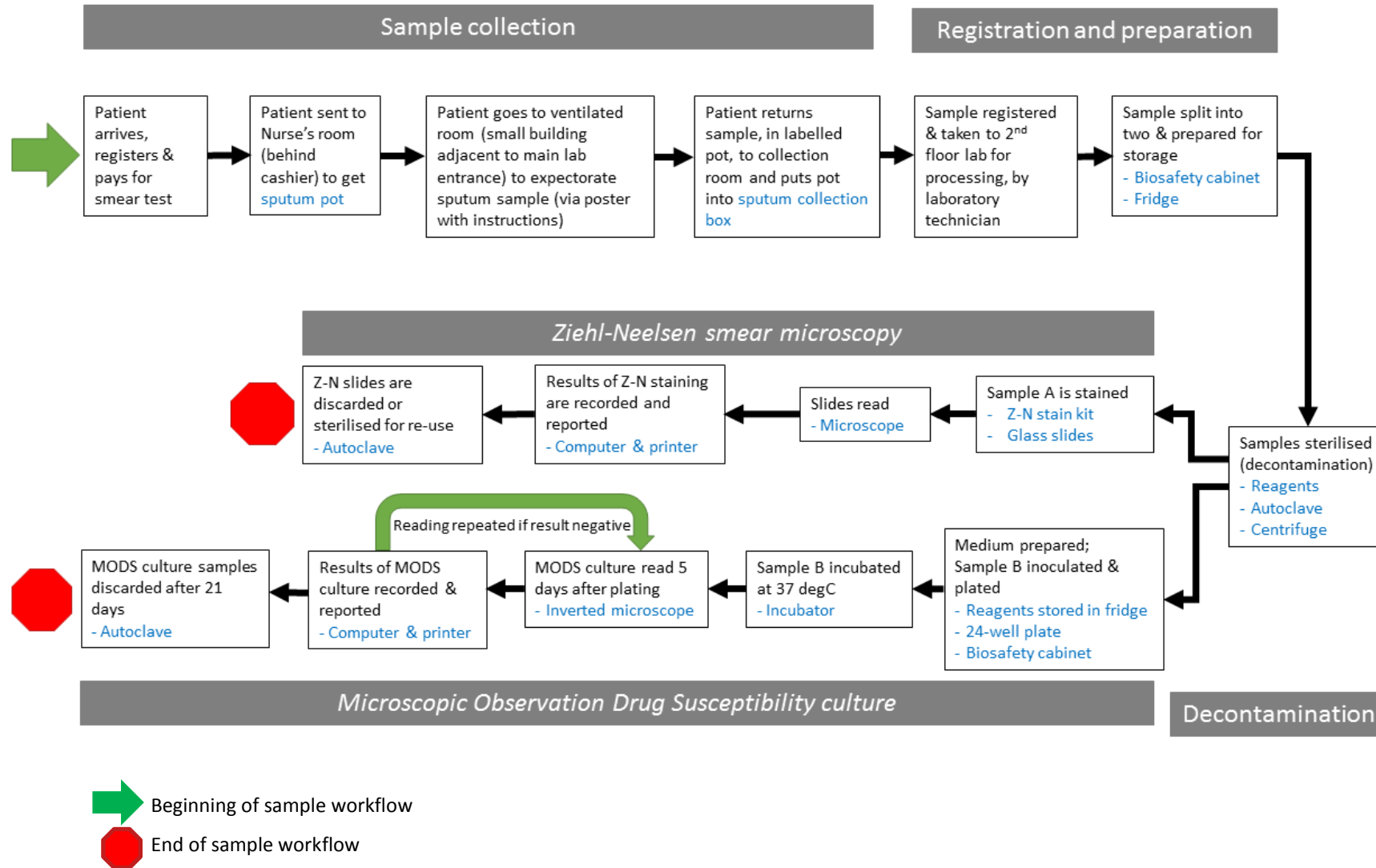
Initial interviews are needed to determine the work flow for the samples being costed and to get referrals and contact information for the individuals to be interviewed for consumable usage, equipment specifications, unit costs, staff time spent on each activity, staff salaries and other compensation, test volume for the laboratory (including the test of interest and as well as all other tests), and capital and recurrent overhead costs.

Step 3. Produce a laboratory workflow

After the initial interviews, you should be able to produce a laboratory workflow (see example in Figure 7-2), which synthesizes information about the processes, resources used and any issues associated with the test. The workflow should capture any additional procedures related to the test that may occur in the laboratory, such as sample collection, sample registration or reporting of results.

This information is best obtained by interviews with staff involved in each component of the test. The laboratory manager or a senior bio-scientist is usually the best person to start with and the list of interviewees may snowball as the process is discussed. It may be easier to separate the procedures for each test early in the process, such as sample collection, sample decontamination, sputum staining, reading of slides, sample storage or disposal, and reporting of results. These initial interviews are also important in sensitising staff to the costing study, demonstrating why the full workflow must be mapped and explaining the need for economic costs rather than using prices established for user charges.

Figure 7-2: Sputum sample workflow for Z-N smear and MODS culture in bacteriology laboratory, Indonesia



Step 4. Perform an inventory of capital items

An inventory is needed for all capital items used for the particular test and for running the laboratory. These include equipment, furniture and building space. The capital items for running the laboratory will be applied to the overhead cost calculation. Capital items that are not used for laboratory operation or the test of interest need not be captured.

Once the inventory is complete, information about the age or approximate year of purchase, expected lifespan and, if possible, the original purchase price or the replacement cost (informed by the current market value) are needed to calculate the annual cost of these items (see Table 7-2). For the building or space occupied by the laboratory where the test is conducted, the square footage and the value of the building or space needs to be obtained. If the test is conducted in a section of a room or building, the size of this smaller space is needed as well.

Table 7-2: List of capital items for Ziehl-Neelsen smear microscopy and MODS culture tests in Indonesia

Item name	Price as new (million IDR)	Year of purchase	Life expectancy	Annual maintenance (million IDR)	Manufacturer	Model	Proportion allocated to Z-N	Proportion allocated to MODS	Source
Test-specific: EQUIPMENT and FURNITURE									
Fridge – samples	3	2013	10		Sharp	NoFrost			Equipment list
Fridge – reagents	3	2013	10		LG	Compressor			Equipment list
Timer (digital)	0.27	2013	5		Hoseki				Vendor website
Vertical laminar flow hood biosafety cabinet with UV light	10.00	2011	10		Nuaire	LabGard Class II, Type B2			Balance sheet
Bunsen burner	Unknown	1960s	50	NA	No name	No name			Laboratory manager
Drying rack	Unknown	1960s	50	NA	No name	No name			Laboratory manager
Microscope	11.68	2013	10	0.83	Olympus	CX21	100%		Vendor website
UV light fixtures (x2)	0.30						100%		Equipment list
Incubator	200	2010	10		New Brunswick	NA			Balance sheet
Micropipette	15	2010	5		NA	NA			Equipment list
Autoclave	25	2010	10		Tomy	ES-315			Balance sheet
Centrifuge (for 15 ml tubes)	100	2010	10		Eppendorf	5804 R			Equipment list
Inverted microscope	150	2009	10		Nikon	Eclipse T5100			Equipment list
Vortex mixer	8	2010	10		NA	NA			Balance sheet
Analytical balance	15	2010	5		NA	NA			Balance sheet
Computer (results)	8	2012	5		Dell	Optix XE	55%	45%	Invoice book
Printer (results)	0.95	2013	5		hp	Laserjet 1300	55%	45%	Invoice book
Air conditioner	?	2013	10	0.175	Sharp	Ion Plasma Cluster	100%		Balance sheet
Overhead: BUILDING SPACE									
Item name	Area (m ²)	Year of data	Life expectancy	Value if sold today (million IDR)	Annual maintenance (million IDR)				Source
Laboratory building (entire)	4725	2012	30	3,658.10	49.00				Renovation quotation report
Land	3195	2012	50	15,985.73	NA				Renovation quotation report
Registration area (incl. sputum collection building, nurse's space, waiting area)	153	2014	30						Area manually measured with tape measure
Bacteriology laboratory (2 nd Floor – Z-N)	60	2014	30						Area manually measured with tape measure
Bacteriology laboratory (3 rd Floor - MODS)	78	2014	30						Area manually measured with tape measure

Step 5. Create lists

Initial lists of resources, costs and staff involved in the conduct of the test should be created and verified or augmented with the laboratory personnel who perform the test.

a. Consumables and reagents

A preliminary list of all consumables used in performing the laboratory tests, along with quantities consumed, can be obtained from standard operating procedures or other literature. Subsequently, in-depth interviews should be performed with relevant staff to confirm the items. All information obtained should be verified as much as possible by a time-motion study or direct observation of the laboratory procedures (see Table 7-2).

b. Unit (input) costs

An initial list of potential sources of unit cost information should be derived from the interviews informing the laboratory workflow. Following refinement, using further information on the facility and relevant literature, create a definitive list containing all the unit costs needed and present this list to the key informants (Table 7-2 and Table 7-3). They can arrange to return the completed list to you, but in practice it is preferable to sit with them and extract all the data needed. In order to do the latter, the key informant must be contacted in advance and given time to identify all the potential databases or documents with the unit cost information, such as procurement lists, balance sheets, or invoice books.

Table 7-3: List of consumables and reagents for sputum collection, Ziehl-Neelsen smear microscopy and MODS culture tests in Indonesia*

Resource name	Unit of purchase	Quantity per unit	Price as new (million IDR)	Quantity per test	Year of purchase	Source/Notes
N95 masks for staff	Box	20	0.5	*each mask lasts 1 week	2014	Hospital balance sheet
Cloth masks for patients & family	Box	50	0.05	2	2014	Balance sheets
Plastic sputum pots with cover	Bag	50	0.175	2	2014	Laboratory technician
Clear plastic bags for pots (12x20cm)	Box	100	0.15	1	2014	Laboratory technician
Toilet tissue	Roll	1	0.004	*each roll lasts 1 week	2014	Balance sheets
Lunch box for sputum storage	Lunch box	1	0.15	*each box lasts ~1 year	2015	Invoice book
Alcohol (70%)	Bottle – 1 litre	1	0.04	*each bottle lasts 1 month	2014	Balance sheets
Marker	Unit	1	0.01	*each lasts ~1 month	2014	Invoice book
Smear glass slides (box- 25x75 mm, 1.1-1.3 mm thick)	Box	72	1.44	2	2014	Balance sheets
Staining kit (Z-N)	Box	40	0.2	2	2014	Balance sheets
Plastic liners for discard bucket	Unit	1	0.002	*replaced every day	2014	Balance sheets
Discard bucket – 5 litres	Unit	1	0.03	*each lasts ~1 year	2014	Balance sheets
Applicator sticks – wooden	Box	100	0.3	2	2014	Balance sheets
Staining rack (drying smear)	Unit	1	0.125	*each rack lasts ~1 year	2013	
Decontamination reagents (hypoclorit)	Bottle – 1 litre	1	0.015	*each bottle lasts 1 month	2014	Balance sheets
Immersion oil	Bottle – 200 ml	2	0.025	*each bottle lasts 1 week	2014	Balance sheets
Paper lens cleaner (for microscopes)	Pack	50	2.5	*each lasts 1 month	2013	Balance sheets
Slide box (to store slides)	Box	100	5.0	2	2013	Invoice book
UV light bulbs	Unit	2	0.7	*each bulb lasts 1 year	2014	Balance sheets
Toner	Unit	1		?	2014	
Paper (A4)	Packet	500 sheets	0.035	3	2015	Balance sheets

*Parts a and b of micro-costing Step 5 are incorporated in Table 3
IDR – Indonesian Rupiah

c. Staff

The job titles (as they would appear on the payroll list) and time spent by each individual involved in every stage of the test should be recorded and measured during a time-motion exercise or by direct observation. The total number of working hours for each staff member is needed for calculating their salary per minute.

d. Recurrent overhead costs

The amount spent per year at the facility level is needed for all of the recurrent overhead costs, including staff compensation, utilities [water and sewerage, electricity, gas, communication (telephone and internet)], cleaning and sterilisation, soft inventory (linens and uniforms), general office supplies, general laboratory or medical supplies, transportation, insurance, rent, administrative activities and food, if applicable. While facilities generally have the same types of recurrent overhead costs, assessing how to allocate those costs to your test will be a key challenge (see Step 7).

Step 6. Complete the spreadsheet

Population of the spreadsheets can begin as soon as data is accessed and adapted to your requirements, but the spreadsheets will be completed and refined only after the interviews and observations in the laboratory have ended. Refining the spreadsheet provides an opportunity to identify any missing data for follow-up (Appendix N).

Step 7. Calculate mean cost per test

The greatest challenge for collecting all data needed is that one is often restricted by time and so scheduling interviews and observation sessions and accessing all the unit cost sources can be onerous.

Calculation of the resource quantities and unit costs are presented separately and combined for calculation of mean cost per test.

a. Pulling the resource quantity data together

The quantity data used in micro-costing studies are staff time, supplies used, square footage, number of tests per year and kilometres driven (if transportation of samples is involved) (Frick, 2009). This type of data collection can be done by accessing administrative databases at a facility, interviews with healthcare providers and administrative staff, patient charts, direct observation, time-motion studies or data from health worker diaries or logs.

Values for the number of tests per year for each piece of equipment used for the test of interest and for the entire laboratory may not always be available. It is useful to ask laboratory personnel to estimate the number of tests performed on an average day and multiply that by the number of days of operation per year.

The outputs of the activity being costed should be quantified (for example, number of tests per year) and further enumerated by type of test for each piece of equipment. For example, when assessing the proportional usage of a bio-safety cabinet, which is usually for sputum samples only, an output number of sputum samples processed per year should be obtained. Alternatively, for a centrifuge, which often has shared usage for blood and sputum samples for various types of tests, the total number of samples and the number of sputum samples processed annually and a subset output of number of Z-N smear samples and MODS samples (i.e. tests of interest) per year should be obtained. The cost allocation for these capital items will then be based on the output activity.

Other potential data to incorporate into a micro-costing study include the wastage proportion of reagents and consumables, re-usage frequency for supplies (e.g. microscope plate), staff and equipment down-time, staff waiting time when analysing tests, and staff time spent on activities such as administrative or management duties. Some top-down costing methods would automatically incorporate these components into their mean cost calculations, but diligence is needed in capturing them in a micro-costing (Cunnamana et al., 2016).

b. Appropriate cost values

Salary information, along with allowances, training and benefits, is most often obtainable from the human resources department of the organisation, but a laboratory manager may know some of these values if they have staff reporting to them directly. The laboratory manager may also be able to provide salary ranges, if not the exact values, for staff categories, which is useful to obtain if there are time constraints in accessing the health facility administrators. Gross salary values are ideal, but if only net salary information is available, make a note of this in your data collection tools, along with the income tax rate for the country, so that gross salaries can be estimated. Since salary information can be sensitive and raises confidentiality concerns, in order to expedite the data collection process, it is important to early request that salary data are mapped to staff positions (e.g. nurse, midwife, and laboratory technician) rather than identifiable individuals.

Capital costs, including equipment, furniture, laboratory space and vehicles, must be annualised; a discount rate, as recommended by the local Ministry of Finance, 3%, was applied to the locally determined life expectancy of the capital items in the Indonesian case study (Walker and Kumaranayake, 2002). The annual cost of maintenance, insurance and any excess freight charges were included before determining the mean capital costs allocated to each test. Equipment maintenance costs may be known by the laboratory manager, but the capital costs will most likely be available from the administrators of the organisation, particularly for older equipment and building values. If there is no centralised register to provide the purchase price of capital goods, you or the member of staff helping you with data collection will most likely be retrieving this information from local dealer estimates, government contracts, or supply records from donors or contractors. If any values are missing for equipment, furniture or vehicles, using external sources such as manufacturer webpages is an alternative method of obtaining capital costs, but these values will be the cost of replacing the goods in the present day rather than the purchase price, which you must account for when calculating the annual value based on the life expectancy from the time of purchase (Creese and Parker, 1994).

The unit costs of test-specific items can often be obtained from the laboratory manager within a health facility or from the finance, accounting or procurement department of a larger laboratory. Expenditure records, rather than budgets are the ideal source.

The cost data collected are normally from different financial years and in different currencies. All values should be converted to a common currency and year, using the beginning of the year present value. In our example, both 2014 Indonesian rupiah (IDR) and United States dollars (USD) were calculated so that the values would be useful within Indonesia and could also be compared against other settings.

c. Mean cost per test

The mean cost per test can be calculated according to cost category (Figure 7-1) (as was done in the sample workbook – Appendix N, or by sub-procedure (for example, sample collection, registration and preparation, decontamination, etc. as shown in Figure 7-2) and combined to produce the mean cost of the laboratory test.

Proportional allocation of annual recurrent overhead costs (excluding staff costs) can also be calculated based on the ratio of the total test output of the laboratory. If the test you are costing is not routinely performed in the laboratory, an alternative approach could be to use the ratio of expected patients by the average number of tests per patient. The square footage ratio of utilised laboratory space to the entire hospital or facility is a common approach for proportional allocation of annualised building space capital costs.

The mean cost per test is the sum of the total test-specific costs (consumables and reagents, equipment and staff) and the allocated capital and recurrent overhead costs (see Box 7-2).

Box 7-2: Indonesia case study: Sputum collection, Ziehl-Neelsen smear microscopy and microscopic observation drug susceptibility tests

Setting: In this example, people with suspected tuberculosis in Bandung, Indonesia were referred to the Balai Laboratorium Kesehatan (BLK), which is a provincial, government owned referral laboratory. They were tested using the Ziehl-Neelsen (Z-N) smear microscopy and microscopic observation drug susceptibility (MODS) culture tests. A wide range of tests are performed at BLK; approximately 170,000 in 2014, of which 2,501 were Z-N and 481 were MODS tests.

The patients arrived at BLK, registered in the reception area on the ground floor and were instructed by a nurse to produce a sputum sample in a sample collection structure ('outhouse'), approximately 20 metres away from the main building, in the same compound. The patients produced a second sputum sample at home early the next morning, which was brought in to the BLK reception within 24 hours.

Work flow: Sputum samples were taken by the nurse to the second floor, where a technician split each sample in half: for Z-N and MODS. The Z-N sample was analysed that day by a technician and results were ready within two to three days. The MODS samples were analysed on Mondays and Thursdays by different laboratory staff on the third floor, so these samples were stored prior to analysis. A positive MODS result can be ready in as little as a day. However, if the sample was negative, it remained in the solution for up to one month before a negative result was confirmed.

Hardcopies of the Z-N and MODS results were collected from the laboratory by the patient and hardcopies were also stored at the laboratory.

Data collection – planning, logistics and understanding the workflow: E-mail communication with the administrators at the BLK about the objectives, process and types of data needed for the micro-costing began two months prior to starting the study. Attempts were made to establish a list of key informants to be interviewed for the workflow, quantity and cost data collection. Enquiries were also made about the process for obtaining permission to interview personnel and collect data. Despite these attempts to have all permission and approval paperwork completed and initiate contact with key informants before going to BLK, key informants were only identified in the first week of starting the micro-costing. During that first week, the BLK microbiologist performing the MODS test was interviewed about the process and quantities when conducting both the Z-N and MODS tests.

Data collection - test quantities and costs: To obtain quantities, specifications and some costs for consumables and equipment, a more detailed interview was conducted with the BLK microbiologist in week two. To obtain overhead costs and salary information, interviews were conducted with the BLK Head Administrator and Head Doctor in week three. Additional overhead costs were later obtained by sending spreadsheets with the information required, for completion by the Head Administrator.

Cost outcome calculation: The mean cost per test (two samples) was determined by combining the test-specific, capital and recurrent overhead costs. Costs are in 2014 Indonesian Rupiah (IDR).

	Supplies, consumables & reagents	Equipment	Staff	Capital overhead	Recurrent overhead	Total costs
Sputum collection – 2 samples	10,377	141	10,691	12,767	10,767	44,742
Z-N smear microscopy – 2 samples	69,100	10,660	33,215	5,007	4,222	122,204
MODS culture – 2 samples	187,297	154,392	43,129	23,468	19,792	428,078

Test-specific costs included consumables, reagents and staff salaries. Staff time, and consumable and reagent quantities were determined by interviewing the BLK microbiologist and confirmed by observation of the analysis processes. The value of staff time was determined from the salary values given by the Head Administrator at BLK and multiplied by time taken (including waiting time) to complete analysis and record results. The Z-N tests were performed in batches of ten and MODS tests were performed twice a week, regardless of the number of samples received.

Capital costs, primarily the equipment used in analysing the AFB and MODS tests, were determined by annualising the equipment. This included the purchase price, when obtained or the current market value, which was divided by the life expectancy of the equipment (after a 3% discount). The annual cost of maintenance was added to this value. The mean capital cost per test utilising each piece of equipment was calculated by dividing the total annualised cost of each piece of equipment by the annual number of tests performed.

Total annual overhead costs for BLK were provided by the Head Administrator. The mean overhead costs per Z-N and MODS tests were calculated by multiplying these annual overhead costs by the proportion of the square footage of the respective laboratories on the second and third floors of the entire building. This was then divided by the total estimated annual number of Z-N and MODS samples analysed respectively by the laboratory.

Lessons learnt: A recent funding application to an external donor for the refurbishment and expansion of BLK meant that most of the capital and recurring overhead costs were readily available. This would usually not be the case and a contingency plan needs to be made to deal with a lack of this data, for example, excluding overhead costs from the mean cost calculation or applying a mark-up value.

Practicalities of micro-costing

Several pragmatic considerations emerged from the case studies in relation to transposing existing methodological guidance into practice.

i. Overhead costs – worth the trouble?

While recurrent overhead costs should ideally be included in the mean cost per test, it may prove difficult to obtain the necessary data and make the proportional allocations sensibly. In a sample of studies included in a review of smear and culture tests costs for multidrug-resistant tuberculosis (Lu et al., 2013) the recurrent overhead cost (excluding salaries) proportion of the total mean cost per test ranged between 3% for various sputum culture media in South Africa (Chihota et al., 2010) and 99% for smear in Thailand (Kamolratanakul et al., 2002). The median proportion was 50% for the 13 laboratory test costings that included overhead costs in Thailand, South Africa and Zambia (Kamolratanakul et al., 2002, Sohn et al., 2009b, Whitelaw et al., 2011, Mueller et al., 2008, Chihota et al., 2010). This is in no way representative of all laboratory tests in LMICs, but suggests that omitting the overhead costs would produce a substantial underestimation of the mean costs and that the effort required to allocate the overhead costs is warranted. Yet, only eight of the 19 (42%) LMIC studies included in the review explicitly indicated that overhead costs were included.

Two key factors influencing overhead costs are the size of the organisation hosting the laboratory and the degree to which laboratory services are integrated with other services. For example, if some laboratory tests are performed in quasi-autonomous departments/institutions (e.g. cancer research institute) hosted by a large hospital, but with independent financial flows, overheads may be quite important. An alternative method for calculating the proportional overhead costs is to add a pre-determined mark-up (Mogyorosy and Smith, 2005) to the mean cost of the test, which should be based on expert opinion familiar with the setting.

ii. How to allocate shared costs?

Allocation of shared costs is not only challenging for overhead costs, but also for the reagents used in the laboratory (which are often used for more than one type of test) or staff who perform more than one type of test. Several methods for proportional allocation exist, but the best method is often unclear. Measuring square footage is a straightforward approach for institutional overhead costs whereas the proportion of tests out of total performed (output) in that laboratory may inform the allocation of laboratory overheads (Creese and Parker, 1994). Activity output allocation however assumes that the different tests are of similar complexity and utilise overhead resources equally. Actual utilisation is more accurate, but requires a complex internal accounting system, which may not be available or easily accessible.

Both output and square footage was used for overhead cost allocation for the Z-N and MODS tests in Indonesia.

iii. Who are your sources?

When costing laboratory diagnostic tests, the laboratory manager is the best initial source of information, but expanding your list of potential contacts is essential. This list could include the financial director, procurement manager of a facility such as a hospital, a grant manager in a research hospital, or administrators in a laboratory or hospital. Knowing who should be on your list of contacts can only be achieved by having a clear understanding of how the organisation or facility works and how the costing study fits into routine services. Interviews conducted early in the process with biomedical staff are invaluable in providing this orientation, but capturing their input may be difficult as they can be unclear about the necessity of their role in the costing activity. They can also provide links or introductions to the staff with the required cost information.

iv. Economic costs

It should be ensured that economic or opportunity cost data are being collected and not tariffs or prices. In practice, this can be difficult to explain to relevant staff. Communicating the difference and the reasons why costs are of interests to economists can require several iterations. Once the ideal data sources have been determined, available data sources should be mapped and time taken to fully understand their content.

v. Consider all pathways

All diagnostic outcomes (true positive, true negative, false positive and false negative) (Dowdy et al., 2011) and their entire test pathways, from sample collection to communicating the test results, need to be costed. An example of the test pathway occurs when a sample is inoculated on three media, and only one of them grows. One then performs particular tests specific to that media, for example application of five different antibiotics to identify the germ. If the sample responds to two of these antibiotics, one then performs an extra test, and so on. At the very least, it is important to distinguish between negative and positive tests because they are unlikely to cost the same. Some form of probabilistic costing is ideal, where the probability of a test being positive (cumulative probability of all node steps being positive) can be calculated. In practice, laboratories rarely keep such detailed records that can be aggregated to produce summary statistics over a substantial time period, but at the very least the likely difference between the costs of various test outcomes should be explored.

vi. Donated goods and volunteered time

Lastly, when conducting a micro-costing study, donated goods and volunteered time can easily be omitted as it requires additional information to be able to place a monetary value on these, but it is important to do so to ensure that the costs are not being underestimated. The simplest approach for including the value of donated goods is to find the current market value of goods that are most similar and include that value in the costing. For volunteered time, the type of activities performed and the level of education

typically required to perform those activities would be a suitable way of assessing the wages that should be paid to individuals performing similar activities. Another approach to placing a value on volunteered time is to determine what paid activity the volunteer could be performing were they not volunteering and use the wage they would get as an indicator for the value of their time. These elements are often not a consideration for costing laboratory services, but is included here so that it isn't omitted when costing other health service activities, for example vaccination or counselling and testing programmes.

Discussion

The steps and examples presented in this paper are not meant to be prescriptive, but demonstrate what has been done and can be done in LMIC settings. There may be other ways of obtaining costs for laboratory diagnostic tests; the approach chosen must be guided by the particular setting, availability of and access to data, format of existing data and the skill set available.

Although our paper gives examples of micro-costing for laboratory diagnostic tests, these methods can also be used to cost other publicly provided services, such as vaccine delivery, radiology tests, point of care tests, screening activities, etc.

The most common concerns when performing a micro-costing include accessing the appropriate individuals and data; sources and type of cost data; and the nuances of the unit cost calculation.

Micro-costing in LMICs requires that planning activities focus on the logistics of data collection, in contrast when conducting similar studies in HICs, where cost accounting data are more easily available in suitable formats. This difference affects how a LMIC cost study is planned. Well before the study begins, collaborators or key personnel to assist with the data collection must be identified and sensitised in order to ensure the required methodological standard. Sufficient research time must be allocated for data collection, cleaning and analysis, accounting for the need to identify and obtain necessary approvals. Interviews, walk-throughs, observations and time-motion studies must be planned

accordingly, with a minimum of two visits: one preliminary visit to familiarise yourself with the setting and aid with planning, one intensive data collection and potentially a third visit for clarification and dissemination. The cost of conducting research must not be neglected and all of these planning considerations will impact on the budget required to perform a micro-costing.

Micro-costing health services in general, and laboratory tests in particular, are not solely a spreadsheet exercise. The process can engage a large number of clinical and non-clinical stakeholders who contribute to various stages of the cost calculation. Costing is also an iterative process where data inputs and analysis require constant validation and adjustment. For these reasons, building an effective and sustainable working relationship with the relevant stakeholders is paramount. You may achieve this by identifying the nature of stakeholders' own interest in cost data and designing the costing exercise so that its intermediate or final outputs can be of use to them. Engaging collaborators or key informants with an interest in cost data and a good working knowledge of the facility's or organisation's culture can also prove invaluable in gaining trust and facilitating the data collection process.

Conclusion

Costing laboratory tests is difficult in high-income countries and even more so in resource-constrained settings. Our experience suggests that micro-costing in LMICs is just as much a social as a technical enterprise. The framework proposed in this paper attempts to bridge the gap between methodological guidance and the practicalities of costing in order to facilitate efficient acquisition of the required cost information. There is no substitute for thorough operational planning of micro-costing studies, which accounts for the organizational realities of the organisation. Otherwise, the promise of high accuracy that micro-costing holds is likely to be largely offset by disproportionately intensive labour and questionable outputs.

**Chapter 8 Costs per accurate diagnosis of bi-directional screening in
Indonesia and Romania: integrating tuberculosis and diabetes
services**

Preamble to Research Paper 3

Screening people with TB for DM seems to be the favoured pathway for identifying concurrent TB and DM, particularly with an increasing awareness of the clinical and economic challenges of TB-DM within the TB community. However, the risk of missing TB in people with DM cannot be denied if DM programmes are not equipped with the information and resources to identify TB.

This paper assessed the costs and accuracy of the algorithms and testing pathways in order to identify the greatest number of patients with concurrent disease for the least amount of money.

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SECTION A – Student Details

Student	Yoko Laurence
Principal Supervisor	Ulla Griffiths
Thesis Title	Strategies to detect and treat concurrent tuberculosis and diabetes in Indonesia, Peru and Romania: costs, operational feasibility and impact on health-related quality of life

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	
When was the work published?	
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Lancet Global Health
Please list the paper's authors in the intended authorship order:	Yoko Laurence, Julia Critchley, Nicolae Pandur, David Moore, Ulla Griffiths
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	See details on the next page
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Student Signature: _____ Date: 17/11/2016

Supervisor Signature: _____ Date: 16/02/2017

Research Paper 3

Costs per accurate diagnosis of bi-directional screening in Indonesia and Romania: integrating tuberculosis and diabetes services

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Author contribution: I designed the costing studies, developed data collection tools for the cost and resource data, and collected the data in Indonesia and Romania. I designed the data analysis plan and performed the analysis, all under the guidance of Ulla

Griffiths. I also performed the diagnostic accuracy analysis for each test, with input from Ulla Griffiths, Julia Critchley, Daniel Grint, David Moore and Nicolae Panduru. I performed the analysis for the cost per accurate diagnosis, which was validated by Ulla Griffiths and Julia Critchley. Lastly, I drafted the manuscript and made revisions based on comments from co-authors.

Abstract

Introduction: There is an emerging syndemic of tuberculosis (TB) and diabetes mellitus (DM), but screening protocols are not well established. The cost per accurate diagnosis of either disease is expected to decrease as the underlying prevalence of the disease in the population increases. We compared the mean costs per accurate diagnosis of various screening algorithms in Indonesia and Romania for detection of concurrent pulmonary TB (PTB) and DM.

Method: Four TB tests were administered to people with diagnosed DM. Two risk scores, three point of care (POC) tests and two blood tests were used to assess people with newly diagnosed TB for DM. In Bandung, Indonesia, people with newly diagnosed TB were recruited and screened for DM from a TB research clinic at a teaching hospital and the directly-observed therapy, short-course clinics at two general hospitals. Patients visiting the DM clinic at a referral hospital were screened for active TB in the hospital's radiology department and in the adjacent reference laboratory. Study participants in Romania were recruited, screened and treated at four government hospitals. DM in-patients at two general hospitals in Craiova were screened for active TB. People being treated for active TB a sanatorium in Gorj county and an infectious diseases hospital in Dolj country, were screened for DM. The diagnostic accuracy (sensitivity and specificity) of each test was determined individually and for combined, stepped diagnostic algorithms, established from consultation with disease specialists and the literature. The diagnostic accuracy for the DM tests were determined against a gold standard of two laboratory glycated haemoglobin tests and for TB tests against the gold standard of smear microscopy followed by culture. Micro-costing of each test was performed from a provider perspective.

Results: In Indonesia, the lowest cost per accurate diagnosis of active PTB was US\$ 3.74 for a single symptom screen. For combined TB tests the lowest cost was US\$ 17.93 for an algorithm of TB symptom screen and smear microscopy. No TB cases in individuals with confirmed DM were identified in Romania. For DM screening, the age screen and the urine dipstick had the lowest costs per accurate diagnosis for an individual test at US\$ 0.08 and US\$ 1.18, respectively in Indonesia and US\$ 1.06 and US\$ 1.85, respectively in Romania. DM screening algorithm with the lowest cost per accurate

diagnosis was age screen with POC random plasma glucose (RPG) at US\$ 1.49 in Indonesia and US\$ 5.64 in Romania. The Omani risk score, which included age and four additional risk screens, combined with the POC RPG was US\$ 2.59 per case accurately diagnosed in Indonesia. The algorithm of urine dipstick with two successive laboratory HbA_{1c} tests amounted to US\$ 10.87 per accurate diagnosis in Romania.

Conclusion: The cost per accurate diagnosis is lower when screening people with TB for DM than screening people with DM for TB. These results can inform the design of screening interventions for concurrent TB-DM within National TB Programmes.

Running head: Costs per accurate diagnosis of concurrent TB and DM

Manuscript word count: 5,512

Key words: provider costs, tuberculosis, diabetes, bi-directional screening, diagnosis, Indonesia, Romania, cost per accurate diagnosis, integration, TB-DM

Introduction

Globally, between a third and a quarter of the population is estimated to have latent tuberculosis infection (LTBI) and there were 10.4 million incident cases of active tuberculosis (TB) in 2015, of which India, Indonesia and China accounted for 45% (Houben and Dodd, 2016, WHO, 2016a). Just as strikingly, in 2015 there were an estimated 415 million adults with diabetes mellitus (DM) and an additional 318 million at risk of DM (IDF, 2015).

The prevalence of DM in people with TB has a wide range. In a Ugandan study the value was 9% for adults 18 to 65 years old diagnosed using a point of care (POC) random blood sugar glucometer (defined as ≥ 200 mg/dL) (Kibirige et al., 2013). The value was much higher in Kerala, India at 44% for people 15 years and over, diagnosed using the laboratory glycated haemoglobin (HbA_{1c}) test (defined as $\geq 6.5\%$) (Balakrishnan et al., 2012).

There are few published data on TB prevalence in people with DM (WHO, 2015b). Historical reports from the 1950s and 1960s cite prevalence rates from 4% in people 40 years and over detected by chest radiography (CXR) in Sweden, to 36% in the same population and using the same screening test in Korea (Jeon et al., 2010). More recent studies show a narrower range between <1% in India and 6% in Ethiopia for smear positive TB (Jali et al., 2013, Amare et al., 2013).

The risk of TB infection is approximately three-fold greater if an individual has DM due to depressed immunity (Jeon and Murray, 2008). Moreover, these patients may have worsened TB treatment outcomes (Baker et al., 2011). One of several reasons for an increased risk of DM in people with TB is prolonged stimulation of the inflammatory system, which ultimately decreases insulin production (Young et al., 2009). While the association between TB and DM is recognised, the temporal relationship between the two diseases is difficult to ascertain and an optimal treatment regimen is therefore not yet established.

Several studies report the cost and cost-effectiveness of various TB diagnostics (Lu et al., 2013, Moliccotti et al., 2014, Nienhaus et al., 2011). Cost and cost-effectiveness studies of DM risk score and other DM tests are solely from high-income countries (Icks et al., 2004, Gillies et al., 2008, Zhang et al., 2003). No studies have shown the cost of integrating TB screening into chronic disease programmes or the cost of integrating DM screening into TB treatment programmes, including Directly Observed Therapy, Short Course (DOTS). However, the cost effectiveness of diagnostic tests is expected to vary according to the prevalence of the underlying disease of interest (Xie et al., 2017).

Our study objectives were to determine and compare the costs of accurate diagnosis of various TB and DM integrated screening strategies in Indonesia and Romania. Data were collected as part of TANDEM (Concurrent Tuberculosis and Diabetes Mellitus: unravelling the causal link and improving care). TANDEM was a multi-disciplinary project generating evidence to enhance clinical care and management of concurrent TB and DM (van Crevel and Dockrell, 2014b). This part of the study was undertaken in two TB endemic countries with an increasing prevalence of DM: Indonesia (TB incidence 395 per 100,000 population; DM prevalence 6.2% adult population) and Romania (TB incidence 84 per 100,000 population; DM prevalence 7% adult population).

Methods

Setting and patient selection - the TANDEM project

TANDEM participants were recruited to a cross-sectional study between December 2013 and June 2016. The sampling frame was all people 18 years and older with new or existing type 2 DM were screened for TB and all people 18 years and older with newly diagnosed active pulmonary TB within 72 hours of treatment initiation were screened for DM at the participating facilities in Indonesia and Romania. The sample size and study power were calculated assuming a 95% confidence interval with precision of +/- 0.15 at each site using the exact mid-P method. Further details on the sampling are given in an accompanying paper by Grint et al. (submitted to Lancet Diabetes Endocrinology (Feb 2017)).

In Bandung, Indonesia, 33 government health facilities were involved in TANDEM (Appendix O). People with suspected TB were referred from 29 primary health centres (Puskesmas) to a TB clinic at the Universitas Padjadjaran Teaching Hospital for TB confirmation and DM screening. People with newly diagnosed TB were also recruited at DOTS clinics in Hasan Sadikin Hospital (RSHS) and Ujung Berung District Hospital. Patients visiting the DM clinic at RSHS were screened for TB in the radiology department and in the adjacent Balai Laboratorium Kesehatan (BLK) building.

In Romania, study participants were recruited, screened and treated at five government hospitals (Appendix P). People with DM were treated as in-patients at the Emergency County Hospital, Craiova (Hospital #1) and the Craiova Philanthropic Municipal Hospital (Hospital #2). People with TB were treated at the Tudor Vladimirescu Runcu Hospital for Lung Diseases in Gorj county (also called a sanatorium) and Victor Babes Clinical Hospital for Infectious Diseases and Pneumology in Dolj county. All patients with TB were treated as in-patients for at least 30 days or until their sputum smear was negative. The remaining five months of TB treatment was through outpatient dispensaries where pneumologists saw patients once per month. DM consultations, glucometers with strips and DM prescriptions were free of charge to patients, but blood and urine tests, as well as administrative fees and some inpatient care, required out-of-pocket payments from patients (Donicova et al., 2011). In Indonesia, services were free and TANDEM patients were reimbursed for their travel costs with a standard fee of IDR 25,000 Rupiah (US\$ 1.92) per visit. Patients in Romania were not compensated.

Screening tests and laboratory diagnostic procedures

A range of data that increases the risk of DM was collected for all people with TB. This allowed established risk scores with a high AUC (FINDRISC) (Brown et al., 2012) and those that had socio-economic settings that were more similar to the TANDEM populations (Indian Risk Score and the Omani Risk Score), as well as new risk scores to be assessed for each patient. In addition to the two risk scores developed from TANDEM data (Full TANDEM Score and the Restricted TANDEM Score), the Omani Risk Score was chosen for this analysis since it performed the best when applied to data from all four TANDEM countries combined ((Grint et al., submitted to Lancet Diabetes Endocrinology

(Feb 2017))). The Omani risk score screened patients on age, DM family history, body mass index (BMI), waist circumference and current hypertension (using systolic and diastolic blood pressure readings) (Al-Lawati and Tuomilehto, 2007). The additional DM screening and diagnostic tests performed on all patients were the POC random plasma glucose (RPG), fasting blood glucose (FBG), POC urine dipstick, POC HbA_{1c} and laboratory HbA_{1c} (Appendix Q).

People with DM were screened for TB using symptom screen and chest x-ray (CXR). Anyone with abnormal CXR were required to produce two sputum samples for the Ziehl-Neelsen (ZN) smear microscopy and culture tests; microscopic observation drug susceptibility (MODS) in Indonesia and the Lowenstein Jensen (L-J) in Romania. Latent TB screening was done using Interferon Gamma Release Assay (IGRA) in Indonesia and tuberculin skin test (TST) in Romania.

The POC RPG and POC HbA_{1c} tests were not used in routine service in any of the study facilities. The urine dipstick test was routinely used, but not by clinicians, which was the procedure in TANDEM. Laboratories in both countries routinely performed both FBG and laboratory HbA_{1c}, although not for people with TB. CXRs were routinely available in all study facilities. TB smear and culture tests were only performed in specialised hospitals in Romania. Hence, DM in-patients had to be transported by ambulance to the Victor Babes Infectious Diseases Hospital in Craiova for collection and analyses of sputum samples. In Indonesia, smear and solid culture tests were available at the Puskesmas and the RSHS Referral Hospital.

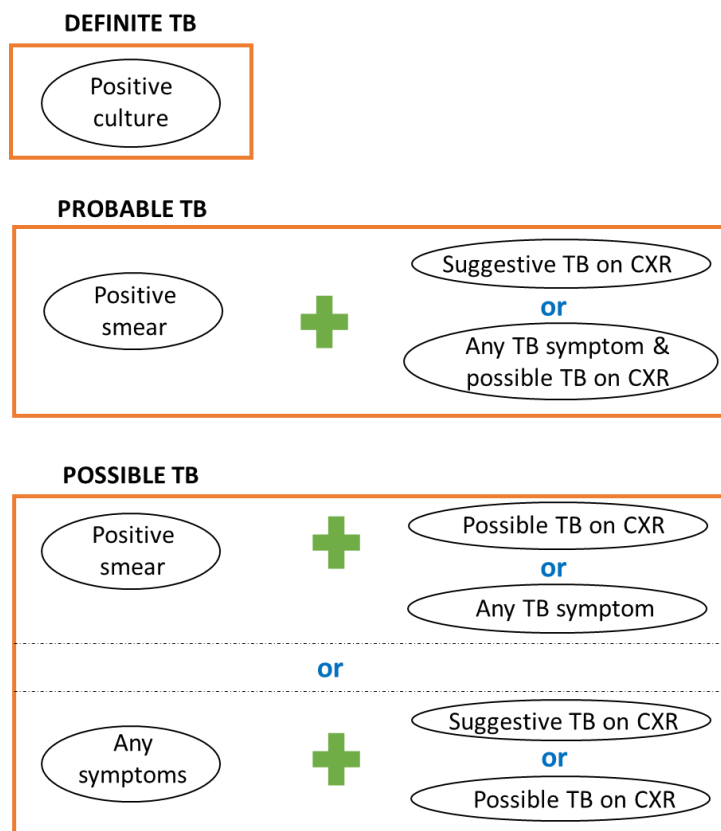
Case definitions

Definite TB was defined as positive sputum culture (Figure 8-1). Probable TB was defined as positive sputum smear and possible or typical TB on CXR. The gold standard for TB diagnosis was smear microscopy followed by a positive sputum culture on at least one of two sputum samples collected.

Two laboratory HbA_{1c} performed on different days was the gold standard for DM diagnosis. The case definition was a result of 6.5% or greater for either laboratory HbA_{1c}

test. In order to comply with the National Glycohemoglobin Standardization Program (NGSP), blood samples were analysed using ion exchange high-performance liquid chromatography at private laboratories in both Indonesia (Prodia) and Romania (Bioclinica) (NGSP, 2010). Prodia is internationally certified by the NGSP while Bioclinica has been certified by the German quality assurance company, Instand eV. Of the two diagnostic tests used in TANDEM, FBG and laboratory HbA_{1c}, the laboratory HbA_{1c} is a more acceptable gold standard for people with TB. The required overnight fasting for FBG is not only inconvenient, but also physically difficult in this population. Laboratory HbA_{1c} and FBG are equally effective for early detection of type 2 DM (Bennett et al., 2007).

Figure 8-1: TB case definitions in TANDEM



Cost data collection

Cost data were collected between February 2014 and July 2015 using the ingredients approach from a provider perspective. Costs were converted into 2014 US dollars using exchange rates of 1 US\$ = 12,420 Indonesian Rupiah and 1 US\$ = 3.66 Romanian Leu

(OANDA, 2016). In any situation where the mean cost for a test was produced for more than one facility, the average and variability (i.e. standard deviation) of the costs were presented.

Test-specific costs

Resource quantities for reagents, consumables and equipment in health clinics, patient wards and laboratories were obtained by interviewing health professionals performing the tests. Time associated with the various activities within each test was also determined from interviews. Quantities and staff time were validated by observing and timing each activity on at least one occasion. Equipment costs were gathered from financial directors of clinics, laboratories and hospitals. Unit costs of reagents and consumables were obtained from the respective Procurement Departments. Items purchased specifically for the study were obtained from invoice books kept by TANDEM administrators. Since the laboratory HbA_{1c} blood analyses were performed at private laboratories, the price charged was used. Blood sample transportation was included in the price in both countries.

Overhead costs

Overhead costs were categorised as either capital or recurrent. Capital costs were collected from facility asset or expenditure records and included building space, land, computers, furniture, general medical equipment, non-medical equipment and vehicles. Recurrent costs gathered from expenditure records included utilities, cleaning, sterilisation, and office supplies. Salaries were extracted from Human Resources payroll databases. See Appendix R for detail by country.

Useful life of capital goods was estimated in line with WHO-CHOICE values (Johns et al., 2003, WHO, 2000), unless otherwise indicated by local personnel. Small equipment (e.g. computer, pipette holder, radiology film cassette) were valued at five years, vehicles at seven years, large equipment (e.g. refrigerator, air conditioner) at 10 years, buildings at 30 years and land at 50 years. All of these items were annualised using a 3% discount rate (Tan-Torres Edejer et al., 2003).

Overhead costs were allocated to patient screening and sample collection based on the physical space used. For laboratories the volume of tests performed as a proportion of total annual tests was used as allocation factor.

We assumed 227 and 253 working days in Indonesia and Romania, respectively, with clinics and laboratories operating between 6.5-10.0 hours per day.

Stepped diagnostic algorithms

Stepped diagnostic algorithms were developed to simulate how bi-directional screening and diagnosis could occur in routine practice.

Screening for TB in people with DM

Stepped diagnostic algorithms included various combinations of TB symptom screen, CXR, smear microscopy and sputum culture. For each algorithm, only patients with positive samples from the subsequent test were assumed to continue screening. Exceptions were smear microscopy and sputum culture; if both tests were included in a particular algorithm, all smear samples would have a sputum culture, as was routine procedure in the study facilities. Smear microscopy was always performed before sputum culture if both tests were in the algorithm. If TB symptom screen was in the algorithm, it was always the first test performed.

Screening for DM in people with TB

Stepped diagnosis for DM tests included various combinations of Omani DM risk score, the three POC tests (RPG, HbA_{1c} and urine dipstick) and the two laboratory tests (FBG and HbA_{1c}). Grint et al. (submitted to *Lancet Diabetes Endocrinology* (Feb 2017)) found that screening for age (≥ 40 years) alone was statistically significant in identifying DM in people with TB as this cut-off value maximised the best overall diagnostic accuracy and provided at least 80% sensitivity. Therefore, the single risk screen of age ≥ 40 years was also included in the diagnostic algorithms. Two restrictions were that the screening tests (age screen, Omani DM risk score, and POC tests) always preceded the diagnostic tests (FBG and laboratory HbA_{1c}) and that the Omani DM risk score, if included, should always

precede all other tests. The order of the other screening tests was not relevant because their outcomes did not impact on each other clinically and practically.

In stepped clinical practice scenarios, people with TB were screened for DM by either POC RPG, POC urine dipstick, Omani risk score or POC HbA_{1c}. If these values were above the cut-off values, patients were tested by either two laboratory HbA_{1c} tests, one laboratory HbA_{1c} followed by a FBG test, or two FBG tests. For additional information on these analyses, see Grint et al. (submitted to *Lancet Diabetes Endocrinology* (Feb 2017)).

Analysis

Diagnostic accuracy of each test was determined from data collected between December 2013 and February 2016 in Indonesia and February 2014 to June 2016 in Romania. Sensitivity and specificity calculations for each test were derived from the true positive and true negative values when compared to the TB and DM diagnostic gold standard tests.

For the POC random tests, the HemoCue[®] machine used in Indonesia produced both capillary and venous plasma but the Quo-Test[™] A1c used in Romania produced capillary only. Venous plasma was the preferred measure but since it was not available in Romania and the glucose estimation in whole blood is approximately 10-15% lower, a conversion factor of 1.12 was used to convert the capillary reading to a plasma reading before comparing the tests for the two countries (Kotwal and Pandit, 2012).

The mean cost per accurate diagnosis was calculated by dividing total cost of diagnosing all study participants using each test or algorithm by the number of true positive and true negative diagnoses. When any given test was performed at more than one of the study facilities in a country, the average cost between facilities was used.

TANDEM patient records were stored and managed in the web-based database system, **Research Electronic Data Capture** (REDCap version 6.9.1; Vanderbilt University, TN, USA, 2016). Costs were analysed in Excel (Microsoft Corporation, Redmond, WA, USA, 2016).

Patient characteristics and diagnostic accuracy were analysed using Stata 14.1 Special Edition (StataCorp LP, College Station, TX, USA, 2015).

Ethics

Ethical approval was received from the London School of Hygiene and Tropical Medicine Research Ethics Committee, the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia and the University of Medicine and Pharmacy of Craiova Committee of Ethics and Academic and Scientific Deontology, Romania.

Results

In Indonesia and Romania there were 809 and 603 people with DM, respectively and 771 and 504 people with TB, respectively, being screened for concurrent disease. The relationship between patient characteristics and baseline disease status is presented in detail in Appendix S, Appendix T and Appendix U.

Diagnostic accuracy

Sensitivity and specificity of TB and DM tests, along with their cut-off values, are shown in Table 8-1. For DM, the POC RPG was the most sensitive test in Indonesia (92.5% [95% CI: 79.6 to 98.4]) and the Omani risk score in Romania (82.5% [95% CI: 70.1 to 91.3]). The urine dipstick was excellent at identifying people without DM in both countries (99.5% [95% CI: 98.6 to 99.9] specificity in Indonesia and 100% [one-sided 97.5% CI: 98.2 to 100] in Romania). The POC HbA_{1c} test performed even better in Indonesia, with a 100% sensitivity [one-sided 97.5% CI: 91.0 to 100].

TB screening and diagnostic tests

Out of 809 people with DM who were screened for TB in Indonesia, 32% (256) were positive for latent and eleven were positive (definite and probable) for active TB (1.4%). A CXR was obtained for 802 of the people with DM, 11.0% of whom had an irregular CXR. Two sputum smear samples were produced by 106 people with DM, of which 4.7% were smear positive and 10.3% had a positive MODS culture. In the stepped diagnosis algorithm, TB symptom screen followed by CXR yielded the most cases of previously undiagnosed DM (n=57), of which nine of the ten true positives were included. The TB symptom screen, CXR and ZN smear identified the largest number of true negatives (775 out of 799).

No people with DM were diagnosed with active TB in Romania, which meant that the diagnostic accuracy of TB tests could not be determined. However, almost half (49%) of the 584 TST results showed LTBI.

Table 8-1: Sensitivity and specificity of screening and diagnostic tests for tuberculosis and diabetes mellitus in Indonesia and Romania

Test	Cut-off	Sensitivity							Specificity:					
		Indonesia				Romania			Indonesia			Romania		
		95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI	95% CI		
TB tests	1 TB symptom screen	any symptom	90.9	58.7	to 99.8	NA	NA	NA	54.9	51.4	to 58.4	NA	NA	NA
	2 Chest x-ray (CXR)	Abnormal suggestive and possible active TB	90.9	58.7	to 99.8	NA	NA	NA	90.1	87.8	to 92.1	NA	NA	NA
	3 Smear microscopy	scanty, 1+, 2+, 3+	36.4	10.9	to 69.2	NA	NA	NA	99	94.5	to 100	NA	NA	NA
	4 Sputum culture	positive	90.9	58.7	to 99.8	NA	NA	NA	100	95.8	to 100*	NA	NA	NA
DM tests	1 Age	≥ 40	82.5	67.2	to 92.7	81.0	68.6	to 90.1	63.1	59.2	to 66.9	47.9	42.7	to 53.1
	2 Omani risk score	≥ 7	84.2	68.7	to 94	82.5	70.1	to 91.3	57.9	53.9	to 61.9	46.1	41	to 51.3
	3 Point of care random plasma glucose (POC RPG)	≥ 6.1 mmol/l	92.5	79.6	to 98.4	71.7	57.7	to 93.2	75.9	72.4	to 79.2	39.0	33.9	to 44.3
	4 Fasting blood glucose (FBG)	≥ 7 mmol/l	64.3	35.1	to 87.2	32.8	21.0	to 46.3	94.5	88.4	to 98	86.7	82.8	to 89.9
	5 Urine dipstick	≥ trace	35.0	20.6	to 51.7	8.3	1.0	to 27	99.5	98.6	to 99.9	100.0	98.2	to 100
	6 Point of care glycated haemoglobin (POC HbA _{1c})	≥ 6.5%	100.0	91.0	to 100*	43.1	29.3	to 57.8	63.5	59.6	to 67.3	87.1	83.1	to 90.4
	7 Laboratory glycated haemoglobin (HbA _{1c})	≥ 6.5%	100.0			100.0			100.0			100.0		

TB-tuberculosis; DM-diabetes mellitus; NA-not applicable

*One-sided, 97.5% confidence interval

DM screening and diagnostic tests

In Indonesia, there were 671 patients with TB with no known previous DM with a laboratory HbA_{1c} test result available. This yielded 40 people (6.0%) with newly diagnosed DM. 28.2% had a positive result with the POC RPG test, 2.6% with urine dipstick, 44.6% with Omani risk score, 39.6% with age screen, and 40.2% with POC HbA_{1c} test. The FBG and repeated FBG diagnostic tests yielded few cases of undetected DM because only 19% of the 671 people with TB were indicated (where RPG≥6.1 mmol/l) to provide a first sample and 1% a second sputum sample.

In Romania 436 patients with TB and no previous DM had a laboratory HbA_{1c} test result; 13.3% of these were diagnosed with DM. For patients with POC RPG test result, 62.4% were positive, 0.9% with urine dipstick, 57.6% with Omani risk score, 16.8% with POC HbA_{1c}, and 56.0% were 40 years or over. A greater proportion of FBG samples were produced in Romania (first FBG 99%; repeated FBG 72%) than in Indonesia.

Unit costs of screening and diagnostic tests

TB screening and diagnostic tests

The mean incremental cost of introducing TB symptom screening for people with DM in an Endocrinology clinic in Indonesia was US\$ 2.07. For DM in-patients at a hospital in Romania this was US\$ 7.50 (Table 8-2). A film CXR costs US\$ 17.51 in Indonesia while a digital CXR in Romania is three times more expensive at US\$ 56.78 (SD=US\$ 4.69). In Indonesia, staff accounted for 84% of the CXR costs while in Romania the majority were overhead recurrent costs at 35%, with staff accounting for 24%. In contrast to the other TB tests, the sputum smear and culture tests were approximately half the costs in Romania than in Indonesia. This is because sputum collection and smear microscopy were performed in specialised Romanian TB hospitals where there is a high volume of sputum samples and staff were proficient in performing the smear microscopy. For culture tests, solid L-J culture was done in Romania while MODS was used in Indonesia. However, as MODS is not the routine test used for suspected TB in Indonesia, the volume of tests performed was not maximised and equipment and some supplies (i.e.

gloves and masks) were being underutilised. The costs per MODS test amounted to US\$ 33.

For detection of LTBI, the IGRA test in Indonesia was US\$ 58.75, which was approximately 22% more than TST for detecting LTBI in Romania. Mean costs were largely driven by the costs of reagents and supplies, accounting for approximately 87% in both tests.

Table 8-2: Mean costs per patient for tuberculosis screening in people with diabetes - Indonesia and Romania (2014 USD)

	Reagents and supplies	Equipment	Staff	Overhead: capital*	Overhead: recurrent**	Total
Indonesia						
TB symptom screen^λ	0.54	0.02	0.74	0.76	0.01	2.07
Chest x-ray^μ	1.61	0.27	14.65	0.97	0.01	17.51
Sputum collection – 2 samples^π	0.80	0.01	0.82	0.98	0.83	3.43
Sputum smear (ZN) – 2 samples^π	5.30	0.82	2.55	0.38	0.32	9.37
Sputum culture (MODS) - 2 samples^π	14.37	11.84	3.31	1.80	1.52	32.83
IGRA^ρ	51.56	0.10	6.53	0.55	0.01	58.75
Romania – Average						
TB symptom screen^α	0.90	0.08	3.09	0.33	3.10	7.50
<i>(SD)</i>	<i>(0.06)</i>	<i>(0.32)</i>	<i>(0.60)</i>	<i>(0.90)</i>	<i>(0)</i>	<i>(0.90)</i>
Chest x-ray^α	0.10	2.34	14.13	4.70	35.51	56.78
<i>(SD)</i>	<i>(9.57)</i>	<i>(5.28)</i>	<i>(6.98)</i>	<i>(4.69)</i>	<i>(0)</i>	<i>(4.69)</i>
Sputum collection – 2 samples^β	0.12	0.19	0.85	0.37	0.88	2.42
Sputum smear (ZN) – 2 samples^β	1.60	0.14	1.67	0.37	0.88	4.66
Sputum culture (L-J) - 2 samples^β	9.43	0.16	7.77	0.37	0.88	18.62
TST^α	41.67	0.53	2.71	0.26	2.97	48.15
<i>(SD)</i>	<i>(0.58)</i>	<i>(0.19)</i>	<i>(1.50)</i>	<i>(0.87)</i>	<i>(0)</i>	<i>(0.87)</i>

TB-tuberculosis; DM-diabetes mellitus; RSHS-Hasan Sadikin Hospital; UNPAD-Universitas Padjadjaran Teaching Hospital; USD-United States dollars; SD-standard deviation
IGRA-Interferon gamma release assay; TST-tuberculin skin test; ZN-Ziehl-Neelsen stain; MODS-microscopic observation drug susceptibility; L-J-Löwenstein Jensen medium

^λRSHS Endocrinology Clinic

^μRSHS Radiology Department

^πBalai Laboratorium Kesehatan

^ρRSHS Endocrinology Clinic (blood draw); UNPAD Immunology Laboratory (blood analysis)

^αMean of Hospital #1 & Hospital #2

^βVictor Babes Hospital

*Capital overhead cost composition explained in Annex 4

**Recurrent overhead cost composition explained in Annex 4

DM screening and diagnostic tests

In Indonesia, mean incremental costs of implementing DM screening into DOTS clinic was US\$ 0.70 for Omani risk score, US\$ 0.65 for urine dipstick and US\$ 1.06 for POC RPG (Table 8-3). The costs of POC HbA_{1c} was substantially higher at US\$ 7.19, explained by the high cost of the test cartridge (95%). Costs of FBG were US\$ 2.06 and laboratory HbA_{1c} US\$ 14.55. Staff time accounted for 53% of the FBG cost. The majority (95%) of the laboratory HbA_{1c} cost was the price charged by a private laboratory. The costs of the screening tests in Romania were between two and ten times more expensive than in Indonesia, largely due to staff time cost and recurrent overheads, which were seven and 24 times higher, respectively. However, while FBG was four times more expensive in Romania, the laboratory HbA_{1c} test was 38% cheaper in Romania, with the blood sample analysis at the private facility costing half of that in Indonesia.

Table 8-3: Mean direct medical provider costs per patient for diabetes screening in people with tuberculosis - Indonesia and Romania (2014 USD)

	Reagents and Supplies	Equipment	Price ^α	Staff	Overhead: capital*	Overhead: recurrent**	Total
Indonesia							
Omani diabetes risk score^{...}	0.01	0.05	NA	0.50	0.14	0.00	0.70
POC RPG^{...}	0.75	0.13	NA	0.14	0.04	0.00	1.06
FBG[‡]	0.83	0.03	NA	1.09	0.11	0.00	2.06
Urine dipstick^{...}	0.48	0.01	NA	0.13	0.03	0.00	0.65
POC HbA_{1c}^{...}	6.90	0.05	NA	0.19	0.05	0.00	7.19
Laboratory HbA_{1c}^{...}	0.46	0.03	13.81	0.20	0.06	0.00	14.55
Romania - AVERAGE							
Omani diabetes risk score^β	0.02	0.01	NA	4.28	0.04	0.05	4.41
<i>(SD)</i>	<i>(0.01)</i>	<i>(0.02)</i>		<i>(2)</i>	<i>(0.05)</i>	<i>(0.05)</i>	<i>(2.08)</i>
POC RPG^β	0.84	0.09	NA	0.87	0.01	0.02	1.83
<i>(SD)</i>	<i>(0.07)</i>	<i>(0.05)</i>		<i>(0.1)</i>	<i>(0.01)</i>	<i>(0.01)</i>	<i>(0.25)</i>
FBG^β	1.14	0.11	NA	6.49	0.17	0.23	8.15
<i>(SD)</i>	<i>(0.11)</i>	<i>(0.05)</i>		<i>(1.95)</i>	<i>(0.14)</i>	<i>(0.09)</i>	<i>(2.12)</i>
Urine dipstick^β	0.93	0.07	NA	0.64	0.01	0.01	1.67
<i>(SD)</i>	<i>(0.17)</i>	<i>(0.1)</i>		<i>(0.4)</i>	<i>(0.01)</i>	<i>(0.01)</i>	<i>(0.69)</i>
POC HbA_{1c}^β	8.53	1.52	NA	1.74	0.02	0.02	11.83
<i>(SD)</i>	<i>(0.45)</i>	<i>(0.12)</i>		<i>(1)</i>	<i>(0.02)</i>	<i>(0.02)</i>	<i>(1.36)</i>
Laboratory HbA_{1c}^β	0.64	0.23	6.86	1.26	0.02	0.02	9.03
<i>(SD)</i>	<i>(0.13)</i>	<i>(0.11)</i>	<i>(0.12)</i>	<i>(0.17)</i>	<i>(0.02)</i>	<i>(0.02)</i>	<i>(0.15)</i>

DM-diabetes mellitus; TB-tuberculosis; USD-United States dollars; SD-standard deviation; POC-point of care; NA-not applicable

RSHS-Hasan Sadikin Hospital; DOTS-directly observed therapy, short-course; RPG-random plasma glucose; FBG-fasting blood glucose; HbA_{1c}-glycated haemoglobin

^αPrice of lab HbA_{1c} analysis by private laboratory

^βMean of Runcu Hospital & Victor Babes Hospital

^{...}RSHS DOTS Clinic

[‡]RSHS DOTS Clinic (blood draw); RSHS Clinical Pathology Laboratory (sample analysis)

*Capital overhead cost composition explained in Annex 4

**Recurrent overhead cost composition explained in Annex 4

Cost per accurate diagnosis

TB screening and diagnostic tests

In Indonesia, the algorithm of TB symptom screen followed by two ZN sputum smears had the lowest cost per accurate diagnosis (US\$ 17.93), and the incremental cost of adding the two smear tests was US\$ 14.20 (Table 8-4). The complete algorithm with TB symptom screen, CXR, two smears followed by two MODS cultures had the highest cost per accurate diagnosis (US\$ 74.75) (Figure 8-2a). This algorithm diagnosed two additional true positives out of 809 patients screened compared to TB symptom screen, CXR and two ZN smears, at an incremental cost of US\$ 35.17 per accurate diagnosis (Table 8-4). The algorithm of CXR followed by two ZN sputum smears was US\$ 33.91 per accurate diagnosis (Figure 8-2b). The reverse of two ZN smears followed by a CXR diagnosed the same number of true positives with only marginally higher costs at US\$ 35.86. Hence, there was only a small difference in costs per accurate diagnosis when the order of the same tests was reversed.

The cost per accurate diagnosis of the gold standard of two ZN sputum smears followed by two MODS cultures on all smear samples was 2.5 times higher than the option of TB symptom screen followed by two sputum smears.

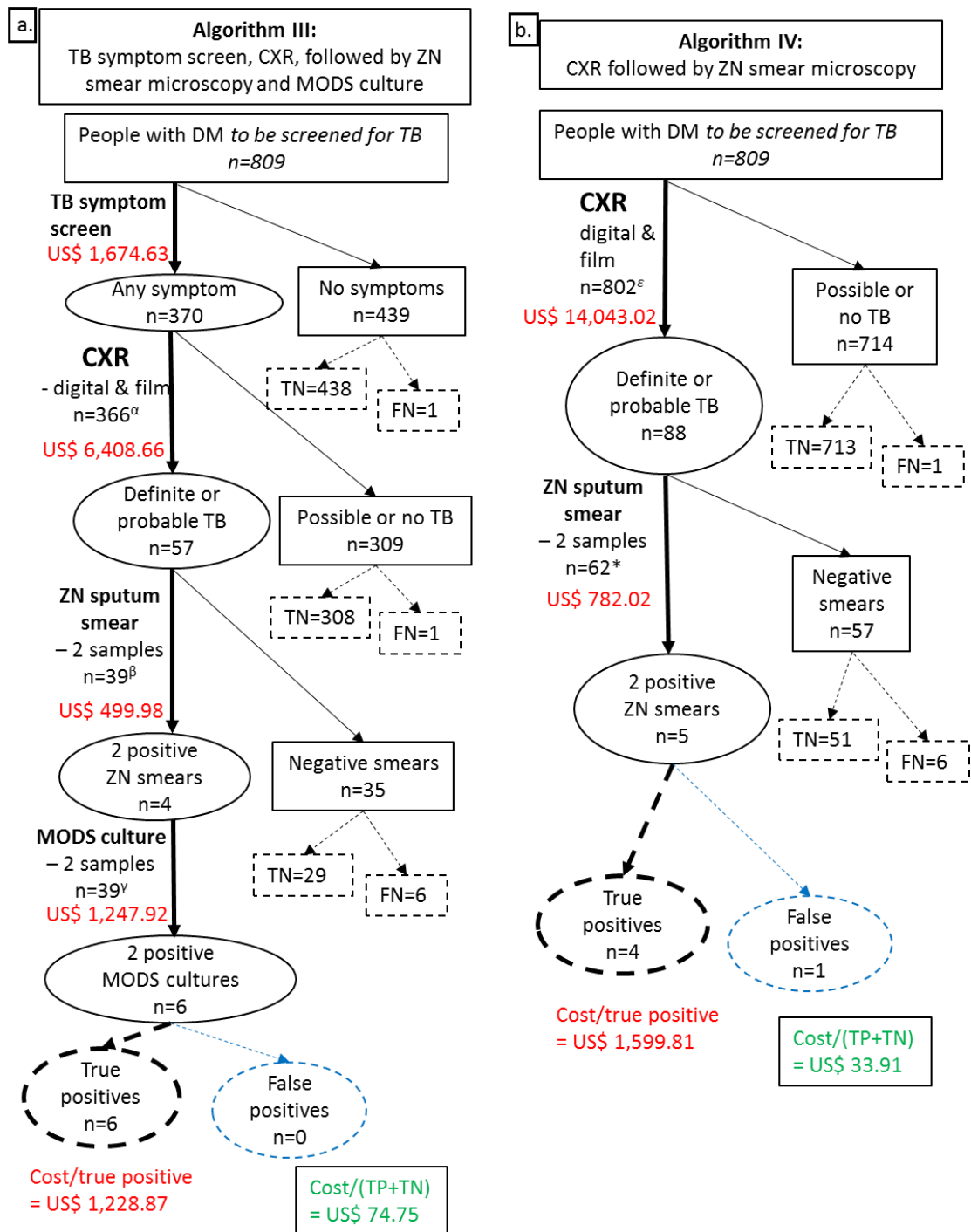
Table 8-4: Cost per accurate diagnosis of tuberculosis screening and diagnostic tests in people with diabetes - Indonesia (2014 USD)

Algorithm		Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost/accurate diagnosis (TP + TN)	Incremental cost (TP + TN)
<i>Smear</i>		112	0.364	0.989	\$12.82	\$1,397.38	\$349.35	\$13.97	
GOLD STANDARD	Smear Culture	112	0.556	1.000	\$45.66	\$4,697.80	\$722.08	\$47.99	\$34.01
<i>Symptom screen</i>		809	0.909	0.549	\$2.07	\$1,674.63	\$167.46	\$3.74	
I	Symptom screen CXR	809	0.818	0.940	\$19.58	\$8,083.29	\$879.54	\$23.95	\$20.22
II	Symptom screen CXR Smear microscopy	809	0.273	0.999	\$32.40	\$8,583.27	\$1,046.20	\$39.58	\$15.62
III	Symptom screen CXR Smear microscopy Culture	809	0.471	1.000	\$65.24	\$9,831.19	\$1,228.87	\$74.75	\$35.17
<i>CXR</i>		802	0.909	0.901	\$17.51	\$14,043.02	\$1,404.30	\$19.42	
IV	CXR Smear microscopy	802	0.364	0.999	\$30.33	\$14,825.04	\$1,599.81	\$33.91	\$14.48
V	CXR Smear microscopy Culture	802	0.500	1.000	\$63.17	\$16,779.02	\$1,848.19	\$67.59	\$33.69
<i>Symptom screen</i>		809	0.909	0.549	\$2.07	\$1,674.63	\$167.46	\$3.74	
VI	Symptom screen Smear microscopy	809	0.273	0.998	\$14.89	\$2,732.28	\$520.01	\$17.93	\$14.20
VII-a	Symptom screen Smear microscopy Culture	809	0.529	1.002	\$47.73	\$5,129.60	\$825.48	\$51.22	\$33.29
VII-b	Symptom screen Smear microscopy CXR	809	0.273	0.998	\$32.40	\$2,802.32	\$543.36	\$41.28	\$23.35
VIII	Symptom screen Smear microscopy Culture CXR	809	0.375	1.000	\$65.24	\$5,252.17	\$845.91	\$71.65	\$20.43

	Algorithm	Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost/accurate diagnosis (TP + TN)	Incremental cost (TP + TN)
	<i>Smear</i>	112	0.364	0.990	\$12.82	\$1,397.38	\$349.35	\$13.97	
IX	Smear microscopy CXR	112	0.364	0.989	\$30.33	\$1,484.93	\$371.23	\$35.86	\$21.89
X	Smear microscopy Culture CXR	112	0.438	1.000	\$63.17	\$4,855.39	\$744.59	\$67.69	\$19.70

USD-United States dollars; TP-true positive; TN-true negative; CXR-chest x-ray; Smear microscopy performed was the Ziehl-Neelsen stain; Culture test used Lowenstein-Jensen solid medium

Figure 8-2: Flowchart of stepped diagnosis pathways for tuberculosis in Indonesia - 2 examples presented



^εMissing CXR tests due to poor quality films or patients not staying for scan, n=7

^αMissing CXR results due to patients not returning for tests, n=4

^βMissing smears due to patients unable to produce or not returning with samples, n=18

^γAll smear samples go on to be tested by culture

*Missing smears due to patients unable to produce samples or not returning with samples, n=26

DM screening and diagnostic tests

In Indonesia and Romania, the single screen with the lowest cost per accurate diagnosis was age 40 or over (US\$ 0.08 and US\$ 1.06, respectively) (Table 8-5 and Table 8-6). This sole risk factor was shown to be highly predictive (AU ROC=0.78 and 0.69 in Indonesia and Romania, respectively) for DM in people with TB ((Grint et al., submitted to Lancet Diabetes Endocrinology (Feb 2017))).

Of the DM testing algorithms assessed the age screen followed by the POC RPG test had the least cost per accurate diagnosis in Indonesia and Romania, at US\$ 1.49 and US\$ 5.64, respectively (Table 8-5 and Table 8-6). In Indonesia, the next cheapest algorithm was Omani risk score and POC RPG at US\$ 2.59 (Table 8-5). In Romania, the urine dipstick was included in the next two cheapest algorithms per case accurately diagnosed: urine followed by two laboratory HbA_{1c} tests (US\$ 10.88) (Figure 8-3a) and the Omani risk score followed by the urine dipstick then two laboratory HbA_{1c} tests (US\$ 10.96) (Table 8-6). In both countries the POC HbA_{1c} followed by two laboratory HbA_{1c} tests had a high cost per accurate diagnosis (US\$ 43.58 and US\$ 52.59, respectively), but the Omani risk score, POC RPG and two laboratory HbA_{1c} tests costed even more per accurate diagnosis in Romania at US\$ 55.76 (Table 8-6).

Table 8-5: Cost per accurate diagnosis of diabetes screening and diagnostic tests in people with tuberculosis - Indonesia (2014 USD)

		Algorithm	Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)	
DM tests - CLINICAL PRACTICE	GOLD STANDARD	Laboratory HbA _{1c} (repeated)	672	1.000	1.000	\$29.10	\$10,112.25	\$260.38	\$29.12	\$14.57	
		POC RPG ≥ 6.1 mmol/l	671	0.925	0.759	\$1.06	\$711.26	\$19.22	\$1.38		
	SCENARIO 1	I	POC RPG Lab HbA _{1c} Lab HbA _{1c}	671	0.833	1.000	\$30.16	\$3,839.51	\$112.46	\$34.84	\$33.47
		II	POC RPG Lab HbA _{1c} FBG	671	0.529	1.000	\$17.67	\$3,490.05	\$96.75	\$19.13	\$17.75
		III	POC RPG FBG >126 mg/dl FBG >126 mg/dl	671	0.000	1.000	\$5.18	\$956.40	\$54.24	\$3.74	\$2.36
		Urine dipstick ≥ trace	664	0.350	0.995	\$0.65	\$431.60	\$30.83	\$0.68		
	SCENARIO 2	IV	Urine dipstick Lab HbA _{1c} Lab HbA _{1c}	664	0.257	1.000	\$29.75	\$824.45	\$64.66	\$31.40	\$30.72
		V	Urine dipstick Lab HbA _{1c} FBG	664	0.071	1.000	\$17.26	\$683.07	\$50.56	\$17.29	\$16.61
		VI	Urine dipstick FBG >126 mg/dl FBG >126 mg/dl	664	0.000	1.000	\$4.77	\$466.62	\$33.33	\$3.18	\$2.50
			Omani risk score ≥ 7	642	0.842	0.579	\$0.70	\$449.40	\$14.04	\$1.18	
	SCENARIO 3	VII	Omani risk score Lab HbA _{1c} Lab HbA _{1c}	642	0.667	1.000	\$29.80	\$4,945.35	\$165.00	\$36.64	\$35.47
		VIII	Omani risk score Lab HbA _{1c} FBG	642	0.467	1.000	\$17.31	\$4,629.24	\$146.73	\$18.38	\$17.20

Chapter 8: Cost of accurate diagnosis for bi-directional screening

		Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)	
SCENARIO 4	IX	Omani risk score								
		FBG >126 mg/dl	642	0.000	1.000	\$4.82	\$1,038.56	\$35.09	\$9.59	
		FBG >126 mg/dl							\$8.42	
		POC HbA _{1c} ≥ 6.0%	665	1.000	0.635	\$7.19	\$4,781.35	\$122.60	\$11.02	
	X	POC HbA _{1c}								
		Lab HbA _{1c}	665	0.913	1.000	\$36.29	\$9,029.95	\$239.85	\$43.58	
		Lab HbA _{1c}								\$32.56
		POC HbA _{1c}								
		Lab HbA _{1c}	665	0.643	1.000	\$23.80	\$8,680.49	\$225.04	\$28.77	
	XI	FBG								\$17.75
		POC HbA _{1c}								
	XII	FBG >126 mg/dl	665	0.000	1.000	\$11.31	\$4,884.35	\$137.31	\$13.59	
FBG >126 mg/dl									\$2.58	
DM tests - RESEARCH	DIAGNOSTIC STRATEGY	Omani risk score ≥ 7	642	0.842	0.579	\$0.70	\$449.40	\$14.04	\$1.18	
		Omani risk score								
		Lab HbA _{1c}	642	0.667	1.000	\$29.80	\$4,945.35	\$165.00	\$36.64	
		Lab HbA _{1c}								\$35.47
		Omani risk score								
		Lab HbA _{1c}	642	0.467	1.000	\$17.31	\$4,629.24	\$146.73	\$18.38	
		FBG								\$17.20
		Omani risk score ≥ 7	642	0.342	0.997	\$1.35	\$634.65	\$28.29	\$1.88	
		Urine dipstick ≥ trace								
		Omani risk score								
Urine dipstick	642	0.242	1.000	\$30.45	\$983.85	\$61.45	\$32.80			
Lab HbA _{1c}										
Lab HbA _{1c}								\$30.92		
XV	Omani risk score									
	Urine dipstick									
	Lab HbA _{1c}	642	0.000	1.000	\$17.96	\$857.02	\$45.08	\$16.43		
XVI	Lab HbA _{1c}									
	FBG								\$14.55	

Chapter 8: Cost of accurate diagnosis for bi-directional screening

	Algorithm	Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)
	Omani risk score \geq 7 POC RPG \geq 6.1 mmol/l	642	0.789	0.886	\$7.89	\$2,505.74	\$82.59	\$10.74	
	Omani risk score POC RPG Lab HbA _{1c}	642	0.625	1.000	\$36.99	\$4,251.74	\$150.97	\$45.66	
XVII	Lab HbA _{1c}								\$34.92
	Omani risk score POC RPG Lab HbA _{1c}	642	0.000	1.000	\$24.50	\$3,964.73	\$130.60	\$25.29	
XVIII	FBG								\$14.55
SCREENING STRATEGY	Omani risk score \geq 7	642	0.842	0.579	\$0.70	\$449.40	\$14.04	\$1.18	
	XIX Omani risk score POC RPG	642	0.789	0.886	\$1.76	\$752.56	\$24.15	\$2.59	\$1.41
	Omani risk score POC RPG	642	0.784	0.960	\$8.95	\$1,449.99	\$48.20	\$12.14	
	XX POC HbA _{1c}								\$10.96
	Omani risk score \geq 7 Urine dipstick \geq trace	642	0.342	0.997	\$1.35	\$634.65	\$28.29	\$1.88	
	Omani risk score Urine dipstick XXI POC HbA _{1c}	642	0.324	1.000	\$8.54	\$735.31	\$36.68	\$9.07	\$7.19
STATISTICAL STRATEGY	Age screen \geq 40	671	0.825	0.631	\$0.05	\$33.55	\$1.02	\$0.08	
	XXII Age POC RPG	671	0.800	0.895	\$1.11	\$315.51	\$9.83	\$1.49	\$1.42
	Age XXIII POC HbA _{1c}	671	0.821	0.861	\$7.24	\$1,931.71	\$60.33	\$10.92	\$10.85
	POC RPG \geq 6.1 mmol/l	671	0.925	0.759	\$1.06	\$711.26	\$19.22	\$1.38	
	POC RPG XXIV POC HbA _{1c}	671	0.923	0.915	\$8.25	\$2,041.41	\$56.17	\$11.53	\$10.15

USD- United States dollars; TP-true positive; TN-true negative

POC-point of care; HbA_{1c}-glycated haemoglobin; RPG-random plasma glucose; FBG-fasting blood glucose

Omani risk score includes assessments of age, waist circumference, body mass index, family history of diabetes and current hypertension status

Table 8-6: Cost per accurate diagnosis of diabetes screening and diagnostic tests in people with tuberculosis - Romania (2014 USD)

		Algorithm	Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)	
DM tests - CLINICAL PRACTICE	GOLD STANDARD	Laboratory HbA_{1c} (repeated)	465	1.000	1.000	\$18.06	\$4,596.27	\$102.96	\$19.32	\$9.63	
		POC RPG \geq 6.1 mmol/l	433	0.717	0.390	\$1.83	\$792.57	\$20.86	\$4.50		
	SCENARIO 1	I	POC RPG Lab HbA _{1c} Lab HbA _{1c}	433	0.196	1.000	\$19.89	\$3,384.18	\$114.33	\$46.64	\$42.14
		II	POC RPG Lab HbA _{1c} FBG	433	0.245	1.000	\$19.01	\$3,355.03	\$101.90	\$34.21	\$29.71
		III	POC RPG FBG >126 mg/dl FBG >126 mg/dl	433	0.075	1.000	\$18.12	\$2,332.31	\$330.43	\$15.62	\$11.12
		Urine dipstick \geq trace	230	0.083	1.000	\$1.67	\$383.36	\$191.68	\$1.84		
	SCENARIO 2	IV	Urine dipstick Lab HbA _{1c} Lab HbA _{1c}	230	0.000	1.000	\$19.73	\$410.45	\$200.71	\$10.87	\$9.03
		V	Urine dipstick Lab HbA _{1c} FBG	230	0.042	1.000	\$18.84	\$409.56	\$208.86	\$19.02	\$17.18
		VI	Urine dipstick FBG >126 mg/dl FBG >126 mg/dl	230	0.042	1.000	\$17.96	\$407.80	\$216.12	\$26.28	\$24.44
			Omani risk score \geq 7	464	0.825	0.461	\$4.41	\$1,922.76	\$40.91	\$8.74	
	SCENARIO 3	VII	Omani risk score Lab HbA _{1c} Lab HbA _{1c}	464	0.500	1.000	\$22.47	\$4,487.28	\$120.35	\$49.37	\$40.64
		VIII	Omani risk score Lab HbA _{1c} FBG	464	0.246	1.000	\$21.59	\$4,513.53	\$113.20	\$42.22	\$33.48

Chapter 8: Cost of accurate diagnosis for bi-directional screening

		Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)			
DM tests - RESEARCH	SCENARIO 4	IX	Omani risk score FBG >126 mg/dl FBG >126 mg/dl	464	0.038	1.000	\$20.71	\$3,569.06	\$326.16	\$24.92	\$16.18	
			POC HbA _{1c} ≥ 6.0%	404	0.431	0.871	\$11.83	\$4,779.32	\$217.24	\$14.66		
			X	POC HbA _{1c} Lab HbA _{1c} Lab HbA _{1c}	404	0.111	1.000	\$29.89	\$5,528.81	\$273.64	\$52.59	\$37.93
			XI	POC HbA _{1c} Lab HbA _{1c} FBG	404	0.176	1.000	\$29.01	\$5,563.63	\$264.66	\$43.61	\$28.95
			XII	POC HbA _{1c} FBG >126 mg/dl FBG >126 mg/dl	404	0.059	1.000	\$28.13	\$5,300.92	\$352.40	\$34.49	\$19.83
				Omani risk score ≥ 7	464	0.825	0.461	\$4.41	\$1,922.76	\$40.91	\$8.74	
		DIAGNOSTIC STRATEGY	XIII	Omani risk score Lab HbA _{1c} Lab HbA _{1c}	464	0.500	1.000	\$22.47	\$4,487.28	\$120.35	\$49.37	\$40.64
			XIV	Omani risk score Lab HbA _{1c} FBG	464	0.246	1.000	\$21.59	\$4,513.53	\$113.20	\$42.22	\$33.48
				Omani risk score ≥ 7 Urine dipstick ≥ trace	464	0.036	1.000	\$6.08	\$2,133.18	\$251.33	\$10.67	
			XV	Omani risk score Urine dipstick Lab HbA _{1c} Lab HbA _{1c}	464	0.000	1.000	\$24.14	\$228.48	\$219.45	\$10.96	\$0.29
			XVI	Omani risk score Urine dipstick Lab HbA _{1c} FBG	464	0.036	1.000	\$23.26	\$227.60	\$227.60	\$19.11	\$8.44

Chapter 8: Cost of accurate diagnosis for bi-directional screening

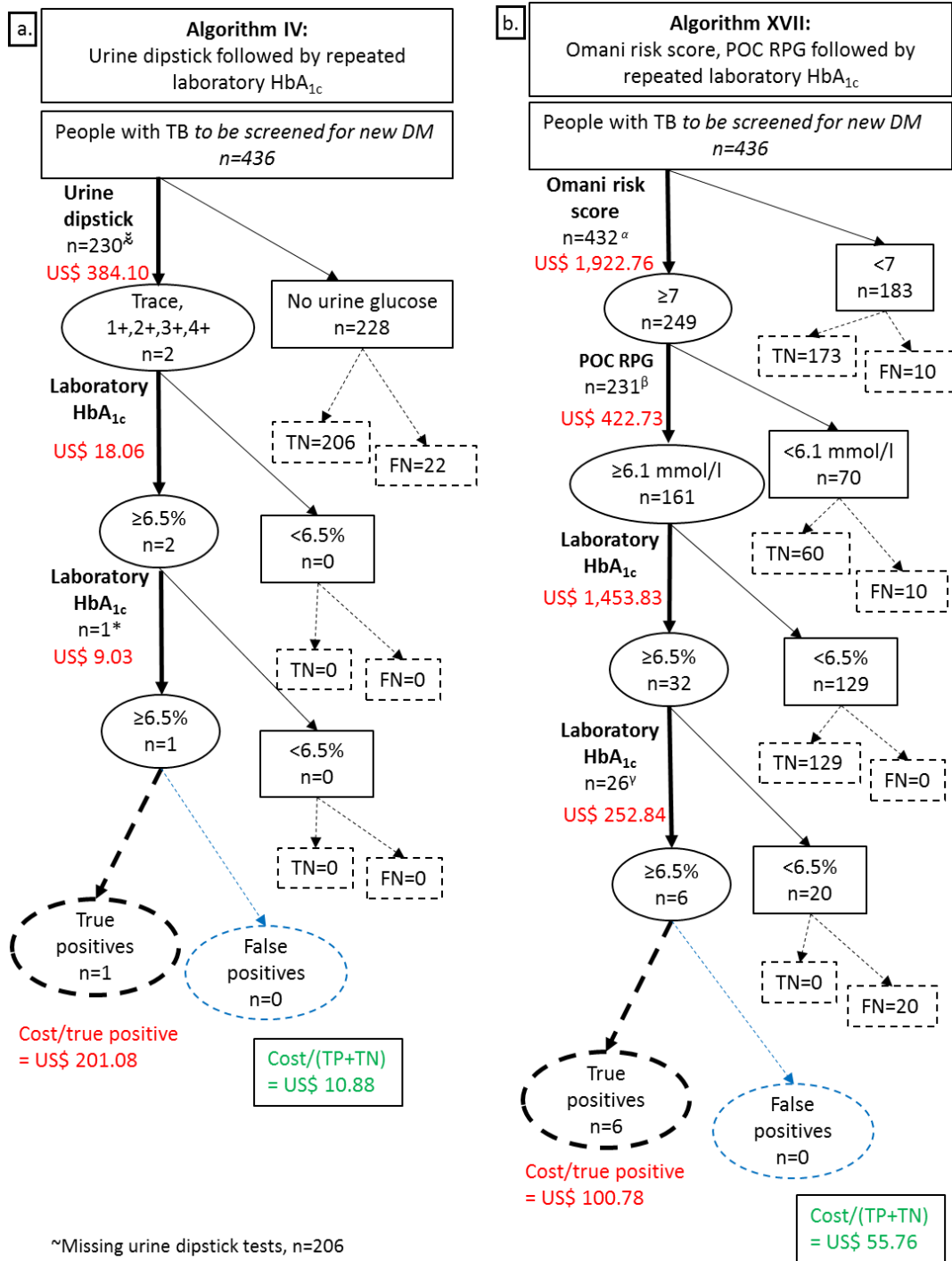
	Algorithm	Total # of people screened	Sensitivity	Specificity	Unit cost	Total cost	Cost per TP	Cost per accurate diagnosis (TP + TN)	Incremental cost (TP + TN)
	Omani risk score ≥ 7 POC RPG ≥ 6.1 mmol/l	464	0.615	0.644	\$6.24	\$2,345.49	\$54.12	\$13.33	
	Omani risk score POC RPG Lab HbA _{1c}	464	0.130	1.000	\$24.30	\$2,129.40	\$100.78	\$55.76	
XVII	Lab HbA _{1c}								\$42.43
	Omani risk score POC RPG Lab HbA _{1c}	464	0.192	1.000	\$23.42	\$2,104.76	\$81.46	\$36.44	
XVIII	FBG								\$23.11
	Omani risk score ≥ 7	464	0.825	0.461	\$4.41	\$1,922.76	\$40.91	\$8.74	
XIX	Omani risk score POC RPG	464	0.615	0.644	\$6.24	\$2,345.49	\$54.12	\$13.33	\$4.59
	Omani risk score POC RPG POC HbA _{1c}	464	0.320	0.931	\$18.07	\$4,226.46	\$171.68	\$29.28	
XX									\$20.54
	Omani risk score ≥ 7 Urine dipstick \geq trace	464	0.036	1.000	\$6.08	\$2,133.18	\$251.33	\$10.67	
	Omani risk score Urine dipstick POC HbA _{1c}	464	0.000	1.000	\$17.91	\$2,145.01	\$251.33	\$10.67	
XXI									\$0.00
	Age screen ≥ 40	436	0.810	0.479	\$0.56	\$241.98	\$5.15	\$1.06	
XXII	Age POC RPG	436	0.604	0.657	\$2.39	\$653.82	\$18.02	\$5.64	\$4.58
	Age POC HbA _{1c}	436	0.353	0.934	\$12.39	\$2,891.90	\$152.37	\$16.29	
XXIII									\$15.23
	POC RPG ≥ 6.1 mmol/l	433	0.717	0.390	\$1.83	\$792.57	\$20.85	\$4.50	
	POC RPG POC HbA _{1c}	433	0.373	0.889	\$13.66	\$3,773.55	\$177.76	\$19.87	
XIV									\$15.37

USD-United States dollars; TP-true positive; TN-true negative

POC-point of care; HbA_{1c}-glycated haemoglobin; RPG-random plasma glucose; FBG-fasting blood glucose

Omani risk score includes assessments of age, waist circumference, body mass index, family history of diabetes and current hypertension status

Figure 8-3: Flowchart of stepped diagnosis pathways for diabetes in Romania - two examples presented



[~]Missing urine dipstick tests, n=206
^{*}Missing laboratory HbA_{1c} results for repeated tests, n=1
^αMissing Omani risk score results, n=4
^βMissing POC RPG tests, n=18
^γMissing laboratory HbA_{1c} results for repeated tests, n=6

Discussion

This is the first study to assess the costs per accurate diagnosis of bi-directional screening for TB and DM. We found that the cost per accurate diagnosis was lower for DM screening in people with TB compared to screening people with DM for TB. The lowest cost per accurate diagnosis was DM age screen and POC RPG algorithm.

Assessing the cost per accurate diagnosis of TB and DM tests in two settings highlighted the country- and disease-specific issues that must be considered when making decisions about the most appropriate approach.

Overhead costs for the screening and diagnostic tests were more difficult to obtain than test-specific costs, but concerted efforts were made to ensure that as many of these costs as possible were included. Overhead costs ranged widely between 1% to 52% of TB test costs, illustrating that making rough assumptions about the importance of overhead costs is not recommended; primary data collection is necessary.

One view in the DM field is that DM screening should occur in two stages; people with risk factors for DM are selected, followed by glucose testing from blood or urine samples (Waugh et al., 2007). There is however debate as to the most useful and cost-effective combination of these tests (Adepoyibi et al., 2013). The diagnostic algorithms explored in this paper were able to investigate potential combinations of tests for lowest cost per accurate diagnosis, but the uncertainty of the values caused by the sensitivity and specificity of the tests must be considered (Ramsey et al., 2005).

The mean costs of the TB tests fall within the range of values reported in other parts of the world, but these were not performed in DM or chronic disease clinics or programmes. Smear tests ranged from US\$ 0.26 in India to US\$ 10.50 in Thailand (Lu et al., 2013), which nestled the costs in Indonesia and Romania of US\$ 6.40 and US\$ 3.54, respectively, for one sputum sample collection and ZN smear test. The mean costs of one combined ZN smear and MODS culture test was US\$ 22.82 in Indonesia, for which there was no comparable published cost assessment, but in Romania one ZN followed

by a L-J test was US\$ 12.85. This is comparable to US\$ 11.13 in Peru and US\$ 14.34 provider costs in Brazil (Lu et al., 2013).

The IGRA test in Indonesia (US\$ 58.75) was approximately 49% more than the same test in South Africa (TB Diagnostics Market Analysis Consortium et al., 2015). The mean cost of the TST in Romania was US\$ 48.15, but the range in other settings was as little as US\$ 5.90 in Brazil (TB Diagnostics Market Analysis Consortium et al., 2014) and US\$ 39.20 in South Africa (Mandalakas et al., 2013).

The mean costs of the fasting glucose and laboratory HbA_{1c} diagnostic tests were US\$ 13.16 and US\$ 14.24 when taken from a cost accounting system in Germany (Icks et al., 2004). The German FBG costs were well above the values in the TANDEM study (Indonesia: US\$ 2.06; Romania: US\$ 8.15) but the laboratory HbA_{1c} costs were similar for Indonesia (US\$ 14.55) despite having very different settings. No TB or DM diagnostic test costs specifically for Indonesia or Romania were found in the literature, nor for the cost of bi-directional screening for pulmonary TB and type 2 DM.

The costs of the screening and diagnostic tests are highly responsive to the volume of tests performed and the choice of consumables used. The costs of integrating bi-directional screening into TB or DM settings are also dependent upon the scale of the implementation, but the costs will decrease as experience is gained, utilisation is increased and if the price of equipment, particularly POC machines, is reduced over time. The start-up costs for equipment, staff training and sensitisation can be minimised if there is cross-programme collaboration by administrators, laboratory personnel and clinicians in TB and chronic disease programmes.

In the general population, random blood glucose and urine glucose testing are considered to be “of limited value” (Borch-Johnsen et al., 2003). Risk score questionnaires are most accurate for high-risk people, but require validation in each new country, though this is still not commonly done.

When using the POC RPG test to screen for DM without a confirmatory diagnostic test, the cut-off value is 11.1 mmol/l or greater. However, in clinical practice the POC RPG test would be repeated unless the patient also has symptoms of DM (such as frequent urination, excessive thirst, weight loss, or blurred vision) (IDF, 2015). This protocol was not explored, but the mean cost per accurate diagnosis would be expected to increase, and the protocol would perform differently in the two countries; in Romania, very few DM false positive people with TB would be identified given the low sensitivity of the test (45.3%) but in Indonesia, the repeated POC RPG could detect a greater proportion of false positives.

Despite the low cost per accurate diagnosis of the urine dipstick, it remains a less favourable option for DM screening due to the low sensitivity (35% in Indonesia and 8% in Romania). Screening by urine dipstick is therefore more likely to miss people with concurrent disease, jeopardising the success of their TB treatment and increasing their risk of relapse (Adepoiyibi et al., 2013). It does, however, remain an affordable option in resource-limited settings that have no other testing options (Restrepo et al., 2013).

HbA_{1c} tests are thought to be the most suitable for establishing chronic hyperglycaemia (as opposed to transitory glycaemia due to TB or other infectious diseases) (Adepoiyibi et al., 2013). Since TB induced hyperglycaemia seems to resolve once TB treatment has begun, HbA_{1c} tests provide glucose levels over the preceding three months and may more accurately diagnose true DM in people with TB, whether the test is performed before or during treatment (Kumpatla et al., 2013).

For detection of suspected TB, a symptom screen is seen as a valuable tool. However, for DM detection, a DM symptom screen would be too broad (for example frequent urination, excessive thirst, lack of interest and concentration, blurred vision) and symptoms may be altogether absent even if a DM diagnosis is warranted. Therefore, DM risk factors, including age, family history of DM, and BMI, were instead used for DM screening.

When recommending a DM POC screening test for people with TB, the POC HbA_{1c} test fares best, but is most cost-effective when combined with at least a diagnostic test, such as repeated laboratory HbA_{1c}. The POC RPG is an easily implementable option (Adepoyibi et al., 2013), with a low cost per accurate diagnosis that decreases when combined with a context specific risk assessment, such as the Omani risk score or simple age screen in people with TB. Both of these POC tests have qualities that are well suited for use in TB programmes. They can be easily implemented into routine DM screening of people with TB without the need for additional infrastructure such as alterations to laboratories or cold storage. The tests also both require minimal additional training or supervision. As discussed earlier, at a single time point, HbA_{1c} tests are able to detect short to long-term glucose levels averaged over three months. They do not require fasting like the FBG or other glucose tolerance tests, which would be a major obstacle for people with TB given the large quantities of anti-TB drugs required for treatment.

An additional benefit is the immediate provision of results; this obviates the need for a follow-up visit to the health facility simply to provide results, thus reducing loss to follow up and the financial and social burden placed on patients for frequent visits to the health facility. Sample collection for both POC tests are by finger prick, which is less invasive than a blood draw but further development of sample collection method would reduce discomfort in already ill patients. In terms of physiological suitability of the tests to people with TB, both tests seemed to be better suited to patients in Indonesia. The POC RPG was twice as sensitive in Indonesia than in Romania; and the POC HbA_{1c} test was eight times (86%) more sensitive with a cut-off of 6.5% but the sensitivity increased from 10% to 44% when the cut-off was reduced to 6.0%. Further investigation into country specific cut-off values could increase the favourability of the POC HbA_{1c} test (Grint et al., submitted to *Lancet Diabetes Endocrinology* (Feb 2017)). The POC RPG is considered to be favourable in terms of costs, with a mean cost per patient of US\$1.06 in Indonesia and US\$ 1.83 in Romania (Adepoyibi et al., 2013). However, the mean costs of the POC HbA_{1c} are still beyond the range that is likely to be acceptable as cost-effective in low- and middle-income countries at US\$ 7.19 and US\$ 11.83, respectively. Provision of

cheaper cartridges by manufacturers would facilitate provision of universal DM screening of people with TB.

The current testing infrastructure and capacity at a health facility is an important factor when considering the implementation of any screening protocol for concurrent disease. Already existing capacity to perform additional tests on a patient would reduce the implementation costs and improve the feasibility of introducing the test. Since sputum smear and culture tests are already performed to an acceptable standard in the Puskesmases and RSHS Referral Hospital in Indonesia, there is scope to have people with DM produce sputum samples without being sent to separate facilities and potentially be lost to follow-up.

It is worth noting that if 'possible' TB cases had been included in the TB case definition (Figure 8-1), the cost per accurate diagnosis would have decreased and the cost per accurate diagnosis of this screening pathway could also have been assessed in Romania, where there were two 'possible' TB cases. Determining the appropriate health professional to interpret the CXR for potential TB in people with DM was challenging, particularly amongst endocrinologists and diabetologists. Computer-assisted detection may be a viable option in the future to improve the diagnostic accuracy.

Conclusion

In environments where both TB and DM burdens are increasing and the challenges of concurrent disease are becoming increasingly apparent, early, cost-effective screening for TB-DM is essential. Screening for DM in people who have TB is the less costly approach per person accurately diagnosed in both Indonesia and Romania. The most suitable algorithm for combined tests in this approach includes the POC RPG and repeated laboratory HbA_{1c} tests in Indonesia; in Romania it was the urine dipstick also followed by repeated laboratory HbA_{1c} tests, with or without the Omani risk score. A combination of POC RPG and an age screen also proved to have the lowest cost per accurate diagnosis in both settings. This comparative analysis of costs of accurate diagnosis for concurrent TB-DM illustrates that understanding the general population profile of DM is important in determining the most cost-effective approach for screening people with TB for the disease.

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End of Research Paper 3

Chapter 9 Operational feasibility of bi-directional screening for tuberculosis and diabetes in Indonesia and Peru

Preamble to Research Paper 4

This paper assessed the operational feasibility of TB screening and diagnostic tests at the end of the screening process, and compared the DM screening and diagnostic tests at the beginning and end of the screening study in Indonesia and Peru. The health care workers responsible for sample collection, analysis and preparation and relaying of results were interviewed using structured questionnaires, with both closed and open-ended responses.

Assessing the feasibility of implementing TB tests into DM services and DM tests into the TB programmes was an objective of the TANDEM work package 1 protocol, led by Professor Julia Critchley. During the planning stages of the micro-costing of the screening and diagnostic tests (see Research Paper 2), it made sense for me to also collect the data for the operational feasibility as many of the same health care staff would need to be interviewed for both activities. Professor Critchley agreed to this and provided guidance and feedback during the tool development and piloting, data collection and data analysis.

In Romania, operational feasibility data were collected electronically at the beginning of the screening study but the data were not adequately backed-up and the device on which the information was stored crashed. Hence, all of the operational feasibility data were lost. For data at the end of the screening studies, after many delays including a nosocomial infection outbreak at the hospital, a decision was made to not collect any further operational feasibility data in Romania. This is the reason that Romania is not included in this paper. The data presented here for Indonesia and Peru are the best quality operational feasibility data collected for TANDEM.

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SECTION A – Student Details

Student	Yoko Laurence
Principal Supervisor	Ulla Griffiths
Thesis Title	Strategies to detect and treat concurrent tuberculosis and diabetes in Indonesia, Peru and Romania: costs, operational feasibility and impact on health-related quality of life

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	
When was the work published?	
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Tropical Medicine & International Health
Please list the paper's authors in the intended authorship order:	Yoko Laurence, Julia Critchley, Finna Pearson, Ulla Griffiths
Stage of publication	Not yet submitted

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	See details on the next page
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 Supervisor Signature: _____ Date: 16/02/2017

Research Paper 4

Operational feasibility of bi-directional screening for tuberculosis and diabetes in Indonesia and Peru

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Author contribution: I designed the questionnaires for the TB and DM tests, with input from Ulla Griffiths, Julia Critchley, Fiona Pearson and Sarah Kerry. With input from TANDEM staff at each site, I piloted and revised the questionnaires. I administered most of the questionnaires in Indonesia, which were translated into Bahasa by three TANDEM staff. I then trained TANDEM staff to administer the remaining questionnaires in Indonesia and Peru. I analysed the data, drafted the manuscript and made revisions suggested by Ulla Griffiths.

Abstract

Introduction: People with tuberculosis (TB) have worsened outcomes if they also develop diabetes mellitus (DM) and vice versa. A European Commission funded study, TANDEM, conducted bi-directional screening for concurrent TB-DM using six DM and five TB tests. The two diseases are often managed through separate disease programmes, implying that bi-directional screening can encounter operational challenges. We sought to determine the operational feasibility of screening people with TB for DM and people with DM for TB in Indonesia and Peru.

Method: Structured questionnaires were administered to all health care workers (HCWs) involved in any of the TANDEM TB screening tests (TB symptom screen, chest x-ray (CXR), interferon gamma release assay, smear microscopy and microscopic observation drug susceptibility (MODS) culture) or DM screening (point of care (POC) random capillary glucose, fasting blood glucose, urine dipstick, and POC and laboratory glycated haemoglobin). The questionnaires were adapted to the particular setting in each country and administered at two time points for the DM tests (the start and end of the bi-directional screening cross-sectional study in the TANDEM project) and at the end of TB screening. Proportion, frequencies, means and medians were estimated for close-ended questions and themes were identified from open text responses. Data were assessed according to seven domains: user friendliness, training and performance time, acceptability by HCWs, perceived patient acceptability, sample and equipment quality, logistics of performing tests and reporting results, and appropriateness of tests.

Results: Although the urine dipstick was user friendly, required the least amount of time to learn and perceived patient acceptability and compliance was high, HCWs felt it was not useful (appropriate) for diagnosing DM in people with TB. POC tests for diagnosing DM were perceived to be the most acceptable to patients, but sample collection by finger pricks was unacceptable. The CXR consistently performed the best in the operational feasibility domains except for appropriateness, where the smear microscopy and MODS culture were reported to be far more useful for diagnosing TB in patients with DM.

Conclusion: Early and accurate bi-directional screening for TB-DM is possible through a practical and operationally feasible model, which was assessed at outpatient clinics in Indonesia and Peru.

Running head: Operational feasibility of TB-DM screening

Manuscript word count: 6,529

Key words: operational feasibility, tuberculosis, diabetes, screening, Indonesia, Peru, acceptability, appropriateness

Introduction

A quarter of the world's population is believed to have latent tuberculosis (TB) infection and there was an estimated 10.4 million new cases of active TB globally in 2015 (Houben and Dodd, 2016, WHO, 2016a). Diabetes mellitus (DM) affects approximately 415 million adults, a 243% increase since 2000 (IDF, 2015, Wild et al., 2004). Thus, many countries with a high burden of TB are also experiencing an increase in the prevalence of DM. A systematic review of observational studies showed that active TB was two to three times more likely to develop in people with DM than in the general population and another systematic review found that TB treatment outcomes were worsened in people with both diseases (Jeon and Murray, 2008, Baker et al., 2011). The prevalence of DM in patients with TB was estimated as 15% in 2012, equating to one million people (Lonnroth et al., 2014).

'Concurrent **Tuberculosis and Diabetes Mellitus**; unravelling the causal link and improving care' (TANDEM), was a project in Indonesia, Peru, Romania and South Africa that sought to identify optimal ways for screening people with TB for DM and the converse through a cross-sectional study. It also defined the requirements of combined treatment of TB and DM through a pragmatic randomised controlled trial (van Crevel and Dockrell, 2014b).

By establishing the best mechanisms for early diagnosis of TB-DM, the care of concurrent disease can be improved. The detection and treatment are delivered, managed and funded through national TB programmes and chronic disease programmes, respectively (Oliveira-Cruz et al., 2003). This separation can result in duplication and inefficiency of resources and it can be challenging to obtain commitment to any non-programme objectives, such as bi-directional screening for TB-DM (Atun et al., 2008).

Operational feasibility in this study was defined as a measure of how well the tests proposed for bi-directional screening performed in identifying people with concurrent TB-DM. It also looked at whether the implementation of the tests provided any opportunities that could be harnessed or identified any barriers in the various healthcare settings in Indonesia and Romania. The focus was the structural and managerial support available to

perform the tests as well as training required and any adverse effects on health care workers or patients.

Costs are an element of operational feasibility but this was assessed in-depth in an accompanying paper (Laurence et al., see Chapter 8), using a different methodology and so was not included in this paper. The study aim was to identify the potential operational challenges from the perspective of health care workers (HCWs) if bi-directional screening were to be integrated into routine practice in Indonesia and Peru. Operational feasibility of implementing DM tests into TB or directly-observed treatment, short-course (DOTS) clinics and TB tests into chronic disease or DM clinics was assessed.

Methods

Description of tests

The tests that were already part of medical services in the respective countries were not modified in any way. The point-of-care (POC) tests were performed according to manufacturer instructions.

DM tests

The manufacturer specifications for the POC DM tests used in Indonesia and Peru to screen people with TB are listed in Table 9-1.

Blood for the laboratory glycated haemoglobin (HbA_{1c}) tests were collected in ethylenediaminetetraacetic acid (EDTA) tubes. The sample tubes were refrigerated until they were delivered to the private laboratories for analysis. The samples were delivered to Prodia in Jakarta, Indonesia and MedLab in Lima, Peru within 24 hours of sample collection. The fasting blood glucose (FBG) tests were performed in public laboratories in Indonesia and Peru.

Table 9-1: Manufacturer specifications of point of care diabetes diagnostic tests used in Indonesia and Peru

<i>Test/machine characteristics</i>	<i>POC RPG</i>	<i>Urine dipstick</i>	<i>POC HbA1c</i>
INDONESIA			
Manufacturer	Roche	GRF Diagnostic	HemoCue®
Model	Accu-Chek® Active Blood Glucose Meter	Uric-3V SG03100 reagent strip	HbA1c 501 Analyzer
Sample type	Finger prick – 1-2 µL (drop of capillary blood)	Urine specimen – 35-60mL	Finger prick – 1-2 µL (drop of blood)
Measurement range	0.6 – 33.3 mmol/L	Negative to ++++ (>110 mmol/L)	4-14%
Direct result readout	Yes – screen only	No – colour comparison chart	Yes – screen and paper tape
Preparation time	90 seconds	N/A	120 seconds
Result time	5-8 seconds	30-60 seconds	5 seconds
Life span of sample strip	18 months	24 months	18 months
PERU			
Manufacturer	Roche	Medi-Test	HemoCue®
Model	Accu-Chek® Active Blood Glucose Meter	Combi-10® SGL	HbA1c 501 Analyzer
Sample type	Finger prick – 1-2 µL (drop of capillary blood)	Urine specimen – 35-60mL	Finger prick – 1-2 µL (drop of blood)
Measurement range	0.6 – 33.3 mmol/L	Negative to ++++ (>110 mmol/L)	4-14%
Direct result readout	Yes – screen only	No – colour comparison chart	Yes – screen and paper tape
Preparation time	90 seconds	N/A	120 seconds
Result time	5-8 seconds	30-60 seconds	5 seconds
Life span of sample strip	18 months	24 months	18 months

TB tests

The type of smear, culture, latent TB infection tests and the image format for chest x-ray (CXR) are listed in Table 9-2. A TB symptom screen, which included questions about recent cough lasting two weeks or more; whether it was a productive cough and if so, whether there was blood in the sputum; breathlessness upon exertion; night sweats; fever; and any unintentional weight loss or gain was also performed in all people with DM.

Table 9-2: Tuberculosis tests description in Indonesia and Peru

	<i>Number of sputum samples collected</i>	<i>Smear method performed</i>	<i>Culture method performed</i>	<i>CXR result format</i>	<i>Latent TB infection test</i>
Indonesia	2	Z-N smear microscopy	MODS	Film and digital	IGRA
Peru	2	Z-N smear microscopy	MODS	Film	IGRA

CXR: chest x-ray; TB: tuberculosis; Z-N: Ziehl-Neelsen; MODS: Microscopic-Observation Drug-Susceptibility assay; IGRA: Interferon Gamma Release Assay

Setting and study population

This study was performed in Bandung, Indonesia and Lima, Peru. In Bandung, patients were screened for concurrent TB-DM at the Endocrinology and DOTS clinics at the Hasan Sadikin Hospital (RSHS) and the TB Research Clinic at the UNPAD Teaching Hospital. In Lima, patients at DOTS clinics at four health care centres (Hospital Huaycan, Centro de Salud San Cosme, Centro Materno Infantil San Jose and Centro de Salud Forteleza) were screened for DM and patients with DM attending the endocrinology clinic at the Maria Auxiliadora Hospital in Miraflores were screened for TB.

The questionnaire participants were purposively sampled and the sampling frame included all clinic, hospital or laboratory staff who attended to any TANDEM patients or their samples, regardless of whether they were hired specifically for the TANDEM study, other research staff or staff involved in the routine services of the facility. The DM test questionnaires for clinicians (doctors and nurses) were administered to staff who performed the POC random plasma glucose (RPG), POC HbA_{1c} or urine dipstick tests, or collected blood samples for the FBG or laboratory HbA_{1c} tests in patients with TB at DOTS clinics. DM questionnaires for laboratory personnel included staff at public health facilities

who performed the FBG analysis on blood samples or private laboratory staff in Indonesia who conducted laboratory analysis of the HbA_{1c} test.

The questionnaires for TB tests were administered to clinicians in the public endocrinology clinics, who performed the TB symptom screen, assisted patients with sputum collection, referred or interpreted CXRs or collected and processed blood samples for the Interferon Gamma Release Assay (IGRA) test for detecting latent TB infection. The remaining TB test questionnaires were administered to publicly funded laboratory personnel (doctors, technicians or other assistants) who prepared or performed analysis of sputum samples for Ziehl-Neelsen (Z-N) smear microscopy, or Microscopic Observation Drug Susceptibility (MODS) culture; conducted radiological examinations for CXRs or analysed IGRA blood samples.

Questionnaire design and data collection

Distinct questionnaires with both open and closed-ended questions were developed for clinic and laboratory staff. The questionnaires contained a section for each TB or DM test performed, developed around seven domains: user friendliness, time for training and performance, perceived patient acceptability, logistics and feasibility of performing the tests and reporting the results, perceived appropriateness of the tests, sample and equipment quality, and accessibility (Medina Lara et al., 2005).

Response options included a five-point ordinal endorsement Likert scale (strongly agree, agree, neither agree nor disagree, disagree and strongly disagree) for the user friendliness domain (Fink, 2003). Dispersed throughout the various domain sections were categorical options (for example agreement: yes/no/don't know, or frequency: never/only when outside the normal range/always); completing numeric values for predetermined units of quantity (percent, count) and time (years/months/weeks/days/hours/minutes); and open ended questions to capture criteria, lists, processes, opinion, comments or description of quality.

User friendliness

The user friendliness domain asked for level of agreement with statements related to the tasks around performing each test. They included the ideal attributes of being technically

undemanding, having training and performance times that were acceptable, requiring minimal supervision to perform the tasks, having a direct result reading and the presence of simple quality control checks.

Training and performance time

The time taken to learn how to perform each test independently was captured, whether the training was done recently for the TANDEM study or part of previous training. HCWs were asked to estimate the time taken to perform the test, including time taken by patients to produce samples and average time taken for results to be returned to clinician or patient.

Acceptability – perceived patient perspective

HCWs were asked to posit on behalf of patients as to reasons for any unwillingness or non-compliance in having the respective tests performed.

Appropriateness

The appropriateness (usefulness) of each test as a diagnostic tool was assessed, including reasons for not being useful.

Quality – samples and equipment

For each HCW interviewed, the proportion of compromised tests, including being lost, destroyed or of poor quality, was captured. They were asked to describe the quality of samples obtained for analysis, with respect to volume and sample properties. They were also asked to describe any internal quality control process, whether they performed them or it was done by someone else; and if supervision of junior staff was done within their facility or department.

The quality of equipment was assessed by determining the frequency of machine maintenance.

Logistics and feasibility

HCWs were asked to describe the processes involved in performing the tests, including any repeat visits by the patient, and the reporting of results to the requesting clinician and patient. They were also asked for the top three reasons for incomplete or compromised

tests in clinic and laboratory. Given these processes and challenges, HCWs were asked to assess the feasibility of performing the test in routine practice, given the current staff capacity.

The logistical feasibility, which assessed the processes for performing each task and combining the tasks (from sample collection to sample analysis to result reporting), differed from the overall operational feasibility of implementing the test, which evaluated the combined outcome of the seven domains.

Accessibility

Questions on accessibility included, where relevant, whether the tests were routinely available and routinely prescribed. When the test was not available, the HCW was asked to identify an alternative test that was used, if any, and why the test was not available or prescribed. The HCW was also asked to identify the nearest facility where the test was available.

Study phases

Validation

The questionnaires were designed in English and pilot tested by administration to health professionals involved in the TANDEM study. Face validity was assessed to determine whether the questions were clear, understandable and asked in a logical order. Content validity was assessed to determine if the information in the questionnaires was accurate and relevant to the issues surrounding screening people with one disease for another disease.

Implementation

Baseline (T_0) questionnaires for DM tests were administered between March 2014 and January 2015; follow-up (T_1) DM questionnaires between March and May 2016; and TB test questionnaires between May and June 2015 (Table 9-3).

Table 9-3: Data collection dates for operational feasibility questionnaires of screening and diagnostic tests in TANDEM

	DM tests – baseline: T ₀	DM tests – follow-up (end of recruitment): T ₁	TB tests – end of recruitment: T ₁
Indonesia	March-April 2014	April-May 2016	May-June 2015
Peru	July and October 2014; January 2015	March 2016	N/A

TANDEM: ‘Concurrent Tuberculosis and Diabetes Mellitus; unravelling the causal link and improving care’

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

In Indonesia, the information sheet, consent form and questionnaire instructions were translated into Bahasa. The remainder of the questionnaire was left in English. When the tool was administered, the questions and options were read out in English and then verbally translated into Bahasa by TANDEM team members who were fluent in both Bahasa and English. In Peru, the questionnaires were translated into Spanish.

Analysis

The participant responses from the paper questionnaires were entered into Excel (Microsoft Corporation, Redwood, WA, USA) using a data entry form. Proportions and measures of central tendency were calculated in Excel. A thematic analysis of open text responses was performed (Braun and Clarke, 2006). This was done by the first author (YVL) initially reading all open text. Codes were then created, such as ‘reasons for urine test not being performed’ or ‘CXR not appropriate for diagnosing TB’. These coded texts from the interviews were then arranged by categories, such as ‘tests performed’, ‘alternative tests performed’ and ‘appropriate tests performed’. These categories were used to generate themes, which were either incorporated with the existing domains, such as appropriateness and used to create new domains, such as logistics and feasibility. All quantitative data in this study were coded in Excel. No internal consistency of questions was performed.

Ethics

Ethical approval was obtained through the London School of Hygiene & Tropical Medicine, the Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; and the Institutional Ethics Committee, Universidad Peruana Cayetano Heredia, Lima, Peru.

Every participant was given an information sheet outlining the objectives of the operational feasibility study and indicating that participation was anonymous, voluntary and could be withdrawn at any time. Informed consent forms were signed by all participants, giving permission for their responses to be anonymously used in this thesis, project reports and any publications arising out of this study. The information sheets and consent forms were presented in Bahasa in Indonesia and Spanish in Peru.

Results

Characteristics of respondents

The majority of responding HCWs were female in both the clinics (91%) and laboratories (68%) (Table 9-4). Median age of clinic staff was 28 years (IQR: 26-29.5) and laboratory staff, 31 years (IQR: 27-35). Only 4% of clinic staff and 28% of laboratory staff were routinely employed by the facility in which they were working. Amongst all staff, 54% were hired by TANDEM to perform tasks only related to the study and 8% were employed by the university affiliated with the health facility and working on several research projects, including TANDEM.

Table 9-4: Characteristics of health care workers performing screening tests in the TANDEM study in Indonesia and Peru (n=48)

	Health centre staff		Laboratory staff	
	(n=23)		(n=25)	
	n	%	n	%
Age (years), [median, IQR]	28	26-29.5	31	27-35
Gender (female)	21	91.3	17	68.0
Employer (TANDEM)	20	87.0	6	24.0
Employer (Health facility)	1	4.3	7	28.0

TANDEM: 'Concurrent Tuberculosis and Diabetes Mellitus; unravelling the causal link and improving care'

DM screening and diagnostic tests

The DM screening and diagnostic tests questionnaires for clinic and laboratory staff (Appendix V and Appendix W) were administered at two time points (Table 9-3). At T_0 , 15 HCWs completed the DM questionnaires (Table 9-5). At T_1 , 12 HCWs responded to the questionnaires, but only four (27% of the T_1 participants) were the same individuals from T_0 . The functional roles in DM screening and diagnosis remained the same however.

Table 9-5: Number of questionnaires completed by activity and time point in Indonesia and Peru

<i>Country</i>	<i>Clinic staff</i>	<i>Laboratory staff</i>	<i>TOTAL</i>	<i>Clinic staff</i>	<i>Laboratory staff</i>	<i>TOTAL</i>	<i>Clinic staff</i>	<i>Laboratory staff</i>	<i>TOTAL</i>
	<i>DM tests – T_0</i>			<i>DM tests – T_1</i>			<i>TB tests – T_1</i>		
<i>Indonesia</i>	5	6	11	5	3	8	7	14	21
<i>Peru</i>	3	1	4	3	1	4	0	0	0
<i>Total</i>	8	7	15	8	4	12	7	14	21

T_0 : within 4 months from start of patient recruitment in TANDEM study

T_1 : within 2 months of ending patient recruitment in TANDEM study

User friendliness

Clinic staff

Amongst clinicians, the urine dipstick had the highest overall satisfaction at T₀, but 24 months later the urine dipstick was equally ranked with the POC RPG test for the highest value (Table 9-6). At T₀ the POC RPG was only one score behind the urine dipstick. The FBG and laboratory HbA_{1c} had the lowest overall satisfaction at T₀ and the laboratory HbA_{1c} dropped one point below the FBG at T₁. Both tests scored consistently low when asked to rate level of agreement with the statement “this test has a direct result reading”.

Table 9-6: User friendliness of DM screening questionnaires in clinic staff in Indonesia and Peru

	Median scores									
	T ₀					T ₁				
	POC RPG	FBG	Urine dipstick	POC HbA _{1c}	Lab HbA _{1c}	POC RPG	FBG	Urine dipstick	POC HbA _{1c}	Lab HbA _{1c}
Technically undemanding	4.5	4	4.5	4	4	4.5	4	5	4	4
Training time acceptable	4	4	4.5	4	4	5	4	5	4	4
Performance time acceptable	5	4	4.5	4	4	4	4	4.5	4	4
Minimal supervision	5	4	4.5	4	3	4.5	4	4	4	4
Direct result reading	5	3	5	4.5	3	4.5	2	5	5	2
Simple quality control checks	3.5	3	4	4	3	4	4	4	4	4
Total score*	27	22	27	24.5	21	26.5	22	27.5	24	22

*Total possible score is 30

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

POC: point-of-care; RPG: random plasma glucose; FBG: fasting blood glucose; HbA_{1c}: glycated haemoglobin

Laboratory staff

For laboratory technicians, the user friendliness of performing blood sample analysis for the FBG and laboratory HbA_{1c} were one point apart initially and garnered the same score of 24 at T₁ (Table 9-7).

Table 9-7: User friendliness of DM screening questionnaires in laboratory staff, Indonesia and Peru

	Median scores			
	T ₀		T ₁	
	FBG	Lab HbA _{1c}	FBG	Lab HbA _{1c}
Technically undemanding	5	4.5	4	4
Training time acceptable	5	4.5	4	4
Performance time acceptable	5	5	4	4
Minimal supervision	4.5	4	4	4
Direct result reading	5	5	4	4
Simple quality control checks	4.5	5	4	4
Total score*	29	28	24	24

*Total possible score is 30

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

FBG: fasting blood glucose; HbA_{1c}: glycated haemoglobin

Training time

Clinic staff

At both time points, 100% of clinic staff reported having performed a FBG, 88% a POC RPG, and 60% a laboratory HbA_{1c} before the start of the TANDEM study (Table 9-8). The values were lower for the urine dipstick and POC HbA_{1c} tests. The experience time ranged from 36 months for the POC HbA_{1c} at T₀ to 66 months for the FBG at T₁. The blood draw for the FBG took the longest to learn, going from 50 hours at T₀ to 59 hours at T₁.

Table 9-8: Clinic staff training and performance times for diabetes tests in Indonesia and Peru

	T ₀					T ₁				
	POC RCPG	FBG	Urine dipstick	POC HbA _{1c}	Laboratory HbA _{1c}	POC RPG	FBG	Urine dipstick	POC HbA _{1c}	Laboratory HbA _{1c}
Proportion of respondents who performed test before TANDEM	88%	100%	50%	25%	60%	88%	100%	38%	13%	60%
Length of time respondents with previous experience have been performing test (in months)	56.6	65.8	55.2	60.0	64.0	48.9	49.2	64.0	36.0	42.0
Time to learn to perform test (in hours)	2.3	58.8	3.6	35.7	16.5	3.4	49.7	2.1	12.4	17.8
Number of times test practised to learn it	3.3	10.6	1.4	3.9	10.8	2.6	5.2	1.6	2.9	2.8
Time to produce urine sample (in minutes)	N/A	N/A	10.6	N/A	N/A	N/A	N/A	15.0	N/A	N/A
Time to perform one test (in minutes)	4.0	8.0	4.5	8.0	6.4	2.1	5.4	3.4	6.4	4.5

N/A: not applicable

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

POC: point-of-care; RPG: random plasma glucose; FBG: fasting blood glucose; HbA_{1c}: glycated haemoglobin

Laboratory staff

All of the laboratory staff interviewed had performed the FGB and laboratory HbA_{1c} analyses prior to the start of TANDEM and had between four and 24 years of experience performing those tests.

Performance time

Clinic staff

The average time for patients to produce and return a urine sample to the HCW for dipstick test increased from 11 to 15 minutes, but the average time for the HCW to perform the test decreased from 5 to 3 minutes from T₀ to T₁ (Table 9-8). The POC RPG took the least amount of time at both time points, at 4 and 2 minutes, respectively. The POC HbA_{1c} test took the longest at 8 and 6 minutes respectively.

Laboratory staff

The mean time taken to perform analysis and complete paperwork for one FBG sample was reported as 8 minutes at T₀ and increased to 10 minutes at T₁ (Table 9-9).

Table 9-9: Laboratory staff training and performance times for diabetes tests in Indonesia and Peru

	T ₀		T ₁	
	FBG	Laboratory HbA _{1c}	FBG	Laboratory HbA _{1c} *
Proportion of respondents who performed test before TANDEM	100%	100%	100%	100%
Length of time respondents with previous experience have been performing test (in months)	90.0	52.0	285.0	120.0
Time to learn to perform test (in hours)	24.0	112.0	74.0	56.0
Number of times test practised to learn it	4.8	60.3	3.8	3.0
Time to complete paperwork (in minutes)	6.9	23.3	7.3	No response
Time to perform one test (in minutes)	1.3	3.0	3.0	Don't know

N/A: not applicable

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

POC: point-of-care; RPG: random plasma glucose; FBG: fasting blood glucose; HbA_{1c}: glycated haemoglobin

Acceptability – perceived patient perspective

Clinic staff

At the start of the cross-sectional study recruitment, none of the respondents indicated reluctance by patients to provide samples for the POC RPG, urine dipstick, POC HbA_{1c} or laboratory HbA_{1c} tests. However, at T₁, 13% of respondents indicated that patients were unwilling to have their fingers ‘pricked’ for the POC RPG and POC HbA_{1c} tests, but no reason was given for this reluctance.

At T₁, 20% of HCWs at DM clinics felt patients were generally non-compliant with the request to fast and unwilling to return to the clinic another day after having fasted. The main reasons mentioned were the distance of the clinic from the patient’s home, and difficulty obtaining additional time off from work.

Appropriateness

Clinic staff

The majority of HCWs felt that the tests were appropriate for diagnosing DM, except the urine dipstick test, which was deemed useful by 75% at T₀, decreasing to 63% at T₁ (Table 9-10). The reasons expressed at T₀ included that glucose would only be present and easily detectable in urine when DM was advanced and therefore the urine dipstick was better for identifying whether there are complications, such as poor renal function, or for detecting advanced DM. Near the end of enrolment, HCWs suggested that the urine dipstick was not useful for diagnosing DM because a more sensitive test (such as FBG or random blood glucose) was needed, particularly in patients with TB. One respondent commented that the perception of colour and matching to the colour chart differed from person to person.

The POC HbA_{1c} was not considered useful for diagnosing DM in only 13% of respondents at T₀, with one respondent commenting that the machine operation requires “special skills” that need to be refined and the test would be considered useful if this was addressed, perhaps by more thorough training. However, no respondents doubted the usefulness of the test at T₁.

Table 9-10: Change in test appropriateness for diagnosing diabetes mellitus from perspective of health care workers in Indonesia and Peru

Test	Proportion of respondents indicating test is useful for diagnosing DM (%)			
	Clinic staff		Laboratory staff	
	T ₀	T ₁	T ₀	T ₁
POC RPG	88	88	N/A	N/A
Urine dipstick	75	63	N/A	N/A
POC HbA_{1c}	88	100	N/A	N/A
FBG	80	100	75	100
Laboratory HbA_{1c}	80	100	100	100

DM: diabetes mellitus; POC: point-of-care; RPG: random plasma glucose; HbA_{1c}: glycated haemoglobin; FBG: fasting blood glucose; N/A: not applicable

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

Laboratory staff

The FBG and laboratory HbA_{1c} tests were considered to be appropriate for diagnosing DM by all respondents in T₁ (Table 9-10). This increased from 75% of respondents at T₀ for the FBG.

Quality – samples

Clinic staff

The proportion of estimated compromised tests decreased between T₀ and T₁, suggesting that clinic staff became more experienced at collecting samples over the 24 month period (Table 9-11). The urine dipstick was consistently reported to have no compromised samples or tests.

Laboratory staff

At T₀, only 33% of respondents indicated that the volume of the FBG samples was usually sufficient, but at T₁, 100% reported that sample volume was sufficient (Table 9-12). The main reason reported for insufficient volume was fragility of veins of older patients.

Quality – equipment

Clinic staff

The POC RPG machines had a down time of one minute at T₀, but after 24 months of use the machines did not function for an average of two days whenever they broke down, which occurred once per year. The average down time of the POC HbA_{1c} machines also increased, but the difference was less striking, going from 12 hours to 16 hours.

The annual frequency of POC RPG machine maintenance decreased from 3.7 times to once per year between T₀ and T₁.

Daily internal quality control checks were reported to happen by 63% of respondents at T₀, but reduced to 38% of respondents at T₁.

Table 9-11: Compromised tests or samples for diabetes mellitus testing as reported by clinic staff in Indonesia and Peru

	T ₀					T ₁				
	POC RPG	FBG	Urine dipstick	POC HbA _{1c}	Laboratory HbA _{1c}	POC RPG	FBG	Urine dipstick	POC HbA _{1c}	Laboratory HbA _{1c}
Number of tests performed (mean)	18	5	20	15	4	577	761	470	343	525
Proportion of staff with a compromised test	50%	80%	0%	25%	20%	50%	40%	13%	38%	20%
Number of compromised tests (mean)	1	0.4	0	0.3	0.2	12	3	0	3	2
Proportion of tests compromised	3%	8%	0%	2%	5%	2%	0.4%	0%	1%	0.3%

T₀: within 4 months from start of patient recruitment in TANDEM study

T₁: within 2 months of ending patient recruitment in TANDEM study

POC: point-of-care; RPG: random plasma glucose; FBG: fasting blood glucose; HbA_{1c}: glycated haemoglobin

Table 9-12: Sample quality for diabetes mellitus tests as reported by laboratory staff at the beginning and end of patient recruitment in Indonesia and Peru

	T ₀		T ₁	
	FBG	Laboratory HbA _{1c}	FBG	Laboratory HbA _{1c} *
Number of tests performed (mean)	0	~2,000	10,514	N/A
Proportion of respondents saying samples usually good quality	100%	100%	100%	N/A
Proportion of respondents saying samples usually sufficient volume	33%	100%	100%	N/A
Proportion of respondents indicating internal quality control performed	100%	---	75%	N/A
Proportion of respondents accurately describing quality control process	100%	---	75%	N/A
Proportion of staff with a compromised test	100%	0%	0%	N/A
Number of compromised tests (mean)	0	0	0	N/A
Proportion of tests compromised	0.0%	0.0%	0.0%	N/A

---: not asked; N/A: not available

*Staff who performed laboratory HbA_{1c} analysis at private laboratories were not accessible in Indonesia at T₁ nor in Peru at T₀ and T₁

Logistics and feasibility of performing tests and reporting results

Clinic staff

For the urine dipstick test, at T₀, 75% of staff reported that the toilet facilities were suitable for patients to produce urine samples, with one respondent in Peru indicating that the space used by patients is a public toilet, which was not clean and was used by many other patients and non-patients. All respondents reported that drinking water was easily available. The values were switched at T₁, with 100% of staff indicating that toilet facilities were suitable, but only 88% that drinking water was easily available, but none provided any suggestions as to how this could be improved.

FBG blood samples were taken to the lab twice daily, according to 40% of respondents, but taken only once a day according to an additional 40% of respondents at T₀. However, once daily was reported by 80% of respondents 24 months later.

The mean time taken for the FBG results to be returned to the clinic and relayed to the patients was two days at T₀, but increased to three days at T₁.

In Indonesia, the mean time taken for the laboratory HbA_{1c} results to be returned to the clinic increased from 3.5 days at T₀ to 8.2 days at T₁.

Patients were always called and asked to visit the clinic for their FBG and laboratory HbA_{1c} test results.

Laboratory staff

Contrary to the information provided by the clinic staff, laboratory staff indicated that FBG samples were brought to the laboratory once weekly at T₀ (reported by 33% of respondents), but this was changed to once daily (reported by 50% of respondents) at T₁.

Accessibility

Clinic staff

At T₀, of the five clinicians interviewed in Indonesia, all indicated that FBG and laboratory HbA_{1c} were currently available at the DOTS clinic in RSHS (outside the TANDEM study). Out of the eight clinicians interviewed about the urine dipstick test in Indonesia and Peru, only 38% (three Indonesian HCWs) said it was available. The POC RPG and HbA_{1c} were reported as being available in the DOTS clinic by 50% and 63% of clinicians, respectively.

At T₁, the proportion of HCWs indicating that the urine dipstick, POC RPG and POC HbA_{1c} tests were available at their facility increased to 63%, 63% and 100%, respectively.

Laboratory staff

At both time points all laboratory technicians in Indonesia (n=3) indicated that the FBG and laboratory HbA_{1c} were available in the facility laboratory as part of routine services. The one laboratory technician interviewed in Peru at both time points consistently stated that analysis of neither blood test was available for patients attending the DOTS clinic.

TB screening and diagnostic tests

A total of 21 HCWs responded to questions about TB tests (Table 9-5). Seven of these performed tasks in the clinic including the TB symptom screen, CXR referral or interpretation, sputum collection for the smear or culture tests or blood collection for the IGRA test (Appendix X), while 14 performed laboratory analysis for the sputum smear, MODS culture, IGRA or performed a CXR in the radiology department (Appendix Y).

User friendliness

Clinic staff

The least user friendly was IGRA blood collection, obtaining a weak Likert score of 2 out of 5 for the statements relating to having a direct result readout and simple quality control checks (Table 9-13).

Table 9-13: User friendliness of TB screening questionnaires in clinic staff in Indonesia and Peru[#]

	Median scores				
	T ₁				
	TB symptom screen	CXR referral	CXR Interpretation	Sputum collection	IGRA blood collection
Technically undemanding	4	3.5	3.5	4	4
Training time acceptable	4	4	4	4	4
Performance time acceptable	4	4	4.5	4	4
Minimal supervision	4	4.5	3.5	4	5
Direct result reading	4	3	3.5	4	2
Simple quality control checks	3	2.5	4	3.5	2
Patients find questions easy to understand	4				
Total score*	27	21.5	23	23.5	21

[#]No health care workers were available in Peru

*Total possible score is 35

T₁: within 2 months of ending patient recruitment in TANDEM study

TB: tuberculosis; CXR: chest x-ray; IGRA: interferon gamma release assay

Laboratory staff

From the perspective of technicians, the CXR was the most user friendly test to perform with a total score of 27 out of 30 (Table 9-14). Sputum smear and MODS culture performed equally well with a total score of 24 each. The least user friendly test was the IGRA analysis, obtaining the lowest score of 2 out of 5 for acceptable training time.

Table 9-14: User friendliness of TB screening questionnaires in laboratory staff in Indonesia and Peru[#]

	Median scores			
	T ₁			
	CXR (radiographer)	Smear analysis	MODS culture analysis	IGRA analysis
Technically undemanding	4.5	4	4	3
Training time acceptable	4.5	4	4	2
Performance time acceptable	4.5	4	4	3
Minimal supervision	4	4	4	3
Direct result reading	5	4	4	4
Simple quality control checks	4.5	4	4	4
Total score*	27	24	24	19

[#]No health care workers were available in Peru

*Total possible score is 30

T₁: within 2 months of ending patient recruitment in TANDEM study

TB: tuberculosis; CXR: chest x-ray; MODS: microscopic-observation direct-susceptibility; IGRA: interferon gamma release assay

Training and performance time

Clinic staff

The IGRA blood collection took the longest amount of time to learn (38 hours) and was practiced for an average of nine times before staff felt comfortable performing the activity (Table 9-15). The TB symptom screen took the least amount of time to learn (0.2 hours), but was practiced the most (20 times).

The total performance time was 5 hours and 50 minutes for CXR interpretation and 42 times as long for the MODS culture, including sputum collection, at 212 hours and 15 minutes.

Table 9-15: Clinic staff training and performance times for tuberculosis tests in Indonesia and Peru[#]

	TB symptom screen	CXR referral	CXR interpretation	Sputum collection	IGRA blood collection
Proportion of respondents who performed test before TANDEM	80%	80%	100%	20%	20%
Length of time respondents with previous experience have been performing test (in months)	75	82	33	24	N/A
Time to learn to perform test (in hours)	0.2	N/A	8	8.1	37.8
Number of times test practised to learn it	20.0	N/A	11.5	4.8	8.5
Time to complete paperwork (in minutes)	N/A	N/A	N/A	N/A	N/A
Time between sample production to delivery to lab for analysis (in minutes)	N/A	N/A	N/A	N/A	258
Time to obtain result of analysis (in minutes)	N/A	1,320	330	Smear: 1,680 Culture: 9,600	7,200
Time to perform one test (in minutes)	N/A	10	20	16.3	8
Time for results to be returned to clinic or given to patient (in minutes)	N/A	6,840	N/A	Smear: 1,320 Culture: 3,120	3,000
Total performance time (in minutes)	N/A	8,170	350	Smear: 3,016 Culture: 12,736	10,466

[#]No health care workers were available in Peru

TB: tuberculosis; CXR: chest x-ray; IGRA: interferon gamma release assay; N/A: not applicable

Laboratory staff

The MODS culture took the longest to learn (180 hours) and was the longest to perform (30 days) but was practiced the least number of times (n=6) to become proficient at performing the test (Table 9-16). The CXR took 23.5 minutes to perform, including time for paperwork and returning the results to the clinic or patient but excluded waiting time.

Table 9-16: Laboratory staff training and performance times for tuberculosis tests in Indonesia and Peru[#]

	CXR	Z-N smear microscopy	MODS culture	IGRA
Proportion of respondents who performed test before TANDEM	100%	100%	83%	67%
Length of time respondents with previous experience have been performing test (in months)	156	18	33	30
Time to learn to perform test (in hours)	77.3	133.3	180.0	40.0
Number of times test practised to learn it	600	20	6	8.3
Time to complete paperwork (in minutes)	7.5	20.0	22.5	120.0
Time between sample production to delivery to lab for analysis (in minutes)	N/A	5.0	408.0	6.0
Time to obtain result of analysis (in minutes)	5.0	480.0	13,440	2.3
Time to perform one test (in minutes)	3.0	6.3	11.5	3.6
Time for results to be returned to clinic or given to patient (in minutes)	8.0	480.0	881.6	2,239.8
Total performance time (in minutes)	23.5	991.3	14,763.7	2,371.8

[#]No health care workers were available in Peru

CXR: chest x-ray; Z-N: Ziehl-Neelsen; MODS: Microscopic Observation Drug Susceptibility; IGRA: interferon gamma release assay; N/A: not applicable

Acceptability – perceived patient perspective

Clinic staff

An average of 88% of patients reported their willingness to participate in the TB symptom screen by HCWs. The main reason reported by HCWs for patients not wanting it was that the patient did not have time or felt too ill. No patients were reported by HCWs as having difficulty completing the TB symptom screen, but the most challenging part of the screen was describing 'shortness of breath' to the patient.

Approximately half (48%) of the patients were estimated to be willing to produce sputum for a smear or culture test. Any unwillingness to produce a sputum sample at the DM clinic was usually because the patient did not have a productive cough and could not produce a sample.

Between 3% and 15% of patients did not comply with the request to go for a CXR. A fear of radiation, stigma associated with TB or not having time to go for the scan were reasons suggested.

The HCWs indicated that an average of 79% of patients were willing to have their blood drawn for an IGRA test. A fear of injections was the only reason given for patient unwillingness.

Laboratory staff

Between 0% and 5% of patients with DM were reported by respondents to not comply with the request to go for a CXR. The reason for non-compliance was usually because the patient was too ill to get to the radiology department, including challenges such as "a lot of TB in the lungs" or gangrene, thus an inability to walk.

Appropriateness

Clinic staff

The smear microscopy and MODS culture tests were deemed to be useful for diagnosing TB by 100% of respondents as long as sample coordination is well done to ensure that both tests are performed on the same sample (Table 9-17). The CXR was seen as a useful test for diagnosing TB by 80% of respondents despite the increased likelihood of abnormal or complicated readings in patients with DM, which are potentially caused by

an enlarged heart, other cardiovascular disease or “old TB” that should really be suggestive of inactive TB. An additional challenge of using CXRs to diagnose TB in Indonesia was that a nurse could only do a referral for a CXR if there is no doctor in the facility and this creates situations where referrals do not happen if the doctor is in the facility, but too busy to do the referral.

The TB symptom screen was seen as appropriate for diagnosing TB by 80% of respondents, but they qualify that the test should include better definitions of the terms in order to improve the understanding of both the clinician and the patient. The respondent who did not find the TB symptom screen useful cautioned that the test was only appropriate for diagnosis if other screens were used with the test.

Only 40% of the clinicians interviewed indicated that the IGRA test was useful for diagnosing TB. Several reasons were listed for it being unsuitable, including it being designed for detecting latent TB only, being a technically demanding test to perform as well as being expensive, with other cheaper options available, such as the Mantoux test.

Table 9-17: Test appropriateness for diagnosing tuberculosis from perspective of health care workers in Indonesia and Peru

Test	Proportion of respondents indicating test is useful for diagnosing TB (%)	
	Clinic staff	Laboratory staff
TB symptom screen	83	N/A
CXR	88	100
Smear microscopy (Z-N)	100	100
MODS culture	100	100
IGRA	50	75

TB: tuberculosis; CXR: chest x-ray; Z-N: Ziehl-Neelsen; MODS: microscopic-observation drug-susceptibility; IGRA: interferon gamma release assay

T₁: within 2 months of ending patient recruitment in TANDEM study

Laboratory staff

The CXR, smear microscopy, MODS culture and IGRA tests were all reported to be useful for diagnosing TB by 100% of laboratory technicians interviewed (Table 9-17). There was a recognition that while the smear was appropriate, culture is the gold standard for TB diagnosis. MODS was identified as being faster and more sensitive than smear and solid culture but with a higher rate of contamination. MODS was identified as the best culture test option but it is not well known and strict quality control measures are needed to ensure a primary contamination rate of under 5%. While the IGRA test was seen as a good option for diagnosing TB, several weaknesses of the test were identified, including an unacceptably high proportion of indeterminate results, the reason for which is often unknown. Potential reasons for indeterminate results included “warm samples occurring during transportation”; low CD4 count of patient; unknown patient medication or other unknown medical history; or tubes shaken because patient moves around when blood being drawn.

Quality – samples

Clinic staff

Staff members performing interpretation of CXRs reported no compromised tests (Table 9-18), but those performing the IGRA blood collection had a high proportion of compromised samples (17%), which were reported to be due to improper processing of the sample in the tube; haemolysis; and using expired tubes. Sputum samples were reported to be compromised for approximately 6% of patients who produced saliva instead of sputum or when the samples were lost due to mislabelling.

Table 9-18: Compromised tests or samples for tuberculosis testing as reported by clinic staff in Indonesia and Peru[#]

	TB symptom screen	CXR referral	CXR interpretation	Sputum collection	IGRA blood collection
Number of tests performed (mean)	360	275	130	45	188
Proportion of staff with a compromised test	N/A	80%	0%	80%	80%
Number of compromised tests (mean)	N/A	17.5	0	4.8	31.7
Proportion of tests compromised	N/A	6.4%	0.0%	10.6%	16.8%

[#]No health care workers were available in Peru

TB: tuberculosis; CXR: chest x-ray; IGRA: interferon gamma release assay; N/A: not applicable

Laboratory staff

All laboratory technicians reported that internal quality control was done for the smear microscopy, MODS culture and IGRA tests, with all respondents accurately describing the process for the smear microscopy and IGRA. An average of 38% of sputum samples were reported to be good quality (Table 9-19). The most common reasons for poor quality samples were dirty or broken containers, and “too much saliva because the patient does not understand how to produce a good sample”. The volume of blood required for the IGRA test was correct in approximately 90% of the samples produced. In cases where there was too much blood in the tube, it was suggested to be caused by the nurse using a syringe or pipette to measure out 1 ml of blood but in reality less than 1 ml of blood being required to reach the 1 ml mark on the tube because of the EDTA chemical already in the blood collection tube.

Internal quality control was performed most frequently (1.5 times) and for the longest amount of time (167 minutes) for the MODS culture test. However, the MODS culture test had the highest proportion of compromised tests (7%) due to spilt, damaged, mislabelled or lost samples, as well as insufficient sputum for analysis. The only reason reported for compromised CXRs (1% of images) was misspelling of patient names so that results could not be matched to the correct patient file. Compromised IGRA tests were reported to be due to wrong caps being used for the IGRA tube; missing labels on tube; low concentration of sample because of too much blood in tube; unknown patient co-morbidities; bubbles in the wells during analysis and incorrectly harvested and processed samples.

Table 9-19: Sample quality for tuberculosis tests as reported by laboratory staff at the end of patient recruitment in Indonesia and Peru[#]

	CXR	Z-N smear microscopy	MODS culture	IGRA
Number of tests performed (mean)	275	3,733	288	236
Proportion of respondents saying samples usually good quality	N/A	38%	86%	97%
Proportion of respondents saying samples usually sufficient volume	N/A	65%	72%	90%
Proportion of respondents indicating internal quality control performed	N/A	100%	100%	100%
Proportion of respondents accurately describing quality control process	N/A	100%	83%	100%
Weekly internal quality control frequency	N/A	0.5	1.5	1.3
Time spent on internal quality control (in minutes)	N/A	86.7	166.7	40.0
Proportion of staff with a compromised test	100%	100%	100%	100%
Number of compromised tests (mean)	2.5	206.7	19.3	3.0
Proportion of tests compromised	0.9%	5.5%	6.7%	1.1%

[#]No health care workers were available in Peru

TB: tuberculosis; CXR: chest x-ray; Z-N: Ziehl-Neelsen; MODS: microscopic-observation drug-susceptibility; IGRA: interferon gamma release assay; N/A: not applicable

Quality – equipment

Laboratory staff

The annual breakdown frequency for the x-ray machine was 0.1 times with a mean down time of two days. The smear microscopy and MODS culture equipment breakdown more frequently each year (0.3 and 0.8 times, respectively) but both had a mean down time of seven days. The CXR, smear and culture equipment were each calibrated once per year by an external supplier. The IGRA equipment was calibrated 4.3 times per year, also by an external supplier.

Logistics and feasibility of performing tests and reporting results

Clinic staff

The test results were reported to be returned to the DM clinic by paper by 80% of the respondents for the smear microscopy, MODS culture and IGRA. Only 20% of respondents indicated that patients were always told the MODS culture results, 40% of respondents performing the CXR referral and smear microscopy said that patients were always told the results and 60% of respondents for the IGRA test.

All the respondents reported that there was sufficient staff to perform CXR interpretation and IGRA blood collection. Only 50% felt there was enough staff at present to perform the CXR referral and 80% shared that opinion for the TB symptom screen and the sputum collection.

Approximately 3% of patients had to return to the health facility on a different day to get a CXR, as reported by staff referring and interpreting the CXRs.

Laboratory staff

When laboratory technicians were interviewed, all indicated that the results for the CXR, MODS culture and IGRA were returned to the clinic using paper results that were delivered by laboratory or clinic staff. For the smear microscopy, 33% of respondents indicated that the paper results were collected by the patient from the laboratory and taken to the clinic. All of the technicians analysing the IGRA blood felt that there was sufficient staff to perform the test in routine service. Only 50% of respondents felt there was sufficient staff for the CXR and MODS culture, and even less (33%) felt there was sufficient staff for the smear microscopy.

Accessibility

Clinic staff

Both of the clinicians interpreting CXRs in Indonesia indicated that the CXR was routinely available at the health facility and routinely prescribed to patients with DM. Of the five doctors interviewed about the TB symptom screen, sputum collection and CXR referrals, none said the symptom screen or sputum collection was available at the health facility. Eighty percent indicated that the CXR was routinely available, but no one said it was

routinely prescribed to people with TB. The main reason for a test not being prescribed to people with TB was because the test was never part of the diagnosis algorithm (CXR and IGRA each by 67% of respondents).

The nearest facilities to the RSHS in Indonesia where sputum collection and the IGRA test were available were five minutes away walking for the sputum collection in another part of the facility and two kilometres for the IGRA test at another public health facility or a private laboratory.

Clinicians at the Endocrinology clinic at RSHS felt that 100% and 58% of patients at the clinic could not access sputum collection or the IGRA blood test, respectively.

Laboratory staff

When technicians were interviewed, 100% indicated that the CXR, sputum smear and IGRA were routinely available at their laboratory but only 67% felt that the MODS culture test was available. The MODS culture test was reported to be unavailable because it was used in projects only (33%) or because the high workload from other tests meant that MODS culture could not be integrated into the laboratory's routine services (17%). The respondents indicated that the solid culture (83%) or the sputum smear (17%) was performed instead of the MODS culture test. The nearest facility to obtain a MODS culture test was reported to be at least five hours and 15 minutes away by one respondent.

Discussion

Key findings

In this study, we reviewed the operational feasibility of HCWs performing DM tests in people with TB at DOTS clinics and TB tests in people with DM at DM clinics. We found that while DM POC tests performed better according to the domains of the study, neither the RPG nor the HbA_{1c} had a clear advantage. For TB diagnosis, CXR performed the best but was not considered to be appropriate for TB diagnosis.

Summary of findings

Despite the urine dipstick performing well in several domains at T₀ and T₁, HCWs never felt that the test was appropriate for diagnosing DM. The POC RPG test was rated well in six of the seven operational feasibility domains at T₀ but its user friendliness, equipment quality, appropriateness and perceived patient acceptability were lower at T₁, with the POC HbA_{1c} test performing better in the equipment quality and appropriateness domains. In terms of identifying a suitable and operationally feasible POC test for diagnosing DM, since the appropriateness of the POC HbA_{1c} test improved over time, suggesting that on-the-job training for the operation of the machine was better at getting convincing HCWs of their usefulness than the extended training times, this should be considered during implementation. Additional concerns that need to be addressed for the POC HbA_{1c} are poor sample quality, compromised tests, and technically demanding operation.

Finger prick is often perceived as a favourable form of sample collection but it was perceived to be less acceptable to patients with TB in Indonesia and Peru than a blood draw for the laboratory HbA_{1c} test. Therefore, identifying a sample collection method that is less invasive than the finger prick could also greatly improve the uptake of DM testing in patients with TB.

CXR was the most operationally feasible test for TB in Bandung from the perspective of clinic and laboratory staff. While many staff acknowledged that the IGRA test detects latent TB infection and therefore not appropriate for diagnosing active TB, the blood collection and analysis processes were thought to be the most feasible in terms of sample collection, analysis and having sufficient staff available to perform these tasks. Analysis of

the test was also favoured because of the short time required for training and the accessibility at various laboratories, once the testing kit was purchased. These findings highlight the type of test for detecting active TB that could have the best uptake by staff.

Limitations of the operational feasibility study

It was difficult identifying some HCWs and getting permission to interview them, but once they committed to the interviews they were fully engaged in the questionnaires and ensured that the information was useful for improving the potential integration of TB and DM services. It was initially hoped that information from TANDEM's online database, REDCap, would be able to supplement and verify these data (e.g. time to perform tests), but the database did not have the capacity to offer this type of validation.

Performing a second round of questions with HCWs for the DM tests helped us understand how or if some of the issues can be resolved. Unfortunately, questions about the TB tests were only asked at one time point because there was no capacity to interview the HCWs near the start of recruitment of patients with DM.

The variability in the quality of the verbal translations from English to Bahasa by three different TANDEM staff is unknown and could not be controlled. There was not enough data from Romania or South Africa due to the lack of capacity to conduct interviews so those countries were not included in the analysis.

We could not calculate the participation rate of the OF study because a sampling frame was not available and it was therefore impossible to capture all of the staff who participated in bi-directional screening activities.

Implications for research

A more detailed analysis of the feasibility of implementing DM screening tests in settings where patients with TB are being diagnosed and treated is needed. From the perspective of HCWs, the themes identified that require additional research include more focused training for clinicians about hyperglycaemia, diabetes and interpreting results of DM screening and diagnostics tests in patients at various stages of TB infection and disease; and better performing POC machines that require less calibration and maintenance. Studies also need to be performed from the perspective of patients being screened for

concurrent disease. In patients who are already ill, it is important to understand what is acceptable for them in terms of additional tests and therefore additional time engaged with the health care system. Interviews with HCWs identified that the most acceptable form of sample collection for patients did not correlate with the most appropriate and feasible diagnostic tests.

Implications for policy

Separate analysis assessing the cost per accurate diagnosis indicated that screening people with TB for DM is less costly per case accurately diagnosed than screening people with DM for TB (Laurence et al., *forthcoming* – Research Paper 3). The former pathway of DM screening would yield more cases given the higher prevalence of DM than active TB in Indonesia and Peru, but the economic burden on the health system is unknown. As the RCT is ongoing at the time of writing, we cannot derive the full cost of bi-directional screening when treatment is included. Without this comprehensive understanding of the cost-effectiveness of detecting and treating people with TB-DM, we recommend further investigation of the implementation of DM tests within vertical TB DOTS programmes in the short term. Additionally, in the long term, ensure that a collaborative relationship is fostered between TB and chronic disease programmes as their integration progresses. While this study did not assess operational feasibility of stepped diagnostic algorithms, this format was previously found to be the most appropriate approach and needs to be considered when developing policies for the detection of DM in people with TB (Laurence et al., *forthcoming* – Research Paper 3).

The most appropriate and feasible screen for DM in patients with TB was the POC HbA_{1c} test but this should be combined with a diagnostic test, such as the laboratory HbA_{1c} test, which was reported to be more acceptable to patients than the FBG test.

Implications for implementation into routine practice

There were challenges for integrating TB and DM services at both the clinical and administrative levels. This was particularly the case for TB tests in Peru (at the endocrinology clinics and laboratories performing analysis for TB tests), where the

TANDEM RCT was discontinued due to inability to engage stakeholders to perform integrated screening and treatment for concurrent TB-DM.

The urine dipstick was the most operationally feasible of DM screening tests but was categorically identified as inappropriate for diagnosing DM in patients with TB. The POC HbA_{1c} test was identified as having been logistically feasible, accessible and appropriate and therefore could be implemented into routine practice if concerns about the sample collection quality and patient acceptability are addressed in collaboration with the manufacturers.

Conclusion

Using the most operational feasible test improves diagnosis and facilitates better care of people with TB-DM. The POC HbA_{1c} was the most operationally feasible test for identifying TB-DM in Indonesia and Peru, but would require further assessment to maximise its ability to improve the care of people with concurrent disease. The CXR was also overwhelmingly identified as the most operationally feasible test for TB in people with DM but only the smear and culture tests were considered appropriate by the HCWs for diagnosing TB, which is an important consideration for successful implementation of diagnostic tests. Therefore, it is still not clear which TB test is the best option. However, the accessibility, training time and logistical feasibility of the blood collection and analysis of the IGRA test are attributes that need to be considered, along with the performance time, user friendliness and acceptability of the CXR and the appropriateness of the smear and cultures tests, if implementation of TB screening in patients with DM is attempted.

End of Research Paper 4

Chapter 10 Health-related quality of life

The data presented in this chapter are not complete since, at the time of analysis in October 2016, TANDEM patients were still being recruited for the RCT in Indonesia. Recruitment ended in February 2017 but patients are still undergoing treatment and follow-up in the RCT. After the recruitment of patients with TB for DM screening in Indonesia, Peru and Romania, patients with TB and DM were initially randomised into the RCT in Indonesia and Romania. However, as discussed in Chapters 1 and 4, the RCT in Romania was discontinued before any patients reached the six-month mark, leaving the RCT functioning in Indonesia only.

Only 27 of the expected 120 patients with TB-DM in Indonesia have completed the 18 months of the DM management. Therefore, the results below are based on preliminary analysis.

10.1 Introduction

TB and DM both independently impact on the subjective well-being of people suffering from the two diseases and the potential complications from either disease, including pleural effusion, pneumothorax, opportunistic infections (such as HIV), heart and blood vessel disease, or nerve, kidney, eye or foot damage. The treatment regimens that are meant to make patients feel better may also worsen the patient-reported outcomes (PRO) before improving it (Atif et al., 2014). The three main domains that are used to capture the health-related quality of life (HRQoL) of patients are physical, mental and social. The combined impact on HRQoL for patients with concurrent TB and DM is not evident from any published literature.

In addition to the primary health outcome of average change in plasma glucose concentration (%), TANDEM measured the baseline HRQoL of all people enrolled with TB as well as that of people in the RCT with TB-DM at key time points: at time of diagnosis, end of TB treatment and end of DM management follow-up.

There are disease specific and generic instruments for measuring HRQoL. A TB specific tool, DR-12 was identified at the beginning of TANDEM, but it had not been used outside of India and the validation of the tool was not thought to be thorough (Dhingra and Rajpal, 2005). Another tool that has been used to assess the HRQoL of people with TB is the St George's Respiratory Questionnaire (SGRQ), but this is not specific to TB (Ralph et al., 2013). The SGRQ was designed to more broadly assess respiratory diseases and while there have been attempts to validate for TB (Pasipanodya et al., 2007), it has not been widely recognised as a TB-specific health outcome measure (Kastien-Hilka et al., 2016a).

Several generic tools have been used to capture the HRQoL of people with TB or with DM. These include the Medical Outcome Study's 36-item short form health survey (SF-36) (Jaber et al., 2016), variations of that instrument with fewer dimensions (e.g SF-6D or SF-12) (Neumann et al., 2014, Wong et al., 2016) (Louw et al., 2016) or revisions to the original tool (e.g. SF36v2) (Kisaka et al., 2016). The World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire was considered to be unsuitable for this study since it measures global quality of life rather than HRQoL (Huang et al., 2006), despite having been previously used to measure HRQoL in people with TB (Aggarwal et al., 2013).

EuroQol's five-dimension, three-level instrument (EQ-5D-3L) is another commonly used generic instrument for describing and valuing HRQoL (Kruijshaar et al., 2010, Grandy et al., 2014). A more reliable and sensitive version of the EQ-5D tool was developed with five levels instead of the previous three levels. This new tool, the EQ-5D-5L (Appendix Z), is validated and has been used to assess the HRQoL in people with DM and is ongoing for people with TB (Matza et al., 2015, Kastien-Hilka et al., 2016b). In addition to the five dimension questions, the EQ-5D-5L also includes a visual analogue scale (EQ VAS).

Since there is no widely accepted, validated TB specific measure for HRQoL, the EQ-5D-5L, a more sensitive version of the EQ-5D-3L with five-levels, was used in this study (Guo et al., 2009, Diel and Lampenius, 2014, Kastien-Hilka et al., 2016a). In addition, the EQ-5D-5L can be used to calculate quality-adjusted life years, which is needed for cost-effectiveness analysis of the DM intervention. This cost-effectiveness analysis will not be

included in this thesis, but upon completion of the RCT. At baseline, the EQ-5D-5L was compared to the EQ VAS and the Karnofsky performance scale index.

The aims of this study were to describe and compare the HRQoL of people with TB only with people with TB-DM before the start of treatment for TB or DM; and to determine the change in HRQoL over time in people receiving treatment for concurrent TB-DM in two DM management groups (standard care versus enhanced intensive monitoring with education and counselling). This is the first known study to assess the quality of life of people with concurrent TB and DM.

10.2 Methods

10.2.1 Data collection and instruments

The HRQoL experienced by adults (18 years and over) diagnosed with active pulmonary TB and in TB treatment for less than 72 hours at the time of DM screening was measured using EuroQol's EQ-5D-5L, which is a generic, validated, PRO measurement tool (Rotterdam, The Netherlands) (Appendix Z). The baseline HRQoL assessment was administered to 1,972 patients with TB recruited for TANDEM in Indonesia, Peru, and Romania (Table 10-1). A sample size of 2,000 people in the three countries was estimated using the exact mid-P method, based on the combined testing approach having a sensitivity of 90%, with an estimated undiagnosed DM prevalence of 8% and a precision (95%) of +/- 0.15 at each site. In Peru and Romania, the self-complete version for tablets was used and in Indonesia, the self-complete version for a laptop was used.

Table 10-1: Sample sizes for EQ-5D-5L profiles for people with TB and TB-DM at baseline and those included in the randomized controlled trial in Indonesia, Romania and Peru

	TB only	TB-DM	Total recruitment	TB-DM included in RCT	Proportion of TB-DM in RCT
Indonesia	685	177*	862	120	67.8%
Romania	421	88*	509	40	45.5%
Peru	549	52	601	0	NA
Total	1,655	317	1,972	160	

TB-tuberculosis; DM-diabetes mellitus; RCT-randomised controlled trial; NA-not applicable

*A total of 105 people with TB-DM were excluded from the randomised controlled trial in Indonesia and Romania; reasons for exclusion included patient refusal, patient lives too far away, HIV positive, MDR-TB, patient too ill due to severe complications, such as renal failure, and already on TB treatment more than 72 hours

In Indonesia, HRQoL (EQ-5D-5L and EQ VAS) data were collected from patients in the RCT at baseline, six, 12, and 18 months. In Romania, HRQoL was collected at baseline only since the RCT was discontinued after initially enrolling 40 people with TB-DM, but before most of the enrolled patients completed the six months of TB and DM treatment. This was due to discordance between the TANDEM and Romanian DM management protocols and the fact that TB clinicians cannot legally provide DM care. A total of 160 patients with TB-DM were enrolled in the RCT in Indonesia and Romania where they received six months of TB and DM treatment and an additional 12 months of follow-up (Table 10-2). As of October 2016, only 27 patients with TB-DM have completed the RCT and 12 months of follow-up in Indonesia.

Table 10-2: EQ-5D-5L data points for people with TB-DM in Indonesia and Romania

	Indonesia	Romania	Total
Baseline	120	40	160
6 months	84	15	99
12 months	49	NA	49
18 months	27	0	27

NA-not applicable

EQ-5D-5L consists of five generic health questions or dimensions that address patient mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each dimension can be assessed by five possible levels of health status that increase in severity, from “1” representing “no problems”, “2” representing “slight problem”, “3” representing “moderate problems”, “4” representing “severe problems” and “5” representing “extreme problems” or “unable to function”. The EQ VAS, which is a vertical, visual analogue scale (VAS) ranging from 0 (the worst health imaginable) to 100 (the best health imaginable), was also administered to patients. The EQ-5D-5L and EQ VAS instruments were included in TANDEM’s electronic case report form (CRF) and administered to all patients by a health professional. The patient was asked to rate their own current health state on that day and the health professional recorded the response in the electronic CRF. The EQ-5D-5L and EQ VAS took approximately five minutes to administer and were the officially translated versions in Bahasa, Peruvian Spanish and Romanian that have been specifically validated for Indonesia, Peru, and Romania, respectively ((EuroQol, 2016)).

The Karnofsky Performance Scale Index was also included for all TANDEM patients. This is a clinician-assessed tool that classifies patients by their level of functional impairment on an 11-point scale ranging from 0%, denoting death, to 100%, denoting no evidence of disease and no symptoms.

In addition to the demographic information collected at baseline, clinical information was also recorded, including smoking status and history, body weight and height, other current treatment regimens or DM complications (including myocardial infarction, heart failure, nephrology, neuropathy, visual impairment or loss). People with serious co-morbidities, including HIV, Type 1 DM, or cancer, were excluded from the RCT.

All data were securely stored in the centralised REDCap database.

10.2.2 Data analysis

In order to determine the health states associated with DM management in people with TB in Indonesia, Peru and Romania, a single weighted index (utility) value was obtained by performing a crosswalk to existing general population value sets. Since there were no population based preference values for any of the TANDEM countries, the value sets for Thailand, the UK and Spain and were used for Indonesia, Peru and Romania, respectively. The range of the index values is -0.452 to 1.000 for Thailand, -0.594 to 1.000 for the UK, and -0.654 to 1.000 for Spain; with 1 representing full health and 0 representing death, and a negative value representing where respondents valued their health status to be worse than death (Lamers, 2007).

The Thai value sets was used for Indonesia as it was considered to be the most culturally similar of the value sets available. Similarly, Spain was used for Romania because it was more culturally similar to Romania than the UK as well as having a 2014 GDP per capita that was close to that of Romania. Despite the UK being culturally very different from Peru, the UK value set has been shown to be a reasonable option for countries without their own value set, particularly in multinational studies, because of its large sample size (Oppong et al., 2013). To assess the degree of uncertainty of the chosen value sets, sensitivity analyses were performed by using the UK value set for Indonesia and Romania and the Thai value set for Peru.

The value sets are based on a survey of the health preferences of the general population of that country using the EQ-5D-3L survey (Kind et al., 1998). The five-level value set for the EQ-5D was mapped or “cross-walked” to the already established three-level value set (van Hout et al., 2012).

People with TB only versus people with TB-DM

At baseline, the frequency and proportion of the health state in each dimension were assessed for people with TB only and for those with TB-DM in Indonesia, Peru and Romania. Pearson’s chi-squared test was used to determine if there was a difference in

HRQoL between the two groups of patients. Where there were five or less responses within a dimension, the Fisher's exact test was used. The 2-sample t-test was used to assess the difference in the mean EQ VAS scores between people with TB only and those with TB-DM.

The health status levels were collapsed from five to three levels (no problem, slight/moderate problems and severe/extreme problems) and to two levels (no problem and any problems). The HRQoL of the two groups was again compared using Pearson's chi-squared test or Fisher's exact test for small cell values.

Simple and multiple linear regression analysis was performed to determine whether there was a difference in the HRQoL utility scores between people with TB only and people with TB-DM when considering the following confounders: sex, age, current smoking status and socio-economic status. A multiple linear regression model was built including all variables in the final model. Since both age and sex influence utility scores and disease status (TB versus TB-DM), interactions between age and sex were assessed. The regression coefficients (β) and p -values from each linear regression model were reported.

People with TB-DM in the standard care and intensive monitoring arms of the RCT

The χ^2 test was used to determine differences in sex, educational level, socio-economic status, employment status, smoking status and DM complications between patients in the standard care and intensive monitoring arms of the RCT at baseline. The Student's t -test was used to investigate the difference in mean values of age between the two RCT arms.

For people with TB-DM in the RCT, the proportions with respect to the patient responses for the five EQ-5D-5L dimensions and the mean EQ VAS value were assessed. The difference in the patient responses for each dimension and at each time point between the two RCT arms was assessed using the Fisher's exact test for the EQ-5D-5L and the two-sample t -test for the EQ VAS.

The Wilcoxon rank sum test then compared the mean ranks of the EQ-5D-5L utility scores at each time point for people in the standard care and intensive monitoring arms of the RCT. The Wilcoxon rank sum test was performed instead of the Student's t-test for the utility scores because they were not normally distributed.

Subsequently, the change over time of the EQ-5D-5L utility scores of people in the two arms of the RCT was assessed using a random effects longitudinal regression. This was assessed at baseline and six months (the end of TB treatment); there were insufficient data points at the 12- and 18-month follow-up periods (Table 10-2) so they were not included in the analysis, but the random effects model will be run again at the end of the study to include all patients and the HRQoL measures at all time points. The model controlled for individual patient characteristics at baseline, including sex, age, smoking frequency, presence of any DM complications and socio-economic status.

Pair-wise correlation between the EQ-5D-5L utility score, EQ VAS, the Karnofsky Index and age was assessed for all patients at baseline. Age and the Karnofsky Index were only captured at baseline so only the correlation between the EQ-5D-5L utility scores and EQ VAS was assessed at six months.

The sample size that was used to measure quality of life is not based on the expected outcome of the EQ-5D-5L, but on the primary outcome of the TANDEM WP2, which is an expected HbA_{1c} difference of 1% between the two intervention arms at six months. Any participant with a missing EQ-5D-5L value was dropped from the analysis. Potential confounders were sex, age, whether the person was a current or previous smoker, socio-economic status (indices derived using principal component analysis – see Chapter 6) and any DM complications.

10.3 Results

10.3.1 Patient characteristics

People with TB only or TB-DM at baseline

During recruitment 862, 601 and 509 people with TB were enrolled into TANDEM in Indonesia, Peru and Romania, respectively, of which 21% (95% CI: 18.0 to 23.3), 9% (95% CI: 6.6 to 11.2) and 17% (95% CI: 14.2 to 20.8) also had DM (Table 10-3).

The mean age at enrolment of patients in Indonesia was 41 years (SD=14.3), 35 years (SD=15.0) in Peru and 44 years (SD=16.0) in Romania. The majority of patients were male (57%, 58% and 70% in Indonesia, Peru and Romania, respectively) and had completed at least secondary school (47%, 60% and 70%, respectively). The ethnic composition in the Indonesian cohort was 87% Sunda and 8% Jawa. In Peru and Romania, the majority (97%) of patients were one ethnicity; Mestizo in Peru and Romanian in Romania.

Participant completion of the baseline EQ-5D-5L questionnaire was 99% in Indonesia, 95% in Peru and 97% in Romania, of which 8%, 8% and 5% had a perfect health state (11111 profile), respectively. Participants in Romania had the highest mean EQ VAS and Karnofsky scores of 81.4 (SD=10.5) and 86.0 (SD=8.3), both out of a total of 100. Both the EQ VAS and Karnofsky scores were lowest in Indonesia at 69.3 (SD=16.7) and 78.6 (SD=13.8), respectively. In Peru, the mean EQ VAS score was 77.3 (SD=37.3) and the mean Karnofsky score was 85.4 (SD=9.33).

Table 10-3: Baseline characteristics of participants with TB and TB-DM in Indonesia, Peru and Romania

Characteristic	Categories	Indonesia n=862		Peru n= 601		Romania n=509	
		n	%	n	%	n	%
Sex	Female	374	43.4	252	41.9	146	28.7
	Male	488	56.6	348	57.9	356	69.9
Age, years	< 40	430	49.9	426	70.9	207	40.7
	≥ 40	432	50.1	177	29.5	297	58.3
Married	No	229	26.6	419	69.7	187	36.7
	Yes	633	73.4	181	30.1	315	61.9
Socio-economic status	Poorest	225	26.1	137	22.8	176	34.6
	Poor	213	24.7	97	16.1	122	24
	Middle income	206	23.9	83	13.8	100	19.6
	Upper middle income	145	16.8	76	12.6	67	13.2
	Richest	66	7.7	65	10.8	26	5.1
	<i>Missing</i>	7	0.8	143	23.8	18	3.5
Educational Level	Up to primary school	299	34.7	99	16.5	48	9.4
	Up to secondary school	162	18.8	142	23.6	98	19.3
	Above secondary school	401	46.5	358	59.6	354	69.5
Employment status	Paid employment	475	55.1	432	71.9	198	38.9
	Unpaid employment	5	0.6	2	0.3	27	5.3
	Looking after home/family	253	29.4	78	13	126	24.8
	Unemployed - seeking work	61	7.1	23	3.8	18	3.5
	Unemployed - unable to work	26	3	10	1.7	0	0
	Student	27	3.1	50	8.3	22	4.3
	Retired	15	1.7	5	0.8	102	20
	Unknown	0	0	1	0.2	16	3.1
Any DM complications ^a	No	788	91.4	575	95.7	490	96.3
	Yes	74	8.6	26	4.3	19	3.7
Disease status	TB only	685	79.5	549	91.3	421	82.7
	TB-DM	177	20.5	52	8.7	88	17.3
Health status	EQ-5D state 11111, n (%)	68	7.9	44	7.3	24	4.7
	EQ-VAS score, mean (SD)	69.3	16.7	77.3	37.3	81.4	10.5
Karnofsky score	Score, mean (SD)	78.6	13.78	85.4	9.33	85.97	8.34

DM-diabetes mellitus; TB-tuberculosis; Q-quintile; VAS-visual analogue scale; SD-standard deviation;

^aDM complications include cataracts, impaired vision, non-healing wounds, angina or heart failure

People with TB-DM receiving standard or intensive DM management in the RCT

In Indonesia, 120 people with TB-DM were randomised to the trial; 60 to the standard care arm and 60 to the intensive monitoring arm. There were 20 people randomised to each arm of the RCT in Romania. Again, the majority were male in both countries and in both RCT arms (see Table 10-4). The mean age in the standard care arm was greater (56.6 years) in Romania than in Indonesia (52.1 years). Approximately 45% of participants in both arms in Indonesia had obtained no more than primary school education while the majority of participants in Romania (85% of intensive monitoring and 70% of standard care) had an education level greater than secondary school.

Approximately a third of trial participants in Indonesia had experienced at least one DM complication at the time of enrolment (intensive arm: 38% and standard arm: 33%), while in Romania 45% of the participants in the intensive monitoring arm and 25% in the standard care arm had at least one DM complication. A perfect health state was reported by 10% of intensive monitoring and 8% of standard care participants in Indonesia, but by none of the intensive monitoring and one (5%) of the standard care participants in Romania. At enrolment, the mean EQ VAS scores were higher in the intensive monitoring arms (72 and 83) than in the standard care arms (68 and 79) for Indonesia and Romania, respectively. However, the mean Karnofsky index scores were more consistent between RCT arms in both Indonesia (approximately 81) and Romania (approximately 87).

As of 22nd October 2016, approximately 70% of trial participants in Indonesia and 50% in Romania had completed the 6-month visit, but one participant in Indonesia did not complete the EQ-5D-5L questionnaire and five did not complete it in Romania (Table 10-2 and Table 10-3). At the 12-month visit, 7.5% (4 out of 53) participants did not complete the questionnaire in Indonesia and 100% have not yet completed it in Romania.

Table 10-4: Characteristics of people in RCT with TB-DM in Indonesia and Romania

Characteristic	Categories	Indonesia		Indonesia		Romania		Romania	
		Intensive monitoring	Standard care	Intensive monitoring	Standard care	Intensive monitoring	Standard care	Intensive monitoring	Standard care
		n= 60	n= 60	n= 60	n= 60	n= 20	n= 20	n= 20	n= 20
		n %	n %	n %	n %	n %	n %	n %	n %
Sex	Female	28	46.7	27	45.0	5	25.0	6	30.0
	Male	32	53.3	33	55.0	15	75.0	14	70.0
Age, years	< 40	5	8.3	3	5.0	1	5.0	3	15.0
	≥ 40	55	91.7	57	95.0	19	95.0	17	85.0
Married	No	5	8.3	8	13.3	1	5.0	2	10.0
	Yes	55	91.7	52	86.7	19	95.0	18	90.0
Socio-economic status	Poorest	12	20.0	15	25.0	4	20.0	1	5.0
	Poor	13	21.7	13	21.7	7	35.0	4	20.0
	Middle income	14	23.3	14	23.3	6	30.0	7	35.0
	Upper middle income	13	21.7	13	21.7	2	10.0	6	30.0
	Richest	7	11.7	5	8.3	1	5.0	1	5.0
Educational level	Primary school and below	28	46.7	27	45.0	1	5.0	1	5.0
	Above primary to secondary	11	18.3	9	15.0	2	10.0	5	25.0
	Above secondary school	21	35.0	24	40.0	17	85.0	14	70.0
Employment status	Paid employment	25	41.7	31	51.7	5	25.0	4	20.0
	Unpaid employment	0	0.0	1	1.7	0	0.0	0	0.0
	Looking after home/family	28	46.7	23	38.3	7	35.0	6	30.0
	Unemployed - seeking work	3	5.0	4	6.7	0	0.0	0	0.0
	Unemployed - unable to work	1	1.7	0	0.0	0	0.0	0	0.0
	Retired	3	5.0	1	1.7	8	40.0	9	45.0
	Unknown	0	0.0	0	0.0	0	0.0	1	5.0
Any DM complications	No	37	61.7	40	66.7	11	55.0	15	75.0
	Yes	23	38.3	20	33.3	9	45.0	5	25.0
Health status at baseline	EQ-5D state 11111, n (%)	6	10.0	4	6.7	0	0.0	1	5.0
	EQ-VAS score, mean (SD)	72.1	16.7	68.1	15.3	83.3	6.7	79.3	6.9
Karnofsky score	Score, mean (SD)	81.7	9.8	81.2	9.0	86.5	4.9	86.5	5.9
Visit completed	Baseline	60	100	60	100	20	100	20	100
	6 months	45	75.0	40	66.7	12	60.0	8	40.0
	12 months	26	43.3	27	45.0	1	5.0	2	10.0
	18 months	16	26.7	15	25.0	0	0.0	0	0.0

DM-diabetes mellitus; TB-tuberculosis; Q-quintile; VAS-visual analogue scale; SD-standard deviation;
^aDM complications include cataracts, impaired vision, non-healing wounds, angina or heart failure

10.3.2 Reported patient health profiles

People with TB only or TB-DM at baseline

There was no statistically significant difference between TB only and TB-DM patient responses at the time of participant enrolment for the dimensions of mobility, performing usual activities and experiencing feelings of anxiety or depression (Table 10-5). In Indonesia more people with TB-DM reported some degree of problem with self-care compared to people with TB only. However, still in Indonesia, more people with TB only reported pain or discomfort compared to those with TB-DM (p -value=0.015), with seven (1%) people indicating that they were unable to function. The opposite scenario occurred in Romania where 21% of people with TB only reported no problems with pain or discomfort while 8% of people with TB-DM reported no problems in this dimension (p -value=0.004).

People with TB-DM reported a lower mean EQ VAS score of 79.3 than people with TB only (81.9) in Romania; while this difference was statistically significant (p -value=0.042) it may not be clinically important. There was a ten-point difference in means in Peru, which may be manifest clinically but this difference was not statistically significant.

Table 10-5: Participant responses to EQ-5D-5L and EQ VAS (health profile) at baseline in Indonesia, Peru and Romania

BASELINE	Indonesia				Peru				Romania						
	TB only (n=685)		TB-DM (n=177)		<i>p</i> -value*	TB only (n=549)		TB-DM (n=52)		<i>p</i> -value*	TB only (n=421)		TB-DM (n=88)		<i>p</i> -value*
	n	%	n	%		n	%	n	%		n	%	n	%	
Mobility															
No problem	421	61.5	97	54.8		415	75.6	35	67.3		341	81.0	63	71.6	
Slight problem	158	23.1	55	31.1		118	21.5	12	23.1		48	11.4	17	19.3	
Moderate problems	65	9.5	18	10.2	0.177	13	2.4	4	7.7	0.053	21	5.0	5	5.7	
Severe problems	27	3.9	6	3.4		1	0.2	1	1.9		3	0.7	3	3.4	
Unable to function	14	2.0	1	0.6		1	0.2	0	0.0		2	0.5	0	0.0	
Missing	0	0.0	0	0.0		1	0.2	0	0.0		6	1.4	0	0.0	
Self-care															
No problem	571	83.4	135	76.3		457	83.2	38	73.1		381	90.5	76	86.4	
Slight problem	54	7.9	31	17.5		84	15.3	11	21.2		27	6.4	8	9.1	
Moderate problems	28	4.1	7	4.0	0.006	5	0.9	2	3.9	0.120	4	1.0	2	2.3	
Severe problems	12	1.8	1	0.6		1	0.2	0	0.0		1	0.2	1	1.1	
Unable to function	18	2.6	3	1.7		0	0.0	0	0.0		2	0.5	0	0.0	
Missing	2	0.3	0	0.0		2	0.4	1	1.9		6	1.4	1	1.1	
Usual activities															
No problem	305	44.5	72	40.7		380	69.2	31	59.6		245	58.2	43	48.9	
Slight problem	179	26.1	53	29.9		158	28.8	19	36.5		127	30.2	35	39.8	
Moderate problems	79	11.5	27	15.3	0.324	8	1.5	2	3.9	0.246	38	9.0	8	9.1	
Severe problems	36	5.3	7	4.0		2	0.4	0	0.0		2	0.5	2	2.3	
Unable to function	86	12.6	16	9.0		0	0.0	0	0.0		2	0.5	0	0.0	
Missing	0	0.0	2	1.1		1	0.2	0	0.0		7	1.7	0	0.0	
Pain/discomfort															
No problem	141	20.6	57	32.2		122	22.2	11	21.2		87	20.7	7	8.0	
Slight problem	301	43.9	64	36.2		323	58.8	28	53.9		285	67.7	65	73.9	
Moderate problems	156	22.8	34	19.2	0.015	64	11.7	9	17.3	0.472	37	8.8	15	17.1	
Severe problems	79	11.5	22	12.4		13	2.4	2	3.9		3	0.7	1	1.1	
Unable to function	7	1.0	0	0.0		0	0.0	0	0.0		0	0.0	0	0.0	
Missing	1	0.2	0	0.0		27	4.9	2	3.9		9	2.1	0	0.0	

BASELINE	Indonesia				<i>p</i> -value*	Peru				<i>p</i> -value*	Romania				
	TB only (n=685)		TB-DM (n=177)			TB only (n=549)		TB-DM (n=52)			TB only (n=421)		TB-DM (n=88)		<i>p</i> -value*
	n	%	n	%		n	%	n	%		n	%	n	%	
Anxiety/depression															
No problem	236	34.5	72	40.7	0.538	133	24.2	6	11.5	0.083	91	21.6	12	13.6	0.466
Slight problem	197	28.8	43	24.3		342	62.3	36	69.2		296	70.3	69	78.4	
Moderate problems	149	21.8	34	19.2		64	11.7	8	15.4		22	5.2	5	5.7	
Severe problems	89	13.0	25	14.1		9	1.6	2	3.9		1	0.2	0		
Unable to function	12	1.8	3	1.7		0	0.0	0	0.0		1	0.2	0		
Missing	2	0.3	0	0.0		1	0.2	0	0.0		10	2.4	2	2.3	
EQVAS score															
Score (mean, SD)	69.42	16.73	68.62	16.4	0.571	78.16	38.57	68.27	17.9	0.068	81.86	10.8	79.34	9.0	0.042
Missing (n, %)	4	0.6	0	0.0		1	0.2	0	0.0		7	1.7	0	0.0	

*Fisher's exact test was used due to small cell values; missing values were not included in analysis

A *p*-value<0.05 was considered to be significant

People with TB-DM receiving standard or intensive DM management

The difference in responses between people with TB-DM in the standard care and intensive monitoring arms of the RCT at different time points was assessed for Indonesia (baseline, six, 12 and 18 months) and Romania (baseline and six months), the two countries where the RCT occurred (Table 10-6 and Table 10-7).

There was no difference in the participant responses to the EQ-5D-5L between the people in the standard care and those in the intensive monitoring arms at any time point in either country (Table 10-6 and Table 10-7).

In Indonesia the EQ VAS score for people with TB-DM is improving over time, but the only significant difference in the mean score between the two RCT arms was at 18 months (p -value=0.021), where counter-intuitively the mean EQ VAS in the intensive monitoring arm (mean=71, SD=22.3) is 16 points less than that of the standard care arm (mean=87, SD=11.0). This may be driven by the domains of usual activities, pain/discomfort and anxiety/depression.

Table 10-6: Participant responses to EQ-5D-5L and EQ VAS (health profile) over four time points in Indonesia

	Baseline				6 months				12 months				18 months			
	Standard care (n=60)		Intensive monitoring (n=60)		Standard care (n=40)		Intensive monitoring (n=44)		Standard care (n=25)		Intensive monitoring (n=24)		Standard care (n=14)		Intensive monitoring (n=13)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Mobility																
No problem	33	55.0	38	63.3	30	50	39	65.0	22	36.7	19	31.7	13	21.7	11	18.3
Slight problem	22	36.7	16	26.7	10	17	5	8.3	3	5.0	4	6.7	1	1.7	1	1.7
Moderate problems	3	5.0	5	8.3	0	0	0	0.0	0	0.0	1	1.7	0	0.0	0	0.0
Severe problems	2	3.3	1	1.7	0	0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.7
Unable to function	0	0.0	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing					20	33	16	26.7	35	58.3	36	60.0	46	76.7	47	78.3
Self-care																
No problem	45	75.0	52	86.7	37	62	44	73.3	24	40.0	24	40.0	13	21.7	11	18.3
Slight problem	13	21.7	8	13.3	2	3	0	0.0	1	1.7	0	0.0	1	1.7	0	0.0
Moderate problems	2	3.3	0	0.0	1	2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Severe problems	0	0.0	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.7
Unable to function	0	0.0	0	0.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Missing					20	33	16	26.7	35	58.3	36	60.0	46	76.7	48	80.0
Usual activities																
No problem	24	40.0	28	46.7	34	57	39	65.0	25	41.7	22	36.7	13	21.7	9	15.0
Slight problem	19	31.7	18	30.0	4	7	5	8.3	0	0.0	2	3.3	1	1.7	3	5.0
Moderate problems	13	21.7	9	15.0	2	3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Severe problems	2	3.3	1	1.7	0	0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Unable to function	2	3.3	3	5.0	0	0	0	0.0	0	0.0	0	0.0	0	0.0	1	1.7
Missing			1	1.7	20	33	16	26.7	35	58.3	36	60.0	46	76.7	47	78.3
	Baseline				6 months				12 months				18 months			

	Standard care (n=60)		Intensive monitoring (n=60)		p-value*	Standard care (n=40)		Intensive monitoring (n=44)		p-value*	Standard care (n=25)		Intensive monitoring (n=24)		p-value*	Standard care (n=14)		Intensive monitoring (n=13)		p-value*
	n	%	n	%		n	%	n	%		n	%	n	%		n	%	n	%	
Pain/discomfort																				
No problem	15	25.0	25	41.7		25	42	28	46.7		21	35.0	17	28.3		11	18.3	9	15.0	
Slight problem	26	43.3	23	38.3		11	18	12	20.0		4	6.7	5	8.3		3	5.0	1	1.7	
Moderate problems	12	20.0	7	11.7	0.229	3	5	4	6.7	0.970	0	0.0	2	3.3	0.355	0	0.0	3	5.0	0.172
Severe problems	7	11.7	5	8.3		1	2	0	0.0		0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0	0	0.0		0	0.0	0	0.0		0	0.0	0	0.0	
Missing						20	33	16	26.7		35	58.3	36	60.0		46	76.7	47	78.3	
Anxiety/depression																				
No problem	24	40.0	29	48.3		29	48	31	51.7		20	33.3	18	30.0		13	21.7	10	16.7	
Slight problem	16	26.7	11	18.3		7	12	10	16.7		4	6.7	4	6.7		0	0.0	1	1.7	
Moderate problems	10	16.7	12	20.0	0.781	3	5	3	5.0	0.867	0	0.0	1	1.7	0.847	1	1.7	0	0.0	0.212
Severe problems	9	15.0	7	11.7		1	2	0	0.0		0	0.0	0	0.0		0	0.0	2	3.3	
Unable to function	1	1.7	1	1.7		0	0	0	0.0		0	0.0	0	0.0		0	0.0	0	0.0	
Missing						20	33	16	26.7		36	60.0	37	61.7		46	76.7	47	78.3	
EQ VAS score																				
Score (mean, SD)	68	15	72	16.7	0.166	85	11	83.6	13.2	0.737	89	8.2	88	10.0	0.847	87	11	71	22.3	0.021
Missing (n, %)	0	0	0	0.0		0	0	0	0.0		0	0	0	0.0		0	0	0	0.0	

VAS-visual analogue scale

*p-values are from Fisher's exact test for EQ-5D-5L responses and 2 sample t-test for EQ VAS

^ap-value is from 1-sided Fisher's exact test

Table 10-7: Participant responses to EQ-5D-5L and EQ VAS (health profile) over two time points in Romania

	Baseline				<i>p-value*</i>	6 months				<i>p-value*</i>
	Standard care (n=20)		Intensive monitoring (n=20)			Standard care (n=6)		Intensive monitoring (n=9)		
	n	%	n	%		n	%	n	%	
Mobility										
No problem	13	65.0	14	70.0	0.731	5	25.0	7	35.0	0.659
Slight problem	7	36.0	5	25.0		1	5.0	2	10.0	
Moderate problems	0	0.0	1	5.0		0	0.0	0	0.0	
Severe problems	0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0.0	0	0.0	
Missing	0	0.0	0	0.0		14	70.0	11	55.0	
Self-care										
No problem	18	90.0	16	80.0	0.475	6	30.0	8	40.0	0.600
Slight problem	2	10.0	3	15.0		0	0.0	1	5.0	
Moderate problems	0	0.0	0	0.0		0	0.0	0	0.0	
Severe problems	0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0.0	0	0.0	
Missing			1	5.0		14	70.0	11	55.0	
Usual activities										
No problem	10	50.0	11	55.0	1.000	6	30.0	7	35.0	0.343
Slight problem	9	45.0	9	45.0		0	0.0	2	10.0	
Moderate problems	1	5.0	0	0.0		0	0.0	0	0.0	
Severe problems	0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0.0	0	0.0	
Missing						14	70.0	11	55.0	
Pain/discomfort										
No problem	3	15.0	4	20.0	0.533	2	10.0	4	20.0	0.545
Slight problem	15	75.0	16	80.0		4	20.0	5	25.0	
Moderate problems	2	10.0	0	0.0		0	0.0	0	0.0	
Severe problems	0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0.0	0	0.0	
Missing						14	70.0	11	55.0	
Anxiety/depression										
No problem	4	20.0	4	20.0	1.000	3	15.0	5	25.0	1.000
Slight problem	14	70.0	15	75.0		3	15.0	3	15.0	
Moderate problems	1	5.0	1	5.0		0	0.0	1	5.0	
Severe problems	0	0.0	0	0.0		0	0.0	0	0.0	
Unable to function	0	0.0	0	0.0		0	0.0	0	0.0	
Missing	1	5.0				14	70.0	11	55.0	
EQ VAS score										
Score (mean, SD)	79	6.9	83	6.7	0.128	90	3.16	88.3	7.1	0.128
Missing (n, %)	0	0	0	0.0		0	0	0	0.0	

VAS-visual analogue scale

**p*-values are from Fisher's exact test for EQ-5D-5L responses and 2 sample t-test for EQ VAS

10.3.1 Association between health utilities and disease status at baseline

People with TB only or TB-DM at baseline

The unadjusted linear regression showed no significant associations for Indonesia (Table 10-8) but that the health utility was better in people with TB only than in people with TB-DM in Peru ($\beta=-0.04$, p -value=0.071) (Table 10-9) and Romania ($\beta=-0.04$, p -value=0.026) (Table 10-10). This remained the case even after exploring interactions between sex and age, particularly in males (Table 10-11). There was no significant relationship between HRQoL and disease status in any country after adjustment for the potential confounders of sex, age, smoking frequency, and socio-economic quintile.

There was a significant association between decreasing health utility and older participants (increasing age) in Indonesia ($\beta=-0.04$, p -value=0.013) (Table 10-8). Evidence of the association became stronger after adjusting for confounders ($\beta=-0.05$, p -value=0.003). There was very strong evidence of an age association for both Peru ($\beta=0.07$, p -value<0.0001) and Romania ($\beta=0.08$, p -value<0.0001), but the direction of the association was opposite that of Indonesia, such that health utility improved for participants 40 and over. After adjusting for confounders the direction of the association changed for both countries (Peru: $\beta=-0.07$, p -value<0.0001; Romania: $\beta=-0.07$, p -value<0.0001) and followed the pattern seen in Indonesia where health utility worsened for people 40 and over.

There was no significant relationship between health utility and sex for any of the countries. This remained unchanged when confounders were adjusted for and when alternative value sets were used to assess the health utility (sensitivity analysis).

There was a stronger association between 'less than daily' smoking and a better health utility in Indonesia ($\beta=0.15$, p -value=0.001) than in Romania ($\beta=0.05$, p -value=0.064) compared to not smoking. In Indonesia, HRQoL is also reported as better in daily smokers ($\beta=0.07$, p -value=0.006) than in non-smokers, but with a weaker association than 'less than daily' smokers. Adjusting for confounders does not change the strength of the

associations seen with frequency of smoking. There was no association between health utility and smoking in Peru.

In Indonesia only, the health utility improved with each wealth quintile increase, but there was no association with socio-economic status in Peru or Romania, even when confounders were adjusted for or when alternative value sets were used.

Table 10-8: Association between health utility and disease status (linear regression - unadjusted and adjusted), Indonesia

Characteristic	Categories	TB only		TB-DM		Unadjusted			Adjusted			
		N	n %	n %	Regression coefficient	(95% CI)		p-value*	RE co-efficient	(95% CI)		p-value**
Overall		862	685	177								
Sex	Female	374	290 42.3	84 47.5	Reference	---	---	---	Reference	---	---	---
	Male	488	395 57.7	93 52.5	-0.008	-0.040	0.024	0.629	-0.026	-0.059	0.007	0.118
Age, years	< 40	430	412 60.1	18 10.2	Reference	---	---	---	Reference	---	---	---
	≥ 40	432	273 39.9	159 89.8	-0.040	-0.072	-0.008	0.013	-0.053	-0.087	-0.019	0.003
Smoking frequency	Not at all	741	586 85.5	155 87.6	Reference	---	---	---	Reference	---	---	---
	Less than daily	31	24 3.5	7 4.0	0.147	0.060	0.234	0.001	0.172	0.085	0.258	<0.0001
	Daily	90	75 10.9	15 8.5	0.073	0.021	0.124	0.006	0.093	0.040	0.146	0.001
Socio-economic status	Poorest	225	186 27.2	39 22.0	Reference	---	---	---	Reference	---	---	---
	Poor	213	172 25.1	41 23.2	0.063	0.019	0.107	0.005	0.060	0.017	0.104	0.007
	Middle income	206	163 23.8	43 24.3	0.08239	0.038	0.127	<0.0001	0.080	0.036	0.124	<0.0001
	Upper middle income	145	110 16.1	35 19.8	0.085	0.036	0.134	0.001	0.090	0.041	0.138	<0.0001
	Richest	66	48 7.0	18 10.2	0.147	0.082	0.211	<0.0001	0.166	0.102	0.230	<0.0001
Disease status	TB only	685	685 100	0 0.0	Reference	---	---	---	Reference	---	---	---
	TB-DM	177	0 0	177 100.0	0.007	-0.033	0.046	0.732	0.025	-0.017	0.067	0.248

TB-tuberculosis; DM-diabetes mellitus; RE-random effects

*p-values are estimated by simple linear regression

**p-values are estimated by multiple linear regression

Analysis is based on the Thailand value set

Table 10-9: Association between health utility and disease status (linear regression - unadjusted and adjusted), Peru

Characteristic	Categories	TB only		TB-DM		Regression coefficient	Unadjusted			RE co-efficient	Adjusted		
		N	n %	n %			(95% CI)	p-value*	(95% CI)		p-value**		
Overall		601	549	52									
Sex	Female	252	225 41	27 51.9		Reference	---	---	---	Reference	---	---	---
	Male	348	323 58.8	25 48.1		0.004	-0.017	0.026	0.695	0.014	-0.013	0.041	0.306
Age, years	< 40	423	414 75.4	9 17.3		Reference	---	---	---	Reference	---	---	---
	≥ 40	177	134 24.4	43 82.7		0.065	-0.087	-0.042	<0.0001	-0.071	-0.101	-0.041	<0.0001
Smoking frequency	Not at all	545	493 89.8	52 100.0		Reference	---	---	---	Reference	---	---	---
	Less than daily	51	51 9.3	0 0.0		-0.029	-0.067	0.008	0.124	-0.041	-0.086	0.005	0.080
	Daily	4	4 0.7	0 0.0		0.058	-0.070	0.186	0.376	0.055	-0.097	0.207	0.479
Socio-economic status	Poorest	137	128 23.3	9 17.3		Reference	---	---	---	Reference	---	---	---
	Poor	97	90 16.4	7 13.5		-0.013	-0.049	0.024	0.500	-0.005	-0.041	0.031	0.783
	Middle income	83	70 12.8	13 25.0		-0.00577	-0.045	0.033	0.771	0.015	-0.024	0.053	0.460
	Upper middle income	76	71 12.9	5 9.6		-0.017	-0.058	0.023	0.402	-0.001	-0.041	0.039	0.948
	Richest	65	57 10.4	8 15.4		0.008	-0.033	0.050	0.699	0.013	-0.028	0.053	0.538
Disease status	TB only	549	549 100	0 0.0		Reference	---	---	---	Reference	---	---	---
	TB-DM	52	0 0	52 100.0		-0.035	-0.073	0.003	0.071	-0.001	-0.049	0.047	0.961

TB-tuberculosis; DM-diabetes mellitus; RE-random effects

*p-values are estimated by simple linear regression

**p-values are estimated by multiple linear regression

Analysis is based on the UK value set

Table 10-10: Association between health utility and disease status (linear regression - unadjusted and adjusted), Romania

Characteristic	Categories	TB only		TB-DM		Unadjusted			Adjusted					
		N	n	%	n	%	Regression coefficient	(95% CI)	p-value*	RE co-efficient	(95% CI)	p-value**		
Overall		509	421		88									
Sex	Female	146	128	30.4	18	20.5	Reference	---	---	---	Reference	---	---	---
	Male	356	286	67.9	70	79.5	0.022	-0.050	0.005	0.111	-0.010	-0.039	0.018	0.486
Age, years	< 40	207	194	46.1	13	14.8	Reference	---	---	---	Reference	---	---	---
	≥ 40	297	222	52.7	75	85.2	0.075	-0.099	-0.050	<0.0001	-0.069	-0.095	-0.042	<0.0001
Smoking frequency	Not at all	319	257	61.0	62	70.5	Reference	---	---	---	Reference	---	---	---
	Less than daily	29	22	5.2	7	8.0	0.051	-0.003	0.104	0.064	0.059	0.005	0.113	0.031
	Daily	155	136	32.3	19	21.6	0.006	-0.021	0.034	0.643	0.014	-0.014	0.042	0.341
Socio-economic status	Poorest	176	146	34.7	30	34.1	Reference	---	---	---	Reference	---	---	---
	Poor	122	99	23.5	23	26.1	0.007	-0.026	0.040	0.666	0.008	-0.024	0.040	0.614
	Middle income	100	80	19.0	20	22.7	0.02534	-0.010	0.060	0.155	0.016	-0.019	0.050	0.374
	Upper middle income	67	61	14.5	6	6.8	0.019	-0.021	0.060	0.349	0.006	-0.034	0.045	0.782
	Richest	26	22	5.2	4	4.5	0.045	-0.014	0.104	0.134	0.024	-0.034	0.083	0.418
Disease status	TB only	421	421	100	0	0.0	Reference	---	---	---	Reference	---	---	---
	TB-DM	88	0	0	88	100.0	-0.037	-0.070	-0.004	0.026	-0.009	-0.043	0.026	0.621

TB-tuberculosis; DM-diabetes mellitus; RE-random effects

*p-values are estimated by simple linear regression

**p-values are estimated by multiple linear regression

Analysis is based on the Spain value set

For the stratified regression to investigate the interaction between age and sex (Table 10-11), there was evidence in Indonesia that HRQoL is better in men with TB-DM than in men with TB only and the regression shows that HRQoL is worse in men 40 and over ($\beta=0.05$, p -value=0.003) than in men under 40 years of age (<40 years old: $\beta=0.09$, p -value=0.008). The pattern was similar in Peru (<40 years old: $\beta=0.08$, p -value=0.02; ≥ 40 years old: $\beta=0.06$, p -value=0.002), but the evidence was weaker in Romania (<40 years old: $\beta=0.07$, p -value=0.069; ≥ 40 years old: $\beta=0.07$, p -value=0.001).

There was no association between HRQoL and disease status in women in either age group.

Table 10-11: Stratified linear regression (age and sex interaction) in people with TB or TB-DM in Indonesia, Peru and Romania

Category	Group 1: Under 40 females (n=448)				Group 2: Under 40 males (n=608)				Group 3: 40 and over females (n=450)				Group 4: 40 and over males (n=745)			
	Regression coefficient*	(95% CI)		p-value**	Regression coefficient*	(95% CI)		p-value**	Regression coefficient*	(95% CI)		p-value**	Regression coefficient*	(95% CI)		p-value**
Indonesia (using Thailand value set)																
TB	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---
TB-DM	0.007	-0.089	0.103	0.890	0.093	0.025	0.162	0.008	0.015	-0.027	0.057	0.482	0.053	0.018	0.087	0.003
Peru (using UK value set)																
TB	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---
TB-DM	-0.001	-0.102	0.100	0.984	0.084	0.013	0.156	0.021	0.008	-0.034	0.051	0.702	0.055	0.020	0.090	0.002
Romania (using Spain value set)																
TB	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---	Reference	---	---	---
TB-DM	-0.008	-0.112	0.097	0.885	0.069	-0.005	0.144	0.069	-0.004	-0.048	0.041	0.874	0.065	0.027	0.103	0.001

*Adjusted for smoking frequency and socio-economic quintile

**p-value is derived from a multiple linear regression model

CI-confidence interval

10.3.2 Health utility scores for EQ-5D-5L using general population value sets

People with TB-DM receiving standard or intensive DM management

In Indonesia, the mean utility score of RCT participants in the standard care and intensive monitoring arms at the four time points are presented in Table 10-12 and at two time points for Romania in Table 10-13, where higher utility scores represent a better HRQoL.

For Indonesia, at 12 and 18 months the mean utility score for people in the intensive monitoring arm was lower than that of people in standard DM care for both the Thai and UK value sets. The mean utility score for the intensive monitoring arm was only lower than that of the standard care arm at six months in Romania using the Spanish value set. The Wilcoxon rank-sum test showed no significant difference in the mean ranks of the utility scores between the RCT arms for either country.

Table 10-12: Difference in EQ-5D-5L utility scores at each time point between people with TB-DM in two arms of an RCT, Indonesia

	Value set	Thailand		<i>p</i> -value*	UK ^α (SA)		<i>p</i> -value*
		mean	SD		mean	SD	
Baseline	Intensive monitoring	0.6636	0.1758	0.1485	0.7208	0.1972	0.1825
	Standard care	0.6110	0.1926		0.6653	0.2240	
6 months	Intensive monitoring	0.8468	0.1381	0.7941	0.8920	0.1004	0.8925
	Standard care	0.8207	0.1875		0.8661	0.1619	
12 months	Intensive monitoring	0.8537	0.1521	0.1457	0.9016	0.1081	0.1523
	Standard care	0.9113	0.1390		0.9402	0.0959	
18 months	Intensive monitoring	0.7846	0.2653	0.1524	0.8168	0.2794	0.1222
	Standard care	0.9157	0.1541		0.9407	0.1078	

*The *p*-values were from the two-sample Wilcoxon rank-sum test

^αThe UK value set was used for data in Indonesia as a sensitivity comparison of the value sets

SD-standard deviation; SA-sensitivity analysis

Table 10-13: Difference in EQ-5D-5L utility scores at each time point between people with TB-DM in two arms of an RCT, Romania

	Value set	Spain		<i>p</i> -value*	UK ^α (SA)		<i>p</i> -value*
		mean	SD		mean	SD	
Baseline	Intensive monitoring	0.8123	0.0978	0.6884	0.7568	0.0759	0.4573
	Standard care	0.8061	0.1067		0.7519	0.0979	
6 months	Intensive monitoring	0.8782	0.1353	1.0000	0.8404	0.1467	0.9047
	Standard care	0.8963	0.0777		0.8382	0.0997	
18 months	Intensive monitoring	NA	NA		NA	NA	
	Standard care	NA	NA		NA	NA	

*The *p*-values were from the Mann-Whitney (Wilcoxon rank-sum) test

^αThe UK value set was used for data in Romania as a comparison to the Spanish dataset. SA-sensitivity analysis

NA-not applicable because not enough data at that time point

10.3.3 Correlation between HRQoL and age

Correlations between the EQ-5D-5L utility scores, EQ VAS, and age and the Karnofsky score were analysed at baseline only since the Karnofsky health utility measurement was only captured at this time point. At baseline, the positive correlations between EQ-5D-5L utility score, EQ VAS score and Karnofsky Performance Scale index were statistically significant in Indonesia, Peru and Romania (Table 10-14). Age was significantly negatively correlated with the EQ-5D-5L utility score and the Karnofsky score in all countries. However, while the EQ VAS decreased with an increase in age, the correlation was significant in Peru ($r=-0.11$, $p=0.006$) and Romania ($r=-0.15$, $p<0.001$) only.

At the six-month follow-up, the EQ-5D-5L utility score was positively correlated with the EQ VAS in Indonesia ($r=0.44$, $p<0.0001$) and Romania ($r=0.86$, $p<0.0001$) only, and negatively correlated with age in Indonesia only ($r=-0.20$, $p=0.0033$). There was no significant correlation between age and EQ VAS at six months in any of the countries.

Table 10-14: Correlation between health-related quality of life value sets and age for people with tuberculosis and diabetes in Indonesia, Peru and Romania

		Baseline						6 months			
		EQ-5D-5L utility score*	<i>p-value</i>	EQ VAS	<i>p-value</i>	Karnofsky score	<i>p-value</i>	EQ-5D-5L utility score*	<i>p-value</i>	EQ VAS	<i>p-value</i>
EQ VAS	Indonesia	0.4691	<0.0001					0.4396	<0.001		
	Peru	0.1263	0.0025					0.3456	0.3279		
	Romania	0.6194	<0.0001					0.8578	<0.001		
Karnofsky	Indonesia	0.6830	<0.0001	0.391	<0.0001						
	Peru	0.5142	<0.0001	0.174	<0.0001						
	Romania	0.7369	<0.0001	0.708	<0.0001						
Age	Indonesia	-0.0878	0.0102	-0.043	0.2071	-0.0849	0.0129	-0.1968	0.0033	-0.051	0.4468
	Peru	-0.2154	<0.0001	-0.113	0.0057	-0.2824	<0.0001	-0.4266	0.2189	-0.252	0.4827
	Romania	-0.3258	<0.0001	-0.150	<0.001	-0.2458	<0.0001	-0.3992	0.1256	-0.312	0.2397

*EQ-5D-5L utility scores for Indonesia are derived from a cross-walk to Thailand population EQ-5D-3L value sets, Peru utility scores are derived from UK population EQ-5D-3L value sets and Romania utility scores are derived from Spain population EQ-5D-3L value sets
VAS-visual analogue scale

As with all of the EQ-5D-5L analysis the values sets used were Thailand for Indonesia, UK for Peru and Spain for Romania. A sensitivity analysis was also performed where the UK value sets were used for Indonesia and Romania and the Thai value set for Peru. The strength of the correlations between the EQ-5D-5L utility scores and the Karnofsky score were mostly unchanged for the sensitivity analysis using alternative value sets (Table 10-15). In Indonesia the correlation between the utility scores (using the alternative UK valuation) and age remained weak but was no longer significant ($r=-0.0513$, $p=0.1343$). In Peru, the correlations between the EQ-5D-5L utility scores (with the Thai valuation) and the other health utility measures did not change as much as may be expected given the cultural differences between Peru and Thailand but this may be because the primary value set for Peru, the UK, was also very different from Peru.

Table 10-15: Correlation between ALTERNATIVE health-related quality of life value sets and age for people with tuberculosis and diabetes in Indonesia, Peru and Romania - sensitivity analysis^a

		Baseline		6 months	
		EQ-5D-5L utility score*	<i>p-value</i>	EQ-5D-5L utility score*	<i>p-value</i>
Indonesia		0.4521	<0.0001	0.3935	<0.0001
Peru	EQ VAS	0.1035	0.0134	0.1972	0.5851
Romania		0.6100	<0.0001	0.7694	<0.001
Indonesia		0.6347	<0.0001		
Peru	Karnofsky	0.5025	<0.0001		
Romania		0.6925	<0.0001		
Indonesia		-0.0513	0.1343	-0.1740	0.0095
Peru	Age	-0.2601	<0.0001	-0.4442	0.1984
Romania		-0.3035	<0.0001	-0.4906	0.0537

*EQ-5D-5L utility scores for Indonesia are derived from a cross-walk to UK population EQ-5D-3L value sets, Peru utility scores are derived from Thailand population EQ-5D-3L value sets and Romania utility scores are derived from UK population EQ-5D-3L value sets

^aFor sensitivity analysis, only EQ-5D-5L utility score values were varied
VAS-visual analogue scale

10.3.4 Effect of DM management on health utility

People with TB-DM receiving standard or intensive DM management

The random effects regression model was applied to Indonesia only since this was the only country that had enough data at more than one time point for the model to run. When using the Thailand value sets, there is weak evidence (regression coefficient=0.05, p -value=0.095) that from baseline to six months, the health utility of people in the intensive monitoring arm is better than that of people receiving standard DM care. There is also weak evidence (regression coefficient=0.05, p -value=0.119) that people in the intensive DM monitoring arm have a better HRQoL over the six months of DM management even after controlling for age, sex, smoking frequency, socio-economic status and the presence of any DM complications. The interaction between age and sex was not considered in this model because of the small sample size.

People who reported smoking 'less than daily' reported a better health utility (regression coefficient=0.12, p -value=0.091) than people who did not smoke. The EQ-5D-5L dimension(s) that captures this improved HRQoL is unknown, but being able to perform 'usual activities' or fewer problems with 'anxiety/depression' could explain it, particularly in people who were previous smokers.

No other characteristics appeared to significantly impact the health utility of people being treated for TB and DM between baseline and six months. The results also remained mostly unchanged when the UK value sets were used instead of the Thailand value sets.

Table 10-16: Effect of DM management on mean utility score of people with tuberculosis and diabetes in standard care versus intensive monitoring arms of RCT between baseline and 6-months, Indonesia using Thailand value sets

Characteristic	Categories	Intervention: intensive DM monitoring		Control: standard DM care		Unadjusted			Adjusted			
		N	n %	n %	Regression coefficient ^α	(95% CI)	p-value*	Regression coefficient ^α	(95% CI)	p-value*		
Overall		120	60	60								
Sex	Female	55	28 46.7	27 45.0	Reference	---	---	---	Reference	---	---	---
	Male	65	32 53.3	33 55.0	0.031	-0.025 0.086	0.281	0.021	-0.040 0.081	0.505		
Age, years (continuous)		120	---	---	-0.001	-0.004 0.002	0.519	-0.001	-0.004 0.002	0.468		
Smoking frequency	Not at all	100	50 83.3	50 83.3	Reference	---	---	---	Reference	---	---	---
	Less than daily	7	3 5	4 6.7	0.122	-0.020 0.264	0.091	0.106	-0.040 0.252	0.155		
	Daily	13	7 11.7	6 10.0	0.063	0.026 0.152	0.163	0.045	-0.052 0.142	0.366		
Socio-economic Status quintiles	Poorest	27	12 20	15 25.0	Reference	---	---	---	Reference	---	---	---
	Poor	26	13 21.7	13 21.7	0.008	-0.078 0.093	0.857	0.004	-0.082 0.091	0.925		
	Middle income	28	14 23.3	14 23.3	0.000	-0.082 0.082	0.999	-0.004	-0.088 0.079	0.917		
	Upper middle income	26	13 21.7	13 21.7	0.044	-0.040 0.128	0.300	0.032	-0.053 0.118	0.461		
	Richest	12	7 11.7	5 8.3	0.007	-0.100 0.114	0.893	-0.003	-0.112 0.105	0.950		
Any DM complications	No	77	37 61.7	40 66.7	Reference	---	---	---	Reference	---	---	---
	Yes	43	23 38.3	20 33.3	-0.019	-0.076 0.039	0.527	-0.022	-0.081 0.037	0.467		
Intervention	Standard care	60	0 0.0	60 100	Reference	---	---	---	Reference	---	---	---
	Intensive monitoring	60	60 100	0 0.0	0.047	-0.008 0.102	0.095	0.045	-0.012 0.102	0.119		

DM-diabetes mellitus

^αThailand general population value set used for utility scores in Indonesia

*p-values are estimated using a random effects regression model

Table 10-17: Effect of DM management on mean utility score of people with TB-DM in an RCT (baseline to 6 months), Indonesia using UK value sets (SENSITIVITY ANALYSIS)

Characteristic	Categories	Intervention: intensive DM monitoring		Control: standard DM care		Unadjusted			Adjusted			
		N	n %	n %	Regression coefficient ^α	(95% CI)	p-value*	Regression coefficient ^α	(95% CI)	p-value*		
Overall		120	60	60								
Sex	Female	55	28 46.7	27 45.0	Reference	---	---	---	Reference	---	---	---
	Male	65	32 53.3	33 55.0	0.035	-0.022 0.091	0.228	0.027	-0.035 0.089	0.387		
Age, years (continuous)		120			0.0001	-0.003 0.003	0.942	0.00001	-0.003 0.003	0.992		
Smoking frequency	Not at all	100	50 83.3	50 83.3	Reference	---	---	---	Reference	---	---	---
	Less than daily	7	3 5	4 6.7	0.126	-0.018 0.271	0.087	0.114	-0.035 0.263	0.133		
	Daily	13	7 11.7	6 10.0	0.056	-0.034 0.147	0.225	0.038	-0.061 0.138	0.452		
Socio-economic Status quintiles	Poorest	27	12 20	15 25.0	Reference	---	---	---	Reference	---	---	---
	Poor	26	13 21.7	13 21.7	0.022	-0.065 0.109	0.618	0.016	-0.072 0.104	0.720		
	Middle income	28	14 23.3	14 23.3	-0.005	-0.089 0.079	0.899	-0.013	-0.098 0.072	0.765		
	Upper middle income	26	13 21.7	13 21.7	0.028	-0.058 0.113	0.530	0.011	-0.076 0.098	0.809		
	Richest	12	7 11.7	5 8.3	-0.002	-0.111 0.107	0.971	-0.015	-0.126 0.096	0.792		
Any DM complications	No	77	37 61.7	40 66.7	Reference	---	---	---	Reference	---	---	---
	Yes	43	23 38.3	20 33.3	-0.024	-0.083 0.035	0.429	-0.024	-0.084 0.036	0.434		
Intervention	Standard care	60	0 0.0	60 100	Reference	---	---	---	Reference	---	---	---
	Intensive monitoring	60	60 100	0 0.0	0.048	-0.008 0.104	0.092	0.048	-0.010 0.105	0.107		

DM-diabetes mellitus

^αUK general population value set used as alternative utility scores for Indonesia

*p-values are estimated using a random effects regression model

10.4 Discussion

At the time of participant enrolment in Peru and Romania, people with TB only had a better HRQoL than people with TB-DM. The association in Peru was weak and no longer significant when adjustment for confounding was performed.

In Indonesia there is weak evidence that people in the intensive DM monitoring arm of the RCT have better HRQoL than people in the standard care arm. Adjustment for confounders reduced the strength of the association.

There is a highly significant positive correlation between the EQ-5D-5L utility scores, the EQ VAS and the Karnofsky Index, indicating that the three HRQoL tools are measuring the same thing. This justifies the decision to perform all the analysis using the utility scores only and not performing additional analysis on the EQ VAS. Correlation between the utility scores, EQ VAS and Karnofsky Index is weakest in Peru, moderate in Indonesia and strong in Romania.

Using both the DR-12 and EQ-5D-5L was considered, so that the two instruments could be compared, but the number of questions being asked of the patients had to be limited, so the decision was made to use the more widely used and language validated EQ-5D-5L only. This is the first study to report the HRQoL of patients with concurrent TB-DM.

There are potentially cultural differences in how people from different countries interpreted the different translations of the 5L descriptive system, particularly since there was no country specific crosswalk for those countries. We attempted to deal with this by using the closest alternatives of Thailand for Indonesia and Spain for Romania. The country with the largest sample size (UK) was used for Peru with the hope that this would compensate for the lack of country specific data. None of the countries where the TANDEM data was collected had value sets that could be used for the HRQoL analysis. This means that the assessments made for the patients in the study were not specific to the cultural and social norms of that setting, and the estimated HRQoL of the participants could be a misrepresentation of their actual HRQoL. The respondents in the crosswalk study performed by EuroQoL were different from those in TANDEM, therefore the calibration of the values to go from 5L to 3L are not equivalent to that of the TANDEM respondents.

Additionally, the value sets are based on stated preference studies (where members of general public are asked to imagine living with various health problems) whereas TANDEM data is based on patients with TB or TB-DM and they will have different opinions about the severity of their health problems.

10.5 Conclusion

Preliminary analysis suggests that the intensive monitoring intervention has resulted in better patient reported HRQoL than the standard DM care available in Indonesia and Romania. Concurrent disease, in this scenario TB and DM, appears to lead to a poorer HRQoL than having TB only but whether this is due to clinical, physiological or social circumstances has not been explored in this analysis.

Chapter 11 Patient costs in Indonesia

This chapter assessed the direct and indirect costs incurred by patients in both arms of the RCT in Indonesia only. Patient costs incurred when seeking treatment for TB and DM were collected by questionnaires included in REDCap.

11.1 Introduction

Patients in the TANDEM RCT with concurrent TB-DM received six months of TB treatment (using the DOTS format) and DM management, which was followed by 12 months of DM management only.

The objective of this chapter was to determine the costs of DM diagnosis and TB-DM treatment in patients with TB-DM from the perspective of the patients in the RCT in Bandung, Indonesia. In addition to presenting the mean costs by category, the coping strategies employed by patients were also explored.

11.2 Methods

The economic burden of TB-DM treatment on patients was assessed by determining the mean out-of-pocket payments and productivity losses reported by the patients in Indonesia who had completed the six months of TB and DM treatment and the additional 12 months of DM follow-up.

The sample size to detect a 1% difference in HbA_{1c} between the two arms of the RCT in Indonesia, Peru and Romania was estimated to be 350 people with TB-DM, accounting for attrition. This was derived by assuming a standard deviation of 2.2, with 90% power at the 5% significance level.

11.2.1 Literature reviews

11.2.1.1 TB treatment costs

A systematic literature review of the costs of treating patients with TB from both the provider and patient perspective was previously described in Chapter 2, Research Paper 1 (Laurence et al., 2015). In Research Paper 1, no papers were identified for Romania but there was one paper for Indonesia, which included aggregated patient out-of-pocket payments for user fees, non-TB medication and transportation, and productivity losses, in addition to provider treatment costs (Mahendradhata et al., 2010). In this study, participating private practitioners were asked to refer people with suspected TB to public health centres where patients would receive six months of directly-observed treatment, short-course (DOTS). Costs incurred from all perspectives were presented for patients who presented directly to the public health centres compared to patients who were referred by the private practitioners. In the former group of patients, out-of-pocket costs for patients amounted to US\$ 50, which was 40% less than the average for the income group. Lost earnings for patients in Indonesia (US\$ 12) were well below the average for the income group (US\$ 238) but the methodology used in each paper for assessing productivity losses varied considerably, if it was described, and it is therefore difficult to assess if this is a true representation of the financial burden of TB treatment for patients in the Indonesian study.

Though there were no papers that presented any form of costs incurred during TB treatment in Romania, as an upper-middle income country (UMIC) it is reasonable to assume that the costs would fall within the range of costs for that income group [patient incurred costs: US\$ 60 (SD: US\$ 868) and productivity losses: US\$ 600 (SD: US\$ 847)]. The Romanian National Tuberculosis Programme (NTP) guidelines state that people with TB must be treated as in-patients in pulmonary hospitals or sanatoria until they are no longer infectious (smear conversion), usually resulting in a hospitalisation period of at least 37 days (WHO and ECDC, 2015). For the remainder of the six months of TB treatment, TB is treated through pulmonary dispensaries that patients must visit weekly or monthly for

monitoring and medication. This case management is different from that of most of the other UMICs included in the review, which followed the DOTS out-patient regimen for the entire six months, therefore it is expected that the patient incurred costs for TB treatment in Romania would be less as there would be no regular transportation costs or user fees while hospitalised and any special dietary requirements would be incurred by the hospital. However, it is reasonable to expect that the household costs for family or friends to visit the hospitalised patient with TB could be higher than in other countries where TB treatment is performed on an out-patient basis. A South African study by Schnippel et al. (2013b) assessed hospitalised management for MDR-TB only. This would have been the closest comparison to the Romanian context but no patient costs were captured in this study.

11.2.1.2 DM treatment costs

A review was conducted by Seuring et al. (2015) on the economic costs of T2DM. There was large variability in the methods used to estimate both direct and indirect costs, as well as the treatment approach (e.g. curing, halting progression or preventing future complications). Comparison between studies is therefore difficult to interpret. Although there was a positive relationship between gross domestic product (GDP) per capita and DM treatment costs, it is still difficult to use the GDP per capita of countries without data to accurately estimate the cost of DM treatment in that setting. All costs in the Seuring et al. (2015) review were presented in 2011 International dollars, to represent purchasing power parity.

It is interesting to note the wide range in cost values between countries in the LMIC group. The average annual productivity costs in LMICs started at Int. \$ 45 in Pakistan in 2006 and was as high as Int. \$ 4,737 in India (2009).

The review period of this review was between January 2001 and October 2014 but no studies published on the cost of DM treatment in Indonesia or Romania were obtained. The study that was closest to Indonesia in terms of geography and GNI per capita was by

Chatterjee et al. (2011) that looked at the annual societal costs of treating people with DM (in- and out-patient care) at a district hospital in Thailand. Indirect costs due to DM and complications, which included the days lost from work or normal activities, leisure time and lost earning capacity from disability or premature mortality, was valued at Int. \$ 649 (2008). The total cost of DM treatment (Int. \$ 1,731) amounted to approximately 18% of the 2011 GDP per capita of Thailand (Int. \$ 9,693), which would then have amounted to approximately Int. \$ 834 in Indonesia in 2011. The cost of informal care accounted for the greatest proportion (28%) of all treatment costs, followed by the cost of permanent disability (19%), mortality costs (18%) and hospital care (11%).

One study was included from Romania's smaller neighbour to the south west, Serbia. The indirect costs associated with DM, including lost earning capacity due to death or disability and absenteeism, was estimated at Int. \$ 187 in 2007 (Biorac et al., 2009) and the total cost of treating DM (valued in 2011) accounted for 17% of the per capita GDP of Serbia, which would be approximately Int. \$ 2,100 in Romania (IMF, 2011).

This review by Seuring et al. (2015) was an update of a previous review of cost-of-illness studies for DM over the period 1970 to 2000 (Ettaro et al., 2004). This earlier review also did not present any relevant studies for Indonesia, a lower-middle income country (LMIC) or Romania, an upper-middle income country (UMIC).

A separate review for Indonesia by Soewondo et al. (2013) assessed both peer-reviewed studies and unpublished data to describe the burden, expenditure, complications, treatment and outcomes of DM in Indonesia up to February 2012. Five references with relevant cost data on DM treatment or complications from DM were identified. Only three of these were published papers that I was able to access, but none presented costs from the perspective of the patient.

For Romania, a study presenting the costs associated with DM treatment along with co-morbid depression was the only paper of the two DM treatment cost papers identified

that was accessible, but patient costs were also not presented here (Chereches et al., 2012).

11.2.1.3 Concurrent TB and DM – economics of screening and treatment

One study sought to address the financial challenges of co-management of TB and DM in LMICs (Sullivan and Ben Amor, 2012). The additional funding needed to treat DM in TB patients in Africa and South East Asia was estimated using yearly DM treatment cost data from Tanzania and India and calculating these values for six months (the same period as DOTS). This was combined with the yield values of finding additional DM cases by screening people with active TB from another study (a literature review of prevalence of bi-directional screening).

11.2.2 Data collection

The patient costs were collected in Indonesian Rupiah and converted into USD based on the 2014 exchange rate of 1 US\$ = 12,420 Indonesian Rupiah (OANDA, 2016). Patients with newly diagnosed TB were interviewed by TANDEM staff clinicians to obtain information on all patient costs incurred due to diagnosis of DM and treatment of concurrent TB-DM. Patient costs included direct medical and transportation costs as well as lost productivity and childcare costs. The cost data collection interviews were conducted using standardised, electronic, interviewer-administered questionnaires that were translated into Bahasa.

Questionnaires regarding transportation and childcare costs were administered at baseline, during the six-month treatment visit and the 18-month follow-up visit (Appendix AA). Questionnaires on direct medical costs and productivity losses were administered at every visit by patients with TB-DM (Appendix AA). These visits included baseline, 2, 3, 6, 12 and 18 months for all patients with TB-DM and four additional time points for people in the intensive DM monitoring arm of the RCT: 2 weeks, 1, 4 and 5 months. At each scheduled visit, all patients were asked about transportation and direct medical costs incurred during any unscheduled health care visit for TB or DM related treatment

(Appendix BB). A health care visit was defined as a visit to a clinician in a private or public setting, a pharmacy, a traditional medicine practitioner or any medical facility to seek care for TB, DM, complications or adverse events. Information on insurance re-imbursements and sources of funds to pay for medical services were also collected.

11.2.3 Data analysis

The analysis tallied the total costs incurred over the 18 months of the RCT. Costs were disaggregated to show the breakdown for medical, transportation and childcare costs and reported lost productivity. Only patients completing the 18 months of care were included.

Medical costs included out-of-pocket payments spent on user fees for consultations with a clinician, registration at a health facility, drugs for TB or DM that were outside the standard treatment regimen or for complications or adverse events, monitoring tests and any hospitalisation. The coping strategy, that is identifying the source of the money used to make any out-of-pocket payments, was asked whenever the patient indicated that medical costs were incurred.

Transportation costs included journeys to and from scheduled and unscheduled health care visits. These costs were provided by the patient if public transportation or a private taxi was used. If the mode of transport was motorcycle or automobile, the distance travelled or journey time was provided by the patient. These values were used to calculate the cost of fuel for a return trip, based on the average fuel efficiency of a motorcycle (2.9 litres per 100 kilometres) or automobile (12.5 litres per 100 kilometres) and subsidised fuel rates provided by the Ministry of the Environment in Indonesia ((Lontoh et al., 2015)).

Productivity losses (to value the time of patients) were calculated using the human capital approach by tabulating the return trip travelling time for any health care visit and the time spent at the health facility including waiting time. This was then multiplied by the 2014 average hourly living wage in Indonesia of US\$ 0.77, derived from a monthly living wage

of 1,746,304 IDR (US\$ 133.94) (BPS, 2016). This wage was used for all patients, including those who were self-employed or unemployed and able to work.

At baseline, the majority (65%) of patients reported that they would be performing unpaid work at home if they had not needed to visit the health facility on that day. Therefore, the living wage in Indonesia was used for all patients since determining the hourly wage of each patient was not possible. It was assumed that employees would work eight hours per day for 227 days per year (or 40 hours in five workdays per week), based on the Julian calendar and Indonesian Government regulations on manpower (Indonesia, 2003).

Any payments made for childcare or care for a dependant was reported by the patient. Any expected insurance reimbursement for payments made relating to treatment of TB or DM was captured. The source of the money used to pay for costs incurred during the 18 months of treatment was reported by the patient whenever any health care expenditure was reported.

The total costs incurred per patient were the sum of medical costs, transport costs, productivity costs and childcare costs.

11.3 Results

A total of 120 patients with TB-DM have been enrolled in the RCT in Indonesia between April 2014 and November 2016. The patient cost analysis in this thesis includes only the 31 patients who have so far completed all 18 months of the RCT as of October 2016 (Table 11-1). There were 15 patients in the standard DM care arm and 16 in the intensive DM monitoring arm.

Table 11-1: Baseline characteristics of TANDEM randomised controlled trial participants with tuberculosis and diabetes in Bandung, Indonesia

Characteristic	Standard DM care (n=15)		Intensive DM monitoring (n=16)	
	n	(%)	n	(%)
Sex				
Female	7	47%	6	38%
Male	8	53%	10	63%
Age, years (mean, SD)	53.25	8.39	54.4	11.64
Employment type				
Non-government	3	20%	2	13%
Self-employed	5	33%	6	38%
Home-maker	6	40%	6	38%
Retired	0	0%	1	6%
Unemployed (able to work)	1	7%	1	6%
Education level attained				
Less than primary school	4	27%	2	13%
Primary school completed	3	20%	5	31%
Secondary school completed	3	20%	1	6%
High school completed	5	33%	4	25%
College/University completed	0	0%	4	25%
Socio-economic status				
Poorest	3	20%	2	13%
Poor	3	20%	4	25%
Middle income	6	40%	1	6%
Upper middle income	2	13%	7	44%
Richest	1	7%	2	13%
Co-morbidities (Charlson)				
Infarction, heart attack, transient ischaemic attack, arrhythmia, heart bypass	1	7%	0	0%
Kidney disease	0	0%	1	6%

The majority of participants were male (58%) and approximately 75% of the participants in either arm of the RCT were self-employed or home-makers. Only two people reported a co-morbidity, one in each arm of the RCT: heart disease in the standard care arm and kidney disease in the intensive monitoring arm.

11.3.1 Medical costs

The mean user fees paid by patients for medical consultations or at a health facility over the 18 months of treatment was US\$ 0.42 in the standard care arm and US\$ 3.84 in the intensive monitoring arm (Table 11-2). The majority (72%) of the total mean costs for intensive monitoring was incurred during three unscheduled visits reported by one patient at the 18-month follow-up visit. Out-of-pocket payments for drugs was higher in the standard care arm (US\$ 3.84) than in the intensive arm (US\$ 2.40). One patient reported paying for drugs in either arm: at the month three treatment visit in the standard arm and at baseline in the intensive arm. The mean cost of tests was US\$ 3.71 in the standard arm and US\$ 14.30 in the intensive arm. Approximately 90% of the payments for tests in the standard arm were incurred during three unscheduled visits reported during the 18-month follow-up visit while more than 90% of the payments for tests in the intensive arm were during five unscheduled visits reported at the 6-month and 18-month visits.

No other direct medical costs have been reported by the patients in the RCT.

11.3.2 Transport costs

In the standard care arm, each patient was required to visit the DOTS clinic at RSHS for TB treatment and DM management six times over the 18 months of the trial, whereas patients in the intensive arm were required to visit the clinic 10 times. However, the mean transportation costs of US\$ 8.23 in the intensive arm, was more than three and a half times that of the standard care arm (US\$ 2.34) (Table 11-2). The transportation costs for unscheduled visits accounted for only 7% of the total transportation costs in both arms. The mean transportation costs per patient per scheduled visit to the clinic were US\$ 0.27 for the standard arm but US\$ 0.77 in the intensive arm.

There was an average of 0.53 unscheduled visits to the clinic in the standard care arm and 1.65 in the intensive monitoring arm, in addition to the six and 10 scheduled visits in the two arms respectively.

Table 11-2: Mean TB-DM patient costs for diagnosis, treatment and transport in Bandung, Indonesia (2014 USD)

Time point	User fees (medical consultation)	User fees (health facility)	Drugs	Tests	Transportation (clinic)	Total mean cost per patient
Standard DM care arm						
Baseline	0.00	0.14	0.00	0.00	0.43	0.55
Unscheduled visits reported at baseline	0.00	0.00	0.00	0.00	0.00	0.00
2 months	0.00	0.00	0.00	0.00	0.35	0.35
3 months	0.00	0.14	3.84	0.38	0.35	4.71
6 months	0.00	0.14	0.00	0.00	0.35	0.49
Unscheduled visits reported at 6 months	0.00	0.00	0.00	0.00	0.00	0.00
12 months	0.00	0.00	0.00	0.00	0.35	0.35
Unscheduled visits reported at 12 months	0.00	0.00	0.00	0.00	0.15	0.15
18 months	0.00	0.00	0.00	0.00	0.35	0.35
Unscheduled visits reported at 18 months	0.00	0.00	0.00	0.66	0.001	0.67
Total	0.00	0.42	3.84	1.05	2.34	7.64
Intensive DM monitoring arm						
Baseline	0.00	0.24	2.40	0.75	0.95	4.34
Unscheduled visits reported at baseline	0.00	0.00	0.00	0.00	0.00	0.00
2 weeks	0.00	0.00	0.00	0.00	0.95	0.95
1 month	0.00	0.00	0.00	0.00	0.95	0.95
2 months	0.00	0.00	0.00	0.00	0.95	0.95
3 months	0.00	0.00	0.00	0.00	0.95	0.95
4 months	0.00	0.00	0.00	0.00	0.95	0.95
5 months	0.00	0.00	0.00	0.00	0.95	0.95
6 months	0.00	0.00	0.00	0.00	0.53	0.53
Unscheduled visits reported at 6 months	0.58	0.00	0.00	3.41	0.52	4.50
12 months	1.92	0.00	0.00	0.00	0.53	2.45
Unscheduled visits reported at 12 months	0.00	0.00	0.00	0.00	0.00	0.00
18 months	0.00	0.00	0.00	0.00	0.00	0.00
Unscheduled visits reported at 18 months	1.10	0.00	0.00	0.72	0.00	1.82
Total	3.60	0.24	2.40	4.88	8.23	19.34

TB-tuberculosis; DM-diabetes mellitus; USD-United States dollar

11.3.3 Productivity and childcare costs

The average transportation time was 54 minutes for patients in the standard care arm and 1 hour and 34 minutes for those in the intensive monitoring arm (Table 11-3). The average time spent at the health centre at baseline for registration and diagnosis was 44 minutes in the standard care arm and more than two times as long at 1 hour and 39 minutes in the intensive monitoring arm.

The mean income lost by patients with TB-DM was US\$ 11.67 and US\$ 29.56 in the standard and intensive monitoring arms, respectively (Table 11-3). In the standard care arm the greatest proportion of income lost was at baseline (15%), the six-month treatment visit (13%) and the 12-month follow-up visit (14%). In the intensive monitoring arm, the proportion of income lost is also highest at the six-month (9%) and 12-month (11%) visits, but the three-month visit also places a heavy economic burden on the patients with 10% (US\$ 3.03) of the income lost occurring at this time point.

The mean cost of productivity losses per visit due to transportation time and time spent at health facility was US\$ 0.83 for patients in the standard DM care arm and 2.5 times more (US\$ 2.11) for those in the intensive monitoring arm.

No payments for childcare or care of dependants were reported.

Table 11-3: Mean income lost per patient with TB-DM in Indonesia (2014 USD)

Time point	Transportation time (minutes)	Time spent at health facility* (minutes)	Total time without income (minutes)	Income lost (USD)
Standard DM care arm				
Baseline	60	74	134	1.73
Unscheduled visits reported at baseline	0	NA	NA	---
2 months	60	34	94	1.21
3 months	60	30	90	1.16
6 months	70	50	120	1.55
Unscheduled visits reported at 6 months	70	NA	70	0.90
12 months	70	54	124	1.59
Unscheduled visits reported at 12 months	70	NA	70	0.90
18 months	47	24	71	0.90
Unscheduled visits reported at 18 months	15	NA	15	0.19
Total	643	266	909	11.67
Average per visit	54	44	65	0.83
Intensive DM monitoring arm				
Baseline	107	67	174	2.23
Unscheduled visits reported at baseline	107	NA	107	1.37
2 weeks	107	98	204	2.62
1 month	107	92	199	2.55
2 months	107	88	195	2.50
3 months	107	130	236	3.03
4 months	107	86	193	2.48
5 months	107	98	205	2.63
6 months	83	130	212	2.72
Unscheduled visits reported at 6 months	83	NA	83	1.06
12 months	83	169	252	3.23
Unscheduled visits reported at 12 months	83	NA	83	1.06
18 months	92	35	127	1.63
Unscheduled visits reported at 18 months	34	NA	34	0.43
Total	1,311	993	2,303	29.56
Average per visit	94	99	165	2.11

TB-tuberculosis; DM-diabetes mellitus; USD-United States dollars; NA-not available

*Includes waiting time

11.3.4 Coping strategies

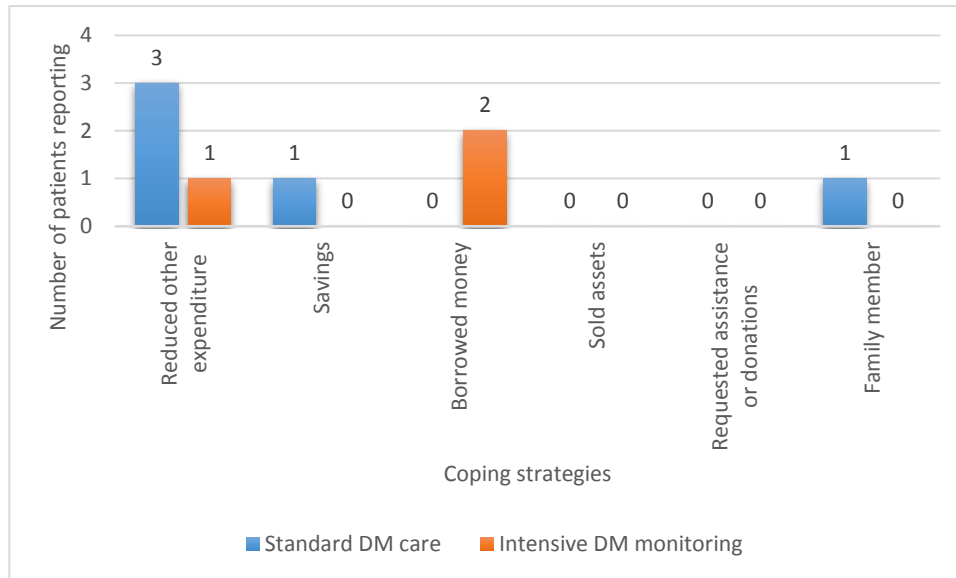
A total of six out of the 31 (19%) patients in the RCT reported some form of coping strategy during their 18 months of treatment. At baseline, four patients (13%) made out-of-pocket payments for medical services, all of whom reported a coping strategy was needed to afford these payments; three patients reduced other expenses and one borrowed money.

Out-of-pocket payments and coping strategies to cover the costs incurred were only reported by one patient at each of the three-month, six-month and 12-month visits. The payments were made by a different patient on each occasion. Use of savings and help from a family member was reported for the three-month visit, reducing other expenses at the six-month visit and borrowing money at the 12-month visit.

Overall, the most common coping mechanism was reducing other expenditure in the standard arm and borrowing money in the intensive arm (Figure 11-1). No patients sold assets, sought assistance from government/charity services or asked for donations.

No insurance reimbursements were reported, so no adjustments were made to the out-of-pocket payments made by patients.

Figure 11-1: Number of patients being treated for TB-DM reporting coping strategies in Bandung, Indonesia*



*For 31 patients in the RCT completing 18 months of treatment and follow-up for TB and DM
TB-tuberculosis; DM-diabetes mellitus; RCT-randomised controlled trial

11.3.1 Mean patient costs per case treated

The mean total patient costs per case of TB-DM treated was two and a half times more in the intensive monitoring arm (US\$ 48.90) than in the standard care arm (US\$ 19.31) (Table 11-4). Lost productivity was the main cost burden (60%) for patients in both arms of the RCT.

During the last 12 months of the RCT, when they are typically receiving DM management only, the costs account for approximately 25% of the total costs to the patient, equating to a monthly cost of US\$ 0.89 and US\$ 0.43 for patients in the intensive monitoring and standard care arms, respectively. The monthly clinic visits required in the intensive monitoring arm during the six months of TB treatment substantially increase the financial burden for patients costing them US\$ 5.28 per month, whereas patients receiving standard DM care during TB treatment incur less than half the costs, at US\$ 1.99 per month, but still 4.5 times more than the monthly cost of DM management only.

In the absence of patient specific data, the average net basic wage for 18 months was calculated as US\$ 2,411, using 2014 Indonesia values. The out-of-pocket expenditure and lost income due to health visits would have accounted for 2% of an employee's income if they received intensive DM monitoring in addition to six months of TB treatment. Receiving the standard DM care available in Bandung as well as the six-month TB regimen would incur costs of less than 1% of the average income earned over 18 months.

Table 11-4: Patient costs per case of TB-DM treated in Bandung, Indonesia (2014 USD)

	Standard DM care				Intensive DM monitoring			
	Diagnosis of concurrent disease (baseline)	TB treatment and DM management (>baseline-6 months)	DM management only (>6-18 months)	Total costs (baseline - 18 months)	Diagnosis of concurrent disease (baseline)	TB treatment and DM management (>baseline-6 months)	DM management only (>6-18 months)	Total costs (baseline - 18 months)
Direct medical costs	0.14	4.49	0.66	5.30	3.39	3.99	3.74	11.11
Direct non-medical costs	0.43	1.06	0.86	2.34	0.95	6.74	0.53	8.23
Indirect costs	1.73	6.36	3.58	11.67	2.23	20.97	6.35	29.56
Total costs per case treated	2.29	11.91	5.10	19.31	6.57	31.70	10.63	48.90

TB-tuberculosis; DM-diabetes mellitus; USD-United States dollars

Direct medical costs includes user fees, drugs and tests; direct non-medical costs includes transportation for clinic visits; indirect costs includes lost income

11.4 Discussion

Very few patients (29%) reported any out-of-pocket payments for consultations, health facilities fees, drugs or tests during the 18 months of treatment and monitoring. This suggests that patients with TB were able to access the free medical services available to them at the point of care through the Jamkesmas national health insurance and the National TB Programme (NTP). In the study, 74% of patients were self-employed or home-makers, and therefore not eligible for national health insurance, making the TB clinic largely responsible for ensuring free healthcare services for patients through the NTP.

The burden of the potential lost wages due to clinic visits was 1.5 times that of the direct out-of-pocket costs incurred during TB-DM treatment. From six to 18 months, when most patients are receiving DM care only, the patient costs are far less per month than when patients are receiving TB and DM treatment, suggesting that TB treatment or complications from concurrent disease contribute a higher financial burden than DM management only.

At baseline, patients were being diagnosed for TB as well as registering for the TANDEM study so it is expected that the average time spent at the health facility at baseline would be greater than at subsequent visits. TB treatment typically ends after six-months, so this visit would also be expected to be longer than the previous health care visits for treatment in order to ensure that ending TB treatment is warranted.

The round trip journey time between the patient's home and the clinic was more than twice as long for patients in the intensive monitoring arm and resulted in almost three times the cost. Patients in the intensive monitoring arm appeared to live further away from the health facility since each mode of transportation (public transportation and motor bicycle) was equally represented in each arm, except for one person taking a taxi in the intensive monitoring arm.

The human capital approach was used to value the productivity losses because the majority of patients in the standard care (73%) and intensive monitoring (76%) arms did

not report to an employer, i.e. they were home-makers or self-employed. Therefore, it was more appropriate to assess the losses from the patient's perspective and capture all the time that potential income was not earned or household/family contributions could not be made due to seeking care (van den Hout, 2010). The friction-cost method assumes that someone else would take over the duties of the patient when seeking care but this is unlikely given the patient characteristics in Bandung, even for long-term absenteeism from self-employed work. Additionally, the time away from productive activities is far less than the standard friction period of six months, after which it is assumed that the patient would be replaced by another worker.

There are several limitations to the patient cost analysis presented here. The lost income reported in this study is likely to be severely underestimated since the time patients had to spend at home because they had infectious TB or were too ill to work or in hospital was not captured. The time spent at the clinic so far, including waiting time, was captured for calculation of the lost productivity. The values obtained are likely to be underestimations since patients may not have left the facility immediately after this interaction with the clinician. Likely reasons for a delayed departure include requiring a test in another part of the health facility, collecting non-TB drugs from a separate health facility pharmacy or waiting for a relative to return to take them home.

Additionally, the impact of patient costs on the household was not captured because household income data was not accessible. This meant that the catastrophic costs could not be assessed, nor the potential of TB-DM to push people and households below the poverty line or for those already below it, even further down. Including the patient costs incurred from the first onset of TB symptoms through to diagnosis of TB, then diagnosis of DM to the end of DM monitoring was not captured in this study either. These early costs could constitute a significant proportion of the patient costs, particularly before uninsured patients become eligible for free health services related to TB and DM, and should be included in future studies about the cost of TB-DM diagnosis and treatment.

The costs of supplements and changes in lifestyle to accommodate more physical activity and a healthier diet were also not captured.

No patient specific costs for detecting or treating TB-DM was identified and the estimates calculated for screening for and treating DM in people with TB in South East Asia (US\$ 3-56 million) were imprecise and the methodology appeared quite crude (Sullivan and Ben Amor, 2012). Therefore, TANDEM is the first study to report the economic burden to patients of diagnosing and treating concurrent TB-DM.

Patient costs have been reported for patients with TB and patients with DM separately in many countries but, despite the high burden of both diseases in Indonesia, there are limited studies reporting patient incurred costs in that setting (Laurence et al., 2015, Seuring et al., 2015 49).

One study in Jogjakarta, Indonesia included the mean total patient costs reported by people with TB only (Mahendradhata et al., 2010). In that study, 58 patients with TB were treated for six months using the DOTS strategy at health centres and reported a mean total cost of \$ 33.75 (2005 USD). Though my study reported total patient costs of US\$ 14.21 and US\$ 38.27 during the first six months of the standard and intensive RCT arms respectively, the study in Jogjakarta included the lost earnings of carers. If carer costs were excluded and the mean costs were inflated to 2014 values in Jogjakarta, the TB treatment costs there (US\$ 51.85) would be greater than the TB-DM treatment costs in Bandung. This could be explained by the financial protection offered to patients in an RCT, even when standard care is costed; avenues for financial protection, such as insurance coverage, are more likely to be explored for patients by the RCT staff, thereby ensuring that patients do not pay for health services that they are entitled to access free of charge.

Andayani and Imaningsih (2007) reported the monthly out-patient costs for DM in Yogyakarta, from the perspective of the patient, as US\$ 19.97. This is far greater than the monthly costs incurred by patients with TB-DM in Bandung, which ranges from US\$ 1.07 for standard DM care to US\$ 2.72 for intensive DM monitoring. Again, we see the effect of national health insurance, which now provides free access to a much wider range of drugs and tests to a larger pool of eligible individuals than was the case in 2004 when the study was conducted in Yogyakarta.

Descriptions of what DM treatment entailed varied considerably and inclusion of DM complications was not consistent, therefore comparison between studies and countries was tenuous, reinforcing why it is difficult to use data from one country to estimate for another. When treatment costs are not well described or disaggregated, they cannot be applied with confidence to other settings, as would have had to occur for Indonesia and Romania since no studies with primary DM treatment costs were identified for either country within Seuring's (2015) global systematic literature review. Methods for assessing productivity losses also varied, partially explaining the reason for such a wide range of values, particularly within country income groups.

A separate review on DM treatment costs specific to Indonesia had monthly costs that were very different, even when comparing two studies that included DM-related complications, appeared to have similar cost components and were set in the same hospital in Yogyakarta. The costing and analysis methods were different, but the papers did not provide enough information to discern where these differences had the greatest impact.

The IDF estimates of the mean DM-related (treatment and management) expenditure per person in 2015 was US\$ 171 (Int. \$471) for Indonesia and US\$ 579 (Int. \$ 1,136) for Romania (IDF, 2015). These values are 11% less in Indonesia and 34% more than the values extracted from the literature searches (**Error! Reference source not found.**). This is perhaps explained by the IDF values not including the costs of DM complications or by a difference in the cost composition, but it is more likely to be due to the estimation method used by the IDF. The IDF method assumed DM expenditure to be two to three times more than in people without DM, and applied an attributional fraction model to the total health expenditure estimates for 2014 (da Rocha Fernandes et al., 2016).

11.5 Conclusion

So few patients with TB-DM reported any out-of-pocket costs that there seems to be much progress in providing universal health coverage for TB-DM care in Bandung. The greatest financial burden for patients with concurrent disease remains the productivity losses incurred by frequent clinic visits. The impact of lost income would be even more severe

when time spent in hospital or at home and unable to work, and time of carers are also included. While improvements can still be made to reduce the burden on patients, 2% expenditure of monthly income on TB-DM treatment is promising, particularly if this remains the case for treatment of patients with TB-DM in routine services.

PART IV – DISCUSSION AND CONCLUSION

Chapter 12 Discussion

The aim of this thesis was to assess the costs, operational feasibility and health-related quality of life impact of various screening and management strategies for patients with concurrent TB and DM in Indonesia, Peru and Romania. The data were collected alongside cross-sectional and RCT studies in the TANDEM project. Patients with TB and patients with DM were recruited at public health facilities in the three countries and screened for DM and TB, respectively. In Indonesia, patients with TB-DM were treated for both diseases for six months and followed-up for an additional 12 months.

The study aim was achieved by focusing on five specific objectives:

1. To compare the mean cost per accurate diagnosis of DM in people with TB, using various algorithms of four screening tests (DM risk score, POC RPG, urine dipstick and POC HbA1c), a diagnostic test (FBG) and the gold standard (laboratory HbA1c), in Indonesia and Romania.
2. To compare the mean cost per accurate diagnosis of TB in people with DM, using various algorithms of two screening methods (TB symptom screen and CXR), and sputum examination (smear and culture), if irregular results were found, in Indonesia and Romania.
3. To evaluate and compare the operational feasibility of various DM screening strategies in persons with TB; and various TB screening strategies in persons with DM, in Indonesia and Peru.
4. To compare the health-related quality of life of patients with concurrent TB-DM receiving 6 months of TB treatment and two different clinical management strategies for DM in Indonesia:
 - a. Standard care: routine practice at each study site;
 - b. Enhanced intensive monitoring, with education and counselling: FBG and clinical review at baseline, 2 weeks, 4 weeks and then monthly until 12 months after TB treatment completion.

5. To compare the patient costs for diagnosis and treatment of concurrent TB-DM during 6 months of TB treatment and two different clinical management strategies for DM in Indonesia:
 - a. Standard care: routine practice at each study site;
 - b. Enhanced intensive monitoring, with education and counselling: FBG and clinical review at baseline, 2 weeks, 4 weeks and then monthly until 12 months after TB treatment completion.

The paper-style format of this thesis allowed me the opportunity to summarise the main results and discuss their implications at the end of each results chapter. This discussion chapter summarises and pulls together the key findings from those distinct topics. Subsequently, study limitations are acknowledged, and contributions to the body of knowledge about integrating TB-DM services, the next steps in the research agenda and potential policy implications are considered. The chapter ends with personal reflections of the entire PhD journey.

12.1 Main research findings

Chapter 6 presented the SES distribution of patients in Indonesia, Peru and Romania, which was developed using a PCA of asset indices. This distribution was a relative measure to compare the SES status of patients in the study, but did not provide absolute values of poverty or income group within the population. The non-durable and durable assets, which were representative of different SES quintiles, varied amongst countries. For instance, having a computer was the strongest indicator of wealth in Indonesia and Romania but this was not the case in Peru, where having a refrigerator or a microwave were found to be the strongest indicators of wealth.

Also, there are socio-cultural and geographic differences between countries that affected which assets were most suitable for assessing SES. In multi-country studies, despite a desire for consistency across sites, different assets may need to be assessed in each country (Howe et al., 2012). For instance, having a flush toilet was the only SES indicator in the sanitation category for Indonesia and Peru while Romania had both flush

toilets and traditional toilets. Even in the poorest quintile, a high proportion of households have flush toilets in Indonesia (77%) and Peru (84%), but in Romania 92% of people in the wealthiest quintile have flush toilets while only 4% of the poorest quintile have one. In Peru, the wealthiest quintile had the greatest proportion (97%) of households with a private water source, but the reverse was true in Romania where the poorest quintile had the greatest proportion (99%) of households with a private water source. This could be explained by the different historical approaches to sanitation infrastructure between Eastern Europe and South America or possibly variation in what was understood by a private water source in the two settings. A private water source and purchasing water were evenly distributed amongst quintiles in Indonesia, suggesting that very little infrastructure for potable water exists in Bandung.

Financial structures or regulation also varies between the three countries; 27% of the wealthiest quintile had a bank account in Peru while this rose to 57% in Romania and 78% in Indonesia. Furthermore, people with DM tended to be wealthier compared to people with TB.

Key programmatic challenges of bi-directional TB-DM screening were assessed in Research Papers 3 and 4. The results of these papers provide evidence from Indonesia, Peru and Romania that screening people with TB for DM has a lower cost per accurate diagnosis compared to screening people with DM for TB. Systematic screening for TB in people with DM should only be considered in settings with a high TB prevalence (at least 100 cases per 100,000 population (Lonroth et al., 2014)).

Some variability in the ranking of the costs per accurate diagnosis for the DM algorithms between Indonesia and Romania suggests that consideration of country profile and disease burden is needed when making assessments about the most appropriate DM diagnostic algorithm in people with TB. This applies particularly to the repeated diagnostic tests after an initial screen. In Research Paper 3, the test combination with the lowest cost per accurate diagnosis was the DM age screen and POC RPG algorithm, at US\$ 1.49 in Indonesia and US\$ 5.64 in Romania. The urine dipstick and repeated FBG algorithm had the second lowest cost per accurate diagnosis in Indonesia, but not in

Romania. The urine dipstick and repeated laboratory HbA_{1c} algorithm had the third lowest cost per accurate diagnosis in Romania, but was far more costly in Indonesia.

In people with TB, who may be experiencing TB induced transitory hyperglycaemia, HbA_{1c} tests are most appropriate for detecting true DM (Adepoyibi et al., 2013). The POC HbA_{1c} test performs well as a screening test, but would need to be combined with a diagnostic test, such as repeated laboratory HbA_{1c}. This algorithm is the second most expensive per accurate diagnosis in Indonesia and Romania, at US\$ 43.58 and US\$ 52.59, respectively.

Data obtained in the costings in the two countries reiterate the guidelines of the micro-costing methodology paper in Chapter 7, which states that it is important to include overhead costs in the cost per test; we saw a range of 1%-52% of TB tests being attributed to overhead costs. Omitting these costs could substantially impact decisions about the most cost-effective diagnostic pathway or algorithm.

Research Paper 4 assessed the operational feasibility of performing DM tests in people with TB attending DOTS clinics and TB tests in people with DM at DM clinics from the perspective of HCWs, in Indonesia and Peru. Operational feasibility was defined using seven domains. The DM POC tests performed well in most domains, but the POC HbA_{1c} test had no clear advantage over the POC RPG test and the urine dipstick was deemed inappropriate (not useful) for diagnosing DM in people with TB. HCWs reported that sample collection by finger prick was not well liked by patients, these samples were compromised more than urine or blood draw and the down time of the POC HbA_{1c} machines increased as the machine aged. Given the clinical and practical preference for the POC HbA_{1c} test (Adepoyibi et al., 2013), if improvements could be made to the sample collection method as well as quality of the samples and equipment, it could be a favoured option for DM screening in DOTS clinics. This is particularly relevant where POC diagnostic tests for HIV in patients with TB have proven to be efficient in increasing diagnosis, improving access to care and early treatment for concurrent disease (Riza et al., 2014, Harries et al., 2010).

The CXR was the most operationally feasible test for TB in people with DM in both Indonesia and Peru, particularly in terms of performance time and accessibility given the already existing infrastructure in these settings.

In Chapter 10, people with TB only were shown to have better HRQoL at baseline than people with TB-DM in Peru and Romania. No difference in HRQoL between these two groups was found in Indonesia, which also had the largest sample size. There is weak evidence that people undergoing intensive DM monitoring have better HRQoL than those in standard care after six months of TB treatment and DM management. The association was further attenuated after adjustment for clinical and demographic confounders, including the SES quintiles generated in Chapter 6. The quintiles were also used to assess the differential effects of SES on HRQoL of patients with TB and TB-DM at baseline. Patient HRQoL measured at baseline improved from the poorest to the wealthiest quintiles for Indonesia only.

In the last results chapter it was shown that very few patients reported making out-of-pocket payments for accessing TB-DM diagnosis and treatment in Indonesia, potentially highlighting the success of augmented universal health coverage in this setting. The burden of out-of-pocket payments and lost productivity was however 2.5 times greater for patients in the intensive DM monitoring arm than those in standard DM care, comprising 2% and less than 1% of the average monthly income, respectively. These proportions can both be considered relatively low, suggesting that TB care in Indonesia has been successful in bringing services close to the patient.

The mean monthly costs for TANDEM patients in the intensive monitoring arm (US\$ 2.72) was approximately US\$ 17 less than the monthly out-patient costs (direct medical out-of-pocket payments only) for DM care (with no complications) in Yogyakarta (Andayani and Imaningsih, 2007). The difference in costs is largely due to the heavy financial burden of DM drugs, which accounted for 96% (US\$ 19.25) of the monthly cost of DM care in the 2004 study. Since the formation of JKN to provide UHC in 2014, there is broader health insurance coverage of the Indonesian population. More patients were

eligible for free DM drugs in TANDEM than in the Yogyakarta study as the number of DM drugs included in the national formulary has increased.

The mean total patient costs during six months of DOTS treatment and standard DM management (US\$ 14.20) was less than half the costs reported (out-of-pocket payments, transportation and productivity losses) in a study in Jogjakarta for patients with TB only (US\$ 33.75) (Mahendradhata et al., 2010). Out-of-pocket payments for consultations, tests and drugs before starting DOTS were included in the Mahendradhata study and accounted for 49% (US\$ 16.56) of the mean total patient costs. These 'before-treatment' costs, where seeking a TB diagnosis can take months and include misdiagnosed treatment, were not included in the TANDEM study. When these costs are removed from the Yogyakarta data, the mean total cost (US\$ 17.19) is still approximately 20% more than the TANDEM values in the standard DM management arm of the RCT (US\$ 14.20). There may have been some financial protection for the patients conferred by participating in the RCT, where staff are more likely to ensure that patients are accessing insurance coverage to pay for health services and minimizing their out-of-pocket payments.

12.2 Strengths and limitations

Collection of some of the economic data was integrated into the TANDEM RCT, thus facilitating access to the data. The epidemiological data, such as the sensitivity and specificity of diagnostic tests, were easily calculated by accessing an online project database (Ramsey et al., 2015). The PCA method provided a relative measure of SES of patients that was methodologically robust and less subject to recall or social desirability bias than collecting income, expenditure or consumption data, and asset index data collection period is shorter than the latter two methods (Filmer and Pritchett, 2001, Gwatkin et al., 2007).

Overall, the PhD journey was very rewarding but there were several challenges along the way that impacted upon the successful conduct of various components of the research. These limitations are presented here.

12.2.1 Data availability and quality

All of the data for this PhD were collected alongside a pragmatic RCT, meaning that the analysis in the thesis was reliant upon the timing and success of the cross-sectional recruitment study and RCT. The operational challenges of conducting a study in busy health facilities alongside overworked and sometimes underappreciated staff, as well as a slower than expected patient recruitment rate for the bi-directional screening caused several delays in cost and operational feasibility data collection. Due to these delays, the RCT is approximately six months behind the proposed schedule and a no-cost extension had to be sought from the funders to ensure that the primary study objective could be met. Hence, at the time of PhD conclusion only preliminary findings were available for the patient costs and HRQoL data and the original objective of performing an economic evaluation had to be modified since the effect of the intervention will not be known until July 2017.

There was some attrition of HCWs for both TANDEM funded staff and those working directly with the health facilities. It is unclear if this attrition was due to staff leaving the facility altogether or performing other duties within the same facility. This staff movement meant that different HCWs were generally interviewed at the first and second time points for the operational feasibility analysis, making it difficult to assess whether HCWs found the DM screening tests easier with time. However, indications of how the health system adapted can be inferred by the high staff turn-over.

The patient cost comparisons for the two arms of the RCT may be underpowered because the sample size of the trial was based on the primary clinical outcome only (Ramsey et al., 2015). This may restrict future economic evaluation hypothesis testing in Indonesia.

As mentioned in Chapter 7, LMICs tend to not have established cost accounting systems. This was the case in Indonesia and Romania and therefore extensive primary data collection was needed to obtain the resource utilisation and unit costs of the diagnostic tests as well as overheads, as presented in Chapter 8. The paper on how to do a micro-costing of laboratory tests in Chapter 7 was my attempt to fill this gap and provide

guidance on the generation of context specific cost data, with the ultimate goal of enabling more accurate and appropriate decision making for countries with limited resources and costing infrastructure. The micro-costing performed in Chapter 8 faced many of the challenges highlighted in Chapter 7. These included obtaining and appropriately allocating shared overhead, equipment and consumable costs.

12.2.2 Biases

Online case report forms were used in the RCT to capture patient data, including asset indices, HRQoL, patient costs and inputs for calculating the sensitivity and specificity of the diagnostic tests. While it is immensely beneficial to have these data collected at the time of the patient visits, these economic and epidemiological data were collected by clinicians, most of whom were not specifically trained to collect them. This may have led to interviewer bias.

Using the asset index approach rather than the consumption or expenditure reporting approaches for estimating SES in TANDEM patients, as presented in Chapter 6, reduced recall bias. However, this may have been replaced by social desirability bias, with patients reporting more assets than they owned to present themselves as being better off than they were. The interviews with the HCWs for the operational feasibility analysis in Chapter 9 and the patient-reported HRQoL in Chapter 10 were also susceptible to social desirability bias.

Some patients with TB-DM refused to participate in the Indonesian RCT because they felt too unwell. Even though RCTs are less affected by selection bias due to the random allocation to different arms of the trial, it was still possible, as those who opted to participate (68%) may be less representative of the entire population of people with TB-DM. This can make the results of the HRQoL, and possibly the patient costs, less generalisable.

The choice of gold standard for DM tests in TANDEM, laboratory HbA_{1c}, may also limit the generalisability of the cost per accurate diagnosis findings. The HbA_{1c} was chosen instead of the traditional gold standard, oral glucose tolerance test, because the latter

is considered to be impractical and disproportionately laborious for people with TB. Given that the WHO has endorsed the use of the laboratory HbA_{1c} as a single diagnostic test, once its availability is expanded, it may become a more common gold standard, particularly for TB-DM.

For the HRQoL analysis no country specific value sets were available for Indonesia, Peru or Romania. Therefore, the cultural and social norms that influence how individuals experience and report their mobility, self-care, usual activities, pain/discomfort and anxiety/depression status were not represented in the utility scores. To address this, sensitivity analyses were performed using value sets from other countries, but there were no differences in the strength or significance of the associations.

12.2.3 Logistical challenges

This multi-country PhD made coordination of data collection challenging, particularly since there were no other economists or researchers with an understanding of health economics at the sites to consistently monitor the data collection process. Before gaining access, obtaining cost data often required many follow-up visits that stretched beyond my three to four week visits to each country.

In order to successfully collect data of a high quality, several trips to each country were needed over the three and a half years of patient recruitment and treatment. The sites are geographically spread across the world and only Romania was easily accessible from my base in London. Therefore, due to limited resources, I was not able to visit all sites as often as needed. This meant that some data collection and data quality control had to be done remotely, which was not ideal. During my visits to the sites, I provided training about costing techniques to TANDEM colleagues. They were then able to follow-up on my cost and resource utilisation data requests and forwarded them to me electronically. I made every effort to thoroughly check the data quality upon receipt, ensuring:

1. Costs, rather than charges, were obtained;
2. Resource units were accurate by comparing with other sites;

3. Preliminary analysis of the costs of diagnostic tests was performed early, to ensure that values were not excessively different from those in literature reviews or if they were, I could explain the differences;
4. Other data validity checks.

12.2.4 Health system constraints

The initial plan for TANDEM during protocol development was that the three countries would conduct the RCT. However, during the bi-directional cross-sectional screening study many obstacles became apparent and Indonesia was the only country that could implement the RCT and comply with the protocol specifications.

In Peru, there were insufficient research staff to support the already overworked health facility staff during both the bi-directional screening and RCT activities (Riza et al., 2014). This was a key reason for not being able to conduct the micro-costing of diagnostic test in Peru. Intensive DM management of patients was meant to occur at the General Hospital in Lima (HAMA), but the logistics of getting patients with TB-DM, many of whom lived hours away by public transport, were in a lower SES and ill, to return to HAMA was difficult to navigate. Additionally, recurrent countrywide strikes by HCWs between 2014 and 2016, led to a restriction of many health care services to emergency care only. These factors exacerbated the situation and after many attempts to engage staff at the HAMA DM Clinic, the RCT was stopped.

Romania also experienced challenges with the RCT. The plan was to engage the diabetologists and family physicians throughout Dolj and Gorj counties who were treating people with DM in the standard care arm of the RCT so they would ensure patient outcomes were reported to TANDEM. DM management in the intensive monitoring arm was to be managed daily by a TANDEM resident doctor affiliated with each of the TB hospitals and overseen by one senior diabetologist based in the capital city of Bucharest, over 200 kilometres away. As many as 40 patients were recruited for the RCT in Romania, but the logistics of continuing the trial became too difficult, especially when it became apparent that the TANDEM DM management protocol did not match regulated DM management in Romania. Clinicians involved in the care of

patients with TB-DM were not prepared to allow the intervention protocol to be implemented. Hence, the RCT in Romania was stopped. These changes with the RCT meant that plans to collect HRQoL and treatment costs data in the three countries were constantly being modified. It also reinforced that many changes within the health system would be needed in Peru and Romania before integration of TB-DM services could realistically be implemented.

From a health systems perspective, the vertical nature of the TB and NCD programmes in Peru and Romania made collaboration between respective programme administrators, and indeed clinicians, challenging, almost impossible at times. In addition to being two distinct programmes that have traditionally had no need to work together, the structures are markedly different. The NTPs in the three countries have successfully implemented an approach that controls TB; patients are registered and evaluated in cohorts and diligently followed-up (Harries et al., 2015). That structure does not exist in the NCD programmes and therefore, even if a patient with TB is diagnosed with DM, a national DM register does not exist in Peru (Seclen et al., 2015). There is a DM register in Romania, but there are delays in registering patients onto it (Mota and Dinu, 2013). The register is controlled at the county level in Romania and patients accessing care in more than one county have poor continuum of care. Additionally, there is a lack of awareness within the medical community about the interactions between TB and DM in all countries.

The above challenges manifested themselves in all TANDEM countries, but the difference in the Indonesian context was political will present at all levels of the public health sector, to address TB-DM. This is evident in the Bali Declaration, which clearly indicates their intention to deal with the syndemic (The Union, 2015a). In Romania, guidelines from the governing health insurance body, NHIH, state that concurrent diseases should be treated separately and make no allowances for programmes to coordinate funds or activities (WHO and ECDC, 2015). The Peruvian government seems to give no official directive for treating concurrent TB-DM (Peru Stop TB Committee, 2009).

Notwithstanding these limitations, the PhD made a number of novel contributions to the field of TB-DM by assessing the costs of TB-DM services, operational feasibility of bi-directional screening and the health-related quality of life of persons with both diseases. These are discussed in the next three sections.

12.3 Contribution to knowledge

This PhD has incorporated health economics methods and epidemiological analysis to produce complementary evidence that supports the screening of people with TB for DM as the most cost-effective route, and highlights potential barriers and opportunities for implementation into routine practice.

If intensive DM monitoring is found to be effective, preliminary analysis suggests that patients who received the intervention will have a better HRQoL than those in standard DM care. Patient costs incurred while receiving TB and DM treatment were greater for those in the intervention arm, driven largely by lost productivity, due to almost twice as many health care visits than in the standard care arm. The incremental patient out-of-pocket costs of DM management over TB treatment appears to be less than the cost of equivalent DM management a decade ago, suggesting that improvements in health insurance coverage can enable the provision of care for concurrent disease without a severe burden on the patient. The main contributions of this thesis are presented according to the fields of health economics and TB-DM services.

12.3.1 Health economics

The diagnostic and patient costs are the first primary cost data available for TB-DM and are an initial step towards conducting economic evaluations of TB-DM services. We would expect the diagnostic costs to be within the range of values for TB and DM tests in disease naïve patients and Chapter 8's discussion confirms this is indeed the case, with the exception of the LTBI tests (IGRA and TST), which are as much as 50% more expensive in patients with DM than stated in the published literature.

The micro-costing paper contributes to the field of health economics by providing a practical guide for obtaining the costs of laboratory tests, and other health technologies, in settings with weak or no cost accounting systems. Common challenges of cost data collection and analysis are presented with potential solutions: obtaining equipment utilisation, allocating of shared costs, costing all relevant diagnostic pathways, and ensuring that overhead costs are included, where possible.

12.3.2 TB-DM services

This is the only known study to administer a HRQoL assessment tool to patients with TB-DM. It offers the patient perspective on the impact of different approaches to DM management while undergoing TB treatment, which can be emotionally, mentally, socially, physically and physiologically overwhelming.

Implementation of bi-directional screening for TB and DM tests was assessed using mostly quantitative approaches. By including the semi-qualitative analysis of the operational feasibility study, some context has been provided to understanding why bi-directional screening is difficult and how this could be addressed.

12.4 Policy implications

International bodies, such as The Union, WHO and World Diabetes Federation have acknowledged the link and burden of TB-DM, and have gone as far as to label it a “looming co-epidemic” (The Union and WDF, 2014, Harries et al., 2011), but no international protocols exist for detecting or treating the concurrent diseases. As a result, it is crucial to synthesise the available evidence with the ultimate goal of informing policies and protocols to manage the syndemic. As discussed in Chapter 1, The Framework by The Union and WHO recommends collaborative activities for addressing the TB-DM syndemic and identifies priority research questions (The Union and WHO, 2011). TANDEM has addressed the majority of the high-priority questions and this PhD supplements this by assessing the costs of detecting concurrent TB-DM, which was a medium priority question.

TANDEM has shown that screening people with TB for DM yields more patients with concurrent disease and my findings supplement these epidemiological data by providing some initial economic and operational evidence that can contribute to the development of policy guidelines for detecting TB-DM through the preferred pathway.

The evidence related to the treatment of concurrent TB-DM is still preliminary, but initial findings from this research suggests that in Indonesia HRQoL is better for patients in the intensive arm, but patient costs are 2.5 times greater than patients in the standard care arm. Transportation costs account for approximately 15% of patient costs for the treatment of TB-DM. The costs incurred by patients prior to a diagnosis of TB or DM (that is the costs while seeking a diagnosis) are not fully captured in this study, but needs to be understood in the Indonesian setting. Hence, policy formulation around TB-DM must consider both patient and provider costs when planning service provision for patients and must explore the feasibility of alternative ways of providing services, such as through communities, health centres, or mobile health facilities.

The preliminary RCT treatment findings can be useful for establishing treatment protocols, particularly from the patient perspective with respect to financial burden and the HRQoL, but should be confirmed if the intervention is shown to be clinically effective.

12.5 Future research agenda

Once the RCT has concluded, the immediate plan is to update the analysis of the HRQoL and patient costs data. Provider treatment cost data collection began in Indonesia in 2016 but can only be completed when the full resource utilisation (captured in the electronic database - REDCap) for DM management and follow-up is available for all patients in the RCT in July 2018. At that time, the incremental costs of DM management and monitoring for TANDEM patients with TB-DM will be calculated and compared. Using a Markov model, the cost-effectiveness of detecting and treating concurrent TB-DM will be assessed. Collaborative efforts have already begun to secure funding to build

a mathematical model to simulate the lifetime effects and costs of concurrent TB-DM treatment.

TANDEM and this PhD stemmed from a need to understand how to detect and treat patients with TB-DM who are already accessing the health system. The long-term goal for this area of research is the integration of DM screening and treatment into routine TB services in various settings.

There were several related analyses that could not be performed in TANDEM and leave unanswered questions. A POC test is the most feasible diagnostic option, particularly for bi-directional screening. There are as yet no simple and accurate POC assays for detecting active TB, but Xpert[®] MTB/RIF, which has been endorsed by the WHO for detecting drug-resistant or HIV-associated PTB, is easy to use and produces results faster than smear microscopy or culture (Lawn et al., 2013, WHO, 2011a). It therefore has the potential to be a useful TB diagnostic tool in people with DM. Although the Xpert[®] MTB/RIF assay was included in TANDEM, it was not assessed in this thesis as there were delays in accessing the test in Indonesia and Peru and inconsistent use across all sites. Future research needs to assess the feasibility, diagnostic accuracy and cost-effectiveness of the Xpert[®] MTB/RIF assay for detecting TB in people with DM, possibly in combination with the CXR (WHO, 2013a, Harries et al., 2015).

No validated TB-specific tools for measuring patient reported quality of life outcomes exists. As discussed in Chapter 1, the DR-12 and SGRQ tools have both been suggested as options for measuring HRQoL in people with TB. Neither tool has been fully validated specifically for this purpose, and this was not possible in TANDEM for people with TB and DM, but is a potential area for additional research.

12.6 Lessons learnt – reflections on a multi-country PhD

The explicit knowledge I have gained during this PhD is illustrated in the thesis. I learnt how to perform systematic literature reviews, conduct micro-costings, achieved an advanced level of data management and analysis skills in Stata, and successfully engaged with multi-disciplinary teams in varied cultural settings. This thesis was a wonderful

combination of health economics methods, analytical epidemiology and project management.

My background is in mathematics and prior to this PhD, I had never worked in TB or DM. Having to obtain detailed knowledge about not just one, but two diseases has pushed the boundaries of my O'Level biology. I have immensely enjoyed learning about the two diseases and about the complications caused by concurrent TB-DM, but this has perhaps been the most unfamiliar part of the PhD. This challenge has been complicated by the fact that while TB-DM is acknowledged to be of public health significance, published research about the epidemiological, clinical and social implications of TB-DM has only begun to flow steadily in the last few years. Therefore, I had to rely heavily on TANDEM colleagues to share their respective expertise in the area.

Upon reflection, I gained a lot of tacit knowledge. My leadership skills have been enhanced over the last four and a half years, and I have become increasingly confident in my ability to coordinate and lead on this large study with several components (socio-economic status, costs, operational feasibility and HRQoL), in three countries. This required refinement of my organisation skills and ensuring document quality control, while allowing context specific components to be incorporated. Since Dr Griffiths and I were the only health economists involved in the TANDEM study, it was crucial to get buy-in from our colleagues, some of whom did not fully appreciate why a health economics component was needed in the study. I found myself becoming a bit of a salesperson for health economics and it took several interactions to ensure that they understood the objectives of my PhD and how those outcomes would add to the success of TANDEM.

Once TANDEM members were on board, I needed to gain the same appreciation and cooperation from people outside the project that I interviewed for data, including clinicians for resource utilisation; department heads, accountants, procurement officers, financial directors, facility directors and their personal assistants for unit costs; HCWs for operational feasibility; and staff involved in any of the TANDEM activities for the patient and sample workflows. I needed to be understood, respected and trusted by

people who spoke different languages, came from different cultures and have different professional backgrounds. Reading body language and the tone of a room, a measure of intuition and a fair amount of emotional intelligence enabled me to do this.

On occasions where I was referred from one individual to the next, who would surely have the data I needed, it was difficult not to get frustrated or overwhelmed, but I persevered. I was not always able to get all the data I wanted, but I obtained enough high quality data to provide novel findings, and I made some friends along the way.

Chapter 13 Conclusion

This thesis provides novel cost, operational feasibility and HRQoL evidence to contribute towards resolving policy and programmatic uncertainty around identifying and managing people with concurrent TB-DM.

As the prevalence of DM continues to increase in settings with a high burden of TB, bi-directional screening should already be happening so that we can get ahead of the syndemic curve and temper it before the doom of DM driven increases in TB cases, as predicted by The Union and WDF, can take hold.

There are lessons to be learnt from the health system structure in Indonesia where patients with concurrent disease are able to access health services with minimal or no out-of-pocket payments. However, clinic visits for TB and DM management can be onerous with patients in the intensive arm requiring an average of 12 visits, whereas those in the standard arm required seven, over the 18 months of the trial. Therefore, decisions about the number of visits needed to effectively manage DM during and after TB treatment are important and should be considered in collaboration with clinical requirements and programme capacity.

While much additional research is still needed to address health system issues for programme integration of bi-directional screening, TB and DM treatment and follow-up for TB recurrence, the evidence generated during this PhD is directly relevant to policy makers, particularly in Indonesia and Romania, but also in settings with a similar burden of TB-DM.

References

- ABUBAKAR, I., LIPMAN, M., MCHUGH, T. D. & FLETCHER, H. 2016. Uniting to end the TB epidemic: advances in disease control from prevention to better diagnosis and treatment. *BMC Med*, 14, 47.
- ADEPOYIBI, T., WEIGL, B., GREB, H., NEOGI, T. & MCGUIRE, H. 2013. New screening technologies for type 2 diabetes mellitus appropriate for use in tuberculosis patients. *Public Health Action*, 3, S10-7.
- AGGARWAL, A. N., GUPTA, D., JANMEJA, A. K. & JINDAL, S. K. 2013. Assessment of health-related quality of life in patients with pulmonary tuberculosis under programme conditions. *Int J Tuberc Lung Dis*, 17, 947-53.
- AL-LAWATI, J. A. & TUOMILEHTO, J. 2007. Diabetes risk score in Oman: a tool to identify prevalent type 2 diabetes among Arabs of the Middle East. *Diabetes Res Clin Pract*, 77, 438-44.
- ALBERTI, K. G., ZIMMET, P. & SHAW, J. 2007. International Diabetes Federation: a consensus on Type 2 diabetes prevention. *Diabet Med*, 24, 451-63.
- ALCALDE-RABANAL, J. E., LAZO-GONZALEZ, O. & NIGENDA, G. 2011. [The health system of Peru]. *Salud Publica Mex*, 53 Suppl 2, s243-54.
- ALISJAHBANA, B., SAHIRATMADJA, E., NELWAN, E. J., PURWA, A. M., AHMAD, Y., OTTENHOFF, T. H. M., NELWAN, R. H. H., PARWATI, I., MEER, J. W. M. V. D. & CREVEL, R. V. 2007. The Effect of Type 2 Diabetes Mellitus on the Presentation and Treatment Response of Pulmonary Tuberculosis. *Clinical Infectious Diseases*, 45, 428-435.
- ALVIN, M. D., MILLER, J. A., LUBELSKI, D., ROSENBAUM, B. P., ABDULLAH, K. G., WHITMORE, R. G., BENZEL, E. C. & MROZ, T. E. 2014. Variations in cost calculations in spine surgery cost-effectiveness research. *Neurosurg Focus*, 36, E1.
- AMARE, H., GELAW, A., ANAGAW, B. & GELAW, B. 2013. Smear positive pulmonary tuberculosis among diabetic patients at the Dessie referral hospital, Northeast Ethiopia. *Infectious Diseases of Poverty*, 2.
- AMEK, N., VOUNATSOU, P., OBONYO, B., HAMEL, M., ODHIAMBO, F., SLUTSKER, L. & LASERSON, K. 2015. Using health and demographic surveillance system (HDSS) data to analyze geographical distribution of socio-economic status; an experience from KEMRI/CDC HDSS. *Acta Trop*, 144, 24-30.
- ANDAYANI, T. M. & IMANINGSIH, I. 2007. Cost analysis of antidiabetic drugs for diabetes mellitus outpatient in Kodya Yogyakarta Hospital. *Malaysian Journal of Pharmaceutical Sciences*, 5, 19-23.
- ANDREWS, J. R., LAWN, S. D., RUSU, C., WOOD, R., NOUBARY, F., BENDER, M. A., HORSBURGH, C. R., LOSINA, E., FREDBERG, K. A. & WALENSKY, R. P. 2012. The cost-effectiveness of routine tuberculosis screening with Xpert MTB/RIF prior to initiation of antiretroviral therapy: a model-based analysis. *AIDS*, 26, 987-995 10.1097/QAD.0b013e3283522d47.
- ASPLER, A., MENZIES, D., OXLADE, O., BANDA, J., MWENGE, L., GODFREY-FAUSSETT, P. & AYLES, H. 2008. Cost of tuberculosis diagnosis and treatment from the patient perspective in Lusaka, Zambia. *Int J Tuberc Lung Dis*, 12, 928-35.

- ATIF, M., SYED SULAIMAN, S. A., SHAFIE, A. A., ASIF, M., SARFRAZ, M. K., LOW, H. C. & BABAR, Z.-U.-D. 2014. Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study. *Health and Quality of Life Outcomes*, 12, 19.
- ATUN, R. A., BENNETT, S. & DURAN, A. 2008. When do vertical (stand-alone) programmes have a place in health systems? *In: WORLD HEALTH ORGANIZATION & EUROPEAN OBSERVATORY ON HEALTH SYSTEMS AND POLICIES (eds.) Health Systems and Policy Analysis*. Copenhagen, Denmark: WHO Regional Office for Europe.
- ATUN, R. A., SAMYSHKIN, Y., DROBNIIEWSKI, F., BALABANOVA, Y., FEDORIN, I., LORD, J. & COKER, R. J. 2006. Costs and outcomes of tuberculosis control in the Russian Federation: retrospective cohort analysis. *Health Policy Plan*, 21, 353-64.
- AYE, R., WYSS, K., ABDUALIMOVA, H. & SAIDALIEV, S. 2010. Household costs of illness during different phases of tuberculosis treatment in Central Asia: a patient survey in Tajikistan. *BMC public health*, 10, 18.
- BADAN PUSAT STATISTIK (STATISTICS INDONESIA), NATIONAL POPULATION AND FAMILY PLANNING BOARD (BKKBN), KEMENTERIAN KESEHATAN (KEMENKES - MOH) & ICF INTERNATIONAL 2013. Indonesia Demographic and Health Survey 2012. Jakarta, Indonesia.
- BAKER, M. A., HARRIES, A. D., JEON, C. Y., HART, J. E., KAPUR, A., LONNROTH, K., OTTMANI, S. E., GOONESEKERA, S. D. & MURRAY, M. B. 2011. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med*, 9, 81.
- BALAKRISHNAN, S., VIJAYAN, S., NAIR, S., SUBRAMONIAPILLAI, J., MRITHYUNJAYAN, S., WILSON, N., SATYANARAYANA, S., DEWAN, P. K., KUMAR, A. M., KARTHICKEYAN, D., WILLIS, M., HARRIES, A. D. & NAIR, S. A. 2012. High diabetes prevalence among tuberculosis cases in Kerala, India. *PLoS One*, 7, e46502.
- BANTUBANI, N., KABERA, G., CONNOLLY, C., RUSTOMJEE, R., REDDY, T., COHEN, T. & PYM, A. S. 2014. High rates of potentially infectious tuberculosis and multidrug-resistant tuberculosis (MDR-TB) among hospital inpatients in KwaZulu Natal, South Africa indicate risk of nosocomial transmission. *PLoS One*, 9, e90868.
- BARLETTA, G., ZANINOTTO, M., FAGGIAN, D. & PLEBANI, M. 2013. Shop for quality or quantity? Volumes and costs in clinical laboratories. *Clin Chem Lab Med*, 51, 295-301.
- BASU, S., YOFFE, P., HILLS, N. & LUSTIG, R. H. 2013. The Relationship of Sugar to Population-Level Diabetes Prevalence: An Econometric Analysis of Repeated Cross-Sectional Data. *PLoS ONE*, 8, e57873.
- BENNETT, C. M., GUO, M. & DHARMAGE, S. C. 2007. HbA(1c) as a screening tool for detection of Type 2 diabetes: a systematic review. *Diabet Med*, 24, 333-43.
- BIORAC, N., JAKOVljeVIC, M., STEFANOVIĆ, D., PEROVIĆ, S. & JANKOVIĆ, S. 2009. [Assessment of diabetes mellitus type 2 treatment costs in the Republic of Serbia]. *Vojnosanit Pregl*, 66, 271-6.
- BOCCHINO, M., GRECO, S., ROSATI, Y., MATTIOLI, G., MARRUCHELLA, A., DE MORI, P., BIBBOLINO, C., GIRARDI, E., SQUARCIONE, S. & SALTINI, C. 2006. Cost determinants of tuberculosis management in a low-prevalence country. *Int J Tuberc Lung Dis*, 10, 146-52.
- BORCH-JOHNSEN, K., LAURITZEN, T., GLUMER, C. & SANDBAEK, A. 2003. Screening for Type 2 diabetes--should it be now? *Diabet Med*, 20, 175-81.

- BPS 2016. Laborer Situation in Indonesia, February 2016/Keadaan Pekerja di Indonesia, Februari 2016. In: STATISTICS, I. B. O. (ed.) *Laborer Situaion in Indonesia*. Jakarta: Badan Pusat Statistik.
- BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qualitative Research in Psychology*, 3, 77-101.
- BROWN, N., CRITCHLEY, J., BOGOWICZ, P., MAYIGE, M. & UNWIN, N. 2012. Risk scores based on self-reported or available clinical data to detect undiagnosed type 2 diabetes: a systematic review. *Diabetes Res Clin Pract*, 98, 369-85.
- BURMAN, W. J., DALTON, C. B., COHN, D. L., BUTLER, J. R. & REVES, R. R. 1997. A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. *Chest*, 112, 63-70.
- BURNS, A. D. & HARRISON, A. C. 2007. Costs of investigating and managing non-residents with possible tuberculosis: New Zealand experience of an international problem. *Respirology*, 12, 262-6.
- CAO, P., TOYABE, S., KURASHIMA, S., OKADA, M. & AKAZAWA, K. 2006. A modified method of activity-based costing for objectively reducing cost drivers in hospitals. *Methods Inf Med*, 45, 462-9.
- CASTELLANOS-JOYA, M., DELGADO-SÁNCHEZ, G., FERREYRA-REYES, L., CRUZ-HERVERT, P., FERREIRA-GUERRERO, E., ORTIZ-SOLÍS, G., JIMÉNEZ, M. I., SALAZAR, L. L., MONTERO-CAMPOS, R., MONGUA-RODRÍGUEZ, N., BAEZ-SALDAÑA, R., BOBADILLA-DEL-VALLE, M., GONZÁLEZ-ROLDÁN, J. F., PONCE-DE-LEÓN, A., SIFUENTES-OSORNIO, J. & GARCÍA-GARCÍA, L. 2014. Results of the Implementation of a Pilot Model for the Bidirectional Screening and Joint Management of Patients with Pulmonary Tuberculosis and Diabetes Mellitus in Mexico. *PLoS ONE*, 9, e106961.
- CENTRAL BUREAU OF STATISTICS (INDONESIA) 2015. Size and Number of Island Areas by Province, 2002-2014. In: DIRECTORATE GENERAL OF PUBLIC ADMINISTRATION (ed.). Jakarta, Indonesia: Ministry of Interior.
- CHAIDIR, L., PARWATI, I., ANNISA, J., MUHSININ, S., MEILANA, I., ALISJAHBANA, B. & VAN CREVEL, R. 2013. Implementation of LED fluorescence microscopy for diagnosis of pulmonary and HIV-associated tuberculosis in a hospital setting in Indonesia. *PLoS One*, 8, e61727.
- CHATTERJEE, S., RIEWPAIBOON, A., PIYAUTHAKIT, P., RIEWPAIBOON, W., BOUPAIJIT, K., PANPUWONG, N. & ARCHAVANUNTAGUL, V. 2011. Cost of diabetes and its complications in Thailand: a complete picture of economic burden. *Health Soc Care Community*, 19, 289-98.
- CHEN, J., ZHANG, R., WANG, J., LIU, L., ZHENG, Y., SHEN, Y., QI, T. & LU, H. 2011. Interferon-gamma release assays for the diagnosis of active tuberculosis in HIV-infected patients: a systematic review and meta-analysis. *PLoS One*, 6, e26827.
- CHERECHE, R. M., LITAN, C. M., ZLATI, A. M. & BLOOM, J. R. 2012. Does co-morbid depression impact diabetes related costs? Evidence from a cross-sectional survey in a low-income country. *J Ment Health Policy Econ*, 15, 127-38.
- CHIHOTA, V. N., GRANT, A. D., FIELDING, K., NDIBONGO, B., VAN ZYL, A., MUIRHEAD, D. & CHURCHYARD, G. J. 2010. Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting. *Int J Tuberc Lung Dis*, 14, 1024-31.

- COLLINS, D. & PARIHATIN, A. 2011. Indonesia National Tuberculosis Program: Planning for Financial Sustainability. *In: MANAGEMENT SCIENCES FOR HEALTH* (ed.). Cambridge, MA, USA: TB CARE I Program: Management Sciences for Health.
- CONTEH, L. & WALKER, D. 2004. Cost and unit cost calculations using step-down accounting. *Health Policy Plan*, 19, 127-35.
- COSTA, J. G., SANTOS, A. C., RODRIGUES, L. C., BARRETO, M. L. & ROBERTS, J. A. 2005. [Tuberculosis in Salvador, Brazil: costs to health system and families]. *Rev Saude Publica*, 39, 122-8.
- CREESE, A. & PARKER, D. 1994. Cost analysis in primary health care: a training manual for programme managers. *In: WHO* (ed.). Geneva, Switzerland: World Health Organization.
- CUNNAMA, L., SINANOVIC, E., RAMMA, L., FOSTER, N., BERRIE, L., STEVENS, W., MOLAPO, S., MAROKANE, P., MCCARTHY, K., CHURCHYARD, G. & VASSALL, A. 2016. Using Top-down and Bottom-up Costing Approaches in LMICs: The Case for Using Both to Assess the Incremental Costs of New Technologies at Scale. *Health Econ*, 25 Suppl 1, 53-66.
- CUSMANO, L. G., MORUA, S., LOGRAN, M., PEREYRA, A. L. & PLAMERO, D. J. 2009. Study of the intangible costs and impact of the household component in the social cost of tuberculosis. *Revista Argentina de Salud Publica*, 1, 18-23.
- DA ROCHA FERNANDES, J., OGURTSOVA, K., LINNENKAMP, U., GUARIGUATA, L., SEURING, T., ZHANG, P., CAVAN, D. & MAKAROFF, L. E. 2016. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. *Diabetes Res Clin Pract*, 117, 48-54.
- DATIKO, D. G. & LINDTJORN, B. 2010. Cost and cost-effectiveness of smear-positive tuberculosis treatment by Health Extension Workers in Southern Ethiopia: a community randomized trial. *PLoS One*, 5, e9158.
- DE OLIVEIRA, M. R., GIOZZA, S. P., PEIXOTO, H. M. & ROMERO, G. A. 2012. Cost-effectiveness of diagnostic for malaria in Extra-Amazon Region, Brazil. *Malar J*, 11, 390.
- DHINGRA, V. K. & RAJPAL, S. 2005. Health related quality of life (HRQL) scoring (DR-12 score) in tuberculosis--additional evaluative tool under DOTS. *J Commun Dis*, 37, 261-8.
- DICK, J. & HENCHIE, S. 1998. A cost analysis of the tuberculosis control programme in Elsies River, Cape Town. *S Afr Med J*, 88, 380-3.
- DIEL, R. & LAMPENIUS, N. 2014. Cost-effectiveness analysis of interventions for tuberculosis control: DALYs versus QALYs. *Pharmacoeconomics*, 32, 617-26.
- DIEL, R., NIENHAUS, A., LAMPENIUS, N., RUSCH-GERDES, S. & RICHTER, E. 2014. Cost of multi drug resistance tuberculosis in Germany. *Respiratory Medicine*, 108, 1677-1687.
- DIEL, R., RUTZ, S., CASTELL, S. & SCHABERG, T. 2012. Tuberculosis: cost of illness in Germany. *Eur Respir J*, 40, 143-51.
- DONICOVA, V., BROZ, J. & SORIN, I. 2011. Health care provision for people with diabetes and postgraduate training of diabetes specialists in eastern European countries. *J Diabetes Sci Technol*, 5, 1124-36.
- DOOLEY, K. E. & CHAISSON, R. E. 2009. Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious Diseases*, 9, 737-746.

- DORMAN, S. E., CHIHOTA, V. N., LEWIS, J. J., SHAH, M., CLARK, D., GRANT, A. D., CHURCHYARD, G. J. & FIELDING, K. L. 2012. Performance characteristics of the Cepheid Xpert MTB/RIF test in a tuberculosis prevalence survey. *PLoS One*, 7, e43307.
- DOWDY, D. W., CATTAMANCHI, A., STEINGART, K. R. & PAI, M. 2011. Is scale-up worth it? Challenges in economic analysis of diagnostic tests for tuberculosis. *PLoS Med*, 8, e1001063.
- DRUMMOND, M. F., SCULPHER, M. J., TORRANCE, G. W., O'BRIEN, B. J. & STODDART, G. L. 2005. *Methods for the Economic Evaluation of Health Care Programmes*, Oxford, UK, Oxford University Press.
- DU TOIT, E., SQUIRE, S. B., DUNBAR, R., MACHEKANO, R., MADAN, J., BEYERS, N. & NAIDOO, P. 2015. Comparing multidrug-resistant tuberculosis patient costs under molecular diagnostic algorithms in South Africa. *Int J Tuberc Lung Dis*, 19, 960-8.
- DYE, C., BOURDIN TRUNZ, B., LÖNNROTH, K., ROGLIC, G. & WILLIAMS, B. G. 2011. Nutrition, Diabetes and Tuberculosis in the Epidemiological Transition. *PLoS ONE*, 6, e21161.
- EL-SONY, A. I. 2006. The cost to health services of human immunodeficiency virus (HIV) co-infection among tuberculosis patients in Sudan. *Health Policy*, 75, 272-9.
- ELAMIN, E. I., IBRAHIM, M. I., SULAIMAN, S. A. & MUTTALIF, A. R. 2008. Cost of illness of tuberculosis in Penang, Malaysia. *Pharm World Sci*, 30, 281-6.
- ERALP, M. N., SCHOLTES, S., MARTELL, G., WINTER, R. & EXLEY, A. R. 2012. Screening of healthcare workers for tuberculosis: development and validation of a new health economic model to inform practice. *BMJ Open*, 2, e000630.
- ETTARO, L., SONGER, T. J., ZHANG, P. & ENGELGAU, M. M. 2004. Cost-of-illness studies in diabetes mellitus. *Pharmacoeconomics*, 22, 149-64.
- EUROPEAN COMMISSION 2009. Language policy of Romania. In: EC (ed.) *Language Policies*. Brussels: European Commission.
- EUROPEAN UNION. 2016. *European Parliament website* [Online]. Available: http://www.europarl.europa.eu/external/html/euenlargement/default_en.htm [Accessed 15/11/2016 2016].
- EUROQOL. 2016. *EQ-5D* [Online]. Available: <http://www.euroqol.org/eq-5d-products/eq-5d-5l.html> [Accessed 14 October 2016 2016].
- EUSEBI, P. 2013. Diagnostic accuracy measures. *Cerebrovasc Dis*, 36, 267-72.
- FAIRALL, L., BACHMANN, M. O., ZWARENSTEIN, M., BATEMAN, E. D., NIESSEN, L. W., LOMBARD, C., MAJARA, B., ENGLISH, R., BHEEKIE, A., VAN RENSBURG, D., MAYERS, P., PETERS, A. & CHAPMAN, R. 2010. Cost-effectiveness of educational outreach to primary care nurses to increase tuberculosis case detection and improve respiratory care: economic evaluation alongside a randomised trial. *Trop Med Int Health*, 15, 277-86.
- FAURHOLT-JEPSEN, D., RANGE, N., PRAYGOD, G., JEREMIAH, K., FAURHOLT-JEPSEN, M., AABYE, M. G., CHANGALUCHA, J., CHRISTENSEN, D. L., GREWAL, H. M. S., MARTINUSSEN, T., KRARUP, H., WITTE, D. R., ANDERSEN, A. B. & FRIIS, H. 2013. Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania. *Tropical Medicine & International Health*, 18, 822-829.

- FILMER, D. & PRITCHETT, L. H. 2001. Estimating wealth effects without expenditure data-or tears: an application to educational enrollments in states of India. *Demography*, 38, 115-32.
- FINK, A. 2003. Responses: choices and measurement. *How to ask survey questions (2nd ed.)*, Sage Publications, California, 56-57.
- FLOYD, K., ARORA, V. K., MURTHY, K. J., LONNROTH, K., SINGLA, N., AKBAR, Y., ZIGNOL, M. & UPLEKAR, M. 2006. Cost and cost-effectiveness of PPM-DOTS for tuberculosis control: evidence from India. *Bull World Health Organ*, 84, 437-45.
- FLOYD, K., HUTUBESSY, R., KLIIMAN, K., CENTIS, R., KHURIEVA, N., JAKOBOWIAK, W., DANILOVITS, M., PEREMITIN, G., KESHAVJEE, S. & MIGLIORI, G. B. 2012. Cost and cost-effectiveness of multidrug-resistant tuberculosis treatment in Estonia and Russia. *Eur Respir J*, 40, 133-42.
- FLOYD, K., SKEVA, J., NYIRENDA, T., GAUSI, F. & SALANIPONI, F. 2003. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. *Int J Tuberc Lung Dis*, 7, S29-37.
- FOSTER, N., VASSALL, A., CLEARY, S., CUNNAMA, L., CHURCHYARD, G. & SINANOVIC, E. 2015. The economic burden of TB diagnosis and treatment in South Africa. *Social Science and Medicine*, 130, 42-50.
- FRICK, K. D. 2009. Micro-Costing Quantity Data Collection Methods. *Medical care*, 47, S76-S81.
- GHAFFARI, S., DORAN, C., WILSON, A., AISBETT, C. & JACKSON, T. 2009. Investigating DRG cost weights for hospitals in middle income countries. *Int J Health Plann Manage*, 24, 251-64.
- GHCC. 2017. *Global Health Cost Consortium* [Online]. Washington, USA. [Accessed 17 July 2017 2017].
- GIBSON, N., BOILLOT, F. & JALLOH, H. 1998a. The cost of tuberculosis to patients in Sierra Leone's war zone. *Int J Tuberc Lung Dis*, 2, 726-31.
- GIBSON, N., BOILLOT, F. & JALLOH, H. 1998b. The cost of tuberculosis to patients in Sierra Leone's war zone. *International Journal of Tuberculosis and Lung Disease*, 2, 726-731.
- GILLIES, C. L., LAMBERT, P. C., ABRAMS, K. R., SUTTON, A. J., COOPER, N. J., HSU, R. T., DAVIES, M. J. & KHUNTI, K. 2008. Different strategies for screening and prevention of type 2 diabetes in adults: cost effectiveness analysis. *Bmj*, 336, 1180-5.
- GOLSHA, R., SHIRAZI, R., SHAFIEE, A., NAJAFIL, L., DASHTI, M. & ROSHANDEL, G. 2009. Pulmonary Tuberculosis And Some Underlying Conditions In Golestan Province Of Iran, During 2001-2005. *Journal of Clinical and Diagnostic Research [serial online]*, 3, 1302-1306.
- GOSPODAREVSKAYA, E., TULLOCH, O., BUNGA, C., FERDOUS, S., JONAS, A., ISLAM, S., RAHMAN, M., HUSSAIN, M. A., HAQUE, M. N., EGWAGA, S., GARDINER, E., PRAYGOD, G., ISLAM, M. A., MANN, G. H., WELLS, W. A. & SQUIRE, S. B. 2014. Patient costs during tuberculosis treatment in Bangladesh and Tanzania: The potential of shorter regimens. *International Journal of Tuberculosis and Lung Disease*, 18, 810-817+i-ii.
- GRANDY, S., LANGKILDE, A. M., SUGG, J. E., PARIKH, S. & SJOSTROM, C. D. 2014. Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. *Int J Clin Pract*, 68, 486-94.

- GRINT, D., ALISJAHBANA, B., PEARSON, F., HILL, P., RIZA, A., RONACHER, K., UGARTE-GIL, C., DOCKRELL, H., VAN CREVEL, R., CRITCHLEY, J. & CONSORTIUM, T. submitted to *Lancet Diabetes Endocrinology* (Feb 2017). Diabetes screening in tuberculosis patients; a diagnostic accuracy analysis of risk scores and laboratory methods in Indonesia, Peru, Romania and South Africa. Submitted to: *Lancet Diabetes Endocrinology*.
- GUO, N., MARRA, F. & MARRA, C. A. 2009. Measuring health-related quality of life in tuberculosis: a systematic review. *Health Qual Life Outcomes*, 7, 14.
- GUZMAN-MONTES, G. Y., OVALLES, R.H., LENIADO-LABORIN, R. 2009. Indirect patient expenses for antituberculosis treatment in Tijuana, Mexico: is treatment really free? *J Infect Dev Ctries*, 3, 778-782.
- GWATKIN, D., RUTSTEIN, S., JOHNSON, K., SULIMAN, E., WAGSTAFF, A. & AMOUZOU, A. 2007. Socio-economic Differences in Health, Nutrition, and Population within Developing Countries: An Overview. In: WORLD BANK (ed.) *Country Reports on HNP and Poverty*. World Bank.
- HARRIES, A. D., KUMAR, A. M., SATYANARAYANA, S., LIN, Y., ZACHARIAH, R., LONNROTH, K. & KAPUR, A. 2016. Addressing diabetes mellitus as part of the strategy for ending TB. *Trans R Soc Trop Med Hyg*, 110, 173-9.
- HARRIES, A. D., KUMAR, A. M. V., SATYANARAYANA, S., LIN, Y., ZACHARIAH, R., LÖNNROTH, K. & KAPUR, A. 2015. Diabetes mellitus and tuberculosis: programmatic management issues. *The International Journal of Tuberculosis and Lung Disease*, 19, 879-886.
- HARRIES, A. D., LIN, Y., SATYANARAYANA, S., NNROTH, K., LI, L., WILSON, N., CHAUHAN, L. S., ZACHARIAH, R., BAKER, M. A., JEON, C. Y., MURRAY, M. B., MAHER, D., BYGBJERG, I. C., ENARSON, D. A., BILLO, N. E. & KAPUR, A. 2011. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. *The International Journal of Tuberculosis and Lung Disease*, 15, 1436-1445.
- HARRIES, A. D., MURRAY, M. B., JEON, C. Y., OTTMANI, S. E., LONNROTH, K., BARRETO, M. L., BILLO, N., BROSTROM, R., BYGBJERG, I. C., FISHER-HOCH, S., MORI, T., RAMAIYA, K., ROGLIC, G., STRANDGAARD, H., UNWIN, N., VISWANATHAN, V., WHITING, D. & KAPUR, A. 2010. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. *Trop Med Int Health*, 15, 659-63.
- HARVARD MEDICAL SCHOOL 2011. The Peruvian National Tuberculosis Control Program. In: ROSENBERG, J., RHATIGAN, J. & KIM, J. Y. (eds.) *Cases in Global Health Delivery*. Boston, MA: Harvard Medical School.
- HAUSLER, H. P., SINANOVIC, E., KUMARANAYAKE, L., NAIDOO, P., SCHOEMAN, H., KARPAKIS, B. & GODFREY-FAUSSETT, P. 2006. Costs of measures to control tuberculosis/HIV in public primary care facilities in Cape Town, South Africa. *Bulletin of the World Health Organization*, 84, 528-536.
- Houben, R. M. & DODD, P. J. 2016. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med*, 13, e1002152.
- HOWE, L. D., GALOBARDES, B., MATIJASEVICH, A., GORDON, D., JOHNSTON, D., ONWUJEKWE, O., PATEL, R., WEBB, E. A., LAWLOR, D. A. & HARGREAVES, J. R. 2012. Measuring socio-economic position for epidemiological studies in low- and

- middle-income countries: a methods of measurement in epidemiology paper. *International Journal of Epidemiology*, 41, 871-886.
- HOWE, L. D., HARGREAVES, J. R. & HUTTLY, S. R. 2008. Issues in the construction of wealth indices for the measurement of socio-economic position in low-income countries. *Emerg Themes Epidemiol*, 5, 3.
- HUANG, I. C., WU, A. W. & FRANGAKIS, C. 2006. Do the SF-36 and WHOQOL-BREF measure the same constructs? Evidence from the Taiwan population*. *Qual Life Res*, 15, 15-24.
- HUAYANAY-ESPINOZA, I. E., GUERRA-CASTANON, F., LAZO-PORRAS, M., CASTANEDA-GUARDERAS, A., THOMAS, N. J., GARCIA-GUARNIZ, A. L., VALDIVIA-BUSTAMANTE, A. A. & MALAGA, G. 2016. Metabolic control in patients with type 2 diabetes mellitus in a public hospital in Peru: a cross-sectional study in a low-middle income country. *PeerJ*, 4, e2577.
- HUDSON, C. P., WOOD, R. & MAARTENS, G. 2000. Diagnosing HIV-associated tuberculosis: reducing costs and diagnostic delay. *Int J Tuberc Lung Dis*, 4, 240-5.
- HUSEREAU, D., DRUMMOND, M., PETROU, S., CARSWELL, C., MOHER, D., GREENBERG, D., AUGUSTOVSKI, F., BRIGGS, A. H., MAUSKOPF, J. & LODER, E. 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Int J Technol Assess Health Care*, 29, 117-22.
- ICKS, A., HAASSTERT, B., GANDJOUR, A., JOHN, J., LOWEL, H., HOLLE, R., GIANI, G. & RATHMANN, W. 2004. Cost-effectiveness analysis of different screening procedures for type 2 diabetes: the KORA Survey 2000. *Diabetes Care*, 27, 2120-8.
- IDF 2011. Diabetes ATLAS. In: UNWIN, N., WHITING, D., GUARIGUATA, L., GHYOOT, G. & GAN, D. (eds.) *IDF Diabetes Atlas*. Fifth ed. Brussels, Belgium: International Diabetes Federation.
- IDF 2014. Global Diabetes Scorecard: Tracking Progress for Action. In: YANEX, B., DODD, S., SCOTT, C. & JACQMAIN, O. (eds.) *Global Diabetes Scorecard*. Brussels, Belgium: International Diabetes Federation.
- IDF 2015. Diabetes ATLAS. In: CAVAN, D., FERNANDES, J. D. R., MAKAROFF, L., OGURTSOVA, K. & WEBBER, S. (eds.) *IDF Diabetes Atlas*. Seventh ed. Brussels, Belgium: International Diabetes Federation.
- IMF 2011. World Economic Outlook Database. *World Economic and Financial Surveys*. Washington, DC, USA: International Monetary Fund.
- IMF 2016. World Economic Outlook Database. *World Economic and Financial Surveys*. Washington, DC, USA: International Monetary Fund.
- INDONESIA, G. O. 2003. Act concerning manpower [Indonesian Labour Law]. In: INDONESIA, T. H. O. R. O. T. R. O. & INDONESIA, T. P. O. T. R. O. (eds.) *Article 5 Subsection (1), Article 20 Subsection (2), Article 27 Subsection (2), Article 28 and Article 33 Subsection (1) of the 1945 Constitution*. Jakarta.
- ISLAM, M. A., WAKAI, S., ISHIKAWA, N., CHOWDHURY, A. M. & VAUGHAN, J. P. 2002. Cost-effectiveness of community health workers in tuberculosis control in Bangladesh. *Bull World Health Organ*, 80, 445-50.
- JABER, A. A., KHAN, A. H., SYED SULAIMAN, S. A., AHMAD, N. & ANAAM, M. S. 2016. Evaluation of Health-Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One*, 11, e0156258.

- JACKSON, S., SLEIGH, A. C., WANG, G. J. & LIU, X. L. 2006a. Poverty and the economic effects of TB in rural China. *Int J Tuberc Lung Dis*, 10, 1104-10.
- JACKSON, S., SLEIGH, A. C., WANG, G. J. & LIU, X. L. 2006b. Poverty and the economic effects of TB in rural China. *International Journal of Tuberculosis and Lung Disease*, 10, 1104-1110.
- JACOBS, B., CLOWES, C., WARES, F., POLIVAKHO, V., LYAGOSHINA, T., PEREMITIN, G. & BANATVALA, N. 2002. Cost-effectiveness analysis of the russian treatment scheme for tuberculosis versus short-course chemotherapy: results from Tomsk, Siberia. *Int J Tuberc Lung Dis*, 6, 396-405.
- JACQUET, V., MOROSE, W., SCHWARTZMAN, K., OXLADE, O., BARR, G., GRIMARD, F. & MENZIES, D. 2006. Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti. *BMC Public Health*, 6, 209.
- JALI, M. V., MAHISHALE, V. K. & HIREMATH, M. B. 2013. Bidirectional screening of tuberculosis patients for diabetes mellitus and diabetes patients for tuberculosis. *Diabetes Metab J*, 37, 291-5.
- JEON, C. Y., HARRIES, A. D., BAKER, M. A., HART, J. E., KAPUR, A., LONNROTH, K., OTTMANI, S. E., GOONESEKERA, S. & MURRAY, M. B. 2010. Bi-directional screening for tuberculosis and diabetes: a systematic review. *Trop Med Int Health*, 15, 1300-14.
- JEON, C. Y. & MURRAY, M. B. 2008. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med*, 5, e152.
- JIMÉNEZ-CORONA, M. E., CRUZ-HERVERT, L. P., GARCÍA-GARCÍA, L., FERREYRA-REYES, L., DELGADO-SÁNCHEZ, G., BOBADILLA-DEL-VALLE, M., CANIZALES-QUINTERO, S., FERREIRA-GUERRERO, E., BÁEZ-SALDAÑA, R., TÉLLEZ-VÁZQUEZ, N., MONTERO-CAMPOS, R., MONGUA-RODRIGUEZ, N., MARTÍNEZ-GAMBOA, R. A., SIFUENTES-OSORNIO, J. & PONCE-DE-LEÓN, A. 2013. Association of diabetes and tuberculosis: impact on treatment and post-treatment outcomes. *Thorax*, 68, 214-220.
- JOHN, K. R., DALEY, P., KINCLER, N., OXLADE, O. & MENZIES, D. 2009a. Costs incurred by patients with pulmonary tuberculosis in rural India. *International Journal of Tuberculosis and Lung Disease*, 13, 1281-1287.
- JOHN, K. R., DALEY, P., KINCLER, N., OXLADE, O. & MENZIES, D. 2009b. Costs incurred by patients with pulmonary tuberculosis in rural India. *Int J Tuberc Lung Dis*, 13, 1281-7.
- JOHNS, B., BALTUSSEN, R. & HUTUBESSY, R. 2003. Programme costs in the economic evaluation of health interventions. *Cost Eff Resour Alloc*, 1, 1.
- KAMOLRATANAKUL, P., HIRANSUTHIKUL, N., SINGHADONG, N., KASETJAROEN, Y., AKKSILP, S. & LERTMAHARIT, S. 2002. Cost analysis of different types of tuberculosis patient at tuberculosis centers in Thailand. *Southeast Asian J Trop Med Public Health*, 33, 321-30.
- KANG, Y. A., CHOI, Y. J., CHO, Y. J., LEE, S. M., YOO, C. G., KIM, Y. W., HAN, S. K., SHIM, Y. S. & YIM, J. J. 2006. Cost of treatment for multidrug-resistant tuberculosis in South Korea. *Respirology*, 11, 793-8.
- KAPUR, A., HARRIES, A. D., LONNROTH, K., WILSON, P. & SULISTYOWATI, L. S. 2016. Diabetes and tuberculosis co-epidemic: the Bali Declaration. *Lancet Diabetes & Endocrinology*, 4, 8-10.

- KARKI, D. K., MIRZOEV, T. N., GREEN, A. T., NEWELL, J. N. & BARAL, S. C. 2007. Costs of a successful public-private partnership for TB control in an urban setting in Nepal. *BMC public health*, 7, 84.
- KASTIEN-HILKA, T., ABULFATHI, A., ROSENKRANZ, B., BENNETT, B., SCHWENKLENKS, M. & SINANOVIC, E. 2016a. Health-related quality of life and its association with medication adherence in active pulmonary tuberculosis- a systematic review of global literature with focus on South Africa. *Health Qual Life Outcomes*, 14, 42.
- KASTIEN-HILKA, T., ROSENKRANZ, B., BENNETT, B., SINANOVIC, E. & SCHWENKLENKS, M. 2016b. How to Evaluate Health-Related Quality of Life and Its Association with Medication Adherence in Pulmonary Tuberculosis – Designing a Prospective Observational Study in South Africa. *Frontiers in Pharmacology*, 7.
- KASUGA, M. 2006. Insulin resistance and pancreatic β cell failure. *Journal of Clinical Investigation*, 116, 1756-1760.
- KHAN, M. A., WALLEY, J. D., WITTER, S. N., IMRAN, A. & SAFDAR, N. 2002. Costs and cost-effectiveness of different DOT strategies for the treatment of tuberculosis in Pakistan. Directly Observed Treatment. *Health Policy Plan*, 17, 178-86.
- KIBIRIGE, D., SSEKITOLEKO, R., MUTEBI, E. & WORODRIA, W. 2013. Overt diabetes mellitus among newly diagnosed Ugandan tuberculosis patients: a cross sectional study. *BMC Infect Dis*, 13, 122.
- KIK, S. V., OLTHOF, S. P., DE VRIES, J. T., MENZIES, D., KINCLER, N., VAN LOENHOUT-ROOYAKKERS, J., BURDO, C. & VERVER, S. 2009. Direct and indirect costs of tuberculosis among immigrant patients in the Netherlands. *BMC public health*, 9, 283.
- KIND, P., DOLAN, P., GUDEX, C. & WILLIAMS, A. 1998. Variations in population health status: results from a United Kingdom national questionnaire survey. *BMJ*, 316, 736-741.
- KISAKA, S. M., RUTEBEMBERWA, E., KASASA, S., OCEN, F. & NANKYA-MUTYOBA, J. 2016. Does health-related quality of life among adults with pulmonary tuberculosis improve across the treatment period? A hospital-based cross sectional study in Mbale Region, Eastern Uganda. *BMC Res Notes*, 9, 467.
- KNIGHT, G. M., GRIFFITHS, U. K., SUMNER, T., LAURENCE, Y. V., GHEORGHE, A., VASSALL, A., GLAZIOU, P. & WHITE, R. G. 2014. Impact and cost-effectiveness of new tuberculosis vaccines in low- and middle-income countries. *Proc Natl Acad Sci U S A*, 111, 15520-5.
- KOTWAL, N. & PANDIT, A. 2012. Variability of capillary blood glucose monitoring measured on home glucose monitoring devices. *Indian J Endocrinol Metab*, 16, S248-51.
- KRUIJSHAAR, M. E., LIPMAN, M., ESSINK-BOT, M. L., LOZEWICZ, S., CREER, D., DART, S., MAGUIRE, H. & ABUBAKAR, I. 2010. Health status of UK patients with active tuberculosis. *Int J Tubers Lung Dis*, 14.
- KUMPATLA, S., ARAVINDALOCHANAN, V., RAJAN, R., VISWANATHAN, V. & KAPUR, A. 2013. Evaluation of performance of A1c and FPG tests for screening newly diagnosed diabetes defined by an OGTT among tuberculosis patients-a study from India. *Diabetes Res Clin Pract*, 102, 60-4.
- LAMERS, L. M. 2007. The transformation of utilities for health states worse than death: consequences for the estimation of EQ-5D value sets. *Med Care*, 45, 238-44.

- LANCET 2014. Indonesia strides towards universal health care. *Lancet*, 383, 2.
- LAOKRI, S., AMOUSSOUHUI, A., OUENDO, E. M., HOUNNANKAN, A. C., ANAGONOU, S., GNINAFON, M., KASSA, F., TAWO, L. & DUJARDIN, B. 2014. A care pathway analysis of tuberculosis patients in Benin: Highlights on direct costs and critical stages for an evidence-based decision-making. *PLoS ONE*, 9.
- LAOKRI, S., DRABO, M. K., WEIL, O., KAFANDO, B., DEMBELE, S. M. & DUJARDIN, B. 2013. Patients are paying too much for tuberculosis: a direct cost-burden evaluation in Burkina Faso. *PLoS One*, 8, e56752.
- LAURENCE, Y. V., GRIFFITHS, U. K. & VASSALL, A. 2015. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *PharmacoEconomics*, 1-17.
- LAWN, S. D., MWABA, P., BATES, M., PIATEK, A., ALEXANDER, H., MARAIS, B. J., CUEVAS, L. E., MCHUGH, T. D., ZIJENAH, L., KAPATA, N., ABUBAKAR, I., MCNERNEY, R., HOELSCHER, M., MEMISH, Z. A., MIGLIORI, G. B., KIM, P., MAEURER, M., SCHITO, M. & ZUMLA, A. 2013. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infect Dis*, 13, 349-61.
- LAZARUS, R. P., KALAISELVAN, S., JOHN, K. R. & MICHAEL, J. S. 2012. Evaluation of the microscopic observational drug susceptibility assay for rapid and efficient diagnosis of multi-drug resistant tuberculosis. *Indian J Med Microbiol*, 30, 64-8.
- LEWIS, M. 2007. Informal payments and the financing of health care in developing and transition countries. *Health Affairs*, 26, 984-997.
- LI, L., LIN, Y., MI, F., TAN, S., LIANG, B., GUO, C., SHI, L., LIU, L., GONG, F., LI, Y., CHI, J., ZACHARIAH, R., KAPUR, A., LONNROTH, K. & HARRIES, A. D. 2012. Screening of patients with tuberculosis for diabetes mellitus in China. *Trop Med Int Health*, 17, 1294-301.
- LI, L. M., BAI, L. Q., YANG, H. L., XIAO, C. F., TANG, R. Y., CHEN, Y. F., CHEN, S. M., LIU, S. S., ZHANG, S. N., OU, Y. H. & NIU, T. I. 1999. Sputum induction to improve the diagnostic yield in patients with suspected pulmonary tuberculosis. *Int J Tuberc Lung Dis*, 3, 1137-9.
- LIENHARDT, C., LONNROTH, K., MENZIES, D., BALASEGARAM, M., CHAKAYA, J., COBELENS, F., COHN, J., DENKINGER, C. M., EVANS, T. G., KALLENIUS, G., KAPLAN, G., KUMAR, A. M., MATTHIESSEN, L., MGONE, C. S., MIZRAHI, V., MUKADI, Y. D., NGUYEN, V. N., NORDSTROM, A., SIZEMORE, C. F., SPIGELMAN, M., SQUIRE, S. B., SWAMINATHAN, S., VAN HELDEN, P. D., ZUMLA, A., WEYER, K., WEIL, D. & RAVIGLIONE, M. 2016. Translational Research for Tuberculosis Elimination: Priorities, Challenges, and Actions. *PLoS Med*, 13, e1001965.
- LIN, Y., LI, L., MI, F., DU, J., DONG, Y., LI, Z., QI, W., ZHAO, X., CUI, Y., HOU, F., ZACHARIAH, R., KAPUR, A., LÖNNROTH, K. & HARRIES, A. D. 2012. Screening patients with Diabetes Mellitus for Tuberculosis in China. *Tropical Medicine & International Health*, 17, 1302-1308.
- LINDELOW, M. 2002. Sometimes more equal than others: how the choice of welfare indicator can affect the measurement of health inequalities and the incidence of public spending. In: UNIVERSITY, O. (ed.). Oxford: Oxford University.
- LITTLETON, J. & PARK, J. 2009. Tuberculosis and syndemics: Implications for Pacific health in New Zealand. *Social Science & Medicine*, 69, 1674-1680.

- LIU, X., THOMSON, R., GONG, Y., ZHAO, F., SQUIRE, S. B., TOLHURST, R., ZHAO, X., YAN, F. & TANG, S. 2007. How affordable are tuberculosis diagnosis and treatment in rural China? An analysis from community and tuberculosis patient perspectives. *Tropical Medicine and International Health*, 12, 1464-1471.
- LONNROTH, K., ROGLIC, G. & HARRIES, A. D. 2014. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. *Lancet Diabetes Endocrinol*, 2, 730-9.
- LONTOH, L., BEATON, C. & CLARKE, K. 2015. Indonesia Energy Subsidy Review: A biannual survey of energy subsidy policies. In: BEATON, C. (ed.) *Global Subsidies Initiative*. Geneva, Switzerland.
- LOUW, J. S., MABASO, M. & PELTZER, K. 2016. Change in Health-Related Quality of Life among Pulmonary Tuberculosis Patients at Primary Health Care Settings in South Africa: A Prospective Cohort Study. *PLoS One*, 11, e0151892.
- LU, C., LIU, Q., SARMA, A., FITZPATRICK, C., FALZON, D. & MITNICK, C. D. 2013. A systematic review of reported cost for smear and culture tests during multidrug-resistant tuberculosis treatment. *PLoS One*, 8, e56074.
- MACINTYRE, C. R., PLANT, A. J. & HENDRIE, D. 2001. Shifting the balance between in-patient and out-patient care for tuberculosis results in economic savings. *Int J Tuberc Lung Dis*, 5, 266-71.
- MAGEE, M. J., BLOSS, E., SHIN, S. S., CONTRERAS, C., ARBANIL HUAMAN, H., CALDERON TICONA, J., BAYONA, J., BONILLA, C., YAGUI, M., JAVE, O. & CEGIELSKI, J. P. 2013. Clinical characteristics, drug resistance and treatment outcomes among tuberculosis patients with diabetes in Peru. *International Journal of Infectious Diseases*, 17, e404-e412.
- MAHENDRADHATA, Y., PROBANDARI, A., AHMAD, R. A., UTARINI, A., TRISNANTORO, L., LINDHOLM, L., VAN DER WERF, M. J., KIMERLING, M., BOELAERT, M., JOHNS, B. & VAN DER STUYFT, P. 2010. The incremental cost-effectiveness of engaging private practitioners to refer tuberculosis suspects to DOTS services in Jogjakarta, Indonesia. *Am J Trop Med Hyg*, 82, 1131-9.
- MANDALAKAS, A. M., HESSELING, A. C., GIE, R. P., SCHAAF, H. S., MARAIS, B. J. & SINANOVIC, E. 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax*, 68, 247-55.
- MAPONGA, C. C., NAZERALI, H., MUNGWINDRI, C., WINGWIRL, M. 1996. Cost Implications of the Tuberculosis/HIV Co-epidemic and Drug Treatment of Tuberculosis in Zimbabwe *Journal of Social and Administrative Pharmacy*, 13.
- MARAIS, B. J., LÖNNROTH, K., LAWN, S. D., MIGLIORI, G. B., MWABA, P., GLAZIOU, P., BATES, M., COLAGIURI, R., ZIJENAH, L., SWAMINATHAN, S., MEMISH, Z. A., PLETSCHETTE, M., HOELSCHER, M., ABUBAKAR, I., HASAN, R., ZAFAR, A., PANTALEO, G., CRAIG, G., KIM, P., MAEURER, M., SCHITO, M. & ZUMLA, A. 2013. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. *The Lancet Infectious Diseases*, 13, 436-448.
- MARCHAND, R., TOUSIGNANT, P. & CHANG, H. 1999. Cost-effectiveness of screening compared to case-finding approaches to tuberculosis in long-term care facilities for the elderly. *Int J Epidemiol*, 28, 563-70.

- MARICA, C. 2009. Pulmonary tuberculosis in Romania at the dawn of the millennium--a major public health issue. *J Med Life*, 2, 207-10.
- MARKS, S. M., FLOOD, J., SEAWORTH, B., HIRSCH-MOVERMAN, Y., ARMSTRONG, L., MASE, S., SALCEDO, K., OH, P., GRAVISS, E. A., COLSON, P. W., ARMITIGE, L., REVUELTA, M. & SHEERAN, K. 2014. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005-2007. *Emerging Infectious Diseases*, 20, 812-821.
- MASOBE, P., LEE, T. & PRICE, M. 1995. Isoniazid prophylactic therapy for tuberculosis in HIV-seropositive patients--a least-cost analysis. *S Afr Med J*, 85, 75-81.
- MATZA, L. S., BOYE, K. S., STEWART, K. D., CURTIS, B. H., REANEY, M. & LANDRIAN, A. S. 2015. A qualitative examination of the content validity of the EQ-5D-5L in patients with type 2 diabetes. *Health Qual Life Outcomes*, 13, 192.
- MAUCH, V., BONSU, F., GYAPONG, M., AWINI, E., SUAREZ, P., MARCELINO, B., MELGEN, R. E., LONNROTH, K., NHUNG, N. V., HOA, N. B. & KLINKENBERG, E. 2013. Free tuberculosis diagnosis and treatment are not enough: patient cost evidence from three continents. *Int J Tuberc Lung Dis*, 17, 381-7.
- MAUCH, V., WOODS, N., KIRUBI, B., KIPRUTO, H., SITIENEI, J. & KLINKENBERG, E. 2011. Assessing access barriers to tuberculosis care with the tool to Estimate Patients' Costs: pilot results from two districts in Kenya. *BMC public health*, 11, 43.
- MEDINA LARA, A., MUNDY, C., KANDULU, J., CHISUWO, L. & BATES, I. 2005. Evaluation and costs of different haemoglobin methods for use in district hospitals in Malawi. *J Clin Pathol*, 58, 56-60.
- MENDEZ-SAMPERIO, P. 2016. Global Efforts in the Development of Vaccines for Tuberculosis: Requirements for Improved Vaccines Against Mycobacterium tuberculosis. *Scand J Immunol*, 84, 204-10.
- MENZIES, N. A., GOMEZ, G. B., BOZZANI, F., CHATTERJEE, S., FOSTER, N., BAENA, I. G., LAURENCE, Y. V., QIANG, S., SIROKA, A., SWEENEY, S., VERGUET, S., ARINAMINPATHY, N., AZMAN, A. S., BENDAVID, E., CHANG, S. T., COHEN, T., DENHOLM, J. T., DOWDY, D. W., ECKHOFF, P. A., GOLDHABER-FIEBERT, J. D., HANDEL, A., HUYNH, G. H., LALLI, M., LIN, H. H., MANDAL, S., MCBRYDE, E. S., PANDEY, S., SALOMON, J. A., SUEN, S. C., SUMNER, T., TRAUER, J. M., WAGNER, B. G., WHALEN, C. C., WU, C. Y., BOCCIA, D., CHADHA, V. K., CHARALAMBOUS, S., CHIN, D. P., CHURCHYARD, G., DANIELS, C., DEWAN, P., DITIU, L., EATON, J. W., GRANT, A. D., HIPPER, P., HOSSEINI, M., MAMETJA, D., PRETORIUS, C., PILLAY, Y., RADE, K., SAHU, S., WANG, L., HOUBEN, R. M., KIMERLING, M. E., WHITE, R. G. & VASSALL, A. 2016. Cost-effectiveness and resource implications of aggressive action on tuberculosis in China, India, and South Africa: a combined analysis of nine models. *Lancet Glob Health*, 4, e816-e826.
- MEYER-RATH, G., SCHNIPPEL, K., LONG, L., MACLEOD, W., SANNE, I., STEVENS, W., PILLAY, S., PILLAY, Y. & ROSEN, S. 2012. The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa. *PLoS One*, 7, e36966.
- MICHAEL, J. S., DALEY, P., KALAISELVAN, S., LATHA, A., VIJAYAKUMAR, J., MATHAI, D., JOHN, K. R. & PAI, M. 2010. Diagnostic accuracy of the microscopic observation drug susceptibility assay: a pilot study from India. *Int J Tuberc Lung Dis*, 14, 482-8.
- MIGLIORI, G. B., AMBROSETTI, M., BESOZZI, G., FARRIS, B., NUTINI, S., SAINI, L., CASALI, L., NARDINI, S., BUGIANI, M., NERI, M. & RAVIGLIONE, M. C. 1999. Cost-comparison

- of different management policies for tuberculosis patients in Italy. AIPO TB Study Group. *Bull World Health Organ*, 77, 467-76.
- MIGLIORI, G. B., KHOMENKO, A. G., PUNGA, V. V., AMBROSETTI, M., DANILOVA, I., RIBKA, L. N., GRZEMSKA, M., SAWERT, H. & RAVIGLIONE, M. C. 1998. Cost-effectiveness analysis of tuberculosis control policies in Ivanovo Oblast, Russian Federation. Ivanovo Tuberculosis Project Study Group. *Bull World Health Organ*, 76, 475-83.
- MILLER, T. L., CIRULE, A., WILSON, F. A., HOLTZ, T. H., RIEKSTINA, V., CAIN, K. P., MOONAN, P. K. & LEIMANE, V. 2013. The value of effective public tuberculosis treatment: an analysis of opportunity costs associated with multidrug resistant tuberculosis in Latvia. *Cost Eff Resour Alloc*, 11, 9.
- MILLER, T. L., MCNABB, S. J., HILSENATH, P., PASIPANODYA, J., DREWYER, G. & WEIS, S. E. 2010. The societal cost of tuberculosis: Tarrant County, Texas, 2002. *Ann Epidemiol*, 20, 1-7.
- MIRZOEV, T. N., BARAL, S. C., KARKI, D. K., GREEN, A. T. & NEWELL, J. N. 2008a. Community-based DOTS and family member DOTS for TB control in Nepal: costs and cost-effectiveness. *Cost Eff Resour Alloc*, 6, 20.
- MIRZOEV, T. N., BARAL, S. C., KARKI, D. K., GREEN, A. T. & NEWELL, J. N. 2008b. Community-based DOTS and family member DOTS for TB control in Nepal: Costs and cost-effectiveness. *Cost Effectiveness and Resource Allocation*, 6.
- MOALOSI, G., FLOYD, K., PHATSHWANE, J., MOETI, T., BINKIN, N. & KENYON, T. 2003. Cost-effectiveness of home-based care versus hospital care for chronically ill tuberculosis patients, Francistown, Botswana. *Int J Tuberc Lung Dis*, 7, S80-5.
- MOGYOROSY, Z. & SMITH, P. 2005. The main methodological issues in costing health care services - A literature review. *CHE Research Paper*. York, UK: Centre for Health Economics, University of York.
- MOH 2010. TB control national strategy in Indonesia: 2010-2014 - Breakthrough Toward Universal Access. In: MINISTRY OF HEALTH (REPUBLIC OF INDONESIA) (ed.) *National Strategic Plan*. Jakarta, Indonesia: Ministry of Health (Republic of Indonesia).
- MOH 2014. Indonesia Health Profile 2013. In: MINISTRY OF HEALTH REPUBLIC OF INDONESIA (ed.). Jakarta, Indonesia.
- MOLICOTTI, P., BUA, A. & ZANETTI, S. 2014. Cost-effectiveness in the diagnosis of tuberculosis: choices in developing countries. *J Infect Dev Ctries*, 8, 24-38.
- MONTES-SANTIAGO, J., FERNANDEZ, C., REY, G. & MEDIERO, A. 2010. [Tuberculosis-related hospitalization in Spain: a cost analysis]. *Enferm Infecc Microbiol Clin*, 28, 358-61.
- MORTON, R. 1694. *Phthisiologia, or, A treatise of consumptions*, London, Sam Smith and Benjamin Walford.
- MOTA, M. & DINU, I.-R. 2013. The Analysis of Prevalence and Incidence of Diabetes Mellitus in Romania. *Romanian Journal of Diabetes Nutrition and Metabolic Diseases*.
- MTWANGAMBATE, G., KALLUVYA, S. E., KIDENYA, B. R., KABANGILA, R., DOWNS, J. A., SMART, L. R., FITZGERALD, D. W. & PECK, R. N. 2014. 'Cough-triggered' tuberculosis screening among adults with diabetes in Tanzania. *Diabet Med*, 31, 600-5.
- MUELLER, D. H., MWENGE, L., MUYOYETA, M., MUVWIMI, M. W., TEMBWE, R., MCNERNEY, R., GODFREY-FAUSSETT, P. & AYLES, H. M. 2008. Costs and cost-

- effectiveness of tuberculosis cultures using solid and liquid media in a developing country. *Int J Tuberc Lung Dis*, 12, 1196-202.
- MUNIYANDI, M., RAJESWARI, R. & BALASUBRAMANIAN, R. 2006. Estimating provider cost for treating patients with tuberculosis under Revised National Tuberculosis Control Programme (RNTCP). *Indian Journal of Tuberculosis*, 53, 12-17.
- MUNIYANDI, M., RAJESWARI, R., BALASUBRAMANIAN, R. & NARAYANAN, P. R. 2008. A Comparison of Costs to Patients with Tuberculosis Treated in a DOTS Programme with Those in a Non-DOTS Programme in South India. *Journal of Health Management*, 10, 9-24.
- NATIONAL INSTITUTE OF STATISTICS 2011. The 2011 Population and Housing Census - Statistic Action of Strategic Importance for Romania. 20-31 October, 2011 ed.
- NEUMANN, A., SCHOFFER, O., NORSTRÖM, F., NORBERG, M., KLUG, S. J. & LINDHOLM, L. 2014. Health-related quality of life for pre-diabetic states and type 2 diabetes mellitus: a cross-sectional study in Västerbotten Sweden. *Health and Quality of Life Outcomes*, 12, 150.
- NGANDA, B., WANG'OMBE, J., FLOYD, K. & KANGANGI, J. 2003. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Machakos District, Kenya. *Int J Tuberc Lung Dis*, 7, S14-20.
- NGSP. 2010. *Harmonizing Hemoglobin A1c Testing: A better A1C test means better diabetes care* [Online]. Missouri, USA: University of Missouri. [Accessed 9 July 2017].
- NICE & BMGF 2014. Bill and Melinda Gates Foundation - Methods for Economic Evaluation Project (MEEP). In: BMGF, INTERNATIONAL, N., (THAILAND), H. I. A. T. A. P. & UNIVERSITY OF YORK, C. F. H. E. (eds.).
- NIENHAUS, A., SCHABLON, A., COSTA, J. T. & DIEL, R. 2011. Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Serv Res*, 11, 247.
- NIETO, E., LOPEZ, L., DEL CORRAL, H., MARIN, D., LOPERA, L. D., BENJUMEA, D., MONTES, F., MOLINA, G. & ARBELAEZ, M. P. 2012a. [Cost-effectiveness of an alternative tuberculosis treatment: home-based guardian monitoring of patients]. *Rev Panam Salud Publica*, 32, 178-84.
- NIETO, E., LÓPEZ, L., DEL CORRAL, H., MARÍN, D., LOPERA, L. D., BENJUMEA, D., MONTES, F., MOLINA, G. & ARBELÁEZ, M. P. 2012b. Costo-efectividad de un tratamiento antituberculoso alternativo: seguimiento a convivientes residenciales de los pacientes. *Revista Panamericana de Salud Pública*, 32, 178-184.
- OANDA. 2016. *Currency Converter* [Online]. Available: <https://www.oanda.com/solutions-for-business/historical-rates/main.html> [Accessed 12/02/2016].
- OKELLO, D., FLOYD, K., ADATU, F., ODEKE, R. & GARGIONI, G. 2003. Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda. *Int J Tuberc Lung Dis*, 7, S72-9.
- OLARU-PETER, S., GRIGORIU, C., BOICULESE, L. V., GRADINARU, A. C., MACOVEI, II, DICULENCU, D. & GRIGORIU, B. 2014. Detection of Mycobacterium tuberculosis growth by direct microscopic observation has a lower cost, higher sensitivity and higher diagnostic value than liquid and solid media cultures. *Indian J Med Microbiol*, 32, 315-7.

- OLIVEIRA-CRUZ, V., KUROWSKI, C. & MILLS, A. 2003. Delivery of priority health services: searching for synergies within the vertical versus horizontal debate. *Journal of International Development*, 15, 67-86.
- OPPONG, R., KAAMBWA, B., NUTTALL, J., HOOD, K., SMITH, R. D. & COAST, J. 2013. The impact of using different tariffs to value EQ-5D health state descriptions: an example from a study of acute cough/lower respiratory tract infections in seven countries. *Eur J Health Econ*, 14, 197-209.
- OZALTIN, A. & CASHIN, C. (eds.) 2014. *Costing of Health Services for Provider Payment: A Practical Manual Based on Country Costing Challenges, Trade-offs, and Solutions*.
- PAAUW, S. 2009. One Land, One Nation, One Language: An analysis of Indonesia's National Language Policy. In: LEHNERT-LEHOUILIER, H. & FINE, A. B. (eds.) *University of Rochester Working Papers in the Language Sciences*. University of Rochester.
- PAHO & WHO 2013. The dual threat of diabetes and tuberculosis in the Americas. In: PAN AMERICAN HEALTH ORGANIZATION (ed.). Washington, DC: Pan American Health Organization, Regional Office for the Americas of the World Health Organization.
- PALMER, C. S., MILLER, B., HALPERN, M. T. & GEITER, L. J. 1998. A model of the cost-effectiveness of directly observed therapy for treatment of tuberculosis. *J Public Health Manag Pract*, 4, 1-13.
- PAN, H. Q., BELE, S., FENG, Y., QIU, S. S., LU, J. Q., TANG, S. W., SHEN, H. B., WANG, J. M. & ZHU, L. M. 2013. Analysis of the economic burden of diagnosis and treatment of tuberculosis patients in rural China. *International Journal of Tuberculosis and Lung Disease*, 17, 1575-1580+i.
- PANG, Y., LI, Q., OU, X., SOHN, H., ZHANG, Z., LI, J., XIA, H., KAM, K. M., O'BRIEN, R. J., CHI, J., HUAN, S., CHIN, D. P. & ZHAO, Y. L. 2013. Cost-Effectiveness Comparison of Genechip and Conventional Drug Susceptibility Test for Detecting Multidrug-Resistant Tuberculosis in China. *PLoS ONE*, 8.
- PANTOJA, A., FLOYD, K., UNNIKISHNAN, K. P., JITENDRA, R., PADMA, M. R., LAL, S. S., UPLEKAR, M., CHAUHAN, L. S., KUMAR, P., SAHU, S., WARES, F. & LONNROTH, K. 2009a. Economic evaluation of public-private mix for tuberculosis care and control, India. Part I. Socio-economic profile and costs among tuberculosis patients. *Int J Tuberc Lung Dis*, 13, 698-704.
- PANTOJA, A., FLOYD, K., UNNIKISHNAN, K. P., JITENDRA, R., PADMA, M. R., LAL, S. S., UPLEKAR, M., CHAUHAN, L. S., KUMAR, P., SAHU, S., WARES, F. & LONNROTH, K. 2009b. Economic evaluation of public-private mix for tuberculosis care and control, India. Part I. Socio-economic profile and costs among tuberculosis patients. *International Journal of Tuberculosis and Lung Disease*, 13, 698-704.
- PASIPANODYA, J. G., MILLER, T. L., VECINO, M., MUNGUIA, G., BAE, S., DREWYER, G. & WEIS, S. E. 2007. Using the St. George Respiratory Questionnaire To Ascertain Health Quality in Persons With Treated Pulmonary Tuberculosis. *Chest*, 132, 1591-1598.
- PEABODY, J. W., SHIMKHADA, R., TAN, C., JR. & LUCK, J. 2005a. The burden of disease, economic costs and clinical consequences of tuberculosis in the Philippines. *Health Policy Plan*, 20, 347-53.

- PEABODY, J. W., SHIMKHADA, R., TAN JR, C. & LUCK, J. 2005b. The burden of disease, economic costs and clinical consequences of tuberculosis in the Philippines. *Health Policy and Planning*, 20, 347-353.
- PERALTA PEREZ, M., PADILLA GONZALEZ, C. M., FUENTES DIAZ, M. & LAZO ALVAREZ, M. A. 2006. Costo del Programa Nacional de Control de la Tuberculosis. Centro Provincial de Higiene y Epidemiologia de Ciudad de La Habana, 2002. *Revista Cubana Medicina Tropical*, 58, 63-7.
- PERU STOP TB COMMITTEE 2009. Multisectoral Strategic Plan for the National Response to Tuberculosis in Peru: 2009-2018 [Plan Estratégico Multisectorial de la Respuesta Nacional a la Tuberculosis en el Perú: 2009 - 2018]. In: MINSa (ed.). Lima, Peru: Ministry of Health in Peru.
- PETER, J. G., THERON, G., POORAN, A., THOMAS, J., PASCOE, M. & DHEDA, K. 2013. Comparison of two methods for acquisition of sputum samples for diagnosis of suspected tuberculosis in smear-negative or sputum-scarce people: a randomised controlled trial. *Lancet Respir Med*, 1, 471-8.
- PICHENDA, K., NAKAMURA, K., MORITA, A., KIZUKI, M., SEINO, K. & TAKANO, T. 2012. Non-hospital DOT and early diagnosis of tuberculosis reduce costs while achieving treatment success. *Int J Tuberc Lung Dis*, 16, 828-34.
- PONCE-DE-LEON, A., GARCIA-GARCIA, M. D. L., GARCIA-SANCHO, M. C., GOMEZ-PEREZ, F. J., VALDESPINO-GOMEZ, J. L., OLAIZ-FERNANDEZ, G., ROJAS, R., FERREYRA-REYES, L., CANO-ARELLANO, B., BOBADILLA, M., SMALL, P. M. & SIFUENTES-OSORNIO, J. 2004. Tuberculosis and Diabetes in Southern Mexico. *Diabetes Care*, 27, 1584-1590.
- POORAN, A., PIETERSON, E., DAVIDS, M., THERON, G. & DHEDA, K. 2013. What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? *PLoS ONE*, 8, e54587.
- PRADO, T. N., WADA, N., GUIDONI, L. M., GOLUB, J. E., DIETZE, R. & MACIEL, E. L. 2011. Cost-effectiveness of community health worker versus home-based guardians for directly observed treatment of tuberculosis in Vitoria, Espirito Santo State, Brazil. *Cad Saude Publica*, 27, 944-52.
- RAJBHANDARY, S. S., MARKS, S. M. & BOCK, N. N. 2004. Costs of patients hospitalized for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*, 8, 1012-6.
- RAJESWARI, R., BALASUBRAMANIAN, R., MUNIYANDI, M., GEETHARAMANI, S., THRESA, X. & VENKATESAN, P. 1999. Socio-economic impact of tuberculosis on patients and family in India. *Int J Tuberc Lung Dis*, 3, 869-77.
- RALPH, A. P., KENANGALEM, E., WARAMORI, G., PONTORORING, G. J., SANDJAJA, TJITRA, E., MAGUIRE, G. P., KELLY, P. M. & ANSTEY, N. M. 2013. High Morbidity during Treatment and Residual Pulmonary Disability in Pulmonary Tuberculosis: Under-Recognised Phenomena. *PLoS ONE*, 8, e80302.
- RAMSEY, S., WILLKE, R., BRIGGS, A., BROWN, R., BUXTON, M., CHAWLA, A., COOK, J., GLICK, H., LILJAS, B., PETITTI, D. & REED, S. 2005. Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health*, 8, 521-33.
- RAMSEY, S. D., WILLKE, R. J., GLICK, H., REED, S. D., AUGUSTOVSKI, F., JONSSON, B., BRIGGS, A. & SULLIVAN, S. D. 2015. Cost-effectiveness analysis alongside clinical

- trials II-An ISPOR Good Research Practices Task Force report. *Value Health*, 18, 161-72.
- RAULINAJTYS-GRZYBEK, M. 2014. Cost accounting models used for price-setting of health services: an international review. *Health Policy*, 118, 341-53.
- RAY, T., SHARMA, N., SINGH, M. & INGLE, G. 2005. Economic burden of tuberculosis in patients attending DOT centres in Delhi. *Journal of Communicable Diseases*, 37, 93-98.
- REICH, M. R., HARRIS, J., IKEGAMI, N., MAEDA, A., CASHIN, C., ARAUJO, E. C., TAKEMI, K. & EVANS, T. G. 2016. Moving towards universal health coverage: lessons from 11 country studies. *Lancet*, 387, 811-6.
- RESTREPO, B. I. 2007. Convergence of the Tuberculosis and Diabetes Epidemics: Renewal of Old Acquaintances. *Clinical Infectious Diseases*, 45, 436-438.
- RESTREPO, B. I., PINO, P. A., ZARATE, I. & MORA-GUZMAN, F. 2013. Dipstick urinalysis for diabetes screening in TB patients. *Int Health*, 5, 157-9.
- RIZA, A. L., PEARSON, F., UGARTE-GIL, C., ALISJAHBANA, B., VAN DE VIJVER, S., PANDURU, N. M., HILL, P. C., RUSLAMI, R., MOORE, D., AARNOUTSE, R., CRITCHLEY, J. A. & VAN CREVEL, R. 2014. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes Endocrinol*, 2, 740-53.
- ROOT, H. F. 1934. The Association of Diabetes and Tuberculosis. *New England Journal of Medicine*, 210, 78-92.
- ROUZIER, V. A., OXLADE, O., VERDUGA, R., GRESELY, L. & MENZIES, D. 2010. Patient and family costs associated with tuberculosis, including multidrug-resistant tuberculosis, in Ecuador. *Int J Tuberc Lung Dis*, 14, 1316-22.
- RUDIANTO, A., SOEWONDO, P., WASPADJI, S., YUNIR, E. & PURNAMASARI, D. 2011. The Indonesian Society of Endocrinology's Summary Article of Diabetes Mellitus National Clinical Practice Guidelines. *Journal of the ASEAN Federation of Endocrine Societies*, 26, 17-19.
- RUIZ, M. G., NUNEZ, L.R., LEZAMA, M.A.S., VALLE, F.C. 2003. Costos de atencipn de la tuberculosis: caso del Instituto Nacional de Enfermedadaes Respiratorias (INER). *Revista Instituto Nacional de Enfermedades Respiratorias*, 16.
- SAMANDARI, T., BISHAI, D., LUTEIJN, M., MOSIMANEOTSILE, B., MOTSAMAI, O., POSTMA, M. & HUBBEN, G. 2011. Costs and consequences of additional chest x-ray in a tuberculosis prevention program in Botswana. *Am J Respir Crit Care Med*, 183, 1103-11.
- SAUNDERSON, P. R. 1995. An economic evaluation of alternative programme designs for tuberculosis control in rural Uganda. *Soc Sci Med*, 40, 1203-12.
- SAWERT, H., KONGSIN, S., PAYANANDANA, V., AKARASEWI, P., NUNN, P. P. & RAVIGLIONE, M. C. 1997. Costs and benefits of improving tuberculosis control: the case of Thailand. *Soc Sci Med*, 44, 1805-16.
- SCHNIPPEL, K., MEYER-RATH, G., LONG, L., MACLEOD, W., SANNE, I., STEVENS, W. S. & ROSEN, S. 2012. Scaling up Xpert MTB/RIF technology: the costs of laboratory- vs. clinic-based roll-out in South Africa. *Trop Med Int Health*, 17, 1142-51.
- SCHNIPPEL, K., MEYER-RATH, G., LONG, L., STEVENS, W. S., SANNE, I. & ROSEN, S. 2013a. Diagnosing Xpert MTB/RIF-negative TB: Impact and cost of alternative algorithms for South Africa. *South African Medical Journal*, 103, 101-106.

- SCHNIPPEL, K., ROSEN, S., SHEARER, K., MARTINSON, N., LONG, L., SANNE, I. & VARIAVA, E. 2013b. Costs of inpatient treatment for multi-drug-resistant tuberculosis in South Africa. *Trop Med Int Health*, 18, 109-16.
- SECLÉN, S. N., ROSAS, M. E., ARIAS, A. J., HUAYTA, E. & MEDINA, C. A. 2015. Prevalence of diabetes and impaired fasting glucose in Peru: report from PERUDIAB, a national urban population-based longitudinal study. *BMJ Open Diabetes Res Care*, 3, e000110.
- SEURING, T., ARCHANGELIDI, O. & SUHRCKE, M. 2015. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. *PharmacoEconomics*, 1-21.
- SHAH, M., CHIHOTA, V., COETZEE, G., CHURCHYARD, G. & DORMAN, S. E. 2013. Comparison of laboratory costs of rapid molecular tests and conventional diagnostics for detection of tuberculosis and drug-resistant tuberculosis in South Africa. *BMC Infect Dis*, 13, 352.
- SHEPARD, J. G., AIREE, A., DAKE, A. W., MCFARLAND, M. S. & VORA, A. 2015. Limitations of A1c Interpretation. *South Med J*, 108, 724-9.
- SINANOVIC, E. & KUMARANAYAKE, L. 2006. Financing and cost-effectiveness analysis of public-private partnerships: provision of tuberculosis treatment in South Africa. *Cost Eff Resour Alloc*, 4, 11.
- SINANOVIC, E., RAMMA, L., VASSALL, A., AZEVEDO, V., WILKINSON, L., NDJEKA, N., MCCARTHY, K., CHURCHYARD, G. & COX, H. 2015. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. *Int J Tuberc Lung Dis*, 19, 172-8.
- SOEWONDO, P. 2011. Current Practice in the Management of Type 2 Diabetes in Indonesia: Results from the International Diabetes Management Practices Study (IDMPS). *Journal of the Indonesian Medical Association*, 61, 474-481.
- SOEWONDO, P., FERRARIO, A. & TAHAPARY, D. L. 2013. Challenges in diabetes management in Indonesia: a literature review. *Global Health*, 9, 63.
- SOHN, H., MINION, J., ALBERT, H., DHEDA, K. & PAI, M. 2009a. TB diagnostic tests: how do we figure out their costs? *Expert Rev Anti Infect Ther*, 7, 723-33.
- SOHN, H., SINTHUWATTANAWIBOOL, C., RIENTHONG, S. & VARMA, J. K. 2009b. Fluorescence microscopy is less expensive than Ziehl-Neelsen microscopy in Thailand. *Int J Tuberc Lung Dis*, 13, 266-8.
- STEFFEN, R., MENZIES, D., OXLADE, O., PINTO, M., DE CASTRO, A. Z., MONTEIRO, P. & TRAJMAN, A. 2010. Patients' costs and cost-effectiveness of tuberculosis treatment in DOTS and non-DOTS facilities in Rio de Janeiro, Brazil. *PloS one*, 5, e14014.
- STEVENSON, C., FOROUHI, N., ROGLIC, G., WILLIAMS, B., LAUER, J., DYE, C. & UNWIN, N. 2007a. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health*, 7, 234.
- STEVENSON, C. R., CRITCHLEY, J. A., FOROUHI, N. G., ROGLIC, G., WILLIAMS, B. G., DYE, C. & UNWIN, N. C. 2007b. Diabetes and the risk of tuberculosis: a neglected threat to public health? *Chronic Illn*, 3, 228-45.
- SUAREZ, P. G., FLOYD, K., PORTOCARRERO, J., ALARCON, E., RAPITI, E., RAMOS, G., BONILLA, C., SABOGAL, I., ARANDA, I., DYE, C., RAVIGLIONE, M. & ESPINAL, M. A. 2002. Feasibility and cost-effectiveness of standardised second-line drug

- treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet*, 359, 1980-9.
- SULLIVAN, T. & BEN AMOR, Y. 2012. The co-management of tuberculosis and diabetes: challenges and opportunities in the developing world. *PLoS Med*, 9, e1001269.
- TAN-TORRES EDEJER, T., BALTUSSEN, R., ADAM, T., HUTUBESSY, R., ACHARYA, A., EVANS, D. B. & MURRAY, C. J. L. (eds.) 2003. *Making Choices in Health: WHO Guide to cost-effectiveness analysis*, Geneva, Switzerland: World Health Organization.
- TB DIAGNOSTICS MARKET ANALYSIS CONSORTIUM, T., STEVENS, W. S., SCHNIPPEL, K., BERRIE, L., GINNARD, J., PERKINS, M. D., BOEHME, C. C., JEFFERSON, C., PANTOJA, A., CHEDORE, P., DENKINGER, C. M., PAI, M. & KIK, S. V. 2015. Market assessment of tuberculosis diagnostics in South Africa, 2012-2013. *Int J Tuberc Lung Dis*, 19, 216-22.
- TB DIAGNOSTICS MARKET ANALYSIS CONSORTIUM, T., TRAJMAN, A., PINTO, M., JUNIOR, R. D. S., FREITAS, M., BOEHME, C. C., GINNARD, J., JEFFERSON, C., PANTOJA, A., KIK, S. V., CHEDORE, P., DENKINGER, C. M. & PAI, M. 2014. Market assessment of tuberculosis diagnostics in Brazil in 2012. *PLoS One*, 9, e104105.
- THE UNION 2015a. Indonesian TB-diabetes consensus signed. *In: INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE* (ed.). Paris, France: International Union Against Tuberculosis and Lung Disease.
- THE UNION 2015b. Taking action against TB-diabetes. *In: INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE* (ed.) *A message from Executive Director Jose Luis Castro*.
- THE UNION & WDF 2014. The looming co-epidemic of TB-diabetes: a call to action. *In: INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE & WORLD DIABETES FOUNDATION* (eds.). Paris, France: International Union Against Tuberculosis and Lung Disease.
- THE UNION & WHO 2011. Collaborative framework for care and control of tuberculosis and diabetes. *In: INTERNATIONAL UNION AGAINST TUBERCULOSIS AND LUNG DISEASE & WORLD HEALTH ORGANIZATION* (eds.). Geneva: World Health Organization.
- THERON, G., POORAN, A., PETER, J., VAN ZYL-SMIT, R., KUMAR MISHRA, H., MELDAU, R., CALLIGARO, G., ALLWOOD, B., SHARMA, S. K., DAWSON, R. & DHEDA, K. 2012. Do adjunct tuberculosis tests, when combined with Xpert MTB/RIF, improve accuracy and the cost of diagnosis in a resource-poor setting? *Eur Respir J*, 40, 161-8.
- TU, H. Z., CHEN, Y. S., LIN, Y. E., TSENG, M. R., HUANG, T. S., TSAI, H. C. & LIU, Y. C. 2011a. Combination of molecular assay and clinical evaluation for early confirmation of tuberculosis cases. *Clin Microbiol Infect*, 17, 712-4.
- TU, H. Z., CHEN, Y. S., LIN, Y. E., TSENG, M. R., HUANG, T. S., TSAI, H. C. & LIU, Y. C. 2011b. Combination of molecular assay and clinical evaluation for early confirmation of tuberculosis cases. *Clinical Microbiology and Infection*, 17, 712-714.
- TUPASI, T. E., GUPTA, R., QUELAPIO, M. I., ORILLAZA, R. B., MIRA, N. R., MANGUBAT, N. V., BELEN, V., ARNISTO, N., MACALINTAL, L., ARABIT, M., LAGAHID, J. Y., ESPINAL, M. & FLOYD, K. 2006. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. *PLoS Med*, 3, e352.
- TURNER, R. D. & BOTHAMLEY, G. H. 2014. Cough and the transmission of tuberculosis. *Journal of Infectious Diseases*.

- UMAR, N. A., ABUBAKAR, I., FORDHAM, R. & BACHMANN, M. 2012. Direct costs of pulmonary tuberculosis among patients receiving treatment in Bauchi State, Nigeria. *Int J Tuberc Lung Dis*, 16, 835-40.
- UNAIDS 2000. Costing guidelines for HIV prevention strategies. In: JOINT UNITED NATIONS PROGRAMMES ON HIV/AIDS (ed.) *UNAIDS Best Practice Collection - Key Material*. Geneva: UNAIDS.
- UNDATA 2016. Country profile. *World Statistics Pocketbook*.
- UNSD 2016. World Statistics Pocketbook. In: DIVISION, U. N. S. (ed.). New York.
- VAN CLEEFF, M. R., KIVIHYA-NDUGGA, L. E., MEME, H., ODHIAMBO, J. A. & KLATSER, P. R. 2005. The role and performance of chest X-ray for the diagnosis of tuberculosis: a cost-effectiveness analysis in Nairobi, Kenya. *BMC Infect Dis*, 5, 111.
- VAN CREVEL, R. & DOCKRELL, H. M. 2014a. TANDEM: understanding diabetes and tuberculosis. *The Lancet Diabetes & Endocrinology*, 2, 270-272.
- VAN CREVEL, R. & DOCKRELL, H. M. 2014b. TANDEM: understanding diabetes and tuberculosis. *Lancet Diabetes Endocrinol*, 2, 270-2.
- VAN DEN HOUT, W. B. 2010. The value of productivity: human-capital versus friction-cost method. *Ann Rheum Dis*, 69 Suppl 1, i89-91.
- VAN HOUT, B., JANSSEN, M. F., FENG, Y. S., KOHLMANN, T., BUSSCHBACH, J., GOLICKI, D., LLOYD, A., SCALONE, L., KIND, P. & PICKARD, A. S. 2012. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*, 15, 708-15.
- VAN RIE, A., PAGE-SHIPP, L., HANRAHAN, C. F., SCHNIPPEL, K., DANSEY, H., BASSETT, J., CLOUSE, K., SCOTT, L., STEVENS, W. & SANNE, I. 2013. Point-of-care Xpert MTB/RIF for smear-negative tuberculosis suspects at a primary care clinic in South Africa. *International Journal of Tuberculosis and Lung Disease*, 17, 368-372.
- VARGAS RUIZ, M., RIOS NUNEZ, L., SALAZAR LEZAMA, M. A. & CANO VALLE, F. 2003. Costos de atencion de la tuberculosis: Caso del Instituto Nacional de Enfermedades Respiratorias (INER). *Revista Instituto Nacional de Enfermedades Respiratorias*, 16, 219-225.
- VASSALL, A., BAGDADI, S., BASHOUR, H., ZAHER, H. & MAAREN, P. V. 2002. Cost-effectiveness of different treatment strategies for tuberculosis in Egypt and Syria. *Int J Tuberc Lung Dis*, 6, 1083-90.
- VASSALL, A., CHECHULIN, Y., RAYKHERT, I., OSALENKO, N., SVETLICHNAYA, S., KOVALYOVA, A., VAN DER WERF, M. J., TURCHENKO, L. V., HASKER, E., MISKINIS, K., VEEN, J. & ZALESKIS, R. 2009. Reforming tuberculosis control in Ukraine: results of pilot projects and implications for the national scale-up of DOTS. *Health Policy Plan*, 24, 55-62.
- VASSALL, A., SEME, A., COMPERNOLLE, P. & MEHEUS, F. 2010. Patient costs of accessing collaborative tuberculosis and human immunodeficiency virus interventions in Ethiopia. *Int J Tuberc Lung Dis*, 14, 604-10.
- VASSALL, A., VAN KAMPEN, S., SOHN, H., MICHAEL, J. S., JOHN, K. R., DEN BOON, S., DAVIS, J. L., WHITELAW, A., NICOL, M. P., GLER, M. T., KHALIQOV, A., ZAMUDIO, C., PERKINS, M. D., BOEHME, C. C. & COBELENS, F. 2011. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. *PLoS Med*, 8, e1001120.
- VILLENA, J. E. 2015. Diabetes Mellitus in Peru. *Ann Glob Health*, 81, 765-75.

- VISWANATHAN, V., KUMPATLA, S., ARAVINDALOCHANAN, V., RAJAN, R., CHINNASAMY, C., SRINIVASAN, R., SELVAM, J. M. & KAPUR, A. 2012. Prevalence of Diabetes and Pre-Diabetes and Associated Risk Factors among Tuberculosis Patients in India. *PLoS ONE*, 7, e41367.
- VLĂDESCU, C., RADULESCU, S. & CASE, S. 2005. The Romanian healthcare system: between Bismark and Semashko. In: SHAKARISHVILI, G. (ed.) *Decentralization in healthcare: Analyses and experiences in Central and Eastern Europe in the 1990s*. Budapest, Hungary: Local Government and Public Service Reform Initiative of the Open Society Institute.
- VLĂDESCU, C., SCINTEE, G. & OLSAVSZKY, V. 2008. *Romania: Health System Review*, Copenhagen, Denmark, WHO Regional Office for Europe.
- VYAS, S. & KUMARANAYAKE, L. 2006. Constructing socio-economic status indices: how to use principal components analysis. *Health Policy and Planning*, 21, 459-468.
- WALKER, D. & KUMARANAYAKE, L. 2002. Allowing for differential timing in cost analyses: discounting and annualization. *Health Policy Plan*, 17, 112-8.
- WANDWALO, E., ROBBERSTAD, B. & MORKVE, O. 2005. Cost and cost-effectiveness of community based and health facility based directly observed treatment of tuberculosis in Dar es Salaam, Tanzania. *Cost Eff Resour Alloc*, 3, 6.
- WAUGH, N., SCOTLAND, G., MCNAMEE, P., GILLETT, M., BRENNAN, A., GOYDER, E., WILLIAMS, R. & JOHN, A. 2007. Screening for type 2 diabetes: literature review and economic modelling. *Health Technol Assess*, 11, iii-iv, ix-xi, 1-125.
- WB 2000. Designing Household Survey Questionnaires for Developing Countries: Lessons from 15 years of the Living Standards Measurement Study. In: GROSH, M. & GLEWWE, P. (eds.). Washington, D.C.: The World Bank.
- WB 2008. Investing in Indonesia's Health: Challenges and Opportunities for Future Public Spending. In: ROKX, C. (ed.) *Health Public Expenditure Review*. Washington, DC: The World Bank.
- WB 2009. Health financing in Indonesia: a reform roadmap. In: ROKX, C., SCHIEBER, G., HARIMURTI, P., TANDON, A. & SOMANATHAN, A. (eds.). Washington, DC.
- WB 2012. World Development Indicators. In: WORLD BANK (ed.). Washington, DC, USA.
- WB 2013. The Nuts & Bolts of Jamkesmas, Indonesia's Government-Financed Health Coverage Program for the Poor and Near-Poor. In: JARIMURTI, P., PAMBUDI, E., PIGAZZINI, A. & TANDON, A. (eds.) *Universal Health Coverage Studies Series (UNICO)*. Washington, DC: The World Bank.
- WB 2016a. GNI per capita, Atlas method (current US\$). *World Bank national accounts data, and OECD National Accounts data files*. Washington, DC, USA.
- WB 2016b. World Development Indicators. In: WORLD BANK (ed.). Washington, DC.
- WEI, X., ZOU, G., WALLEY, J., YIN, J., LONNROTH, K., UPLEKAR, M., WANG, W. & SUN, Q. 2014. China tuberculosis policy at crucial crossroads: Comparing the practice of different hospital and tuberculosis control collaboration models using survey data. *PLoS ONE*, 9.
- WEIS, S. E., FORESMAN, B., MATTY, K. J., BROWN, A., BLAIS, F. X., BURGESS, G., KING, B., COOK, P. E. & SLOCUM, P. C. 1999. Treatment costs of directly observed therapy and traditional therapy for Mycobacterium tuberculosis: a comparative analysis. *Int J Tuberc Lung Dis*, 3, 976-84.

- WEISS, P. 1954. [Geography of diseases in Peru in relation to the climatic zones]. *An Fac Med Lima*, 37, 601-27.
- WHITE, J. R. 1997. Combination Oral Agent/Insulin Therapy in patients with Type II Diabetes Mellitus. *Clinical Diabetes*, 15.
- WHITE, V. L. & MOORE-GILLON, J. 2000. Resource implications of patients with multidrug resistant tuberculosis. *Thorax*, 55, 962-3.
- WHITELAW, A., PETER, J., SOHN, H., VILJOEN, D., THERON, G., BADRI, M., DAVIDS, V., PAI, M. & DHEDA, K. 2011. Comparative cost and performance of light-emitting diode microscopy in HIV-tuberculosis-co-infected patients. *Eur Respir J*, 38, 1393-7.
- WHO 1988. Estimating costs for cost-effectiveness analysis: Guidelines for managers of diarrhoeal diseases control programmes. *In: WORLD HEALTH ORGANIZATION* (ed.). Geneva: WHO.
- WHO 2000. CHOosing Interventions that are Cost Effective (WHO-CHOICE). *Useful Life*. Geneva: World Health Organization.
- WHO 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. *In: WORLD HEALTH ORGANIZATION* (ed.). Geneva: World Health Organisation.
- WHO 2008. Integrated Health Services. *In: WORLD HEALTH ORGANIZATION* (ed.) *Technical Brief*. Geneva: World Health Organization.
- WHO 2009. A brief history of tuberculosis control in Indonesia. *In: WORLD HEALTH ORGANIZATION* (ed.). Geneva, Switzerland.
- WHO 2010a. Global Tuberculosis Report 2010. Geneva: World Health Organization,.
- WHO 2010b. Treatment of tuberculosis: guidelines. *In: WORLD HEALTH ORGANIZATION* (ed.) 4th ed. Geneva: World Health Organization.
- WHO 2011a. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. *In: WORLD HEALTH ORGANIZATION* (ed.) *Policy statement*. Geneva, Switzerland: World Health Organization.
- WHO 2011b. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. *In: WORLD HEALTH ORGANIZATION* (ed.). Geneva: World Health Organisation.
- WHO 2012. Global Tuberculosis Report 2012. *In: WORLD HEALTH ORGANIZATION* (ed.) *Global Tuberculosis Report*. Geneva: World Health Organization.
- WHO 2013a. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. *In: WORLD HEALTH ORGANIZATION* (ed.) *Policy updates*. Geneva, Switzerland: United Nations.
- WHO 2013b. Global strategy and targets for tuberculosis prevention, care and control after 2015. December 2013 ed.
- WHO 2013c. Systematic screening for active tuberculosis: principles and recommendations. *In: WORLD HEALTH ORGANIZATION* (ed.). Geneva, Switzerland.
- WHO. 2013d. *Tuberculosis - Key facts* [Online]. Geneva, Switzerland: WHO. [Accessed August 11 2013].

- WHO 2014a. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. *In: WORLD HEALTH ORGANIZATION (ed.) Companion handbooks*. Geneva, Switzerland: United Nations.
- WHO 2014b. Health System Financing Country Profile: Peru, 2014. *National Health Accounts*. Geneva, Switzerland: World Health Organization.
- WHO 2014c. Noncommunicable diseases country profiles. *Noncommunicable Diseases (NCD) Country Profiles*. Geneva, Switzerland: World Health Organization.
- WHO 2015a. The End TB Strategy. *In: WORLD HEALTH ORGANIZATION (ed.) Fact Sheets*. Geneva, Switzerland: United Nations.
- WHO 2015b. Global Tuberculosis Report 2015. *In: WORLD HEALTH ORGANIZATION (ed.) Global Tuberculosis Report*. Geneva: World Health Organization.
- WHO 2015c. Multidrug-resistant Tuberculosis (MDR-TB). *In: WORLD HEALTH ORGANIZATION (ed.) Fact Sheets*. Geneva, Switzerland: United Nations.
- WHO 2015d. Tuberculosis control in the South-East Asia Region. *In: WORLD HEALTH ORGANIZATION (ed.) Annual TB Report 2015*. India: World Health Organization - Regional Office for South-East Asia.
- WHO 2015e. Tuberculosis country profiles. *Global Tuberculosis Report 2015*. Geneva, Switzerland: World Health Organization.
- WHO 2015f. Use of high burden country lists for TB by WHO in the post-2015 era. *In: WORLD HEALTH ORGANIZATION (ed.) Discussion paper*. Geneva, Switzerland: Global TB Programme.
- WHO 2015g. World Health Statistics 2015. *In: WORLD HEALTH ORGANIZATION (ed.) World Health Statistics*. Geneva.
- WHO 2016a. Global Tuberculosis Report 2016. *In: WORLD HEALTH ORGANIZATION (ed.) Global Tuberculosis Report*. Geneva: World Health Organisation.
- WHO 2016b. Tuberculosis control in the South-East Asia Region. *In: WORLD HEALTH ORGANIZATION (ed.) Annual TB report 2016*. India: World Health Organization - Regional Office for South-East Asia.
- WHO & ECDC 2015. Review of the national tuberculosis programme in Romania: 10-21 March 2014. *In: COLOMBANI, P. D. (ed.)*. Copenhagen, Denmark: WHO Regional Office for Europe.
- WIBOWO, Y., SUNDERLAND, B. & HUGHES, J. 2016. Pharmacist and physician perspectives on diabetes service delivery within community pharmacies in Indonesia: a qualitative study. *Int J Pharm Pract*, 24, 180-8.
- WIDYAHENING, I. S., VAN DER GRAAF, Y., SOEWONDO, P., GLASZIOU, P. & VAN DER HEIJDEN, G. J. 2014. Awareness, agreement, adoption and adherence to type 2 diabetes mellitus guidelines: a survey of Indonesian primary care physicians. *BMC Fam Pract*, 15, 72.
- WILD, S., ROGLIC, G., GREEN, A., SICREE, R. & KING, H. 2004. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 27, 1047-53.
- WILKINSON, D., FLOYD, K. & GILKS, C. F. 1997. Costs and cost-effectiveness of alternative tuberculosis management strategies in South Africa--implications for policy. *S Afr Med J*, 87, 451-5.
- WILLIAMS, R., VAN GAAL, L., LUCIONI, C. & BOARD, C.-A. 2002. Assessing the impact of complications on the costs of Type II diabetes. *Diabetologia*, 45, S13-7.

- WONG, C. K., LAM, C. L., WAN, E. Y., CHAN, A. K., PAK, C. H., CHAN, F. W. & WONG, W. C. 2016. Evaluation of patient-reported outcomes data in structured diabetes education intervention: 2-year follow-up data of patient empowerment programme. *Endocrine*, 54, 422-432.
- WURTZ, R. & WHITE, W. D. 1999. The cost of tuberculosis: utilization and estimated charges for the diagnosis and treatment of tuberculosis in a public health system. *Int J Tuberc Lung Dis*, 3, 382-7.
- WYSS, K., KILIMA, P. & LORENZ, N. 2001. Costs of tuberculosis for households and health care providers in Dar es Salaam, Tanzania. *Trop Med Int Health*, 6, 60-8.
- XIA, H., SONG, Y. Y., ZHAO, B., KAM, K. M., O'BRIEN, R. J., ZHANG, Z. Y., SOHN, H., WANG, W. & ZHAO, Y. L. 2013. Multicentre evaluation of Ziehl-Neelsen and light-emitting diode fluorescence microscopy in China. *Int J Tuberc Lung Dis*, 17, 107-12.
- XIE, X., SINCLAIR, A. & DENDUKURI, N. 2017. Evaluating the accuracy and economic value of a new test in the absence of a perfect reference test. *Res Synth Methods*.
- XU, Q., JIN, S. G. & ZHANG, L. X. 2000. Cost effectiveness of DOTS and non-DOTS strategies for smear-positive pulmonary tuberculosis in Beijing. *Biomed Environ Sci*, 13, 307-13.
- XU, X., GROSSETTA NARDINI, H. & RUGER, J. 2014. Micro-costing studies in the health and medical literature: protocol for a systematic review. *Systematic Reviews*, 3, 47.
- YITAYAL, M., ASEFFA, A., ANDARGIE, G., WASSIE, L. & ABEBE, M. 2014. Assessment of cost of tuberculosis to patients and their families: a cross-sectional study at Addet Health Center, Yilmana Densa District, Amhara National Regional State. *Ethiop Med J, Suppl 1*, 23-30.
- YOUNG, F., CRITCHLEY, J. A., JOHNSTONE, L. K. & UNWIN, N. C. 2009. A review of co-morbidity between infectious and chronic disease in Sub Saharan Africa: TB and diabetes mellitus, HIV and metabolic syndrome, and the impact of globalization. *Global Health*, 5, 9.
- ZHANG, P., ENGELGAU, M. M., VALDEZ, R., BENJAMIN, S. M., CADWELL, B. & NARAYAN, K. M. 2003. Costs of screening for pre-diabetes among US adults: a comparison of different screening strategies. *Diabetes Care*, 26, 2536-42.
- ZOU, G., WEI, X., WITTER, S., YIN, J., WALLEY, J., LIU, S., YANG, H., CHEN, J., TIAN, G. & MEI, J. 2013. Incremental cost-effectiveness of improving treatment results among migrant tuberculosis patients in Shanghai. *International Journal of Tuberculosis and Lung Disease*, 17, 1056-1064.

Appendices

Appendix A: Full electronic search strategies

7th January 2013

EMBASE and Medline - using Ovid search interface

(cost* OR finance OR economic burden).mp

AND

(treatment OR management OR drugs OR medication OR DOTS OR directly observed treatment).mp

AND

(tb OR tuberculosis OR MDR#tb OR XDR#TB OR multi?drug resistant tuberculosis).mp

OR

(cost* OR finance OR eco mic burden).mp

AND

(diagnos* OR screen* OR chest x-ray OR chest radiography OR sputum* OR smear OR test* OR skin test OR xpert OR (case adj3 (find* OR detection))).mp

AND

(tb OR tuberculosis OR MDR#tb OR XDR#TB OR multi?drug resistant tuberculosis).mp

[Limits: 'human' and 'year' = 1990-current]

15th January 2013

NHS EED (National Health Service Economic Evaluation Database)

'tuberculosis'

AND

'cost'

[Any field; limits]

CEA Registry (Cost-effectiveness analysis Registry)

'tuberculosis'

[Full search contents]

LILACS (Literatura Latino Americana em Ciencias da Saude or Latin American and Caribbean Health Sciences Literature) – using Virtual Health Library Service

'tuberculosis'

AND

'treatment'

AND

'cost'

[Words]

Appendix B: Quality assessment for studies with provider costs only

First author	Country	Number of patients in study sample	Ingredient approach used	Sources for resource use and unit costs well explained	Year of cost data reported	Main cost categories reported	Descriptive statistics presented
HICs (n=15)							
MacIntyre (MacIntyre et al., 2001)	Australia	269	X	X	X		
Floyd (Floyd et al., 2012)	Estonia, Russia	354	X	X	X	X	
Marchand (Marchand et al., 1999)	Canada	11			X		
Bocchino (Bocchino et al., 2006)	Italy	92	X		X	X	X
Miller (Miller et al., 2013)	Latvia	63	X	X	X	X	X
Burns (Burns and Harrison, 2007)	New Zealand	45	X			X	
Migliori (Migliori et al., 1998)	Russia	NA	X	X	X	X	
Atun (Atun et al., 2006)	Russia	1,749	X			X	X
Montes-Santiago (Montes-Santiago et al., 2010)	Spain	NA			X	X	
Tu (Tu et al., 2011a)	Taiwan	161					
Palmer (Palmer et al., 1998)	USA	178	X	X	X	X	
Weis (Weis et al., 1999)	USA	659	X	X	X	X	
Wurtz (Wurtz and White, 1999)	USA	92	X	X	X	X	
Eralp (Eralp et al., 2012)	UK	NA		X	X		
White (White and Moore-Gillon, 2000)	UK	9	X	X	X	X	
UMICs (n=11)							
Samandari (Samandari et al., 2011)	Botswana	NA	X		X		

First author	Country	Number of patients in study sample	Ingredient approach used	Sources for resource use and unit costs well explained	Year of cost data reported	Main cost categories reported	Descriptive statistics presented
Xu (Xu et al., 2000)	China	NA	X				
Peralta Perez (Peralta Perez et al., 2006)	Cuba	223	X		X	X	
Ruiz (Ruiz, 2003)	Mexico	NA	X	X	X	X	
Suarez (Suarez et al., 2002)	Peru	298	X	X	X	X	
Masobe (Masobe et al., 1995)	South Africa	NA	X	X	X	X	
Dick (Dick and Henchie, 1998)	South Africa	NA	X	X	X	X	
Schnippel (Schnippel et al., 2013b)	South Africa	121	X	X	X	X	X
Sinanovic (Sinanovic and Kumaranayake, 2006)	South Africa	1,182	X	X	X	X	
Pooran (Pooran et al., 2013)	South Africa	NA	X	X	X	X	
Kamolratanakul (Kamolratanakul et al., 2002)	Thailand	98	X	X	X	X	
LMICs (n=1)							
El-Sony (El-Sony, 2006)	Sudan	1797				X	
LICs (n=1)							
Maponga (Maponga, 1996)	Zimbabwe	300	X		X		

HICs: High-income countries, UMICs: Upper-middle income countries, LMICs: Lower-middle income countries, LICs: Low-income countries, NA: Not applicable

Appendix C: Quality assessment for studies with provider and patient costs

First author	Country	Number of patients in study sample	Patient interviews	Ingredient approach used*	Sources for resource use and unit costs clearly explained	Main cost categories reported	Descriptive statistics presented	Methods for valuing productivity loss clearly explained	Sources for productivity costs assumptions justified
HICs (n=10)									
Diel (Diel et al., 2012)	Germany	3510		X	X	X		X	X
Diel (Diel et al., 2014)	Germany	65		X	X	X	X	X	X
Migliori (Migliori et al., 1999)	Italy	682		X	X	X		X	X
Kik (Kik et al., 2009)	Netherlands	60	X	NA	X	X	X	X	X
Jacobs (Jacobs et al., 2002)	Russia	98	X	X	X	X		X	X
Kang (Kang et al., 2006)	South Korea	21		X	X	X	X	X	X
Rajbhandary (Rajbhandary et al., 2004)	USA	13		X	X	X	X	X	X
Burman (Burman et al., 1997)	USA	107		X	X	X		X	
Marks (Marks et al., 2014)	USA	135		X	X		X	X	
Miller (Miller et al., 2010)	USA	54				X			
UMICs (n=18)									
Cusmano (Cusmano et al., 2009)	Argentina	30	X	X		X		X	
Moalosi (Moalosi et al., 2003)	Botswana	50	X	X	X	X		NA	NA

First author	Country	Number of patients in study sample	Patient interviews	Ingredient approach used*	Sources for resource use and unit costs clearly explained	Main cost categories reported	Descriptive statistics presented	Methods for valuing productivity loss clearly explained	Sources for productivity costs assumptions justified
Costa (Costa et al., 2005)	Brazil	214	X	X	X	X			X
Steffen (Steffen et al., 2010)	Brazil	218	X	X		X	X	X	X
Prado (Prado et al., 2011)	Brazil	130	X	X	X	X		X	X
Jackson (Jackson et al., 2006a)	China	160	X	NA	X	X	X	X	X
Liu (Liu et al., 2007)	China	889	X	NA	X			NA	NA
Pan (Pan et al., 2013)	China	316	X	NA		X	X		
Wei (Wei et al., 2014)	China	293	X	NA	X			NA	NA
Zou (Zou et al., 2013)	China	198	X	X	X	X		X	X
Nieto	Colombia	150	X	X	X	X	X	X	X
Rouzier (Rouzier et al., 2010)	Ecuador	104	X	NA	X	X		X	X
Elamin (Elamin et al., 2008)	Malaysia	30	X	X	X	X		X	X
Guzman-Montes (Guzman-Montes, 2009)	Mexico	180	X	NA	X	X		NA	NA
Fairall (Fairall et al., 2010)	South Africa	1,999	X	X	X	X		NA	NA
Foster (Foster et al., 2015)	South Africa	175	X	NA	X	X		X	X
Wilkinson (Wilkinson et al., 1997)	South Africa	48	X	X	X	X		NA	NA

First author	Country	Number of patients in study sample	Patient interviews	Ingredient approach used*	Sources for resource use and unit costs clearly explained	Main cost categories reported	Descriptive statistics presented	Methods for valuing productivity loss clearly explained	Sources for productivity costs assumptions justified
Sawert (Sawert et al., 1997)	Thailand	NA		Not clear		X		X	
LMICs (n=16)									
Vassall (Vassall et al., 2002)	Egypt, Syria	285	X	X	X			X	
Floyd (Floyd et al., 2006)	India	354	X	X	X	X	X	X	
John (John et al., 2009b)	India	100	X	NA	X	X	X	X	X
Muniyandi (Muniyandi et al., 2008)	India	896	X	NA	X	X	X	X	X
Pantoja (Pantoja et al., 2009a)	India	1,138	X		X	X		X	
Rajeswari (Rajeswari et al., 1999)	India	304	X	NA	X			X	X
Mahendradhata (Mahendradhata et al., 2010)	Indonesia	108	X		X	X	X		
Mauch (Mauch et al., 2011)	Kenya	258	X	NA	X	X	X	X	X
Nganda (Nganda et al., 2003)	Kenya	87	X	X	X	X	X	X	X
Umar (Umar et al., 2012)	Nigeria	255	X	NA	X	X	X	NA	NA
Khan (Khan et al., 2002)	Pakistan	337	X		X	X			

First author	Country	Number of patients in study sample	Patient interviews	Ingredient approach used*	Sources for resource use and unit costs clearly explained	Main cost categories reported	Descriptive statistics presented	Methods for valuing productivity loss clearly explained	Sources for productivity costs assumptions justified
Peabody (Peabody et al., 2005a)	Philippines	NA		NA	NA			X	X
Tupasi (Tupasi et al., 2006)	Philippines	117	X	X	X	X		NA	NA
Vassall (Vassall et al., 2009)	Ukraine	285	X	X	X	X			
Aspler (Aspler et al., 2008)	Zambia	103	X	NA	X	X	X	X	X
Mauch (Mauch et al., 2013)	Dom. Republic [§] , Ghana, Vietnam	543	X	NA	X	X		X	X
LICs (n=18)									
Gospodarevskaya (Gospodarevskaya et al., 2014)	Bangladesh, Tanzania	190	X	NA	X	X		X	X
Islam (Islam et al., 2002)	Bangladesh	38	X	X	X	X		X	
Laokri (Laokri et al., 2014)	Benin	245	X	NA	X	X	X	NA	NA
Laokri (Laokri et al., 2013)	Burkina Faso	242	X	NA	X	X	X	NA	NA
Pichenda (Pichenda et al., 2012)	Cambodia	277	X						
Datiko (Datiko and Lindtjorn, 2010)	Ethiopia	229	X	X	X		X	X	X

First author	Country	Number of patients in study sample	Patient interviews	Ingredient approach used*	Sources for resource use and unit costs clearly explained	Main cost categories reported	Descriptive statistics presented	Methods for valuing productivity loss clearly explained	Sources for productivity costs assumptions justified
Vassall (Vassall et al., 2010)	Ethiopia	184	X	NA	X	X	X		
Yitayal (Yitayal et al., 2014)	Ethiopia	279	X	NA		X	X	X	X
Jacquet (Jacquet et al., 2006)	Haiti	84	X			X		X	
Floyd (Floyd et al., 2003)	Malawi	181	X	X	X	X		X	X
Karki (Karki et al., 2007)	Nepal	50	X	X	X	X			
Mirzoev (Mirzoev et al., 2008a)	Nepal	50	X	X	X	X		X	
Gibson (Gibson et al., 1998a)	Sierra Leone	72	X	NA	X	X		NA	NA
Aye (Aye et al., 2010)	Tajikistan	204	X	NA	X	X	X	X	X
Wandwalo (Wandwalo et al., 2005)	Tanzania	145	X	X	X	X		X	X
Wyss (Wyss et al., 2001)	Tanzania	191	X			X			X
Okello (Okello et al., 2003)	Uganda	94	X	X	X	X		X	X
Saunderson (Saunderson, 1995)	Uganda	34	X	X	X	X			

*Ingredient approach can only be used for provider costs and is non-applicable for studies that only included patient costs

§Dominican Republic is an upper middle-income country

HICs: High-income countries, UMICs: Upper-middle income countries, LMICs: Lower-middle income countries, LICs: Low-income countries, NA: Non-applicable

Appendix D: Provider mean DS-TB treatment costs per patient (2014 US\$)

First author	Country	Intervention chosen	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
HIC (n=19)								
MacIntyre (MacIntyre et al., 2001)	Australia	In-patient	---	---	---	---	---	7,516
Marchand (Marchand et al., 1999)	Canada	DOTS with 33 days in hospital	---	---	---	---	---	10,091
Diel (Diel et al., 2012)	Germany	Hospital and outpatient	11,824	2,584	---	---	---	14,408
Bocchino (Bocchino et al., 2006)	Italy	Integrated in- and outpatient management	19,261	---	4,055	2,027	NI	25,343
Migliori (Migliori et al., 1999)	Italy	DOT	---	---	---	---	---	25,086
Miller (Miller et al., 2013)	Latvia	DOTS	12,467	2,606	110	---	NI	15,182
Burns (Burns and Harrison, 2007)	New Zealand	DOT in non-resident population	8,359	489	320	2,000	2,977	14,144
Atun (Atun et al., 2006)	Russia	Russian Federation TB Control	2,512	1044	---	277	NI	3,833
Jacobs (Jacobs et al., 2002)	Russia	Individualised DOTS treatment	---	---	---	---	---	1,107
Migliori [31]	Russia	New treatment strategies for all patients	---	---	---	---	---	3,898
Montes-Santiago (Montes-Santiago et al., 2010)	Spain	Hospitalisation only	9,252	NI	NI	NI	NI	9,252
Tu (Tu et al., 2011b)	Taiwan	DOT – 56% inpatient; 44% outpatient	---	---	---	---	---	1,023

First author	Country	Intervention chosen	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
Eralp (Eralp et al., 2012)	UK	DOTS	---	---	2,901	157	2,096	5,154
White [15]	UK	TB treatment costs	---	---	---	---	---	12,848
Burman (Burman et al., 1997)	USA	DOT	---	632	311	635	366	1,945
Miller (Miller et al., 2010)	USA	Total TB costs in a county in Texas	12,514	---	---	124	10,497	23,134
Palmer (Palmer et al., 1998)	USA	Universal DOT	---	---	---	---	---	29,638
Weis (Weis et al., 1999)	USA	DOT – public hospital	14,073	NI	654	1,505	1,129	17,361
Wurtz (Wurtz and White, 1999)	USA	Traditional therapy – public hospital	---	---	---	---	---	57,559
Average costs			11,283 (8)	1,471 (5)	1,392 (6)	961 (7)	3,413 (5)	14,659 (19)
UMIC (n=19)								
Cusmano (Cusmano et al., 2009)	Argentina	DOTS	NI	15	9	25	NI	49
Moalosi (Moalosi et al., 2003)	Botswana	Home-based DOT	813	658	29	---	284	1,784
Samandari (Samandari et al., 2011)	Botswana	DOT	NI	360	12	NI	NI	372
Costa (Costa et al., 2005)	Brazil	Treatment in state of Salvador	---	---	---	---	---	181
Prado (Prado et al., 2011)	Brazil	Health worker supervision	NI	118	47	19	258	442

First author	Country	Intervention chosen	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
Steffen (Steffen et al., 2010)	Brazil	DOTS	NI	NI	NI	NI	NI	677
Xu (Xu et al., 2000)	China	DOTS	NI	NI	71	54	NI	125
Zou (Zou et al., 2013)	China	DOTS - incentives vs. no incentives	---	---	---	---	1,233	1,233
Nieto (Nieto et al., 2012b)	Columbia	DOTS increased guardian supervision	---	---	---	---	---	321
Peralta Perez (Peralta Perez et al., 2006)	Cuba	DOTS	---	---	208	289	---	498
Elamin (Elamin et al., 2008)	Malaysia	DOT at chest clinic in Penang state	6	28	86	80	65	266
Ruiz (Vargas Ruiz et al., 2003)	Mexico	National costs	---	---	---	---	---	4,971
Dick (Dick and Henchie, 1998)	South Africa	DOT community	---	318	47	96	777	1,239
Fairall (Fairall et al., 2010)	South Africa	DOT only	12	17	3	3	NI	34
Masobe (Masobe et al., 1995)	South Africa	Isoniazid prophylactic therapy	455	23	11	27	359	875
Sinanovic (Sinanovic and Kumaranayake, 2006)	South Africa	DOT with nurses	NI	493	592	65	NI	1,150
Wilkinson (Wilkinson et al., 1997)	South Africa	DOT community	614	148	46	---	7	815
Kamolratanakul (Kamolratanakul et al., 2002)	Thailand	New smear +	---	---	202	81	164	448

First author	Country	Intervention chosen	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
Sawert (Sawert et al., 1997)	Thailand	DOTS	---	---	130	22	329	481
Average costs			380 (5)	218 (10)	107 (14)	69 (11)	386 (9)	840 (19)
LMIC (n=10)								
Vassall (Vassall et al., 2002)	Egypt	DOTS	---	187	---	37	---	223
Floyd (Floyd et al., 2006)	India	Public-private mix DOTS (Delhi)	---	---	16	3	38	58
Pantoja (Pantoja et al., 2009a)	India	Public-private mix DOTS	1	6	13	35	44	99
Mahendradhata (Mahendradhata et al., 2010)	Indonesia	Private practitioner DOTS referral	---	---	---	---	---	526
Nganda (Nganda et al., 2003)	Kenya	DOT decentralised	68	114	61	7	13	262
Khan (Khan et al., 2002)	Pakistan	Community health workers	NI	11	43	93	16	163
Peabody (Peabody et al., 2005b)	Philippines	DOTS	---	---	---	---	---	155
El-Sony (El-Sony, 2006)	Sudan	DOTS health facility HIV-	392	---	48	135	16	591
Vassall (Vassall et al., 2002)	Syria	DOTS primary health care	---	56	---	20	---	76
Vassall (Vassall et al., 2009)	Ukraine	DOTS implementation in Mariupol and Kyiv (2003)	400	77	52	50	NI	579
Average costs			215 (4)	75 (6)	39 (6)	48 (8)	25 (5)	273 (10)

First author	Country	Intervention chosen	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
LIC (n=11)								
Islam (Islam et al., 2002)	Bangladesh	Current programme with no CHW	---	---	22	3	66	91
Pichenda (Pichenda et al., 2012)	Cambodia	Non-hospital DOT	---	---	---	---	---	108
Datiko (Datiko and Lindtjorn, 2010)	Ethiopia	DOTS community	---	9	33	---	33	74
Jacquet (Jacquet et al., 2006)	Haiti	DOTS expansion	---	---	---	---	---	1,311
Floyd (Floyd et al., 2003)	Malawi	DOT decentralised	75	13	25	2	9	124
Karki (Karki et al., 2007)	Nepal	DOTS Public-private partnership	---	---	---	---	107	107
Mirzoev (Mirzoev et al., 2008b)	Nepal	DOTS community	---	---	22	---	63	85
Wandwalo (Wandwalo et al., 2005)	Tanzania	DOT community	---	22	25	---	64	111
Okello (Okello et al., 2003)	Uganda	DOTS community	181	94	57	---	29	360
Saunderson (Saunderson, 1995)	Uganda	DOT ambulatory care	NI	170	166	52	28	416
Maponga (Maponga, 1996)	Zimbabwe	Costs of TB/HIV co-epidemic	NI	NI	45	NI	NI	45
Average costs			128 (2)	61 (5)	49 (8)	19 (3)	50 (8)	258 (11)
Total average costs			4,909	396	308	273	780	6,667
<i>Proportion</i>			<i>73.6%</i>	<i>5.9%</i>	<i>4.6%</i>	<i>4.1%</i>	<i>11.7%</i>	<i>99.9%</i>

---: Cost not itemized

NI: Cost not included

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, TB: Tuberculosis, DOT: Directly Observed Treatment, DOTS: Directly Observed Treatment, short-course, CHW: Community health worker, HIV: human immunodeficiency virus, UK: United Kingdom, USA: United States of America

Appendix E: Provider mean MDR-TB treatment costs per patient (2014 US\$)

First author	Country	Hospitalisation	Outpatient	Drugs	Diagnostic and monitoring tests	Other	Total
HIC (n=10)							
Floyd [28]	Estonia	8,007	1,589	3,956	560	1,888	16,000
Diel (Diel et al., 2012)	Germany	32,435	83,175	---	---	---	115,610
Diel (Diel et al., 2014)	Germany	28,757	---	50,451	2,055	---	81,262
Miller [54]	Latvia	40,473	2,706	3,474	---	---	46,653
Floyd [28]	Russia	6,493	434	6,404	1,424	2,618	17,373
Kang [21]	South Korea	3,521	---	1,652	1,663	---	6,836
White [15]	UK	99,954	2,937	22,980	424	1,016	127,311
Burman [9]	USA	181,909	9,575	12,313	1,080	---	204,876
Marks (Marks et al., 2014)	USA	87,619	---	57,870	---	---	145,488
Rajbhandary [20]	USA	41,612	30,627	---	---	---	72,239
Average		53,078 (10)	18,720 (7)	19,887 (8)	1,201 (6)	1,841 (3)	83,365 (10)
UMIC (n=7)							
Samandari [49]	Botswana	NI	NI	3,244	NI	1,735	4,979
Costa [38]	Brazil	NI	---	---	---	---	4,828
Xu [32]	China	NI	NI	1,758	82	NI	1,840
Suarez [33]	Peru	NI	839	1,364	171	1,568	3,942
Pooran [53]	South Africa	80	712	2,390	1,013	72	4,267
Schnippel [52]	South Africa	12,033	---	280	174	179	12,666
Kamolratanakul [35]	Thailand	NI	315	3,277	310	562	4,464
Average		6,056 (2)	622 (3)	2,052 (6)	350 (5)	823 (5)	5,284 (7)
LMIC (n=1)							
Tupasi [59]	Philippines	201	218	2930	397	2567	6,313
LIC (n=1)							
Pichenda [86]	Cambodia	---	---	---	---	---	1,218
Total average costs		41,776	12,102	11,623	779	1,356	67,637
<i>Proportion</i>		<i>61.8%</i>	<i>17.9%</i>	<i>17.2%</i>	<i>1.2%</i>	<i>2.0%</i>	<i>100.1%</i>

---: Cost not itemized

NI: Cost not included

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries,

LIC: Low-income countries, UK: United Kingdom, USA: United States of America

Appendix F: Mean DS-TB treatment costs reported by patients (2014 US\$)

First author	Country	User fees	Drugs	Transport	Other*	Total (no productivity)	Productivity loss
HIC (n=6)							
Diel (Diel et al., 2012)	Germany	NI	NI	NI	NI	NI	3,003
Migliori (Migliori et al., 1999)	Italy	NI	NI	NI	NI	NI	6,246
Kik [21]	Netherlands	107	---	---	379	486	3,576
Jacobs [34]	Russia	NI	NI	260	NI	260	450
Burman [9]	USA	NI	NI	NI	NI	NI	1,469
Miller [22]	USA	NI	NI	NI	NI	NI	2,062
Average		107 (1)	---	260 (1)	379 (1)	373 (2)	2,801 (6)
UMIC (n=19)							
Cusmano (Cusmano et al., 2009)	Argentina	NI	NI	7	NI	7	46
Moalosi [36]	Botswana	120	16	---	771	889	---
Costa [38]	Brazil	12	---	50	74	136	332
Prado [48]	Brazil	---	---	10	10	20	11
Steffen [47]	Brazil	5	108	10	42	165	148
Jackson [41]	China	55	118	21	421	614	1,018
Liu [42]	China	---	---	---	---	472	NI
Pan (Pan et al., 2013)	China	1,421	---	342	1,762	3,525	3,048
Wei (Wei et al., 2014)	China	---	---	---	---	238	NI
Zou (Zou et al., 2013)	China	---	---	42	1,512	1,554	310
Nieto [50]	Colombia	---	---	---	---	344	NI

First author	Country	User fees	Drugs	Transport	Other*	Total (no productivity)	Productivity loss
Mauch (Mauch et al., 2013)	Dominican Republic	45	5	2	129	180	1,085
Rouzier [46]	Ecuador	4	---	62	168	234	481
Elamin [43]	Malaysia	---	---	725	128	853	167
Guzman-Montes [44]	Mexico	344	---	272	827	1,443	---
Fairall [45]	South Africa	3	---	2	NI	5	NI
Foster (Foster et al., 2015)	South Africa	---	---	14	44	58	106
Wilkinson [28]	South Africa	---	NI	---	NI	116	---
Sawert [29]	Thailand	NI	NI	NI	NI	NI	444
Average		221 (9)	62 (4)	120 (13)	491 (12)	603 (18)	600 (12)
LMIC (n=17)							
Vassall [57]	Egypt	---	---	---	4	4	26
Mauch (Mauch et al., 2013)	Ghana	24	19	3	57	103	278
Floyd [60]	India	70	17	NI	NI	87	---
John [65]	India	---	---	---	---	42	636
Muniyandi [63]	India	---	---	---	---	32	52
Pantoja (Pantoja et al., 2009a)	India	31	---	---	---	31	NI
Rajeswari [55]	India	---	---	---	---	95	181
Mahendradhata [67]	Indonesia	20	13	14	3	50	12
Mauch (Mauch et al., 2011)	Kenya	---	---	---	70	70	368
Nganda [75]	Kenya	133	20	---	41	194	

First author	Country	User fees	Drugs	Transport	Other*	Total (no productivity)	Productivity loss
Umar [68]	Nigeria	38	63	13		114	
Khan [56]	Pakistan	9	15	---	4	28	30
Peabody [58]	Philippines	---	---	---	---	123	
Vassall [57]	Syria	---	---	---	7	7	10
Vassall [66]	Ukraine	35	---	---	33	68	
Mauch (Mauch et al., 2013)	Vietnam	131	1	7	234	373	996
Aspler [62]	Zambia	---	---	---	12	12	27
Average		55 (9)	21 (7)	9 (4)	47 (10)	84 (17)	238 (11)
LIC (n=19)							
Gospodarevskaya (Gospodarevskaya et al., 2014)	Bangladesh	9	NI	14	173	196	63
Islam (Islam et al., 2002)	Bangladesh	4	NI	15	NI	19	11
Laokri (Laokri et al., 2014)	Benin	7	29	4	78	118	
Laokri [87]	Burkina Faso	---	---	---	---	104	
Pichenda [86]	Cambodia	58	---	31	68	157	393
Datiko [82]	Ethiopia	---	---	---	7	7	9
Vassall [83]	Ethiopia	---	---	122	158	280	148
Yitayal (Yitayal et al., 2014)	Ethiopia	26	4	49	142	220	200
Jacquet (Jacquet et al., 2006)	Haiti	299	---	---	351	650	364

First author	Country	User fees	Drugs	Transport	Other*	Total (no productivity)	Productivity loss
Floyd [74]	Malawi	31	9	---	72	112	
Karki [79]	Nepal	46	---	10	19	76	245
Mirzoev [80]	Nepal	---	---	---	---	25	25
Gibson (Gibson et al., 1998b)	Sierra Leone	8	---	---	32	40	
Aye [81]	Tajikistan	55	126	118	168	467	775
Gospodarevskaya (Gospodarevskaya et al., 2014)	Tanzania	5	NI	57	150	212	139
Wandwalo [77]	Tanzania	---	---	---	10	10	18
Wyss [72]	Tanzania	64	---	32	1	97	825
Okello [76]	Uganda	24	21	---	54	98	
Saunderson [69]	Uganda	---	---	---	58	58	252
Average		49 (13)	38 (5)	45 (10)	96 (16)	155 (19)	248 (14)
Total average costs		101	36	82	212	432	700
<i>Proportion</i>		<i>23.3%</i>	<i>8.5%</i>	<i>19.1%</i>	<i>49.1%</i>	<i>100.0%</i>	

*Other patient costs typically include, but are not limited to, non-TB drugs, food, drink, vitamins, traditional medicines, accommodation

---: Cost not itemized

NI: Cost not included

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, USA: United States of America

Appendix G: Mean MDR-TB treatment costs reported by patients (2014 US\$)

First author	Country	User fees	Drugs	Transport	Other*	Total (no productivity)	Productivity loss
HI (n=5)							
Diel (Diel et al., 2014)	Germany	NI	NI	NI	NI	NI	22,352
Kang [21]	South Korea	NI	NI	21	NI	21	9,959
Burman [9]	USA	NI	NI	NI	NI	NI	25,677
Marks (Marks et al., 2014)	USA	NI	NI	NI	NI	NI	136,802
Rajbhandary [20]	USA	NI	NI	NI	NI	NI	51,230
Average		NI	NI	21 (1)	NI	21 (1)	49,204 (5)
UMIC (n=2)							
Costa [38]	Brazil	20	---	90	271	381	295
Rouzier [46]	Ecuador	4	---	266	669	938	6,770
Average		12 (2)	---	178 (2)	470 (2)	660 (2)	3,532 (2)
LMIC (n=1)							
Tupasi [59]	Philippines	909	---	---	707	1,616	0
LIC (n=1)							
Pichenda [86]	Cambodia	103	---	18	285	406	1,256
Total average costs		259	0	99	483	841	28,260
<i>Proportion</i>		<i>30.8%</i>	<i>0.0%</i>	<i>11.7%</i>	<i>57.4%</i>	<i>99.9%</i>	

*Other patient costs include, but are not limited to, non-TB drugs, food, drink, accommodation, repairs to the home

---: Cost not itemized

NI: Cost not included

HIC: High-income countries, UMIC: Upper-middle income countries, LMIC: Lower-middle income countries, LIC: Low-income countries, USA: United States of America

Appendix H: Full electronic search strategies for TB diagnostic costs

Tuesday 18th August, 2015:

Embase and Medline database - using Ovid search interface

1. (cost* or finance or economic* or expenditure*).af.
2. With limits (human and yr="1990-Current")
3. (tb or tuberculosis or drug#resistant#tb or xdr#tb or multi?drug resistant tuberculosis or mycobacterium tuberculosis).af.
4. With limits (human and yr="1990-Current")
5. (diagnos* or screen* or chest x-ray or chest radiography or sputum* or smear or culture or test* or skin test or Xpert or (case adj3 (find* or detection))).af.
6. With limits (human and yr="1990-Current")
7. 4 AND 6
8. 7 AND 2

Tuesday August 18th, 2015:

Centre for Reviews and Dissemination (CRD) database (DARE, NHS EED and HTA)

'tuberculosis'

AND

'diagnosis'

AND

'cost'

In any field and publication year from '1990' to '2015'

Tuesday August 18th, 2015:

CEA Registry

'tuberculosis'

(Full Search Contents)

Friday August 21st, 2015:

EconLit database - using Ovid search interface

1. (cost* or financ* or economic* or expenditure*).af. [Results: 844,248]
2. With limits (yr="1990-Current") [Results: 714,320]

-
3. (tb or tuberculosis or drug#resistant#tb or xdr#tb or multi?drug resistant tuberculosis or mycobacterium tuberculosis).af. [Results: 201]
 4. With limits (human and yr="1990-Current") [Results: 194]
 5. (diagnos* or screen* or chest x-ray or chest radiography or sputum* or smear or culture or test* or skin test or Xpert or (case adj3 (find* or detection))).af. [Results: 102,934]
 6. With limits (human and yr="2000-Current") [Results: 97,193]
 7. 4 AND 6 [Results: 33]
 8. 7 AND 2 [Results: 27]

Friday August 21st, 2015:

LILACS (Latin American and Caribbean Health Sciences Literature) - using the Virtual Health Library

Search

'tuberculosis'

AND

'diagnosis'

AND

'cost'

(Full Search Contents)

Wednesday 2nd September, 2015:

PubMed database

((("mycobaterium tuberculosis" OR "tb" OR "tuberculosis") AND ("cost" OR "finance" OR "economic evaluation" OR "expenditure") AND ("diagnosis" OR "screening" OR "chest x ray" OR "chest radiography" OR "sputum smear" OR "sputum culture" OR "skin test" OR "xpert" OR "detection"))

With limits (Humans, Full text and Text availability="01/01/1990-04/09/2015")

Appendix I: TANDEM Ethics Approvals - LSHTM

London School of Hygiene & Tropical Medicine
 Keppel Street, London WC1E 7HT
 United Kingdom
 Switchboard: +44 (0)20 7636 8636
www.lshtm.ac.uk



Observational / Interventions Research Ethics Committee

Dr. Jackie Cliff
 Prof of Immunology and Special Advisor for overseas projects
 Department of Immunology and Infection (IID)
 LSHTM

30 July 2015

Dear Dr. Cliff

Study Title: TANDEM 1: Concurrent Tuberculosis and Diabetes: Improving care through bi-directional screening and unravelling the causal link through study of genetic susceptibility factors

LSHTM Ethics Ref: '6449 - 2'

Thank you for your application for the above amendment to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Other	130704_Patient_Information_DM_V2	04/07/2013	2
Other	TANDEM_Protocol_1_v5	29/07/2015	5
Covering Letter	9599-2_amendment_response_to_provisional_decision	29/07/2015	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: <http://leo.lshtm.ac.uk>

Additional information is available at: www.lshtm.ac.uk/ethics

Yours sincerely,

Professor John DH Porter
 Chair

ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

Improving health worldwide

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Observational / Interventions Research Ethics Committee

Hazel Dockrell
 Professor of Immunology
 & Special Advisor to the Director on Overseas Programmes
 IID / ITD
 LSHTM

9 August 2013

Dear Professor Dockrell,

Study Title: TANDEM - concurrent tuberculosis and diabetes: Clinical monitoring, microbiological and immunological effects of diabetes during TB treatment
LSHTM ethics ref: 6465

Thank you for your letter of 6 August 2013, responding to the Interventions Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM ethics application	n/a	17/06/2013
Protocol	4	06/08/2013
Patient Information and Informed Consent for patients with pulmonary TB	2	04/07/2013
Patient Information and Informed Consent for patients with Diabetes	2	04/07/2013
Patient Information and Informed Consent for Healthy Volunteers		
Patient Information and Informed Consent for PK study of metformin		
Screening TB patients for DM	1	16/05/2013

After ethical review

Any subsequent changes to the application must be submitted to the Committee via an E2 amendment form. All studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor John DH Porter
 Chair
ethics@lshtm.ac.uk
<http://intra.lshtm.ac.uk/management/committees/ethics/>

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Observational / Interventions Research Ethics Committee

Hazel Dockrell
 IID / ITD
 LSHTM

18 December 2013

Dear Professor Dockrell,

Study Title: Concurrent Tuberculosis and Diabetes: Improving care through bi-directional screening and unravelling the causal link through study of genetic susceptibility factors
LSHTM ethics ref: 6449
LSHTM amend no: A473

Thank you for your application of 28 November 2013 for the amendment above to the existing ethically approved study and submitting revised documentation. The amendment application has been considered by the Observational Committee.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above amendment to research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval for the amendment having been received, where relevant.

Approved documents

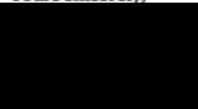
The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
LSHTM amendment application	n/a	
131124 Protocol 1 TANDEM	3	24 Nov 2013

After ethical review

Any further changes to the application must be submitted to the Committee via an E2 amendment form. The Principal Investigator is reminded that all studies are also required to notify the ethics committee of any serious adverse events which occur during the project via form E4. An annual report form (form E3) is required on the anniversary of the approval of the study and should be submitted during the lifetime of the study. At the end of the study, please notify the committee via form E5.

Yours sincerely,



Professor John DH Porter
 Chair
ethics@lshtm.ac.uk
<http://www.lshtm.ac.uk/ethics/>

Appendix J: TANDEM Ethics Approvals – UNPAD, Indonesia



KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
 FAKULTAS KEDOKTERAN UNIVERSITAS PADJADJARAN
KOMITE ETIK PENELITIAN KESEHATAN
 HEALTH RESEARCH ETHICS COMMITTEE
 Afiliasi: Komisi Nasional Etik Penelitian Kesehatan (KNEPK)
 NIH-USA: IORG-IRB Number: 00008626, FWA for the Protection of Human Subject: 00018324

KETERANGAN PERSETUJUAN ETIK
ETHICAL CLEARANCE

Nc.: 377/UN6.C2.1.2/KEPK/PN/2012

Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Padjadjaran Bandung, dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian kesehatan dan menjamin bahwa penelitian berjalan sesuai dengan pedoman *International Conference on Harmonisation - Good Clinical Practice (ICH-GCP)* dan aturan lainnya yang berlaku, telah mengkaji dengan teliti dan menyetujui proposal penelitian berjudul:

The Health Research Ethics Committee Faculty of Medicine Universitas Padjadjaran Bandung, in an effort to protect the basic rights and welfare of the subject of the health research and to assure that a research operates in accordance with International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines and other applicable laws and regulations, has thoroughly reviewed and approved a research proposal entitled:

"MENJAJAK HUBUNGAN KASUAL ANTARA PENYAKIT TUBERKULOSIS (TB) DAN DIABETES MELITUS (DM) UNTUK MENINGKATKAN MUTU PENATALAKSANAAN PENYAKIT TB DAN DM YANG TERJADI BERSAMAAN"

Nama Peneliti Utama <i>Name of the principal investigator</i>	: Bachtli Alisjahbana
Nama Peneliti Lain <i>Name of other the principal investigators</i>	: Rovina Ruslami
Nama Institusi <i>Name of institution</i>	: TB-HIV Working Group LPPM Fakultas Kedokteran Universitas Padjadjaran

Ditetapkan di : Bandung
 Specified in
 Tanggal : 11 - 10 - 2013
 Date

Ketua,
 Chairman



Prof. Dr. Firman F. Wirakusumah, dr., SpOG-K
 NIP. 19480115 197302 1 001

Keterangan/notes:

Peretujuan etik ini berlaku selama satu tahun sejak tanggal ditetapkan.

Pada akhir penelitian, laporan pelaksanaan penelitian harus diserahkan ke Komite Etik Penelitian Kesehatan.

Jika ada perubahan protokol dan/atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian.

This ethical clearance is effective for one years from the due date

In the end of the research, progress and final summary report should be submitted to the Health Research Ethics Committee.

Should there be any modification and/or extension of the study, the Principal Investigator is required to resubmit the protocol for approval.



KEMENTERIAN PENDIDIKAN DAN KEBUDAYAAN
FAKULTAS KEDOKTERAN UNIVERSITAS PADJADJARAN
KOMITE ETIK PENELITIAN KESEHATAN
HEALTH RESEARCH ETHICS COMMITTEE

Afiliasi: Komisi Nasional Etik Penelitian Kesehatan (KNEPK)
NIH-USA IORG-IRB Number: 00008626, FWA for the Protection of Human Subject: 00019324

Amandemen dari persetujuan etik nomor : 487/JUN6.C2.12/KEPK/PN/2013
Amendment of ethical approved number

PERSETUJUAN ETIK
ETHICAL APPROVAL

No: 05 /JUN6.C2.1.2/KEPK/PN/2014

Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Padjadjaran Bandung, dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian kesehatan dan menjamin bahwa penelitian berjalan sesuai dengan pedoman *International Conference on Harmonisation - Good Clinical Practice (ICH-GCP)* dan aturan lainnya yang berlaku, telah mengkaji dengan teliti protokol penelitian sebelumnya berjudul:
The Health Research Ethics Committee Faculty of Medicine Universitas Padjadjaran Bandung, in an effort to protect the basic rights and welfare of the subject of the health research and to assure that a research operates in accordance to International Conference on Harmonisation - Good Clinical Practice (ICH-GCP) guidelines and other applicable laws and regulations, after conducting review on the research protocol entitled:

"MENGUAK HUBUNGAN KALSA, ANTARA PENYAKIT TUBERKULOSIS (TB) DAN DIABETES MELITUS (DM) UNTUK MENINGKATKAN MUTU PENATALAKSANAAN PENYAKIT TB DAN DM YANG TERJADI BERSAMAAN"

Nama Peneliti Utama : Bachli Alisjahbana
Name of the principal investigator

Nama Peneliti Lain : Rovina Ruslami
Name of other the principal investigators

Nama Institusi : TB-HIV Working Group
Name of institution
LPPM-Fakultas Kedokteran
Universitas Padjadjaran

Protokol tersebut dapat disetujui pelaksanaannya
Has hereby declared that the protocol approved.

Ditetapkan di : Bandung
Specified in

Tanggal : 5 - 02 - 2014
Date

K e l u a,
Chairman,

Prof. Dr. Firman F. Wirakusumah, dr., SpOG-K
NIP. 19480115 197302 1 001

Keterangan/notes:

Persetujuan etik ini berlaku selama satu tahun sejak tanggal ditetapkan.

Pada akhir penelitian, laporan pelaksanaan penelitian harus diserahkan ke Komite Etik Penelitian Kesehatan.

Jika ada perubahan protokol dan/atau perpanjangan penelitian, harus mengajukan kembali permohonan kajian etik penelitian.

This clinical clearance is effective for one years from the due date.

In the end of the research, progress and final summary report should be submitted to the Health Research Ethics Committee



KEMENTERIAN PENDIDIKAN DAN KERUDAYAAN
 FAKULTAS KEDOKTERAN UNIVERSITAS PADJADJARAN
KOMISI ETIK PENELITIAN KESEHATAN
HEALTH RESEARCH ETHICS COMMITTEE
 Jl. Prof. Djender No. 38 Bandung 40131
 Telp. & Fax: (021) 2535677 email: kek@unpad.ac.id

PERPANJANGAN PERSETUJUAN ETIK
CONTINUING ETHICAL APPROVAL

No. Reg.: 0616030229

No: 23 F. UKS.C1.3.2KEP/PM/2015

Komisi Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Padjadjaran Bandung, dalam upaya melindungi hak asasi dan kesejahteraan subjek penelitian kesehatan dan menjamin bahwa penelitian yang menggunakan formulir surveil/registrasi/surveilensi/Epidemiologi/humaniora/sosial Budaya/Bahan Biologi Tersimpan/Sel Punca dan non klinis lainnya berjalan dengan memperhatikan implikasi etik, hukum, sosial dan non klinis lainnya yang berlaku, telah mengkaji kembali dengan teliti proposal penelitian berjudul:

The Health Research Ethics Committee Faculty of Medicine Universitas Padjadjaran Bandung, in order to protect the rights and welfare of the health research subject, and to guaranty that the research using survey questionnaire/register/surveillance/epidemiology/humaniora/social-cultural/archived biological materials/stem cell/other non clinical materials, will carried out according to ethical, legal, social implications and other applicable regulations, has been thoroughly reviewed the proposal entitled:

"MENYUKAI HUBUNGAN KARSINOM ANTARA PENYAKIT TUBERKULOSIS (TB) DAN DIABETES MELITUS (DM) UNTUK MENINGKATKAN MUTU PENATALAKSANAAN PENYAKIT TB DAN DM YANG TERJADI BERSAMAAN"

Nama Peneliti Utama : Bacthi Alisjahbana, dr., SpPD-KPTI, PhD
 Name of the principal investigator

Pembimbing/Peneliti Lain : Rovina Ruslami, dr., SpPD., PhD
 Supervisor/Other Researcher

Nama Institusi : Pusat Studi TB-HIV
 Name of institution : Fakultas Kedokteran
 Universitas Padjadjaran

proposal tersebut dapat disetujui dan dilanjutkan pelaksanaannya.
 the research has been approved to be continued.

Ditetapkan di : Bandung
 Specified in
 Tanggal : 07 - 04 - 2015
 Date



Dr. Elmar F. Wirakusumah, dr., SpOG-K
 NIP. 19490115 197302 1 001

Keterangan/notes:
 Persetujuan etik ini berlaku selama satu tahun sejak tanggal ditetapkan.
 This ethical clearance is valid for one year from the due date.
 Pada akhir penelitian, laporan pelaksanaan penelitian harus diserahkan ke Komisi Etik Penelitian Kesehatan.
 In the end of the research, progress and final summary report should be submitted to the Health Research Ethics Committee.
 Jika ada perubahan atau yang mengenai protokol penelitian, perpanjangan penelitian, atau mengajukan kembali permohonan kajian etik penelitian.
 If there be any protocol modification or demand about extension of the study, the Principal Investigator is required to resubmit the protocol for approval.
 Jika ada kejadian serius yang tidak diingini (SITD) harus segera dilaporkan ke Komisi Etik Penelitian Kesehatan.
 If there are Serious Adverse Events (SAE) should be immediately reported to the Health Research Ethics Committee.

Appendix K: TANDEM Ethics Approvals - UPCH, Peru



UNIVERSIDAD PERUANA
CAYETANO HEREDIA

Vicerrectorado de Investigación
Dirección Universitaria de Investigación,
Ciencia y Tecnología - DUICI

CONSTANCIA 227-31-13

El Presidente del Comité Institucional de Ética (CIE) de la Universidad Peruana Cayetano Heredia certifica que el proyecto de investigación señalado a continuación fue **APROBADO** por el Comité de Ética. La aprobación incluyó los documentos finales descritos en anexo a la presente constancia.

Título del proyecto : "Comorbilidad Tuberculosis y Diabetes: Mejorando el cuidado a través del tamizaje bidireccional y descifrando la relación de causalidad a través del estudio de factores genéticos de susceptibilidad"

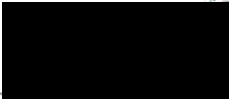
Código de inscripción : 61069


Investigadores : David Moore, César Ugarte Gil

La **APROBACION** considera el cumplimiento de los estándares de la Universidad, los lineamientos Científicos y éticos, el balance riesgo/beneficio, la calificación del equipo investigador y la Confidencialidad de los datos, entre otros.

Cualquier enmienda, desviaciones, eventualidad deberá ser reportada de acuerdo a los plazos y normas establecidas. El investigador reportará cada seis meses el progreso del estudio y alcanzará un informe al término de éste. La aprobación tiene vigencia desde la emisión del presente documento hasta el **02 de Septiembre del 2024**. Los trámites para su renovación deberán iniciarse por lo menos 30 días previos a su vencimiento.

Lima, 02 de Septiembre del 2013


Dr. Alfonso Gushiken Maza
Presidente (a)
Comité Institucional de Ética en Investigación



2/20

Av. Honorio Degado 430, Lima 31 / Apartado Postal 4314, Lima 100, Telefax: 482 4541
Teléfono: 319-0000 Anexo: 2271 / 2542
e-mail: duici@oficinas-upch.pe <http://www.upch.edu.pe/vr/inve/duici/>



UNIVERSIDAD PERUANA
CAYETANO HEREDIA

Vicerrectorado de Investigación
Dirección Universitaria de Investigación,
Ciencia y Tecnología - DUICIT

CONSTANCIA 93 - 39- 13

El Presidente del Comité Institucional de Ética (CIE) de la Universidad Peruana Cayetano Heredia hace constar que el proyecto de investigación señalado a continuación fue **APROBADO** por el Comité de Ética.

Título del Proyecto : "Comorbilidad Tuberculosis y Diabetes: Monitorio clínico y efectos microbiológicos e inmunológicos de la diabetes durante el tratamiento para TB"
Codigo de inscripción : 62093
Investigador principal : Dr. César Ugarte Gil

La aprobación incluye los documentos finales descritos a continuación:

1. Protocolo de Investigación, versión 1.2 de fecha 23 de febrero del 2014.
2. Consentimiento Informado, versión 2 de fecha 13 de marzo del 2014
3. Consentimiento Informado para el estudio de expresión genética, versión 1.1 de fecha 13 de marzo del 2014

La **APROBACIÓN** considera el cumplimiento de los estándares de la Universidad, los lineamientos Científicos y éticos, el balance riesgo/beneficio, la calificación del equipo investigador y la Confidencialidad de los datos, entre otros.

Cualquier enmienda, discusiones, eventualidad deberá ser reportada de acuerdo a los plazos y normas establecidas. El investigador reportará cada seis meses el progreso del estudio y alcanzará un informe al término de éste. La aprobación tiene vigencia desde la emisión del presente documento hasta el **23 de marzo del 2015**. Si aplica, los trámites para su renovación deberán iniciarse por lo menos 30 días previos a su vencimiento.

Lima, 24 de marzo del 2014






Fredy Cancihuanán Rivera, MD MPH PhD
Presidente
Comité Institucional de Ética en Investigación

/s/ang

Av. Honorio Delgado 430, Lima 31 / Apartado Postal, 4314, Lima 100, Telefax: 482-4541
Teléfono: 318-0000 Anexo: 2271 / 2542
e-mail: duict@oficinas-upch.pe <http://www.upch.edu.pe/virtiva/duict/>

Appendix L: TANDEM Ethics Approvals - UMFCV, Romania

 <p style="margin: 0;">Ministry of Education, Research, Youth and Sport UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA</p>  <p style="margin: 0;">Committee of Ethics and Academic and Scientific Deontology</p>		
No. 94 / 06.09.2013		
<p>Ethical Approval of Research Project</p>		
<p><i>For the study (research project)</i> Concurrent Tuberculosis and Diabetes: Improving care through bi-directional screening and unravelling the causal link through study of genetic susceptibility factors</p>		
<p><i>Project coordinator:</i> Professor Hazel Dockrell <i>Scientific coordinator:</i> Dr. Reinout van Crevel <i>TANDEM - P8-UMFCV coordinator:</i> Dr. Mihai Ioana</p>		
<p>We confirm that the guidelines of the Ethical University Code of The University of Medicine and Pharmacy from Craiova were consulted and all ethical issues and implications related to the above study were considered. The study procedures were followed in accordance with these guidelines.</p>		
<p>Ethical principles were followed underlying the Declaration of Helsinki and the University Code of Ethics on the proper conduct of research, together with the codes of practice established by the medical ethics code.</p>		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 5px;"> Ethical Approval: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> </td> </tr> <tr> <td style="padding: 5px;"> Date: 06.09.2013 </td> </tr> </table>	Ethical Approval: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>	Date: 06.09.2013
Ethical Approval: Yes <input checked="" type="checkbox"/> No <input type="checkbox"/>		
Date: 06.09.2013		
<p><i>Signature of Ethics Committee Chairman,</i> Liliana Noxac, PhD., MD.</p> 		
<p>2 Petru Rareș Street, 200349, Craiova, Dolj, ROMANIA Phone: + 40 351 443522; Fax: +40 251 593077; E-mail: etica@webmail.umfcv.ro</p>		



Ministry of Education, Research, Youth and Sport
**UNIVERSITY OF MEDICINE AND PHARMACY
 OF CRAIOVA**
 Committee of Ethics and Academic and Scientific Deontology



No. 95 / 06.09.2013

Ethical Approval of Research Project

For the study (research project)

Concurrent Tuberculosis and Diabetes: Clinical monitoring, and microbiological and immunological effects of diabetes during TB treatment

Project coordinator: Professor Hazel Dockrell

Scientific coordinator: Dr. Reinout van Crevel

TANDEM - P8-UMFCV coordinator: Dr. Mihai Ioana

We confirm that the guidelines of the Ethical University Code of The University of Medicine and Pharmacy from Craiova were consulted and all ethical issues and implications related to the above study were considered. The study procedures were followed in accordance with these guidelines.

Ethical principles were followed underlying the Declaration of Helsinki and the University Code of Ethics on the proper conduct of research, together with the codes of practice established by the medical ethics code.

Ethical Approval: Yes No
 Date: 06.09.2013

Signature of Ethics Committee Chairman,
Liliana Novac, PhD., MD.



2 Petru Rares Street, 200349, Craiova, Dolj, ROMANIA
 Phone: +40 351 443522; Fax: +40 251 593077; E-mail: etica@webmail.umfcv.ro

Appendix M: TANDEM case report form

Date: ___/___/___

BASELINE (DAY 0) CRF

Date of Birth: _____ (MM/DD/YYYY)

Gender: Male Female

A. Smoking	
A1. Do you currently smoke tobacco?	Daily Less than daily Not at all
A2. Did you smoke tobacco daily in the past?	Yes No
A3. In the past, did you smoke tobacco daily, less than daily or not at all? (If respondent smoked "daily" and "less than daily", response is "daily")	Daily Less than daily Not at all
A4. How long has it been since you last smoked daily?	___Years or ___Months
A5. Why did you stop smoking daily?	Advised by doctor pressure from friends /family health reasons (I was feeling unwell) health reasons (to remain healthy) economic reasons (cost of smoking cigarettes) other (please state) [can tick more than one box]
A6. How old were you when you first started smoking tobacco?	___Years old
A7. Before you became sick, on average, how many cigarettes (or equivalent) did you smoke on the days that you currently smoke?	___per day <input type="checkbox"/> check if >0 but <1/ day
A8. Before you became sick, approximately how many times in a typical week have you been exposed to the tobacco smoke of others at home, work or in public places (where exposure is for a minimum of five consecutive minutes each time)?	Not at all A few times a day on some days Many times a day on some days A few times a day on many days Many times a day on many days

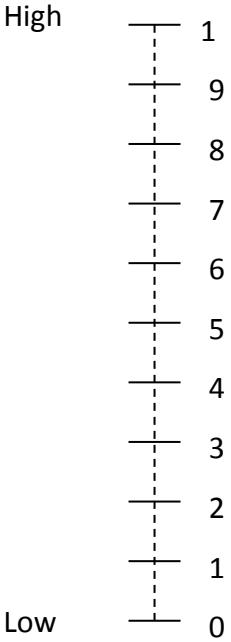
C. Alcohol Use	
C1. Have you consumed an alcoholic drink within the past 12 months ?	Yes <input type="checkbox"/> No <input type="checkbox"/>
C2. During the past 12 months, how frequently have you had at least one alcoholic drink? <i>(READ RESPONSES, USE SHOWCARD)</i>	Daily <input type="checkbox"/> 5-6 days per week <input type="checkbox"/> 1-4 days per week <input type="checkbox"/> 1-3 days per month <input type="checkbox"/> Less than once a month <input type="checkbox"/>
C4. Before you became sick, in a typical month, on how many occasions did you have at least one alcoholic drink? C5. Before you became sick, in a typical month when you drank alcohol, on average , how many standard alcoholic drinks did you have during one drinking occasion? <i>(USE SHOWCARD)</i> C6. Before you became sick, in a typical month, what was the largest number of standard alcoholic drinks you had on a single occasion, counting all types of alcoholic drinks together?	— — Don't know 77 — — Don't know 77 — — Don't Know 77 No change Increase Reduced Stopped
C7. Have you changed (increased or reduced) your intake of alcohol [over what time period, past 12 months maybe]?	Health reasons (feeling unwell, Health reasons (wanted to stay well)
C8. If reduced or stopped drinking, why have you reduced or stopped drinking?	Family pressure Economic reasons (cost of buying alcohol) Advice from a doctor Other (please state)

D. Corticosteroids		
D6	Are you currently taking any corticosteroid medication? (e.g. hydrocortisone dexamethosone,	Yes 1 No 2

	prednisolone, Prednisone, local brand names?)	
D7	If yes,	Oral Inhaled Topical
D8	If yes, for how long have you been taking this medication (months, weeks?)	_____weeks ____months

E. Socio economic information		
E1. What is the highest level of education you have completed?	No formal schooling <input type="checkbox"/> Less than primary school <input type="checkbox"/> Primary school completed <input type="checkbox"/> Secondary school completed <input type="checkbox"/> High school completed <input type="checkbox"/> College/University completed <input type="checkbox"/> Post graduate degree <input type="checkbox"/> Refused <input type="checkbox"/>	
E2. What is your <i>[insert relevant ethnic group / racial group / cultural subgroup / others]</i> background ?	<i>[Locally defined]</i> <i>[Locally defined]</i> <i>[Locally defined]</i> Other (specify) _____ Refused	
E3. Are you married?	Yes <input type="checkbox"/> No <input type="checkbox"/> Refuse to answer <input type="checkbox"/>	
E4. What religion do you follow?	Christian <input type="checkbox"/> Muslim <input type="checkbox"/> Hindu <input type="checkbox"/> African Traditional <input type="checkbox"/> No religion <input type="checkbox"/> Other (specify) _____ Refused <input type="checkbox"/>	
E5. How many people, including yourself, live in your	Number of people __	
E6. With whom to you live?	Alone <input type="checkbox"/> Children <input type="checkbox"/> Other family <input type="checkbox"/> Friends <input type="checkbox"/> Partner <input type="checkbox"/> Refused <input type="checkbox"/>	
	Government employee <input type="checkbox"/>	

<p>E7. Which of the following best describes your main work status over the past 12 months?</p>	<p>Non-government employee <input type="checkbox"/> Self-employed <input type="checkbox"/> Non-paid <input type="checkbox"/> Student <input type="checkbox"/> Homemaker <input type="checkbox"/> Retired <input type="checkbox"/> Unemployed (able to work) <input type="checkbox"/> Unemployed (unable to work) <input type="checkbox"/> Refused <input type="checkbox"/></p>
<p>E8. If employed, what is your current occupation?</p>	
<p>E9. Do you have a bank account? (savings, checking, current, etc.)</p>	<p><input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Refused</p>
<p>E10. Where you live, do you</p>	<p><input type="checkbox"/> Rent a room in a house <input type="checkbox"/> Rent a house/self-contained flat <input type="checkbox"/> Own <input type="checkbox"/> Live with family <input type="checkbox"/> Not have a usual place to live <input type="checkbox"/> Live in a shelter (homeless) <input type="checkbox"/> Other (Specify)_____</p>
<p>E11. What is your main source of water for drinking and cooking?</p>	<p><input type="checkbox"/> Private connection to pipeline <input type="checkbox"/> Private well <input type="checkbox"/> Public taps/standpipe <input type="checkbox"/> Public well <input type="checkbox"/> Neighbours <input type="checkbox"/> Water vendor <input type="checkbox"/> Spring <input type="checkbox"/> River, stream, lake, pond <input type="checkbox"/> Rainwater <input type="checkbox"/> Bottled water <input type="checkbox"/> Other (Specify)_____</p>
<p>E12. What toilet facility do you have in your house?</p>	<p><input type="checkbox"/> Flush toilet <input type="checkbox"/> Traditional latrine <input type="checkbox"/> Ventilated improved pit latrine <input type="checkbox"/> Bowl/bucket <input type="checkbox"/> Other (Specify)_____</p>

<p>E13. Do you own any of the following items? (check all that apply)</p>	<ul style="list-style-type: none"> <input type="checkbox"/> Stove <input type="checkbox"/> Refrigerator <input type="checkbox"/> Microwave <input type="checkbox"/> Washing machine <input type="checkbox"/> Air conditioning <input type="checkbox"/> Fan <input type="checkbox"/> Computer <input type="checkbox"/> Television 	<ul style="list-style-type: none"> <input type="checkbox"/> DVD player <input type="checkbox"/> Radio/CD player <input type="checkbox"/> Camera <input type="checkbox"/> Mobile phone <input type="checkbox"/> Bicycle <input type="checkbox"/> Motorcycle/scooter <input type="checkbox"/> Car or truck
<p>E14. Using the scale on the right, how well off do you think your household is in relation to other households in your neighbourhood/street?</p> <p>E15. Using the scale on the right, how well off do you think your household is in relation to other households in your town/city/etc.?</p>		

Costs of travel to health facility today:

1. How long did it take to get here from your home (*include the journey time and any waiting for transport*)
- Minutes |_|_|
Hours |_|_|
Unknown |_|_|_|
2. What kind of transport did you use to reach this health facility?
- Walking (go to Q11)
 Public transport (go to Q9)
 Taxi (go to Q9)
 Self-driven car (go to Q10)
3. If you paid for transportation to reach the facility, how much did you pay?
- IDR/PEN/RON _____
4. If you used a private car to get here, please estimate the distance travelled, one way. (*if unable to estimate indicate residence*)
- Kilometres |_|_|
Residence _____

Costs incurred at the health facility today:

5. Did you pay for the care you received today?
- No
 Yes
 Not sure
6. If yes, how much did you pay for the care given?

	User fees – medical professional	User fees – health facility	Drugs	Tests	Physical rehabilitation services	Other payments (specify)
Payment made: <i>0 - no payment</i> <i>999 - don't know</i> <i>888 - NA</i>						
Outstanding payments:						

7. Where did the money come from to pay these expenses? (multiple responses allowed)
- Cutting down on other expenses
 Using savings
 Borrowing
 Selling assets
 Asking for donations
 Other, specify _____

Insurance coverage:

8. Will you receive insurance reimbursement for any of the payments you made today?
- No
 Yes
 Not sure
9. If yes, how much do you expect to be reimbursed?
- IDR/PEN/RON _____
 Not sure

Opportunity costs:

10. How much time did you spend at the health facility today? _____hours _____minutes
11. If you weren't here today, what would you be doing? (Multiple responses allowed)
- Unpaid work at home
 Paid work
 Other (specify) _____
12. Did you have to make alternative arrangements for childcare or caring for other dependants in order to come here today?
- No (End of questionnaire)
 Yes (Go to Q19)
 Refuse to answer
13. Who is taking care of your dependants/child(ren) while you are here?
- Other family member or friend
 Paid childcare
 Refuse to answer
14. How much did you pay for that care today?
- IDR/PEN/RON _____

F Contraceptives

F.1 Current contraceptive use

None Yes Not Asked

F2. If yes, specify:

- Pill
 3 month inject
 2 month inject
 1 month inject IUD
 Implant
 None of these

F3. If using pill or injection, do you know the name of your contraceptive? No Yes

If yes, provide name: _____

F4. How long have you used this contraceptive? Days__ or Weeks__ or Months ____ or Years_____

G TB Symptoms

G1. Coughing: Yes No

G2. Duration: ≤2 weeks 2-4 weeks > 4 weeks Don't know

G3. Sputum production:
Do you produce sputum (cough up phlegm)?:

- Yes
 No

G4. If yes (produces sputum) do you cough up blood?

- No
 Specks only
 Clear blood

G5. Breathlessness upon exertion?

- Yes
 No
 No answer

G6. Night sweats (*need to change pyjamas or linen*):

No Yes

G7. Unintentional Weight Loss/Gain in last 3 months:

Loss (10kg +) Loss (5-10 kg) Loss (<5kg) No change Gain (<5kg) Gain(>5 kg)

OR When did you begin to feel ill? _____ months/ weeks/ days

If weight change, how much by? ___kg (- for weight loss, + for weight gain)

G8. Chest pain:

No Yes

G9. In the past, have you ever been diagnosed with TB? Yes No Don't know

(If G9- yes) When were you diagnosed with TB? _____Month [is this last occasion if more than one previous diagnosis?]

_____Year

For how many months did you receive treatment/ take medication for TB?

<2 months 2-4 months 4-6 months >6 months

Did your physician tell you that you had completed the regimen? Yes No Don't know

G10. [Fieldworker] Have you already begun treatment for this instance of TB? Yes No

H. DM risk related questions

H1. Frequent thirst

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H2. Pain during walking with need to slow down

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H3. Shortness of breath when walking with people of same age

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H4. Exercises in leisure time (before becoming sick)

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H5. Physically demanding job/ occupation? (before becoming sick)

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H6. Before you became sick, were you physically active for 30 minutes a day, including physical activity during work, leisure or regular routine? This includes activities such as walking to market, carrying shopping.

<input type="checkbox"/> Yes	<input type="checkbox"/> No
------------------------------	-----------------------------

H7. Number of parents with diabetes

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> Don't know
----------------------------	----------------------------	----------------------------	-------------------------------------

H7a Number of children

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3+	<input type="checkbox"/> Don't know
----------------------------	----------------------------	----------------------------	-----------------------------	-------------------------------------

H8b. Number of children with diabetes

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3+	<input type="checkbox"/> Don't know
----------------------------	----------------------------	----------------------------	-----------------------------	-------------------------------------

H8a Number of siblings

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3+	<input type="checkbox"/> Don't know
----------------------------	----------------------------	----------------------------	-----------------------------	-------------------------------------

H9b. Number of siblings with diabetes

<input type="checkbox"/> 0	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3+	<input type="checkbox"/> Don't know
----------------------------	----------------------------	----------------------------	-----------------------------	-------------------------------------

H11. How often do you eat fruit or vegetables?

<input type="checkbox"/> Everyday	<input type="checkbox"/> Not everyday
-----------------------------------	---------------------------------------

H12 Have you ever been told by a doctor or other health worker that you have raised blood pressure or hypertension?

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
------------------------------	-----------------------------	-------------------------------------

H13 Have you been prescribed any antihypertensives?

<input type="checkbox"/> Currently	<input type="checkbox"/> In the Past	<input type="checkbox"/> Never	<input type="checkbox"/> Don't know
------------------------------------	--------------------------------------	--------------------------------	-------------------------------------

H14. Have you ever been told that you had gestational diabetes (high sugar during pregnancy, in any pregnancy)

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
------------------------------	-----------------------------	-------------------------------------

H15. Have you ever delivered a large baby (over 4kg)

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Don't know
------------------------------	-----------------------------	-------------------------------------

H16. IF yes, please record weight if known

[Note to fieldworkers - If more than one baby please record largest]

--	--

H. History of DM

H15. Has a doctor ever told you that you have diabetes?

Yes No

H16 If yes, when were you told you had diabetes?

_____month _____year

H17. Are you taking any medication to manage your diabetes?

- Insulin
- Metformin
- Other oral anti-diabetic drugs
- Anti-hypertensives
- Statins
- Aspirin
- Other drugs
- No medication

IH18. If yes, please state how long you have been using this medication: (enter 999 for don't know)

____Years
____Months

H19. Have you been using any other medication to manage your diabetes?

Yes/No/ Don't Know

H20. If yes, how many times have you been admitted to hospital because of your diabetes in the last year?

H21. If yes, how many times have you been admitted to hospital because of your diabetes in the last 5 years?

H22. If yes, what is the longest overnight stay you have had in hospital?

_____nights

J. Peripheral Vascular disease

J1 Has patient ever lost a limb or digit (not through trauma)?

Yes No

J2 Previous bypass or stenting surgery in limbs

Yes No

J3 Previous or current non-healing wound(>3 months)

Yes No

Cardiovascular complications

J4 Previous stroke

Yes No

J5 Previous heart attack

Yes No

J6 Previous bypass or stenting heart surgery

Yes No

J7 Diagnosed (are you on medication?) angina or heart failure

Yes No

Eye pathology

J8 Previous cataract or laser eye surgery

Yes No

J9 Known Glaucoma(Are you on treatment for increased eye pressure?)

Yes No

J10 Acquired blindness in one or both eyes(not trauma)

Yes No

J11 Do you have difficulty seeing/ disturbed vision

Yes No

J12 If J12=yes, How long for? _____Months _____Years

J13 Having treatment for renal failure?

Yes No

K. Vital Signs	
K1 Temperature <input type="checkbox"/> °C <input type="checkbox"/> °F _____	K2. Resp Rate (<i>bpm</i>) _____
	K3. Pulse rate (<i>bpm</i>) _____
K4. Systolic blood pressure _____mmHg	
K5. Diastolic blood pressure _____mmHg	
Anthropometry	
K6. Karnofsky score: _____% K7. Anaemic conjunctivae*: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not Done K8. Weight: _____kg K9. Height: _____m K10. Upper arm circumference: _____cm (smaller or non-dominant arm) K11. Waist circumference _____cm K12. Hip circumference _____cm K13. Positive lung auscultation*: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not Done K14. Presence of a BCG Scar? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not done *From this appointment or recent medical assessment by clinician	Karnofsky score: <ul style="list-style-type: none"> • 100% - normal, no complaints, no signs of disease • 90% - capable of normal activity, few symptoms or signs of disease • 80% - normal activity with some difficulty, some symptoms or signs • 70% - caring for self, not capable of normal activity or work • 60% - requiring some help, can take care of most personal requirements • 50% - requires help often, requires frequent medical care • 40% - disabled, requires special care and help • 30% - severely disabled, hospital admission indicated but no risk of death • 20% - very ill, urgently requiring admission, requires supportive measures or treatment • 10% - moribund, rapidly progressive fatal disease

L. Sample Collection			
Tick		Sample ID	Time taken
L1	Sputum <input type="checkbox"/> Collected <input type="checkbox"/> Collected overnight Counseled patient/subject on overnight sputum collection: <input type="checkbox"/> Not done <input type="checkbox"/> Done <input type="checkbox"/> Induced <input type="checkbox"/> Spot collection <input type="checkbox"/> Could not produce sample		
L2	Blood – Lab Hb1Ac (2ml EDTA tube)		
L3	Blood – Creatinine, RBG, ALT/AST and Serum (4ml plain tube - 2ml serum, 0.5ml Creatinine, 0.5ml RBG, 0.5ml ALT/AST)		
L4	Blood – Patient DNA/ Plasma (2ml EDTA tube)		
L5	Blood – RNA (2.5ml Pax-Gene tube)		
L6	Blood – HIV (0.5ml)		
L7	Blood- Haemoglobin		
L8	Blood –Diluted WBA		
L9	Urine		
L10	CXR booked for ___/___/___ or CXR ID		

M. DM Tests			
		Result	
M1. Urine dipstick	<input type="checkbox"/> 0 <input type="checkbox"/> trace <input type="checkbox"/> 1+ <input type="checkbox"/> 2+ <input type="checkbox"/> 3+ <input type="checkbox"/> 4+ <input type="checkbox"/> Not taken		
M5. Proteinuria	<input type="checkbox"/> =0 <input type="checkbox"/> trace <input type="checkbox"/> 1+ <input type="checkbox"/> 2+ <input type="checkbox"/> Not done <input type="checkbox"/> Refused		
M3. Random Plasma Glucose POC	_____ mmol per l (from Hemocue POC test)		
M4. POC Hb1Ac	_____ stored as % or mmol per mol. (from Hemocue POC)		
M6. Rapid HIV test result:	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not done <input type="checkbox"/> Refused	If Yes, second HIV test taken:	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not done <input type="checkbox"/> Refused
M7. (If Female) POC Pregnancy test	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not done <input type="checkbox"/> Refused		
M8. Fasting plasma glucose (if random plasma glucose \geq 6.1 mmol/l)			
Exclusion from the Bioprofiling study			
<input type="checkbox"/> Pregnant <input type="checkbox"/> HIV +ve <input type="checkbox"/> Already started TB treatment <input type="checkbox"/> Already taking DM meds <input type="checkbox"/> Known Multiple Drug Resistance <input type="checkbox"/> Steroid usage <input type="checkbox"/> Serious Comorbidity i.e. Rheumatoid arthritis (Please state) _____ <input type="checkbox"/> Any other reason patient not able to participate _____			



INSTRUCTIONS:

Text in yellow should be adapted to your setting.

Tool for estimating costs of **type of tests in town, country**

This tool has been adapted to estimate mean costs of **bi-directional TB and DM screening**. The outputs of the tool are:

- (1) **Total resources** used at the **Hasan Sadikin Hospital** for providing TB screening services in persons with DM
- (2) **Total resources** used at the **Hasan Sadikin Hospital** for providing DM screening services in persons with TB
- (3) **Costs per patient** according to screening test or tool
- (4) **Estimates of the costs of various combinations of screening tests**, such as **TB symptom screen with CXR**

The results can be used to:

- (1) **Compare costs and outcomes between different facilities within Indonesia and in other countries**
- (2) **Assess efficiency of how service delivery is organized and whether it can be improved**
- (3) **Plan and budget for maintaining current service delivery or expanding to bi-directional screening**
- (4) **Input data for modelling the cost-effectiveness of bi-directional screening for TB and DM**

Instructions and briefing on methodology

Instructions:

1. The grey cells are input cells where you need to enter data. The blue cells are calculation cells that generate the results. You should not enter data in these.
2. Some data has already been entered into the grey cells (e.g. in the "X-ray specific" worksheet). The cost data needed are for the items already identified in the item row.
3. Please use the "Notes" column to explain any values that are not in the spreadsheet unit, provide more detail on the source or method of calculation of the data, or anything else that you think I should know or would be of interest.
4. Economic costs are needed, NOT tariffs or rates.

Methodology:

The cost data collection method used in this study is the "ingredient approach". This entails multiplying the resource quantities by their respective unit costs.

Resources could include health worker time, quantity of drugs supplies and consumables, proportion of capital, recurrent or overhead costs, etc. The unit costs to be captured include capital, recurrent, overhead, test-specific and patient specific.

Capital versus recurrent costs

Capital costs are items that have a useful life or more than one year, such as vehicles, medical equipment, buildings and one-off training programmes. Recurrent costs are those items that are used up during a year and usually purchased regularly (e.g. yearly, monthly, weekly, daily or irregularly but frequently).

To be able to combine capital and recurrent costs in a useful manner, all costs must be presented on an annual basis, as fixed value costs. Capital costs are annualised by spreading their value over their expected lifetime. Future values are discounted to account for the fact that resources are tied up in these items.

Overhead costs

Overhead costs are resources used for the overall running of the laboratory within the hospital, which do not vary much with the number of patients. These include administration, laundry services, electricity, etc.

In this tool, each patient seen at the hospital are allocated overhead costs equally, no matter if DM, TB, or TB-DM.

If overhead costs amount to IDR 100,000,000,000 per year and the hospital treats a total of 200,000 patients per year, shared costs

are IDR 500,000 per patient.

Test specific costs

These are supplies, consumables, equipment and staff that are specific to the screening, diagnostic and monitoring tests within the TANDEM study. Some resources may be shared (e.g. incubator in the lab or nurses in the clinic), which will be proportionally allocated.

Other costs may be applied to a specific test only (e.g. AccuCheck machine for the POC random capillary glucose test or vacutainer needle for blood draw).

Patient specific costs

These costs vary according to the number of patients. Examples are drugs and medical supplies.

In this tool, these costs will be collected from TANDEM patient records in REDCap.

Resource	Useful life (life expectancy)*	<i>*Unless otherwise stated</i>
Equipment (small & computers)	5	
Equipment (large)	10	
Buildings	30	
Land	50	
Vehicles	5	
Initial training	30	

Allocating shared costs:

Buildings	Percentage of floor space or staff involved in intervention?
Staff	Percentage of time
Equipment	Percentage of time the equipment is used for a particular intervention
Utilities	Percentage of floor space or staff involved in intervention?
Maintenance	Percentage of floor space or staff involved in intervention?

Description of hospital	
Name of FACILITY:	
Address of facility:	
Name of hospital director:	
Name of medical director:	
Name of financial director:	
Name of administrative director:	
Name of HR director:	
Name of head of accounting:	
Name of head of supplies:	
Name of head of procurement:	
Name of DEPARTMENT:	
Name of radiologist:	
Name of radiographer (HoD):	
Names of resident doctors (radiology):	
Name of DEPARTMENT:	
Name of endocrinologists:	
Name of endocrinology nurses:	
Name of resident doctors (endocrinology):	
Name of field nurses (TANDEM):	
Names of resident field doctors (TANDEM):	
Name of DEPARTMENT:	
Name of pulmonologists:	
Name of pulmonology nurses:	
Names of resident doctors (pulmonology):	
Name of DEPARTMENT:	
Name of ClinPath doctor:	
Name of ClinPath analysts:	
Facility ownership:	Yes/No Specify ownership
Government	
Church	
NGO	
Private for profit	
Size of catchment population:	
Describe catchment population	

Appendix N - Sample micro-costing spreadsheet - Facility description

Description of hospital					
Physical facilities:	Yes/No	Number	Shared w/ other	Facility name in	Notes
			services?		
Registration office - general			Yes/No		
Endocrinology Clinic					
Common area					
Consultation room - doctor					
Nurses' consultation room (also					
TANDEM room for screening patients)					
Sputum collection room					
DOTS clinic					
Common area					
Consulation area					
TB-DM education & counselling area					
Convalesing area					
Pharmacy					
Laboratory - Clinical Pathology					
Common area					
Sample collection - 2nd floor					
Sample analysis - 3rd floor					
ClinPath Secretariat (admin & accounting)					
Radiology department					
Common area					
X-ray room					
X-ray control room					
X-ray processing room					
TB ward					
Internal medicine ward					
Emergency room					

Appendix N - Sample micro-costing spreadsheet - Facility description

Description of hospital			
	VALUE	YEAR	NOTES
Number of hospital beds:			
Number of patients per year (entire hospital)			
Number of ER beds			
Number of beds for DM patients:			
Number of beds for TB patients:			
Opening hours of hospital:			
Operating hours of radiology department*:			
Operating hours of endocrinology clinic:			
Operating hours of DOTS clinic:			
Operating hours of Clinpath lab*:			
Emergency hours:			

Parameter assumptions

Parameter name

Year of evaluation:
 No. of months evaluated:
 No. of days in a month:
 No. of weeks in a month:
 No. of days in a year:
 No. workdays in a year
 No. of working minutes in a year
 Exchange rate **IDR to USD**
 Exchange rate **Euro to IDR**
 Exchange rate **USD to IDR**
 Exchange rate **NZD to IDR**
 Discount rate

Value	Source
	Assumption
	Assumption
	Assumption
	Julian calender
	Assumption
	Assumption
	Assumption
	http://www.oanda.com/currency/historical-rates
	http://www.oanda.com/currency/historical-rates/
	http://www.oanda.com/currency/historical-rates/
	http://www.oanda.com/currency/historical-rates/
	WHO Generalised CEA Guide (Tan-Torres et al., 2003)

Mean cost per patient per screening test (Hospital, Town, Country)

Test	Cost components (Year Currency)					Total
	Reagents and Supplies	Equipment	Staff	Overhead: capital*	Overhead: recurrent*	
TB symptom screen	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
CXR	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
IGRA	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
FBG	#DIV/0!	#DIV/0!	#DIV/0!	#REF!	#REF!	#DIV/0!

Test	Cost components (Year USD)					Total
	Reagents and Supplies	Equipment	Staff	Overhead: capital*	Overhead: recurrent*	
TB symptom screen	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
CXR	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
IGRA	#DIV/0!	#REF!	#DIV/0!	#REF!	#REF!	#DIV/0!
FBG	#DIV/0!	#DIV/0!	#DIV/0!	#REF!	#REF!	#DIV/0!

*Overhead costs include buildings, utilities and other laboratory running costs

Appendix N: Sample micro-costing spreadsheets - Hospital overhead

HOSPITAL - Overhead costs																								
Mean overhead cost	Value (IDR) Per Year	Year of data	Calculation method	Value (IDR) Per Day	Total Patients/day	Value (IDR) Per Day Per Patient																Notes		
Overhead cost per in-patient bed-day (Capital + recurrent) (IDR)							If known, cost per in-patient bed-day (IDR)	Year of data	Explanation of source or calculation method	Year of purchase	Approximate life expectancy from new (years)	Frequency of maintenance (per year)	Annual cost of maintenance (IDR)	Annualisation factor	Annualised capital costs (IDR)	Total annual costs (IDR)	Proportion of overhead costs specific to radiology department	Proportion of overhead costs specific to clinical pathology laboratory	Proportion of overhead costs specific to endocrinology clinic	Proportion of overhead costs specific to DOTs clinic	Proportion of overhead costs specific to emergency room	Proportion of overhead costs specific to internal medicine ward	Proportion of overhead costs specific to TB ward	
EXAMPLE ONLY																								
Hospital building (entire)	10,000		600,000,000,000	NA	10,000	25,000	60,000	2013	Valuation for insurance				100,000,000			0	0	0	0	0	0	0	0	
Vehicles	Don't know		950,000,000,000	NA				2014	Assets records	various	5	3x per year	100,000,000	#REF!	#REF!	#REF!	Don't know	Don't know	Don't know	Don't know	Don't know	Don't know	Don't know	
Utilities - water				20,000,000	1		3,000	2015	Expenditure books							Don't know	0	0	0	0	0	0	0	
Overhead																								
Capital costs																								
Hospital building (entire)											50			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
Radiology (including waiting/common area, clinician and technician space, admin space, x-ray and x-ray control rooms, x-ray processing room)														#REF!	#REF!	#REF!	100.00%	NA	NA	NA	NA	NA	NA	
ClinPath Lab - blood collection area														#REF!	#REF!	#REF!	NA	#DIV/0!	NA	NA	NA	NA	NA	
ClinPath lab - blood analysis area														#REF!	#REF!	#REF!	NA	#DIV/0!	NA	NA	NA	NA	NA	
Endocrinology clinic (incl. waiting area, screen space, admin space, patient space)														#REF!	#REF!	#REF!	NA	NA	100.00%	NA	NA	NA	NA	
DOTs clinic (incl. waiting area, clinician space, admin space, patient space and pharmacy)														#REF!	#REF!	#REF!	NA	NA	NA	100.00%	NA	NA	NA	
Emergency room department														#REF!	#REF!	#REF!	NA	NA	NA	NA	100.00%	NA	NA	
Internal medicine ward														#REF!	#REF!	#REF!	NA	NA	NA	NA	NA	100.00%	NA	
TB ward														#REF!	#REF!	#REF!	NA	NA	NA	NA	NA	NA	100.00%	
Land (entire hospital grounds)											50			#REF!	#REF!	#REF!	NA	NA	NA	NA	NA	NA	100.00%	
Computers											5			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
Furniture											10			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
General medical equipment (e.g. office equipment, software, air conditioners, generators, etc.)											20			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
General non-medical equipment (e.g. vehicles (ambulances, trucks, motorcycles, bicycles)											10			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
Other capital overhead costs (overhead for Eyckman Building (UNPAD) - education and research)											15			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
											50			#REF!	#REF!	#REF!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	
TOTAL CAPITAL COSTS														#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	
Recurrent costs																								
ALL UTILITIES?																	IDR -	NA	0.60%	0.21%	NA	4.76%	NA	NA
Utilities - water																	IDR -	NA	NA	NA	NA	NA	NA	NA
Utilities - electricity																	IDR -	NA	NA	NA	NA	NA	NA	NA
Utilities - gas																	IDR -	NA	NA	NA	NA	NA	NA	NA
Utilities - telephone																	IDR -	NA	NA	NA	NA	NA	NA	NA
Utilities - internet																	IDR -	NA	NA	NA	NA	NA	NA	NA
Utilities - generator fuel or other electricity back-up																	IDR -	NA	NA	NA	NA	NA	NA	NA
Laundry services																	IDR -	NA	NA	NA	NA	NA	NA	NA
Sterilisation																	IDR -	NA	NA	NA	NA	NA	NA	NA
Cleaning supplies																	IDR -	NA	NA	NA	NA	NA	NA	NA
General administrative or operations (printing/photocopying, health advertising, etc.)																	IDR -	NA	NA	NA	NA	NA	NA	NA
General lab and medical supplies																	IDR -	NA	NA	NA	NA	NA	NA	NA
General office supplies																	IDR -	NA	NA	NA	NA	NA	NA	NA
Other non-medical supplies/consumables (uniforms, linens, etc.)																	IDR -	NA	NA	NA	NA	NA	NA	NA
Patient/Staff food																	IDR -	NA	NA	NA	NA	NA	NA	NA
Training																	IDR -	NA	NA	NA	NA	NA	NA	NA
Transportation																	IDR -	NA	NA	NA	NA	NA	NA	NA
Routine repairs and maintenance																	IDR -	NA	NA	NA	NA	NA	NA	NA
Rent, if applicable																	IDR -	NA	NA	NA	NA	NA	NA	NA
Other recurrent overhead costs																	IDR -	NA	NA	NA	NA	NA	NA	NA
TOTAL RECURRENT COSTS																	IDR 0	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!	#DIV/0!
TOTAL OVERHEAD (capital and recurrent) COSTS																	IDR 0	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!
Annual proportional allocation																	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!	#REF!

	Start	End
Operating days of X-ray department per week		
Operating days of clinpath lab per week		
Operating days of endocrinology clinic per week		
Operating days of TB clinic per week		
Operating days of hospital per week		

Annual values	Number per year	Year of data
Total number of hospital admissions		
Number of ER admissions		
Number of internal medicine ward admissions		
Number of TB ward admissions		
Number of hospital patients		
Number of ER patients		
Number of internal medicine in-patients		

Number of TB patients in DOTS clinic per year		
Number of TB in-patients		
Number of in-patient bed days (entire hospital)		
Number of bed days (TB)		
Number of in-patient bed days (internal medicine ward)		
Number of in-patient bed days (TB ward)		

KEY:	
Input a value	
Need to follow-up	
Value needs to be verified	Red font
Not applicable to this facility	NA
Data is not available right now but will provide later	ND
Value not available at all	Don't know

Appendix N: Sample micro-costing spreadsheet - Hospital staff

RSHS - Staff costs

Resource	Quantity	Total gross* monthly salary (IDR)	Total gross* monthly benefits and allowances (incl. housing, childcare, hazard pay, pension, etc.) (IDR)	Total gross* overtime (IDR)	Total gross* monthly training (IDR)	Total gross* monthly incentives or bonuses (IDR)	Total number of working hours per month	Year of data	Proportion specific to radiology department	Proportion specific to endocrinology clinic	Proportion of overhead costs specific to DOTS clinic	Proportion of overhead costs specific to internal medicine ward	Proportion of overhead costs specific to TB ward	Proportion specific to clinical pathology laboratory	Notes
EXAMPLE ONLY															
Doctors	207	800,000,000	650,000,000	500,000,000	75,000,000	N/A	33,120	2014	1.5%				5.0%	2.5%	
Overhead															
<i>Staff - general</i>															
Doctors															
Nurses															
Technicians															
Administrative															
Auxilliary															
Other staff categories?															
<i>Staff - specialised</i>															
Doctors - radiologist															
Doctors - endocrinologist															
Doctors - pulmonologists															
Doctors - clinical pathology laboratory															
Resident doctors - radiology department															
Resident doctors - endocrinology department															
Resident doctors - pulmonology department															
Resident doctors - clinical pathology laboratory															
Nurses - radiology department															
Nurses - endocrinology department															
Nurses - pulmonology department															
Technicians - clinical pathology laboratory															
Radiographers															
Couriers - for sample or CXR film transfer															
Porters - for patient transfers															

*If gross value (before taxes) not available, provide net (after taxes) value and indicate in "Notes" section the taxation percentage

KEY:	
Input a value	
Need to follow-up	
Data needs to be verified	Red font
Not applicable to this facility	NA
Data is not available right now but will provide later	ND
Value not available at all	Don't know

Appendix N: Sample micro-costing spreadsheet - Smear microscopy specific

Costs per smear microscopy (Facility name)																			
Resource	Average quantity per order	Price as new (RON)	Quantity per test	Year of purchase	Approx. life expectancy - from new (years)	Frequency of maintenance (per year)	Annual cost of maintenance (RON)	Brand name	Manufacturer	TANDEM - new (Y/N)	Year of data	Annualisation factor	Annualised capital costs	Proportion allocated to sputum (collection or analysis)	Sub-total	Mean cost per patient (RON)	Mean cost per patient (USD)	Notes/source	
EXAMPLE																			
Culture tubes	100	RON 1,000	3							N	2013				RON 30	RON 30	USD 30.00		
Computer	1	RON 3,000		2011	5	0.33333333	RON 100	MacBook Pro	Apple	N	2013	4.58	RON 600	55%	#DIV/0!	#DIV/0!	#DIV/0!	*Computer is maintained every 3 years.	
TEST SPECIFIC COSTS																			
<i>Supplies - consumables</i>																			
SPUTUM COLLECTION																			
N95 masks for staff (box)															#DIV/0!	#DIV/0!	#DIV/0!	*box lasts 2 months	
Cloth masks for patients & family members before interview (box)															#DIV/0!	#DIV/0!	#DIV/0!		
Plastic pots with cover for sputum collection															#DIV/0!	#DIV/0!	#DIV/0!	3 containers per patient for each sputum sample	
Clear plastic zip lock bags (12x20)															#DIV/0!	#DIV/0!	#DIV/0!	1 ziplock bag for 3 sputum pots; Source: Ule (Nury) at TANDEM clinic	
Labels with barcodes (for TANDEM)															#DIV/0!	#DIV/0!	#DIV/0!	Source: TANDEM invoice book	
Cotton - 500gr															#DIV/0!	RON 0.00	USD 0.00	*Each order lasts 2 months.	
Lunch box for sputum storage (before collection by lab personnel)															#DIV/0!	#DIV/0!	#DIV/0!	Each box lasts ~ 1 year. Source: TANDEM invoice book	
Sputum box/container at lab															#DIV/0!	#DIV/0!	#DIV/0!	Lasts ~ 1 year	
Alcohol (70%) - 50 mL bottle															#DIV/0!	#DIV/0!	#DIV/0!	*10 litres lasts 6 months.	
Paper towels for sterilizing container (roll) - 2 per set															#DIV/0!	#DIV/0!	#DIV/0!	Lasts ~ 1 month	
Gloves (latex)															#DIV/0!	#DIV/0!	#DIV/0!	VB Balance Sheet for Laboratories - 2015	
Marker															#DIV/0!	#DIV/0!	#DIV/0!	Lasts ~ 1 month	
																		USD 0.00	
															TOTAL	#DIV/0!	#DIV/0!	#DIV/0!	
SMEAR MICROSCOPY ANALYSIS																			
Smear glass slides (box - 26mm x 76mm, 1.1-1.3 mm thick)															#DIV/0!	#DIV/0!	#DIV/0!	3 slides per patient for each sputum sample	
Staining kit (Z-N)															#DIV/0!	#DIV/0!	#DIV/0!	Each kit can process 40 slides; kit contains smear stain, decolouriser, counterstain. Website: http://www.licitatie-publica.ro/licitatie/kit-colorare-ziehl-neelsen?searchProfileId=&user=6113e7ce52384f4a88d1c991780b464c&token=&uid=587c49aa-1a97-11e3-a05d-002e55f16dc8	
Distilled water (5L)															#DIV/0!	#DIV/0!	#DIV/0!	Each set of reagents lasts for 6 months; Website: http://www.dedeman.ro/ro/auto/accesorii-auto/apa-distilata/apa-distilata-5l.html	
Plastic liners for discard bucket															#DIV/0!	#DIV/0!	#DIV/0!	*Assume liner is replaced every day --> 5 liners per week	
Discard bucket - 7.5L															#DIV/0!	#DIV/0!	#DIV/0!	*Assume bin lasts ~ 1 month	
Applicator sticks - wooden (100 in a box)															#DIV/0!	#DIV/0!	#DIV/0!	3 sticks per patient for each sputum sample	
Decontamination reagents (hypoclorite) (1L bottle)															#DIV/0!	#DIV/0!	#DIV/0!	*Assume 3 litres lasts ~ 1 month	
Immersion oil (2ml bottle)															RON 0.00	#DIV/0!	#DIV/0!	*Assume 118 ml lasts ~ 6 months	
Paper lens cleaner (for microscopes) (pack)															#DIV/0!	#DIV/0!	#DIV/0!	Website: http://www.skywatcher.ro/Microa/ulei_de_imersie.htm	
UV light bulb (LBA 55W)															#DIV/0!	#DIV/0!	#DIV/0!	*Assume each pack lasts ~ 1 month; microscope lens is cleaned at the end of every day.	
Hand disinfectant (Sterillium) - 1000 ml															#DIV/0!	#DIV/0!	#DIV/0!	How many UV lights in lab? *Assume each bulb lasts ~ 2 months	
Surface cleaner (Bode Bacillo AF) - 1000 ml															#DIV/0!	#DIV/0!	#DIV/0!	*3 bottles lasts entire BK lab ~ 1 month	
															#DIV/0!	#DIV/0!	#DIV/0!	*3 bottles lasts entire BK lab ~ 1 month	
Toner															#DIV/0!	#DIV/0!	#DIV/0!	VB Balance Sheet for Laboratories - 2015	
Paper (packets of 500 sheets)															#DIV/0!	#DIV/0!	#DIV/0!	Lasts ~ 1 month? - approximately 20 tests or checks per patient per month?	
Other supplies...															#DIV/0!	#DIV/0!	#DIV/0!	VB Balance Sheet for Laboratories - 2015	
															TOTAL	#DIV/0!	#DIV/0!	#DIV/0!	

Costs per smear microscopy (Facility name)																			
Resource	Average quantity per order	Price as new (RON)	Quantity per test	Year of purchase	Approx. life expectancy - from new (years)	Frequency of maintenance (per year)	Annual cost of maintenance (RON)	Brand name	Manufacturer	TANDEM - new (Y/N)	Year of data	Annualisation factor	Annualised capital costs	Proportion allocated to sputum (collection or analysis)	Sub-total	Mean cost per patient (RON)	Mean cost per patient (USD)	Notes/source	
EXAMPLE																			
Culture tubes	100	RON 1,000	3							N	2013				RON 30	RON 30	USD 30.00		
Computer	1	RON 3,000		2011	5	0.33333333	RON 100	MacBook Pro	Apple	N	2013	4.58	RON 600	55%	#DIV/0!	#DIV/0!	#DIV/0!	*Computer is maintained every 3 years.	
Equipment																			
SPUTUM COLLECTION																			
Refrigerator for samples (4-8 degC)													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	Source: taken from Sputum culture values. Needed if patient produces sample after 12 noon (which is when samples are taken to lab each day for smear analysis)
													0.00	#DIV/0!		#DIV/0!	#DIV/0!	#DIV/0!	
															TOTAL	#DIV/0!	#DIV/0!	#DIV/0!	
SMEAR MICROSCOPY ANALYSIS																			
Timer (digital)													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	Website: http://malvi.ro/timer-si-cronometru-digital-alb-tfa.html?utm_source=shopmania&utm_medium=pc&utm_campaign=direct_link
Biosafety cabinet - vertical laminar flow hood, with UV light													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Balance Sheet (13.06.16)
Fridge/freezer													0.00	#DIV/0!	50%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
Drying rack (drying over sink)																			
Slide rack (drying stained slides - 100)																			
Slide box (to store slides) - holds 100 slides?													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	http://www.skywatcher.ro/MicroCel/preparate.htm The box can store slides for 33 patients, with 3 slides each.
Bunsen burner													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	http://www.skywatcher.ro/microscope.htm bunsen/
Microscope (optical)													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
Technical balance													0.00	RON 0.00	100%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
UV light fixture													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
Computer (electronic recording of AFB results)													0.00	#DIV/0!	100%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
Computer & printer (for reports)													0.00	#DIV/0!	6%	#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
Other resources...													0.00	#DIV/0!		#DIV/0!	#DIV/0!	#DIV/0!	VB 2015 Equipment Values (13.06.16)
															TOTAL	#DIV/0!	#DIV/0!	#DIV/0!	
Transportation																			
Staff - labour																			
	Quantity	Net* monthly salary (RON)	Net* monthly benefits (including overtime) (RON)	Monthly training (CME incl.) (RON)	Total number of working hours per month	Time spent on sputum smear per patient (minutes)	Total # of expected TANDEM patients per month	Total # of sputum smears (incl TANDEM) per month	Total # of NON-sputum smear tests per month	Total # laboratory tests conducted per month	Year of data	Salary per minute	Proportion allocated to sputum (collection or analysis)	Sub-total	Mean cost per patient (RON)	Mean cost per patient (USD)	Notes/source		
SPUTUM COLLECTION																			
Doctor (TB ward) - assess patient and order test???					152	0	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00		
Nurse (TB ward) - for sputum collection and delivery					152	5	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00	VB inpatients are brought to BK lab by ward nurse; VB outpatients (i.e. DM patients for Hospital #1 or #2 being screened for TB) are brought by ambulance (1-2 hours of transportation)	
														TOTAL	RON 0.00	RON 0.00	USD 0.00		
SMEAR MICROSCOPY ANALYSIS																			
Laboratory doctor - smear analysis					152	0	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00		
Biologist - smear analysis					152	15	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00	*Monitors process --> spends 2 hours per week on all AFB tests. 125-150 non-TB tests are conducted per week at BLK.	
Laboratory technicians - smear analysis					152	5.175	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00		
Cleaning staff (shared with ClinPath Lab) - sputum collection and analysis					152	5	0	0		1457	1457	2015	RON 0.00		RON 0.00	RON 0.00	USD 0.00		
Other staff																			
*Taxation of salary = x%																			
TOTAL SPUTUM COLLECTION SPECIFIC COSTS															RON 0.00	RON 0.00	USD 0.00		
TOTAL SPUTUM SMEAR MICROSCOPY ANALYSIS SPECIFIC COSTS															#DIV/0!	#DIV/0!	#DIV/0!		

OVERHEAD COSTS			
	Bacteriology Laboratory	Proportion of BK Lab overhead for capital costs	Proportion of BK Lab overhead for recurrent costs
Total Annual Overhead Costs for BK Lab	RON 43,529	30%	70%
Total number of BK Lab tests per year (2014)	17,484		
Overhead costs per sputum collection (2014) (RON)	RON 4.98	RON 1.48	RON 3.50
Overhead costs per sputum collection (2014) (USD)	USD 1.26	USD 0.37	USD 0.88
Overhead costs per smear microscopy analysis (2014) (RON)	RON 4.98	RON 1.48	RON 3.50
Overhead costs per smear microscopy analysis (2014) (USD)	USD 1.26	USD 0.37	0.882410269

SUMMARY DATA		
Total number of DM patients screened for TB (sputum smear)		
Total number of sputum smears conducted		
Number of sputum smears per patient	2	
Cost per patient (sputum collection) - test specific	#DIV/0!	#DIV/0!
Cost per patient (smear analysis) - test specific	#DIV/0!	#DIV/0!
Cost per patient (sputum collection) - overhead	RON 4.98	USD 1.26
Cost per patient (smear analysis) - overhead	RON 4.98	USD 1.26
Total cost per patient (sputum collection)	#DIV/0!	#DIV/0!
Total cost per patient (smear analysis)	#DIV/0!	#DIV/0!
COST PER PATIENT for SPUTUM SMEAR (incl. COLLECTION)	#DIV/0!	#DIV/0!

	Start	End
Operating hours of BK laboratory per day	8:00 AM	3:00 PM
Operating days of BK laboratory per week	Monday	Friday
Operating hours of hospital per day	24 hours	
Operating days of hospital per week	Monday	Sunday

	Number	Year of data	Source
Number of all bacteriology lab tests per year			
Number of smear microscopy tests per year			
Number of smear microscopy patients per year			
Number of TANDEM DM patients per day			
Number of TANDEM DM patients per week			
Number of TANDEM DM patients per month			
Number of TANDEM DM patients per year			

KEY:	
Input a value	
Human resources	
Need to follow-up	
Need to verify	Red text
Not applicable to this facility	NA
Data is not available right now	ND
Data not available at all	Don't know

*Source (sputum culture specific costs): Dowdy, 2008. Impact and CE of culture for diagnosis of TB in HIV+ Brazilian adults. PLoSone.

Appendix O: TANDEM health facility and hospital characteristics in Indonesia, 2013-2016

Characteristic	Hasan Sadikin Referral Hospital				UNPAD TANDEM	Ujung Berung District Hospital	Balai Laboratorium Kesehatan	Puskesmas (29 facilities)
	- Endocrinology clinic	- Radiology Department	- DOTS clinic	- Clinical Pathology Laboratory	- TB clinic	- DOTS clinic	- Bacteriology	
Location	Bandung city				Bandung city	Bandung district (east)	Bandung city	Bandung district
Setting	Urban				Urban	Urban	Urban	Urban and peri-urban
Service range	Adult clinic for people with type 1, 2, gestational DM & other endocrine conditions	Adult and paediatric	Adult DS- MDR-TB treatment & paediatric TB drug collection	All tests & TB	Adult TB/MDR-TB patients; paediatric TB for meds only	NA	Reference laboratory	Primary health centres
Disease screened	TB	TB	DM	DM	DM	DM	TB	DM
Disease focus of facility	DM	All patients	TB	No specialty	TB	TB	No specialty*	TB
Number of patients/ tests per year	~8,000 DM patients ~11,350 visits	89,592 x-rays	~2,270 TB patients ~6,800 visits	1,226,364 tests	~24,000 patients	NA	~3,000 smear & culture Culture (solid) - 481	~ 50,000 patients
Type and number of staff	Consultant endocrinology - 1 Doctors (internal med resident) - 5 Nurse - 3 Admin - 2 Nutritionist - 1 Courier - 1 Porter - 1	Resident doctor - 1/week Radiologist - 10 Radiographer - 38 Nurse - 27	Consultant pulmonologist - 1 Doctor (head TB programme) - 1 TB nurse - 1 Pharmacist - 1 Admin - 1	Laboratory doctor - 15 Sr. Resident Doctor - 1 Medical Technologist - 10	Sr. Doctor - 1 Pulmonologist - 1 Resident Dr - 1 (for TANDEM only) Nurse (TB) - 1 Admin - 1 Pharmacist - 1	NA	Laboratory technicians (for smear/culture) - 8	An average Puskesmas: Doctor - 4 (2 GPs, 2 dentists) Nurse - 4 Midwives - 4 Pharmacist - 1 Lab Tech - 1 Admin - 4 Auxiliary - 1
Funder/ ownership	Provincial				Provincial	NA	Provincial	Department of Health
Hours of operation	M-F: 08:00 - 15:00	M-F: 07:00 - 15:30	M-F: 07:30 - 15:30	24 hours	M-F: 07:30 - 15:30	M-F: 07:30 - 15:30	M-F: 07:30 - 16:00	M-Sa: 07:30 - 14:00

*Haematology, immunology, bacteriology, virology, environmental health, radiology, ultrasound, ECG

NA-not available; TB-tuberculosis; DS-drug susceptible; MDR-multidrug-resistant; DM-diabetes mellitus; DOTS-directly observed treatment, short-course;

Puskesmas-Primary Health Centre; Hospital #1-The Emergency County Hospital, Craiova; Hospital #2-The Craiova Philanthropic Municipal

Appendix P: TANDEM health facility and hospital characteristics in Romania, 2013-2016

Characteristic	Hospital #1			Hospital #2		Victor Babes			Runcu		
	- DM ward	- Radiology Department	- Medical Laboratory Department	- Internal Medicine ward	- Radiology Department	- Pneumology (with TB) ward	- BK Lab	- BioChem Lab	- Radiology Department	- TB ward (Section II)	- Microbiology Laboratory
Location	Dolj			Dolj		Gorj			Dolj		
Setting	Urban			Urban		Urban			Rural		
Service range	Reference hospital: Adult type 1 & 2 inpatients	Adult and paediatric	Haematology, immunology, biochemistry, microbiology	City hospital	Adult and paediatric	Infectious diseases: 3 TB wards (adult male, adult female, paediatric)	Bacteriology (sputum samples)	Blood and urine samples	Adult & paediatric radiology & medical imaging	Pulmonary diseases	Sputum, blood and urine samples
Disease screened	TB	TB	TB	TB	TB	DM	TB	DM	TB	DM	DM
Disease focus of facility	DM	All non-infectious diseases	No specialty	Internal medicine	All non-infectious diseases	TB	TB	TB	Infectious diseases	TB	TB
Number of patients/ tests per year	~1,200 patients 65,717 for entire hospital	117,212 x-rays	1,281,721 tests	~43 DM patients	12,659 x-rays	~867 TB patients for each adult pneumology ward ~7,867 for entire hospital	17,484 tests	301,600 tests	~42,030 x-rays	385 patients	22,053 tests
Type and number of staff	Diabetologist – 11 Nurse - 15	Radiologist – 26 Rad. Res Dr - 52	Lab doctor - 13 Nurse - 33 Biochemist - 13 Biologist - 5 Chemist - 9 Physicist - 1	Doctor - 1 Sr. Nurse - 4 Nursing assistant - 2 Cleaning staff - 1	Physicist - 1 Radiologist - 6 Nurse - 8 Cleaning staff - 1	Doctors – 11 Nurse – 32 Radiology nurse – 3 Nurse's aide – 6 Medical records – 2 Orderly - 14	Doctor - 1 Biologist - 2 Technician - 2 Cleaning staff - 1	Lab Doctor - 6 Biologist - 8 Nurse - 17 Orderly - 3	Radiologist - 3 Nurse - 17 Orderly - 3	Pulmonologist – 3 Nurse – 10 Pharmacist – 1 (entire hospital) Laboratory staff – 7 (entire hospital) Admin – 14 (entire hospital) Auxiliary - 60 (entire hospital)	Biologist - 1 Chemist - 1 Nurse (lab) - 5
Funder/ ownership	Local Authority - City Hall of Craiova			Local Authority - City Hall of Craiova		Local Authority - City Hall of Craiova			Gorj County Council		
Hours of operation	24 hours (doctors: 08:00 - 15:00)	24 hours	24 hours	24 hours	24 hours	24 hours	M-F: 08:00 - 15:00		24 hours	24 hours	M-F: 08:00 - 15:00

TB-tuberculosis; DM-diabetes mellitus; BK-bacteriology; BioChem-Biological Chemistry

Hospital #1-The Emergency County Hospital, Craiova; Hospital #2-The Craiova Philantropic Municipal Hospital; Victor Babes-The Victor Babes Clinical Hospital for Infectious Diseases and Pneumology; Runcu-The Tudor Vladimirescu Runcu Hospital for Lung Diseases

Appendix Q: Characteristics of screening and diagnostic tests for tuberculosis and diabetes mellitus in Indonesia and Romania

	Test name	Format	Available in routine service	Specimen	Person to collect sample	Time to collect sample	Facility where sample collected
TB tests	1 TB symptom screen	5 questions: blood in sputum , breathlessness upon exertion , night sweats , unintentional weight loss/gain , fever	Not in DM patients	N/A	Doctor	20 minutes	Indonesia: RSHS Endocrinology Clinic Romania: H#1 DM ward, H#2 Internal Medicine ward
	2 Chest x-ray (CXR)	Digital and film (Indonesia); digital only (Romania)	Yes	Indonesia: digital and film Romania: digital	Radiographer	Indonesia: 150 Romania: 20 minutes	Indonesia: RSHS Radiology Department Romania: H#1 & H#2 Radiology Departments
	3 Smear microscopy	Ziehl-Neelsen stain	Romania: in Infectious Disease Hospitals only Indonesia: yes	Sputum x2 (1 at clinic, 1 early morning)	Nurse	30 minutes or 1 day	Indonesia: RSHS, BLK Romania: H#1 DM ward, VB
	4 Sputum culture	MODS technique using Middlebrook broth (Indonesia) or solid medium Lowenstein-Jensen (Romania)	Romania: Infectious Disease Hospitals Indonesia: yes	Sputum	Nurse	<i>Smear sample used</i>	Indonesia: RSHS, BLK Romania: VB
	5 Interferon Gamma Release Assay (IGRA) – Indonesia	QuantiFERON® analysis kit	No	Whole blood - 3ml	Nurse/phlebotomist	25 minutes (including transport)	RSHS DM ward
	6 Tuberculin skin tests (TST) – Romania	Injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm	No	Measurement of induration (reaction)	Nurse	10 minutes	H#1 DM ward; H#2 Internal Medicine ward
DM tests	1 Omani risk score	5 questions: age , BMI , waist circumference , hypertensive state (at time of study) , family history of diabetes	No	N/A	Nurse/doctor	22 minutes	Indonesia: UNPAD Romania: Runcu, VB
	2 POC random plasma glucose (RPG)	Point of care machine in clinic or in patient's room	No	blood from finger prick	Nurse/doctor	5 minutes	Indonesia: UNPAD Romania: Runcu, VB
	3 Fasting blood glucose (FBG)	Blood draw from arm	Yes	Whole blood - 2 ml	Nurse/phlebotomist	Indonesia: 22 minutes (including transport) Romania: 10 minutes	Indonesia: UNPAD Romania: Runcu, VB
	4 Urine dipstick	Urine sample collected at any time	Indonesia: no Romania: samples tested in laboratories only	Urine	Nurse/doctor	Indonesia: 5 minutes (depending on patient) Romania: 60 minutes (including transport)	Indonesia: UNPAD Romania: Runcu, VB
	5 POC glycated haemoglobin (HbA _{1c})	Point of care machine in clinic or in patient's room	No	blood from finger prick	Nurse/doctor	10 minutes	Indonesia: UNPAD Romania: Runcu, VB
	6 Laboratory glycated haemoglobin (HbA _{1c})	Blood draw from arm	Yes, but no international certification	Whole blood - 2ml EDTA	Nurse/phlebotomist	10 minutes	Indonesia: UNPAD Romania: Runcu, VB

TB-tuberculosis; DM-diabetes mellitus; NA-not applicable; BMI-body mass index; EDTA-Ethylenediaminetetraacetic acid; POC-point of care; mins-minutes
RSHS-Hasan Sadikin Hospital; H#1-Hospital #1 (The Emergency County Hospital, Craiova); H#2-Hospital #2 (The Craiova Philanthropic Municipal Hospital); BLK-Balai Laboratorium KesehatanI; VB-The Victor Babes Clinical Hospital for Infectious Diseases and Pneumology; Runcu-The Tudor Vladimirescu Runcu Hospital for Lung Diseases; UNPAD- Universitas Padjadjaran; CXR-chest x-ray;
MODS-microscopic observation drug susceptibility

	Test name	Person to analysis	Time for result	Facility where analysis performed	Diagnosis range	TANDEM diagnosis cut-off values	Next step
TB tests	1	TB symptom screen	Doctor	2 minutes	Indonesia: RSHS Endo Clinic Romania: H#1 DM ward, H#2 Internal Medicine ward	0 to 5 for the presence of the five key symptoms	Suggestive TB: CXR or sputum smear presence of ≥1 of 5 key symptoms
	2	Chest x-ray (CXR)	Radiologist or pulmonologist	40 minutes	Indonesia: RSHS Radiology Department Romania: H#1 & H#2 Radiology Departments	Positive TB, suggestive TB, not suggestive TB, not TB	Abnormal: positive TB, suggestive TB Sputum smear
	3	Smear microscopy	Bacteriology technician	3 days	Indonesia: BLK Romania: VB	1. Negative = 0/ 100 view field 2. Scanty = 1-9 per 100 3. Positive = ≥ 10 per 100 (+1=10-99 per 100; +2=1-10 per 50; +3>10 per 20)	Positive and scanty Culture
	4	Sputum culture	Bacteriology technician	Indonesia: 14-28 days Romania: National protocol: ≤ 60 days	Indonesia: BLK Romania: VB	Negative Positive	Positive Active TB diagnosed
	5	Interferon Gamma Release Assay (IGRA) – Indonesia	Clinical Pathology doctor or technician	60 minutes	UNPAD Immunology Lab	Positive, negative, indeterminate	Positive Latent TB infection diagnosed
	6	Tuberculin skin tests (TST) – Romania	Pulmonologist or trained diabetologist	15 minutes	H#1 DM ward; H#2 Internal Med ward	Induration measurement at 72 hours after injection: 0 - 40 mm	≥ 5, 10 or 15 mm Latent TB infection diagnosed
DM tests	1	Omani risk score	Nurse/doctor	3 minutes	Indonesia: UNPAD Romania: Runcu, VB	0 to 25	≥ 7 Confirmatory screening or diagnostic test
	2	POC random plasma glucose (RPG)	Nurse/doctor	2 minutes	Indonesia: UNPAD Romania: Runcu, VB	0.6 to 33.3 mmol/L	DM: ≥ 11.0 mmol/L Suspected DM: ≥ 6.1 mmol/L FBG
	3	Fasting blood glucose (FBG)	Clinical Pathology doctor or technician	Indonesia: 10 mins Romania: 70 mins (including report)	Indonesia: RSHS Clinical Pathology lab Romania: Runcu, VB	NA	DM: ≥ 7.0 mmol/L Suspected DM: ≥ 6.1 mmol/L Repeat FBG or laboratory HbA _{1c} test
	4	Urine dipstick	Nurse/doctor	2 minutes	Indonesia: UNPAD Romania: Runcu lab, VB lab	0, Trace, 1+, 2+, 3+, 4+	Trace, 1+, 2+, 3+, 4+ Confirmatory screening or diagnostic test
	5	POC glycated haemoglobin (HbA _{1c})	Nurse/doctor	5 minutes	Indonesia: UNPAD Romania: Runcu, VB	4 to 14%	≥ 6.5% Diagnostic test
	6	Laboratory glycated haemoglobin (HbA _{1c})	Clinical Pathology doctor or technician	Indonesia: 24 hrs Romania: up to 10 days	Indonesia: Prodia Private lab Romania: Bioclinica Private lab	NA	≥ 6.5% DM diagnosed

TB-tuberculosis; DM-diabetes mellitus; NA-not available; BMI-body mass index; EDTA-Ethylenediaminetetraacetic acid; POC-point of care; mins-minutes

RSHS-Hasan Sadikin Hospital; H#1-Hospital #1 (The Emergency County Hospital, Craiova); H#2-Hospital #2 (The Craiova Philanthropic Municipal Hospital); BLK-Balai Laboratorium KesehatanI; VB-The Victor Babes Clinical Hospital for Infectious Diseases and Pneumology; Runcu-The Tudor Vladimirescu Runcu Hospital for Lung Diseases; UNPAD- Universitas Padjadjaran; CXR-chest x-ray; MODS-microscopic observation drug susceptibility

Appendix R: Overhead cost composition for mean costs of screening and diagnostic tests in Indonesia and Romania**Capital overhead costs**

For the Balai Laboratorium Kesehatan (BLK) building in Indonesia, the capital overhead costs for the sputum collection, Ziehl-Neelsen (ZN) smear and culture (MODS) tests include the maintenance of the buildings, computers and vehicles; the current value of the land and building; and other assets such as computers, furniture and vehicles. At the Hasan Sadikin Hospital (RSHS), capital overhead costs include building maintenance; the current value of the land and building; and other assets such as computers, general medical and non-medical equipment and vehicles.

The capital overhead costs for the TB symptom screen, chest x-ray and tuberculin skin tests performed at Hospital #1 and Hospital #2 in Romania include the building maintenance; and assets such as furniture and general medical equipment. Hospital #2 includes additional costs of computers general non-medical equipment and vehicles. The costs at Victor Babes Hospital for sputum collection, smear microscopy (Z-N) and culture (Lowenstein-Jensen) only includes the re-sale value of the entire hospital.

Recurrent overhead costs

At BLK in Indonesia, recurrent overhead costs include utilities, laundry services, sterilisation, cleaning, general office supplies and transportation. At RSHS, only utilities are included.

In Romania, the recurrent overhead costs at Hospital #1 and Hospital #2 include utilities, linens, uniforms, sterilisation, cleaning, general office supplies, medical and laboratory supplies, transportation, rent, and general operations (administrative). The recurrent overhead costs at the Victor Babes hospital include utilities only.

Appendix S: Characteristics of patients screened - narrative

Methods

The characteristics of patients with TB and DM being screened for concurrent disease were evaluated by descriptive analysis (frequencies and proportions), followed by Student's t-test and Pearson's chi-square. The dependent variable was TB or DM cohort at baseline before bi-directional screening. Independent variables were age, sex, ethnicity, marital status, having a bank account, education level and work status. To assess whether any characteristics were associated with disease status (TB patients versus DM patients) after adjustment for confounding, multivariate analysis was performed using a multiple logistic regression model including all independent variables, separately for Indonesia and Romania.

Results

The age, sex, marital status, education level and work status were all significantly different between the DM and TB cohorts in both countries. Mean age of people with DM was higher in both Indonesia and Romania (59 and 58 years, respectively) than for people with TB (40 and 44 years, respectively) (Appendix T). With each year of life, the likelihood of developing DM increased by 11% in Indonesia and 6% in Romania (Appendix U). While the proportion of females was larger than males in people with DM (63% in Indonesia and 53% in Romania), the majority of patients with TB were male (57% and 71%, respectively). In both countries, unmarried people were more likely to have TB than married people (86% versus 42% in Indonesia and 60% versus 40% in Romania, $p < 0.001$). This association persisted when controlling for age using a logistic regression (OR=2.97 and 1.48, respectively). People who attended college or above were more likely to have DM than any other education level (73%, $p < 0.001$) (Appendix U). Students and unemployed people were 1.91 and 2.45 times more likely to have DM than those in paid employment in Indonesia and Romania, respectively (95% CI 1.27-2.87, $p = 0.002$ and 95% CI 1.66-3.62, $p < 0.001$).

Ethnicity and having a bank account were statistically different between people with TB and those with DM in Indonesia only. The ethnic distribution of patients did not proportionally represent that of the respective countries, but the majority ethnic groups (84% Sundanese in Indonesia and 98% Romanian in Romania) reflected the demographic composition of the study regions. (Badan Pusat Statistik (Statistics Indonesia) et al., 2013, National Institute of Statistics, 2011) In Indonesia, Sunda were more likely to have TB than Jawa or other Indonesian ethnicities (51% versus 37% or 40%, $p < 0.001$).

Appendix T: Patient characteristics for people screened in TANDEM study, Indonesia and Romania 2013-2016

	INDONESIA					ROMANIA				
	People with DM		People with TB		<i>p</i> -value*	People with DM		People with TB		<i>p</i> -value*
	(n=809)		(n=771)			(n=603)		(n=504)		
Age, mean (SD) (in years)	58.6	(10.3)	39.7	(14.3)	<0.001 ^α	58.2	(11.9)	43.6	(16)	<0.001 ^α
Sex (female), count (%)	511	(63.2)	332	(43.1)	<0.001	321	(53.2)	146	(29)	<0.001
Ethnicity, count (%)										
Sunda	649	(80.2)	674	(87.4)	<0.001					
Jawa	104	(12.9)	60	(7.8)						
Other Indonesian ethnicities	56	(7.0)	37	(4.9)						
Romanian						588	(97.5)	491	(97.4)	0.097 ^β
Rroma						7	(1.2)	12	(2.4)	
Education level, count (%)										
No formal schooling	12	(1.5)	7	(0.9)	<0.001	10	(1.7)	8	(1.6)	<0.001
Some primary school	55	(6.8)	66	(8.6)		8	(1.3)	2	(0.4)	
Primary school completed	182	(22.5)	178	(23.1)		66	(11)	38	(7.5)	
Secondary school completed	153	(18.9)	150	(19.5)		201	(33.3)	98	(19.4)	
High school completed	229	(28.3)	306	(39.7)		247	(41)	327	(64.9)	
College/University completed	159	(19.7)	62	(8)		58	(9.6)	27	(5.4)	
Postgraduate degree	19	(2.4)	2	(0.3)		3	(0.5)	0	(0)	
Unknown	0	(0)	0	(0)	10	(1.7)	4	(0.8)		
Married (yes), count (%)	771	(95.3)	552	(71.6)	<0.001	471	(78.1)	315	(62.5)	<0.001
Bank account (yes), count (%)	345	(42.7)	226	(29.3)	<0.001	178	(29.5)	150	(29.8)	0.835
Work status, count (%)										
Government employee	46	(5.7)	8	(1)	<0.001	16	(2.7)	11	(2.2)	<0.001
Private sector employee	53	(6.6)	265	(34.4)		67	(11.1)	95	(18.9)	
Self employed	104	(12.9)	163	(21.1)		10	(1.7)	92	(18.3)	
Volunteer or unpaid	12	(1.5)	4	(0.5)		6	(1)	27	(5.4)	
Student	0	(0)	27	(3.5)		2	(0.3)	22	(4.4)	
Homemaker	353	(43.6)	215	(27.9)		112	(18.6)	126	(25)	
Retired	165	(20.4)	13	(1.7)		361	(59.9)	102	(20.2)	
Unemployed (able to work)	21	(2.6)	53	(6.9)		18	(3)	18	(3.6)	
Unemployed (unable to work)	55	(6.8)	23	(3)		0	(0)	0	(0)	
Unknown	NA	NA	NA	NA	11	(1.8)	11	(2.2)		

*Pearson's chi-squared test, unless otherwise stated

^αStudent *t*-test for continuous age variable

^βFisher's exact test (1-sided)

NA-not applicable

Appendix U: Multivariate analysis, Indonesia and Romania 2013-2016

Variable	Indonesia		Romania	
	OR*	(95% CI)	OR*	(95% CI)
Age	1.11	(1.10-1.13)	1.06	(1.05-1.07)
Sex				
Female		<i>Reference</i>		<i>Reference</i>
Male	0.31	(0.21-0.45)	0.38	(0.28-0.52)
Ethnicity				
Sunda		<i>Reference</i>		
Jawa	1.33	(0.85-2.06)		
Other Indonesian ethnicities	1.5	(0.80-2.83)		
Romanian				<i>Reference</i>
Roma			0.58	(0.20-1.68)
Education level				
No more than primary school completed		<i>Reference</i>		<i>Reference</i>
Between secondary and high school completed	2.07	(1.52-2.83)	1.29	(0.77-2.15)
College and above	4.84	(2.93-8.00)	3.74	(1.75-8.02)
Marital status				
Married	2.97	(1.81-4.90)	1.48	(1.04-2.09)
Not married		<i>Reference</i>		<i>Reference</i>
Bank account				
Yes	1.23	(0.90-1.70)	1.01	(0.72-1.42)
No		<i>Reference</i>		<i>Reference</i>
Work status				
Paid employment		<i>Reference</i>		<i>Reference</i>
Unpaid employment	1.19	(0.81-1.75)	1.52	(1.00-2.33)
Unemployed/Student	1.91	(1.27-2.87)	2.45	(1.66-3.62)

*Reference is disease status = TB



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

Operational Feasibility Questionnaire: diabetes screening tests - TANDEM nursing staff

INFORMATION SHEET:

The objective of this questionnaire is to determine the acceptability, accessibility and feasibility of performing the diabetes (DM) screening tests on tuberculosis (TB) patients within the TANDEM project. It is hoped that these questions will determine how to successfully implement DM screening tests into routine TB services in the future.

You will be asked to complete this questionnaire twice: near the beginning of the TANDEM study and again shortly before the end of the TANDEM study.

All responses will be kept confidential and any publication will attribute responses to broad professional categories, not individuals. Only members of the TANDEM team will view the completed questionnaires.

If, after this interview has ended, you have any further questions or wish to withdraw your responses, please contact:

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(PhD candidate – health economics)
Phone: +44 753 111 4253
E-mail: yoko.laurence@lshtm.ac.uk
Websites: www.lshtm.ac.uk
www.tandem-fp7.eu

Questionnaire #: _____



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

**Operational Feasibility Questionnaire: diabetes screening tests
- TANDEM nursing staff**

CONSENT FORM:

I, _____ (participant name), agree to participate in this operational feasibility study and complete this questionnaire.

I understand the purpose of this questionnaire.

All of my questions or concerns have been addressed.

PARTICIPANT NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

INTERVIEWER NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

DATE: _____

Questionnaire #: _____

Operational Feasibility Questionnaire: diabetes screening tests - TANDEM nursing staff

START TIME: _____ (please record the start time of the interview)

INSTRUCTIONS (to be read to the interviewee)

I will read the questions to you and capture your response in this paper. Take as much time as you need to respond. Please answer the questions from your own perspective as it relates to your work in the TANDEM study.

Study identifier

1. Facility name _____ 2. Date of interview
|_|_|day|_|_|month|_|_|_|_|year
3. Questionnaire number _____
|_|_|_|

Interviewee information

4. First name: _____ 6. Gender:
5. Surname: _____ Male
 Female
7. Date of birth _____
|_|_|day|_|_|month|_|_|_|_|year
8. Job title _____
9. Employer
 TANDEM
 University
 Ministry of Health
 Health facility/hospital
 Other _____

Test 1: Point of care (POC) Random Capillary Blood Glucose (RCG)

10. Is this test currently being done at your facility (outside the TANDEM project)? No Yes
11. If no, what test is done in its place? _____
12. Is use of the test reliant on an electricity supply? No Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
13. This test is technically undemanding for you	5	4	3	2	1
14. The amount of time needed for training in order for you to become proficient in using this test was acceptable	5	4	3	2	1
15. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
16. Minimal supervision is required for you to perform this test	5	4	3	2	1
17. This test has a direct result reading	5	4	3	2	1
18. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

19. Before the start of the TANDEM project did you already know how to perform the RCG test?

- No
 Yes

20. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

21. How long did it take to learn the method for performing this test?

_____ days _____ hours _____ minutes

22. How many times did you practice this test to learn the method? _____

23. How long does it take you, on average, to perform the RCG test on one patient? _____ minutes

Patient participation and other issues:

24. In general, are patients reluctant to have their finger pricked for this test?

- No
- Yes

25. If yes, what are some of the issues?

26. Have you ever had a compromised (e.g. damaged, lost or mislabelled) RCG test for the TANDEM project?

- No
- Yes

27. If yes, please indicate the top three reasons for compromised RCG tests:

1. _____

2. _____

3. _____

28. How many RCG tests have you performed since the start of the TANDEM project?

29. Out of all the RCG tests that you have performed so far, how many have been compromised?

30. How often has the POC RCG machine been maintained?

- Never
- _____ times a month/ year (**select ONE time division**)
- I don't know

31. If never, how often should the POC RCG machine be maintained?

_____ times a month/ year (**select ONE time division**)

32. How often does the POC RCG machine break down?

Questionnaire #: _____

- Never
- _____ times a month/ year (**select ONE time division**)
- I don't know

33. On average, how long is the machine usually not working, when it breaks down?

_____ months _____ weeks _____ days _____ hours _____ minutes

- I don't know
- Not applicable

34. In your opinion, do you think this test is a useful way of diagnosing DM?

- No
- Yes

35. If no, please give reasons why you think so:

36. Are there any additional comments you would like to make about the RCG test?

Test 2: Fasting Blood Glucose (FBG)

37. Is this test currently being done at your facility (outside the TANDEM project)?
- No
 Yes - go to question 35
 Not applicable – go to question 35
38. If no, what test is done in its place? _____
39. Is use of the test reliant on an electricity supply?
- No
 Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
40. This test is technically undemanding for you	5	4	3	2	1
41. The amount of time needed for training in order for you to become proficient in using this test was acceptable	5	4	3	2	1
42. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
43. Minimal supervision is required for you to perform this test	5	4	3	2	1
44. This test has a direct result reading	5	4	3	2	1
45. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

46. Before the start of the TANDEM project did you already know how to perform the FBG test?

- No
 Yes

47. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

48. How long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

49. How many times did you practice this test to learn the method? _____

50. How long does it take you, on average, to perform the FBG test on one patient (from starting the blood draw to storing the blood sample to be sent to the lab)? _____ minutes

Patient participation and other issues:

51. Do patients usually comply with the fasting requirement for the FBG test?

- No
- Yes
- Don't know

52. If the patient is required to return to a health facility the following day in order to ensure fasting is done, what is the usual reaction of patients to this request? (Describe)

53. How often are blood samples for FBG usually picked-up for delivery to the SUN laboratory?

- Twice daily
- Once daily
- Once weekly
- Other, specify _____ times per *day/week/month* (**select ONE**)

54. How long do the results take, on average, to be returned from the national public laboratory to the clinic?

_____ weeks _____ days _____ hours

55. When are patients told the results of the FBG test?

- Never
- Always
- Only when outside the normal range
- Other, specify _____

56. How long after the results are returned to the clinic from the national public laboratory are patients told the results?

_____ months _____ weeks _____ days _____ hours _____ minutes

57. How are patients told the results?

- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____

58. Have you ever had a compromised (e.g. haemostasis, damaged, lost, mislabelled, due to machine failure, etc.) FBG sample for the TANDEM project?

- No
- Yes

Questionnaire #: _____

59. If yes, please indicate the top three reasons for compromised FBG samples:

1. _____

2. _____

3. _____

60. How many FBG blood draws have you performed since the start of the TANDEM project?

61. Out of all the FBG samples that you collect so far, how many have been compromised?

62. In your opinion, do you think this test is a useful way of diagnosing DM?

- No
 Yes

63. If no, please give reasons why you think so:

64. Are there any additional comments you would like to make about the FBG test?

Test 3: Urine dipstick

65. Is this test currently being done at your facility (outside the TANDEM project)?
- No
 Yes – go to question 63
 Don't know – go to question 63

66. If no, what test is done in its place? _____

67. Is use of the test reliant on an electricity supply?
- No
 Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
68. This test is technically undemanding for you	5	4	3	2	1
69. The amount of time needed for training in order for you to become proficient in using this test was acceptable	5	4	3	2	1
70. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
71. Minimal supervision is required for you to perform this test	5	4	3	2	1
72. This test has a direct result reading	5	4	3	2	1
73. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

74. Before the start of the TANDEM project did you already know how to perform the urine dipstick test?

- No
 Yes

75. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

76. How long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

77. How many times did you practice this test to learn the method? _____

Questionnaire #: _____

78. How long does it usually take for patients to produce a urine sample?

_____ hours _____ minutes

Other, explain _____

79. How long does it take you, on average, to perform the urine dipstick test for one patient (once you already have the sample from the patient)?

_____ hours _____ minutes _____ seconds

Patient participation and other issues:

80. Do you have difficulty getting patients to agree to do the urine dipstick?

- No
 Yes

81. If yes, what are some of the issues?

82. Are the toilet facilities suitable for patients to give a urine sample?

- No
 Yes

83. If no, what needs to be improved?

84. Is there water easily available from the health facility for patients if they need it in order to give a urine sample?

- No
 Yes

Questionnaire #: _____

85. If no, how can it be improved?

86. Have you ever had a compromised (e.g. damaged, lost, mislabelled results or difficult to interpret reading when compared to manufacturer's colour chart) urine sample for the TANDEM project?

- No
- Yes

87. If yes, please indicate the top three reasons for compromised urine samples:

1. _____

2. _____

3. _____

88. How many urine dipstick tests have you performed since the start of the TANDEM project?

89. Out of all the urine dipstick tests that you have performed so far, how many have been compromised?

90. In your opinion, do you think the urine dipstick is a useful way of diagnosing DM?

- No
- Yes

91. If no, please give reasons why you think so:

Questionnaire #: _____

92. Are there any additional comments you would like to make about the urine dipstick test?

Test 4: Point of care (POC) HbA1c test

93. Is the POC HbA1c test offered at this health facility (outside of the TANDEM project)?

- No
- Yes – go to question 91
- I don't know – go to question 91

94. If no, what test is done in its place? _____

95. Is use of the test reliant on an electricity supply? No Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
96. This test is technically undemanding for you	5	4	3	2	1
97. The amount of time needed for training in order for you to become proficient in using this test is acceptable	5	4	3	2	1
98. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
99. Minimal supervision is required for you to perform this test	5	4	3	2	1
100. This test has a direct result reading	5	4	3	2	1
101. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

102. Before the start of the TANDEM project did you already know how to perform the POC HbA1c test?

- No
- Yes

103. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

104. How long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

105. How many times did you practice this test to learn the method? _____

Questionnaire #: _____

106. How long does it take you, on average, to get the results for each POC HbA1c test?

_____ hours _____ minutes

107. How many individual tests, on average, do you perform each week? _____

Quality control:

108. Is internal quality control done for the POC HbA1c test?

- No – go to question 107
 Yes

109. If yes, how often do you do it?

_____ times per day/week/month (**select ONE**)?

110. If yes, please describe the process.

Logistics and other issues:

111. Are patients usually willing to have their finger pricked?

- No
 Yes

112. If no, what are the most common reasons for patient unwillingness?

113. Has a POC HbA1c sample for TANDEM ever been compromised (e.g. damaged, lost, mislabelled, machine failure, etc.) in the clinic?

- No
 Yes

Questionnaire #: _____

114. If yes, please indicate the top three reasons for compromised POC HbA1c samples:

1. _____

2. _____

3. _____

115. How many POC HbA1c tests have you performed since the start of the TANDEM project?

116. Out of all the POC HbA1c tests that you have done so far, how many have been compromised?

117. How often has the POC HbA1c machine maintained?

Never

_____ times a month/ year (**select ONE time division**)

I don't know

118. If never, how often should the POC HbA1c machine be maintained?

_____ times a month/ year (**select ONE time division**)

119. How often does the POC HbA1c machine break down?

Never

_____ times a month/ year (**select ONE time division**)

I don't know

120. On average, how long is the machine usually not working, when it breaks down?

_____ years _____ months _____ weeks _____ days

I don't know

Not applicable

121. In your opinion, do you think the POC HbA1c is a useful way of diagnosing DM?

No

Yes

Questionnaire #: _____

122. If no, please give reasons why you think so:

123. Are there any additional comments you would like to make about the POC HbA1c test?

Test 5: Gold Standard – Laboratory HbA1c

124. Is this test currently being done at your facility (outside the TANDEM project)?
- No
 Yes – go to question 121
 Don't know – go to question 121

125. If no, what test is done in its place? _____

126. Is use of the test reliant on an electricity supply?
- No
 Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
127. This test is technically undemanding for you	5	4	3	2	1
128. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
129. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
130. Minimal supervision is required for you to perform this test	5	4	3	2	1
131. This test has a direct result reading	5	4	3	2	1
132. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

133. Before the start of the TANDEM project did you already know how to perform the laboratory HbA1c test?

- No
 Yes

134. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

135. How long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

136. How many times did you practice this test to learn the method? _____

137. How long does it take you, on average, to perform each laboratory HbA1c test?

_____ hours _____ minutes

Questionnaire #: _____

138. How many individual tests, on average, do you perform each week? _____

Patient participation and other issues:

139. Do you have difficulty getting patients to agree to have their blood drawn for the laboratory HbA1c?

- No
 Yes

140. If yes, what are some of the issues?

141. How long after the patient's sample is taken is the sample picked-up for delivery to the SUN laboratory?

_____ hours _____ weeks _____ days

142. How long does it usually take to get the results from the national public laboratory?

_____ weeks _____ days

143. When are patients told the results of the laboratory HbA1c test?

- Always
 Only when outside the normal range
 Other, please specify _____

144. How long after the results are returned from national public laboratory are patients told the results?

_____ weeks _____ days _____ hours _____ minutes

145. How are patients told the results?

- Phone
 Asked to visit the clinic
 Other, please specify _____

146. Have you ever had a compromised (e.g. damaged, lost or mislabelled) laboratory HbA1c sample for the TANDEM project?

- No
 Yes

147. If yes, please indicate the top three reasons for compromised laboratory HbA1c samples:

1. _____

Questionnaire #: _____

2. _____

3. _____

148. How many laboratory HbA1c tests have you performed since the start of the TANDEM project?

149. Out of all the laboratory HbA1c tests that you have done so far, how many have been compromised?

150. In your opinion, do you think the laboratory HbA1c test is a useful way of diagnosing DM?

- No
- Yes

151. If no, please give reasons why you think so:

152. Are there any additional comments you would like to make about the laboratory HbA1c test?

END TIME: _____ (please record the end time of the interview)



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

Operational Feasibility Questionnaire: diabetes screening tests - Laboratory staff

INFORMATION SHEET:

The objective of this questionnaire is to determine the acceptability, accessibility and feasibility of performing the diabetes (DM) screening tests on tuberculosis (TB) patients within the TANDEM project. It is hoped that these questions will determine how to successfully implement DM screening tests into routine TB services in the future.

You will be asked to complete this questionnaire twice: near the beginning of the TANDEM study and again shortly before the end of the TANDEM study.

All responses will be kept confidential and any publication will attribute responses to broad professional categories, not individuals. Only members of the TANDEM team will view the completed questionnaires.

If, after this interview has ended, you have any further questions or wish to withdraw your responses, please contact:

Ms. Yoko Laurence
(PhD candidate – health economics)
Phone: +44 753 111 4253 (UK)
E-mail: yoko.laurence@lshtm.ac.uk
Websites: www.lshtm.ac.uk
www.tandem-fp7.eu

Questionnaire #: _____



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

**Operational Feasibility Questionnaire: diabetes screening tests
- Laboratory staff**

CONSENT FORM:

I, _____ (participant name), agree to participate in this operational feasibility study and complete this questionnaire.

I understand the purpose of this questionnaire.

All of my questions or concerns have been addressed.

PARTICIPANT NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

INTERVIEWER NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

DATE: _____

Questionnaire #: _____

Operational Feasibility Questionnaire: diabetes screening tests - Laboratory staff

START TIME: _____ (please record the start time of the interview)

INSTRUCTIONS (to be read to the interviewee)

I will read the questions to you and capture your response on this paper. Take as much time as you need to respond. Please answer the questions from your own perspective as it relates to your work in the TANDEM study.

Study identifier

1. Facility name _____ 2. Date of interview
|_|_|day|_|_|month|_|_|_|_|year
3. Questionnaire number |_|_|_|

Interviewee information

4. First name: _____ 6. Gender:
5. Surname: _____ Male
 Female
7. Date of birth |_|_|day|_|_|month|_|_|_|_|year
8. Job title _____
9. Employer
 TANDEM
 University
 Ministry of Health
 Health Centre/Hospital
 Laboratory – public
 Laboratory - private
 Other _____

Questionnaire #: _____

Test 1: Fasting Blood Glucose (FBG)

10. Is this test currently being performed at your facility (outside the TANDEM project)? No
 Yes

11. If no, what test is done in its place? _____

12. Is use of the test reliant on an electricity supply? No
 Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
13. This test is technically undemanding for you	5	4	3	2	1
14. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
15. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
16. Minimal supervision is required to perform this test	5	4	3	2	1
17. The analysis for this test has a direct result reading	5	4	3	2	1
18. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

19. Before the start of the TANDEM project did you already know how to perform the analysis of the FBG test?

No
 Yes

20. If yes, how long have you been performing this test?

_____ weeks _____ months _____ years

21. How long did it take to learn the method for performing this test?

_____ days _____ hours _____ minutes

Questionnaire #: _____

22. How many times did you practice this test to learn the method? _____

23. How long does it take you, on average, to complete the paperwork (registration, insurance, payment, etc.) for each FBG test?

_____ minutes _____ hours

24. How long do the results take, on average, to be given to the patient (from the time the patient gives blood to collection of results)?

_____ weeks _____ days _____ hours

25. Is the analysis of the FBG done in batches?

- No
 Yes

26. If no, how long does it take you, on average, to do the analysis for each FBG test?

_____ minutes

27. If yes, how many samples are analysed for FBG in each batch?

28. How long, on average, does it take you to complete the analysis of one batch?

_____ minutes _____ hours

29. How many batches or individual tests, on average, are run each day? **(Select ONE below and state average number)**

- Batches _____
 Individual tests _____

Quality control:

30. Is internal quality control done for the FBG test?

- No
 Yes

31. If yes, how often?

_____ times per day/week/month **(select ONE)?**

32. If yes, please describe the process.

Questionnaire #: _____

33. How much time is spent on the internal quality control and calibration process for batch 1 of tests?

_____ hours _____ minutes _____ seconds

34. Number of tests in batch 1 _____

35. If applicable, how much time is spent on the internal quality control and calibration process for batch 2 of tests?

_____ hours _____ minutes _____ seconds

36. Number of tests in batch 2 _____

Logistics and other issues:

37. Do patients usually comply with the fasting requirements (e.g. return the following day) for the FBG test?

- No
- Yes
- Do not know

38. If no, please state reasons for not complying.

39. Are the samples usually of good quality (whole blood, plasma, etc.)?

- No
- Yes

40. If no, why are they not usually of good quality?

Questionnaire #: _____

41. Are the samples usually sufficient for the test (e.g. volume)?

- No
- Yes

42. If no, why?

43. Has an FBG sample ever been compromised (e.g. damaged, lost, mislabelled) in your laboratory?

- No
- Yes

44. If yes, please indicate the top three reasons for compromised FBG samples:

1. _____

2. _____

3. _____

45. How many FBG tests have you analysed since the start of the TANDEM project?

46. Out of all the FBG samples that you analysed so far, how many have been compromised?

47. In your opinion, do you think the FBG is a useful way of diagnosing DM?

- No
- Yes

48. If no, please give reasons why you think so:

Questionnaire #: _____

49. Are there any additional comments you would like to make about the laboratory FBG test?

END TIME: _____ (please record the end time of the interview)

Questionnaire #: _____

Test 2: Gold Standard - Laboratory HbA1c test

50. Is the laboratory HbA1c test (outside of the TANDEM project) offered at this health facility?

- No
- Sometimes
- Yes
- I don't know

51. If yes, please respond to the statement:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The laboratory HbA1c test is always available at this facility	5	4	3	2	1

52. If no, what test is done in its place? _____

53. If sometimes, why is it not available?

- Faulty machinery
- Reagents unavailable
- Other, please explain _____

54. If a laboratory HbA1c test is not available at the facility, how far from this health facility is the closest facility at which patients would get the test done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

55. What kind of facility is it?

- Private
- Another public health centre
- Other, specify _____

56. What proportion of patients are not able to get a prescribed laboratory HbA1c at this facility?

_____ %

57. Is use of the test reliant on an electricity supply? No Yes

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
58. This test is technically undemanding for you	5	4	3	2	1

Questionnaire #: _____

59.	The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
60.	The amount of time needed for to perform this test is acceptable	5	4	3	2	1
61.	Minimal supervision is required for you to perform this test	5	4	3	2	1
62.	This test has a direct result reading	5	4	3	2	1
63.	There are simple quality control checks	5	4	3	2	1

Training and test performance time:

64. Before the start of the TANDEM project did you already know how to perform the laboratory HbA1c test?

- No
 Yes

65. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

66. How long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

67. How many times did you practice this test to learn the method? _____

68. How long does it take you, on average, to do the paperwork for each batch of laboratory HbA1c tests?

_____ hours _____ minutes

69. Is the analysis of the laboratory HbA1c done in batches?

- No
 Yes

70. If no, how long does it take you, on average, to do the analysis for each laboratory HbA1c test?

_____ minutes

70. If yes, how many samples are analysed for laboratory HbA1c in each batch?

72. How long, on average, does it take you to complete the analysis of one batch?

_____ hours _____ minutes

73. How many batches or individual tests, on average, do you run each day? (**Select ONE below and state average number**)

Questionnaire #: _____

- Batches _____
- Individual tests _____

Quality control:

74. Is internal quality control done for the laboratory HbA1c test?

- No
- Yes

75. If yes, how often?

_____ times per day/week/month (**select ONE**)?

76. If yes, please describe the process.

77. How much time do you spend on the internal quality control and calibration process for batch 1 of tests?

_____ hours _____ minutes _____ seconds

78. Number of tests in batch 1 _____

79. How much time do you spend on the internal quality control and calibration process for batch 2 of tests?

_____ hours _____ minutes _____ seconds

80. Number of tests in batch 2 _____

Logistics and other issues:

81. Do you generally receive samples in a timely manner?

- No
- Yes

82. Are the samples usually of good quality (whole blood, plasma, etc.)?

- No
- Yes

Questionnaire #: _____

83. If no, why are they not usually of good quality?

84. Are the samples usually sufficient for the test (e.g. volume)?

- No
- Yes

85. If no, why?

86. Has a laboratory HbA1c sample for TANDEM ever been compromised (e.g. damaged, lost, mislabelled, due to machine failure, etc.) in your laboratory?

- No
- Yes

87. If yes, please indicate the top three reasons for compromised laboratory HbA1c samples:

1. _____
2. _____
3. _____

88. Out of every 25 laboratory HbA1c samples that you analyse, how many are compromised?

89. In your opinion, do you think this test is a useful way of diagnosing DM?

- No
- Yes

90. If no, please give reasons why you think so:

Questionnaire #: _____

91. Are there any additional comments you would like to make about the laboratory HbA1c test?

END TIME: _____ (please record the end time of the interview)



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests - Clinic staff

INFORMATION SHEET:

The objective of this questionnaire is to determine the acceptability, accessibility and feasibility of performing the tuberculosis (TB) screening and diagnostic tests on patients with diabetes mellitus (DM) within the TANDEM project. It is hoped that these questions will determine how to successfully implement TB screening and diagnostic tests into routine DM services in the future.

All responses will be kept confidential and any publication will attribute responses to broad professional categories, not individuals. Only members of the TANDEM team will use this information.

If, after this interview has ended, you have any further questions or wish to withdraw your responses, please contact:

Ms. Yoko Laurence
(Health Economist)
Phone: +44 753 111 4253 (UK)
E-mail: yoko.laurence@lshtm.ac.uk
Websites: www.lshtm.ac.uk
www.tandem-fp7.eu

Questionnaire #: _____

Questionnaire #: _____



**Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link
and improving care**

**Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests
- Clinic staff**

CONSENT FORM:

I, _____ (participant name), agree to participate in this operational
feasibility study and complete this questionnaire.
I understand the purpose of this questionnaire.
All of my questions or concerns have been addressed.

PARTICIPANT NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

INTERVIEWER NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

DATE: _____

Questionnaire #: _____

Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests - Clinic staff

START TIME: _____ (please record the start time of the interview)

INSTRUCTIONS (to be read to the interviewee)

I will read the questions to you and capture your response on this paper. Take as much time as you need to respond. Please answer the questions from your own perspective as it relates to your work in the TANDEM study.

Study identifier

1. Facility name _____
2. Date of interview |__|__|day|__|__|month|__|__|__|__|year
3. Questionnaire number |__|__|__|

Interviewee information

4. First name _____
5. Surname _____
6. Gender Male
 Female
7. Date of birth |__|__|day|__|__|month|__|__|__|__|year
8. Job title _____
9. Employer TANDEM
 Universidad Peruana Cayetano Heredia
 Health Centre
 Other, please specify _____

Test 1: TB symptom screen

TB symptom screen includes questions on:

Cough (recent)
Cough duration
Sputum production
Blood in sputum
Breathlessness upon exertion
Night sweats
Unintentional weight loss or gain
When started to feel ill
Previous TB diagnosis
Previous TB treatment

10. Is any TB symptom screen test currently being done routinely at your facility (outside the TANDEM project)?

- No
 Yes
 Don't know

11. If no, is any TB screen in patients with DM done in its place?

- No
 Yes

12. If yes, what is done in its place? _____

User friendliness:

		Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
13.	This test is technically undemanding for you	5	4	3	2	1
14.	The amount of time needed for training in order for you to become proficient in performing this test was acceptable	5	4	3	2	1
15.	The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
16.	Minimal supervision is required for you to perform this test	5	4	3	2	1
17.	This test has a direct result reading	5	4	3	2	1
18.	There are simple quality control checks	5	4	3	2	1
19.	Patients find the questions easy to understand	5	4	3	2	1

Training and test performance time:

20. Before the start of the TANDEM project did you already know how to perform the TB symptom screen?

- No
 Yes

21. If yes, how long have you been performing the screen?

_____ years _____ months _____ weeks

22. How long does it take you, on average, to perform the TB symptom screen on one patient? _____ minutes

23. How many times, on average, do you perform the TB symptom screen per week (TANDEM and non-TANDEM)?

24. Are there sufficient skilled personnel to perform TB symptom screens of patients with DM in each site if this was rolled out into routine practice?

- No
 Yes
 Don't know

Patient participation and other issues:

25. Approximately what proportion of patients with DM are willing to be symptom screened for TB?

_____ %

Don't know

26. What are some of the reasons for unwillingness to be screened?

27. In general, do patients with DM have difficulty answering any of the questions in the TB symptom screen?

- No
 Yes

28. Which questions are the most difficult?

29. Approximately how many TB symptom screens in patients with DM have you performed since the start of the TANDEM project?

Questionnaire #: _____

30. In your opinion, do you think this is a useful way of screening for TB in patients with DM?

- No
- Yes

31. If no, please give reasons why you think so:

32. Are there any additional comments you would like to make about the TB symptom screen?

Test 2: Chest x-ray (CXR) – REFERRAL ONLY

33. Is the CXR routinely **available** at this health facility (outside of the TANDEM project)?

- Yes, go to #34
- No, go to #35
- I don't know, go to #39

34. If yes, is the CXR routinely **prescribed** at this clinic (outside of the TANDEM project)?

- Yes, go to #39
- No, go to #35

35. If no to #33 or #34, why is the CXR not available or prescribed?

- No x-ray machine
- Never part of the diagnosis algorithm for patients at this clinic
- Faulty machinery
- Supplies unavailable
- Trained staff unavailable
- Other, please explain _____

36. If no to #33, how far from this health facility is the closest facility at which patients would get one done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

37. What kind of facility is it?

- Private
- Another public health centre
- Other, specify _____

38. Approximately what proportion of patients are not able to get a prescribed CXR at this facility due to the issues in 35 above?

_____ %.

- Don't know

39. Is an electricity supply needed to perform a CXR referral?

- No
- Yes

40. Do you refer patients to the radiology department for CXRs?

- No
- Yes

Questionnaire #: _____

41. If no, who refers them? _____

42. Do you interpret the CXR?

- No
 Yes

43. If no, who interprets it? _____

User friendliness of CXR referral (answer ONLY if conducting CXR referrals):

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
44. After the symptom screen it is easy to know whether a patient should be referred for a CXR	5	4	3	2	1
45. The amount of time needed for training in order for you to become proficient in knowing when to refer a patient for a CXR was acceptable	5	4	3	2	1
46. The amount of time needed for you to decide whether to refer a patient with DM for a CXR (using the screening algorithm) is acceptable	5	4	3	2	1
47. Minimal supervision is required for you to decide whether to refer a patient for a CXR	5	4	3	2	1
48. The algorithm for referring a patient for a CXR has a direct result	5	4	3	2	1
49. There is supervision of junior staff to ensure correct referral of a patient for a CXR	5	4	3	2	1

Training and test performance time (for CXR referral – answer ONLY if conducting CXR referrals):

50. Before the start of the TANDEM project did you already have criteria for referring a DM patient for a CXR to screen for TB?

- No
 Yes

Questionnaire #: _____

51. If no, how is the decision made to send DM patients for a CXR if there is a suspected respiratory illness?

52. If yes, how long have these criteria existed at your facility?

_____ years _____ months _____ weeks

Don't know

53. If yes, what are the TB screening criteria for CXR referral (in patients with DM) at your facility?

54. How long does it take you, on average, to refer one patient with DM for a CXR?

_____ minutes _____ hours _____ days

Patient participation and other issues:

55. Approximately what proportion of patients with DM comply with the request to go for a CXR?

_____ %

Don't know

56. What are some of the reasons for non-compliance?

Questionnaire #: _____

57. Approximately what proportion of patients with DM have to return to the health facility in order to get the CXR?

_____ %

58. How long does it take, on average, for CXR results (for patients with DM) to be returned from the radiology department to the clinician (to be interpreted or with the interpretation report)?

_____ weeks _____ days _____ hours

59. What is the format of the CXR?

- Film
- Electronic
- Other, please specify _____

60. How are the results of the CXR returned to the DM clinic (from where the patient was first referred)?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or radiology _____
- Online system
- E-mail
- Other, please specify _____

61. When are patients with DM told the results of the CXR?

- Never
- Always
- Only when there is an abnormal reading
- Only if they ask for it
- Other, please specify _____

62. To the best of your memory, how long after the results are returned to the clinic are patients with DM told the results? – **MINIMUM time**

_____ months _____ weeks _____ days _____ hours _____ minutes

63. To the best of your memory, how long after the results are returned to the clinic are patients with DM told the results? – **MAXIMUM time**

_____ months _____ weeks _____ days _____ hours _____ minutes

64. How are patients with DM told the results?

- In person during their next scheduled visit at the clinic
- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____

Questionnaire #: _____

65. Have you ever had a compromised (e.g. damaged, lost, mislabelled, incorrectly performed, etc.) DM patient CXR for the TANDEM project?

- No
- Yes

66. If yes, please indicate the top three reasons for compromised CXRs (for patients with DM):

1. _____

2. _____

3. _____

67. Approximately how many patients with DM have you **referred for a CXR** since the start of the TANDEM project?

_____ patients

68. Out of all the **CXRs that you ordered** so far, approximately how many have been compromised?

69. In your opinion, do you think the CXR is a useful way of screening patients with DM for TB?

- No
- Yes

70. If no, please give reasons why you think so:

71. Are there any additional comments you would like to make about the CXR?

Questionnaire #: _____

Test 2: Chest x-ray (CXR) – Interpretation/reading by clinician or pulmonologist

72. Is the CXR routinely **available** at this health facility (outside of the TANDEM project)?

- Yes, go to #73
- No, go to #74
- I don't know, go to #78

73. If yes, is the CXR routinely **prescribed** at this clinic (outside of the TANDEM project)?

- Yes, go to #78
- No, go to #74

74. If no to #72 or #73, why is the CXR not available or prescribed?

- No x-ray machine
- Never part of the diagnosis algorithm for patients at this clinic
- Faulty machinery
- Supplies unavailable
- Trained staff unavailable
- Other, please explain _____

75. If no to #72, how far from this health facility is the closest facility at which patients would get one done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

76. What kind of facility is it?

- Private
- Another public health centre
- Other, specify _____

77. Approximately what proportion of patients are not able to get a prescribed CXR at this facility due to the issues in 74 above?

_____ %.

- Don't know

78. Is an electricity supply needed to perform a CXR?

- No
- Yes

79. Do you refer patients to the radiology department for CXRs?

- No
- Yes

Questionnaire #: _____

80. If no, who refers them? _____

81. Do you interpret the CXR?

- No
 Yes

82. If no, who interprets it? _____

User friendliness of CXR INTERPRETATION (answer ONLY if interpreting CXRs):

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
83. The CXR is technically undemanding for you to interpret	5	4	3	2	1
84. The amount of time needed for training in order for you to become proficient in interpreting the CXR was acceptable	5	4	3	2	1
85. The amount of time needed for you to interpret the CXR is acceptable	5	4	3	2	1
86. Minimal supervision is required for you to interpret the CXR	5	4	3	2	1
87. The CXR has a direct result reading	5	4	3	2	1
88. There are quality control checks of the CXR reading	5	4	3	2	1

Training and test performance time (for CXR INTERPRETATION – answer ONLY if interpreting CXRs):

89. Before the start of the TANDEM project did you already know how to interpret a CXR for TB in patients with DM?

- No
 Yes

90. If yes, how long have you been performing this?

_____ years _____ months _____ weeks

91. Approximately how long did it take you to learn to interpret CXRs in patients with DM?

_____ days _____ hours _____ minutes

92. Approximately how many times did you practice interpreting CXRs in patients with DM to learn the method?

93. How long does it take you, on average, to interpret the CXR for one patient with DM (from reading to writing a report)? _____ minutes

Questionnaire #: _____

94. Are there sufficient skilled personnel to interpret these x-rays of patients with DM at this facility if this screening algorithm was rolled out into routine practice?

- No
- Yes
- Don't know

Patient participation and other issues:

95. Approximately what proportion of patients with DM do not comply with the request to come for a CXR?

_____ %

- Don't know

96. What are some of the reasons for non-compliance?

97. Approximately what proportion of patients with DM have to return to the radiology department in order to get the CXR?

_____ %

- Don't know

98. How long does it take, on average, for CXR results (for patients with DM) to be returned from the radiology department to the clinician (with the interpretation report)?

_____ weeks _____ days _____ hours

99. What is the format of the CXR?

- Film
- Electronic
- Other, please specify _____

Questionnaire #: _____

100. How are the results of the CXR returned to the DM clinic (from where the patient was first referred)?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or radiology _____
- Online system
- E-mail
- Other, please specify _____

101. When are patients with DM told the results of the CXR?

- Never
- Always
- Only when there is an abnormal reading
- Only if they ask for it
- If I remember
- Other, please specify _____
- Don't know

102. How are patients with DM told the results?

- In person during their next scheduled visit at the clinic
- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____
- Don't know

103. Have you ever had a compromised CXR (e.g. damaged, lost, mislabelled, incorrectly performed, etc.) for DM patients in the TANDEM project?

- No
- Yes

104. If yes, please indicate the top three reasons for compromised CXRs (for patients with DM):

1. _____

2. _____

3. _____

Questionnaire #: _____

105. Approximately how many **CXR interpretations** for patients with DM have you performed since the start of the TANDEM project?

_____ CXRs

106. Out of all the **CXRs that you interpreted** so far for TANDEM, approximately how many have been compromised?

107. In your opinion, do you think the CXR is a useful way of screening patients with DM for TB?

- No
- Yes

108. If no, please give reasons why you think so:

109. Are there any additional comments you would like to make about the CXR?

END TIME: _____ (please record the end time of the interview)

Test 3: Sputum collection

110. Is sputum collection routinely **done** at the DM clinic in your health facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

111. If no, why is it usually not done?

- Never prescribed for DM patients
- Trained staff unavailable (e.g. to instruct patients on proper sputum production techniques, etc.)
- Inadequate infrastructure (e.g. no designated room for producing sputum, etc.)
- Supplies unavailable (e.g. sputum pots, request forms, etc.)
- Other, please explain _____
- Don't know

112. If no, what is done in its place? _____

113. If sputum collection cannot be done at the clinic, how far is the closest space at which there is infrastructure for patients to produce a sputum sample?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

114. What kind of facility is it?

- Another part of this facility or hospital
- Private (lab or health centre)
- Another public health centre
- Other, specify _____

115. Approximately what proportion of patients who are required to provide a sputum sample are **NOT** able to do so at this facility due to the issues in 111 above?

_____ %

- Don't know

116. Is an electricity supply needed in order for patients to produce sputum?

- No
- Yes

Questionnaire #: _____

User friendliness of sputum collection:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
117. Guiding patients with DM to produce a sputum sample is technically undemanding	5	4	3	2	1
118. The amount of time needed for training in order for you to become proficient in facilitating sputum production is acceptable	5	4	3	2	1
119. The amount of time needed for you to perform the sputum collection with the DM patient is acceptable	5	4	3	2	1
120. Minimal supervision is required for you to help a patient with DM produce sputum	5	4	3	2	1
121. There is a direct reading to indicate when the sputum sample is adequate	5	4	3	2	1
122. There are quality control checks for the sputum sample	5	4	3	2	1

Training and test performance time:

123. Before the start of the TANDEM project did you already know how to perform sputum collection in patients with DM?

- No
 Yes

124. If yes, how long have you been performing sputum collection?

_____ years _____ months _____ weeks

125. How long did it take you to learn the method for sputum collection in patients with DM?

_____ days _____ hours _____ minutes

126. How many times did you practice to learn how to correctly guide patients to produce sputum?

127. From how many patients with DM, on average, do you collect sputum each week? _____

128. How long does it take you, on average, to collect sputum from a patient with DM?

_____ weeks _____ days _____ hours

Questionnaire #: _____

129. Are there sufficient trained personnel to perform sputum collection at your DM clinic if AFB smear and MODS were rolled out into routine practice for DM patients with suspected TB?

- No
- Yes

Quality control:

130. Is quality control done for the sputum collected?

- No
- Yes

131. If yes, how often do you do it?

Every _____ patients?

132. If yes, please describe the process.

133. How much time is spent on the quality control for the sputum collection in patients with DM?

_____ hours _____ minutes _____ seconds

Patient participation and other issues:

134. Approximately what proportion of patients with DM are willing or able to produce a sputum sample?

_____ %

135. What are the most common reasons for patient unwillingness or inability to produce a sputum sample?

Questionnaire #: _____

136. Are the facilities for sputum expectoration appropriate?

- No
- Yes

137. If no, what needs to be improved?

138. How long does it take, on average, for AFB smear results (for patients with DM) to be returned to the clinic from the laboratory?

_____ weeks _____ days _____ hours

139. How long does it take, on average, for culture results (for patients with DM) to be returned to the clinic from the laboratory?

_____ weeks _____ days _____ hours

140. How are the results of the AFB smear returned to the DM clinic (where the patient was first screened)?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or laboratory _____
- Online system
- E-mail
- Other, please specify _____

141. How are the results of the culture returned to the DM clinic (where the patient was first screened)?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or laboratory _____
- Online system
- E-mail
- Other, please specify _____

Questionnaire #: _____

142. When are patients with DM told the results of the AFB smear test?

- Never
- Always
- Only when there is an abnormal result
- Only if they ask for it
- If I remember
- Other, specify _____

142. When are patients with DM told the results of the culture test?

- Never
- Always
- Only when there is an abnormal result
- Only if they ask for it
- If I remember
- Other, specify _____

143. Approximately how long after the results are returned to the clinic from the laboratory are patients with DM told the AFB smear results?

_____ months _____ weeks _____ days _____ hours _____ minutes

144. Approximately how long after the results are returned to the clinic from the laboratory are patients with DM told the culture results?

_____ months _____ weeks _____ days _____ hours _____ minutes

145. How are patients with DM told the AFB smear results?

- In person during their next scheduled visit at the clinic
- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____

146. How are patients with DM told the culture results?

- In person during their next scheduled visit at the clinic
- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____

147. Has a sputum sample for TANDEM patients with DM ever been compromised (e.g. damaged, lost, mislabelled, equipment failure, etc.) in the clinic?

- No
- Yes

Questionnaire #: _____

148. If yes, please indicate the top three reasons for compromised sputum samples:

1. _____

2. _____

3. _____

149. Approximately how many sputum samples from patients with DM have you collected since the start of the TANDEM project?

150. Out of all the sputum samples that you have collected so far in patients with DM, how many have been compromised?

151. In your opinion, do you think the AFB smear is a useful way of diagnosing TB?

- No
 Yes

152. If no, please give reasons why you think so:

153. In your opinion, do you think culture is a useful way of diagnosing TB?

- No
 Yes

154. If no, please give reasons why you think so:

Questionnaire #: _____

155. Are there any additional comments you would like to make about sputum collection?

Test 4: Quantiferon test for latent TB infection (QFT) – blood draw

156. Is the QFT offered at this health facility (outside of the TANDEM project)?

- Yes
- No
- I don't know, go to #163

157. If yes, is the QFT routinely **prescribed** at this clinic?

- Yes
- No

158. If no, why is it usually not available or prescribed?

- Never part of the diagnosis algorithm for patients at this clinic
- Faulty equipment
- Trained staff unavailable
- Supplies unavailable
- Other, please explain _____

159. If no, what test is done in its place? _____

160. If a QFT is not routinely available at the facility, how far from this health facility is the closest facility at which patients would get one done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

161. What kind of facility is it?

- Private
- Another public health centre
- A TB clinic
- Other, specify _____

162. Approximately what proportion of patients are not able to get a prescribed QFT at this facility due to the issues in 158 above?

_____ %

163. Is an electricity supply needed to perform the QFT test?

- No
- Yes

Questionnaire #: _____

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
164. This QFT blood draw is technically undemanding for you	5	4	3	2	1
165. The amount of time needed for training in order for you to become proficient in performing the QFT blood draw is acceptable	5	4	3	2	1
166. The amount of time needed for you to perform the QFT blood draw is acceptable	5	4	3	2	1
167. Minimal supervision is required for you to perform the QFT blood draw	5	4	3	2	1
168. The IGRA blood draw has a direct result reading when completed	5	4	3	2	1
169. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

170. Before the start of the TANDEM project did you already know how to perform the QFT test blood draw in patients with DM?

- No
 Yes

171. If yes, how long have you been performing the blood draw for this test?

_____ years _____ months _____ weeks

172. How long did it take you to learn how to perform the blood draw for this test?

_____ days _____ hours _____ minutes

173. How many times did you practice the blood draw to learn the method? _____

174. How long does it take you, on average, to perform the blood draw for the QFT test?

_____ hours _____ minutes

175. How many individual tests, on average, do you perform each week? _____

176. How long does it take, on average for the QFT blood sample to be delivered to the laboratory for analysis?

_____ weeks _____ days _____ hours

Questionnaire #: _____

Quality control:

177. Is supervision of junior staff done for the QFT test blood draw?

- No
 Yes

178. If yes, how often do you do it?

_____ times per day/week/month (**select ONE**)?

179. If yes, please describe the process.

180. How long does this process take?

_____ hours _____ minutes _____ seconds

Patient participation and other issues:

181. Approximately what proportion of patients with DM are willing to have their blood taken for the QFT test?

_____ %

182. What are the most common reasons for patient unwillingness?

183. How long does it take, on average, for the results of the QFT test (for patients with DM) to be returned to the DM clinic from the laboratory?

_____ weeks _____ days _____ hours

Questionnaire #: _____

184. How are the results of the QFT returned to DM clinic (where the blood draw was done)?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or laboratory _____
- Online system
- E-mail
- Other, please specify _____

185. When are patients with DM told the results of the QFT test?

- Never
- Always
- Only when there is an abnormal reading
- Only if they ask for it
- If I remember
- Other, specify _____

186. Approximately how long after the results are returned to the clinic from the laboratory are patients with DM told the results?

_____ months _____ weeks _____ days _____ hours _____ minutes

187. How are patients with DM told the results?

- In person during their next scheduled visit at the clinic
- Over the phone
- Called and asked to visit the clinic for the results
- Other, specify _____

188. Has a QFT sample for TANDEM ever been compromised (e.g. damaged, lost, mislabelled, equipment failure, etc.) in the clinic or laboratory?

- No
- Yes

189. If yes, please indicate the top three reasons for compromised QFT samples:

1. _____

2. _____

3. _____

Questionnaire #: _____

190. How many QFT blood draws have you performed on patients with DM since the start of the TANDEM project?

191. Out of all the QFT blood draws that you have done so far on patients with DM, how many have been compromised?

192. In your opinion, do you think the QFT is a useful way of diagnosing TB in patients with DM?

- No
- Yes

193. If no, please give reasons why you think so:

194. Are there any additional comments you would like to make about the QFT test?

END TIME: _____ (please record the end time of the interview)



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests - Laboratory staff

INFORMATION SHEET:

The objective of this questionnaire is to determine the acceptability, accessibility and feasibility of performing the tuberculosis (TB) screening and diagnosis tests on patients with diabetes mellitus (DM) within the TANDEM project. It is hoped that these questions will determine how to successfully implement TB screening and diagnosis tests into routine DM services in the future.

All responses will be kept confidential and any publication will attribute responses to broad professional categories, not individuals. Only members of the TANDEM team will view the completed questionnaires.

If, after this interview has ended, you have any further questions or wish to withdraw your responses, please contact:

Ms. Yoko Laurence
(Health Economist)
Phone: +44 753 111 4253 (UK)
E-mail: yoko.laurence@lshtm.ac.uk
Websites: www.lshtm.ac.uk
www.tandem-fp7.eu

Questionnaire #: _____

Questionnaire #: _____



Concurrent Tuberculosis and Diabetes Mellitus: unraveling the causal link and improving care

**Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests
- Laboratory staff**

CONSENT FORM:

I, _____ (participant name), agree to participate in this operational feasibility study and complete this questionnaire.

I understand the purpose of this questionnaire.

All of my questions or concerns have been addressed.

PARTICIPANT NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

INTERVIEWER NAME: _____ (BLOCK LETTERS)

SIGNATURE: _____

DATE: _____

Questionnaire #: _____

Operational Feasibility Questionnaire: tuberculosis screening and diagnostic tests - Laboratory staff

START TIME: _____ (please record the start time of the interview)

INSTRUCTIONS (to be read to the interviewee)

I will read the questions to you and capture your response on this paper. Take as much time as you need to respond. Please answer the questions from your own perspective as it relates to your work in the TANDEM study.

Study identifier

1. Facility name _____
2. Date of interview |__|__|day|__|__|month|__|__|__|__|year
3. Questionnaire number |__|__|__|

Interviewee information

4. First name _____
5. Surname _____
6. Gender Male
 Female
7. Date of birth |__|__|day|__|__|month|__|__|__|__|year
8. Job title _____
9. Employer TANDEM
 Universidad Peruana Cayetano Heredia
 Health Centre
 Other, please specify _____

Questionnaire #: _____

Test 2: Chest X-ray (CXR) - RADIOGRAPHER

10. Is the CXR routinely **available** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

11. Is the CXR routinely **prescribed** at this facility for DM (outside of the TANDEM project)?

- Yes
- No
- I don't know

12. If no, why is it usually not available or prescribed?

- No equipment to do a CXR
- Faulty machinery
- Supplies unavailable
- Trained staff unavailable
- Other, please explain _____

13. If no, what test is done in its place? _____

14. If no, how far from this facility is the closest facility at which patients would get one done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

15. What kind of facility is it?

- Private
- Another public health centre
- Other, specify _____

16. Approximately what proportion of patients are not able to get a prescribed CXR at this facility due to the issues in 12 above?

_____ %

- Don't know

17. Is an electricity supply needed to perform a CXR?

- No
- Yes

Questionnaire #: _____

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
18. This test is technically undemanding for you to perform	5	4	3	2	1
19. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
20. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
21. Minimal supervision is required to perform this test	5	4	3	2	1
22. The CXR has a direct result reading	5	4	3	2	1
23. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

24. Before the start of the TANDEM project did you already know how to perform the CXR in patients with DM?

- No
 Yes

25. If yes, how long have you been performing this test?

_____ weeks _____ months _____ years

26. Approximately how long did it take you to learn the method for performing the CXR in patients with DM?

_____ days _____ hours _____ minutes

27. Approximately how many times did you practice the CXR to learn the method? _____

28. How long does it take you, on average, to complete the paperwork (registration, insurance, payment, etc.) for each CXR?

_____ minutes _____ hours

29. How many CXR are performed each week by you?

Questionnaire #: _____

30. How long, on average, does it take you to complete the CXR on one patient (from the time the patient arrives to when the CXR is completed)?

_____ minutes _____ hours

31. How long do the results take, on average, to be sent back to the health facility or given to the patient (from the time the patient has the CXR to when the film or the report is ready)?

_____ weeks _____ days _____ hours

32. Are there sufficient skilled personnel to perform CXRs if this test was rolled out into routine practice for DM patients with suspected TB?

- No
- Yes
- Don't know

Quality control and machinery:

33. Is internal quality control done for the CXR?

- No
- Yes

34. If yes, how often?

_____ times per day/week/month (**select ONE**)?

35. Do you perform the internal quality control?

- No
- Yes

36. If yes, please describe the process.

37. If no, who performs it?

- Another technician from this laboratory
- Supplier (external)
- Other person, please explain _____

Questionnaire #: _____

38. How much time is spent on the internal quality control of the x-ray machine?

_____ hours _____ minutes _____ seconds

39. Is the x-ray machine calibrated?

- No
- Yes

40. If yes, how often?

_____ times per day/week/month (**select ONE**)?

41. Do you perform the x-ray machine calibration?

- No
- Yes

42. If yes, please describe the process.

43. If no, who performs it?

- Another technician from this laboratory
- Supplier
- Other person, please explain _____

44. How much time is spent on the calibration of the x-ray machine?

_____ hours _____ minutes _____ seconds

45. How often has the x-ray machine been maintained?

- Never
- _____ times a week/month/ year (**select ONE time division**)
- I don't know

46. If never, how often should the x-ray machine be maintained?

_____ times a week/month/ year (**select ONE time division**)

Questionnaire #: _____

47. How often does the x-ray machine break down?

- Never
- _____ times a week/month/ year (select ONE time division)
- I don't know

48. On average, how long is the machine usually not working, when it breaks down?

_____ months _____ weeks _____ days _____ hours _____ minutes

- I don't know
- Not applicable

Logistics and other issues:

49. Approximately what proportion of patients with DM have difficulty completing a CXR?

_____ %

- Don't know

50. What are some of the reasons for not completing a CXR?

51. How long does it usually take to obtain the CXR film/electronic image?

_____ weeks _____ days

52. How are the results of the CXR returned to the DM clinic/patient?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or radiology _____
- Online system
- E-mail
- Patient collects paper results and takes to DM clinic
- Other, please specify _____

Questionnaire #: _____

53. When are patients told the results of the CXR?

- Never
- Always
- Only if there is an abnormal result
- Only if they ask for it
- Don't know
- Other, please specify _____

54. How are patients told the results?

- Over the phone
- Called and asked to visit the clinic
- On their next scheduled visit
- Don't know
- Other, please specify _____

55. Has a CXR for a patient with DM ever been compromised (e.g. damaged, lost, mislabelled) in your department?

- No
- Yes

56. If yes, please indicate the top three reasons for compromised CXRs:

1. _____

2. _____

3. _____

57. How many CXRs have you performed since the start of the TANDEM project?

58. Out of all the CXRs that you performed so far, how many have been compromised?

Questionnaire #: _____

59. In your opinion, do you think the CXR is a useful way of screening patients with DM for TB?

- No
- Yes

60. If no, please give reasons why you think so:

61. Are there any additional comments you would like to make about the CXR?

END TIME: _____ (please record the end time of the interview)

Questionnaire #: _____

Test 3: Sputum smear – acid fast bacilli (AFB) test

62. Is the AFB test routinely **available** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

63. Is the AFB test routinely **prescribed** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

64. If no, why is it usually not available?

- Faulty machinery
- Trained staff unavailable
- Reagents unavailable
- Other supplies unavailable
- Other, please explain _____

65. If no, what test is done in its place? _____

66. If an AFB test is not available at this facility, how far from this facility is the closest facility at which patients would get the test done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

67. What kind of facility is it?

- Private
- Another public health centre/laboratory
- Other, specify _____

68. Approximately what proportion of patients are not able to get a prescribed AFB at this facility due to the issues in 62 above?

_____ %

- Don't know

69. Is an electricity supply needed to perform an AFB test? No Yes

Questionnaire #: _____

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
70. This test is technically undemanding for you	5	4	3	2	1
71. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
72. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
73. Minimal supervision is required to perform this test	5	4	3	2	1
74. The analysis for this test has a direct result reading	5	4	3	2	1
75. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

76. Before the start of the TANDEM project did you already know how to perform the AFB?

- No
 Yes

77. If yes, how long have you been performing this test?

_____ weeks _____ months _____ years

78. Approximately how long did it take to learn the method for performing this test?

_____ weeks _____ days _____ hours

79. Approximately how many times did you practice this test to learn the method? _____

80. How long does it take you, on average, to complete the paperwork (registration, insurance, payment, etc.) for each AFB?

_____ minutes _____ hours

81. Is analysis of the AFB test done in batches?

- No
 Yes

Questionnaire #: _____

82. If no, how long does it take you, on average, to complete the AFB analysis for one patient (from the time the sample arrives to when the AFB test is completed)?

_____ minutes _____ hours

83. If yes, how many AFB samples do you analyse in each batch?

84. How long, on average, does it take you to complete the analysis of one batch?

_____ hours _____ minutes

85. How many batches or individual tests, on average, do you run each week? **(Select ONE below and state average number)**

- Batches _____
 Individual tests _____

86. How long do the results take, on average, to be given to the patient (from the time the AFB analysis is complete to when the report is given to the patient or returned to the clinician)?

_____ weeks _____ days _____ hours

87. Are there sufficient skilled personnel to perform AFBs if this test was rolled out into routine practice for DM patients with suspected TB?

- No
 Yes
 Don't know

Quality control and machinery:

88. Is internal quality control done for the AFB test?

- No
 Yes
 Don't know

Questionnaire #: _____

89. If yes, how often?

_____ times per day/week/month (**select ONE**)?

90. Do you perform the internal quality control?

- No
- Yes

91. If yes, please describe the process.

92. If no, who performs it?

- Another technician from this laboratory
- Supplier (external)
- Don't know
- Other person, please explain _____

93. How much time is spent on the internal quality control for the AFB test?

_____ hours _____ minutes _____ seconds

94. Approximately what proportion of the samples are of good quality?

_____ %

- Don't know

95. What are the most common reasons for poor quality samples?

Questionnaire #: _____

96. Approximately what proportion of the samples are the correct quantity (volume)?

_____ %

Don't know

97. What are the most common reasons for the incorrect quantity?

98. Is the equipment used for the AFB test calibrated?

No
 Yes

99. If yes, how often?

_____ times per day/week/month (**select ONE**)?

101. Do you perform the calibration for the AFB test?

No
 Yes
 Not applicable

100. If yes, please describe the process.

102. If no, who performs it?

Another technician from this laboratory
 Supplier
 Other person, please explain _____

Questionnaire #: _____

103. How much time is spent on calibration for the AFB test?

_____ hours _____ minutes _____ seconds

104. How often has the equipment for the AFB been maintained?

- Never
 _____ times a week/month/ year (**select ONE time division**)
 I don't know

105. If never, how often should the AFB equipment be maintained?

_____ times a week/month/ year (**select ONE time division**)

106. How often does the equipment for the AFB test break down?

- Never
 _____ times a week/month/ year (**select ONE time division**)
 I don't know

107. On average, how long is the equipment usually not working when it breaks down?

_____ months _____ weeks _____ days _____ hours _____ minutes

- I don't know
 Not applicable

Logistics and other issues:

108. How long after the patient produces a sputum sample is the sample delivered to your laboratory?

_____ hours _____ weeks _____ days

- Don't know

109. How long does it usually take to obtain results for the AFB test?

_____ weeks _____ days

Questionnaire #: _____

110. How are the results of the AFB returned to the DM clinic?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or laboratory _____
- Online system
- E-mail
- Patient collects paper results and takes to DM clinic
- Other, please specify _____

111. When are patients told the results of the AFB test?

- Never
- Always
- Only if there is a positive result
- If they ask for it
- If I remember
- Don't know
- Other, please specify _____

112. How are patients told the results?

- Over the Phone
- Called and asked to visit the clinic for result
- On their next scheduled visit
- Don't know
- Other, please specify _____

113. Has there ever been a compromised (e.g. damaged, lost or mislabelled) AFB sample for the TANDEM project?

- No
- Yes
- Don't know

114. If yes, please indicate the top three reasons for compromised AFB samples:

1. _____

2. _____

3. _____

115. How many AFB tests have you performed since the start of the TANDEM project?

Questionnaire #: _____

116. Out of all the AFB tests that you have done so far, how many have been compromised?

117. In your opinion, do you think the AFB test is a useful way of diagnosing TB in persons with DM?

- No
- Yes

118. If no, please give reasons why you think so:

119. Are there any additional comments you would like to make about the AFB test?

Questionnaire #: _____

Test 4: Sputum culture

120. Is the culture test routinely **available** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

121. Is the culture test routinely **prescribed** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

122. If no, why is it not available or prescribed?

- Faulty machinery
- Trained staff unavailable
- Equipment unavailable
- Reagents unavailable
- Other supplies unavailable
- Other, please explain _____

123. If no, what test is done in its place? _____

124. If a culture test is not available at the facility, how far from this facility is the closest facility at which patients would get the test done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

125. What kind of facility is it?

- Private
- Another public health centre/laboratory
- Other, specify _____

126. Approximately what proportion of patients are not able to get a prescribed culture test at this facility due to the issues in 122 above?

_____ %

- Don't know

127. Is an electricity supply needed to perform the culture test?

- No
- Yes

Questionnaire #: _____

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
128. This test is technically undemanding for you	5	4	3	2	1
129. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
130. The amount of time needed for to perform this test is acceptable	5	4	3	2	1
131. Minimal supervision is required for you to perform this test	5	4	3	2	1
132. This test has a direct result reading	5	4	3	2	1
133. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

134. Before the start of the TANDEM project did you already know how to perform the culture test?

- No
 Yes

135. If yes, how long have you been performing this test?

_____ years _____ months _____ weeks

136. Approximately how long did it take you to learn the method for performing this test?

_____ days _____ hours _____ minutes

137. Approximately how many times did you practice this test to learn the method? _____

138. Is the analysis of the culture done in batches?

- No
 Yes

139. If no, how long does it take you, on average, to complete the culture analysis for one patient (from the time the sample arrives to when the culture test is completed)?

_____ hours _____ minutes

140. If yes, how many culture samples do you analyse in each batch?

Questionnaire #: _____

141. How long, on average, does it take you to complete the analysis of one batch?

_____ hours _____ minutes

142. How many batches or individual tests, on average, do you run each week? **(Select ONE below and state average number)**

- Batches _____
- Individual tests _____

143. How long does it take you, on average, to complete the paperwork (registration, insurance, payment, etc.) for each culture test?

_____ hours _____ minutes

144. How long do the results take, on average, to be given to the patient (from the time the culture analysis is complete to when the report is given to the patient or returned to the clinician)?

_____ weeks _____ days _____ hours

145. Are there sufficient skilled personnel to perform the culture test if it was rolled out into routine practice for DM patients with suspected TB?

- No
- Yes
- Don't know

Quality control and machinery:

146. Is internal quality control done for the culture test?

- No
- Yes

147. If yes, how often?

_____ times per day/week/month (**select ONE**)?

149. Do you perform the internal quality control?

- No
- Yes

148. If yes, please describe the process.

Questionnaire #: _____

150. If no, who performs it?

- Another technician from this department
- Supplier (external)
- Other person, please explain _____

151. Approximately how much time is spent on the internal quality control of the culture test?

_____ hours _____ minutes _____ seconds

152. Approximately what proportion of the samples are of good quality?

_____ %

- Don't know

153. What are the most common reasons for poor quality samples?

154. Approximately what proportion of the samples are the correct quantity (volume)?

_____ %

- Don't know

155. What are the most common reasons for the incorrect quantity?

Questionnaire #: _____

156. Is the equipment used for the culture test calibrated?

- No
- Yes
- Don't know

157. If yes, how often?

_____ times per day/week/month (**select ONE**)?

158. If yes, please describe the process.

159. Do you perform the calibration of the equipment used for the culture test?

- No
- Yes

160. If no, who performs it?

- Another technician in this department
- Supplier
- Other person, please explain _____

161. How much time is spent on the calibration of the equipment used for the culture test?

_____ hours _____ minutes _____ seconds

- Don't know

162. How often has the equipment used for the culture test been maintained?

- Never
- _____ times a week/month/ year (**select ONE time division**)
- I don't know

Questionnaire #: _____

163. If never, how often should the equipment used for the culture test be maintained?

_____ times a week/month/ year **(select ONE time division)**

164. How often does the equipment used for the culture test break down?

Never

_____ times a week/month/ year **(select ONE time division)**

I don't know

165. On average, how long is the equipment usually not working, when it breaks down?

_____ months _____ weeks _____ days _____ hours _____ minutes

I don't know

Not applicable

Logistics and other issues:

166. How long after the patient produces a sputum sample is the sample delivered to your laboratory?

_____ hours _____ weeks _____ days

Don't know

167. How long does it usually take to obtain results for the culture test?

_____ weeks _____ days

168. How are the results of the culture test returned to the DM clinic?

Paper results – by post

Paper results – by staff, specify if staff from clinic or laboratory _____

Online system

E-mail

Patient collects paper results and takes to DM clinic

Other, please specify _____

169. When are patients told the results of the culture test?

Never

Always

Only if there is a positive result

If they ask for it

If I remember

Don't know

Other, please specify _____

Questionnaire #: _____

170. How are patients told the results?

- Over the Phone
- Called and asked to visit the clinic for result
- On their next scheduled visit
- Don't know
- Other, please specify _____

171. Has there ever been a compromised (e.g. damaged, lost or mislabelled) culture sample for the TANDEM project?

- No
- Yes

172. If yes, please indicate the top three reasons for compromised culture samples:

1. _____

2. _____

3. _____

173. How many culture tests have you performed since the start of the TANDEM project?

174. Out of all the culture tests that you have done so far, how many have been contaminated?

175. Out of all the culture tests that you have done so far, how many have been compromised (not including contamination)?

176. In your opinion, do you think the culture test is a useful way of diagnosing TB in persons with DM?

- No
- Yes

Questionnaire #: _____

177. If no, explain why.

178. Are there any additional comments you would like to make about the culture test?

Questionnaire #: _____

Test 5: QuantiFERON (QFT) or Interferon gamma release assay (IGRA)

179. Is the QFT **available** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

180. Is the QFT **prescribed** at this facility (outside of the TANDEM project)?

- Yes
- No
- I don't know

181. If no, why is it usually not available?

- Faulty machinery
- Trained staff unavailable
- QFT kit unavailable
- Supplies unavailable
- Not part of the hospital algorithm for TB diagnosis
- Other, please explain _____

182. If no, what test is done in its place? _____

183. If an QFT test is not available at the facility, how far from this facility is the closest facility at which patients would get one done?

_____ km OR _____ minutes by car/bus/foot (**select ONE**)

184. What kind of facility is it?

- Private
- Another public health centre/laboratory
- Other, specify _____

185. Approximately what proportion of patients are not able to get a prescribed QFT at this due to the issues in 181 above?

- Don't know

186. Is an electricity supply needed to perform the QFT test? No Yes

Questionnaire #: _____

User friendliness:

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
187. This test is technically undemanding for you	5	4	3	2	1
188. The amount of time needed for training in order for you to become proficient in this test is acceptable	5	4	3	2	1
189. The amount of time needed for you to perform this test is acceptable	5	4	3	2	1
190. Minimal supervision is required to perform this test	5	4	3	2	1
191. The analysis for this test has a direct result reading	5	4	3	2	1
192. There are simple quality control checks	5	4	3	2	1

Training and test performance time:

193. Before the start of the TANDEM project did you already know how to perform the QFT test?

- No
 Yes

194. If yes, how long have you been performing this test?

_____ weeks _____ months _____ years

195. Approximately how long did it take to learn the method for performing this test?

_____ days _____ hours _____ minutes

196. Approximately how many times did you practice this test to learn the method? _____

197. How long does it take you, on average, to complete the paperwork (registration, insurance, payment, etc.) for each QFT?

_____ minutes _____ hours

198. Is analysis of the QFT test done in batches?

- No
 Yes

Questionnaire #: _____

199. If no, how long does it take you, on average, to complete the QFT analysis for one patient (from the time the sample arrives to when the QFT test is completed)?

_____ minutes _____ hours

200. If yes, how many QFT samples do you analyse in each batch?

201. How long, on average, does it take you to complete the analysis of one batch?

_____ hours _____ minutes

202. How many batches or individual tests, on average, do you run each week? (**Select ONE below and state average number**)

- Batches _____
 Individual tests _____

203. How long do the results take, on average, to be given to the patient (from the time the QFT analysis has been performed to when the report is given to the patient or returned to the clinician)?

_____ weeks _____ days _____ hours

204. Are there sufficient skilled personnel to perform the QFT test if it was rolled out into routine practice for DM patients with suspected TB?

- No
 Yes
 Don't know

Quality control and machinery:

205. Is internal quality control done for the QFT test?

- No
 Yes

206. If yes, how often?

_____ times per day/week/month (**select ONE**)?

Questionnaire #: _____

207. Do you perform the internal quality control?

- No
- Yes

208. If yes, please describe the process.

209. If no, who performs it?

- Another technician from this laboratory
- Supplier (external)
- Other person, please explain _____

210. Approximately how much time is spent on the internal quality control for the QFT test?

_____ hours _____ minutes _____ seconds

211. Approximately what proportion of the samples are of good quality?

_____ %

- Don't know

212. What are the most common reasons for poor quality samples?

Questionnaire #: _____

213. Approximately what proportion of the samples are the correct quantity (volume)?

_____ %

Don't know

214. What are the most common reasons for samples having the incorrect quantity (volume)?

215. Is the equipment used for the QFT test calibrated?

No
 Yes

216. If yes, how often?

_____ times per day/week/month (**select ONE**)?

217. Do you perform the calibration for the QFT test?

No
 Yes

218. If yes, please describe the process.

Questionnaire #: _____

219. If no, who performs it?

- Another technician from this laboratory
- Technician from another laboratory
- Supplier
- Other person, please explain _____

220. Approximately how much time is spent on the calibration for the equipment for the QFT test?

_____ hours _____ minutes _____ seconds

- I don't know

221. How often has the equipment for the QFT been maintained?

- Never
- _____ times a week/month/ year (**select ONE time division**)
- I don't know

222. If never, how often should the equipment used to perform the QFT test be maintained?

_____ times a week/month/ year (**select ONE time division**)

- Not applicable

223. How often does the equipment used for the QFT test break down?

- Never
- _____ times a week/month/ year (**select ONE time division**)
- I don't know

224. On average, how long is the equipment usually not working when it breaks down?

_____ months _____ weeks _____ days _____ hours _____ minutes

- I don't know
- Not applicable

Logistics and other issues:

225. How long after the blood is drawn is the sample delivered to your laboratory?

_____ hours _____ weeks _____ days

- Don't know

226. How long does it usually take to obtain results for the QFT test?

_____ weeks _____ days _____ hours

Questionnaire #: _____

227. How are the results of the QFT returned to the DM clinic?

- Paper results – by post
- Paper results – by staff, specify if staff from clinic or laboratory _____
- Online system
- E-mail
- Patient collects paper results and takes to DM clinic
- Other, please specify _____

228. When are patients told the results of the QFT test?

- Never
- Always
- Only if there is a positive result
- Don't know
- Other, please specify _____

229. How are patients told the results?

- At next scheduled follow-up visit
- Phone
- Asked to visit the clinic
- Don't know
- Other, please specify _____

230. Has a QFT test ever been compromised (e.g. damaged, lost, mislabelled, indeterminate) in your laboratory?

- No
- Yes

231. If yes, please indicate the top three reasons for compromised QFT tests:

1. _____

2. _____

3. _____

232. How many QFT tests have you performed since the start of the TANDEM project?

Questionnaire #: _____

233. Out of all the QFT tests that you performed so far, how many have been compromised?

234. In your opinion, do you think the QFT test is a useful way of diagnosing TB in persons with DM?

- No
- Yes

235. If no, please give reasons why you think so:

236. Are there any additional comments you would like to make about the QFT test?

END TIME: _____ (please record the end time of the interview)

Appendix Z: EuroQol's EQ-5D-5L questionnaire - English version



Health Questionnaire

English version for the UK

SAMPLE

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

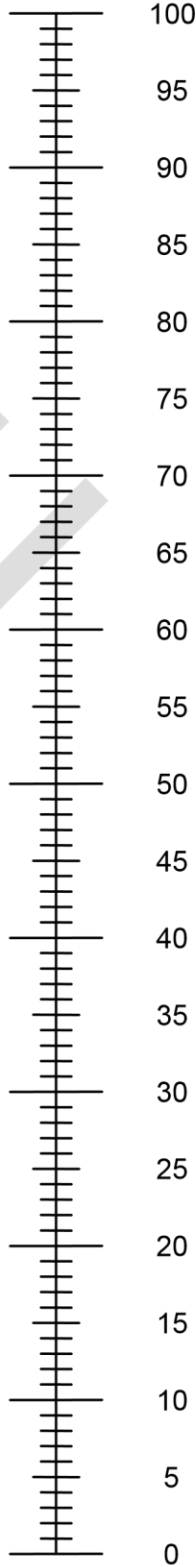
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health you can imagine



The worst health you can imagine

Appendix AA: Patient costs questionnaire for Indonesia

Costs of travel to health facility today:

1. How long did it take to get here from your home (*include the journey time and any waiting for transport*)

Minutes |_|_|
Hours |_|_|
Unknown |_|_|_|

2. What kind of transport did you use to reach this health facility?

Walking (go to Q11)
 Public transport (go to Q9)
 Taxi (go to Q9)
 Self-driven car (go to Q10)

3. If you paid for transportation to reach the facility, how much did you pay?

IDR/PEN/RON _____

4. If you used a private car to get here, please estimate the distance travelled, one way. (*if unable to estimate indicate residence*)

Kilometres |_|_|
Residence _____

Costs incurred at the health facility today:

5. Did you pay for the care you received today?

No
 Yes
 Not sure

6. If yes, how much did you pay for the care given?

	User fees - medical professional	User fees - health facility	Drugs	Tests	Physical rehabilitation services	Other payments (specify)
Payment made: <i>0 - no payment</i> <i>999 - don't know</i> <i>888 - NA</i>						
Outstanding payments:						

7. Where did the money come from to pay these expenses? (multiple responses allowed)
- Cutting down on other expenses
 - Using savings
 - Borrowing
 - Selling assets
 - Asking for donations
 - Other, specify - _____

Insurance coverage:

8. Will you receive insurance reimbursement for any of the payments you made today?
- No
 - Yes
 - Not sure
9. If yes, how much do you expect to be reimbursed?
- IDR/PEN/RON _____
- Not sure

Opportunity costs:

10. How much time did you spend at the health facility today? _____hours _____minutes
11. If you weren't here today, what would you be doing? (Multiple responses allowed)
- Unpaid work at home
 - Paid work
 - Other (specify) _____
12. Did you have to make alternative arrangements for childcare or caring for other dependants in order to come here today?
- No (End of questionnaire)
 - Yes (Go to Q19)
 - Refuse to answer
13. Who is taking care of your dependants/child(ren) while you are here?
- Other family member or friend
 - Paid childcare
 - Refuse to answer
14. How much did you pay for that care today?
- IDR/PEN/RON _____

Appendix BB: Data collection form for unscheduled visits by patients with TB-DM in TANDEM

Study ID	_____
[Revise wording?] Since the last time we saw you for a study visit, have you had any unscheduled visits to a health care provider?	Yes No Don't know
How many visits did you make?	_____
Date of visit 1 (to best estimation)?	_____
How accurate do you think that date is?	To the day 1-3 days Within a week Within 2 weeks Within a month
Who saw you?	Tandem Fieldworker/ Nurse Tandem Doctor Doctor Nurse Other
If other, please specify	_____
What was the reason for the visit?	Side effects from drugs Not responding to treatment Hypoglycaemic event Other
If other, please specify	_____
Outcome of the visit	No change in medication Change in medication Admission Other

If other, please specify	_____
Did you pay to see the doctor or nurse on that unscheduled visit?	No Yes
If yes, how much?	_____ IDR/PEN/ROM
Did you pay for any tests, medication or anything else prescribed at that visit?	No Yes
If yes, how much?	_____ IDR/PEN/ROM
If yes, include details on what was purchased.	_____
How much time was spent at the visit, including travel time?	_____ hours _____ minutes
What type of transportation did you take to go to that visit?	Walking Public transport Taxi Self-driven car Motor bike/scooter Other, please specify _____
If public transport or taxi, how much did it cost? If self-driven car or motor bike/scooter, what is distance from home to health facility (or where do you live)?	_____ IDR/PEN/ROM _____
Comments	_____
Date of visit 2 (to best estimation)?	_____
How accurate do you think that date is?	To the day 1-3 days Within a week Within 2 weeks

	Within a month
Who saw you?	Tandem Fieldworker/ Nurse Tandem Doctor Doctor Nurse Other
If other, please specify	_____
What was the reason for the visit?	Side effects from Not responding to treatment Hypoglycaemic event Other
If other, please specify	_____
Outcome of the visit	No change in medication Change in medication Admission Other
If other, please specify	_____
Did you pay to see the doctor or nurse on that unscheduled visit?	No Yes
If yes, how much?	_____ IDR/PEN/ROM
Did you pay for any tests, medication or anything else prescribed at that visit?	No Yes
If yes, how much?	_____ IDR/PEN/ROM
If yes, include details on what was purchased.	_____
How much time was spent at the visit, including travel time?	_____ hours _____ minutes
What type of transportation did you take to go to that visit?	Walking Public transport Taxi Self-driven car

	Motor bike/scooter Other, please specify _____
If public transport or taxi, how much did it cost? If self-driven car or motor bike/scooter, what is distance from home to health facility (or where do you live)?	_____ IDR/PEN/ROM _____
Comments	_____
Date of visit 3 (to best estimation)?	_____
How accurate do you think that date is?	To the day 1-3 days Within a week Within 2 weeks Within a month
Who saw you?	Tandem Fieldworker/ Nurse Tandem Doctor Doctor Nurse Other
If other, please specify	_____
What was the reason for the visit?	Side effects from drugs Not responding to treatment Hypoglycaemic event Other
If other, please specify	_____
Outcome of the visit	No change in medication Change in medication Admission Other
If other, please specify	_____
Did you pay to see the doctor or nurse on that unscheduled visit?	No Yes
If yes, how much?	_____ IDR/PEN/ROM

<p>Did you pay for any tests, medication or anything else prescribed at that visit?</p>	<p>No Yes</p>
<p>If yes, how much?</p>	<p>_____IDR/PEN/ROM</p>
<p>If yes, include details on what was purchased.</p>	<p>_____</p>
<p>How much time was spent at the visit, including travel time?</p>	<p>_____hours _____minutes</p>
<p>What type of transportation did you take to go to that visit?</p>	<p>Walking Public transport Taxi Self-driven car Motor bike/scooter Other, please specify _____</p>
<p>If public transport or taxi, how much did it cost? If self-driven car or motor bike/scooter, what is distance from home to health facility (or where do you live)?</p>	<p>_____IDR/PEN/ROM _____</p>
<p>Comments</p>	<p>_____</p>