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Cost Effectiveness of a Line Probe Assay Test Compared to Standard Drug Susceptibility Testing for the Detection of Multi-Drug Resistant Tuberculosis in a South African HIV Population

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Cost Effectiveness of a Line Probe Assay Test Compared to Standard Drug Susceptibility Testing for the Detection of Multi-Drug Resistant Tuberculosis in a South African HIV Population

by

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For My Parents
My First and Greatest Teachers

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Cost Effectiveness of a Line Probe Assay Test Compared to Standard Drug Susceptibility Testing for the Detection of Multi-Drug Resistant Tuberculosis in a South African HIV Population

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Supervisor: Karen Rascati

Over the last few years the World Health Organization (WHO) has endorsed several tests for the rapid detection of multidrug-resistant tuberculosis (MDR-TB) in resource-poor settings. The objective of this study was to compare the cost-effectiveness of a line probe assay test (less than one week for results) to conventional (bacterial culture) drug susceptibility testing (one month for results) for the detection of MDR-TB in an HIV-positive South African population by estimating the incremental cost-effectiveness ratio (ICER) per disability-adjusted life-year (DALY) averted. Costs of testing, drug treatment, hospitalization, as well as estimates for mortality, treatment success, and failure rates were obtained from literature sources, the South African Department of Health, the WHO, the Foundation of Innovative Diagnostics (FIND), and expert opinion. The willingness-to-pay threshold for a DALY averted was pre-set at 3 times the 2009 GDP per capita (about $17,400) for South Africa.

In the base-case scenario for a prevalence of 30% of MDR-TB among HIV-positive patients, the average cost per person for the line probe assay testing strategy was

$3,539/0.458 DALY averted and the conventional testing approach was $3,011/0.430 DALY averted. The base-line ICER was about $18,800 per DALY averted – about $1,400 above the pre-set threshold. In sensitivity analyses, the model was robust to changes in prevalence (± 50%); costs (± 10%), and probabilities of death, success and failure (± 20%). However, when the treatment success rate for the line probe assay test was increased to 60% (one of the targets set by WHO in TB treatment) the ICER was below the willingness-to-pay level (i.e., cost-effective). The probabilistic sensitivity analysis showed there is a 70% chance that the additional cost of the line probe assay, compared with conventional testing, was less than $30,000 per DALY averted. However, the model may have underestimated the benefits of the line probe assay because it did not account for a decrease in the transmission of the disease due to earlier treatment nor did it measure any benefits more than a year after testing.

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ABBREVIATIONS

Antiretroviral	ARV
Bacille Calmette-Gue`rin	BCG
Directly observed therapy, short course	DOTS
Drug resistant tuberculosis	DR-TB
Drug susceptibility testing	DST
Disability-adjusted life-year	DALY
Extensively drug resistant tuberculosis	XDR-TB
False Negative	FN
False Positive	FP
Foundation for Innovative New Diagnostics	FIND
Food and Drug Administration	FDA
Human immunodeficiency virus	HIV
Incremental cost-effectiveness ratio	ICER
Incremental net benefit	INB
International Classification of Diseases	ICD-10
Latent tuberculosis infections	LTBI
Life year gained	LYG
Millennium Development Goals	MDGs
Multi-drug resistant tuberculosis	MDR-TB
Mycobacterium Tuberculosis	M. Tuberculosis
New diagnostics working group	NDWG
Quality-adjusted life-years	QALY

Quality Assessment of Studies of Diagnostic Accuracy	QUADAS
STAndards for the Reporting of Diagnostic Accuracy Studies	STARD
True Negative	TN
True Positive	TP
Tuberculosis	TB
Joint United Nations Programme on HIV/AIDS	UNAIDS
World Health Organization	WHO

CHAPTER 1

Tuberculosis,

Multi-Drug Resistant Tuberculosis,

and

Extensively Drug Resistant Tuberculosis

In Chapter 1, a brief background on pulmonary tuberculosis disease and tuberculosis drug resistance is provided. Definitions of multi-drug resistant and extensively drug resistant tuberculosis are provided. Additionally, methods used to diagnose and treat pulmonary tuberculosis are outlined. At the end of the chapter, information on the World Health Organization's Millennium Goals and STOP TB partnership are presented.

1.1 BACKGROUND

In 1882, Robert Koch, a German scientist, isolated the *Mycobactreium Tuberculosis (M. Tuberculosis),* a bacillus which causes the infectious disease known as Tuberculosis (TB).[1] The World Health Organization (WHO) defines tuberculosis as "an airborne infectious disease that is preventable and curable," if precautions and treatment to reduce spread of the disease are strictly adhered to.[2] However, drug resistance poses a major challenge to the management of this disease, ultimately resulting in poor patient outcomes, including increased morbidity and mortality levels, and development and

spread of resistant strains of the disease. Two main reasons cited for treatment failure and resistance are: (1) use of inadequate or incorrect pharmacological agents; and (2) non-adherence to therapy.[1] Patients can become resistant to treatment by acquiring resistance or through primary resistance where the infection occurs through a drug resistant strain of the bacteria.[3] Resistance to therapy was apparent even in the 1940s when drugs to treat tuberculosis were only being discovered.[1] Migliori and Bishai report that in 1948, the British Medical Research Council found that many patients treated for TB with streptomycin monotherapy developed resistance to the treatment.[1] Over the decades, resistance to TB treatment has been amplified, resulting in the emergence of multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB).

1.2 MULTI-DRUG RESISTANT AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS

Multi-drug resistant tuberculosis (MDR-TB) is defined as "mycobacterium tuberculosis resistant to at least rifampicin and isoniazid." Extensively drug resistant tuberculosis (XDR-TB) includes resistance to rifampicin and isoniazid but also includes "resistance to any fluoroquinolone and to at least one of the three following injectable drugs used in anti-tuberculosis treatment: capreomycin, kanamycin and amikacin." [4]

1.3 EPIDEMIOLOGY OF MDR-TB AND XDR-TB

The WHO estimated that almost 500 000 new cases of MDR-TB occur each year because of improper management and treatment. Many of these new cases occur in what is now referred to as the 27 high-burden MDR-TB and XDR-TB countries, "Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, the Democratic Republic of Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, the Republic of Moldova, Myanmar, Nigeria, the Philippines, the Russian Federation, Pakistan, South Africa, Tajikistan, Ukraine, Uzbekistan and Vietnam."[5-7] See Table 1.1.

Table 1.1. High Burden MDR-TB and XDR-TB Countries

• Armenia • Azerbaijan • Bangladesh • Belarus • Bulgaria • China • The Democratic Republic of Congo • Estonia • Ethiopia • Georgia • India • Indonesia • Kazakhstan • Kyrgyzstan	• Latvia • Lithuania • The Republic of Moldova • Myanmar • Nigeria • The Philippines • The Russian Federation • Pakistan • South Africa • Tajikistan • Ukraine • Uzbekistan • Vietnam

The five countries with the highest number of existing TB cases are India, China, Indonesia, Nigeria and South Africa - with approximately 2.0 million, 1.3 million, 530

000, 460 000, and 460 000 cases, respectively. [8] As part of the Global Plan to reduce TB, the WHO has set an MDR-TB and XDR-TB treatment target of 1.4 million cases by the year 2015. The costs associated with this diagnosis and treatment initiative were estimated to be $16.9 million. Costs for all cases are expected to rise from $700 million in 2009 to $4.4 billion in 2015.[8]

Human Immunodeficiency Virus (HIV) co-infection further complicates the TB crisis. The World Health Organization reported in 2007 that there were 9.7 million incident cases of TB worldwide, and approximately 1.37 million (14%) of these individuals were living with HIV. [6] HIV/AIDS and TB continue to remain in the top 10 leading causes of death in low- and middle-income countries.[9] Even in the United States, XDR-TB is a deadly disease. From 83 XDR-TB cases reported from 1993 to 2007; 26 (35%) cases died during treatment.[10] In California between 1993 and 2006; majority of cases of XDR-TB were international, some of whom who had arrived within the Unites States within the last 6 months.[11] Similar results were found in Canada where the majority of drug resistant cases of TB can be linked to recent immigrants.[12]

The World Health Organization has identified South Africa (Africa), Russia (Eastern Europe) and India (Asia) as areas of particular interest because each of these regions poses a unique epidemiological challenge. Africa is currently faced with a serious HIV crisis. It is well documented that TB is one of the main opportunistic infections associated with HIV, resulting in a high mortality in HIV positive patients co-infected with TB.[13] Eastern Europe has a high TB but low HIV burden, and India reports high absolute numbers of TB and HIV. In the Russian Federation, substance abuse has been

associated with non-adherence to TB medication and default from treatment programs leading to MDR-TB; research has shown that treatment failure is higher in extensively resistant forms of the disease.[14-16] Poverty, social issues, over-crowded prisons, and political structures have also contributed to the growing crisis in Russia.[17-19] In the Russian Oblast (South western region of the country), introducing treatment plans and social support systems for the poor helped improve incidence, prevalence and mortality of TB.[20]

There are published research reports of HIV and TB in India indicating over 2 million HIV/AIDS cases in India, coupled with an estimated 1.8 million new cases of TB per annum.[21] If these TB patients are left undiagnosed and untreated in India the MDR-TB rates in the region would also worsen.[22-24] A study in Gujarat, India showed that while MDR-TB prevalence among new TB patients may be low, re-treated TB patients are more likely to develop resistance to medication.[25] If TB is left undetected, it will cause worsening health in the patient, can result in death for the patient, and will spread through the community, which in turn results in increasing costs of health care at the patient and community level. Reports show that in Sub-Saharan Africa mortality is high in the first year of diagnosis of TB because of the late stage at which the disease is diagnosed.[26] Managing and containing TB, particularly the drug resistant type, requires a multifaceted approach. Prompt diagnosis, appropriate and effective initiation and continuation of treatment, and patient follow-up are essential. Of primary concern is the correct and prompt diagnosis of multi-drug resistant tuberculosis.

1.4 DIAGNOSIS OF TUBERCULOSIS

Reaching a diagnosis for pulmonary TB consists of several steps. First, tests to determine if the tuberculosis bacteria are present must be conducted. Once confirmation of infection is made, other tests, including chest x-rays and sputum testing, must be performed to determine if the patient has a latent or active form of the disease. Finally, advanced sputum testings are conducted to determine if resistant strains of the disease are present.

Two tests are usually used to determine if a patient has been infected with TB bacteria: (1) TB skin test (Mantoux Skin Test); and (2) TB blood test.[27-29]

During a TB skin test a small amount of tuberculin is injected into the skin, usually in an area of the lower arm. The results are generally confirmed within 48 to 72 hours of tuberculin administration.[30, 31] A positive skin test consists of a reaction at the injection site. Patients who have received a Bacille Calmette-Gue`rin (BCG) vaccination - the only recommended vaccination for the prevention of tuberculosis in many parts of the world or had repeated tuberculin skin testing performed might also react to the tuberculin skin test, resulting in false positive test results.[31-33]

Tuberculosis blood tests (interferon-gamma release assays) assess the body's immune system response to the TB bacteria.[28] Results are generated within 24 to 48 hours. The Food and Drug Administration (FDA) has approved three TB blood tests to be

used for the confirmation of the presence of TB bacteria: (1) The QuantiFERON®-TB Gold test (QFT-G), (2) QuantiFERON®-TB Gold In-Tube test (GFT-GIT), and (3) T-SPOT®.*TB* test.[27]

The tuberculin skin and blood tests confirm if a patient has been infected with the TB bacteria. However, these tests do not provide any information as to whether the patient has a latent TB infection or active TB disease. Chest X Rays, smear microscopy, and sputum cultures are used to confirm the presence of active TB disease.[27] Table 1.2 shows the advantages and disadvantages of microscopy versus culture tests.

Table 1.2 Advantages and Disadvantages of Tuberculosis Microscopy versus Culture Testing

Test	Advantage	Disadvantage
Sputum Smear Microscopy	• Gold standard to detect TB in developing countries • Highly specific especially in areas with a high TB incidence • Relatively fast	• Results depend on bacterial load of the sputum specimen • Results affected by training of staff • Insensitive test – detects approximately 50% of TB cases • Sensitivity is low in children and HIV patients (approximately 20%) • Cannot detect drug resistance • Burden on patient (patient has to visit clinic several times before a diagnosis is made) • Costly (transportation cost of specimen to the laboratory)
Culture of TB bacteria on liquid or solid media	• More sensitive than smear microscopy • Can be used for drug resistance testing • Growth on liquid culture is rapid vs slower growth on solid medium	• Biological safety cabinets and specialized staff required, making testing difficult in resource-poor settings • Time consuming because of the slow growth of the bacilli • Results must be transported back to the clinic

Source:World Health Organization. New Laboratory Diagnostic Tools for Tuberculosis Control. Available at: http://apps.who.int/tdr/publications/non-tdr-publications/diagnostic-tool-tb/pdf/diagnostic-tool-tb.pdf.Accessed September 1, 2009.

The New Diagnostics Working Group (NDWG), is part of the WHO STOP TB Partnership and is actively involved in providing information on new and old diagnostics in TB management. The NDWG describes three diagnostic tools used in the detection of TB, which have already been endorsed and adopted by the WHO.[31] (Table 1.3)

Table 1.3 Tuberculosis Testing Tools Endorsed by the World Health Organization

Test	Methodology	Advantages	Disadvantages
Liquid Culture: Broth based culture systems	Fluorescence is added to a liquid culture, enriched with oxygen. If bacteria are present, the bacteria will use the oxygen present causing the fluorescence to be detected under UV light. Testing for drug susceptible bacteria is conducted in a similar manner. If the bacteria are susceptible to the drug, the growth of the bacteria will be slowed, the oxygen will not be fully consumed and fluorescence will not be detected under the UV light.	• The system has undergone rigorous testing • Results from liquid culture mediums are produced faster than solid culture mediums. • Diagnosis can be reached in 1 to 2 weeks (same for drug susceptibility testing) • Automated systems have a sensitivity and specificity = 100%.	• Costly • Liquid media are more easily contaminated compared to solid media
Molecular Line Probe Assay Test	A strip, which detects tuberculosis bacteria as well as mutations noted in drug resistance	• Sensitivity = approximately 97% • Specificity = 98%	• Performance of the test may vary depending on epidemiological setting and type of bacterial mutation • Requires skilled laboratory technicians • Conventional and drug susceptibility testing is still needed to confirm the diagnosis of MDR-TB, confirm negative cases, and to assess XDR-TB
Strip Speciation	Used to confirm the presence of *M. Tuberculosis* complex in liquid or solid cultures	• Produces results within 15 minutes • Comparable to other methods of *M. tuberculosis* detection • Sensitivity = 98.6% • Specificity = 97.9% • Can detect *M. Tuberculosis* even when mixed with other bacteria	• Detects *M. Tuberculosis* complex but does not identify strains of *M. tuberculosis*

Source: World Health Organization. New Laboratory Diagnostic Tools for Tuberculosis Control. Available at: http://apps.who.int/tdr/publications/non-tdr-publications/diagnostic-tool-tb/pdf/diagnostic-tool-tb.pdf. Accessed: September 1st 2009.

In Summary there are several diagnostic tests that can be used for the detection of Active TB, Latent TB and Drug resistant TB. Pai and colleagues summarized the description of several diagnostic tests and these are shown in Table 1.4.[34]

Table 1.4 Tuberculosis Diagnostic Tests

Diagnostic Test	Description	Disease/Site
Diagnosis of Active TB		
Sputum smear microscopy	Microscopic observation of stained acid fast bacilli	Pulmonary TB
Nucleic acid amplification tests	Isolation, replication, and detection of nucleic acid sequences specific for Mycobacterium tuberculosis	Pulmonary and extrapulmonary TB
Commercial serological antibody detection tests	Detection of host antibody response to *Mycobacterium tuberculosis* antigens	Pulmonary and extrapulmonary TB
Noncommercial (in-house) serological antibody detection tests	Detection of host antibody response to *Mycobacterium tuberculosis* antigens	Pulmonary TB
Adenosine deaminase (ADA)	Detection of host cellular enzyme released by lymphocytes in response to live intracellular pathogens	TB pleuritis, pericarditis, peritonitis
Interferon-gamma (IFN-g)	Measurement of IFN-g	TB pleuritis
Phage amplification assays	Detection of Mycobacterium tuberculosis-specific phage viruses, after their infection and amplification of live MTB	Pulmonary TB
Automated liquid cultures	Detection of changes in oxygen, carbon dioxide, or pressure resulting from bacterial growth	Pulmonary TB
Diagnosis of Latent TB		
Tuberculin skin test (TST)	Measurement of induration as a result of exposure to intradermal tuberculin	Latent TB infection
T-cell-based interferon-g release assays	Measurement of IFN-g released from lymphocytes when stimulated by Mycobacterium tuberculosis specific antigens	Latent TB infection

Table 1.4 (continued)

Diagnosis of Drug Resistance		
Phage amplification assays	Detection of *Mycobacterium tuberculosis*-specific phage viruses, after their infection and amplification of live MTB inhibition of growth in presence of antituberculous drugs	Rapid detection of rifampicin resistance
Line probe assays: INNO-LiPA Rif.TB [LiPA] and GenoType MTBDR assay	Detection of genetic sequences associated with resistance (after extraction and amplification) using immobilized probes and colorimetric development	Rapid detection of rifampicin resistance
Colorimetric redox indicators	Determination of MIC using microdilution, followed byaddition of reagent which will become reduced in the presence of actively growing MTB resulting in a color change	Rapid detection of rifampicin and isoniazid resistance
Nitrate reductase assays	Direct or indirect inoculation of drug-free and drug-containing media containing KNO3. Addition of Greiss reagent detects early growth by reacting with enzymatic byproduct and resulting in a color change.	Rapid detection of rifampicin and isoniazid resistance
Microscopic observation drug susceptibility	Direct or indirect inoculation of drug-free and drug-containing liquid media, followed by examination using an inverted microscope to detect early growth[35]	Rapid detection of rifampicin and isoniazid resistance
Thin layer agar	Direct or indirect inoculation of drug-free and drug-containing solid media, followed by examination using a microscope to detect early growth[35]	Rapid detection of rifampicin and isoniazid resistance

Taken From: Pai M, Minion J, Steingart K, Ramsay A. New and improved tuberculosis diagnostics: evidence, policy, practice, and impact. *Curr Opin Pulm Med.* May 2010;16(3):271-284.[34]

1.5 MULTI-DRUG RESISTANT AND EXTENSIVELY DRUG RESISTANT DIAGNOSTIC SERVICES

Tuberculosis is usually diagnosed by laboratory culture or microscopy methods. It can take 6-10 weeks for culture results, but with microscopy the results can be obtained within a day. Chest X-rays, clinical response to antibiotics to exclude pneumonias, and clinical response to TB therapy are also considered as part of the TB diagnosis.[36]

In order for a definite diagnosis of drug resistant tuberculosis (DR-TB) to be made, *Mycobactrium tuberculosis* must be isolated on a culture medium, and drug susceptibility testing (DST) must be conducted. Currently, a lack of laboratory facilities and other resource constraints particular to individual countries makes it difficult or impossible to conduct DST.

In 2008, the WHO updated guidelines for the management of TB. Recommendations for the management of drug susceptible and drug resistant Tuberculosis include:[4]

- All patients suspected of DR-TB need access to laboratory services for adequate and timely diagnosis of DR-TB;
- Laboratories should develop a proficiency to test for isoniazid and rifampicin resistance as a minimum and then consider DST of other drugs;

- Laboratories should develop DST of the fluoroquinolones and second-line injectable agents where adequate capacity and expertise exist;
- Laboratories should follow all standardized protocols for infection control and bio-safety;
- Quality control and quality assurance should be in place for microscopy, culture and DST.

International consensus on DST for first-line TB drugs exists. However, the same is not true for second-line agents. Microscopy for acid-fast bacilli has a major disadvantage in that it cannot distinguish between drug susceptible and drug-resistant *Mycobactrium tuberculosis* or between different types of species of the bacteria. [4]

A number of different techniques are available for DST, including direct and indirect "culturing of *M.Tuberculosis* drugs to detect inhibition of growth."[5] In the direct testing approach, a "drug-containing and drug-free media is inoculated directly with a concentrated specimen (results available within 3 weeks)."[5] The indirect method (egg-based Lowenstein-Jensen Medium or agar based 7H11 medium) involves inoculation of drug with a pure culture grown from a patient's specimen, and is regarded as the gold standard of DST (results can take up to 6 to 10 weeks).[37]

Newer technologies are directed toward rapid testing because conventional DST methods can take time to produce results and in many clinical environments, patients are lost to follow-up before results are obtained. This delay can result in no treatment, inappropriate treatment, mutation of resistant strains, and spread of drug-resistant strains

among patients (especially amongst immuno-compromised patients). Information on the cost-effectiveness and cost-benefit of these rapid procedures is also of interest to the WHO, especially in resource-poor locations.[38]

As mentioned earlier, MDR-TB is defined as *M. Tuberculosis* resistant to at least rifampicin or isoniazid treatment. The WHO reports that where first-line agents are used to fight TB, resistance to rifampicin is almost always associated with a resistance to isoniazid. Therefore, the rapid rifampicin resistance tests can be used as a marker for MDR-TB. This procedure is regarded as a reliable, but incomplete, method because conventional DST is still the "gold standard." The WHO recommends rapid rifampicin resistance testing in "high-risk MDR-TB settings (including high burden HIV settings)"[31]

At present, XDR-TB can only be diagnosed through the laboratory approach, which usually produces results in 14 days.[5] Overall, even conventional DST can be limited by misclassification, cross-resistance, reliability, and reproducibility issues. When tools are assessed, the WHO advises that the following aspects be considered: evidence-base; the epidemiological setting the test will be implemented in; the time the test takes to produce results; costs; regulatory and quality control issues; safety (TB is a contagious disease and health care professionals should not be put at risk); and ability of health care professionals to use the test.[38] The line probe assay test is a test proposed by the WHO for rapid detection of resistance to rifampicin therapy alone or rifampicin therapy in combination with isoniazid.[38]

1.6 THE LINE PROBE ASSAY TEST

The line probe assay testing procedure involves a series of rapid chemical reactions. During this rapid testing procedure, DNA is extracted from the clinical specimen thought to contain the *M. Tuberculosis* bacteria. Polymerase chain reaction amplification, using "molecular grade water and Taq polymerase," is conducted and the products are "hybridized with specific oligonucleotide probes on a strip." [38] If resistance is present, colored bands appear on the strip and can be confirmed by the naked eye. The tests are currently under patent but are available for use. During the clinical trial phase rapid testing was not suggested as a replacement for conventional DST. The rapid test was intended for quick use (results available within 48 hours), but follow-up with the conventional "gold standard" DST was still recommended. [38] However, policy on the use of the test has changed and rapid technology is now being for first line testing in many parts of the world including South Africa. In March 2008, the WHO convened an expert panel and other key players in tropical diseases to assess available data on line probe assays in order to determine recommendations for their use. The data collected included: (1) published literature; (2) laboratory validation studies; and (3) laboratory and field demonstrations conducted to assess the performance and feasibility of implementation.

A literature search by the WHO resulted in two line probe assays with proven efficacy being identified: [38]

1. Inno-LiPA Rif TB (Belgium) – used to isolate *M.tuberculosis* grown on solid culture; and
2. Genotype MTBDR and Genotype MTBDR*plus* assays (Germany) – used on solid and liquid culture and smear positive pulmonary specimens.

Both tests are polymerase chain reaction-based, hybridization, assays capable of simultaneously detecting *M.tuberculosis* complex and specific mutations in the rpoB gene, which confirms rifampicin resistance. The latter test (Genotype MTBDR*plus*) also simultaneously detects specific mutations in the *KatG* gene, confirming high-level isoniazid resistance as well as those in the *inHa* gene confirming low-level isoniazid resistance. Data from systematic reviews and meta-analyses were used by the WHO to evaluate assay performance results and are presented in Table 1.5 below.[39] The results presented are for Inno-LiPA Rif TB (Belgium) compared.[31, 38, 40]

Table 1.5 Summary of Data From Systematic Reviews And Meta-Analyses Used To Evaluate Assay Performance Results. The Results Are In Comparison To Conventional DST Methods.[38]

	Inno-LiPA Rif TB
Number of Studies	Based on 12 of 14 studies
Sensitivity	>95%
Specificity	100%
Pooled Sensitivity	0.97 (95% CI 0.95-0.98)
Pooled Specificity	0.99 (95% CI 0.95-1.00)
Overall Discriminatory Ability of the Assay	99%
Overall Accuracy	97%

Similar results were obtained for the Genotype MTBDRplus assay

Take From: World Health Organization. Molecular line probe assays for rapid screening of patients at risk of multi-drug resistant tuberculsis (MDR-TB). Available at: http://www.who.int/tb/features_archive/policy_statement.pdf. Accessed: September 1st 2009.

According to a policy statement by the WHO, four studies that applied Inno-LiPA Rif TB directly to specimens showed 100% specificity, and sensitivity ranging from 80 to 100%. The expert group concluded that Inno-LiPA Rif TB was a highly sensitive and specific test for the detection of rapid rifampicin resistance.[38]

Although the line probe assay tests are unable to detect XDR-TB the WHO believes that detecting MDR-TB through line probe assay technology ultimately also helps improve the diagnosis rates and prognosis for XDR-TB.[41]

The test does necessitate certain requirements, which may be difficult to meet in resource-poor settings. Some of the requirements are microbiological safety cabinets, test tubes, reagents, and personal protective equipment such as gloves. [38]

The Foundation of Innovative Diagnostics (FIND) and Hain Lifescience partnered to test a line probe assay test, MTBDRplus, in South Africa. FIND conducted field studies testing the line probe assay in 4 provinces in South Africa testing over 20 000 patients suspected of having MDR-TB.[42]

In April 2009, ministers of health met in Beijing, China to discuss "key bottlenecks" preventing wide scale effective implementation and follow-through of MDR-TB and XDR-TB diagnosis and treatment. These bottlenecks included: (1) "Forecasting the control of MDR-TB epidemics; (2) Addressing the gaps in TB Control; (3) Addressing the gaps in TB control" (i.e. poor infrastructure within hospital systems preventing patients from being referred to other institutions for adequate treatment); (4) "Providing XDR-TB management and care; (5) Addressing the health workforce crisis; (5) Responding to the laboratory bottleneck; (6) Ensuring access to quality-assured anti-TB medicines" (7) Restricting the availability of anti-TB drugs" (i.e. regulating unregulated "over the counter sales" of TB drugs to prevent unnecessary use and promote resistance); "(8) Prioritizing TB infection control; (9) Maximizing research opportunities to address MDR-TB and XDR-TB", and (10) Financing MDR-TB and XDR-TB control and care."[43] This type of intensified response involving strong local and global leadership

and financing; health care restructuring, and improved diagnostic testing is required in the current HIV and TB crisis.[44]

1.7 DRUG TREATMENT AND DRUG RESISTANCE

Standard TB treatment consists of a 2-month intensive daily dosing treatment phase (combination of isoniazid, rifampicin, pyrazinamide, and ethambutol treatment), followed by a 4-month daily or thrice weekly continuation-dosing phase. The continuation phase can consist of isoniazid in combination with rifampicin alone or isoniazid in combination with rifampicin and ethambutol treatment. Tables 1.6 and 1.7 show the combinations of drugs and dosing used as standard TB treatment. [45]

In the past, three times weekly dosing was grouped with directly observed short course treatment, a strategy where nurses administered medication to patients to enhance proper adherence to treatment. Currently, the three times weekly regimen is not as commonly used because of the burden it places on the health system, and sometimes shortage of staff prevents this service from being delivered.

Table 1.6. Standard Anti-Tuberculosis Drugs Used in the Intensive and Continuation Phases of Tuberculosis Treatments[45]

Option	Initiation Phase	Continuation Phase	Dosing
Option 1	2 Months Treatment With: Isoniazid Rifampicin Pyrazinamide Ethambutol	4 Months Treatment with: Isoniazid Rifampicin	Daily
Option 2	2 Months Treatment With: Isoniazid Rifampicin Pyrazinamide Ethambutol	4 Months Treatment with: Isoniazid Rifampicin Ethambutol	3 Times a Week

Taken From: World Health Organization. Treatment of Tuberculosis Guidelines - Fourth Edition 2010 Available from: http://www.who.int/tb/publications/tb_treatmentguidelines/en/. Accessed July 10th 2010.

Table 1.7 Recommended Standard Adult Dosing Regimens for First-Line Anti-Tuberculosis[45]

Drug	Recommended Dose			
	Daily		3 Times Per Week	
	Dose and Range mg/kg body weight	Maximum (mg)	Dose and Range mg/kg body weight	Daily Maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	-
Ethambutol	15 (15–20)	–	30 (25–35)	–

Taken From: World Health Organization. *Treatment of Tuberculosis Guidelines - Fourth Edition* 2010 July 10th 2010; Available from: http://www.who.int/tb/publications/tb_treatmentguidelines/en/

MDR-TB treatment consists of five categories based on efficacy of the drugs, drug class and how often the drug has been used in the past. Table 1.8 shows the WHO grouping of MDR-TB treatment. At the minimum, the recommendation is for MDR-TB treatment to consist of at least four drugs in the intensive and continuation phase. When the drug resistance pattern or the effectiveness of the drug treatment is unknown, it is recommended that more than four drugs be used.

Table 1.8. Groupings of Drugs Used in the Treatment of Multidrug Resistant Tuberculosis [45]

Group	Drug
Group 1: First-line oral agents	Pyrazinamide Ethambutol Rifabutin
Group 2: Injectable agents	Kanamycin Amikacin Capreomycin Streptomycin
Group 3: Fluoroquinolones	Levofloxacin Moxifloxacin Ofloxacin
Group 4: Oral bacteriostatic second-line agents	Para-Aminosalicylic Acid Cycloserine Terizidone Ethionamide Protionamide
Group 5: Agents with unclear role in treatment of drug resistant-TB	Clofazimine Linezolid Amoxicillin/Clavulanate Thioacetazone Imipenem/Cilastatin High-Dose Isoniazid (High-Dose) Clarithromycin

Taken From: World Health Organization. *Treatment of Tuberculosis Guidelines - Fourth Edition* 2010 July 10th 2010; Available at: http://www.who.int/tb/publications/tb_treatmentguidelines/en/

Resistance to treatment emerges due to poor adherence to drug treatment, and inappropriate pharmacological treatment (for example, monotherapy). Testing the patient for resistant strains and individualized treatment is needed to combat this disease. However, many of the 27 high-burden TB countries do not have the resources to provide individualized treatment. Therefore, standard protocols are adopted, which contribute to the resistance patterns noted today. Resistance to the most powerful first-line anti-tuberculosis drug, isoniazid, can emerge rapidly, followed by resistance to the second most powerful drug, rifampicin. Other agents, such as pyrazinamide, ethambutol and streptomycin, have proven to be less than effective in preventing the spread of resistance among second-line drugs. It is apparent that occurrence and spread of resistance happens rapidly. In a letter to the Editor of the European Respiratory Journal, Dr Migliori. from the WHO Collaborating Centre for TB and Lung Diseases and other TB researchers reiterated the call for robust prospective studies to help determine what treatment regimens can provide the best chance of MDR and XDR-TB cures.[46] However, overall researchers also recognize that the spread of MDR-TB and XDR-TB, since the first cases were discovered in South Africa, was a direct result of a delay in diagnosis.

1.8 STOP TB PARTNERSHIP - WORLD HEALTH ORGANIZATION

In the year 2000, World Leaders at a meeting at the United Nations adopted the Millennium Development Goals (MDGs). The MDGs consist of eight broad measureable targets set for the year 2015 to address the needs of developing countries: "(1) combat extreme poverty and hunger; (2) increase access to education; (3) promote gender equality; (4) decrease childhood mortality; (5) improve maternal health; (6) halt and reverse the spread of HIV/AIDS, Malaria, TB and other infectious diseases; (7) ensure environmental sustainability; and (8) develop global partnerships for development"[47] As part of Millennium Development Goal 6, to decrease the spread of TB, the WHO launched the STOP TB partnership. The STOP TB partnership is sometimes regarded as a successor to the Directly Observed Therapy Short course (DOTS) strategy. Directly observed therapy in TB management was initiated around 1995 to ensure acceptable medication adherence among TB patients. Patients received TB treatment under direct medical supervision at local clinics or through mobile clinic services. The STOP TB partnership includes DOTS in addition to other TB management components including: expanding collaborative HIV/AIDS and TB initiatives; strengthening health systems (*including upgrading diagnostic services and laboratories*); building private and public health partnerships; empowering communities, and promoting research. [48, 49] A study conducted in Estonia, Latvia, Lima, Manila and Tomsk, describing MDR-TB programs, frequency of MDR-TB drugs used in the programs, and treatment outcomes showed that in resource limited or low-income countries MDR-TB management through collaborative

programs can produce results closer to high income countries. In these low-income regions, treatment was successful in 70% of all (N=1047) new and previously treated patients.[50]

As part of the STOP TB Partnership, the WHO created the Global Laboratory Initiative to strengthen laboratory facilities and promote the use of rapid detection technology to test for resistant strains of TB. [8] Costs for such programs are high, and the WHO is working with each of the 27 countries to set up individual budgets with some of the funding coming from the Global Fund.

Development of new pharmacological agents will be expensive and may only complicate the resistance patterns - particularly in areas where patient education is poor and patients continue to be non-adherent. An essential initiative to address the global TB crisis lies in the early detection of resistant strains (i.e. improve case finding), short effective treatment regimens (i.e. improve case management), and development of post TB exposure vaccines.[51-54] The Foundation of Innovative Diagnostics (FIND), based in Geneva, Switzerland, is working closely with the WHO to develop new rapid diagnostics for infectious diseases like TB and Malaria, which negatively affect the developing world.[55] Due to for-profit companies finding little financial incentive to develop new diagnostics and vaccines for the developing world, and government-funded health care systems in the developing world finding it difficult to pay for the new technologies; FIND is using public-private partnerships to negotiate prices of novel diagnostic agents so low- and middle-income countries can benefit from the new diagnostics.[56, 57] The line probe assay test is one example of a rapid test that has been developed, distributed and

currently under field studies coordinated by FIND's efforts in South Africa.[55] Pharmacoeconomic cost studies can be used to model costs and probabilities to determine how clinicians and decision makers can use resources, like the line probe assay test developed by FIND, most effectively for the timely detection of resistant strains.

CHAPTER 2

Economic Analyses and Tuberculosis

In Chapter 2, an outline of pharmacoeconomic analyses is provided. Additionally, a summary of selected cost-effectiveness studies on tuberculosis diagnostic algorithms, diagnostics tests, and treatment is provided in this chapter.

2.1 PHARMACOECONOMICS AND COST STUDIES

Pharmacoeconomics "identifies, measures, and compares the costs and consequences of pharmaceutical products and services."[58] There are four main types of pharmacoeconomic analyses: (1) cost-minimization analysis (CMA), (2) cost-effectiveness analysis (CEA), (3) cost-utility analysis (CUA), and (4) cost-benefit analysis (CBA).[59]

2.2 COST-MINIMIZATION ANALYSIS

Cost-minimization is the simplest type of pharmacoeconomic analysis. A CMA is a comparison of input costs of two or more interventions or drugs that are assumed to have equivalent outcomes.[59]

2.3 COST-EFFECTIVENESS ANALYSIS

A second type of a pharmacoeconomic analysis is a cost-effectiveness analysis. It is the most common type of pharmacoeconomic analysis, where costs are measured in monetary units (e.g., U.S. dollars) and outcomes are measured in natural health units (e.g. number of lives saved or number of patients cured). [59] The goal of cost-effectiveness analyses is to identify a drug or diagnostic procedure (i.e., any health intervention) that has the greatest health benefit but costs the lowest per unit output. Usually two or more health interventions are compared in a cost-effectiveness analysis and the outcomes of the individual interventions must be measured in the same health units. [60] The perspective of a cost-effectiveness study can be that of a health care provider or a societal perspective, among others. Examples of provider perspectives include direct costs associated with testing and screening, and medical services rendered. Examples of patient perspective costs include out-of-pocket costs for the patient, productivity costs, and loss of time. In general, costs for TB diagnostics can include: "physical infrastructure, chemicals reagents and consumables, human resources, training and quality assurance, and transport of specimens." [60] Effectiveness can be measured in terms of reduced transmission rates, number of TB cases detected, and speed of diagnosis.[61]

To evaluate how one treatment/diagnostic compares to another in terms of costs and outcomes, an incremental cost-effectiveness ratio (ICER) is calculated. The ICER is calculated as the difference in costs over the difference in outcomes. If a negative ICER is obtained, then one treatment, referred to as the dominant treatment, is more effective

but less costly. If on the other hand, one treatment costs more but is also more effective, then the ICER provides information on how much one extra unit in improvement costs. Cost-effectiveness grids (represented as a table showing different levels of effectiveness against different levels of costs) and cost-effectiveness planes are also used to illustrate results from a cost-effectiveness analysis. Another newer measure seen in the literature, similar to the ICER is the incremental net benefit ratio (INB). The INB overcomes the disadvantage of the subjectivity that can occur with the use of an ICER. For example, in instances where one drug costs more but is more effective, it is left up to the decision maker's judgment to determine if the drug is worth the cost for each unit of outcome. The maximum willingness-to-pay for a particular disease is represented in the INB equation. A positive INB value is considered cost-effective and a negative value is not considered to be cost-effective.[59] Although a potential disadvantage of this method is that a value must be assigned to the willingness-to-pay amount in an INB calculation, this procedure is still considered acceptable because a sensitivity analysis is conducted using a range of willingness-to-pay values.[59]

2.4 COST-UTILITY ANALYSIS

In a cost-utility analysis, inputs are measured in dollar amounts and outcomes are most commonly represented as quality-adjusted life years (QALYs) or disability-adjusted life-years (DALYs). The QALY is a measure of the patient's preference based on mortality and morbidity associated with a particular disease. Various methods are used to determine a patient's utility including: (1) Rating Scale, (2) Standard Gamble, and (3)

Time Tradeoff. Using one of these three methods, patients are questioned on what preference between death and perfect health they have for a particular disease state. This value, referred to as a utility, is then multiplied by the length of life for the option chosen, resulting in a value known as the QALY. The QALY can fall anywhere between 0.0 (death) and 1.0 (perfect health).[59] DALYs are "the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability."[62]

2.5 COST-BENEFIT ANALYSIS

In a cost-benefit analysis, both costs and outcomes/benefits are compared in monetary units. Costs in the analysis can include direct medical (e.g., testing and medication), direct non-medical costs (e.g., travel costs for the patient to receive treatment) and indirect costs (lost productivity time/lost time from work). Benefits can be described as direct, indirect and intangible. Direct benefits can include direct and indirect medical savings. Indirect benefits include productivity benefits measured in terms of the human capital approach or a patient's willingness-to-pay. Finally, intangible benefits include benefits such as a patient's reduction in pain, again measured by the patient's willingness-to-pay. Cost-benefit ratios are used to represent cost-benefit results. If the benefit-to-cost ratio is over 1.0, then the service or intervention in question is considered cost beneficial.[59]

2.6 DECISION ANALYSIS

Decision analysis is an economic method used to compare two or more different options. In pharmacoeconomics research, decision analysis can be used to compare the cost-effectiveness of different treatments. Cost and probabilities are used to determine which of the treatments under investigation produce the best outcome at the lowest cost. Six steps have been identified in decision analysis. Firstly, the specific objective or decision of the study needs to be identified. Secondly, the alternatives/treatments that will be compared must be specified. Thirdly, a decision tree (read from left to right) is constructed outlining the specific alternatives. Choice, chance, and terminal nodes appear on the branches of a decision tree to represent the choice between the two alternatives, the probability of one event over another, and the outcome for each alternative, respectively. A probability of event and cost is assigned to each branch after a chance node. Fourthly, costs for each branch from the chance node to the terminal node are summed, while the probabilities for the same branches are multiplied. Fifthly, the total costs for the branch is then multiplied by the product of the probabilities for that branch. All the "cost multiplied by probability" totals are then summed to obtain the average cost for each alternative. An ICER (change or difference in costs divided by the change in outcomes) is then calculated. Decision makers can then use their discretion to determine if the outcome is worth the calculated cost. Finally, a sensitivity analysis should be conducted to determine if results change with a change in assigned probabilities and costs.[59] A decision analysis assumes that patients do not transition between health states,

and the outcomes are generally simple and straightforward (for example cured vs. death). In the case of more complex disease states that vary over time and where patients may transition between different health states, a Markov model analysis may produce more useful results.[59]

2.7 MARKOV MODELING ANALYSIS

In a Markov model analysis, the disease state is identified, the possibility of transitioning between different health states are determined, a cycle length is assigned, and transition probabilities, costs, and outcomes between health states is estimated and assigned. Unlike a decision analysis, a Markov model takes time into account in the model.

Cohort and Monte Carlo simulations are two types of calculations used in Markov analyses. In a cohort simulation, a hypothetical group of patients are transitioned from one common health state through one cycle of the analysis. The process is repeated using the same (Markov chain analysis) or different probabilities (Markov process analysis). A cohort simulation like a decision analysis does not account for uncertainty in the model. Monte Carlo simulation accounts for uncertainty in the model by passing a single patient through the cycle. Costs and probabilities are calculated for that patient. Then other patients are passed one at a time through the analysis. However, each patient may follow a different path. Monte Carlo simulation can account for patient level and statistical-level uncertainty.[59]

2.8 LITERATURE ON DECISION ANALYSIS RELATED TO TUBERCULOSIS DIAGNOSTIC TESTS

Studies have been conducted on cost-effectiveness and cost analysis of TB related to diagnosis and treatment. One of these studies, published in the late 1990's, was a cost-effectiveness study conducted in the US, which showed that empiric tuberculosis therapy lowers mortality and cost per person treated when rapid diagnostic testing is used. Rapid diagnostic referred to conventional (results available in 22.3 to 31.8 days) and radiometric culture isolation (results available in 9.3 to 16.8 days). Initiating treatment in HIV- infected patients awaiting test results decreased average mortality by 2% ("at a cost of $8000 per life saved").[63]

More studies have been conducted in recent years on persons who are exposed to *Mycobacterium tuberculosis* who can either develop latent TB infection or active TB disease. Tuberculin skin testing is used to detect the presence of an infection but can be costly if all people who are exposed are tested. In the United States, researchers from the University of Alabama conducted a study to compare the cost-effectiveness of two contact investigation models: the concentric circle versus the contact priority model. The "concentric circle approach" categorizes individuals exposed to TB as high, medium or low risk. Tuberculin skin testing is then conducted, starting with the high risk group and continued until the "rate of the positive skin tests equals the prevalence of the latent tuberculosis infection in the community." The prevalence of latent TB in the community was estimated to be 10%. The "contact priority model" uses a decision rule to categorize

patients into different risk groups and it was assumed that using the latter model would result in a lower number of skin tests being conducted annually (20% less tests annually) and therefore a certain degree of loss in disease control. The researchers used a decision analysis to determine the cost-effectiveness of both approaches. The findings were summarized as follows: Simulating 1000 individuals through the model resulted in the contact priority model saving $45,000. However, an estimated 0.5 additional TB cases would occur. Overall, the researchers concluded that the contact priority model (i.e., the algorithm) reduced costs with limited loss of disease control.[64]

In Canada, treatment of latent TB infections is recommended in individuals who come into contact with a person who had a positive tuberculin skin test (≥5mm). A Markov model was constructed to evaluate the cost-effectiveness of latent TB infection therapy depending on certain risk factors including: tuberculin skin test size, closeness to contact, age, ethnicity, and Calmette-Gue`rin or BCG vaccination status. The results indicated that the preventative treatment recommended at the time of the study in Canada was cost-effective for certain groups of individuals. The preventative treatment was not cost-effective for "nonhousehold Canadian-born (nonaboriginal)" or foreign-born contacts 10 years of age older. However, preventative treatment (without screening) was cost-effective in individuals less than 10 years of age who did not receive BCG vaccination. The researchers found that such preventative therapy would result in an incremental net monetary benefit of $25 for each contact investigated if the willingness-to-pay was set at $50,000/QALY Canadian dollars. [65]

Diel et al. conducted a cost-benefit analysis using decision analysis methods to

compare two approaches (QuantiFERON TB Gold in Tube and the tuberculin skin test) to test for latent TB infection. The comparison considered each test alone or the QuantiFERON test as a follow-up to the tuberculin test results. Hepatotoxicity related to the isoniazid preventative treatment, and early post-exposure to TB were also considered in the model. The researchers found that costs were the lowest but fewer TB cases were diagnosed when the QuanitFERON test was used alone.[66] In Mexico, cost-effectiveness results showed that the QunatiFERON-TB Gold for the detection of LTBI was cost-effective in preventing 78 cases of active TB (incremental cost per case prevented: US$529) over a 20-year period.[67] The QuantiFERON test has been considered superior to the tuberculin test because the former test requires a single consultation and results are not affected by a BCG vaccination. However, study results showing the costs and effectiveness of the QuantiFERON test are conflicting depending on the type of patient and BCG vaccine used. Using a Markov model, researchers in the United States showed that the QuantiFERON test was less costly but superior to the tuberculin test, irrespective of BCG vaccination, when testing health care workers.[68] However, when Marra et al. constructed a similar model considering ethnicity in addition to BCG use, the QuantiFERON test was cost-effective compared with the tuberculin test when used in selected groups of patients only, specifically patients who were vaccinated with BCG (incremental net benefit ratio = $3.70 Canadian Dollars per contact). When the prevalence, reactivation rates of TB, and adherence to treatment were varied, the QuantiFERON test became cost-effective among patients who were not BCG vaccinated.[69]

One study conducted in a resource-poor setting in Brazil showed that conducting TB cultures in a group of HIV positive patients who were suspected of having TB was cost-effective. The cost of one negative culture test for solid and liquid media was $17.52 and $23.50 United States dollars, respectively. [70]

Markov cost-effectiveness analyses have been conducted in South African, Brazilian and Kenyan settings comparing (1) a hypothetical point of care test (with a hypothesized 70% sensitivity, 95% specificity and cost of $20 per test) to (2) sputum testing alone, (3) sputum testing in conjunction with the hypothetical test, and (4) sputum testing with TB culture. Using these sensitivity, specificity and cost estimates, sputum smear testing was more cost-effective ($38 to $131 DALY averted) than the hypothetical new test. Sputum smear in conjunction with the hypothetical test averted 46-49% more DALYs per 1000 TB suspects ($170-$625 per DALY averted) compared to the sputum smear test alone. The hypothetical test plus sputum smear was more costly but more effective than the sputum smear plus TB culture test in the majority of scenarios. The results for use of the hypothetical test were sensitive based on the following characteristics of the test: specificity, sensitivity, cost, detection rate and discounting rate.[71]

Other work conducted involves the comparison of the cost-effectiveness of the T-SPOT.TB assay to the tuberculin skin test for detection of latent TB infection. A 20-year Markov model showed that using T-SPOT.TB alone or in combination with the tuberculin skin test to screen for latent tuberculosis infection before initiating treatment was cost-effective at (Euro) 11,621 in a 20-year-old cohort and (Euro) 23,692 in a 40-

year-old cohort, respectively.[72] See Table 2.1 for summary of study results of these selected studies.

Table 2.1 Summary of Cost-Effectiveness Studies on TB Testing

Study	Type of Test	Costs	Outcomes	Results
Pisu, M., et al., *Targeted Tuberculosis Contact Investigation Saves Money Without Sacrificing Health.* Journal of Public Health Management and Practice, 2009. **15**(4): p. 319-327	Comparison of two contact investigation strategies used to determine which patients exposed to TB cases should undergo tuberculin skin testing	• Costs associated with skin testing • Follow up costs for contacts with a positive skin test • Treatment for latent tuberculosis infection • Treatment of active tuberculosis disease	• Number of active tuberculosis cases • Number of life years attained	• Incremental cost-effectiveness ratios were used and were represented as the average cost of preventing one additional tuberculosis case or gaining one additional life year • The concentric circle approach was identified as being more effective but also more costly. The cost of prevention of one additional case of TB was $92 934 and the cost to gain one additional life year was $185 920 with the concentric circle approach • Results were sensitive to changes in the cost and likelihood of disease reactivation
Tan, M.C., et al., *Cost-effectiveness of LTBI treatment for TB contacts in British Columbia.* Value Health, 2008. **11**(5): p. 842-52	Evaluated the cost-effectiveness of latent tuberculosis infection by comparing (1) No screening versus (2) testing TB contacts and treating TB contacts with a positive test versus (3) treat all TB contacts	• Physicians visits • Latent Tuberculosis Infection management and treatment • Hospitalizations • Diagnosis and treatment of active TB cases • Contact Investigations	• Incremental cost per QALY gained • Incremental cost per active TB case prevented	• When QALYs were used as the outcome measure, the test and treat group was the most cost-effective compared to the other two groups. However, in non household Canadian and foreign born contacts ≥ 10 years old the do not test option was most cost-effective, irrespective of BCG vaccination status, and in household contacts age <10 years who were not vaccinated with BCG the treat all TB contacts was most cost-effective. • Similar results occurred when cost per active TB case was used as the treatment measure. In household contacts age <10 years who were not vaccinated with BCG the treat all TB contacts was most cost-effective

Table 2.1 (continued)

Diel, R., et al., *Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany.* Respir Med, 2009. **103**(12): p. 1838-53	To compare whole blood QuantiFERON TB Gold in tube (QFT) and the tuberculin skin test (TST) to detect latent tuberculin infection.	• Cost of treatment of TB disease • Cost of screening for latent TB infection • Cost of preventative treatment • Cost of hepatotoxic side effects • Cost of second chest x ray	• Tuberculosis disease including the cost of absenteeism • Hospitalization due to hepatitis induced by Isoniazid treatment • Death due to drug induced hepatitis • Latent tuberculosis infection without progression to disease	• Cost of using the QFT alone (215.79 Euro) was lower than using QFT in conjunction with TST (227.89 Euro) or TST alone (232.58 Euro). • In all the cases hospitalization due to isoniazid induced hepatitis did not influence the outcome • Preventative treatment using the QFT alone resulted in detection of fewer TB cases
Burgos JL, Kahn JG, Strathdee SA, et al. Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *Int J Tuberc Lung Dis.* Aug 2009;13(8):962-968.	Cost-effectiveness of QuantiFERON-TB Gold in-Tube (QFT-GIT)	• Cost of screening • Cost of treatment • Cost of Isoniazid induced Hepatitis Toxicity • HIV testing • Fixed costs for coordinating the program • Start Up costs • Tb Management Costs	• Incremental cost per latent TB infection case detected • Incremental cost per active TB case averted • Cost per QALY	• Incremental cost per latent tuberculosis infection case detected was US$730 • Incremental cost per active TB case prevented US$529 • Incremental cost per QALY gained was US$108

Table 2.1 (continued)

de Perio, M.A., et al., *Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers.* Arch Intern Med, 2009. **169**(2): p. 179-87.	Cost-effectiveness of interferon Gamma Release Assays (QuantiFERON-TB Gold in Tube test and QuantiFERON-TB Gold test) vs Tuberculin Skin Tests (TST) in Health Care Professionals	• TST cost • QFT costs • Isoniazid treatment costs • Hepatitis • Treatment of active TB and MDR-TB	• QALYs	• Both Gamma release assays were less costly and more effective than the skin testing option
Marra, F., et al., *Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts.* Int J Tuberc Lung Dis, 2008. **12**(12): p. 1414-24	To compare the cost-effectiveness of QuantiFERON-TB Gold (QFT-G) to tuberculin skin testing in the detection of latent TB infection	• Costs of testing included staff time, equipment, consumables, and commercial kits. • Physician Visits • Tuberculosis treatment • Hospitalization • Contact screening • Management of latent or active disease	• QALYs	• Using QFT-G in BCG-vaccinated contacts was the most cost-effective (Net monetary value $3.70 Canadian Dollars per contact). • Tuberculin testing was suggested in all other contacts
Dowdy, D.W., et al., *Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults.* PLoS One, 2008. **3**(12): p. e4057	Sputum smear microscopy with expanded TB culture testing using solid and liquid media vs sputum smear microscopy alone	• Cost of testing including the reagents • Cost of transporting specimens	• Disability adjusted life years (DALYs)	For 1000 HIV positive patients suspected of having TB compared to sputum smear alone: • TB culture with solid media would avert 8 TB deaths, would lead to incorrect treatment of 44 patients, and would avert "37 DALYs at a cost of $36 per TB suspect or $962 per DALY averted" • TB culture with liquid media will avert one further death, cause 35 additional unnecessary treatments, avert an additional 8 DALYs at a cost of $22 per TB suspect. A final estimated incremental cost-effectiveness ratio of $2751 per DALY was obtained for liquid media compared to the solid media test indicating that liquid media was dominated.

Table 2.1 (continued)

Dowdy, D.W., M.A. O'Brien, and D. Bishai, *Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis.* Int J Tuberc Lung Dis, 2008. **12**(9): p. 1021-9	Comparison of (1) hypothetical point-of-care diagnostic test with a range of specificity and sensitivity values, (2) sputum smear microscopy, (3) sputum smear plus the hypothetical test and (4) sputum smear plus TB culture. The main comparison was between the hypothetical test and the sputum smear microscopy plus hypothetical test. Decision model for South Africa, Brazil and Kenya.	• Cost of testing	• Expected costs • TB infections prevented • DALYs	• In all three countries, sputum smear testing was more cost-effective ($38 to $131 DALY averted) then a hypothetical test with a 70% sensitivity, 95% specificity, and at a cost of $20 • Sputum smear plus hypothetical test averted 46-49% more DALYs per 1000 TB suspects ($170-$625 per DALY averted) compared to the sputum smear alone • The hypothetical test plus sputum smear was more costly but more effective than the sputum smear plus TB culture test in the majority of scenarios
Diel, R., P. Wrighton-Smith, and J.P. Zellweger, *Cost-effectiveness of interferon-gamma release assay testing for the treatment of latent tuberculosis.* Eur Respir J, 2007. **30**(2): p. 321-32	Comparison of cost-effectiveness of the new T-SPOT.TB assay versus the tuberculin skin test (TST) for screening TB contacts for latent infection	• Cost of screening and treatment of latent TB infection • Cost of illness • Direct diagnostic and treatment costs • Indirect costs e.g. days lost from work	• Number of cases of TB disease avoided • Life Years Gained (LYG)	• Skin testing was cost-effective in the 15 mm cut off in younger patients (26.451 Euros per LYG) • T-SPOT.TB was cost-effective at 11 621 and 23 692 Euros per life year gained in all age groups • Compared to TST, the number of cases of TB disease avoided by using T-SPOT.TB was lower (18 vs 50)

2.9 A SUMMARY OF A COST-EFFECTIVENESS STUDY ON RAPID TESTING FOR MULTI-DRUG RESISTANT TB

One study estimated the cost-effectiveness of various rapid MDR-TB tests compared to traditional drug susceptibility testing. The study was conducted in Lima, Peru and published in 2008.[73]

The researchers conducted a cost-effectiveness analysis comparing four rapid susceptibility tests to conventional drug susceptibility testing using various MDR-TB prevalence groups (2%, 5%, 20%, and 50%). The conventional drug susceptibility test was that of the indirect proportion method of Löwenstein-Jensen Medium (IDLJ) and the remaining four tests were rapid tests (FASTPlaque-Response, INNO-LiPA, DLJ, and MTT assay). The patient data used in this study were obtained from clinical trial data. Costs included: cost of the test, cost savings from avoiding unnecessary drug treatment while waiting for test results, and cost of false positive test results. The major outcome measure was the cost per DALY averted. The unit cost for four of the five tests ranged from $25 to $42. The fifth test, INNO-LIPA, had a much higher unit cost of $112. Results showed that DLJ had the lowest cost per case detected for all the prevalence groups ($3913 for 2%, $1522 for 5%, $326 for 20% and $87 for 50%). Additionally, DLJ had the lowest cost per DALY averted including cost savings due to reduced transmissions ($41 for each DALY averted). [73]

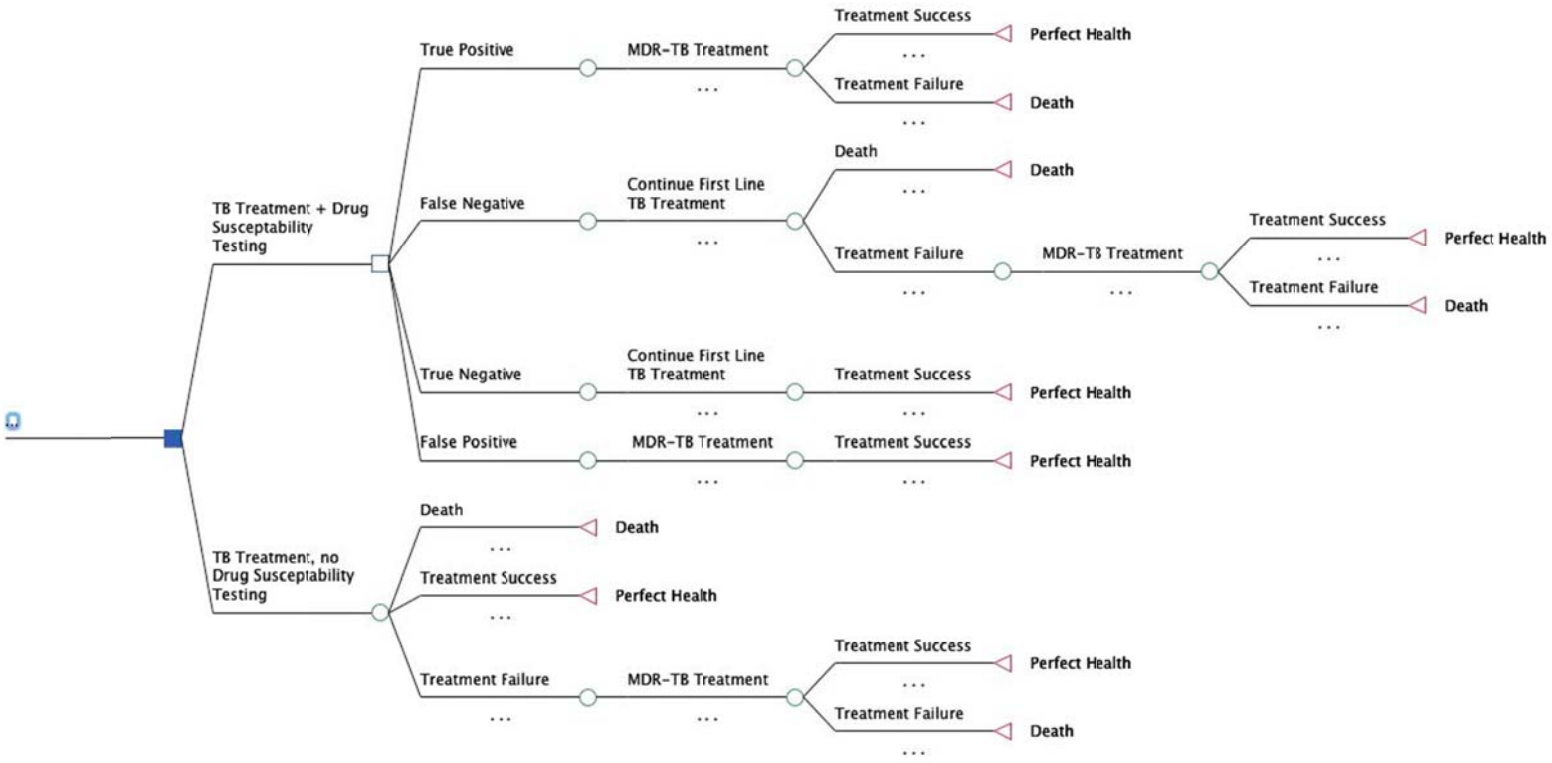
Table 2.2 provides a summary of some of the important prevalence, cost, probability and outcome measures used in this study. Figure 2.1. shows the decision tree used in the study.

Table 2.2 Summary of a Cost-Effectiveness Study of Rapid Multi-Drug Resistant Tuberculosis Diagnostic Techniques in Lima, Peru

Summary of Costs, Probabilities, Assumptions, Outcome Measures and Sensitivity Analyses Used in The Study
Costs
• Costs and cost-effectiveness estimates were calculated for patient groups with 2%, 5%, 20%, and 50% prevalence of MDR-TB." These rates were used because they correspond to what is commonly found in the WHO surveillance data.
• Average cost per case for each diagnostic test was calculated using the following costs: cost of the test, cost savings from using the correct drug earlier/avoiding use of unnecessary drug treatment while waiting for results, and cost of false positives which included the cost of treatment
• Other costs included: indirect costs (overhead costs) and direct costs ("buildings, equipment, training, transportation, supplies, salaries, and utilities").[73] Contamination test costs and cost of invalid tests were also included in the model.
• The ingredients approach was used when calculating the cost of the test. Using this method, the amount of ingredients used are multiplied by the price per unit.
• Staff time and quantities used were measured by technicians in the laboratory
Assumptions
• It was assumed that patients would receive a standardized MDR-TB treatment regimen
• Two percent of patients were estimated to die while waiting for MDR-TB treatment
• Patients would be switched to MDR-TB treatment within 7 days of the drug susceptibility test
• Drug susceptibility testing would occur at 0 months and that patients would remain infectious for 2 months after treatment was initiated.
• All false negative patients were assumed to remain infectious during the entire study
• The indirect proportion method on Löwenstein-Jensen medium (IDLJ) was used as the comparator in this study and was assumed to have a specificity and sensitivity of 98%.
Outcome
• Average cost per disability-adjusted life-years (DALYs) was obtained for each testing procedure and was the main outcome measure
Sensitivity Analysis
• Various sensitivity analyses were conducted on the following variables: prices (±10%), sensitivities (±2%), specificities (±2) and efficiency assumptions (±5%)

Acuna-Villaorduna, C., et al., Cost-effectiveness analysis of introduction of rapid, alternative methods to identify multidrug-resistant tuberculosis in middle-income countries. Clin Infect Dis, 2008. 47(4): p. 487-95.

Figure 2.1 Decision Tree – Acuna Villaorduna et al., 2008[73]



Source: Acuna-Villaorduna, C., et al., Cost-effectiveness analysis of introduction of rapid, alternative methods to identify multidrug-resistant tuberculosis in middle-income countries. Clin Infect Dis, 2008. 47(4): p. 487-95.

2.10 LITERATURE ON DECISION ANALYSIS RELATED TO TUBERCULOSIS TREATMENT

Cost-effectiveness studies have been conducted on costs and effectiveness of the treatment of latent TB treatment infections (LTBI), especially in immigrants to the United States. There have also been a few studies on the cost-effectiveness of directly observed therapy short course (DOTS). Details (aim, methods, study assumptions, costs, and results) on selected literature are presented in Table 2.3.[74-77] Latent TB infection refers to an underlying form, and not an active form of pulmonary tuberculosis. Directly observed therapy short course refers to the manner in which the drug is administered to patients. The DOTS approach refers to health care professionals supervising the administration of the TB drug to patients as compared to the self-administered treatment approach.

Finnell et al. investigated at what rate of isoniazid resistance should an alternative TB treatment regimen (e.g., rifampin for 6 months) be considered for immigrant children who are entering the United States with LTBI. Four options were compared using a decision analysis framework that considered costs associated with medication, medication administration, and side effects of treatment. The four treatment options included: (1) isoniazid for 9 months; (2) rifampin for 6 months; (3) a combination of isoniazid and rifampin therapy; or (4) no treatment. Results showed that rifampin treatment cost the lowest. However, the result was sensitive to the isoniazid resistance rate in the country of the child's origin. When all variables were taken into consideration in the model Rifampin remained least costly as long as the isoniazid resistance rate of the

country of origin from which the child emigrated from was ≥ 11%. Combination treatment (e.g., isoniazid for 9 months and rifampin for 6 months) appeared to be the most effective but was also the more expensive approach.[74]

Khan et al. compared four treatment approaches: tuberculin skin testing followed by treatment with: 1) no intervention; (2) isoniazid and pyrodoxine (Vitamin B6) daily for nine months; (3) rifampin daily for four months, or (4) rifampin and pyrodoxine for two months for the treatment of LTBI among immigrants entering the United States from various developing nations. Rifampin monotherapy was the dominant treatment irrespective of the immigrant's country of origin. However, in some regions the combination of rifampin with pyrazinamide was the least costly and most effective approach.[75]

In 2006, a study was published on the estimated costs and potential benefits of DOTS expansion in Haiti. Although the results of this study are no longer relevant due to a natural disaster that affected the country in 2009, the Markov model that was developed in this study gave researchers an idea of the potential societal cost savings from an expansion of the country's DOTS strategy. It was assumed that DOTS expansion would reach 100% of publicly funded clinics in Haiti, case detection rates would increase from 49% to 70%, and treatment success would increase from 71 to 85%. The DOTS expansion was projected to prevent 63 080 TB cases and 52 120 TB related deaths in Haiti. Societal savings from such an expansion were calculated to be $131 million over a 20-year period. [76]

Costs of directly observed therapy have also been compared to self-administered therapy. As would be expected the type of costs used in the analysis influences the cost-effectiveness results regarding DOTS vs. self-administered therapy. From the perspective of the health care system, if the patient time costs were excluded from the analysis then DOTS was the more cost-effective approach ($2785 vs. $10 529). With the inclusion of patient time costs, DOTS was the more expensive approach ($2117 vs. $1339). However if patient time costs associated with treatment failure was included in the analysis, then DOTS cost less ($3999 vs. $12 167). [77] (Table 2.3)

Table 2.3 Summary of Studies on Decision Analysis and Tuberculosis Resistance and Treatment

Citation	Aim	Methods	Assumptions	Costs	Results
Finnell, S.M., J.C. Christenson, and S.M. Downs, *Latent tuberculosis infection in children: a call for revised treatment guidelines.* Pediatrics, 2009. **123**(3): p. 816-22.[74]	It is recommended for immigrant children with latent TB infection (LTBI), isoniazid (INH) therapy be used for 9 months. However this recommendation does not take resistance into account. The study set out to determine at what rate of isoniazid resistance should an alternative regimen (other than the 9 month recommendation) of isoniazid be considered Treatment 1: INH for 9 months. Treatment 2: Rifampin for 6 months Treatment 3: Combination of 1 and 2 No treatment	• Decision tree evaluating three TB regimens and no treatment option for LTBI treatment in pediatric cases • Societal perspective	• The likelihood of resistant TB infection in immigrant children reflects the prevalence of resistance in the child's country of origin, • Treatment of latent TB infection provides lifelong benefit by reducing the subsequent risk of reactivation • Treatment with a drug to which the organism is resistant provides no benefit in reducing the risk of reactivation • There is no synergism of the combined treatment beyond that of the more effective drug • Reactivation leads to pulmonary TB	• Cost of medication • Administration costs • Cost of side effect of the drug (liver failure)	• Results were presented as cost and cost per case of TB prevented • Rifampin was found to cost the lowest, but this result was sensitive to the isoniazid resistance rate of the country from where the child immigrated to the United States (least costly for areas with a rate ≥ 11%) • The most effective treatment was isoniazid plus rifampin. However this combination type treatment was expensive and would cost more than $1million per reactivation case prevented.

Table 2.3 (continued)

Khan, K., et al., *Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States.* N Engl J Med, 2002. **347**(23): p. 1850-9.[75]	To compare four treatment approaches (1) no intervention, (2) tuberculin skin testing followed by treatment with "300 mg of isoniazid plus 25 mg of pyridoxine daily for nine months, (3), 600 mg, or rifampin daily for four months, or (4) 600 mg of rifampin plus 15 to 20 mg of pyrazinamide per kilogram of body weight daily for two months."	• A decision analysis was conducted on a hypothetical cohort adult immigrants from developing nations who entered the United States in the year 2000. • The developing nations included: China, Philippines, South Korea, Vietnam, East Asia and the Pacific, India, South Asia, Mexico, Haiti, Latin American and the Caribbean, Eastern Europe and Central Asia, Middle East and North America, an Sub Saharan Africa.	• Prevalence of latent infection among the immigrants was equal to the prevalence of TB infection in the immigrants country of origin • Drug resistance patterns in this cohort reflect the drug resistance patterns seen in foreign born individuals who developed disease within 5 years of entry into the United States • The development of active TB disease after the immigrant enters the United States is due to the reactivation of TB disease acquired in the persons place of birth • Treatment of latent TB disease provides life long benefit by reducing the occurrence of active TB disease • If a patient is resistant to a drug, then that drug will provide no benefit in the future • "Presence of resistance to either rifampin or pyrazinamide reduces the effectiveness of the combined regimen by 50%" • Immigrants have a very small risk of HIV infection at the time of entry into the United States • Deaths occur on average within 2 months of being diagnosed with active disease • If a patient experiences an adverse drug reaction during treatment the patient will have an unscheduled ambulatory clinic visit • Immigrants have been exposed to non tuberculosis mycobacteria or have received the BCG vaccination	• Transportation costs • Cost of interpreters • Laboratory test costs • Treatment costs • Cost of adverse drug reactions • Hospitalization costs	• Screening immigrants into the US for latent TB will be economically beneficial. • Over a one year period, 9000 to 10 000 active TB cases would be prevented, resulting in a savings of $60 to $90 million US dollars • Rifampicin monotherapy was dominated in all regions • However, in the following regions: Vietnam, Haiti, and the Philippines, rifampin plus pyrazinamide was the most effective and least expensive.

Tale 2.3 (continued)

Jacquet, V., et al., *Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti.* BMC Public Health, 2006. **6**: p. 209.[76]	To estimate the costs and benefits of Directly Observed Treatment Shortcourse (DOTS) expansion in Haiti from the government, and societal perspectives.	• A Markov decision analysis to compare the current national TB program to DOTS expansion	• DOTS expansion would reach 100% of government health centers in Haiti within 3 years • Case detection would increase from 49% (current WHO estimate) to 70% • Treatment success would increase from 71% to 85% • Treatment failure would remain unchanged • TB mortality would remain unchanged • Rates with initial drug resistance would not change during the entire DOTS expansion • HIV prevalence would not change during the entire DOTS expansion • Hospitalizations would decrease by two thirds with DOTS expansion • Number of patients investigated for each new case of TB would increase from 4 to 16 • Retreatment and resistance cases would be treated with second line TB drugs (49% cure and 12% mortality) • DOTS expansion would result in a 6% decrease in TB annual TB incidence (a similar pattern was noted in Peru after DOTS implementation	**Government Costs**: • TB-related health care costs • DOTS implementation and expansion • Drug costs **Societal Costs** • Government costs • Out of pocket costs • Lost wages including family members time for caring for ill patient • Productivity loss due to morbidity and mortality	• The expansion program was projected to prevent 63 080 TB cases and 52 120 TB related deaths • Total societal savings from the expansion program was calculated to be $131 million, over a 20 year period

Table 2.3 (continued)

Burman, W.J., et al., *A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis.* Chest, 1997. **112**(1): p. 63-70.[77]	To conduct a cost-effectiveness analysis to compare self administered therapy to directly observed therapy (DOT)	A decision analysis model was used to compare cure and failure rates with self-administered therapy vs. directly observed therapy. Failure rates of both therapies were expanded to drug susceptible and multi drug resistant TB Results were analyzed from the perspective of a tuberculosis control program and health care system	• Treatment failures would occur during treatment or within 6 months of completing treatment • Identification of treatment failure within 12 months of diagnosis did not require discounting of costs but discounting was used in the case of MDR-TB where treatment was assumed to continue for 2 years after diagnosis • Patients who were diagnosed with MDR-TB were assumed to be hospitalized directly after diagnosis for three months in order to be isolated and receive intravenous drugs • 80% of patients who experience initial treatment failure would be hospitalized for an average of 14 days • Treatment of MDR-TB was assumed to be a standard treatment of ofloxacin, cycloserine, ethionamide, and capreomycin for 6 months follwed by 18 months of treatment with oral agents. • Oral outpatient treatment for MDR-TB treatment was assumed to administered via DOTS for 5 days a week and then as self administered treatment over the weekends • Patients with drug susceptible TB would not work for 3.5 weeks after diagnosis • Patients with MDR-TB would not work for 3 months after diagnosis	• TB drugs • Nursing cost • Sputum Culture • Chest Radiograph • Serum bilirubin and asparate aminotransferase test • Delivery of DOT dose • Costs of treatment failures which included the cost of diagnosis and hospitalization,	• From the perspective of the tuberculosis control program DOT was dominant ($1405 vs $2314) resulting in cost savings of $90900 • Results from the perspective of the health care system were dependent on whether patient time costs were included. When patient time costs were excluded, DOT cost-effective ($2785 vs. $10 529). However when patient time costs were included, the initial cost of DOT was higher than with self-administered therapy ($2117 vs. $1339). When patient time costs associated with treatment failures were included DOT had a lower cost compared to self administered treatment ($3999 vs. 1$2167)

2.11 Cost-Effectiveness of Diagnostic Tests

Cost-effectiveness studies are more common among drug treatments than diagnostic tests because it is difficult to determine the incremental cost per number of years saved for diagnostic tests. With diagnostic tests it is easier to determine the incremental cost per case detected using specificity and sensitivity values. False positive, false negative, true positive and true negative test results are used in the analyses. Treatment approaches and life expectancy gains and losses are then established. Time frames used in the cost-effectiveness of diagnostic tests are dependent on the type of disease under study. Short-term time periods are used for curable diseases. However, longer time frames are used if the disease spans over a lifetime or many years. Most importantly, cost-effectiveness analyses for diagnostic tests are presenting clinical and cost information for clinicians to make choices for patients, therefore results in these analyses must be robust and sensitivity analyses must be conducted to reduce bias.[78, 79]

2.12 Limitations in Cost-Effectiveness Studies of TB Diagnostics

In resource-poor settings, because financial support might be limited, it is important that any monetary investments be supported by evidence. Cost-effectiveness studies can help guide the decision making process, and should therefore be conducted with care. Unfortunately, in TB research there are several limitations with regard to cost-effectiveness studies on diagnostics and treatment. It is reported that there is a large variability in outcome measures related to TB management. For example, transmission rates among patients are difficult to measure. Furthermore, the effectiveness of many TB tests is based on sensitivity and specificity estimates, which are obtained from comparison of the diagnostic test in question to some "gold standard." Currently, there are no guidelines on how to evaluate the costs of a diagnostic test. In addition, costs which are important in conducting the test, are often excluded from studies. Examples of these costs include training staff on the use of the test, and technical support. It is recommended that researchers stipulate what costs were used in determining the effectiveness of the diagnostic test. Researchers are in the process of developing a standardized tool, which would provide guidance on how to conduct cost and cost-effectiveness studies on diagnostic tests. [60]

Diagnostic tests should be implemented cautiously depending on the sensitivity, specificity, reliability, and cost of the test. Using pharmacoeconomics and modeling techniques, researchers can estimate the cost-effectiveness of using novel diagnostic tests in many diseases, including infectious diseases such as TB. However, Walker advises

that “methodological challenges, including specification of appropriate alternatives, measuring costs, and measuring outcomes” can be experienced during simulations. The cost-effectiveness results will depend on the characteristics of the test, treatment practices, resources or environment in which the test will be implemented, epidemiological factors, HIV rates, and other factors such as acceptability and training of health care professionals. [36]

CHAPTER 3

TUBERCULOSIS AND HIV IN SOUTH AFRICA

3.1 INTRODUCTION

A brief background on South Africa, and epidemiological information on the HIV, TB and MDR-TB outbreak are provided in Chapter 3. A problem statement, the study objectives, and study hypotheses are also provided here.

3.2 SOUTH AFRICA: BACKGROUND

South Africa is situated on the southern tip of Africa, and has a population of approximately 50 million (Figure 1 and Table 3.1). In 2009 the Gross Domestic Product per capita was $5786. (Figure 1 and Table 3.1). Currently the country has in place treatment guidelines for the management of Tuberculosis.

Taken From: http://www.routes.co.za/map.html[80]

Table 3.1. Background Information on South Africa

Population of South Africa	49 667 628
Provinces in South Africa: 1. Eastern Cape 2. Free State 3. Gauteng 4. Kwa-Zulu Natal 5. Limpopo Province 6. Mpumalanga 7. Northern Cape 8. North West Province 9. Western Cape	9
GDP per capita (2009)	$5786
Tuberculosis and Multidrug-Resistant Tuberculosis Guidelines Available	Yes

In 2001, approximately 4.7 million South Africans had HIV (including cases where AIDS had not developed or cases showing no symptoms of AIDS).[81] By 2008, the Joint United Nations Program on HIV/AIDS reported an estimated 5.7 million South Africans were HIV positive.[82] The rising South African HIV epidemic and previous governing policies which made access to health care difficult for certain groups of South Africans have contributed to the country having one of the highest TB and HIV burdens in the world.[83]

Karim et al. reported: "Despite constituting just 0.7% of the world's population, South Africa accounted for 17% (about 5.5 million people) of the global burden of HIV in 2007."[83] HIV positive patients are more likely to develop TB because of a compromised immune system and TB is the leading cause of deaths among HIV positive

patients.[84] The high HIV rate coupled with poor TB medication adherence and resistance to TB medication has resulted in a TB crisis and more recently (2006), an MDR-TB and XDR-TB outbreak in South Africa.[85] Perhaps Wells et al. provide the best description for the dual crisis describing HIV and multidrug resistant co-infection as the "perfect storm".[52] In one small study from Msinga, South Africa, MDR-TB and XDR-TB re-infections were primarily due to exogenous infection (re-infection strains differing from the initial strain of infection). In this study, 15 of the 17 patients with differing strains of infection were also HIV positive.[3]

According to Karim et al., TB was first noted in South Africa in the 17th century, with the incidence increasing during the 20th century.[83] Statistics from the 1960s indicate that there were about 350 cases per 100 000 population per year. These numbers decreased in the 1970s, but it is not clear if a misrepresentation was present, because when the Apartheid rule was abolished in the 1990s and all South Africans were taken into account during calculation of national statistics, an increase in TB cases was noted. In the "1994-1997 Anti-tuberculosis Drug Resistance in the World Report", published by the WHO, no statistics were provided for South Africa, because the country had just achieved democracy and the statistics were not available.[86] However, by 2002, drug resistance statistics were beginning to be generated for South Africa.[87]

The directly observed therapy short course (DOTS) strategy assisted in TB control efforts in South Africa. However, the HIV epidemic diminished the effect of DOTS, which resulted in a rise in opportunistic TB infections.[83] TB rates increased more than four times (163 per 100 000 to 628 per 100 000) over a 20-year period (1986-2006).

Over 70% of patients with newly diagnosed TB also have HIV. [48] Table 3.2 summaries some of the epidemiological TB and HIV estimates (2008) from South Africa.

Table 3.2. Epidemiological Burden of MDR-TB in South Africa.

Variable	Best Estimate (Range)	Source
Total Number of Estimated Cases of MDR-TB	13 000	[88]
Percentage MDR-TB among new TB cases (95% CI), 2002	1.8 (1.5-2.3)	[88]
Percentage MDR-TB among previously treated TB cases (95% CI), 2002	6.7 (5.5-8.1)	[88]
Number of MDR-TB among incident new and relapse cases (95% CI), 2002	10 000 (7 500-13000)	[88]
Number of incident acquired MDR-TB cases (95% CI), 2002	2 800 (1900–3900)	[88]
Number of MDR-TB among incident total TB cases (95% CI), 2002	13000 (10000-16000)	[88]
Number of TB patients who had drug susceptibility testing, 2008	68087	[48]
Number of MDR-TB cases found among the 68 087 patients who had drug susceptibility performed, 2008	6219	[48]
Expected number of MDR-TB cases to be treated, 2009 2010	 5662 6071	[48]

Estimates shown, are World Health Organization Estimates for the year 2008, unless otherwise indicated

3.3 MDR-TB AND XDR-TB OUTBREAK IN SOUTH AFRICA

In 2006, an outbreak of MDR- and XDR-TB occurred in Kwa-Zulu Natal South Africa.[89] During this time, 72 (39%) of 185 culture-confirmed patients from a rural clinic in Tugela Ferry had MDR-TB. Additionally, 53 patients were diagnosed with XDR-TB. Forty-four of the 53 XDR-TB patients were tested for HIV and were HIV negative. However, the number of XDR-TB cases rose and by December 2006, up to 300 cases were identified throughout South Africa.[85, 90] In addition, the mortality rate associated with TB more than doubled from 1990 to 2006 ("78 per 100 000 population to 218 per 100 000 population"). [83] Karim et al. also reported that the WHO estimates indicated "8238 (2%) of the 453 929 new tuberculosis cases and 5796 (7%) of 86 642 tuberculosis re-treatment cases had MDR tuberculosis in 2006."[83] In 2008, the WHO reported that an estimated 13 000 patients with incident TB developed MDR-TB in South Africa (Table 3.2). [88] However, to date, no statistics are available for the prevalence rates of MDR-TB among HIV positive patients, although prevalence rates from the outbreak in 2006 indicate that over 30% patients had MDR-TB.

A case-control study was conducted from 2005 to 2007 at the Tugela Ferry site in South Africa to determine predictors of MDR-TB and XDR-TB in a high HIV prevalence area. At that time (2007) the TB, MDR-TB, and XDR-TB rate in the community was 1100, 118, and 72 per 100 000 population respectively. Three patient groups consisting of 116, 123 and 139 TB, MDR-TB and XDR-TB cases respectively were studied. Previous

TB treatment failure and prior hospitalization were strongly correlated with MDR-TB (adjusted odds ratio 51.7 [CI 6.6 - 403.7] and adjusted odds ratio 3.8 [CI 1.1 - 13.3] respectively), and XDR-TB (adjusted odds ratio 51.5 [CI 6.4- 414.0] and adjusted odds ratio 6.1 [CI 1.8 – 21.0] respectively). HIV was associated with a significant risk of XDR-TB (Adjusted odds ratio 8.2[1.3 – 52.6]) compared with MDR-TB (adjusted odds ratio 1.4 [CI 0.5-4.0]). Andrews et al. also reported that more MDR-TB and XDR-TB patients were receiving ARV treatment, and that at the same site unpublished research showed that more HIV patient's MDR-TB and XDR-TB remained undiagnosed. Andrews et al. stressed the importance of rapid diagnostic testing to avoid loss of gains from money invested in the ARV treatment program in South Africa.[91]

3.4 TREATMENT OF MDR-TB IN SOUTH AFRICA

According to the South African Department of Health guidelines for the treatment of MDR-TB, a standard MDR-TB treatment approach consists of a six-month intensive phase of treatment with five drugs: (kanamycin, ethionamide, pyrazinamide, levofloxacin, and terizidone), followed by an 18-month continuation phase with four drugs: (ethionamide, pyrazinamide, levofloxacin, and terizidone). Ideally, drugs are administered in a hospital.[92] Tables 3.3 and 3.4 show drugs and recommended dosage ranges for the treatment of MDR-TB.

Table 3.3 South African Department of Health Approach for the Intensive Phase of MDR-TB Treatment in Adults[92]

Patient Weight	Drug	Dosage
<33kg	Kanamycin	15-20 mg/kg
	Ethionamide	15-20 mg/kg
	Pyrazinamide	30-40 mg/kg
	Levofloxacin	750 mg
	Terizidone	15-20mg/kg
33-50kg	Kanamycin	500-750mg
	Ethionamide	500mg
	Pyrazinamide	1000-1750mg
	Levofloxacin	750mg
	Terizidone	750mg
51-70kg	Kanamycin	1000mg
	Ethionamide	750mg
	Pyrazinamide	1750-2000mg
	Levofloxacin	750mg
	Terizidone	750mg
>70kg	Kanamycin	1000mg
	Ethionamide	750mg-1000mg
	Pyrazinamide	1750-2500mg
	Levofloxacin	750mg-1000mg
	Terizidone	750mg-1000mg

Source: Department of Health Republic of South Africa. Management of Drug Resistant Tuberculosis in South Africa 2010.

Table 3.4 South African Department of Health for the Continuation Phase of MDR-TB Treatment[92]

Patient Weight	Drug	Dosage
33-50kg	Ethionamide	500
	Pyrazinamide	1000-1750mg
	Levofloxacin	750mg
	Terizidone	750mg
51-70kg	Ethionamide	750mg
	Pyrazinamide	1750-2000mg
	Levofloxacin	750mg
	Terizidone	750mg
>70kg	Ethionamide	750mg-1000mg
	Pyrazinamide	2000mg-2500mg
	Levofloxacin	750mg
	Terizidone	750mg-1000mg

Source: Department of Health Republic of South Africa. Management of Drug Resistant Tuberculosis in South Africa 2010.

A second or individualized approach to treatment can also be considered. However, the individualized approach requires some skill in ranking the drugs with regard to their effectiveness in terms of drug susceptibility results, and may not be commonly used.[92]

3.5 HOSPITALIZATION AND DRUG RESISTANT TB IN SOUTH AFRICA

Patients who are diagnosed with MDR-TB in South Africa should be hospitalized

for a period of 6 months during the intensive phase of their treatment. In a report by the Center for Global Health Policy, Dr. Sarita Shah from the Albert Einstein School of Medicine discussed the issue of hospitalizations and resistance in South Africa. According to Dr. Shah, there are centralized hospitals in South Africa to treat MDR-TB. However, overcrowding caused by large numbers of current patients and influx of new cases sometimes forces medical staff to discharge patients early (example after three or four months of intensive treatment instead of the required 6 months hospitalization). Many of these patients default and do not return for the continuation phase of treatment. This reduces success rates of treatment and promotes transmission in the community.[93]

3.6 COST-EFFECTIVENESS STUDIES CONDUCTED ON TB AND MDR-TB IN SOUTH AFRICA

Several studies were conducted on the costs and effectiveness of TB treatment in the 1990s in an attempt to determine the value of DOTS. For example, one study looked at the economic feasibility of directly observed treatment when compared to conventional TB treatment for a group of adult patients with new cases of tuberculosis receiving TB care in Hlabisa district in Kwa-Zulu Natal, South Africa.[94] Directly Observed Therapy Short Course (DOTS) treatment was less expensive than conventional treatment from the perspective of the health care system and patient. Overall, DOTS cost less than conventional treatment ($740.90 vs. $2047.70) because of reduced hospital stay. The

DOTS strategy was also more cost-effective per patient cured [$890 for DOTS vs. $2095 for the (best case) and $3700 (worst case) for conventional treatment].[94]

The results and estimates of many of the studies conducted in the 1990s and early parts of the last decade are limited because of the epidemiological changes that have taken place in South Africa with regard to TB disease.

Recent studies on cost-effectiveness of TB diagnostics include the study by Dowdy et al. discussed in detail in Chapter 2. Dowdy et al. evaluated the cost-effectiveness of a hypothetical test to detect TB in South Africa, which showed that increasing sensitivity from 50% to 100% increased the incremental DALYs averted from 75 to 152 and the cost per TB suspect from $40 to $50.

Additionally, limited cost-effectiveness studies have been conducted on TB alone. However, cost-effectiveness and cost utility studies have been conducted on the introduction of antiretroviral treatment for South African HIV patients.

In 2004, a report was published on the assessment of the cost-effectiveness and cost utility of providing ARV treatment to public sector South African patients. The outcomes were cost per life year gained and quality-adjusted life-year gained with or without ARV treatment (in patients with CD4 cell counts < 200 cells/μl). The research was conducted in three public sector clinics in Khayelitsha, South Africa. Costs of medication and capital costs including "medical equipment, furniture, and staff training" were included in the Markov model. The findings showed that ARV cost 13 754 South

African Rand per QALY vs no ARV at 14 189 South African Rand per QALY. The ICER per QALY on ARV is R13 621. The researchers concluded that initiating treatment in HIV positive patients with a CD4 count <200 cells/µl is cost-effective. Treatment with ARV's also resulted in a gain in life expectancy of 6.06 years (6.79 QALYs on ARV vs 1.59 QALYs for no ARV). Results were sensitive to cost of ARV and CD4 cell counts. This study provided some of the first cost-effectiveness results for a government funded ARV program in South Africa. However, assumptions surrounding treatment regimens and short patient follow up times were listed as possible limitations of the study.[95]

3.7 TREATMENT OUTCOMES ASSOCIATED WITH TB, MDR-TB, XDR-TB AND HIV IN SOUTH AFRICA

Researchers have worked with the WHO to define the following terms as possible outcomes of TB treatment: cure, completion of treatment (however no culture result present), treatment failure, death, default (patient stops taking treatment), patient transferred out of one TB treatment clinic/program to another (patient may or may not continue TB treatment), and treatment success (patient is cured after course of TB treatment).[96] One study that investigated default rates in a group of patients with MDR-TB in Kwa-Zulu Natal, South Africa found the following percentages for each of the following outcomes in a group of 1209 MDR-TB patients: cure [491 (41%)]; completed ([35 (2.9%)]; failed [208 (17%)]; died [223 (18%)], and defaulted [252 (21%)].[97] A

similar pattern of outcomes was published for Cape Town, South Africa where over an 11-year period outcomes for 747 MDR-TB patients were studied. Outcomes published for the 491 (66%) patients who received treatment were: cured or completed treatment [239 (49%)]; failed [27 (5%)]; died [68 (14%)]; defaulted [144 (29%)]; transferred [(10 (2%)]; remained on treatment [(3; (1%)].[98] Here it can been seen that there is an 50% probability of treatment failure and success in MDR-TB patients in South Africa.

Connolly et al. examined the effect of HIV on TB mortality in Hlabisa district, South Africa from 1991 to 1995. There were 258 cases of death among 2376 TB cases with available outcomes data in this district during this period. Risk of death in TB patients infected with the HIV virus was 2.4 times higher (95% Confidence Interval: 1.7-3.5) than patients who were HIV negative. Risk of death was also higher (1.4 times, 95% Confidence Interval: 1.1-1.8) in HIV infected patients vs. those whose HIV status was unknown.[99] The probability of death in HIV negative patients remained constant at about 1% per month. However, in HIV positive patients, the probability of death appeared to rise on average by an estimated 3% per month. Overall mortality at the end of the study period was 18.5% in HIV positive patients and 6.8% in HIV negative patients. TB related deaths among HIV patients without ARV treatment was 16-35% and 4-9% in HIV uninfected patients.[99-101]

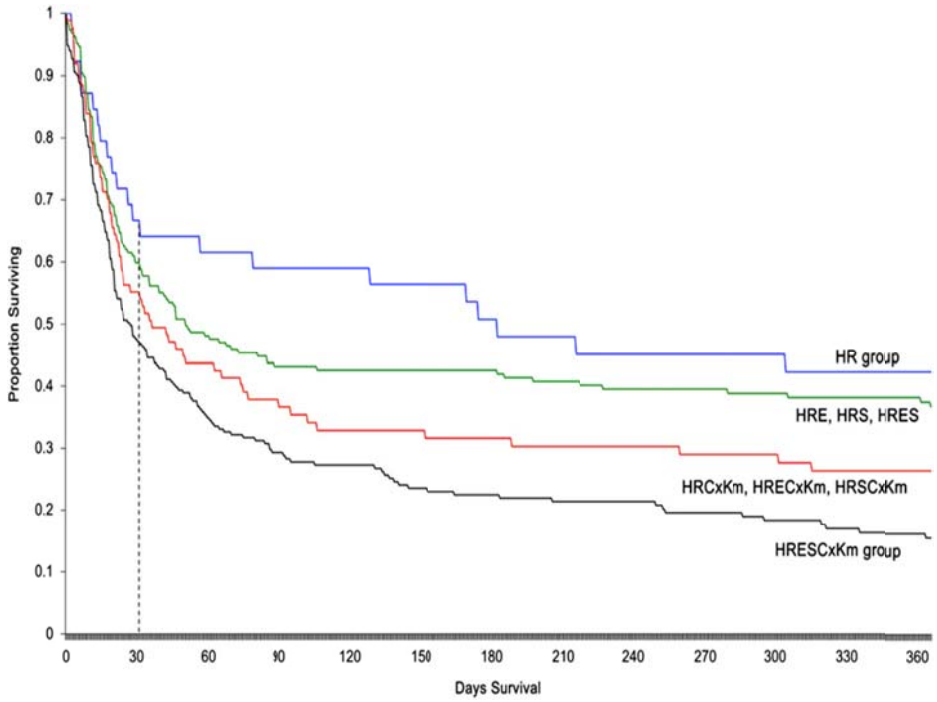
In a study (1995) conducted among 28 522 South African non-white miners, there were 376 cases of TB and 190 (50%) of the TB positive patients had HIV. In addition HIV positive patients had a higher mortality rate than HIV negative patients. (13% vs 0.5%).[101, 102]

In all of these studies the patients were on first line TB drugs including Rifampicin, Isoniazid, Ethambutol and Pyrazinamide.[99, 101, 102]

The largest retrospective observational study on mortality related to MDR-TB and XDR-TB cases in a high HIV setting took place in Tugela Ferry, South Africa. Patient data were collected from medical records between the years 2005 and 2007. Between these years 272 MDR-TB and 382 XDR-TB patients were identified. Patients were treated with standard TB treatment prior to being diagnosed with drug resistant TB. Results for drug susceptibility testing took 6-8 weeks to return and patients who had confirmed TB were referred and treated at a hospital in Durban, South Africa. Treatment consisted of "a standardized regimen of Kanamycin, ciprofloxacin, ethionamide, ethambutol (if susceptible), pyrazinamide (if susceptible), and terizidone or cycloserine (if ethambutol resistant) for 6 months (intensive phase) and continued on this regimen, without Kanamycin for an additional 18 months".[103] More than half of the patients who had drug resistant TB (75% of MDR-TB and 69% of XDR-TB patients) were treated for TB in the past year. Almost all (90% of the drug-resistant groups also had HIV. Thirty-day mortality was nearly 40% in the MDR-TB group. (range =34%-54%) This high 30-day mortality indicates the need for rapid diagnostic tests. [103] Patient's survival rates are shown in Figure 3.2.

Figure 3.2 Kaplan-Meier Survival Curve for Patients with Multi-Drug Resistant and Extensively Drug Resistant Tuberculosis in South Africa.

"Graph shows multidrug-resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB), 2005 to 2007(log-rank, P , 0.0001). Letters indicate drugs to which isolate was resistant: H, Isoniazid; R, Rifampin; E, Ethambutol; S, Streptomycin; Cx, Ciprofloxacin; Km, Kanamycin. " Taken from: Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med.* Jan 1 2010;181(1):80-86.



A similar study was conducted in the same area (Msinga, Kwa-Zulu Natal) from 2005 to 2006. During this period 1539 patients were tested for drug resistance using traditional drug susceptibility testing. From this group 221 patients were diagnosed with MDR-TB and 53 XDR-TB. Dates of death were available for 42 of these patients and all died within an average of 16 days of diagnosis (range=6-37days) showing high XDR-TB

fatality.[104] Case records for 195 of 227 XDR-TB cases were analyzed from four government funded XDR-TB facilities in South Africa. Eighty-three patients died before initiation of treatment (n=21) or during follow up (n=62). One hundred and seventy four patients were treated and all were HIV positive. There was no significant difference in death ($p>0.05$) between patients with HIV infection (34 of 82 patients) and those without HIV infection (28 of 92 patients). However, there were significantly fewer deaths ($p<0.0.5$) in HIV patients who were on ARV treatment. Culture conversion was low; achieved in 33 (19%) of 174 patients. [105] In an editorial on these findings, representatives from the WHO commented that access to ARV treatment is paramount in the current HIV/TB crisis; and culture conversion in these patients was low indicating the need for quicker diagnosis and initiation of second line TB treatment.[106]

Lawn et al. summarize mortality information from two HIV treatment initiation cohort studies in South Africa.[107, 108] In Cape Town, approximately 30 deaths per 100 person years occurred in the month leading up to the initiation of ARV medication. According to Lawn et al. this accounted for 67% of deaths in the first three months of ARV initiation.[107, 108] A higher percentage of death, 87%, prior to initiation of treatment was noted in other areas of South Africa. [107, 109]

3.8 Overview of Laboratory Capacity within South Africa

Worldwide approximately US$ 1 Billion is spent on diagnosing TB cases annually.[110, 111] This type of expenditure must be justified by good case detection rates within countries.[112]

In South Africa the National Health Laboratory Service (NHLS) conducts all pathology testing for all (100%) government (publically) funded health centers. In addition to testing for the presence of communicable diseases the services include testing for chronic disorders, and cancer. There are 349 laboratories located throughout South Africa.[113] Recently one of the laboratories in South Africa together with the Foundation of Innovative Diagnostics (FIND), provided support to Lesotho (a landlocked country within South Africa) to renovate and expand TB testing in Lesotho. The South African laboratory was able to provide external quality control. The expansion of testing in Lesotho from 100 TB cultures per month to nearly 1000 cultures per month is proof that laboratory expansion is possible in the developing world when adequate training and investment of funds is provided. In Lesotho, the total cost for laboratory expansion, consumables and training was approximately US $550 000.[114] Similar expansion is underway throughout South Africa. South Africa is currently using the rapid Genotype MDR-TB*plus* test for detection of multidrug-resistant TB as confirmed by two laboratories in Kwa-Zulu Natal and the Western Cape Town.

3.9 COSTS OF TB AND HIV IN SOUTH AFRICA

South Africa has a two-tier health care system: (1) public/(South African government funded); and (2) private health insurance. The HIV and TB crisis weighs heavily on the government-funded clinics where patients cannot afford private health insurance. Human suffering and health care costs associated with HIV and TB are immense. Millions of South African Rands are spent on making antiretroviral medication available to patients as well as developing specialized clinics referred to as antiretroviral (ARV) clinics where patients receive treatment and monitoring for their HIV infection.[115]

Harling and Wood report that information on healthcare expenditures in South Africa is limited and that few studies have estimated the costs of ARV programs. They summarize studies that estimated the average cost of ARV treatment provision in South Africa, and show that the cost per patient per year for ARV can range from $1023 to $2502 for public clinics, and can be as high as $2761 per patient per year in the private sector.[116] Lawn et al. conducted a 3-year prospective cohort study to determine the impact of TB on ARV programs in South Africa. The researchers reported "prevalent and incident TB were associated with greater than two-fold increased mortality risk." [84, 117] Although limited data are available, Lawn et al. reported that the leading cause of death in HIV patients in sub-Saharan Africa appears to be TB.[84] A course of anti-tuberculosis medication for the treatment of uncomplicated pulmonary tuberculosis can cost approximately $20/month to treat. However, the costs of treating MDR-TB are approximately 50 to 200 times higher and are due to the specialized drugs required to

treat the disease, and the extended periods of hospitalization that are required for effective management of MDR-TB.[88] A concern is that MDR-TB will worsen the HIV/AIDS situation in South Africa and negate positive results from the investment made by the South African government toward the HIV initiative by reducing quality of life and increasing mortality in patients with HIV. Additionally, the chances of spread of MDR-TB, especially among immuno-compromised patients and health care professionals, are always a concern. Among South African patients diagnosed with HIV and receiving antiretroviral treatment, a diagnosis of MDR-TB has the potential to reduce the financial benefits provided by a healthcare system already in dire straits.[117-120] Public health care steps suggested to contain the crisis include: improving the tuberculosis case detection and cure rate, integrating HIV and TB services, and identifying and treating drug-resistant TB. A prospective study in which 119 patients co-infected with TB and HIV were followed over a period of 12 months, in Kwa-Zulu Natal, South Africa and who received integrated TB and HIV care, showed lower mortality rates among patients (11% in the study vs 25-40% pre ARV treatment rates), and improved visit and treatment adherence (93% of visits and 99% of all ARV doses were adhered to).[121]

Estimations of hospitalizations costs for TB and HIV patients treated in South Africa are limited. One study on unit costs of inpatient days in public hospitals in South Africa showed that costs for medical patients range between US $37.23 and US $70.86.[122] The WHO listed a much higher cost for treating patients at the tertiary level in South Africa (approximately $180 from 2005 data).[123]

A major priority for South Africa should be the early diagnosis of drug resistant TB (DR-TB). It was recommended that drug susceptibility testing (DST) "should be conducted in at least 85% of re-treatment cases" in South Africa because of the public health concern the disease presents.[83]

3.10 PROBLEM STATEMENT

Tuberculosis multi-drug resistance patterns that have been detected in the last decade can be attributed to inappropriate prescribing of, and poor adherence to, TB drug treatment. New drug formulations have the potential to make the problem worse, by increasing the spread of resistance if not adhered to. Therefore, alternative strategies must be implemented to curb the problem of drug resistance. Researchers have stressed the importance for general TB case detection rates in South Africa to be increased from an estimated 62% to 70%, which was suggested as an acceptable case detection rate by the WHO.[83] An alternative method, and perhaps more effective method compared to the development of new drugs, is rapid diagnosis and detection technology. Rapid detection may allow for earlier treatment and reduced patterns of spread of the disease in the community.[83] However, limited data exist on the use of rapid TB diagnostic tests. Secondly, HIV adds to the TB burden. *Many patients who are HIV positive succumb to TB rather than the HIV/AIDS virus.* South Africa provides an example of the challenge the presence of both diseases poses to the management of each condition. The South African government provides free Anti-Retroviral (ARV) treatment to HIV patients without health insurance. However, many of these patients die due to opportunistic

infections such as TB. It is proposed that early testing of South African patients on antiretroviral medication (funded by the South African Department of Health), using rapid detection tests for the possible presence of MDR-TB could be cost saving compared to conventional drug susceptibility culture testing.[100, 124]

The objective of this study is to estimate the ICER per DALY averted to measure and compare the cost-effectiveness of using a line probe assay test versus conventional drug susceptibility testing to detect the presence of multi-drug resistant tuberculosis (MDR-TB) in a simulated South African population diagnosed with HIV. The simulation will include the cost of the diagnostic tests, cost of first- and second-line tuberculosis drugs, and costs of hospitalizations.

3.11 STUDY OBJECTIVES

The objectives of this study are:

1. To develop a decision analysis tree in order to compare the use of the rapid line probe assay diagnostic test to conventional drug susceptibility culture testing. using valuations obtained from expert opinion, literature, and country-specific cost data collected by the World Health Organization and Foundation of Innovative Diagnostic on (1) probabilities, (2) costs and (3) disability-adjusted life-years associated with the use of the line probe assay test and sputum/conventional culture testing.
2. To estimate the average direct medical costs associated with the use of the line probe assay test and sputum/conventional culture testing.

3. To estimate the average DALYs associated with the use of the line probe assay test and sputum/conventional culture testing.
4. To determine whether the use of the line probe assay test to isolate multi-drug resistant tuberculosis is a cost-effective approach in a South African government-funded health care setting, based on incremental cost per disability-adjusted life-year gained estimates.

3.12 STUDY HYPOTHESES

Objective 1 involves model development and the collection of information from the literature and through expert opinion and does not require the development of hypotheses.

The following three hypotheses based on Objectives 2,3 and 4 were tested.

Hypothesis 1:

The average direct medical cost associated with the line probe assay test is greater than the average cost associated with the use of conventional drug susceptibility testing.

$$\text{Average Cost}_{\text{line probe assay test}} > \text{Average Cost}_{\text{conventional drug susceptibility testing}}$$

Hypothesis 2:

The average DALYs associated with the line probe assay test is lower (= better quality of life) than the average DALYs associated with the use of conventional drug

susceptibility testing.

$\text{Average DALYs}_{\text{line probe assay test}} < \text{Average DALYs}_{\text{conventional drug susceptibility testing}}$

Hypothesis 3:

The incremental cost-effectiveness ratio per DALY averted for the line probe assay test, compared to conventional drug susceptibility testing, will be an acceptably low number (e.g., ≤ three times the 2009 Gross Domestic Product per capita for South Africa: $17361).

CHAPTER 4

METHODOLOGY

4.1 INTRODUCTION

This chapter covers the following methodological aspects of the study: (1) a description of the development of the decision tree; (2) prevalence estimates; (3) costs, probabilities and outcome estimates used in the model; (4) information on sources for the costs, probabilities, and outcome estimates; (5) assumptions of the model; and (6) analyses (including sensitivity analyses) that were conducted in the study.

4.2 ETHICAL APPROVAL

The study used a hypothetical cohort of patients and estimates from the literature. The Institutional Review Board at The University of Texas at Austin provided an exemption from ethical approval for this study.

4.3 SOURCES OF DATA

Estimates for the following variables were used in this study: prevalence of MDR-TB; costs of testing for MDR-TB; probabilities of obtaining successful test results based on sensitivity and specificity values of the tests; treatment outcomes related to death (mortality), success and failure for tuberculosis; costs of MDR-TB treatment and

TB treatment; hospitalization outcomes, and mortality outcomes. Gaps in WHO estimate information were filled from other literature sources/scientific research studies conducted on HIV, TB and MDR-TB in Cape Town and Kwa-Zulu Natal (South Africa). Information was also gathered from experts in the field of TB and HIV. Costs on testing and treatment were collected directly from National Health laboratory services in South Africa, field study reports published by the Foundation of Innovative Diagnostics (FIND), the global laboratory division at the WHO, and the Department of Health in South Africa. Hospitalization costs were obtained from the WHO and literature sources. Disability-adjusted life-years (DALYs) were estimated from global disease burden sources and literature sources. In some cases, the DALY estimates were based on less extensive forms of tuberculosis disease in HIV patients.

A careful record of all estimated values used was maintained and is presented in the results section. These estimates were varied in a sensitivity analysis.

4.4 WORLD HEALTH ORGANIZATION ESTIMATES

The World Health Organization (WHO) requires national Tuberculosis (TB) control programs in the 27 high-burden tuberculosis countries "to complete an electronic data collection form focusing on case notifications, treatment outcomes, implementation of the STOP TB strategy and financing of TB control programs. These data are stored in WHO's global TB database and are used to produce an annual assessment of the status of the global TB epidemic and progress in TB control." [125]

The WHO has published a global report on the burden of TB disease every year on March 24th, World TB day, since 1997. The published estimates are derived from the Departments of Health within individual countries (including surveillance systems such as death registries and case notifications), research studies, and expert opinion. Two data collection forms are used to collect data. A short form is used to collect information from high-income countries, and a long form is used to collect information from high TB burden countries.[48]

The following are examples of the types of information collected from individual countries:[48]

- Case notifications
- Treatment outcomes broken down by gender, age and HIV
- An overview of services for the diagnosis and treatment of TB
- Laboratory diagnostic services
- Human resource development
- Drug management
- TB and HIV initiatives
- Management of drug resistant TB
- TB control in vulnerable populations and high-risk groups
- Health system strengthening (e.g., upgrading diagnostic laboratories) and the integration of TB control in primary health care
- TB infection control
- Adoption and use of technologies
- Budget of national TB control programs

- Utilization of general health services
- TB expenditures

In 2009, the WHO began collecting this information online (http://www.stoptb.org/tme), and found that the online response rate was high, with 198 out of 204 countries (97%) that were requested to report information responding online. One of the major limitations to publishing estimates early in the year is that some of the information is from two years prior to the publication. Therefore, from 2010 onwards the WHO has decided to publish estimates in October. October 2010 marks the latest information that was published by the WHO. [48]

Table 4.1 Definition of Estimates and Sources Used by the World Health Organization in Obtaining Prevalence, Incidence and Mortality Tuberculosis Estimates[48]

Estimate	WHO Definition	Sources
TB Incidence	New and relapse cases of TB occurring in a one-year period	• No direct incidence measures are available because no country has undertaken a nationwide incident TB survey due to the large sample sizes required and country financial constraints • Expert opinion • Calculated indirectly from prevalence and mortality estimates • Notification data received from countries on new and relapse cases • Using estimates from the proportion of cases detected, the following equation was used to estimate incidence during workshops held by the WHO: *Incidence = case notifications/proportion of cases detected* • Using measurements of mortality for South Africa, incidence was calculated using the following equation: Incidence = total deaths/proportion of death among incident cases
TB Prevalence	Number of TB cases at a given point in time	• National population-based surveys • Generally only include adults • Exclude extra pulmonary TB as well as smear negative and culture negative TB
Mortality	Death caused by TB, according to the 10th revision of the International Classification of Diseases.	• Vital registration systems within countries in which causes of death are coded according to the ICD-10 • Mortality statistics generally exclude deaths in HIV-positive TB cases
Estimates of prevalence of HIV among incident cases of TB	Not applicable	• Estimated from country-specific data • Measured indirectly using the following equation: $t=h\rho/1+h(\rho-1)$ "where t is the HIV prevalence among incident TB cases, *h* is HIV prevalence in the general population and ρ is the incident rate ratio or the incidence rate of TB in HIV-positive people divided by the incidence rate of TB in HIV-negative people," obtained through UNAIDS data

WHO = World Health Organization

4.5 TARGET POPULATION

The hypothetical target population is adult (≥18 years) South African HIV-infected TB patients who are eligible to receive ARV and TB treatment from publicly or government funded health care facilities in South Africa.

4.6 PERSPECTIVE

The study was conducted from the perspective of the South African Department of Health, as the majority of South African patients seeking TB and HIV treatment are treated at publicly/government-funded clinics.

4.7 ALTERNATIVES

Two alternatives were compared, the Gentotype MDR-TB*plus* rapid line probe assay diagnostic test recently adopted by the South African government for the detection of MDR-TB and traditional/conventional drug susceptibility testing, which involves culturing of bacteria.

4.8 PREVALENCE DATA

Unfortunately, recent data from 2010 South African country level data published by the WHO do not yet provide estimates of MDR-TB prevalence for an HIV patient

population on ARV treatment suspected of having MDR-TB. The prevalence of MDR-TB in an HIV-positive patient population in South Africa receiving antiretroviral treatment was assumed from an outbreak region of South Africa on the east coast of the country (Kwa-Zulu Natal).

4.9 PROBABILITIES

The following probabilities were included in the model:

(1) Probabilities of true positive (correct diagnosis), true negative (correct diagnosis), false positives, and false negatives;

(2) Probabilities of treatment success versus failure;

(3) Mortality estimates (probabilities of dying).

True positives, true negatives, false positives and false negatives were calculated using baseline prevalence rates of MDR-TB in HIV patients (obtained from the literature) and the following 2x2 epidemiology table.[126]

Table 4.2: Relationship between Sensitivity, Specificity, True Positive, True Negative, False Positive and False Negative Values for the Detection of MDR-TB

		Disease	
		Patient MDR +	**Patient MDR -**
Test	**+ MDR**	True Positive (TP)	False Positive (FP)
	- MDR	False Negative (FN)	True Negative (TN)
		Sensitivity =TP /(TP + FN)	Specificity = TN /(FP + TN)

4.10 COST DATA

The study was conducted from the perspective of the South African Department of Health; therefore, direct medical costs were included.

The following direct medical costs were included in the model:

(1) Cost of the screening test including false positive and false negative test results [line probe assay tests (Genotype MTBDR*plus)* versus drug susceptibility testing];

(2) Cost of tuberculosis medication and costs of standard MDR-TB treatment regimens; and

(3) Costs of hospitalizations.

a) Adjustment of Costs

All costs were adjusted to US dollars using appropriate and current Rand-US dollar conversions. United States dollars was selected to represent the costs because other cost-effectiveness studies on TB diagnostics have used United States dollar (US $) values, and this allowed for an easy comparison between the present study and previous literature.

Past costs were adjusted to present value using Consumer Price Index inflation rates from South Africa. If costs were available in South African Rands, inflation was accounted for before the conversion to US dollars; if costs for South Africa were available in US dollar values, then consumer price index inflation rates were accounted for on the US dollar value. Since costs were compared for a one-year time period, discounting was not needed.

b) Cost of Diagnostic Tests

Two diagnostic options were compared. Diagnostic testing costs for conventional culture versus the Genotype MTBDRplus (line probe assay test) from South Africa were published in an Expert Group Report by the World Heath Organization. However, the cost of usual drug susceptibility testing was obtained from the National Health Laboratory Service in South Africa and compared to the values obtained from the WHO report on line probe assay tests. The costing information negotiated through the South African Laboratories, WHO and the Foundation for Innovative Diagnostics (FIND) were

selected for best estimates. The total cost for each testing procedure were confirmed through two laboratories in South Africa.

c) Cost of Drug Treatment

The cost of drug treatment included costs of a standard regimen of TB drugs used before confirmation of MDR-TB diagnosis and the cost of a standard regimen of MDR-TB treatment if the patient was diagnosed with MDR-TB. These costs were obtained through the Kwa-Zulu Natal Pharmaceutical Services.

d) Hospitalization Costs

Hospitalization/inpatient costs for a medical patient (i.e., non surgical) for tertiary government-funded South African hospitals were obtained from the WHO and a literature source – Olukoga et al.[122] These are hospitals where patients without private insurance seek medical care. The two cost values (i.e., WHO and Olukoga et al.) were compared and the second estimate[122] which included more background information on how the inpatient cost for a medial patient was calculated (e.g., utilities, building, equipment) was selected for the model.

4.11 OUTCOME MEASURE

The average DALY averted was assessed for each diagnostic approach. Incremental cost-effectiveness ratios were calculated to compare the incremental cost per DALY averted for each of the tests. Although no acceptable willingness-to-pay or threshold value has been identified in the literature for South Africa to date, one study in

Peru (South America) considered an incremental "cost per QALY that was less than the per capita Gross Domestic Product for Peru to be highly cost-effective."[127] The researchers considered "three times the per capita GDP to be a threshold beyond which an intervention would be considered too expensive."[127] The per capita GDP at the time in Peru was $2,360.[127] Using Gross Domestic Product as a measure is regarded as an acceptable method to assess cost-effectiveness in resource poor settings and this method is commonly used in the literature.

4.12 DECISION TREE DESIGN

A decision tree (Appendix A) was developed using previous literature on rapid MDR-TB testing as a guideline [73] However, the tree was revised based on the recommendations of experts from the University of Cape Town, Foundation of Innovative Diagnostics and a clinician who worked on the cost-effectiveness study in Peru. The model covers the perspective of the South African Government Public Health Care System. The tree compares two alternatives: (1) the line probe assay test; and (2) conventional drug susceptibility testing through culturing of bacteria. Outcomes of death, treatment success and treatment failure were assessed in terms of DALYs averted. All analyses were performed using TreeAge Software.[128]

Time Horizon: The hypothetical cohort of HIV/TB patients were followed over a 1-year period from time of sputum sample to the end of a one-year period (365-day period).

4.13 ASSUMPTIONS

Several assumptions were made in this model and are outlined here:

- It was assumed that MDR-TB treatment began when a positive test result was obtained from the laboratory.
- Because of the limited information on the prevalence of MDR-TB among HIV patients (with and without ARV access) the prevalence was assumed to be as high as the prevalence rate noted during the 2006 outbreak in South Africa
- One-month mortality associated with awaiting test results was assumed to be equal to the rate within the Tugela Ferry outbreak.
- 1% of treated patients die from the end of month 1 until the end of the 12 month period (noted from the literature for HIV negative patients). This death rate was assumed for the true positive arm of both test branches. This percentage of death, using Kaplan Meier calculations, provided a one-year mortality that was noted in the literature for MDR-TB positive patients in Tugela Ferry.
- A standard treatment course for a 51-70 kg/patient was used to determine costs for TB and MDR-TB treatment regimens.
- Diagnosing patients in a shorter time period, with a rapid test (Genotype MDR-TB*plus*), would reduce the probability of death.

- Test results for the conventional drug susceptibility testing were obtained in 28 days and treatment was initiated in 28 days.
- Test results for the line probe assay test were obtained in 7 days and treatment was initiated in 7 days.

4.14 SUMMARY OF MODEL INPUT VARIABLES

Cost, probability and outcome estimates obtained from the literature and through expert opinion were used in this study. Table 4.3 summaries these estimates of costs and probabilities for the analysis. For each alternative, a hypothetical cohort was followed for a one-year period.

Estimates of the prevalence of MDR-TB among HIV-positive patients were obtained from the Gandhi et al. study published on the outbreak of MDR-TB in South Africa in 2006. The WHO recognizes this high estimate in a range for low-to-middle income countries. Other probability and cost estimates were obtained through literature sources, the South African Department of Health, and expert opinion.

Table 4.3 List of Variables and Sources

Variables		Source
Prevalence	Prevalence of MDR-TB in HIV Patients	Gandhi et al.[103]
Cost Variables	Cost of Diagnostic Tests Line Probe Assay Traditional Drug Susceptibility Testing	World Health Organization Expert Group Report on Molecular Line probe assays for Rapid Screening of Patients at Risk of Multi-Drug Resistant Tuberculosis (MDR-TB) National Health Laboratory Service in South Africa
	MDR-TB Treatment: Intensive Phase Continuation Phase	South African Department of Health, South African Pharmaceutical Services and MDR-TB Treatment Guidelines
	TB Treatment Intensive Phase Continuation Phase	South African Department of Health, South African Pharmaceutical Services and MDR-TB Treatment Guidelines
	Hospitalization	World Health Organization and Olukoga et al. [122]
Variables Related to Treatment	• Days on MDR-TB Treatment • Days on TB Treatment	National TB treatment guidelines in South Africa National TB treatment guidelines in South Africa
Variables Related to Effectiveness of the Tests	• Diagnostic Tests Sensitivity Values • Diagnostic Tests Specificity Values	World Health Organization Expert Group Report on Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multi-Drug Resistant Tuberculosis
Mortality	• Probability of death for patients with HIV and TB • Probability of death for patients with MDR-TB and HIV	Gandhi et al.[104] Gandhi et al.[121] Assumptions
Success	• Successfully complete intensive phase of MDR-TB and continue with continuation phase of MDR-TB treatment • Successfully complete a 6 month course of TB Treatment	Shean et al.[98] Gandhi et al. [121] Expert opinion Assumptions
Failure	• Fail MDR-TB treatment • Fail TB Treatment	Shean et al.[98] Assumptions Expert Opinion
Outcome Measure	• Disability-adjusted life-year estimates	World Health Organization[129] Assumption

MDR-TB = Multi-drug resistant tuberculosis and TB = Tuberculosis

4.15 SENSITIVITY ANALYSIS

A one-way sensitivity analysis was conducted for each cost and probability variable. A tornado diagram was constructed to indicate the variables that showed the most change. A probabilistic sensitivity analyses was performed on all variables simultaneously. Triangular distributions were used for all probability distributions and Gamma distributions were used for the cost estimates. Range estimates for sensitivity analyses were limited in the literature. Therefore, when ranges were not available, estimates for costs, probability, and mortality estimates were varied by ± 10-20%, and sensitivity and specificity estimates were varied by ±2%.[73] These are commonly used variations in the literature when ranges are not available.

4.16 EXPERT OPINION

Several individuals with an expertise in tuberculosis research including clinicians, pulmonologists, economists and microbiologists served as experts on this study. These experts were based in the US, Peru, South Africa, and Geneva (FIND and WHO). Input was obtained from FIND and WHO. The development of the initial proposal was based on input from the Global Laboratory Division with the WHO. At several stages throughout the study, these experts were contacted for guidance on the development of the model and comments on the clinical relevance of the model. Our primary discussion points on decision analysis versus Markov analysis, success and failure rates, the benefits

of the commercial line probe assay tests, and definitions of treatment initiation rates are summarized here:

a) Decision Analysis versus Markov Analysis

- For cost-effectiveness analyses on diagnostics for infectious diseases, a decision analysis approach is preferred to Markov modeling because it is very difficult to define the health states for infectious diseases using the cyclical pathways in a Markov model, especially if patients are only going to be tested once during the time horizon.
- It was advised that benefits should be determined in terms of DALYs averted. This was a suggestion made based on the experience from the study conducted in Peru and DALY estimates available from the WHO.
- Originally, the decision tree had 3 major branches:

    1. Line probe assay plus conventional drug susceptibility testing;
    2. Conventional drug susceptibility testing; and
    3. No testing.

    In branch 1 (line probe assay test and conventional drug susceptibility testing), the question arose if the two tests would be used simultaneously in South Africa or would the line probe assay be used as a screening tool, and only those patients with positive results will be further tested with the conventional drug susceptibility test. This was an important consideration because combining the tests will increase the diagnostic

accuracy but also increases costs and delays in treatment. It was then proposed that if the South African health ministry was considering implementing the line probe assay, then a better approach would be to evaluate the line probe assay vs. the conventional drug susceptibility testing approach. This is the approach that was selected because the policy in South Africa indicated that the line probe assay test will be increasingly used as mainstream testing in South Africa. We were interested in assessing cost-effectiveness of testing approaches (rapid and conventional); therefore, the no testing branch was not included in this model.

- Initially patients could progress from treatment failure to death or failure to XDR-TB to death. The question arose as to why XDR-TB to death was incorporated when it is difficult to determine how many patients can live with this type of disability. It was therefore advised that the terminal node should end with success, failure and death.
- In the false negative branch, initially all patients were assumed to develop XDR-TB and die because they would receive inappropriate treatment. However, based on expert opinion, a more conservative approach was advised to allow patients to fail treatment and continue living with XDR-TB.
- In the base-case analysis, it was advised that the estimates of true positives and true negatives can be calculated as fractions of total positives and total negatives, respectively, given sensitivity and specificity values from the literature and assumed prevalence rates.
- Finally, because results were dependent on prevalence of the disease (MDR-TB), experts advised that it was very important to make calculations using a base MDR-TB

prevalence among HIV-positive patients and then conduct a sensitivity analysis on the range of prevalence values.

b) Success and Failure Rates

- When considering conventional drug susceptibility testing, a 50% success and failure rate for MDR-TB and XDR-TB are the best estimates for South Africa as indicated by literature sources and expert opinion.[98]

c) The Benefits of the Commercial Line Probe Assay Tests

- Genotype MTBDR*plus* is an appropriate Line Probe Assay test to assess for South Africa – it is currently being used in laboratories in South Africa following clinical trials.
- The main benefits of rapid TB diagnostic tests are that (1) it decreases the transmission due to rapid diagnosis, and (2) treatment can be initiated sooner. Earlier diagnosis usually leads to early treatment, which may improve the outcomes for patients. In this cost-effectiveness study, the benefit of decreased mortality due to earlier initiation of treatment was used to incorporate the benefit of the test. Unfortunately, there is still no clear data available in the literature on success rates of treatment related to the use of the line probe assay test. Success rates have been published for patients who were tested with conventional testing. Assumptions and expert opinions were used in selecting success and failure rates associated with earlier

versus later diagnosis. Sensitivity analyses were strongly encouraged for mortality and uncertain success rates.

d) Definitions of Treatment Initiation

- In using earlier treatment initiation as a benefit of the line probe assay test, a definition of time-to-initiation of treatment had to be agreed upon. There were several definitions of time to initiation of treatment proposed:
    1. Treatment could be initiated from the time the patient experiences symptoms or,
    2. Time patient presents to a health care facility or

In this study, the time-to-diagnosis and initiation of treatment was defined as the time from when the sputum sample was taken to the time when the laboratory generated the result. The reason this definition was selected was because there are actual mortality numbers for time-to-result (awaiting test results for one month) available in the literature versus no numbers for the other definitions. The drawback of using time to generation of test result as a marker for time to initiation of treatment is that in reality it may take several more days for a health care worker in the clinic to see the diagnostic result and sometimes the test result is actually never communicated to the patient or treatment is not initiated. The fact that not all patients will be initiated on treatment in this time frame was a limitation in this economic model. The large difference in the time to obtaining test result (7 days vs 28 days) provides enough of an advantage to reduce mortality. Twenty-

eight days was used as the turn-around time for the conventional testing approach because mortality estimates for a 28-day period were available in the literature. An assumption on mortality was then generated using the 7-day versus 28-day advantage of the line probe assay test. Time-lines for the two testing procedures are shown in Appendix B. The conventional testing approach lags by one month in terms of continuation phase treatment because of delay in testing procedures.

CHAPTER 5

RESULTS

5.1 INTRODUCTION

Results for each of the study objectives are presented in Chapter 5. The final decision tree, costs, (screening and treatment costs), probabilities (transition and mortality estimates), and the full range of assumptions used in the cost-effectiveness analysis are presented in Chapter 5. Detailed results from the cost-effectiveness analysis (average costs, average DALYs, incremental cost-effectiveness ratios and sensitivity analyses) are also presented here. The results are broken up into two major sections. The first section looks at background information on the tests, disease and decision tree. The second section addresses the results based on the objectives and hypotheses of the study.

5.2 SECTION 1: DIAGNOSTIC TESTS

Background information on the diagnostic tests are provided in this section.

a) The Line Probe Assay Test: Genotype MTBDR*plus* assay

Genotype MTBDR*plus* assay is "a polymerase chain reaction (PCR) amplification and reverse hybridization assay for detecting RIF and INH resistance. The assay detects mutations in the r*poB* gene for RIF resistance, the KatG gene for high-level INH

resistance, and the *inhA* gene for low-level INH resistance directly from smear positive sputum. Results are available within 1-7 days."[130]

In a diagnostic performance study conducted on 536 specimens (97% produced interpretable results) in Cape Town, South Africa, researchers from the Foundation of innovative diagnostics (FIND) and the National TB Reference Laboratory found that the Genotype MTBDR*plus* had a sensitivity of 99, 94 and 99% for rifampicin, isoniazid and MDR-TB. Similarly, the "specificity for detection of rifampicin, isoniazid, and MDR-TB resistance was 99, 100, and 100% respectively".[130] Findings from this study are shown in Table 5.1.[130]

Table 5.1: Summary of Sensitivity and Specificity Values

	Rifampicin	Isoniazid	Multidrug Resistance
Sensitivity	98.9 (94.3–100.0)	94.2 (88.4–97.6)	98.8 (93.7–100.0)
Specificity	99.4 (98.0–99.9)	99.7 (98.3–100.0)	100 (99.0–100.0)*
Overall Accuracy	99.3 (98.1–99.9)	98.2 (96.5–99.2)	99.8 (98.8–100.0)
Positive Predictive Value	97.9 (92.7–99.7)	99.1 (95.3–100.0)	100 (95.8–100.0)*
Negative Predictive Value	99.7 (98.5–100.0)	97.9 (95.8–99.2)	99.7 (98.5–100.0)

Values are percentages with 95% confidence interval in parentheses.

* One-sided, 97.5% confidence interval.

Taken From: Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med.* Apr 1 2008;177(7):787-792[130]

Results for line probe assay tests can be obtained within 8 hours. However, in the high-volume clinic that the Genotype MTBDR*plus* was tested in, the results were usually reported within 2 working days. When transport time, time to perform the testing, and reporting of results were considered, the total estimated turn-around time was estimated to be 7 days. Seven days was used as the base-case estimate in this study.

Since 2010, South African laboratories have been rolling out the line probe assay test to detect MDR-TB in patients as confirmed by a laboratory in the Western Cape Town and Kwa-Zulu Natal. [130, 131] The treatment guidelines call for the use of Hain

Genotype MTBDR*plus* Test on specimens. However, some laboratories may still follow the conventional approach. Previously (prior to 2011), while clinical trials were underway, it was recommended that rapid testing with the line probe assay be followed up with conventional testing. However, currently, if the laboratory uses the line probe assay test, no follow up with the conventional testing is recommended within the first month of initiation of treatment. An expert from the laboratory in South Africa therefore recommended comparing only the line probe assay to conventional testing in a decision analysis without including the cost of the conventional testing in the line probe assay branch. This is because the policy is in transition regarding these tests and it appears like rapid testing will be used as mainstream testing in the future in South Africa. The cost of the test as negotiated by FIND and the South African government is 188.52 South African Rands (equivalent to approximately $28.10). The price was confirmed through two NHLS laboratories in South Africa (Western Cape and Kwa-Zulu Natal).

b) Conventional Drug Susceptibility Test

Investigation through two laboratories in South Africa (Western Cape and Kwa-Zulu Natal) confirmed that in South Africa the MIGIT Liquid Culture system was commonly used to test all TB cultures, and for routine INH / RIF / Streptomycin / Kanamycin / Ciprofloxacin susceptibility testing if indicated among patients who receive treatment through government-funded programs. The conventional test was regarded and still is regarded as the gold standard in many parts of the world because of its high specificity and sensitivity values of 99% or more. The laboratories conduct INH/ RIF as

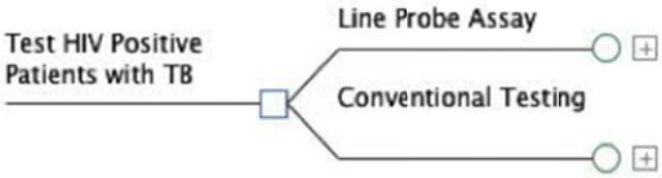
first-line (i.e., MDR-TB) and only test other drugs for second-line resistance (i.e., XDR-TB) if requested by the doctor. Using these methods, specimens are cultured and bacteria take time to grow. Therefore, the cultures can take up to 4 to 8 weeks (or up to 56 days) to produce results. The charge for conventional drug susceptibility testing is 66.67 South African Rands (equivalent to approximately $19) per drug tested confirmed through the NHLS in Kwa-Zulu Natal.

The costs and value/effectiveness of the line probe assay compared to the conventional testing approach cannot be assessed solely in terms of sensitivity and specificity values. The value of better effectiveness of the line probe assay test lies in its ability to produce results sooner for an infectious disease.

5.3 DECISION TREE RESULT

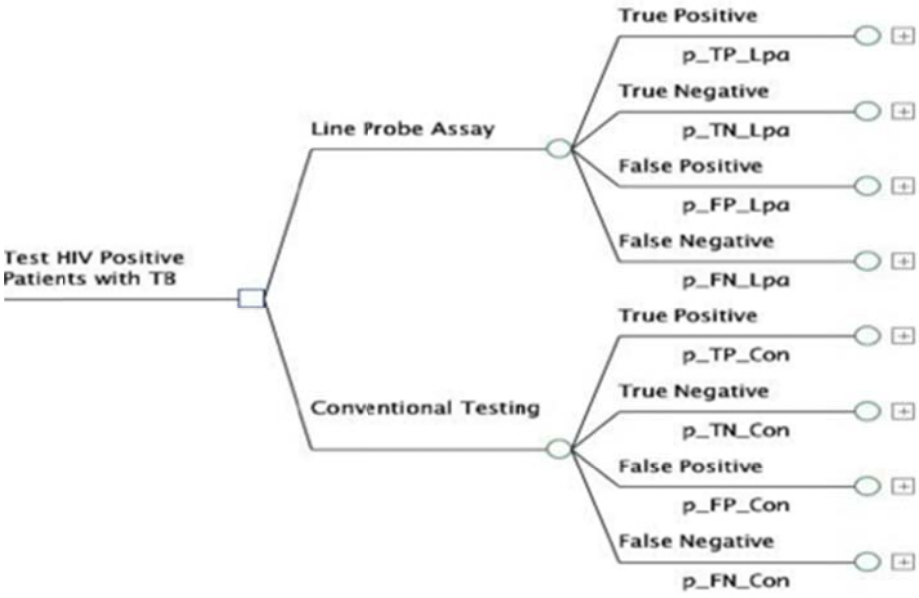
The final decision tree was derived by consulting literature sources and expert opinions and is displayed in Appendix A. The tree is based primarily on the tree used by Acuna-Villaorduna et al. in a similar cost-effectiveness study in Peru.[73] The model was assessed looking at the incremental cost per disaility-adjusted life-year (DALY) averted. Figure 5.1 shows that two testing approaches were assessed:

Figure 5.1: Decision Tree Choice Node



For each testing branch, there were four possible pathways that were assessed: false positives, false negatives, true positive and true negatives.

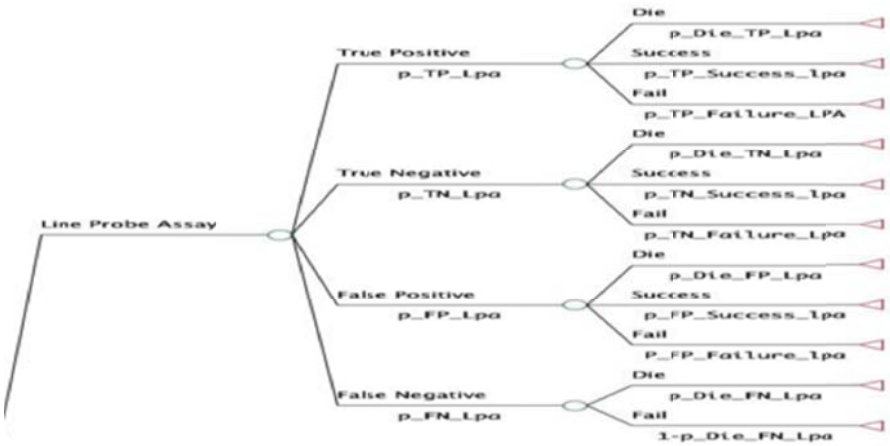
Figure 5.2: True Positive, True Negative, False Positive, False Negative Pathways



In both testing branches, the true positive, true negative, and false positive branches terminate in die, success and failure. The false negative branch terminates in

die or fail. Figure 5.3 shows the terminal branches for the line probe assay (the same pathways were used for the conventional testing approach).

Figure 5.3 Terminal Branches



5.4 DURATION OF MDR-TB

Through WHO reports, Zignol et al. state that the exact duration of an MDR-TB episode cannot be established. However, the infection is assumed to last longer than 1.64 years, which is the estimated length of a drug susceptible form of TB.[132] In this study, the estimates were analyzed over a one-year period because reliable mortality estimates were only available for one year.[92]

5.5 DEFINITIONS OF VARIABLES IN THE MODEL

The hypothetical cohorts of patients are all HIV-positive patients who have TB. When tested for MDR-TB with either diagnostic test, four scenarios can present themselves: (1) True Positive test results (patient is correctly diagnosed as MDR-TB positive); (2) True Negative test results (patient is correctly diagnosed as MDR-TB Negative); (3) False Positive test results (patient is incorrectly diagnosed as MDR-TB positive); and (4) False Negative test results (patient is incorrectly diagnosed as MDR-TB negative). Table 5.2 summarizes each of the definitions used in the model.

Table 5.2: Variable Definitions Used in the Model

Path	**Definition**
True Positive	Test result *correctly* indicates that patient has MDR-TB and patient receives MDR-TB treatment
True Negative	Test result *correctly* indicates patient does not have MDR-TB and patient continues with TB treatment
False Positive	Test result *incorrectly* indicates that patient has MDR-TB and patient receives unnecessary MDR-TB treatment
False Negative	Test result *incorrectly* indicates patient does not have MDR-TB and patient continues with inappropriate TB treatment
Treatment Success	Patient is not cured of MDR-TB but has successfully completed the intensive phase of MDR-TB treatment, is still living with MDR-TB but on a successful course of completing continuation phase of MDR-TB treatment
Treatment Failure	Patient fails MDR-TB and has likely developed an extensive form of the disease
Death	Patient dies by the end of the one year time horizon

5.6 MDR-TB PREVALENCE IN HIV PATIENTS IN SOUTH AFRICA

In 2010, the WHO reported that 35% of HIV-positive TB patients who received treatment from the public health sector in South Africa were on ARV treatment. Unfortunately, WHO estimates are still not available for the prevalence of MDR-TB among HIV-positive South African patients. However, cohort studies from South Africa provided estimates for prevalence of MDR-TB among HIV-positive patients. Estimates from Tugela Ferry showed that MDR-TB HIV co-infection rates could be as high as 90%.[103] Tugela Ferry is where the outbreak of MDR-TB was noted in 2006 and presents a very high prevalence rate for MDR-TB. The latest (2010) TB AND MDR-TB profile for South Africa is summarized in Table 5.3.

Table 5.3: Tuberculosis Estimates from South Africa

Estimate	Value (Range)
Estimated % of all new TB cases with MDR-TB	1.8 (1.5-2.3)
Estimated % of all retreated cases with MDR-TB	6.7 (5.5 -8.1)
Total Number of Estimated Cases of MDR-TB in 2008 (Thousands)	13 (10-16)
Notified cases of MDR-TB in 2009	7343
Cases of MDR-TB enrolled in treatment	4143
Expected number of MDR-TB cases to be treated in 2011	8642

Taken From: World Health Organization. *Global Tuberculosis Control 2010*.[133]

The prevalence of MDR-TB among HIV positive patients was assumed from the study conducted by Gandhi et al. in a very high MDR-TB/HIV prevalence area (where MDR-TB outbreak was first noted in 2006) in Kwa-Zulu Natal and estimated to be 30%. This prevalence value was varied by ±50% of the total prevalence in sensitivity analyses.

5.7 Calculation of True Positive, True Negative, False Positive and False Negative Results

True positive, true negative, false positive and false negative values were estimated using a baseline MDR-TB prevalence rate of 30% among HIV-positive patients. The base-case estimate for the sensitivity and specificity values for the line probe assay and conventional drug susceptibility testing used was 99% and 99%, respectively. Although the literature from clinical trials cautioned using the line probe assay test on its own, policy surrounding the use of this test is changing; follow up with conventional drug susceptibility testing is no longer required, and the sensitivity and specificity for the base-case model were assumed to be equal.[38]

Line Probe Assay: Sensitivity and Specificity values of 99% were used.

Conventional Drug Susceptibility Testing: Sensitivity and Specificity values of 99% were used.

The following formulas were used to calculate the true positive, true negative, false positive and false negative test results in TreeAge.

Equation A:

Sensitivity = True Positive/(True Positive + False Negative)

= True Positive/Prevalence

Equation B:

True Positive + False Negative = Prevalence

False Negative = Prevalence – True Positive

False Negative = Prevalence – (Sensitivity x Prevalence)

Equation C:

Specificity = True Negative/(True Negative + False Positive)

= True Negative/No Disease

Equation D:

True Negative + False Positive = No Disease

False Positive = No Disease - True Negative

= No Disease – (Spec x No Disease)

Assuming that 100 patients were tested with a line probe assay test with a sensitivity and specificity of 99% and 99% respectively, the true positive, true negative, false positive and false negative results were calculated as follows for the both tests.

If there is a 30% prevalence of MDR-TB among HIV-positive patients, then 30 out the 100 patients will have the disease. That means in a group of patients, 30 patients will have MDR-TB irrespective of whether they were diagnosed as being positive or not (i.e., the number of true positives and number of false negatives must equal 30). Using this reasoning, if the sensitivity (% of actual positives who are correctly diagnosed as being positive) is 99%, the true positive and false negative values were calculated as follows using sensitivity and specificity equations.

Box 1: Calculation of True Positive and False Negative Test Results

If Prevalence of MDR-TB in TB HIV/AIDS patients = 30%

In a cohort of 100 hypothetical patients, 30 patients would have MDR-TB

IF

Sensitivity = True Positive / (True Positive + False Negative) = 30% = 0.30

If X = True Positive

And True Positive + False Negative = People who have MDR-TB = 30

X/0.30 = 0.99

X = 0.99 x 0.3

X = 0.297

Therefore, probability of True Positives = 0.297

False Negatives = Total Patients who have the disease – True Positives

False Negatives = 0.3 – 0.297

False Negatives = 0.003

Similarly if the prevalence of MDR-TB among HIV positive patients is 30%, this means 70 (100-30) patients in a cohort of 100 patients do not have MDR-TB.

Box 2: Calculation of True Negative and False Positive Test Results

If Prevalence of MDR-TB in TB HIV/AIDS patients = 30%

No disease = 1-0.30=0.70

In a cohort of 100 hypothetical patients, 70 patients would have MDR-TB

Specificity= True Negative / (True Negative + False Positive) = 0.70

If X = True Negative

And True Negative + False Positive = People who do not have MDR-TB = 0.70

X/0.70 = 0.99

X = 0.99 x 0.70

X = 0.693

Therefore, probability of True Negatives = 0.693

False Positives = Total Patients who *do not* have the disease – True Negatives

False Positives = 0.70- 0.693

False Positive =0.007

Given a sensitivity and specificity of 99%, 69.3% will be diagnosed correctly as MDR-TB negative and 0.007% of the patients will be diagnosed as being positive when

they really do not have the disease. Table 5.4 shows the break-down of true positive, true negative, false positive, and false negative MDR-TB test results.

Table 5.4 Assumed True Positive, True Negative, False Positive and False Negative Test Probabilities for the Line Probe Assay Test

	Patient MDR +	**Patient MDR -**	**Total**
TEST MDR +	0.297	0.007	0.304
TEST MDR –	0.003	0.693	0.696
Total	0.3	0.7	1.00

MDR= Multi-Drug Resistant Tuberculosis

5.8 TB AND MDR-TB MORTALITY ESTIMATES

According to Gandhi et al., up to 40% of patients in the high-prevalence area died within 30 days of sputum collection. In a study conducted at multiple centers in South Africa, for the patients with extensively drug-resistant tuberculosis, proportion of patients surviving after one month of initiation of treatment was 90%. The LPA takes 7 days to produce results and culturing via the conventional test can take up to 28-56 days. Therefore, as part of the assumption that producing test results 3 weeks earlier would give the patient a better chance of survival, a survival analysis calculation was conducted

assuming that in the first month 40% of patients would die in the conventional testing group while awaiting test results and in the line probe assay group 10% of patients would die while awaiting test results (annual death rate was previously noted for patients in the literature from the MDR-TB outbreak region and multi-centers in South Africa, and the rate produced mortality results similar to those seen in the literature; approximately 40-50% of patients die after a one-year period when treatment was delayed). We therefore assumed a constant death rate per month (for those treated) of 1% until the end of 12 months until the proportion at risk was comparable to those noted in the literature from the Tugela Ferry outbreak region and a multi-center study conducted in South Africa.[103] The proportion surviving in the conventional group was equal to 46.28%, which is comparable to data from the outbreak in a high prevalence area in South Africa. Calculations are shown in Appendix C.

5.9 Direct Medical Costs Associated with the MDR-TB Screening

At the time this study was conducted, the Department of Health adopted the Genotype MDR-TB*plus* test as an adequate testing procedure. Therefore, the clinical trial costs were not used in the study (shown together with adjusted values in Appendix D; rather the 2011 costs were obtained from the NHLS in South Africa. The cost per test was negotiated at 188.52 South African Rands and is provided by the NHLS laboratories.

The cost per conventional drug susceptibility testing was 66.67 South African Rands per drug tested. The cost of the test would be 66.67 South African Rands x 2 for INH and RIF is assumed to be conducted. The total cost would therefore be 133.34 South African Rands (year 2011).

The present day cost for the line probe assay test and the conventional drug susceptibility testing using a current exchange rate of R6.71 South African Rands to 1 US $ would be:

Line Probe Assay Test: R188.52 / 6.71 = US $28.10

Conventional Drug Susceptibility Testing: R133.34 / 6.71 = US $19.87

5.10 DIRECT HOSPITALIZATION COSTS FOR SOUTH AFRICA

Hospitalization costs were available from the WHO and literature sources. Costs for hospitalization from the WHO are outlined in Appendix E. The cost per bed (minus treatment and diagnostic costs but including personnel, and food) was US $108.51 (2005). The WHO hospitalization cost was not included as a base cases estimate because it was not clear what components constituted the total cost. Hospitalization costs were obtained from a study conducted by Olukoga et al., in 2002 (published in 2007). Unit costs for medical inpatients for one day of hospitalization in a government hospital in South Africa ranged from US $37.23-US $70.86.[122] The costs consisted of personnel, equipment, materials, drugs (not MDR-TB treatment), utilities and buildings. The $37.23

estimate was used because it originated from a well-known government hospital (Osindisweni) in Kwa-Zulu Natal, South Africa.

5.11 Present Value Adjustments for Hospitalization Costs Associated with MDR-TB

The costs were adjusted to present value using the South African Consumer Price Index Inflation Rate for the years 2002 to 2011. During the adjustment, inflation per year up to the current year is represented as (1 + inflation value) and then multiplied by the available cost estimate. General consumer price index inflation rates were available for 2002 to 2008. The consumer price index inflation rates for 2002 to 2008 were 0.08, 0.067, 0.012, 0.036, 0.058, 0.09, and 0.115, respectively. Hospital consumer price index inflation rates were available for 2009, 2010 and 2011 (May 2011) and were 0.10, 0.07 and 0.058, respectively.

$37.23 x [1+0.08] x [1+0.067] x [1+0.012] x [1 + 0.036] x [1 + 0.058] x [1 + 0.09] x [1 + 0.115] x [1 + 0.10] x [1 + 0.007] x [1 + 0.058] = $67.78

5.12 Cost of First-Line TB and MDR-TB Medication

Drug costs were calculated for TB and MDR-TB using a standard treatment regimen recommended in the MDR-TB treatment guidelines and also commonly seen in

the literature. A current version of the Provincial Medical Supply Center (called the Provincial Pharmaceutical Supply Depot) catalogue was obtained from pharmaceutical services in Kwa-Zulu Natal, South Africa. The catalogue listed all TB medicines currently available and their costs for South Africa. The costs obtained were inclusive of the levy applied as a handling cost by Provincial Pharmaceutical Supply Depot. The price lists are confidential, because drug suppliers are competing for the market. Therefore, as requested by the Department of Health, individual prices are not published here.

The drug costs were available for each drug in the regimen as July 2011 costs and were published in South African Rands. Regimen costs were calculated using a standard regimen stipulated in the South African MDR-TB treatment guidelines. This regimen includes Kanamycin, ofloxacin, ethionamide, ethambutol and pyrazinamide. A one-month supply was assumed to be 4 weeks or (7days x 4weeks = 28 days). A current exchange rate of R6.71 South African Rands to 1 US $ was used (Table 5.5) to convert cost in South African Rands to US dollars. Daily costs and total regimen cost for the TB and MDR-TB treatment are shown in South African Rands and US $ in Table 5.5.

Table 5.5 Rand and US Dollar Value Amounts

Variable	South African Rands (R)	US Dollar ($)
Daily Cost of first line TB treatment (Intensive phase)	5.14	0.77
Daily Cost of first line TB treatment (Continuation phase)	2.85	0.42
Daily Cost of MDR-TB treatment (Intensive phase)	24.22	3.61
Daily Cost of MDR-TB treatment (Continuation phase)	21.37	3.18

5.13 Disability-Adjusted Life-Year Estimates Used in the Model

A disability-adjusted life-year is the 1-year of healthy life lost, actual life lost and life lost through disability.[129] For each of the DALY values, a quality-adjusted life-year value (or DALY averted) was calculated by subtracting the DALY value from a value of 1 (Table 5.6). Dowdy et al. have used 0.1 increment decreases to adjust for more advanced levels of diseases; therefore, in the case of MDR-TB and "failure", we use 0.1 lower.

Table 5.6. Disability-Adjusted Life-Year Values

Disease States	**DALY**	**QALY (1- DALY)**
HIV-positive with ART access	0.236	0.8 (0.7 was assumed as a more conservative estimate)
HIV-positive and TB	0.5	0.5 (From Dowdy et al.[71] based on Active TB and HIV disease obtained from WHO estimation)[129]
HIV-positive and MDR-TB	Assumed	0.4 (Assumed to be 0.1 less than living with HIV and TB disease therefore 0.5-0.1=0.4)
Failure (Extensively drug-susceptible TB)	Assumed	0.3 (Assumed to be 0.1 less than living with MDR-TB and HIV disease therefore 0.4-0.1= 0.3)

Sources: World Health Organization. *The global burden of disease : a comprehensive assessment of mortality and disability from diseases,*: Harvard School of Public Health on behalf of the World Health Organization and the World Bank ; Distributed by Harvard University Press; 1996.
Dowdy DW, O'Brien MA, Bishai D. Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis *Int J Tuberc Lung Dis.* 2008;12(9):1021-1029.
TB= Tuberculosis
HIV=Human Immuno-deficiency Virus
DALY=Disability-Adjusted Life-Year
QALY= Quality-Adjusted Life-Year

The QALYs used for each branch are shown in Table 5.7. Additionally in Appendix C, costs and QALYs for each branch are outlined. Kaplan-Meier mortality

calculations for the true positive branches for each of the tests are also shown in Appendix C.

Table 5.7: Quality-Adjusted Life-Years (Qalys) As Inputted Into Payoff Effectiveness For Each Branch

Result	**Branch**	**QALY**
True Positive	Die	0
	Success	0.4
	Failure	0.3
True Negative	Die	0
	Success	0.7
	Failure	0.5
False Positive	Die	0
	Success	0.65**
	Failure	0.45**
False Negative	Die	0
	Failure	0.3

**Assumed to be 0.05 less than success and failure in the true negative branch because of 6 months of hospitalization during acute/intensive treatment phase.

A summary of all costs, probabilities and assumptions used in the base-case model are outlined in Table 5.8.

Table 5.8 Base-Case Estimates

Variable	Base-case Estimate	Source
Treatment Variables		
Daily Cost of first line TB treatment (Intensive phase)	$0.77	South African Department of Health
Daily Cost of first line TB treatment (Continuation phase)	$0.42	South African Department of Health
Number of days Intensive Phase (TB)	56	South African Department of Health
Number of days Continuation Phase (TB)	112	South African Department of Health
Cost of 1 week of TB Treatment	$5.39	South African Department of Health
Cost of 1 month of TB Treatment	$21.56	South African Department of Health
Total TB cost for 6 months (56 days intensive phase and 112 continuation phase)	$90.16	South African Department of Health
Daily Cost of MDR-TB treatment (Intensive phase)	$3.61	South African Department of Health
Daily Cost of MDR-TB treatment (Continuation phase)	$3.18	South African Department of Health
Number of months Intensive Phase (MDR-TB)	6 months	South African Department of Health
Number of months Continuation Phase (MDRTB)	6 months: line probe assay 5 months: conventional *	South African Department of Health

Table 5.8 (continued)

Probability of Death from TB	0.11	Gandhi et al[121]
Probability of Success and Failure from TB and MDR-TB Medication	0.5	Shean et al[98] Expert Opinion
Probability of Death for False Negative Result	0.5	Gandhi et al.[103]
Hospitalization		
Hospitalization cost per day	$67.78	Olukoga et al.[122]
Number of Months of Hospitalization	6 months	South African MDR-TB Treatment Guidelines
Test Variables		
Line Probe Assay Cost	$28.10	WHO Foundation of Innovative Diagnostics
Annual mortality: True positive MDR-TB patients tested with line probe assay	0.19	Assumed
Time to Diagnosis: Line Probe Assay Benefit assumed in terms of higher success rate and lower mortality	7 days	Field Testing of Line Probe Assay Test
Line Probe Assay: Sensitivity	99%	WHO and Foundation of Innovative Diagnostics
Line Probe Assay: Specificity	99%	WHO and Foundation of Innovative Diagnostics
Cost of Conventional Testing	$19.87	National Health Laboratory Services in South Africa
Annual mortality: True positive MDR-TB patients tested with conventional test	0.46	Assumption Gandhi et al.[103]
Time to Diagnosis: Conventional Test	28 days	Field Testing of Conventional Test
Conventional Test: Sensitivity	99%	National Health Laboratory Service
Conventional Test: Specificity	99%	National Health Laboratory Service

*Time Horizon in the model was 1 year; patients on the conventional testing branch lag in treatment by one month.

TB=Tuberculosis; MDR-TB=Multi-drug Resistant Tuberculosis

5.14 SECTION 2: AVERAGE DIRECT MEDICAL COSTS OF SCREENING

The average total cost per person for the line probe assay testing strategy was $3538.98/0.458 DALY averted and the conventional testing approach was $3011.08/0.430 DALY averted.

Table 5.9 includes the average costs, DALYS averted and incremental cost-effectiveness ratios for each of the testing procedures. Hypothesis 1 stated that the average cost of the line probe assay test will be greater than the average cost of conventional drug susceptibility testing. The average cost associated with the line probe assay test was higher than the conventional drug susceptibility test. Therefore, Hypothesis 1 is accepted. Hypothesis 2 stated the average DALY of the line probe assay test will be lower (= higher QALY) compared to the conventional drug susceptibility testing. The average DALYs averted (i.e., QALYs gained) based on the line probe assay test were higher (0.458) than the DALYs averted using the conventional test (0.430). Therefore, Hypothesis 2 is accepted. Hypothesis 3 stated that the incremental cost-effectiveness ratio per DALY averted for the line probe assay test, compared to conventional drug susceptibility testing, will be ≤ three times the 2009 Gross Domestic Product per capita for South Africa. The incremental effectiveness was 0.02 DALY averted. The line probe assay test had a higher cost but also a higher effectiveness. The base-line incremental cost-effectiveness ratio was $18,786 per DALY averted (QALY gained) which was greater than 3 times the 2009 GDP ($17,361) for South Africa. Therefore, Hypothesis 3 is rejected.

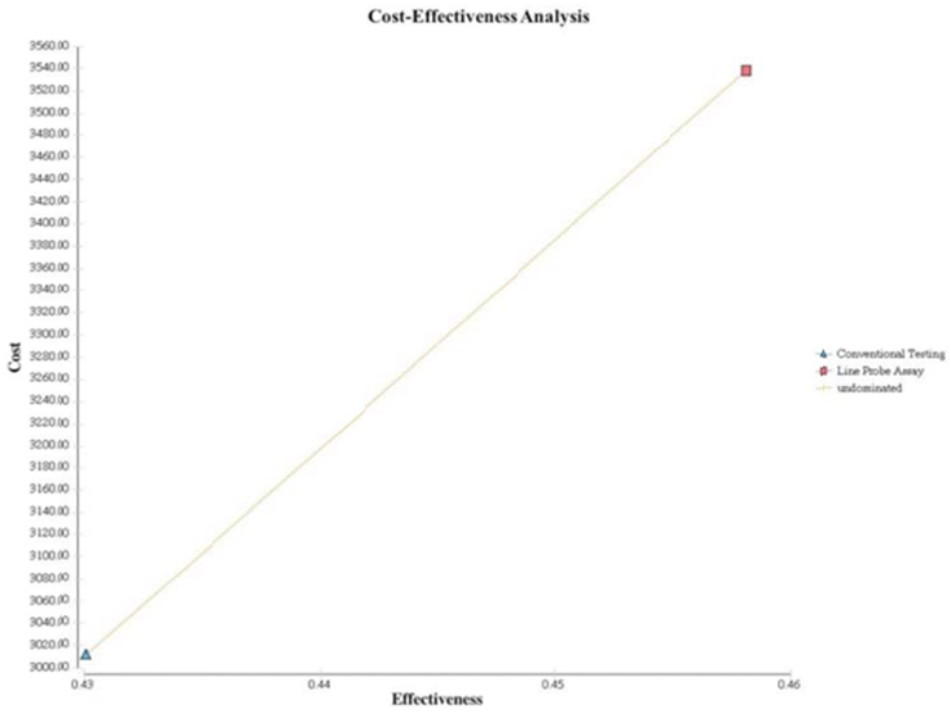
Table 5.9: Cost-Effectiveness Rankings

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness	Incremental Effectiveness	Incremental Cost Effectiveness Ratio (ICER) ($)
Conventional Testing	3,011.08	0	0.430	0	0
Line Probe Assay	3,538.98	527.90	0.458	0.028	18,800

Results show that the line probe assay test was undominated

The cost-effectiveness graph (Figure 5.4) clearly shows that the higher effectiveness of the line probe assay test (0.458) comes at a higher cost ($3,538.98). The difference in effectiveness was only 0.028.

Figure 5.4 Cost-effectiveness Graph



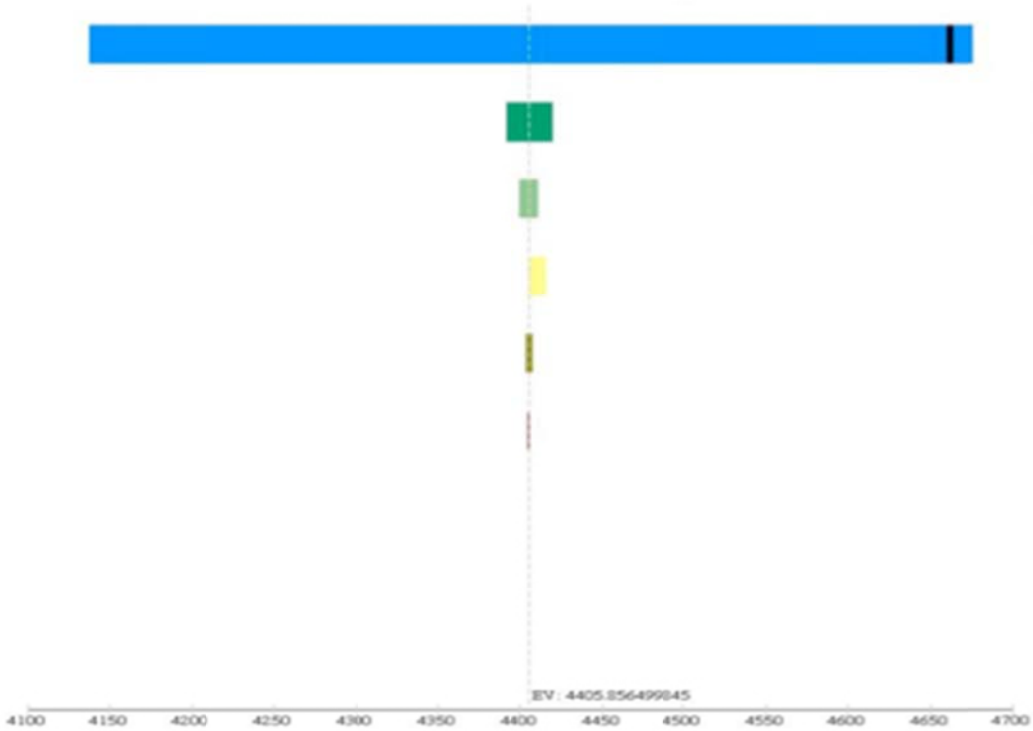
*(Difference in effectiveness only 0.028)

5.15 TORNADO DIAGRAM FOR COSTS

A tornado diagram shows which variables have the greatest impact on a decision analysis model. Tornado diagrams were produced for all cost variables, probabilities, and prevalence estimates. Results shown in Figure 5.5 indicate that hospitalization costs have

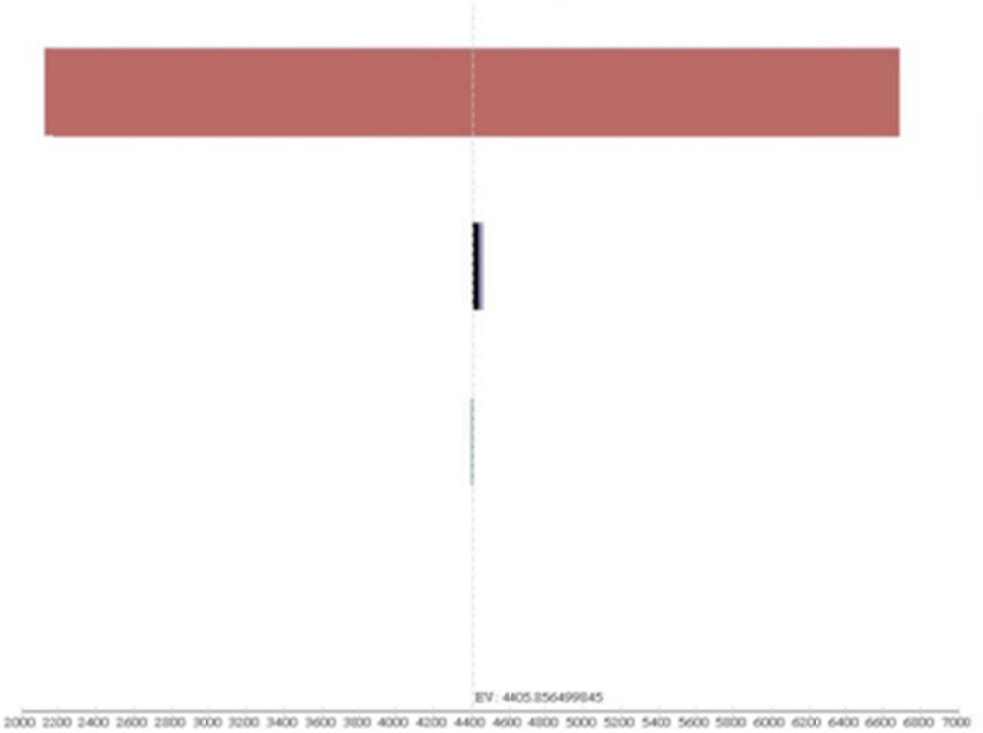
the greatest impact on the model. The tornado diagrams are plotted separately (Figures 5.5. and 5.6) to show the difference in the variables that had the greatest impact on the model.

Figure 5.5 Tornado Diagram: Cost Variables



Hospital	Intensive Phase MDR-TB Treatment	TB Treatment for 6 months	MDR-TB 5 months Continuation Phase Treatment	Conventional Test	TB Treatment for one Month	TB Treatment 7 Days	Line Probe Assay Test	MDR-TB 6 months Continuation Phase Treatment

Figure 5.6 Tornado Diagram: Prevalence and Probabilities



Prevalence	**Line Probe Assay: Probability of True Positive Successful Treatment**	**Conventional Test: Probability of Death True Positive**	**Line Probe Assay: Probability of Death True Positive**

5.16 SENSITIVITY ANALYSES

A one-way sensitivity analysis was conducted on the hospitalization variables (±10%), prevalence estimate (±50%), mortality estimates for both tests (± 20%), and the probability of treatment success variable in the true positive line probe assay branch (varied down by 20% and up to a value of 60%). Findings (Table 5.10) were robust

ranging from $15,572 to $20,413. For all the sensitivity analyses (except true positive success branch), the ICER is greater than the willingness-to-pay value ($17,361) for South Africa. When the true positive success rate for the line probe assay test is increased to a success rate of 60%, which the WHO hopes to achieve in resource poor settings, the ICER falls below the willingness-to-pay level to $15,572.

Table 5.10 Parameters Assessed in the One-Way Sensitivity Analysis

Parameters	Base-case Parameter	Lower-bound of Parameters	Upper Bound of Parameters	ICER at Lower Bound	ICER at Upper Bound	Result
Prevalence	0.30	0.15	0.45	$19,072	$18,691	undominated
Costs						
Hospitalization (Cost_Hospitalizaiton)	$11,387	$10,248	$12,525	$17,159	$20,413	undominated
Mortality						
True Positive – Conventional Test (p_Die_TP_Con)	0.46	0.368	0.552	$19,295	$18,535	undominated
True Positive – Line Probe Assay Test (p_Die_TP_LPA)	0.19	0.152	0.228	$18,677	$18,930	undominated
Success Rate						
True Positive Success Rate_ LPA (p_TP_Success_LPA)	0.405	0.324	0.60*	$20,547	$15,572	undominated

*Minimum success rate wanting to be achieved by World Health Organization

5.17 PROBABILISTIC SENSITIVITY ANALYSIS

A probabilistic sensitivity analysis was conducted on the hospitalization variable, prevalence variable, mortality variables on the die branch of the true positive branch for both tests, and the success variable of the line probe assay true positive branch.

In the probabilistic sensitivity analysis, the mean cost for the line probe assay test and conventional testing was $4,974.83 (sd=$2,288.92; range=$508.37-$1,9418.94) and $4,238.21 (sd=$1,963.80, range=$440.78-$16,655.00) respectively. The mean effectiveness was 0.46 (sd=0.02; range=0.42-0.52) and 0.43 (0.02; range=0.37-0.48) for the line probe assay and conventional test, respectively.

Figure 5.7 shows the cost-effectiveness scatterplot. For the majority of the iterations in the probabilistic sensitivity analysis, the line probe assay test appears to have a higher cost but also a higher effectiveness.

Figure 5.7 Scatterplot for the Line Probe Assay Test Compared to the Conventional Drug Susceptibility Testing

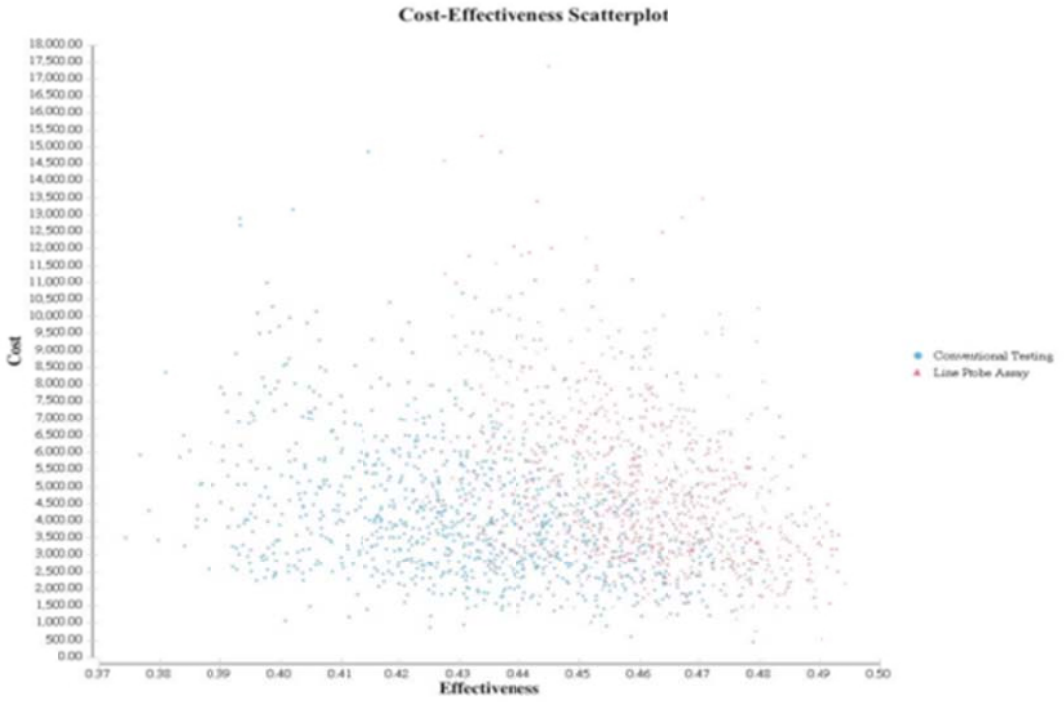


Figure 5.8 shows the acceptability curve from the probabilistic sensitivity simulation showed. There is a 70% probability that the additional cost of the line probe assay test, compared with conventional testing, is less than $30,000 per DALY averted. The actual data points above and below the willingness-to-pay values are shown in Table 5.11.

Figure 5.8 Probabilistic Sensitivity Analysis: Acceptability Curve

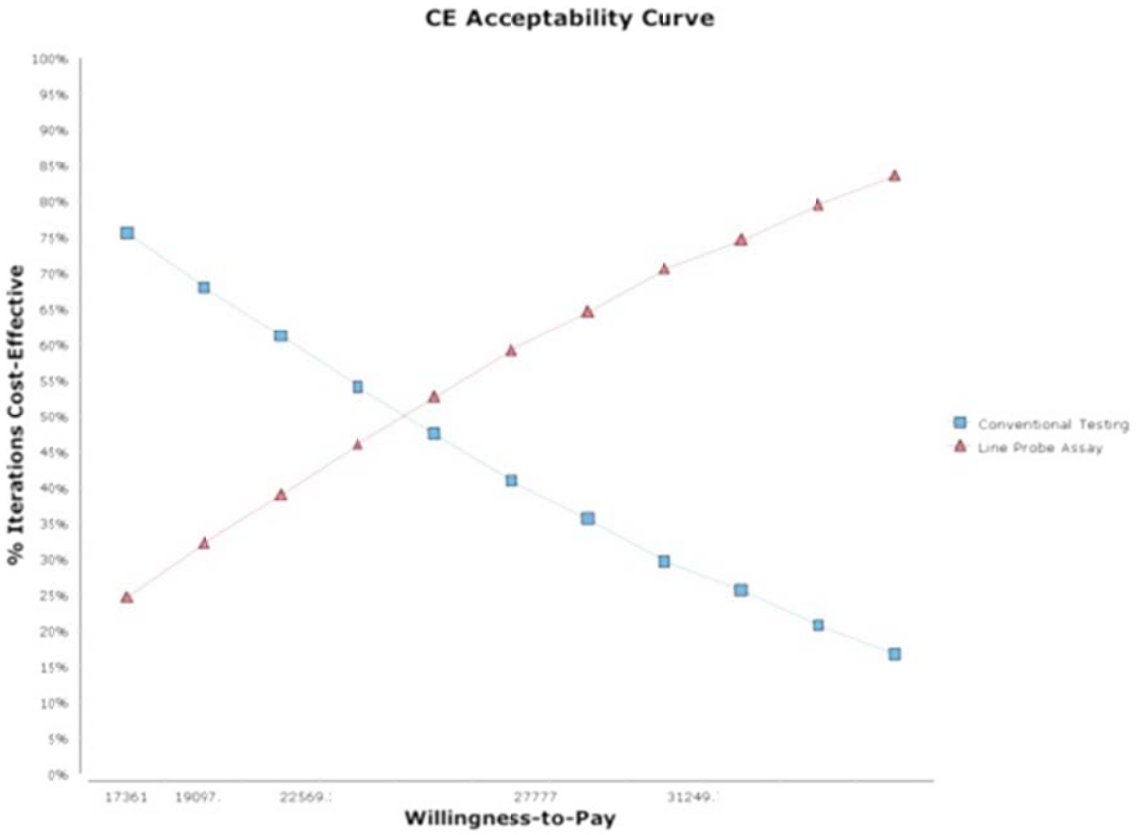


Table 5.11 Acceptability Curve Proportions

Willingness-to-Pay	**Line Probe Assay Test**	**Conventional Drug Susceptibility Testing**
17,361*	0.245	0.755
19,074	0.318	0.682
20,787	0.384	0.616
22,500	0.456	0.544
24,213	0.523	0.477
25,926	0.587	0.413
27,639	0.641	0.359
29,352	0.702	0.298
31,065	0.742	0.258
32,778	0.786	0.214
34,491	0.829	0.171

*Willingness-to-pay for South Africa

CHAPTER 6

DISCUSSION AND CONCLUSIONS

6.1 INTRODUCTION

A comparison of the study results to existing literature related to cost-effectiveness of diagnostics for South Africa and other low-to-middle income countries is summarized in Chapter 6. A summary of limitations and recommendations are also presented in Chapter 6.

6.2 COMPARISON TO THE LITERATURE

In the past, several studies have been conducted on the cost-effectiveness of TB diagnostics (not rapid technology). Only one study focused on the cost-effectiveness of rapid MDR-TB tests in low-to-middle-income countries.[73]

In that study, which was conducted in Peru, two rapid and three conventional drug susceptibility testing approaches were rated as cost-effective when compared to the GDP of Peru. The rapid test FASTPlaque-response was the least cost-effective approach of the drug susceptibility testing approaches ($272 per DALY averted). The current study has a much higher average DALY averted/QALY gained, greater than the willingness-to-pay due to the high hospitalization costs (>$10,000) for 6 months that were included in our model. Hospitalization costs were not included and TB treatment costs were also lower

(120 days for the Peruvian study versus 6 months MDR-TB treatment in the current study) in the previous analysis. The Peruvian study considered a transmission model (a US based model) in their analysis, assuming that there were 6 close contacts per MDR-TB patient who had on average 8 hours of contact with the MDR-TB patient per day. We did not include a transmission component in our model since the US model may not be applicable to the South African setting. The exclusion of the transmission model greatly limits the benefits of the line probe assay test since the results are provided in 7 days vs 28 days or more with the conventional test; and therefore if patients are tested with the line probe assay test and receive a test result earlier and are treated sooner there is potential for less spread of disease in the community. Adopting a transmission model would likely improve the cost-effectiveness of the line probe assay test, but would also likely require a great deal of additional assumptions being added to the model. Also in contrast to our analysis, the benefit of initiating treatment sooner was not considered in the model. In the current study, we assumed benefit of the line probe assay test in that the results were provided 3 weeks earlier. Using Kaplan Meier survival analyses calculations we assumed mortality would occur at a rate of 1% per month over a one-year period to a mortality rate noted for conventional drug susceptibility testing in survival analysis drug resistant literature for South Africa. The ideal model would consider the transmission component, as well as consider earlier initiation of treatment and decreased mortality.

Most recently, information from conference proceedings from the International AIDS Society Conference from the 17th of July 2011 show that the Foundation of Innovative Diagnostics is in the process of assessing the cost-effectiveness of the Xpert/Rif TB test in South Africa. The Xpert MTB/RIF, a rapid TB/rifampicin-resistance diagnostic, has been recently endorsed by the WHO and is recommended for investigating tuberculosis suspects for tuberculosis and rifampicin resistance. The

conference abstract briefly shows that the Xpert test had an ICER of $1860/year-of-life saved (YLS). The full report has not been published so it is difficult to assess what costs were included (and if hospitalization costs or transmission were included in the model). The test was assessed for a 3% incident rate of MDR-TB in South Africa.[134] In the current study we use a much higher prevalence rate as noted from 2006 published estimates for a very high MDR-TB outbreak region of the country.[103]

6.3 Challenges Experienced in Economic Modeling on Diagnostics for the Detection of TB

Throughout this study, several methodological challenges were encountered including incorporating the value of the line probe assay test with the limited information available from "real life" data and use of the test. Therefore, several assumptions needed to be made while developing the decision analysis model. It was interesting that in late July (July 26th 2011), prior to completion of this dissertation, Dowdy et al. published a paper outlining several of the challenges of economic analysis relating to TB testing, many of which were also encountered while building the current model. Dowdy, a leading researcher in the field of diagnostic technologies asks a very relevant question from the perspective of economic modeling and rapid tests – "Is a scale up worth it?" Dowdy then proceeds to discuss three main challenges experienced in building economic models to address the cost-effectiveness of TB diagnostics. These three key challenges, have also been encountered in the current model. These challenges include: assessing the

cost of the false positive disease, estimating the clinical impact of a new rapid diagnostic test, and the setting of cost-effectiveness thresholds. False positive results are difficult to estimate because of the costs associated with the morbidity incurred by the patient for a disease they were not treated for (but were treated for MDR-TB Tuberculosis instead).[135] Also false positives and the use of inappropriate MDR-TB treatment can promote the emergence of further resistant strains. In the current study, we assumed that all patients enter treatment (i.e., patients who default/drop out of treatment were not taken into consideration). This assumption is a limitation as the patient drop-out rates can be as high as 20% or more in Africa.[97]

The model and the limitations of the study will be discussed in further detail.

6.4 LIMITATIONS OF THE STUDY

Limitations of the model include:

- Success and failure rates were assumed and estimated from literature sources.
- A transmission model was not considered in the study which may have underestimated the value of obtaining a positive test result in a week with the line probe assay test, because patients would ideally be quarantined and treated in a shorter period of time and therefore transmission would be reduced in the community.
- Benefits beyond one year were not considered.

- The model does not consider adverse effects and patient dropouts from treatment. All patients are assumed to receive treatment.
- All false positive patients receive a full course of treatment and hospitalization
- Assumptions were made regarding outcome measures and mortality estimates.

A discussion on success rates, published estimates and cost comparisons follows.

6.5 SUCCESS RATES

Ravigilone provided commentary on a study regarding the control of drug resistant TB in Lima, Peru. In the Peruvian study, patients were tested for drug resistance, but received treatment with at least five-second-line drugs while awaiting test results. Despite several biases including an "exceptionality bias" because the study site in Lima, Peru was associated with strong organization support including governmental support, members of the WHO believe that the successful treatment approach in Peru is achievable in other resource poor settings. Ravigilone suggested that the success of this necessary intervention was dependent on a strong partnership and financial commitment by all stakeholder groups and should be an example to other TB programs throughout the developing world.[136] In a separate letter to the editor, Dheda et al. commented that a 60% treatment success rate was impressive but that caution should be exercised when extrapolating these findings to the African setting. Dheda and colleagues stressed that treatment outcomes for drug-resistant patients were poor and that the roll out of rapid diagnostic tests were equally as important as initiating specialized treatment regimens.[137]

Cheruvu and Bhadriraju commented that cost-effectiveness analysis ("cost per averted death due to TB" and cost per QALY) of the Peruvian treatment strategy would provide more evidence of the value of the program in Peru.[138] Researchers are currently conducting a cost-effectiveness study in Peru on the MDR-TB management strategy – which indicated that 60% of patients were cured, and in future, these results will be made available for a comparison to the present study.[139] In our model the impact of the 60% success rate in the line probe assay group was compared with the conventional testing group in a sensitivity analysis. We assumed that patients who were tested earlier could achieve a higher success rate if they are initiated on treatment within one week in the line probe assay group. When we applied the 60% success assumption, the ICER dropped from above the willingness-to-pay to approximately $15,000, which is below the willingness-to-pay threshold.

6.6 Published Estimates from Studies

Available global estimates come from organizations such as the United Nations, WHO, the United Nations Children's Fund (UNICEF), and academic institutions engaged in research.[140] Country-level data is available for public use through registries.[141] One major limitation of global estimates is that they are "best guesses" regarding health and death measurements at the country level.[142] Mortality data can be biased and underrepresented because much of the information comes from well-developed and structured programs. [107] In addition, omitting opportunistic infections or even omitting the diagnosis of HIV/AIDS might result in incorrectly or inappropriately recording

causes of death among HIV/AIDS patients. Furthermore, many patients might die in rural areas without a physician present.[143] After overall analysis and mathematical processes are completed, the presentation of final global estimates might be very different from the initial data collected. Additionally, researchers who utilize data presented by the WHO, UNICEF and other institutions need to understand the biases (statistical and political) that may be present in the collection of patient and health system information.[140] Academic institutions also have a responsibility to improve the collection of data through research projects and development and implementation of new innovations (e.g., improved medical recording systems in low- to middle- income countries).[144] In this study, we used high prevalence estimates from a region in South Africa where an MDR-TB outbreak took place. This limits the generalizability of the study results to areas within South Africa that may have a low prevalence of MDR-TB. The South African government and the WHO are in the process of generating prevalence estimates of MDR-TB in HIV patients in South Africa. The Gandhi et al., estimate, although limited, provides a picture of the costs associated with outbreak proportions.

As part of a series of five articles, Peter Byass suggested the following for global data estimates: [140]

- "Work towards better availability and quality data"
- "Enhance country capacity to develop, analyze, and interpret local data"
- "Develop common data standards"
- "Focus on better data rather than more complex estimation methods"

- "Improve robustness of data and methodologies used in estimates"
- "Manage a gradual transition from estimates to measurements"

The same concerns hold true for the reporting of sensitivity, specificity, positive predictive values and negative predictive values from tests. Tools such as the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) and STAndards for the reporting of Diagnostic Accuracy Studies (STARD) have been developed to assess the quality and reporting of diagnostic test results. Fontela et al., report that recently published infectious disease (HIV, malaria and TB) diagnostic reports have not been following the QUADAS and STARD guidelines and the diagnostic reports are "low to moderate quality." In the current cost-effectiveness analysis, diagnostic test characteristics published by FIND, WHO and collaborative investigators were used. It could not be determined if the test results met all the recommended standards of reporting results. [145]

6.7 COST COMPARISONS

One study in the United Kingdom showed that the mean average cost for treating patients with MDR-TB was as high as 60 000 British Pounds annually.[146] In the US, average inpatient costs per MDR-TB patient were US $25 853 (hospital stay only), per the Centers for Disease Control.[147] In South Africa, six-month hospitalization cost per patient was calculated to be approximately $11000 (including personnel cost, utilities and equipment and building costs).

The WHO reported high hospitalization costs for patients at government-funded health centers at $108.51 (Year 2005) per hospital bed (See Appendix E) per day.[123] We were unaware of what cost components made up the total hospitalization cost published but the WHO and costing experts from South Africa agreed with our decision to use a more conservative cost estimate. Hospitalization costs were confirmed with a costing expert in South Africa, who confirmed that these costs were realistic estimates. He also advised that we include costs for specialized MDR-TB personnel .We included personnel cost, but not specific to MDR-TB. Additionally, cost of transporting specimens, cost of wastage and other diagnostic costs are not included. However, the cost of each testing procedure is the current cost charged to the Department of Health from two major National Health Service laboratories in South Africa.

Hospitalization costs appeared to have the greatest impact on the model. This is an interesting observation as this is one of the first cost-effectiveness studies conducted on diagnostic tests to take into consideration hospitalization of patients. In the Peruvian study, MDR-TB patients are managed at home and the costs of hospitalizations were not included in the model. Therefore, the ICER for one DALY (approximately $18000) averted in the current study is much higher than the Peruvian study (between $2 and $94 per DALY). [73] South Africa is currently testing home-based MDR-TB care in the Eastern Region of South Africa (Kwa-Zulu Natal). Early results show that the home-based care model might be an appropriate model to reduce patient loads at hospitals in the region. Overall study results show that time to initiation of treatment (84 days versus 106.5 days), sputum smear (59 vs. 92 days, P = 0.055) and culture conversion (85 days vs. 119

days, P = 0.002) was lower for the home-based patients compared with the hospital-based patients. These encouraging results should be accepted with caution because transmission in the community still remains a challenge.[148]

There is concern that simple cost-effectiveness analyses like the current analysis may take away from the need for real community-based cost studies on infectious diseases in Africa.[149] Costing studies on HIV/AIDS, TB, MDR-TB are required in South Africa and Africa. While conducing this study, it became increasingly difficult to obtain costs associated with training, adverse events and societal costs. Therefore, these costs were eliminated from the study. This study was conducted to produce evidence while large-scale field studies are still underway. Additionally evidence from another decision analysis may differ greatly depending on the estimates used.[150] In this study, we conducted a sensitivity analysis to provide evidence at varying costs and incidence.

Other limitations of this model include the termination after 1 year. However, with the extensively drug resistant disease being as unpredictable as it is we, do not assess what occurs in patient's post 1-year follow up. Therefore, DALYs were not discounted in this model. We also made assumptions about the DALY estimates that were not available from the literature. We assumed that MDR-TB would reduce patients' QALY by 0.1 and a further 0.1 when a more extensive form of the disease was present (i.e., in the case of treatment failure of MDR-TB treatment). Additionally, we assumed

that a patients' QALYs would be further reduced by 0.05 in the event of hospitalization with an incorrect diagnosis of MDR-TB.

6.8 Conclusion and Recommendations for Future Research

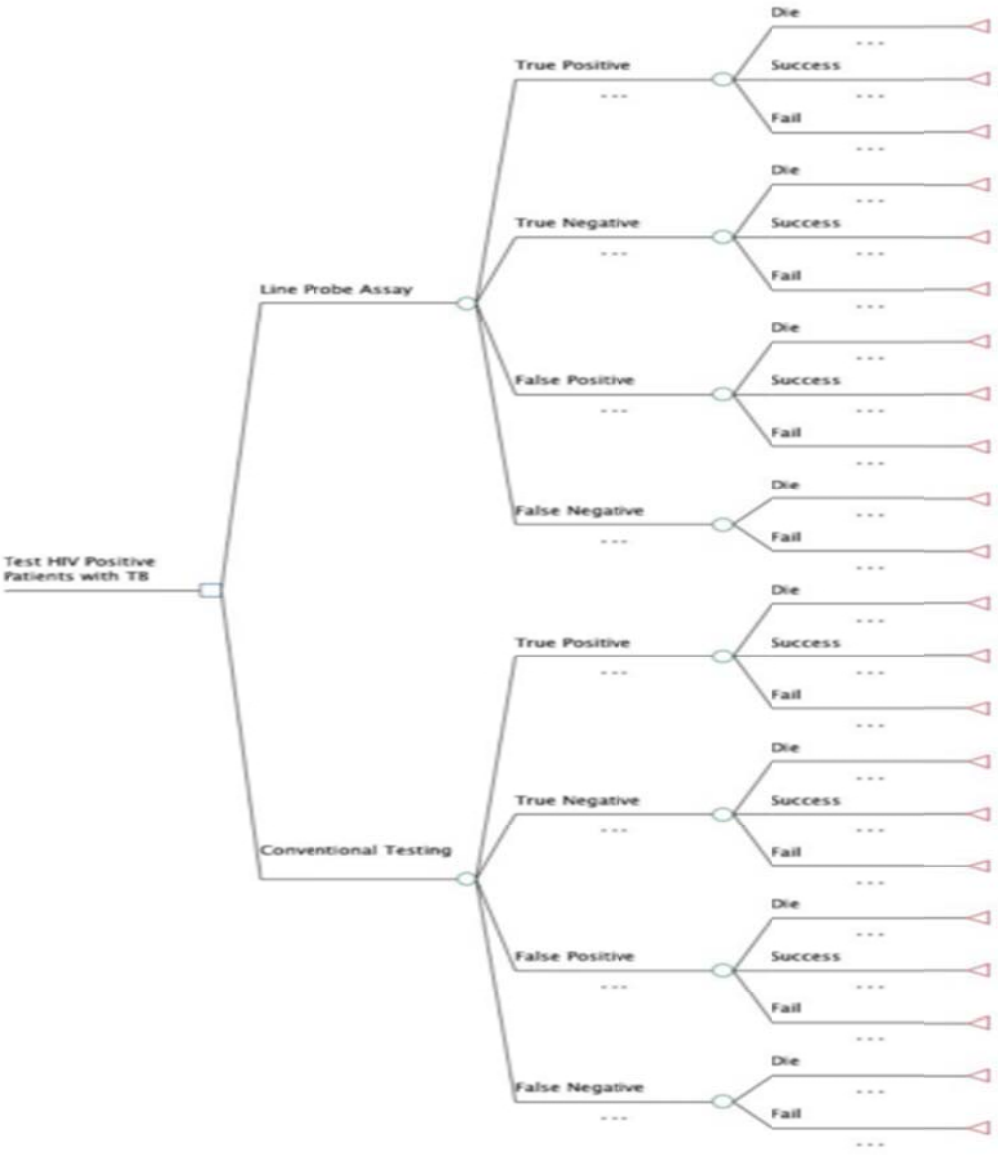
There are two major areas of research recommended: (1) costing studies; and (2) disease transmission models for South Africa. There is very limited cost information on the treatment for tuberculosis patients, resistant patients or retreatment cases. Cost studies are required to estimate costs of treatment, hospitalization, TB medical personal, transportation of specimens, patient costs and productivity costs for patients. Researchers in Cape Town, South Africa are currently conducting costing studies on extensive drug resistant forms.

Secondly, adding a transmission component to the current model would reduce the limitations of the current model. Gandhi et al. report from published research: "modeling studies have shown that when a patient with infectious drug-resistant tuberculosis is admitted to such a setting (i.e., hospitals), up to 50% of the patients exposed on that ward can become infected within 24 hours". [151] As noted, the cost of the line probe assay test is higher than the conventional drug susceptibility testing. Sensitivity and specificity are very similar between the two tests. However, the time to diagnosis sets the line probe assay apart from conventional testing therefore until the transmission model is added to the current model the results should be accepted with caution. The future consideration of the transmission model should be estimated from the perspective of society (e.g., number of household contacts infected) and from the

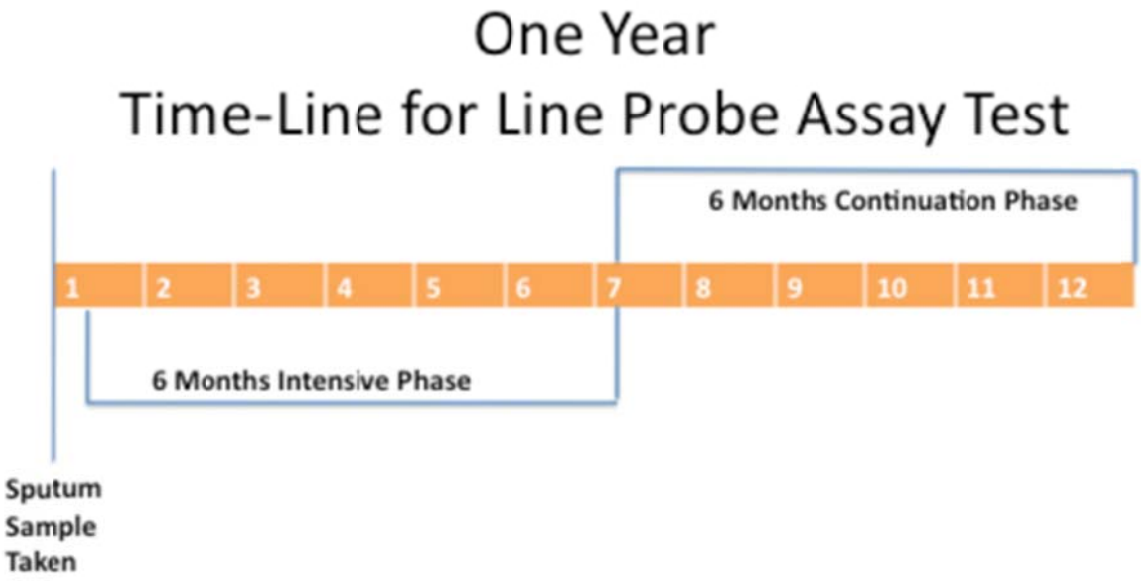
perspective of the South African government (e.g., how many patients require funded treatment).

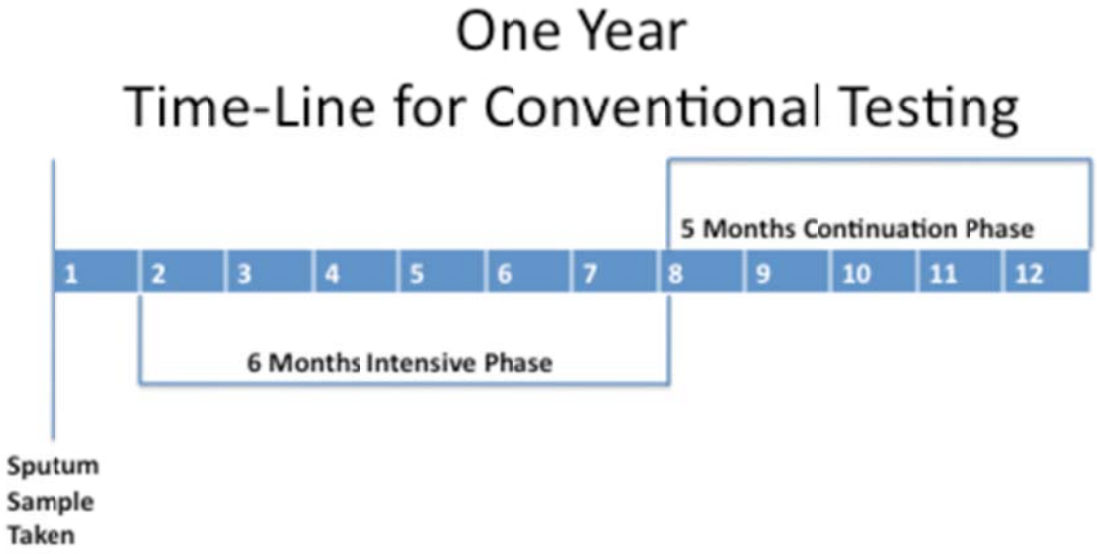
In order to harness the full impact of rapid diagnostic technology, a structured approach to the management of MDR-TB is required to prevent patients from being lost to follow up and to ensure that patients are treated in a timely manner to cure disease and to prevent transmission of the disease within the community. This will take a commitment from many key players including, patients, communities, caregivers, health care professionals, and the South African government.

APPENDIX A: DECISION TREE


Test HIV Positive Patients with TB
Line Probe Assay
Conventional Testing
True Positive
True Negative
False Positive
False Negative
Die
Success
Fail

APPENDIX B: ONE-YEAR TIME LINE FOR BOTH TESTING PROCEDURES


One Year
Time-Line for Line Probe Assay Test
6 Months Continuation Phase
1
2
3
4
5
6
7
8
9
10
11
12
6 Months Intensive Phase
Sputum
Sample
Taken


One Year
Time-Line for Conventional Testing
5 Months Continuation Phase
1
2
3
4
5
6
7
8
9
10
11
12
6 Months Intensive Phase
Sputum
Sample
Taken

APPENDIX C: SURVIVAL CALCULATION FOR PROBABILITY OF DEATH IN TRUE POSITIVE BRANCH AND DESCRIPTION OF BRANCHES USED IN TREE

Conventional Test Mortality Calculation

Time Period	At Risk	Percentage At Risk	Percentage Died	Percentage Live	Died	Survived	Kaplan- Meier Survival Probability Estimate
Time 0: Test	100.00	100.00					
End Month 1	60.00	60.00	0.40	0.60	40.00	60.00	0.6
End Month 2	59.40	99.00	0.01	0.99	0.60	59.40	0.594
End Month 3	58.81	99.00	0.01	0.99	0.59	58.81	0.58806
End Month 4	58.22	99.00	0.01	0.99	0.59	58.22	0.5821794
End Month 5	57.64	99.00	0.01	0.99	0.58	57.64	0.576357606
End Month 6	57.06	99.00	0.01	0.99	0.58	57.06	0.57059403
End Month 7	56.49	99.00	0.01	0.99	0.57	56.49	0.56488809
End Month 8	55.92	99.00	0.01	0.99	0.56	55.92	0.559239209
End Month 9	55.36	99.00	0.01	0.99	0.56	55.36	0.553646817
End Month 10	54.81	99.00	0.01	0.99	0.55	54.81	0.548110348
End Month 11	54.26	99.00	0.01	0.99	0.55	54.26	0.542629245
End Month 12	53.72	99.00	0.01	0.99	0.54	53.72	0.537202953

Mortality= 100-53.72=46.28
Mortality=1-0.54=0.46

Line Probe Assay Mortality Calculation

Time Period	At Risk	Percentage At Risk	Percentage Died	Percentage Live	Died	Survived	Kaplan- Meier Survival Probability Estimate
Time 0: Test	100.00	100.00					
End Month 1	90.00	90.00	0.10	0.90	10.00	90.00	0.9
End Month 2	89.10	99.00	0.01	0.99	0.90	89.10	0.891
End Month 3	88.21	99.00	0.01	0.99	0.89	88.21	0.88209
End Month 4	87.33	99.00	0.01	0.99	0.88	87.33	0.8732691
End Month 5	86.45	99.00	0.01	0.99	0.87	86.45	0.864536409
End Month 6	85.59	99.00	0.01	0.99	0.86	85.59	0.855891045
End Month 7	84.73	99.00	0.01	0.99	0.86	84.73	0.847332134
End Month 8	83.89	99.00	0.01	0.99	0.85	83.89	0.838858813
End Month 9	83.05	99.00	0.01	0.99	0.84	83.05	0.830470225
End Month 10	82.22	99.00	0.01	0.99	0.83	82.22	0.822165523
End Month 11	81.39	99.00	0.01	0.99	0.82	81.39	0.813943868
End Month 12	80.58	99.00	0.01	0.99	0.81	80.58	0.805804429

Mortality= 100-80.58=19.42
Mortality=1-0.81=0.19

Cost Variables

Cost Variable Name	Value ($)
Cost_1month_TBTX	21.56
Cost_5months_MDR_TB_ContinuationPhaseTX	445.20
Cost_6months_MDR_TBContinuationPhaseTx	534.24
Cost_Con	19.87
Cost_Hospitalization	11,387.04
Cost_IntensivePhase_MDR_TBTX	606.48
Cost_LPA	28.10
Cost_TBTX_6months	90.16
Cost_TBTX_7Days	5.39

Line Probe Assay: True Positive Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.19	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	6294.68*	0
Success	0.405	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	12561.25	0.4
Failure	0.405	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	12561.25	0.3

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Line Probe Assay: True Negative Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.110	Cost_Con+ Die_TB_Cost_HalfCycleCorrection	73.18*	0
Success	0.445	Cost_LPA+ Cost_TBTX_6months	118.26	0.7
Failure	0.445	Cost_LPA+ Cost_TBTX_6months	118.26	0.5

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Line Probe Assay: False Positive Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.110	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	6294.68*	0
Success	0.445	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	12561.25	0.65
Failure	0.445	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_6months_MDR_TBContinuationPhaseTx	12561.25	0.45

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Line Probe Assay: False Negative Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.5	Cost_Con+ Die_TB_Cost_HalfCycleCorrection	73.18*	0
Failure	0.5	Cost_LPA+ Cost_TBTX_6months	118.26	0.3

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Conventional Test: True Positive Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.460	Cost_Con+ Die_Cost_CON_MDR_TBTX_HalfCycleCorrection	6250.01*	0
Success	0.270	Cost_Con+ Cost_1month_TBTX+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_5months_MDR_TB_ContinuationPhaseTX	12480.15	0.4
Failure	0.270	Cost_Con+ Cost_1month_TBTX+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_5months_MDR_TB_ContinuationPhaseTX	12480.15	0.3

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Conventional Test: True Negative Branch

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.110	Cost_Con+ Die_TB_Cost_HalfCycleCorrection	64.95*	0
Success	0.445	Cost_LPA+ Cost_TBTX_6months	110.03	0.7
Failure	0.445	Cost_LPA+ Cost_TBTX_6months	110.03	0.5

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Conventional Test: False Positive

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.110	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_5months_MDR_TB_ContinuationPhaseTX	6250.01*	0
Success	0.445	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_5months_MDR_TB_ContinuationPhaseTX	12480.15	0.65
Failure	0.445	Cost_LPA+ Cost_TBTX_7Days+ Cost_IntensivePhase_MDR_TBTX+ Cost_Hospitalization+ Cost_5months_MDR_TB_ContinuationPhaseTX	12480.15	0.45

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

Conventional Test: False Negative

Branch	Base-case Probability	Costs	Total Cost	QALYS
Die	0.5	Cost_Con+ Die_TB_Cost_HalfCycleCorrection	64.95*	0
Failure	0.5	Cost_Con+ Cost_TBTX_6months	110.03	0.3

*Half cycle correction applied to all costs beside the cost of the test
QALYs = Quality Adjusted Life Years

APPENDIX D: COSTS OF DIAGNOSTIC TESTS FROM CLINICAL TRIALS CONDUCTED BY FOUNDATION OF INNOVATIVE DIAGNOSTICS IN CONJUNCTION WITH THE WORLD HEALTH ORGANIZATION

During clinical trials, the cost of screening with the line probe assay test per screen was estimated to be between US $17.36-$18.87.[38] The cost of confirmatory testing or the cost of traditional drug susceptibility testing to confirm test results was US $ 24.66-34.48.[38] These costs were published in 2008 and were adjusted to present value before inputting into the model. The following table lists the cost per screening procedure prior to price negotiation.

Costs of Conventional Culture and Drug Susceptibility Testing relative to Genotype MTBDR*plus* in NHLS laboratories, South Africa. Taken from: Expert Group Report on Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multi-Drug Resistant Tuberculosis (MDR-TB)

Unit Cost (USD)*	**Cape Town**	**Johannesburg***
Conventional Culture and Drug Susceptibility Testing (DST)		
Decontamination	2.26	3.18
Primary culture	7.82	11.35
Acid-fast bacilli (AFB) microscopy confirmation	2.57	2.99
DST (isoniazid and rifampicin)	12.01	16.96
Total	24.66	34.48
Genotype MTBDR*plus*		
Decontamination	2.26	3.18
Acid-fast bacilli (AFB) microscopy confirmation	1.00	1.44
Resistance detection (isoniazid and rifampicin)	15.61	12.74
Total	18.87	17.36

*Diagnostic costs will be standardized using Consumer Price index inflation rates from the United States and South Africa.

Source: World Health Organization. Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multi-Drug Resistant Tuberculosis (MDR-TB) Available at: http://search.who.int/search?q=molecular+line+probe+assays+for+rapid+screening+of+patients+at+risk+of+multidrug+resistant+tuberculosis+and+may+2008+&btnG=Search&spell=1&ie=utf8&site=default_collection&lr=lang_en&client=WHO&proxystylesheet=WHO&output=xml_no_dtd&oe=UTF8&sitesearch=&sort=date%3AD%3AL%3Ad1&entqr=3&ud=1. Accessed: September 1, 2009

Present Value Adjustments for Direct Medical Costs Associated with MDR-TB Screening

Costs of diagnostic tests, including costs of decontamination; confirmation of acid-fast bacilli and cost of resistance testing were published in 2008 by the World Health Organization and Foundation of Innovative Diagnostics. The South African General Consumer Price Inflation Rate and medical product inflation rate were used to adjust costs. The medical product inflation rate for 2008 was not provided through the South African Statistics Bureau and therefore, the general consumer price inflation rate in 2008 of 0.115 was used. The 2009, 2010, and 2011 (May 2011) consumer price inflation values for medical products were 0.119, 0.063, 0.058 respectively. The costs of the diagnostic tests (published in US $) and collected in 2008 were multiplied by these Consumer Price Index inflations rates for South Africa. Calculations are shown below.

Conventional Drug Susceptibility Testing (Range: $24.66-$34.48)

24.66 x [1 + 0.115] x [1 + 0.119] x [1 + 0.063] x [1 + 0.058] = $31.14

34.48 x [1 + 0.115] x [1 + 0.119] x [1 + 0.063] x [1 + 0.058]= $43.54

Line Probe Assay (Range: $17.36-$18.87)

17.36 x [1 + 0.115] x [1 + 0.119] x [1 + 0.063] x [1 + 0.058]= $24.35

18.87 x [1 + 0.115] x [1 + 0.119] x [1 + 0.063] x [1 + 0.058]= $26.47

APPENDIX E: THE WORLD HEALTH ORGANIZATION HOSPITALIZATION COSTS

Taken from World Health Organization Website[123]
(http://www.who.int/choice/costs/unit_costs/en/index.html)
South Africa

"Estimates of Unit Costs for Patient Services for South Africa"

"The table on Hospital Costs presents the estimated cost per hospital stay and per outpatient visit by hospital level[1]. Unit costs are specific to public hospitals, with occupancy rate of 80% and representing the "hotel" component of hospital costs, i.e., excluding drugs and diagnostic tests and including other costs such as personnel, capital and food costs."

"The table on Health Centre Costs presents cost per visit for primary care facilities, i.e. health centers, at different levels of population coverage. It includes all cost components including depreciated capital items but excludes drugs and diagnostics."

The results are presented in International dollars units (2005)."[123]

HOSPITAL COSTS	
Cost per bed day by hospital level*	
	Int $ 2005
Primary	60.89
Secondary	79.44
Tertiary	**108.51**
Cost per outpatient visit by hospital level*	
	Int $ 2005
Primary	20.90
Secondary	29.64
Tertiary	43.84
HEALTH CENTRE COSTS	
Cost per visit at health centre by population coverage for a 20 minute visit**	
	Int $ 2005
50%	9.06
80%	10.68
95%	16.20

* Public facility, 80% occupancy rate, excludes drugs and diagnostics ** public facility, at different population coverage, excludes drugs and diagnostics

Adjustment of World Health Organization cost for Inflation:
$108.51 x [1 + 0.036] x [1 + 0.058] x [1 + 0.09] x [1 + 0.115] x [1 + 0.10] x [1 + 0.007] x [1 + 0.058] = $130

“

REFERENCES

1. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is "science" enough to tackle the epidemic? *European Respiratory Journal.* 2007;29(3):423-427.
2. World Health Organization. Tuberculosis (TB). http://www.who.int/tb/en/. Accessed September 1st 2009
3. Andrews JR, Gandhi NR, Moodley P, et al. Exogenous Reinfection as a Cause of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis in Rural South Africa. *Journal of Infectious Diseases.* Dec 2008;198(11):1582-1589.
4. World Health Organization. Guidelines for the programmatic management of drug resistant tuberculosis. Emergency update 2008. . http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf. Accessed September 1st 2009
5. World Health Organization. Global Tuberculosis Control 2009. Epidemiology, Strategy, Financing. 2009; http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf. Accessed September 1st 2009.
6. World Health Organization. Health Ministers to accelerate efforts against drug-resistant tuberculosis. http://www.who.int/mediacentre/news/releases/2009/tuberculosis_drug_resistant_20090402/en/. Accessed September 1st 2009
7. Wright A, Zignol M, Van Deun A, et al. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet.* May-Jun 2009;373(9678):1861-1873.
8. Donald PR, van Helden PD. The Global Burden of Tuberculosis - Combating Drug Resistance in Difficult Times. *New England Journal of Medicine.* Jun 2009;360(23):2393-2395.
9. Kent MM, Yin S. *Controlling Infectious Diseases.* 2006
10. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993-2007. *JAMA.* Nov 12 2008;300(18):2153-2160.
11. Banerjee R, Allen J, Westenhouse J, et al. Extensively drug-resistant tuberculosis in California, 1993-2006. *Clin Infect Dis.* Aug 15 2008;47(4):450-457.
12. Alexander PE, De P. The emergence of extensively drug-resistant tuberculosis (TB): TB/HIV coinfection, multidrug-resistant TB and the resulting public health threat from extensively drug-resistant TB, globally and in Canada. *Can J Infect Dis Med Microbiol.* Sep 2007;18(5):289-291.
13. Chaisson RE, Martinson NA. Tuberculosis in Africa - Combating an HIV-driven crisis. *New England Journal of Medicine.* Mar 2008;358(11):1089-1092.

14. Gelmanova IY, Keshavjee S, Golubchikova VT, et al. Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bull World Health Organ.* Sep 2007;85(9):703-711.
15. Keshavjee S, Gelmanova IY, Farmer PE, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. *Lancet.* Oct 18 2008;372(9647):1403-1409.
16. Kourbatova EV, Borodulin BE, Borodulina EA, del Rio C, Blumberg HM, Leonard MK, Jr. Risk factors for mortality among adult patients with newly diagnosed tuberculosis in Samara, Russia. *Int J Tuberc Lung Dis.* Nov 2006;10(11):1224-1230.
17. Keshavjee S, Gelmanova IY, Pasechnikov AD, et al. Treating multidrug-resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. *Ann N Y Acad Sci.* 2008;1136:1-11.
18. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Lomakina OB, Kourbatova EV. Social support and incentives programme for patients with tuberculosis: experience from the Russian Federation. *Int J Tuberc Lung Dis.* Nov 2007;11(11):1210-1215.
19. Jakubowiak WM, Bogorodskaya EM, Borisov SE, Danilova ID, Kourbatova EV. Risk factors associated with default among new pulmonary TB patients and social support in six Russian regions. *Int J Tuberc Lung Dis.* Jan 2007;11(1):46-53.
20. Zolotova E. Russian oblast is model in fight against TB. *Bull World Health Organ.* May 2007;85(5):329-331.
21. Swaminathan S, Narendran G. Hiv and Tuberculosis in India. *J. Biosci.* 2008;33(4):527-537.
22. Singh M, Chauhan DS, Gupta P, et al. In vitro effect of fluoroquinolones against Mycobacterium tuberculosis isolates from Agra & Kanpur region of north India. *Indian J Med Res.* May 2009;129(5):542-547.
23. Jain A, Mondal R, Prasad R, Singh K, Ahuja RC. Prevalence of multidrug resistant Mycobacterium tuberculosis in Lucknow, Uttar Pradesh. *Indian J Med Res.* Sep 2008;128(3):300-306.
24. Tahir M, Sharma SK, Rohrberg DS, Gupta D, Singh UB, Sinha PK. DOTS at a tertiary care center in northern India: successes, challenges and the next steps in tuberculosis control. *Indian J Med Res.* May 2006;123(5):702-706.
25. Ramachandran R, Nalini S, Chandrasekar V, et al. Surveillance of drug-resistant tuberculosis in the state of Gujarat, India. *Int J Tuberc Lung Dis.* Sep 2009;13(9):1154-1160.
26. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. *J Infect Dis.* Aug 15 2007;196 Suppl 1:S15-27.
27. Centers for Disease Control and Prevention. Tuberculosis (TB): Testing & Diagnosis. 2010 http://www.cdc.gov/tb/topic/testing/default.htm. Accessed September 10th 2010.

28. Pai M, Menzies D. Interferon-gamma release assays: what is their role in the diagnosis of active tuberculosis? *Clin Infect Dis.* Jan 1 2007;44(1):74-77.
29. Pai M, Kalantri S, Dheda K. New tools and emerging technologies for the diagnosis of tuberculosis: part I. Latent tuberculosis. *Expert Rev Mol Diagn.* May 2006;6(3):413-422.
30. Pai M, O'Brien R. New diagnostics for latent and active tuberculosis: state of the art and future prospects. *Semin Respir Crit Care Med.* Oct 2008;29(5):560-568.
31. World Health Organization. New Laboratory Diagnostic Tools for Tuberculosis Control. http://apps.who.int/tdr/publications/non-tdr-publications/diagnostic-tool-tb/pdf/diagnostic-tool-tb.pdf. Accessed September 1st 2009.
32. Small PM, Fujiwara PI. Management of tuberculosis in the United States. *N Engl J Med.* Jul 19 2001;345(3):189-200.
33. Garwood P. New tools for an old disease. *Bull World Health Organ.* May 2007;85(5):331-332.
34. Pai M, Minion J, Steingart K, Ramsay A. New and improved tuberculosis diagnostics: evidence, policy, practice, and impact. *Curr Opin Pulm Med.* May 2010;16(3):271-284.
35. Minion J, Leung E, Menzies D, Pai M. Microscopic-observation drug susceptibility and thin layer agar assays for the detection of drug resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis.* Oct 2010;10(10):688-698.
36. Walker D. Economic analysis of tuberculosis diagnostic tests in disease control: how can it be modelled and what additional information is needed? *Int J Tuberc Lung Dis.* 2001 5(12):1099-1108.
37. Ramachandran R, Paramasivan C. What is new in the diagnosis of Tuberculosis? Part II; Techniques for drug susceptability testing. . *Indian Journal of Tuberculosis* 2003 50 197-202.
38. World Health Organization. Molecular Line Probe Assays for Rapid Screening of Patients at Risk of Multi-Drug Resistant Tuberculosis (MDR-TB) http://www.who.int/tb/features_archive/policy_statement.pdf. Accessed Septemeber 1st 2009
39. Morgan M, Kalantri S, Flores L, Pai M. A commercial line probe assay for the rapid detection of rifampicin resistance in Mycobacterium tuberculosis: a systematic review and meta-analysis. *BMC Infect Dis.* 2005;5:62.
40. Bwanga F, Hoffner S, Haile M, Joloba ML. Direct susceptibility testing for multi drug resistant tuberculosis: A meta-analysis. *Bmc Infectious Diseases.* May 2009;9.
41. Wise J. Fast action urged to halt deadly TB. *Bull World Health Organ.* May 2007;85(5):328-329.
42. Foundation of Innovative Diagnostics. *Annual Report.* 2008
43. World Health Organization. *A ministerial meeting of high M/XDR-TB Burden countries. Addressing the key bottlenecks hampering the prevention and scale-up of M/XDR-TB control and patient care.* 2009.

44. Ghebreyesus TA, Kazatchkine M, Sidibe M, Nakatani H. Tuberculosis and HIV: time for an intensified response. *Lancet.* May 22 2010;375(9728):1757-1758.
45. World Health Organization. Treatment of Tuberculosis Guidelines - Fourth Edition http://www.who.int/tb/publications/tb_treatmentguidelines/en/. Accessed July 10th 2010.
46. Migliori GB, Sotigu, G, D'Arcy Richardson M, Centis R, Facchini A, Guenther G, Spanevello A, Lange C. MDR-TB and XDR-TB: Drug Resistance and Treatment Outcomes *European Respiratory Journal.* 2009 34(3):778-779.
47. United Nations Development Programme. What you need to know about the Millennium Development Goals http://www.undp.org/mdg/basics.shtml. Accessed October 20th 2010.
48. World Health Organization. Global Tuberculosis Control. A Short Update to the 2009 Report 2009 http://www.who.int/tb/publications/global_report/2009/update/en/index.html. Accessed 20th September 2010.
49. Cobelens FG, Heldal E, Kimerling ME, et al. Scaling up programmatic management of drug-resistant tuberculosis: a prioritized research agenda. *PLoS Med.* Jul 8 2008;5(7):e150.
50. Nathanson E, Lambregts-van Weezenbeek C, Rich ML, et al. Multidrug-resistant tuberculosis management in resource-limited settings. *Emerg Infect Dis.* Sep 2006;12(9):1389-1397.
51. Mabey D, Peeling RW, Ustianowski A, Perkins MD. Diagnostics for the developing world. *Nat Rev Microbiol.* Mar 2004;2(3):231-240.
52. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis.* Aug 15 2007;196 Suppl 1:S86-107.
53. Lonnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. *Lancet.* May 22 2010;375(9728):1814-1829.
54. Young DB, Perkins MD, Duncan K, Barry CE, 3rd. Confronting the scientific obstacles to global control of tuberculosis. *J Clin Invest.* Apr 2008;118(4):1255-1265.
55. Perkins MD, Small PM. Partnering for better microbial diagnostics. *Nat Biotechnol.* Aug 2006;24(8):919-921.
56. Wallis RS, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. *Lancet.* May 29 2010;375(9729):1920-1937.
57. Das P, Horton R. Tuberculosis--time to accelerate progress. *Lancet.* May 22 2010;375(9728):1755-1757.
58. Bootman JL TR, McGhan WF. *Principles of pharmacoeconomics*. 3rd ed. Cincinnati, OH: Harvey Whitney Books Co.; 2005.
59. Rascati KL. *Essentials of pharmacoeconomics*. Philadelphia: Lippincott Williams & Wilkins; 2009.

60. Sohn H, Minion J, Albert H, Dheda K, Pai M. TB diagnostic tests: how do we figure out their costs? *Expert Rev Anti Infect Ther.* Aug 2009;7(6):723-733.
61. New Diagnostics Working Group of the STOP TB Partnership. Pathway to better diagnostics for tuberculosis. A blueprint for the development of TB diagnostics 2009; http://www.stoptb.org/wg/new_diagnostics/. Accessed September 9th 2010.
62. World Health Organization. DALYs / YLDs definition. 2010; http://www.who.int/mental_health/management/depression/daly/en/. Accessed October 6th 2010
63. Brewer TF, Heymann SJ, Ettling M. An effectiveness and cost analysis of presumptive treatment for Mycobacterium tuberculosis. *Am J Infect Control.* Jun 1998;26(3):232-238.
64. Pisu M, Gerald J, Shamiyeh JE, Bailey WC, Gerald LB. Targeted Tuberculosis Contact Investigation Saves Money Without Sacrificing Health. *Journal of Public Health Management and Practice.* Jul-Aug 2009;15(4):319-327.
65. Tan MC, Maeea CA, Sadatsafavi M, et al. Cost-effectiveness of LTBI treatment for TB contacts in British Columbia. *Value Health.* 2008;11(5):842-852.
66. Diel R, Schaberg T, Loddenkemper R, Welte T, Nienhaus A. Enhanced cost-benefit analysis of strategies for LTBI screening and INH chemoprevention in Germany. *Respiratory Medicine.* Dec 2009;103(12):1838-1853.
67. Burgos JL, Kahn JG, Strathdee SA, et al. Targeted screening and treatment for latent tuberculosis infection using QuantiFERON-TB Gold is cost-effective in Mexico. *Int J Tuberc Lung Dis.* Aug 2009;13(8):962-968.
68. de Perio MA, Tsevat J, Roselle GA, Kralovic SM, Eckman MH. Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. *Arch Intern Med.* Jan 26 2009;169(2):179-187.
69. Marra F, Marra CA, Sadatsafavi M, et al. Cost-effectiveness of a new interferon-based blood assay, QuantiFERON-TB Gold, in screening tuberculosis contacts *Int J Tuberc Lung Dis.* 2008;12(12):1414-1424.
70. Dowdy DW, Lourenco MC, Cavalcante SC, et al. Impact and Cost-Effectiveness of Culture for Diagnosis of Tuberculosis in HIV-Infected Brazilian Adults. *Plos One.* Dec 2008;3(12).
71. Dowdy DW, O'Brien MA, Bishai D. Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis *Int J Tuberc Lung Dis.* 2008;12(9):1021-1029.
72. Diel R, Wrighton-Smith P, Zellweger JP. Cost-effectiveness of interferon-gamma release assay testing for the treatment of latent tuberculosis. *Eur Respir J.* 2007;30(2):321-332.
73. Acuna-Villaorduna C, Vassall A, Henostroza G, et al. Cost-effectiveness analysis of introduction of rapid, alternative methods to identify multidrug-resistant tuberculosis in middle-income countries. *Clin Infect Dis.* Aug 15 2008;47(4):487-495.
74. Finnell SME, Christenson JC, Downs SM. Latent Tuberculosis Infection in Children: A Call for Revised Treatment Guidelines. *Pediatrics.* Mar 2009;123(3):816-822.

75. Khan K, Muennig P, Behta M, Zivin JG. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N Engl J Med.* Dec 5 2002;347(23):1850-1859.
76. Jacquet V, Morose W, Schwartzman K, et al. Impact of DOTS expansion on tuberculosis related outcomes and costs in Haiti. *BMC Public Health.* 2006;6:209.
77. Burman WJ, Dalton CB, Cohn DL, Butler JR, Reves RR. A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. *Chest.* Jul 1997;112(1):63-70.
78. Mushlin AI, Ruchlin HS, Callahan MA. Costeffectiveness of diagnostic tests. *Lancet.* Oct 20 2001;358(9290):1353-1355.
79. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health.* Jan-Feb 2003;6(1):9-17.
80. Map of South Africa http://www.routes.co.za/map.html. Accessed July 15th 2011.
81. Joint United Nations Programme on HIV/AIDS. *Epidemiological Fact Sheet on HIV and AIDS. Core Dataon Epidemiology and Response. South Africa. September 2008 Update.* 2008
82. Joint United Nations Programme on HIV/AIDS. *South Africa, July 2008: Country Situation.* 2008.
83. Abdool Karim SS, Churchyard GJ, Addool Karim Q, Lawn SD. HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response *Lancet.* 2009;374(9693):921-933.
84. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. *Aids.* Aug 2006;20(12):1605-1612.
85. Singh JA, Upshur R, Padayatchi N. XDR-TB in South Africa: no time for denial or complacency. *PLoS Med.* Jan 2007;4(1):e50.
86. World Health Organization. *Anti-tuberculosis drug resistance in the world (1994-1997).*
87. World Health Organization. *Anti-tuberculosis drug resistance in the world. Report 4 (2002-2007).* 2008.
88. World Health Organization. Multidrug and Extensively drug-resistant TB (M/XDR-TB) 2010 Global Report on Surveillance and Response. 2010; http://www.who.int/tb/features_archive/m_xdrtb_facts/en/index.html. Accessed 24th October 2010.
89. Published in Partnership with Umsinyathi District Management. The Msinga Experience: Tuberculosis MDR/XDR. Lessons Learned From South Africa 2005-2009. . 2009.
90. Dorman SE, Chaisson RE. From magic bullets back to the magic mountain: the rise of extensively drug-resistant tuberculosis. *Nat Med.* Mar 2007;13(3):295-298.

91. Andrews JR, Shah NS, Weissman D, Moll AP, Friedland G, Gandhi NR. Predictors of multidrug- and extensively drug-resistant tuberculosis in a high HIV prevalence community. *Plos One.* 2010;5(12):e15735.
92. Department of Health Republic of South Africa. Management Drug Resistant Tuberculosis2010.
93. Center for Global Health Policy. *Death by Drug- Resistant TB and How to Stop It.* 2010.
94. Floyd K, Wilkinson D, Gilks C. Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *BMJ.* Nov 29 1997;315(7120):1407-1411.
95. Cleary C BA, McIntyre D, Coetzee D. *Cost Effectiveness of Antiretroviral Treatment for HIV-Postive Adults in a South African Township.* 2004
96. Laserson KF, Thorpe LE, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* Jun 2005;9(6):640-645.
97. Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. *Int J Tuberc Lung Dis.* Apr 2010;14(4):413-419.
98. Shean KP, Willcox PA, Siwendu SN, et al. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992-2002. *Int J Tuberc Lung Dis.* Oct 2008;12(10):1182-1189.
99. Connolly C, Davies GR, Wilkinson D. Impact of the human immunodeficiency virus epidemic on mortality among adults with tuberculosis in rural South Africa, 1991-1995. *Int J Tuberc Lung Dis.* Nov 1998;2(11):919-925.
100. Howard AA, El-Sadr WM. Integration of tuberculosis and HIV services in sub-Saharan Africa: lessons learned. *Clin Infect Dis.* May 15 2010;50 Suppl 3:S238-244.
101. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *Aids.* Jan 26 2001;15(2):143-152.
102. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. *Am J Respir Crit Care Med.* Mar 1999;159(3):733-740.
103. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med.* Jan 1 2010;181(1):80-86.
104. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet.* Nov 2006;368(9547):1575-1580.
105. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet.* May 22 2010;375(9728):1798-1807.

106. Migliori GB, Sotgiu G. XDR tuberculosis in South Africa: old questions, new answers. *Lancet.* May 22 2010;375(9728):1760-1761.
107. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *Aids.* Oct 2008;22(15):1897-1908.
108. Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *Aids.* Dec 2005;19(18):2141-2148.
109. Fairall LR, Bachmann MO, Louwagie GM, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Arch Intern Med.* Jan 14 2008;168(1):86-93.
110. World Health Organization/ UNDP/World Bank Special Programme for Research in Tropical Diseases (TDR) and the Foundation of Innovative New Diagnostics. *Diagnostics for Tuberculosis: Global Demand and Market Potential.* 2006
111. Nantulya VM. *Getting Diagnostics into Countries* Geneva: Global Forum for Health Research 2008.
112. Pai M, Ramsay A, O'Brien R. Comprehensive new resource for evidence-based TB diagnosis. *Expert Rev Mol Diagn.* Oct 2009;9(7):637-639.
113. National Health Laboratory Service. NHLS About Us (Homepage). http://www.nhls.ac.za/?page=about_us&id=16.
114. Paramasivan CN, Lee E, Kao K, et al. Experience establishing tuberculosis laboratory capacity in a developing country setting. *Int J Tuberc Lung Dis.* Jan 2010;14(1):59-64.
115. Bateman C. ARV compliance--the new battle terrain. *S Afr Med J.* Aug 2004;94(8):602-603, 605.
116. Harling G, Wood R. The evolving cost of HIV in South Africa: changes in health care cost with duration on antiretroviral therapy for public sector patients. *J Acquir Immune Defic Syndr.* Jul 1 2007;45(3):348-354.
117. Andrews JR, Shah NS, Gandhi N, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: Implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. *Journal of Infectious Diseases.* Dec 2007;196:S482-S490.
118. Bateman C. SAMA leads the way with ARV roll-out. *S Afr Med J.* 2004;94(1):17-18.
119. Bateman C. "One Shot" to kill MDR-TB-or risk patient death *S Afr Med J.* 2007;97(12):1233-1236.
120. Shenoi SV, Escombe AR, Friedland G. Transmission of drug-susceptible and drug-resistant tuberculosis and the critical importance of airborne infection control in the era of HIV infection and highly active antiretroviral therapy rollouts. *Clin Infect Dis.* May 15 2010;50 Suppl 3:S231-237.
121. Gandhi NR, Moll AP, Lalloo U, et al. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study. *J Acquir Immune Defic Syndr.* Jan 1 2009;50(1):37-43.

122. Olukoga A. Unit costs of inpatient days in district hospitals in South Africa. *Singapore Med J.* Feb 2007;48(2):143-147.
123. World Health Organization. Unit Costs for Patient Services. http://www.who.int/choice/costs/unit_costs/en/index.html.
124. Scano F, Vitoria M, Burman W, Harries AD, Gilks CF, Havlir D. Management of HIV-infected patients with MDR- and XDR-TB in resource-limited settings. *International Journal of Tuberculosis and Lung Disease.* Dec 2008;12(12):1370-1375.
125. World Health Organization. Download Data From Who's Global TB Website. http://www.who.int/tb/country/en/. Accessed April 1st 2010.
126. Fletcher R.H. FSW. *Clinical Epidemiology. The Essentials.* Fourth Edition ed. Philadelphia: Lippincott Williams & Wilkins 2005.
127. Resch SC, Salomon JA, Murray M, Weinstein MC. Cost-effectiveness of treating multidrug-resistant tuberculosis. *PLoS Med.* Jul 2006;3(7):e241.
128. TreeAge Software Inc. TreeAge Pro Software 2011 http://www.treeage.com/.
129. World Health Organization. *The global burden of disease : a comprehensive assessment of mortality and disability from diseases,*: Harvard School of Public Health on behalf of the World Health Organization and the World Bank ; Distributed by Harvard University Press; 1996.
130. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med.* Apr 1 2008;177(7):787-792.
131. Jassal M, Bishai WR. Extensively drug-resistant tuberculosis. *Lancet Infect Dis.* Jan 2009;9(1):19-30.
132. Zignol M, Hosseini MS, Wright A, et al. Global incidence of multidrug-resistant tuberculosis. *J Infect Dis.* Aug 15 2006;194(4):479-485.
133. World Health Organization. *Global Tuberculosis Control.* 2010.
134. Andrews J, Lawn SD, Rusu C, et al. Cost-effectiveness of Xpert MTB/RIF for screening for tuberculosis prior to antiretroviral therapy in South Africa. *International Aids Society Conference* 2011
135. Dowdy DW, Cattamanchi A, Steingart KR, Pai M. Is Scale-Up Worth It? Challenges in Economic Analysis of Diagnostic Tests for Tuberculosis. *PLoS Med.* 2011 8(7).
136. Raviglione MC. Facing extensively drug-resistant tuberculosis--a hope and a challenge. *N Engl J Med.* Aug 7 2008;359(6):636-638.
137. Dheda K, Shean K, Badri M. Extensively Drug-Resistant Tuberculosis. *The New England Journal of Medicine.* 2008;359(22):2390.
138. Cheruvu M., B. S. Extensively Drug-Resistant Tuberculosis. *The New England Journal of Medicine.* 2008 359(22):2390-2391.
139. Mitnick CD, Bayona JN, Becerra MC. Extensively Drug-Resistant Tuberculosis: The Authors Reply. *The New England Journal of Medicine.* 2008 359(22):2391.

140. Byass P. The imperfect world of global health estimates. *PLoS Med.* 2010;7(11):e1001006.
141. Boerma JT, Mathers C, Abou-Zahr C. WHO and global health monitoring: the way forward. *PLoS Med.* 2010;7(11):e1000373.
142. The PLoS Medicine Editors. Can we count on global health estimates? *PLoS Med.* 2010;7(11):e1001002.
143. Sankoh O. Global health estimates: stronger collaboration needed with low- and middle-income countries. *PLoS Med.* 2010;7(11):e1001005.
144. Murray CJ, Lopez AD. Production and analysis of health indicators: the role of academia. *PLoS Med.* 2010;7(11):e1001004.
145. Fontela PS, Pant Pai N, Schiller I, Dendukuri N, Ramsay A, Pai M. Quality and reporting of diagnostic accuracy studies in TB, HIV and malaria: evaluation using QUADAS and STARD standards. *Plos One.* 2009;4(11):e7753.
146. White VL, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. *Thorax.* Nov 2000;55(11):962-963.
147. Rajbhandary SS, Marks SM, Bock NN. Costs of patients hospitalized for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis.* Aug 2004;8(8):1012-1016.
148. Heller T, Lessells RJ, Wallrauch CG, et al. Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis.* Apr 2010;14(4):420-426.
149. Simpson KN. Economic modeling of HIV treatments. *Curr Opin HIV AIDS.* May 2010;5(3):242-248.
150. Braithwaite RS, Roberts MS, Justice AC. Incorporating quality of evidence into decision analytic modeling. *Ann Intern Med.* Jan 16 2007;146(2):133-141.
151. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet.* May 22 2010;375(9728):1830-1843.