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Cost-effectiveness of chest x-ray screening for diagnosis and treatment of inactive pulmonary tuberculosis in a high-incidence country

by

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ABSTRACT

Treatment of individuals with inactive pulmonary tuberculosis has been shown to prevent cases of tuberculosis and improve quality-of-life at a “reasonable” cost in North America. The economic feasibility of screening and treatment of inactive pulmonary tuberculosis has not been established in South Africa, a country with an increasing tuberculosis epidemic. As such, cost-effectiveness and cost-utility analyses were performed to determine the benefits and costs of a chest x-ray screening and treatment programme for individuals with inactive pulmonary tuberculosis in South Africa. Comparing this intervention with usual care, the incremental cost per QALY gained and the cost per active case of tuberculosis prevented were 31,043 Rand and 17,384 Rand respectively. Screening and treating individuals thirty-five years of age and older instead of individuals fifteen years of age and older and use of miniature chest x-rays for screening instead of conventional chest radiography improved the economic attractiveness of the proposed programme.

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1.1 Overview

Providing antibiotic therapy to individuals with inactive pulmonary tuberculosis has been shown to be effective at preventing the development of tuberculosis disease in multiple studies world wide.[1-16] This preventive strategy has also been shown to be cost-effective by traditional standards in high-income countries.[17-21] Given the results of these studies, tuberculosis guidelines in high-income countries recommend that individuals with inactive pulmonary tuberculosis be treated for latent tuberculosis infection (LTBI).[1-24] However, the cost-effectiveness of screening for and treating individuals with inactive pulmonary tuberculosis has not been studied in Africa, the continent with the highest incidence of tuberculosis per capita in the world.[25] Given the number of people potentially requiring screening in Africa, the cost of screening and treating individuals with inactive pulmonary tuberculosis, and the monetary constraints that exist in the South African public health system, an economic evaluation of screening and treatment of inactive pulmonary tuberculosis in a South African setting is performed. This information will help decision makers determine if this preventive strategy or alternate tuberculosis control programmes should be introduced in South Africa to help contain the escalating tuberculosis epidemic.[26]

1.2 Economic Evaluation

1.2.1 Scarcity and Opportunity Cost

Economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences".[27] Health care resources are limited, and decisions need to be made to maximize the benefit obtained from health care spending. If money is spent on a new health care initiative, this money is not available to fund other health care programmes: In economic terms this is called the opportunity cost of the new programme.[27] The South African National Tuberculosis Programme (NTP) receives a limited financial budget each year to provide tuberculosis care to patients. If a new screening system is developed to detect and treat cases of inactive pulmonary tuberculosis, the money spent on this screening programme would not be available to purchase, for example, new lab equipment to improve the diagnosis of pulmonary tuberculosis. Therefore, the opportunity costs of choosing to fund the new screening programme are the health benefits that would have been accrued if the new laboratory equipment had been purchased. In making health care resource allocation decisions, the goal is to minimize opportunity costs and select the most economically efficient treatments.

1.2.2 Efficiency in Health Economics

The efficiency of a health care intervention is the relationship between the resources spent on that health care intervention and the health benefits obtained.[27] One of the goals of economic assessment in health care is to assess the relative efficiency of different health care interventions.

Technical efficiency examines the most efficient way of delivering health benefits to a certain group of patients within a designated budget.[27,28] An example of this would be assessing the most efficient way to treat smear-positive pulmonary tuberculosis patients, either admitting these patients to hospital or managing these patients as outpatients. The most efficient programme can be determined by assessing the relative costs and benefits of these two treatment options.

Allocative efficiency involves the comparison of different groups of patients and how to distribute health care resources efficiently between these groups of patients. An example of allocative efficiency would be to assess the relative efficiency of a treatment programme for multi-drug resistant tuberculosis patients and a treatment programme of anti-retroviral (ARV) treatment for Human Immunodeficiency Virus (HIV) positive individuals living in South Africa. The more efficient programme would be allocated the funds to establish a treatment programme for their respective patient group.

In order to measure efficiency, economic evaluation is used to systematically assess the costs and benefits of competing health care strategies and assist in the choice between them.[27] If a new technology costs less than conventional care and provides more benefit it is said to be the dominant strategy and should be adopted by decision makers. Alternatively, if the new technology costs more and provides less benefit than conventional care it is said to be dominated by the alternative and should not be adopted. However, in most economic evaluations, the therapy being assessed costs more and

provides more benefit than its relevant comparator.[27] In some situations, the new therapy costs less, but also provides less benefit. Decision making in these two situations is difficult and in these situations an incremental analysis should be performed.[27]

Incremental analyses assess how much more money will be spent on an intervention and how much more benefit will be obtained. An incremental cost-effectiveness ratio can be calculated to express the above information:

(Cost A - Cost B) / (Effect A – Effect B)

Utilizing the cost-effectiveness ratio, decision makers have to determine how much more they are willing or able to spend (willingness-to-pay) to obtain the added benefit, or alternatively how much health benefit they are willing to give up for a decrease in cost. [27]

1.2.3 Types of Economic Evaluations

1.2.3.1 Cost Effectiveness Analysis

All types of economic evaluation assess the cost of the health care intervention in monetary terms, but they differ in how they measure the clinical benefit.[27] In cost-effectiveness analysis (CEA), benefits are reported in clinical outcomes appropriate for the group of patients being studied, for example number of new cardiac events in patients with previous myocardial infarction prescribed differing anti-cholesterol medications.[27] In this study, conventional care (no screening nor treatment of inactive pulmonary tuberculosis) is compared to a chest x-ray screening and treatment programme to detect

and treat those with inactive pulmonary tuberculosis. The clinical effect is the number of cases of tuberculosis that develop over a twenty year period. Therefore, the incremental cost per active case of tuberculosis prevented can be calculated. The results of this study can be compared to other studies on tuberculosis prevention that report a cost per active case of tuberculosis prevented. This study can therefore address technical efficiency; which of the studied tuberculosis prevention programmes for at risk patients is the most efficient at preventing active cases of tuberculosis.[27]

1.2.3.2 Cost Utility Analysis

Another type of economic analysis that can be performed is a cost-utility analysis (CUA).[27] In this type of analysis, health outcomes are expressed in a common rubric that measures both the quantity and quality of life such as quality-adjusted life-years (QALYs), disability-adjusted life-years (DALYs), or healthy years equivalent (HYEs).[27] Using these measures, a person's overall quality of life with a specific health outcome (morbidity) and the quantity of life (mortality) can be reported in a single value that can be compared between different patient groups and disease conditions.[27]

1.2.3.2.1 Measurement of patient utility

In order to determine the "quality" of different health outcomes, an individual's preferences for different health states must be determined. These preferences can be measured directly using methods such as time-trade off and standard gamble, or indirectly utilizing pre-scored multi-attribute health status classification systems such as the Health Utilities Index (HUI) and the EuroQol.[27] The utility of a health outcome has a

specific meaning in health economics. Utility is a measure of preference that is made under conditions of uncertainty (following the expected-utility theory) and is ordered in a cardinal (not ordinal) fashion.[27]

The standard gamble technique is one method of directly assessing preferences for different health states.[27] This method measures cardinal preferences for health outcomes under conditions of uncertainty and is based on the expected utility theory.[27] Thus, preferences measured with this method can be appropriately referred to as utilities.[27] In order to assess preference, individuals must choose between two alternative treatment states for the same health outcome. Alternative one is the "gamble" choice, the treatment of the health outcome of interest (for example tuberculosis) will either cause a person to immediately return to perfect health (with a varying probability) or the treatment will cause immediate death.[27,28] Alternative two is to remain in the specific health state (tuberculosis) for the same period of time as the perfect health state. The probability of returning to perfect health in alternative one is varied until the person completing the standard gamble assessment is indifferent to the choice; they do not have a preference for either alternative one or alternative two. This probability is the health utility score of the specified health state where perfect health is one and immediate and certain death is zero.[27,28]

Health preferences can also be measured using pre-scored multi-attribute health status classification systems.[27,28] These questionnaires provide a ranking system of different aspects of health that can be quickly completed by patients. For example, the EuroQol

health status assessment questionnaire has five measurements of health status where individuals rank themselves from 1 to 3 on measures of mobility, self-care, ability to perform usual activities, pain, and anxiety.[27] Members of the public have previously performed direct measures of preference for the different health states described with this classification system using the time trade-off method.[27] A scoring system derived from the time-trade off preference assessment is used to transform the ranking of the attributes in the EuroQol questionnaire to a utility measurement.[27] This indirect method of assessing health preferences is quicker and easier for individuals to perform than the direct methods, but the scoring system is based on a specific group's preferences for certain health states.[27] In the case of the EuroQol, three thousand adult members of the United Kingdom performed the direct method of preference assessment for conditions described by the ranking system in the EuroQol questionnaire. Thus, when using this multi-system attribute system, you are assuming that the health preferences of the group that completed the direct method of preference assessment accurately represents the health preferences of the group of individuals you are studying.

1.2.3.2.2 Quality-adjusted life years

Using one of the above-described methods, the "quality"of an individual"s life with a certain health condition (ie the utility) can be estimated. QALYs are calculated by multiplying the utility of a specific health state by the length of time an individual remains in that health state. Perfect health is represented by a utility score of one and death represented by a utility score of zero.[27] For example, the QALY of an individual with pulmonary tuberculosis can be calculated over a one year time period. If this patient

was healthy for six months, and then was diagnosed and treated for pulmonary tuberculosis for six months (assuming the utility of tuberculosis disease is 0.62) the QALY of that individual is expressed by the formula shown below:

QALY = (time in perfect health x utility of perfect health) + (time with tuberculosis x utility of tuberculosis)

This individual would have a QALY of 0.81 over one year compared to a fully healthy individual with a QALY of 1. Stated in another way, the individual would have lost 0.19 QALYs due to pulmonary tuberculosis over a one-year time period.

DALYs are another measure used to combine both the morbidity and mortality of health states into one metric.[27] DALYs are based on the principle of the loss of healthy life where one represents death (complete loss of healthy life) and zero represents complete health with no disability (no loss of healthy life). DALYs preference measures for disease states were obtained by grouping diseases into severity classes and assigning quality weights for the severity classes based on expert opinion.[27] DALYs are adjusted based on age so that the loss of quality or quantity of life during the years of prime productivity are weighted higher than loss of life at the extremes of age.

The measurement of health preferences for disease states differs between QALYs and DALYs. DALYs have implicit value judgment about the utility of life at differing ages while QALYs are assumed to be equal regardless of age.[27] DALYs also include implicit

discounting, the value of life now outweighs the quality of life in the future. Unless additional discounting is calculated in an economic assessment, the utility scores used to create a QALY are the same for health states now or in the future. DALY health preference measurements are based on expert opinion while QALY utilities are based on patient or societal preferences for different health states obtained using direct and indirect methods to assess preference.

1.2.3.2.2 Cost-utility in inactive pulmonary tuberculosis

In this study, a cost-utility analysis is performed using quality-adjusted life-years as the measure of health benefit in the assessment of conventional treatment for inactive pulmonary tuberculosis compared to screening and treatment of inactive pulmonary tuberculosis. This study reports the incremental cost per QALY of the screening and treatment program for inactive pulmonary tuberculosis. The benefit of using a CUA rubric is that the incremental cost per QALY of the chest x-ray and screening program for inactive pulmonary tuberculosis can be compared to potential health programmes in other patient groups. For example, this proposed programme can be compared to a comprehensive ARV treatment package for HIV positive patient in South Africa by reporting the incremental cost per QALY gained.

1.2.4 Components of an Economic Evaluation

Guidelines have been developed to ensure the quality of economic evaluation in the health care field. This study will follow the Canadian guidelines, Guidelines for the Economic Evaluation of Health Technologies: Canada.[31] In addition, for issues directly

related to costing of tuberculosis treatment, it will refer to the Guidelines for Cost and Cost-effectiveness Analysis of Tuberculosis Control published through the World Health Organization.[32]

According to the Canadian guidelines, the baseline assessment in an economic evaluation should be an incremental assessment of the differences in costs and benefits of the new programme being assessed compared to an appropriate comparator.[31] There should be adequate effectiveness data available on the new programme and the following issues must be considered and addressed in the economic evaluation:

1.2.4.1 Perspective

The perspective of an economic evaluation provides the framework for the analysis.[28] Essentially, the economic evaluation is being performed for a certain group of people who will use the information provided in the analysis to make health care decisions.[27,28] In Canada, the public health system is the main provider of health care and thus a public payer perspective should be taken for assessments performed in Canada.[31] In South Africa, there is both a public health system and a private health system. The majority of tuberculosis care in South Africa is provided by the public health system and as such a public payer perspective will be taken for this analysis.

A societal perspective can also be taken in an economic analysis. This perspective tries to assess the total cost and benefit to society of the introduction of a new health care

programme.[27] A societal perspective is the most comprehensive economic evaluation but requires costing information outside of the health care system.[28]

1.2.4.2 Costing

While costs in economic evaluations are always reported in monetary terms, different costs can be included in an analysis depending upon the perspective taken for the analysis.[27] The base-case analysis in this study will examine costs from a public payer perspective as recommended by the Canadian guidelines.[31]

Costing requires the measurement of the quantities of resources used and the unit cost (price) of those resources.[27,28] Therefore, if a public payer perspective is taken the quantity and price of health care resources used in this system needs to be determined, these are termed direct costs. These costs include the cost of the therapy and personnel directly related to the care of patients. In this analysis, the health care costs of diagnosing and treating an individual with inactive pulmonary tuberculosis would include the cost of the chest x-ray and sputum assessment for diagnosis, the cost of the medication to treat individuals identified with inactive pulmonary tuberculosis, and the cost of physician and nursing time to assess and manage the patient.

The costs to the health care system also include the capital cost and the overhead cost of diagnosing and treating patients with inactive pulmonary tuberculosis. The capital cost is the cost to purchase major capital assets required by a programme. For example, if new

clinic space must be purchased to enable a screening programme to perform chest x-ray and sputum assessments this would be the capital cost of the new programme.

Overhead costs also need to be measured in the costing assessment. These costs are comprised of resources that are used that serve more than one department or programme. For example, if the new tuberculosis screening clinic was also utilized for childhood vaccinations, shared expenses such as office administration cleaning costs would have to be apportioned according to the utilization of these resources by the tuberculosis screening programme.[27,28]

It is controversial if future unrelated health care costs should be included in an economic analysis. If mortality rates decrease and people live longer due to a new health intervention, is it appropriate to account for the costs of their additional health expenditures? Given that there is little data on these future costs, at the present time these health care expenditures are often not included in economic evaluation.[27,28]

If a health perspective other than that of a public payer is taken in an economic analysis, additional costing categories must be considered. When performing an economic analysis with a societal perspective, the costs of the health condition and intervention to society need to be included in the analysis.[27,28] The costs related to patient's time and loss of productivity need to be assessed. If an individual requires eight weeks off work for a surgical procedure, then society has lost eight weeks of productivity from that individual. These costs should be captured as the average wage lost during the time the

patient could not be at work.[28] If an individual dies due to their health condition, some economists advocate for including the cost of this loss of productivity. Other economists feel that the effect of loss of life is already captured in the outcome measurement and by counting lost productivity the loss of life of an individual is being double counted.[28]

1.2.4.3 Time Horizon

The time horizon is the length of time that benefits and costs are accrued in an economic analysis.[31] The time horizon should be long enough to capture the relevant costs and benefits of the intervention.[31] The proven long-term effectiveness of the intervention being assessed should also be considered when determining the time horizon of an economic assessment.[31] If long-term effectiveness data is unavailable, and it is thought important that the time horizon be extended beyond the proven effectiveness of an intervention, a sensitivity analysis around the length of time the effectiveness lasts should be performed.[31]

1.2.4.4 Discounting

Discounting of costs and benefits is performed in an economic evaluation because the costs and benefits of a programme do not always occur at the same time.[27] People have a positive rate of time preference; they have a preference for benefits now as opposed to benefits in the future and a preference to pay for things later as opposed to now.[28] Given this preference, the costs and benefits of a programme that will occur in the future are rated at a lower “discounted” rate than costs and benefits that occur in the present. The Canadian guidelines recommend that both the outcomes and the costs of an intervention

that occur in the future be discounted at a 5% rate. The recommended discount rate varies between published guidelines and different discount rates are assessed in this analysis.

1.2.5 Performance of an economic analysis

1.2.5.1 Economic evaluation as part of a randomized controlled trial

When economic evaluation occurs as part of a randomized-placebo controlled study or a cohort study, the costs incurred by the individuals in the study are captured. Economic assessments performed in conjunction with randomized controlled trials offer the benefit of direct patient-specific cost capture with accurate efficacy information.[27,28] However, there are limitations with this approach. The efficacy outcome of a randomized-placebo controlled trial may not be representative of the true effectiveness of the intervention when used in a real world setting.[28] In addition, the costing information may not be generalizable to a non-trial programme. Randomized controlled trials may not take place over long time periods and thus there may be an inadequate follow-up period to accurately determine the long term benefits or detriments of a given intervention.[27,28] Finally, the choice of comparator required in a randomized controlled trial may not be the appropriate choice for an economic analysis. If the comparator is placebo and not the current or conventional treatment, the wrong economic evaluation will be performed.[27,28]

1.2.5.2 Decision Analysis

Given the limitations of economic evaluations being performed as part of a study, decision analysis methods have been developed to perform an economic evaluation

outside of an ongoing trial or to complement analyses done alongside a clinical trial. Decision analysis is defined as a systematic approach to decision making under conditions of uncertainty.[27] In order to perform a decision analysis, the decision problem must be identified and bound, the problem must be structured over time, the information that is required to perform the analysis must be determined and obtained, and at the end, the preferred course of action must be chosen.[28]

There are different techniques of decision modeling that are available to perform an economic evaluation.[27-30] A simple tree model can assess costs, benefits, and clinical outcomes and works well over short time periods and single clinical output states.[27-30] However, if individuals are followed over long time periods and have clinical events that may occur more than once, a simple tree will become "bushy" and hard to manage.[27-30] Markov modeling is useful in these situations.[27-30, 33] A Markov model establishes a cohort of "individuals" to cycle through different Markov states accruing costs and benefits.[33] Individuals spend a certain amount of time in a particular state (cycle time) before transitioning to the same state, a new state, or a previous clinical state.[33]An absorbing state must exist in a Markov model, where no costs or benefits are accrued. In this economic evaluation of chest x-ray screening and treatment of inactive pulmonary tuberculosis in South Africa, Markov modeling is the appropriate technique to use as individuals need to transition from being infected with tuberculosis to developing tuberculosis disease with differing probabilities over a long-time period.[27-30]

1.2.5.3 Economic evaluation using both methods

In many circumstances, it is appropriate to utilize both techniques of economic evaluation to assess the costs and benefits of a health intervention. Efficacy and direct costs of the health intervention of interest can be directly measured from a clinical trial. Long-term costing and outcomes not measured during the trial can be estimated by using modeling techniques. In this economic evaluation, the prevalence of inactive pulmonary tuberculosis is obtained from a recent epidemiologic survey in Cape Town with the long-term effects modeled using decision analysis over a twenty year time period.

1.3 Clinical Background

1.3.1 Overview of Tuberculosis

Tuberculosis is a chronic infection caused by the bacterium, *Mycobacterium tuberculosis*.[22-26] Approximately two billion people in the world are infected with *M. tuberculosis*, but it is estimated that only one in ten infected individuals will develop tuberculosis disease in their lifetime.[23-26] Infection with *M. tuberculosis* can be detected either through a skin test (tuberculin skin test) or a blood test that measures the response of the immune system to tuberculin antigen.[23,24] Tuberculosis disease most commonly occurs in the lungs (65% of cases), termed pulmonary tuberculosis, but can develop in any organ system in the body.[22] Individuals with pulmonary tuberculosis present with cough, weight loss and often have chest x-ray evidence of upper lung cavitation and fibrosis.[22] Pulmonary tuberculosis is diagnosed by seeing the bacteria in respiratory secretions (smear-positive disease) or growing the bacteria from respiratory secretions (smear-negative culture positive disease).[22] Individuals with active pulmonary tuberculosis can spread disease to others via respiratory secretions that contain the

mycobacterium.[22] The more bacteria present in the respiratory secretions (smear positive disease), the more likely the disease will be transmitted to others.[22-26] Individuals diagnosed with tuberculosis are treated with antibiotics for a minimum of six months to kill the bacterium and cure the disease.[20-26] The World Health Organization (WHO) estimated that there were 8.9 million new cases of tuberculosis disease world-wide in 2004, resulting in 1.7 million deaths.[25]

Currently Africa is the only region in the world with increasing rates of tuberculosis.[25] The incidence of tuberculosis has more than doubled in South Africa in the last 6 years, from 338 per 100,000 in 1998, to 718 per 100,000 in 2004.[25] Comparatively, the incidence of tuberculosis in Canada has remained stable over the last several years at less than 10 per 100,000.[23] The increasing incidence of tuberculosis in Africa is thought to be due to the large number of individuals co-infected with the Human Immunodeficiency Virus (HIV).[25] Individuals with HIV have impairment of the immune pathway that controls the proliferation of *M. tuberculosis*. This immunosuppression causes high rates of tuberculosis disease in individuals with HIV infection who are co-infected with *M. tuberculosis*.[23]

With the extremely high incidence rates of tuberculosis in South Africa, it is not surprising that tuberculosis is one of the top three causes of decreased life expectancy and disability in South Africa.[34] Additional interventions need to be introduced to help control the current tuberculosis epidemic in Africa as the current standard of care is not preventing the increasing epidemic.

1.3.2 Efficacy and cost-effectiveness of tuberculosis control methods

The goal of a tuberculosis control programme is to decrease the incidence, morbidity, and mortality of tuberculosis disease.[25] In order to accomplish this goal the programme must aim to diagnose and appropriately treat individuals with tuberculosis disease, prevent individuals from becoming infected with *M. tuberculosis*, and prevent individuals already infected with *M. tuberculosis* from developing disease. A tuberculosis programme must accomplish the above goals within a limited budget thus it is important to utilize the control methods that are most effective and cost-effective.

1.3.2.1 Treatment of smear-positive pulmonary tuberculosis

The most efficacious and cost-effective way to control tuberculosis is to adequately diagnose and treat individuals with infectious (smear-positive) pulmonary tuberculosis.[22-26,35-37] Not only does treatment substantially decrease the patient's own morbidity and mortality, it also prevents the spread of tuberculosis to others. [22-26,35,36] The World Health Organization (WHO) directly observed treatment, short-course (DOTS) strategy is the current world-wide recommendation for the diagnosis and treatment of smear-positive pulmonary tuberculosis.[25] The goal of the DOTS strategy is to detect at least 70% of the new smear positive pulmonary cases and successfully treat 85% of these individuals using a short-course antibiotic regime over six months.[25]

Diagnosis and short-course treatment of smear-positive pulmonary tuberculosis has been shown to be economically attractive in an African setting, ranging from 1 to 40 US dollars per DALY gained.[35,36]

At the present time, there is 98% DOTS coverage in South Africa with assumed case detection rates of 96 %.[25] However, cure rates are below the 85% recommendation of the WHO.[25] Therefore, the first priority in controlling the current tuberculosis epidemic in South Africa is to improve cure rates in smear-positive pulmonary tuberculosis patients to the WHO recommended targets.[25,26]

1.3.2.2 Treatment of smear-negative pulmonary tuberculosis

Individuals who have smear-negative pulmonary tuberculosis, cost more money to diagnose, have lower fatality rates and infect fewer individuals with *M. tuberculosis* compared to those with smear-positive pulmonary tuberculosis.[22-26,35.] Therefore, treating individuals with smear-negative pulmonary tuberculosis is not as economically attractive as treating smear-positive pulmonary tuberculosis.[35] However, the cost is considered to be a reasonable expense in South Africa with a reported cost range of 100 to 400 US dollars per case of smear-negative pulmonary tuberculosis diagnosed and treated, and is currently funded by the South African National Tuberculosis Programme (NTP).[26,35]

1.3.2.3 Active case finding

The above described DOTS strategy promoted by the WHO focuses on diagnosing and treating those individuals with pulmonary tuberculosis who present to medical services (passive case finding). Attempting to diagnose all pulmonary cases of tuberculosis disease in a given population has been attempted with chest x-ray screening, symptom inquiry, and sputum examination (active case finding).[35-37] These studies have diagnosed more individuals with pulmonary tuberculosis than passive case finding but always at significant cost.[23,35,37]

1.3.2.3.1 Chest x-ray screening

Chest x-ray screening has been used for active case finding for the last seventy years.[23,35,37] Mass radiography campaigns were originally implemented prior to the availability of treatment for tuberculosis to detect cases earlier than passive case finding in the hopes of decreasing tuberculosis case fatality.[37] In addition, individuals found to have infectious pulmonary tuberculosis on chest radiography were isolated to prevent subsequent infection of other individuals.[37] Chest x-ray screening for active pulmonary tuberculosis was effective at detecting additional cases of pulmonary tuberculosis, but with the advent of excellent outpatient treatment of tuberculosis in high-income countries, the significant cost of the mass radiography programmes, and the declining incidence of tuberculosis in high-income countries, mass chest radiography is no longer used for population screening in North America.[23,24,37,38] Currently in Japan, population mass radiography for the detection of active cases of pulmonary tuberculosis is still being used but is thought to be an expensive health intervention at 4.4 million yen (42,872 Canadian dollars) to detect a case of tuberculosis.[39]

Currently, active case finding in North America and Europe with chest x-ray screening is performed for groups of individuals with a high background incidence of tuberculosis. Immigrants to Canada, the United States, and Europe from high tuberculosis incidence countries are screened for active pulmonary disease with chest x-rays prior to immigration or upon arrival to the low-incidence country.[23,24,40] High risk groups within low-incidence countries have also been targeted for regular chest x-ray assessment.[23,24,37] Studies have examined the yield of chest x-ray screening for active tuberculosis cases in prisoners, individuals with HIV infection, and the homeless population.[37,41] The cost of chest x-ray screening for active case finding differs between these high risk groups.[37,41] Cost-effectiveness analyses have shown that the cost to prevent a case of tuberculosis is dependent upon the background prevalence of pulmonary tuberculosis in the group targeted for screening, the compliance of individuals for chest x-ray screening, and the assurance that appropriate treatment is given.[23,24,37]

Active case finding with chest radiography has been performed in South Africa as part of prevalence surveys of tuberculosis but is not routinely used for population screening at this time.[26,37] South African gold miners have an extremely high risk of tuberculosis because of the joint effects of silica exposure and HIV infection, and are routinely screened with chest radiography to detect pulmonary tuberculosis.[37] In this cohort, chest x-ray screening has detected tuberculosis cases prior to smear positivity, creating potential for decreasing mortality and secondary infections.[37]

1.3.2.4 Prevention of *M. tuberculosis* infection

The only available vaccine against tuberculosis, the BCG vaccine, has been widely utilized in high tuberculosis incidence countries for several years.[26,42] The reported efficacy of the vaccine to prevent pulmonary tuberculosis in adults ranges from 0 to 80%, thus it is unclear if this vaccine is currently helpful at preventing smear-positive adult pulmonary tuberculosis and the spread of infection to others.[35] However, the vaccine has been shown to provide good protection against disseminated and meningeal tuberculosis in childhood, diseases with high morbidity and mortality.[35, 42] The cost-effectiveness of the BCG vaccine has been estimated at fifty US dollars per DALY gained and is currently used in South Africa.[26,35,42]

1.3.2.5 Prevention of development of tuberculosis disease

As mentioned above, only 10% of immuno-competent individuals infected with *M. tuberculosis* develop tuberculosis disease.[22] Prevention strategies in those with tuberculosis infection and at high risk of developing disease are commonly used in the high-income countries in the world.[23,24,43] Individuals with tuberculosis infection and factors that increase the risk of developing tuberculosis disease are prescribed antibiotics to kill *M. tuberculosis* and thus prevent the subsequent development of tuberculosis disease, termed treatment of latent tuberculosis infection (LTBI).

1.3.2.5.1 LTBI treatment in HIV/AIDS patients

HIV infection and Acquired Immune Deficiency Syndrome (AIDS) confer the highest risk of developing tuberculosis disease after infection.[22,24,35] Individuals with HIV and

tuberculosis co-infection develop tuberculosis disease at a rate of approximately 6.7 % per annum.[22,24,35] Multiple studies have demonstrated that treatment of LTBI in HIV positive individuals prevents the development of tuberculosis disease. HIV positive individuals in high-income countries with tuberculosis infection are offered treatment for latent tuberculosis infection (LTBI).[22-24] Recent studies of the cost-effectiveness of HIV/AIDS interventions in Africa have demonstrated that tuberculin skin testing and treatment of LTBI in HIV positive individuals is economically feasible, costing 169-288 US dollars per DALY gained.[35,44-46] With this evidence, the South African NTP introduced testing and treatment of LTBI for HIV positive individuals in South Africa in 2004.[26]

1.3.2.3.2 LTBI treatment of contacts of tuberculosis patients

Individuals who have recently been infected with *M. tuberculosis* after exposure to a known infectious case of pulmonary tuberculosis are also at high risk of developing tuberculosis disease.[22-24] Contact investigation and treatment of infected household contacts has been shown to reduce the risk of developing tuberculosis disease by 60-80%.[35] Two studies have examined the cost-effectiveness of contact tracing and isoniazid treatment of infected household contacts of smear-positive pulmonary tuberculosis patients. [20,47] This intervention was found to be cost-saving: contact tracing and treatment resulted in fewer cases of tuberculosis and cost less than its comparator, no contact tracing in household members exposed to infectious cases of pulmonary tuberculosis.[20,47] Therefore, the cost-effectiveness of contact tracing should be assessed as a tuberculosis control method in South Africa as it is not routinely practiced at this time.

1.3.3 Effectiveness of treatment of inactive pulmonary tuberculosis

Another group of individuals with latent tuberculosis infection at high risk of developing tuberculosis disease are individuals with chest x-ray (CXR) abnormalities consistent with post-primary tuberculosis who have never been treated for tuberculosis disease and do not have evidence of current active pulmonary tuberculosis, termed inactive pulmonary tuberculosis in this study.[23,24] Multiple studies have demonstrated that individuals with inactive pulmonary tuberculosis have a six to thirteen times higher rate of developing active tuberculosis disease than tuberculin skin test positive individuals with normal chest x-rays.[1-16] Studies in North America, Europe, Africa, and Hong Kong have demonstrated significantly reduced rates of tuberculosis disease in individuals with inactive pulmonary tuberculosis treated with anti-tuberculous medications.[3-16]

The largest study of treatment of inactive pulmonary tuberculosis was a randomized placebo-controlled trial of 28,000 individuals in Eastern Europe with inactive pulmonary tuberculosis (IUAT trial).[3] In this study, individuals had to have stable chest x-ray abnormalities consistent with inactive pulmonary tuberculosis for one year prior to entry.[3] Individuals were randomly assigned to treatment with isoniazid, of differing durations, or placebo .[3] There was a 21 % reduction in tuberculosis disease at five years in the 12 week regime, 65% reduction in the 24 week regime, and a 75% reduction of tuberculosis disease in the 52 week regime using an intention-to-treat analyses.[3] The major side-effect of isoniazid treatment was hepatitis, occurring in 0.48% of individuals with a 3% case fatality rate.[3]

Another study of isoniazid preventive treatment of inactive pulmonary tuberculosis was performed in a high tuberculosis incidence area.[11-13] The background incidence of tuberculosis in this Alaskan community was 916 per 100,000 similar to current case rates in South Africa.[11-13,25] Households were randomly selected to receive isoniazid preventive therapy for 12 months or placebo.[11-13] The background prevalence of disease was determined with chest x-ray examinations and tuberculin skin testing. In the individuals who were shown to have chest x-ray abnormalities consistent with inactive pulmonary tuberculosis and negative sputum assessment for tuberculosis disease, there was a 60% reduction of tuberculosis disease development over a total of 19 years of follow-up.[11-13]

Similar randomized placebo controlled trials of isoniazid treatment of inactive pulmonary tuberculosis disease have shown similar risk reductions as the above two studies.[3-16] These studies have been performed on distinct populations, in areas with lower incidence of tuberculosis, and for shorter periods of time but have found similar results, a decrease in tuberculosis disease of between 60 and 75% in individuals with inactive pulmonary tuberculosis treated with isoniazid.[3-16]

Based on these studies, individuals found to have inactive pulmonary tuberculosis are offered LTBI treatment in Canada and the United States.[23,24]

1.3.4 Chest x-ray screening to detect inactive pulmonary tuberculosis

Currently, there are no chest x-ray screening programmes specifically designed to detect and treat inactive pulmonary tuberculosis. However, in low-incidence tuberculosis countries, as discussed above, chest x-ray screening for active case finding in immigrants from high-incidence countries has been in place for several years.[23,24,40] Individuals found to have inactive pulmonary tuberculosis during the screening process are referred for assessment to public health clinics and offered treatment.[23,24,40] However, the immigration chest x-ray screening process is not specifically designed to detect inactive pulmonary tuberculosis.

1.3.5 Cost-effectiveness of treatment of inactive pulmonary tuberculosis

The cost-effectiveness of treatment of inactive pulmonary tuberculosis has been assessed in multiple studies.[17-21] A cost-effectiveness analysis was performed using data from the above-described IUAT trial on inactive pulmonary tuberculosis.[17] This study compared the incremental cost and benefit of providing isoniazid treatment for latent tuberculosis infection for differing lengths of time. The 24 week regime was found to be the most cost-effective regime with a cost of 7,112 US dollars per case of tuberculosis prevented.[17]

A more recent study compared different treatment regimens for inactive pulmonary tuberculosis to a no treatment comparator.[18] This decision analysis examined the costs and benefits of treating a cohort of individuals with inactive pulmonary tuberculosis with either isoniazid for twelve months, rifampin and isoniazid for four months, or no treatment.[18] Treating individuals with inactive pulmonary tuberculosis with isoniazid or

isoniazid and rifampin was cost-saving when compared to the no-treatment comparator.[18] However, the costs of detecting inactive pulmonary tuberculosis disease were not modeled in this analysis.

A Canadian study has examined the cost-effectiveness of different screening strategies to detect and treat tuberculosis infection and tuberculosis disease in individuals immigrating to Canada.[19] No screening, chest x-ray screening, and tuberculin skin test screening was modeled for different cohorts of immigrants arriving to Canada.[19] Chest x-ray screening with treatment of both active and inactive pulmonary tuberculosis in a sub-Saharan cohort was estimated to cost 3,943 Canadian dollars (16,781 Rand) per active case of tuberculosis prevented.[19] This study did not include the costs to develop and co-ordinate the screening strategy adopted.[19]

A study performed in the United States examined the cost-effectiveness of treating immigrants identified with inactive pulmonary tuberculosis during their screening assessment with isoniazid compared to a no follow-up or treatment comparator.[21] Providing treatment for immigrants with inactive pulmonary tuberculosis was found to be cost-saving, preventing cases of tuberculosis and costing less than the no treatment of inactive pulmonary tuberculosis comparator.[21] However, this study did not include the cost of immigration chest x-ray screening and detection of those with inactive pulmonary tuberculosis.[21]

These studies would suggest that screening and treatment of inactive pulmonary tuberculosis in a sub-Saharan African cohort may be a cost-saving intervention.[17-21] However, no cost-effectiveness studies have been published that examine the role of a chest x-ray screening programme to detect and treat inactive pulmonary disease in an African population.

1.3.6 Inactive pulmonary tuberculosis in Cape Town, South Africa

The prevalence of tuberculosis and inactive pulmonary tuberculosis has recently been assessed in two neighbouring urban communities in the Tygerberg district of Cape Town, South Africa.[48,49] Fifteen percent of households in these two communities were randomly selected for this Lung Health Survey, and tuberculosis prevalence information was collected as part of this assessment.[48,49] Individuals completed a lung health questionnaire including questions about current or previous tuberculosis treatment and symptoms of active pulmonary tuberculosis.[48,49] Tuberculin skin testing, chest radiography, sputum microscopy, and sputum cultures were also performed on this randomly-selected cohort.[48,49] The information on inactive pulmonary tuberculosis and active pulmonary tuberculosis available from this recent tuberculosis prevalence study provides the framework for the development of the decision analysis model that is used herein to address the study question.[48,49]

1.4 Study Proposal

Given the increasing epidemic of tuberculosis in South Africa that is not controlled with current tuberculosis programmes, and studies that have demonstrated that it may be cost-

saving to treat individuals with inactive pulmonary tuberculosis, an economic evaluation was designed to assess the cost-effectiveness and cost-utility of chest x-ray screening and treatment of inactive pulmonary tuberculosis in an urban community of Cape Town, South Africa. This community has a high incidence of active pulmonary tuberculosis (341/100,000) and relatively low prevalence of HIV co-infection (12.4%), factors that are hypothesized to improve the cost-effectiveness of this intervention.[48,49] Prevalence information will be used from the above-described Lung Health Survey and chest x-ray screening will be presumed to be undertaken as a one-time public health intervention to decrease the incidence of tuberculosis in this cohort.[48,49]

Chapter 2: Objectives

2.1 Primary objective

To determine the incremental cost per quality adjusted life year (QALY) gained of chest x-ray screening and treatment of inactive pulmonary tuberculosis in individuals fifteen years of age and older in Cape Town, South Africa compared to current conventional care

2.2 Secondary objective

To determine the cost per case of tuberculosis prevented by the proposed screening and treatment programme compared with current conventional care

Chapter 3: Methods

3.1 Type of analysis

This study compares two alternatives in a tuberculosis control programme in Cape Town, South Africa: usual care which includes no assessment or treatment of inactive pulmonary tuberculosis, versus chest x-ray screening and treatment of inactive pulmonary tuberculosis.

This study is a cost-effectiveness study; the cost and number of cases of tuberculosis disease are calculated for the different treatment cohorts. A cost-utility analysis is also performed; the cost per QALY gained is calculated. An incremental analysis is performed to determine the differences in costs and benefits in these two treatment strategies for inactive pulmonary tuberculosis.

3.2 Target Audience

The target audience selected is the public payer health system. In South Africa, a government health system provides health care to those who cannot afford private health care through health insurance or out-of-pocket expenses.[26] In contrast to the management of other diseases, all costs of treating tuberculosis are borne by the government health system and most patients on private health insurance elect to receive free treatment through the state system.[26] The primary audience is the public health officials in charge of allocating a budget to tuberculosis control services. This cost-effectiveness analysis will allow direct comparison between chest x-ray screening and treatment of inactive pulmonary tuberculosis to other tuberculosis control initiatives by reporting a cost per case of tuberculosis prevented.

Decision makers working in the public health system outside of tuberculosis control are also presumed to be an audience. A cost-utility analysis was also performed so that the chest x-ray screening and treatment of inactive pulmonary tuberculosis control strategy can be compared to other health care initiatives by reporting an incremental cost per QALY.

3.3 Viewpoint

The reference case viewpoint is that of a public payer for health care services. The public health system in South Africa pays for the vast majority of tuberculosis treatment, thus the cost and benefits of initiating a tuberculosis screening program would be borne by the public health system. In addition, a societal perspective will be examined in a scenario analysis; for this analysis relevant indirect costs will be included.

3.4 Treatment comparator

In this analysis, chest x-ray screening and treatment of inactive pulmonary tuberculosis was compared to a no screening nor treatment of inactive pulmonary tuberculosis comparator as this is the current management practice for inactive pulmonary tuberculosis in South Africa.[26]

3.5 Time horizon

A time horizon of twenty years is selected as studies of treatment of inactive pulmonary tuberculosis had a maximum follow-up time period of twenty years.[3-16] In addition, previous cost-effectiveness analyses on inactive pulmonary tuberculosis treatment have

utilized a twenty year time horizon, and thus direct comparison between this study and previous studies is possible.[17-21]

3.6 Markov decision analysis model

A model was constructed using TreeAge Software to calculate the costs of chest x-ray screening and treatment of patients found to have inactive pulmonary tuberculosis to the current strategy, no screening nor treatment (Figure 1).[33]

In the group that is screened with chest x-rays to detect inactive pulmonary tuberculosis, a certain portion of individuals will decline to be screened and are assumed to have the same outcome as those who are not screened (Figure 1). Chest x-ray screening will separate those with normal chest x-rays from those with abnormal chest x-ray consistent with inactive pulmonary tuberculosis. Those who declined screening or were in the no screening arm will enter the relevant Markov state based on probabilities determined from the Lung Health Survey.[48,49]

Those who are found to have chest x-ray abnormalities consistent with inactive pulmonary tuberculosis in the screening arm will undergo testing to ensure that they do not have active pulmonary tuberculosis with a sputum smear and culture (Figure 1). Individuals identified as having inactive pulmonary tuberculosis will be offered treatment for inactive pulmonary tuberculosis with isoniazid for six months, whereas individuals identified with active pulmonary tuberculosis will be treated for pulmonary tuberculosis disease. Due to diagnostic inaccuracies, some people who are screened will have

incorrect test results. Thus, a small proportion of patients in the screening arm will incorrectly enter the "inactive pulmonary tuberculosis" state, either without an underlying *M tuberculosis* infection or with active pulmonary tuberculosis. These patients will inappropriately receive isoniazid treatment, thus being exposed to treatment-associated risks and unnecessary costs.

Individuals who are offered screening but decline and those in the no screening arm are assumed to have the same prevalence of chest-ray abnormalities, prevalence of tuberculosis infection, and incidence of active tuberculosis disease; however, as they do not receive treatment for tuberculosis disease or latent tuberculosis infection they will enter into different initial Markov states. Their initial Markov states are: normal chest x-ray, inactive pulmonary tuberculosis without treatment, and tuberculosis disease without treatment.

All individuals remain in their initial Markov state for a 6 month time period, the treatment length for inactive pulmonary tuberculosis with isoniazid. As described above, and based on the results from the Lung Health Survey, individuals enter one of seven Markov states: normal chest x-ray, post-treatment of inactive pulmonary tuberculosis, post-treatment of tuberculosis disease, inactive pulmonary tuberculosis no treatment for LTBI, treatment of tuberculosis without a screening program, and death. (Figure 2) The only further state that can be entered is the tuberculosis retreatment arm for individuals who have received treatment for tuberculosis disease and develop tuberculosis disease a second time.

Individuals transition though the Markov cycles for a 20 year period, 39 cycles after their initial Markov state, accruing costs and benefits. Individuals are at risk of dying from tuberculosis, dying from other causes, developing tuberculosis, or remaining well. If an individual has been treated for tuberculosis once, they are at risk of contracting tuberculosis for a second time.

3.7 Outcome measurements

The source of clinical and costing information is detailed in Tables 1-9 and outlined in the relevant sections below.

3.7.1 Screening Probabilities

3.7.1.1 Prevalence of inactive pulmonary tuberculosis

Figure 1 demonstrates the decision pathways for screening of inactive pulmonary tuberculosis. Chest x-ray prevalence information used to construct the screening probabilities in this decision analysis are obtained from the Lung Health Survey in Cape Town, South Africa described in section 1.3.5.[48,49]

Information was collected on 3,483 individuals 15 years of age and older, 339 individuals were excluded from further analysis as they either had a previous history of tuberculosis or were actively being treated for tuberculosis.[48,49] A screening program designed to detect and treat latent tuberculosis infection would not offer screening to individuals previously or currently being treated for tuberculosis disease.[23-26] The uptake of chest x-

ray screening was estimated to be 0.745, the proportion of individuals who presented for chest x-ray assessment out of the 3144 individuals in this survey deemed appropriate for a screening program.[48,49] This uptake measure may be an overestimation of the acceptance of a screening programme as individuals had already agreed to the tuberculosis prevalence study prior to being sent for chest x-ray screening. Therefore, a wide sensitivity analysis is performed on this variable.

One hundred and fifty-nine of 2,340 chest x-rays performed were found to have parenchymal abnormalities consistent with inactive pulmonary tuberculosis (0.0679).[48,49] A sensitivity analysis is performed utilizing a chest x-ray prevalence of any tuberculosis abnormalities of 0.085 from this study.[48,49] This chest x-ray categorization group includes chest films with evidence of pleural changes, calcified pulmonary nodules and calcified lymph nodes thought to be the result of tuberculosis infection.[48,49] These types of chest x-ray abnormalities have not been shown to confer a significant risk of subsequent tuberculosis disease development.[1-16] Thus, this prevalence estimate is used as the high end of a sensitivity analysis. A second sensitivity analysis is performed utilizing an abnormal chest x-ray prevalence estimate from a large grouped analysis of several tuberculosis prevalence studies performed throughout South Africa.[50] This meta-analysis reports a prevalence of abnormal chest films consistent with previous tuberculosis disease of 0.132.[50] This chest x-ray prevalence estimate of inactive pulmonary tuberculosis includes individuals with previously treated tuberculosis disease, thus overestimated individuals who would participate in a screening program. However,

it does provide information on prevalence of chest x-ray abnormalities for all of South Africa.[50]

3.7.1.2 Diagnostic accuracy of chest x-ray

It is difficult to model the diagnostic accuracy of chest x-ray for the diagnosis of inactive pulmonary tuberculosis as there is no gold standard test for tuberculosis infection. Tuberculin skin testing and interferon gamma blood testing (IGRA), both used to document tuberculosis infection, can be falsely positive and falsely negative.[22-24] Therefore, in an individual with an abnormal chest x-ray consistent with inactive pulmonary tuberculosis and a negative test for tuberculosis infection, a clinician will be unclear as to which diagnostic test is correct. Given these difficulties, the diagnostic accuracy of chest x-ray and tuberculin skin testing was modeled in several ways in this decision analysis.

In the base analysis it is assumed that chest x-ray abnormalities consistent with inactive pulmonary tuberculosis accurately represented those with tuberculosis infection. In a sensitivity analysis, the positive predictive value (PPV) of an abnormal chest x-ray is calculated using the formula below and assuming the tuberculin skin test to be the gold standard for tuberculosis infection and better than chest x-ray at determining tuberculosis infection.[51]

PPV= (prevalence x sensitivity)/((prevalence x sensitivity) + (1-prev)(1-specificity))

Both a five and a ten mm tuberculin skin test result is modeled as indicative of tuberculosis infection in individuals with inactive pulmonary tuberculosis.[23,26] A five mm or greater tuberculin skin test is considered a positive test in those with abnormal chest radiographs and HIV co-infection while a ten mm test is considered positive in those at lower risk of developing tuberculosis, thus both positive criteria are considered.[23,26] Sensitivity and specificity results of chest x-ray assessment for inactive pulmonary tuberculosis is obtained both from the literature and from the Lung Health Survey to calculate the positive predictive values.[19,48,49,52] A sensitivity analysis is performed with a low positive predictive value (0.866) and a high positive predictive value (0.941) from these calculations.

3.7.1.3 Prevalence of active tuberculosis

In individuals with parenchymal abnormalities on chest x-ray consistent with past or present tuberculosis, active pulmonary tuberculosis disease must be ruled out with sputum microscopy and culture for *M. tuberculosis.*[23-26] In the Lung Health Study, 104 out of 159 individuals with presumed inactive pulmonary tuberculosis had sputum microscopy and culture performed, 16 out of the 104 (15.3%) were sputum culture positive for *M. tuberculosis*.[48,49] Thus, the prevalence of active pulmonary tuberculosis disease in those with abnormal chest x-rays tested with sputum smear and microscopy was estimated to be 0.153.[48,49] The sensitivity of a single sputum sample for smear microscopy and culture is estimated to be 87%, with a range from 84 to 90%.[19,52-55] Specificity of a positive sputum culture for pulmonary tuberculosis is estimated to be 99% from previously published data.[19,52-55] Using these estimates, the negative predictive

value (NPV) of one negative sputum smear and culture was calculated using the formula below and found to be 97.7%.[51]

NPV=

(specificity x (1-prevalence))/((1-sensitivity)x prevalence)+(specificity x (1-prevalence))

3.7.2 Transition probabilities for Markov tree

Individuals enter into five main initial Markov states at the end of the screening process: normal chest x-ray, inactive pulmonary tuberculosis with treatment for LTBI (screening) or without treatment (no screening), and tuberculosis disease with treatment (screening) or without treatment (no screening) (Figures 1). Two small subgroups of individuals are also identified in the screening process due to diagnostic errors: abnormal chest x-ray without tuberculosis infection inappropriately treated for latent tuberculosis infection and active pulmonary tuberculosis inappropriately treated for latent tuberculosis infection. Individuals in the initial Markov states are assigned probabilities of living or dying, developing tuberculosis disease, or developing a complication of treatment of inactive pulmonary tuberculosis based on information from the literature. These probabilities determine how individuals cycle through the Markov tree.

3.7.2.1 Incidence of tuberculosis

3.7.2.1.1 Base case estimate

The most uncertain and potentially influential transition probabilities relate to the risks of developing tuberculosis in people with normal chest x-rays, inactive pulmonary

tuberculosis prescribed preventative therapy, and inactive pulmonary tuberculosis who did not receive preventive therapy in South Africa. It has been shown in large population studies that individuals with chest x-rays consistent with inactive pulmonary tuberculosis have a six to thirteen times increased risk of developing tuberculosis than individuals known to be infected with *M. tuberculosis* with normal chest x-rays.[1,2] Only two studies have examined the long-term incidence of tuberculosis in individuals with abnormal chest x-rays in Africa.[15,16] This cohort was comprised of men working in the South Africa gold mining industry with progressive upper lobe fibrotic chest x-ray changes suggestive of active pulmonary tuberculosis disease with negative sputum smears and cultures.[15,16] Fifty-eight percent of the individuals in this cohort developed bacteriologically proven tuberculosis over a five year period.[15,16] This cohort is not directly applicable to population screening as the study only involved men, there was evidence of progressive changes on chest x-ray (most other studies have demonstrated stability of lesions), and there were additional risk factors for the development of tuberculosis disease in the cohort.[15,16] As such, using estimates of tuberculosis disease incidence from this cohort of individuals with inactive pulmonary tuberculosis would likely overestimate the risk of disease development. Alternatively, if the incidence estimates from North American studies are utilized, the incidence of tuberculosis development in those with inactive pulmonary tuberculosis will be underestimated. The usual estimate of the risk of reactivation of tuberculosis for HIV negative individuals infected with *M. tuberculosis* with normal chest radiography is 0.001 per annum.[19] As mentioned above, the risk of reactivation of tuberculosis in those with abnormal upper lobe fibrotic changes is considered to be between six to thirteen times higher, resulting in a risk of reactivation of

0.006 to 0.013 per annum.[1,2,19] However, the incidence of all new pulmonary tuberculosis cases was 0.00283 in Cape Town in 2001, significantly higher than the estimate of immunocompetent individuals with normal chest radiography.[56] This highlights the concern of using data obtained in one group of individuals to model effects for a different cohort.

Given the above concerns, the transition probabilities of tuberculosis development are modeled using information from the large randomized controlled trials on isoniazid treatment for inactive pulmonary tuberculosis and Cape Town tuberculosis disease cumulative incidence.[1-17,56] The incidence of new cases of pulmonary tuberculosis in Cape Town, South Africa in 2001 was 0.002883 (283.3/100,000).[56] Only new cases of tuberculosis should develop from the screening cohort in this model as this decision analysis model excluded individuals with previously treated tuberculosis disease. Therefore, individuals from this cohort should be developing tuberculosis disease for the first time (new tuberculosis disease), as opposed to their second or third episode of tuberculosis disease (re-treatment tuberculosis disease). The base case utilized the incidence of pulmonary tuberculosis, as opposed to all disease forms of tuberculosis, as most treatment studies on inactive pulmonary tuberculosis monitored for the development of pulmonary tuberculosis.[3-16] Results from 2001 were used to avoid any impact of the Lung Health Survey on tuberculosis incidence in Cape Town.[48,49] In this model, Markov cycles are 6 months of length, the time period required to treat latent tuberculosis infection with isoniazid and treat an individual for tuberculosis disease. Thus, one year

cumulative incidence must be converted to 6 month risks of developing tuberculosis disease as shown in the formula below:

Rate = -ln (1-p)/t

So for incidence of all new cases of pulmonary tuberculosis

Rate =-ln (1-0.002883)/1

= 0.002887

The six month incidence was calculated utilizing the following formula:

CI=1-e(-(rate x t))

CI= 1-e(-(0.002887163 x 0.5))

CI=0.001443

Thus, the six month incidence of new pulmonary tuberculosis cases in Cape Town, South Africa in 2001 for those with normal chest x-ray was presumed to be 0.00144.[51]

Individuals with inactive pulmonary tuberculosis are estimated to have a 6-13 times higher incidence of developing tuberculosis disease than individuals with normal chest x-rays. [1,2,22-24] While this estimate is high, and may represent an overestimate of the risk of developing tuberculosis in Cape Town with an abnormal chest x-ray consistent with inactive pulmonary tuberculosis, it is significantly lower than the six month incidence estimate from the South African study of 0.1553.[15,16] These risks were then converted to

6 month cumulative incidence as above and the lower value was assumed to the correct value in the base case analysis (0.00869), with the higher estimate (0.01908) used in a sensitivity analysis.

3.7.2.1.2 Incidence of tuberculosis: Chest x-ray stratification

The problem with the above estimation is that the known incidence of new pulmonary tuberculosis disease in Cape Town includes individuals with both previously normal and previously abnormal chest films. To try to correct for this, the five year incidence of new pulmonary tuberculosis disease was calculated as above (0.0144). From the Lung Health Survey, 93.3% of individuals were presumed to have normal chest films and 6.7% of individuals were presumed to have abnormal films consistent with inactive pulmonary tuberculosis.[48,49] Individuals with the chest films consistent with inactive pulmonary tuberculosis were presumed to develop tuberculosis disease six times more frequently than those with normal films.[1,2,48,49] Solving for the equation shown below, the five year incidence of tuberculosis disease in those with normal films is 0.01074 and in those with abnormal films is 0.06441.

$$0.067(6x) + 0.933x = 0.01432$$

The six month incidence risks are calculated as above resulting in a six month incidence of tuberculosis disease in those with normal films of 0.00101 and 0.0066 in those with previously abnormal chest films. A sensitivity analysis is performed utilizing these values.

3.7.2.2 Effectiveness of treatment for inactive pulmonary tuberculosis

The effectiveness of treatment of LTBI in individuals with fibrotic chest x-rays consistent with inactive pulmonary tuberculosis has been well-established in large clinical trials.[3-16] The IUAT study of 28,000 individuals with inactive pulmonary tuberculosis was used to calculate the decreased risk of developing tuberculosis after preventive treatment with isoniazid.[3] This study examined the effect of different durations of isoniazid treatment in 28,000 individuals with upper lobe fibrotic changes consistent with inactive pulmonary tuberculosis shown to be stable over a one year period prior to entry in the study.[3] This study demonstrated a 65% reduction in the five year incidence of pulmonary tuberculosis in this group with 6 months of isoniazid therapy with an intention-to-treat analysis.[3] Therefore, a relative risk of 0.35 of developing tuberculosis disease was applied to those people identified to have inactive pulmonary tuberculosis and treated with isoniazid for six months. Thus, the estimate of the six month incidence of tuberculosis disease in those with inactive pulmonary tuberculosis who have undergone treatment for latent tuberculosis infection is 0.00296. The incidence of tuberculosis disease development in those with treated inactive pulmonary tuberculosis is calculated in a similar method for the other incidence estimates described above and shown in Table 2.

3.7.2.3 Mortality

The risk of death in the initial Markov states of normal chest x-ray and all inactive pulmonary tuberculosis states is modeled on mortality rates in Cape Town in 2001.[57] Mortality in the tuberculosis disease states is modeled on tuberculosis case fatality rates

in Cape Town in 2001.[56] As tuberculosis case fatality is assessed in the tuberculosis disease states, and tuberculosis is one of top three causes of death in Cape Town, tuberculosis deaths were removed from the total mortality risks and then calculated as above into 6 month risks, shown in Table 3.[57] The total number of deaths in Cape Town for 2001 for individuals 15 years of age or older was 21,341, excluding deaths from tuberculosis (1339) and using census data from 2001 (2,327,729), the risk of dying from any condition other than tuberculosis in a year was calculated at 0.0086 with a six month risk of 0.0043.[57]

3.7.2.4 Risks of treatment of inactive pulmonary tuberculosis

The morbidity and mortality risk from treatment for latent tuberculosis disease is modeled for all individuals prescribed isoniazid treatment for inactive pulmonary tuberculosis. All preventive treatment regimes for LTBI may cause hepatitis which is rarely fatal.[58-72] Latent tuberculosis infection treatment is currently not used in inactive pulmonary tuberculosis in Africa and, as such, rates of INH-associated hepatitis are not available for this African cohort. There are rates of hepatitis in LTBI treatment studies in individuals with HIV in Africa, but results in HIV patients may not accurately reflect hepatitis rates in non-HIV individuals.[58,73-75] Therefore, for this model, the baseline rates of hepatitis and hepatitis fatality are taken from the same study as the treatment outcome results for inactive pulmonary tuberculosis.[3,17] In that study, liver enzyme serum testing to detect isoniazid-related hepatitis was not performed. However, individuals were seen monthly while on treatment to monitor for symptoms of hepatitis and ensure compliance with isoniazid treatment.[3,17] This clinical hepatitis monitoring strategy is similar to the

current South African NTP recommendations for the use of isoniazid preventive treatment.[26] The guidelines recommend the use of isoniazid therapy for prevention of tuberculosis in individuals who do not have known liver disease or alcoholism. Monitoring for hepatitis is performed clinically when individuals obtain their monthly supply of medications.[26] Adherence is also monitored during these monthly visits, as occurred in the IUAT study.[3,17,26] The risk of hepatitis with six months of isoniazid preventive treatment and clinical monitoring is 0.0048, with the risk of dying from hepatitis of 0.031.[3,17]

3.7.2.5 Risks due to diagnostic error

As shown in Figure 1, if individuals are incorrectly diagnosed with inactive pulmonary tuberculosis on chest x-ray when they have not been infected with *M. tuberculosis*, they will receive treatment for latent tuberculosis infection in the screening arm of the decision analysis model with no benefit. After receiving their 6 months of isoniazid, patients transition to the normal chest x-ray branch as they are not at increased risk of developing tuberculosis disease.

In addition, due to diagnostic errors in the diagnosis of tuberculosis disease, a small number of individuals who have active pulmonary tuberculosis will be incorrectly diagnosed with inactive pulmonary tuberculosis in the screening branch and started on isoniazid preventive treatment instead of four drug full treatment of tuberculosis disease. Individuals in this arm would receive LTBI treatment for six months and then transition to the tuberculosis disease treatment (outside of a screening program). The effects of

inappropriate LTBI therapy have been assessed in the LTBI treatment studies in inactive pulmonary tuberculosis.[3-16] There was no evidence of increased mortality, treatment failure, or isoniazid resistance in individuals who were diagnosed with tuberculosis disease while on LTBI treatment for inactive pulmonary tuberculosis.[3-16,76] Thus, in the base case analysis, mortality was presumed to be the same as in the LTBI treatment arm and individuals were then transitioned to the tuberculosis treatment arm. In scenario analysis, the worst case was assumed with individuals having the same risk of death as in the tuberculosis treatment arm and then transitioning to the retreatment arm, assuming they had developed resistant disease.

3.7.2.6 Pulmonary tuberculosis treatment outcomes

In this decision analysis model, individuals may be found to have pulmonary tuberculosis during the screening process, have pulmonary tuberculosis not yet diagnosed, have pulmonary tuberculosis disease and are inappropriately prescribed treatment for inactive pulmonary tuberculosis due to diagnostic error, or develop pulmonary tuberculosis during the 20 year Markov cycle (Figures 1 and 2).

The outcomes of patients treated for active pulmonary tuberculosis in Cape Town, South Africa are shown in Table 5.[56] In the base case analysis, the case fatality risk for new cases of pulmonary tuberculosis disease was assumed to be 0.044; a risk of 0.074 was used in sensitivity analysis, the case fatality risk for all form of tuberculosis disease.[56] Those successfully treated for tuberculosis (0.848), are transitioned into the post-treatment tuberculosis disease Markov state. Those who failed treatment or interrupted

their treatment were presumed to have required retreatment for pulmonary tuberculosis and entered the retreatment tuberculosis Markov state. Individuals in the post-treatment of tuberculosis disease remained in this state, died based on mortality risks as explained above, or developed re-treatment tuberculosis based on the six-month incidence risk of re-treatment tuberculosis in Cape Town (0.000725).[56] Outcomes for re-treatment pulmonary tuberculosis are shown in Table 5, individuals died based on case-fatality risk of retreatment pulmonary tuberculosis (0.068), were successfully treated for retreatment pulmonary tuberculosis disease and re-entered the post-treatment of tuberculosis disease branch of the Markov analysis, or failed treatment. Those who failed retreatment were re-entered into the retreatment branch of the analysis. Very few individuals entered into this pathway, but as it may represent an over-prescribing of treatment costs, a scenario analysis will be performed where all individuals who fail retreatment are presumed to be adequately treated and transitioned to the post-treatment of tuberculosis branch (best case) or presumed to have died (worse case).

3.7.2.6.1 Tuberculosis screening outcomes

Individuals diagnosed with active pulmonary tuberculosis in a screening program are detected prior to seeking medical attention. A study out of the Netherlands examined the differences in tuberculosis severity and infectiousness between immigrants diagnosed as part of a screening protocol and those diagnosed outside of a screening program.[77] They documented no significant differences in cure rates or mortality rates between individuals diagnosed within a screening program and those diagnosed outside of a screening program, thus the same success rate and case fatality rate is presumed.[56] There were

significant differences between the screened and unscreened cases in terms of symptoms, infectiousness and hospitalization rates that will be discussed in the utility, costing, and sensitivity analyses sections below.[77]

In the no screening branch of this decision analysis, there will be people who have active pulmonary tuberculosis that has not yet been diagnosed. The mortality of this group is presumed to be the same as the case-fatality associated with treated tuberculosis, 0.044.[56] Individuals who survive, will then transition to the tuberculosis treatment without screening branch.

3.7.3 Outcomes of the economic evaluation

3.7.3.1 Cost effectiveness analysis

The outcome assessed in this cost-effectiveness analysis is the number of cases of tuberculosis disease that develop over a 20 year period in the management strategies. An incremental analysis will determine the difference in number of cases of tuberculosis disease that develop in each cohort and report the cost per case of tuberculosis disease prevented.

3.7.3.2 Cost utility analysis

The outcome measurement in the cost-utility analysis is the number of quality-adjusted life years (QALYs) obtained with chest x-ray screening and treatment of inactive pulmonary tuberculosis compared to the QALYs obtained with current care.

In the base case scenario, the utility for a patient with tuberculosis in the non-screened branch of the decision model is estimated at 0.66 based on results obtained in both a physician-proxy survey and directly from members of the public using the time trade off method (Table 6).[78,79] However, given the large range of reported utilities for tuberculosis in the literature, a utility score rangeof 0.45 to 0.96 was considered in sensitivity analyses.[17,21,67,70,72,78-83] The utility for patients with pulmonary tuberculosis detected within a screening program has not been reported in the literature. A study on immigrants diagnosed with tuberculosis in the Netherlands found that individuals diagnosed with tuberculosis as part of a screening program were symptomatic 37% of the time compared to 100% symptom complaint in those diagnosed outside of a screening program, suggesting that patients with tuberculosis detected in a screening program might have a higher quality of life.[77] The Lung Health Survey found that 67% of individuals diagnosed with active pulmonary tuberculosis in this study were symptomatic at the time of the screening process.[48,49] Thus, the utility for patients with tuberculosis diagnosed in a screening program is estimated by assuming those individuals in a screening program that were symptomatic had the same utility as individuals diagnosed with tuberculosis outside of screening program and those without symptoms were assumed to have a utility of 1.

The utility for patients undergoing retreatment of tuberculosis is presumed to be the same as that for a new case of tuberculosis as there is no reported utility measures for retreatment tuberculosis available in the literature.

The utility of inactive pulmonary tuberculosis without treatment was presumed to be the same as a normal individual, one. The utility for individuals with inactive pulmonary tuberculosis disease prescribed treatment for latent tuberculosis infection is 0.93, ranging from 0.9 to 1. [17,21,67,70,72,78-83] The impact of isoniazid-related hepatitis on quality of life has only been assessed in a systematic fashion in a physician-proxy survey with a utility of 0.62.[70] A sensitivity analysis will be performed utilizing other values reported in the literature for isoniazid-related hepatitis as well as values found in hepatitis patients not related to isoniazid (Table 4). [17,21,67,70,72,78-83]

3.7.4 Discounting

A five percent discount rate is applied to all outcomes and costs that will occur in the future as per the Canadian guidelines for the economic evaluation of health technologies.[31] A sensitivity analysis will be performed utilizing values of 0 and 3%.[31]

3.8 Cost measurement and valuation

Individual cost estimates are provided in Table 8. Component costing is shown in Table 9. All costs are reported in 2005 South African Rand inflated using the consumer price index of South Africa.[84] One Canadian dollar is currently equivalent to 6.05 South African Rand.[85] The base case analysis assumes a health provider perspective and thus only direct costs are included.[31] A scenario analysis examines the cost per QALY gained using a societal perspective, and as such indirect costs are included in that analysis.[31]

3.8.1 Cost of screening

The cost of screening individuals for inactive pulmonary tuberculosis is estimated from costs incurred to complete the Lung Health Survey in Cape Town.[48,49] Capital costs and salary costs are included in the analysis, while research costs (data analyst) are excluded.[31] Individualized costs are added to the base screening costs. Individuals who decline screening are prescribed the base cost of screening without any additional individualized cost as they would not have presented for assessment. All individuals who accept screening are assigned the cost of screening in addition to the cost of a chest x-ray.[86] Individuals with normal chest x-rays would not have any further investigations performed. [48,49] Individuals with abnormal chest films would have a sputum smear and culture performed.[87]

3.8.2 Cost of treatment for inactive pulmonary tuberculosis

The cost of treatment for inactive pulmonary tuberculosis is calculated as shown in Table 9. Isoniazid therapy for six months is used as the treatment regimen for inactive pulmonary tuberculosis patients in this study as it is the recommended treatment regime for LTBI in the South African NTP and has been shown to be cost-effective in previous studies on inactive pulmonary tuberculosis.[18,26] The base case analysis models the cost of LTBI treatment in individuals with inactive pulmonary tuberculosis on the current management and treatment recommendations for LTBI infection in the South African NTP guidelines.[26] The guidelines recommend that individuals are clinically assessed for liver disease and risk factors that increase the risk of liver disease.[26] If no risks of liver toxicity are elucidated on the clinical assessment, individuals are started on isoniazid and continue treatment for six months. Once a month individuals are assessed clinically for

compliance and symptoms of hepatotoxicity.[26] Thus the costs of six months of isoniazid treatment and the cost of 6 clinic visits are the component costs calculated for LTBI treatment for those with inactive pulmonary tuberculosis in this model. The cost of isoniazid is obtained from the 2002 pharmaceutical price list for South Africa.[88] The clinic visit cost is obtained from a study performed in Cape Town, South Africa, that examined the cost of treating tuberculosis patients in outpatient settings.[89] The clinic cost represents the average cost of a clinic visit for a tuberculosis patient. This cost included the costs of personnel, equipment, and proportion of clinic space utilized. The capital costs associated with the clinic use were annualized using a discount rate of 8%.[89]

3.8.3 Cost of hepatitis

Individuals on treatment for LTBI have a risk of developing isoniazid-related hepatitis while on therapy.[3-21,58-75] The outpatient cost of a case of hepatitis is assumed to be the cost of two additional clinic visits and the cost of liver enzyme testing on two occasions, the first visit for assessment and diagnosis of hepatotoxicity and the second visit to ensure resolution.[17-21,58-75,89,90] The incidence of hospitalization with isoniazid-related hepatitis ranges from 0 to 10% in the literature, with length of hospitalization ranging from 7 to 14 days.[3-21,58-75] A 5% hospitalization rate and 7 day length of stay is used in the base case analysis with sensitivity analysis encompassing the above ranges. The estimated cost of hospitalization is discussed in Section 3.8.3.2.

Individuals who develop hepatitis while on isoniazid are not continued nor re-introduced to latent tuberculosis infection treatment.[26] Therefore, once diagnosed with hepatitis, the

costs of isoniazid and monthly clinic visits should not be accrued in this cohort of individuals with inactive pulmonary tuberculosis who develop hepatitis.[26] In the IUAT study, 67% of hepatitis cases occurred during the first twelve weeks of therapy.[3,18] Thus, the cost of LTBI treatment in 67% of the hepatitis cohort will be accrued over twelve weeks and the cost of LTBI treatment will be accrued over the entire twenty-four weeks in the other 33% of individuals.[3,18]

3.8.4 Cost of treatment of tuberculosis

3.8.4.1 Outpatient care

Individuals diagnosed with tuberculosis disease must take a minimum of six months of antibiotic treatment to adequately kill the bacteria and obtain a cure.[22-26] The first two months of therapy are termed the intensive phase of treatment and individuals are commenced on four antibiotics.[22-26] The last four months of therapy involve treatment with at least two antibiotics to which the organism is known to be sensitive.[22-26] The costs of clinical outpatient care of new tuberculosis disease patients is obtained from a previous study performed in two communities in Cape Town, South Africa.[89] 1997 US dollar estimates were converted into Rand and inflated to 2005 prices.[84,85] This cost-effectiveness study examined the costs and outcomes of providing directly-observed-therapy (DOT) in two different ways, either providing witnessed medication delivery by a nurse at the health clinic or with a community supervisor.[89] In the base analysis, an average of the outpatient costs for each comparator was used, with a sensitivity analysis for the lower and higher cost of outpatient care of tuberculosis patients.[89]

The cost of out-patient therapy for retreatment tuberculosis is obtained from the same study and calculated as above.[89] Individuals who have already been diagnosed and treated for tuberculosis disease on a previous occasion are at risk of having resistant *M. tuberculosis*.[22-26] They are commenced on treatment with at least five antibiotics and maintained on therapy for at least 8 months of treatment.[22-26] Thus, the cost of retreatment tuberculosis is higher than that of new tuberculosis.[89]

3.8.4.2 Inpatient care

The cost for hospital care of tuberculosis patients in Cape Town is estimated from the literature. The costs of an inpatient day at the regional and tertiary hospitals in the Tygerberg district in Cape Town are obtained from a study that examined the cost of managing HIV positive individuals with anti-retroviral therapy in Cape Town.[91] In this study, patient–specific costs, recurrent overhead costs (hotel costs), and capital costs were calculated for HIV positive individuals admitted to a regional hospital and a tertiary hospital in Cape Town.[91] Patient-specific costs for tuberculosis patients admitted to these hospitals are not available, thus the estimate of the patient-specific costs for HIV positive individuals admitted to hospital is assumed to be the same with a wide range reported in the sensitivity analyses. Recurrent overhead costs were calculated by subtracting capital and patient-specific expenditure for the total expenditure at each facility and dividing by the patient day equivalent (measure that determines the cost of an inpatient day relative to the cost of an outpatient visit).[91] Hospitalization costs due to isoniazid hepatitis are calculated as above.

The inpatient cost of a retreatment tuberculosis disease case is assumed to be the same as a new case of tuberculosis. The only costs that will differ are medication costs, higher for retreatment cases.[89] Therefore, the daily medication cost to treat tuberculosis disease, either a new case or a re-treatment case, will be added to the daily cost of inpatient tuberculosis care.

3.8.4.2.1 Proportion of tuberculosis patients hospitalized

It is estimated that 10% of tuberculosis patients are admitted to hospital in South Africa.[92] The average length of stay for a tuberculosis patient in a community-based tuberculosis treatment programme in South Africa is 17.8 days.[93] Individuals diagnosed with tuberculosis disease within a screening program in this Markov model will have a different hospitalization rate. In a recent study, patients diagnosed with tuberculosis disease within a screening program were found to have a significantly decreased risk of hospitalization (RR 0.33) but once admitted to hospital had the same length of stay.[77] Therefore, a 3.3% hospitalization rate with a 17.8 day stay is modeled in the base case analysis for individuals diagnosed with tuberculosis disease in the screening branch of the Markov model.

The retreatment tuberculosis cohort is prescribed the same hospitalization and length of stay as the non-screened tuberculosis disease cohort. In sensitivity analysis, a longer length of stay and higher hospitalization rate is assessed.

3.8.5 Societal costing

A societal perspective is taken in a scenario analysis. Costs accrued will include transportation costs and work time lost for screening assessment, clinic visits, and hospitalization. Transportation and income costs are obtained from a study on cost-effectiveness of outpatient tuberculosis care.[89]

3.9 Sensitivity and Scenario analyses

Uncertainty will be assessed in sensitivity and scenario analyses, as outlined in the sections below and presented in detail in Tables 12 through 15.

3.9.1 Sensitivity analyses

A previous review of cost-effectiveness studies in treating those with latent tuberculosis infection identified the tuberculosis disease risk, the tuberculosis case fatality risk, and the isoniazid hepatitis case fatality rates as the major source of variability in the results between these studies.[59] Therefore a one-way sensitivity analysis will be performed for these three variables utilizing values reported in the literature and presented in Table 10.

3.9.1.1 Incidence of tuberculosis and HIV

HIV disease could not be directly modeled in this analysis as HIV status was not collected in the Lung Health Survey.[48,49] However, HIV is one of major reasons for the increasing epidemic of tuberculosis in South Africa.[26] It is estimated that fifty percent of the cases of tuberculosis disease in South Africa are co-infected with HIV.[26] Individuals known to be co-infected with HIV and *M. tuberculosis* are offered treatment for latent tuberculosis in South Africa to prevent the development of tuberculosis disease.[26] These

individuals would therefore not be entered into a screening and treatment programme for inactive pulmonary tuberculosis as they would already be candidates for LTBI treatment.

A sensitivity analysis is performed to try to estimate the incidence of tuberculosis disease development in individuals with inactive pulmonary tuberculosis and without HIV co-infection in South Africa. It is assumed in this analysis that all individuals with HIV and *M. tuberculosis* co-infection have been previously identified and not entered into the chest x-ray screening programme. It is therefore further assumed that 50% of the five year incidence of tuberculosis disease in Cape Town is due to HIV co-infection and thus not preventable using this chest x-ray screening programme as individuals with HIV would be excluded from screening. This is modeled as a worst case analysis as individuals with unknown HIV infection and evidence of inactive pulmonary tuberculosis disease on chest x-ray would obtain significant benefit from the diagnosis and treatment of inactive pulmonary tuberculosis. With these assumptions, and utilizing the calculations shown in section 3.7.2.1, the 6 month incidence of tuberculosis disease in HIV negative individuals with previously normal chest films is estimated to be 0.000537 and 0.00326 in HIV negative individuals with chest x-rays previously consistent with inactive pulmonary tuberculosis.

3.9.1.2 Effectiveness of treatment of inactive pulmonary tuberculosis

3.9.1.2.1 Resistance of *M. tuberculosis*

Given that the effectiveness of LTBI treatment in those with inactive tuberculosis is not well-established in an African setting, LTBI effectiveness will be subjected to sensitivity

analyses. One possible difference between the original studies and the current situation in Cape Town is the resistance pattern of *M. tuberculosis*. Individuals infected with a resistant strain of *M. tuberculosis* will not receive any preventive benefit if the organism is resistant to the prescribed antibiotic. [22-26] If there is a large number of individuals who are infected with resistant bacteria, tuberculosis preventive therapy may not be as effective as reported in the original studies of inactive pulmonary tuberculosis and this is modeled in this decision analysis.[3-16] The resistance of *M. tuberculosis* to isoniazid, the preventive medication prescribed to treat inactive pulmonary tuberculosis in this model, was 5.2% in the Western Cape Province in 2001.[94] If it is assumed that all individuals with inactive pulmonary tuberculosis in the IUAT trial were infected with *M. tuberculosis* sensitive to isoniazid, and assuming a 5.2% isoniazid resistance rate in this cohort, the effectiveness of isoniazid preventative therapy is reduced from a 65% decreased incidence of active tuberculosis disease at five years to a 58% decreased incidence at five years.[3,94]

3.9.1.2.2 Reactivation versus Reinfection

The effectiveness of treatment for individuals with inactive pulmonary tuberculosis has been questioned in high-incidence tuberculosis areas. A significant proportion of studies that examined the effects of treatment of inactive pulmonary tuberculosis were performed in low tuberculosis incidence countries.[3-10] In high incidence countries such as South Africa, individuals who develop tuberculosis disease on a second occasion may have reactivated dormant mycobacteria (endogenous reactivation) and have tuberculosis disease due to the same strain of *M. tuberculosis* or have become re-infected with a new

strain of *M. tuberculosis* (exogenous reinfection).[95] It is assumed in low incidence countries that the majority of individuals with chest x-ray evidence of inactive pulmonary tuberculosis will develop tuberculosis disease from organisms that reside in the lung scars and thus prescribing preventive therapy will kill these bacteria and prevent the development of tuberculosis disease.[22-24] However, in high tuberculosis incidence countries it is unclear if individuals who have chest x-ray evidence of inactive pulmonary tuberculosis who develop tuberculosis disease, reactivate the dormant bacilli or are re-infected given the high background incidence of disease. One study out of Cape Town has demonstrated that in individuals with a second episode of tuberculosis disease, 75% of cases were due to exogenous re-infection and not due to endogenous re-activation.[95] Thus, a prevention strategy may only be effective for 25% of cases of tuberculosis disease that develop in individuals with inactive pulmonary tuberculosis on chest x-ray, and this is modeled in a sensitivity analysis. It is important to note that studies on preventive therapy in high tuberculosis incidence areas have shown similar effectiveness as the IUAT trial and thus this estimate of effectiveness is thought to be reasonable and used in the base case analysis.[11-16] Effectiveness in only 25% of individuals is modeled as a worst-case scenario.[95]

3.9.1.3 Costing

Details of costing sensitivity analyses are summarized in Table 13.

3.9.1.3.1 Cost of screening

A sensitivity analysis is performed with the range of the screening base costs from the Lung Health Study.[48,49] A sensitivity analysis is performed that examines the base costs of screening in individuals that decline to participate in the chest x-ray screening programme. Assigning the full base cost of screening to this group likely overestimates the true base costs in this cohort. Costs in this group are therefore estimated to be 50% less than the base costs of the individuals who accepted screening in a sensitivity analysis.

An additional sensitivity analysis is performed using costing information from a functioning screening and treatment program for detection and treatment of latent tuberculosis infection in HIV patients in Cape Town.[46] The screening costs available in this study are the cost for the clinic space, administration of screening process, nursing time, and diagnostic procedures completed prior to initiation of LTBI treatment in HIV positive patients.[46]

3.9.1.3.2 Cost of treatment of inactive pulmonary TB

Outpatient clinic costs for clinic visits during isoniazid treatment are estimated on clinic costs for tuberculosis patients.[89] This clinic cost may represent an overestimation of the costs of clinic time for those being treated for latent tuberculosis infection as they are not symptomatic at outset of treatment and are on substantially less medications than tuberculosis disease patients, likely resulting in fewer complications and less time being spent at the clinic visit. Therefore a sensitivity analysis was performed utilizing clinic

cost information for HIV positive patients treated for latent tuberculosis infection in primary care facilities in Cape Town.[46]

3.9.1.3.3 Cost of isoniazid-related hepatitis

The costs of isoniazid-related hepatitis are estimated using South African costing information and hospitalization rates from North America as preventive treatment is not routinely prescribed in South Africa for inactive pulmonary tuberculosis.[58-75] A sensitivity analysis is performed using direct costing information for isoniazid-related hepatitis in South Africa in HIV patients prescribed isoniazid.[96]

3.9.1.3.4 Cost of hospitalization

As mentioned in section 3.8.4.2, direct patient-specific costs for tuberculosis patients admitted to the regional and tertiary hospital in the Tygerberg district are not available, thus costs associated with HIV patients admitted to these hospital are used as estimates.[82] A 50% adjustment of patient-specific costs is assessed in the sensitivity analyses given this assumption. A further sensitivity analysis is performed with costing information for the average patient admitted to hospital in South Africa.[97] The percentage of tuberculosis patients admitted to each category of hospital is not available in Cape Town, therefore a sensitivity analysis will be performed assuming all tuberculosis patient inpatient care is in either the district, regional or tertiary care hospital. The base case analysis will assume all care is provided in a regional hospital.[91, 97]

A range of hospitalization rates is assessed in sensitivity analysis as multiple studies have shown a significant impact of hospitalization rates on the cost-effectiveness of tuberculosis treatment programs.[98-102]

An additional sensitivity analysis is performed, varying the length of stay in hospital from 4 to 21 days, the range reported in the literature.[17-21,98-102]

3.9.2 Scenario analyses

Scenario analyses are also performed to examine uncertainty within this decision model and are outlined and reported in Table 14.

3.9.2.1 Screening

3.9.2.1.1 Miniature chest x-ray screening

Miniature chest x-ray screening has been utilized for tuberculosis prevalence studies and for active case finding.[23,37,41,103] Miniature chest x-rays are less expensive than full size films but require an initial capital cost to purchase specialized equipment. [41,103] The use of miniature chest films for screening instead of full-size chest imaging is assessed in a scenario analysis. In the Lung Health Survey, conventional radiography was used for chest imaging.[48,49] In the base scenario analysis, miniature chest radiographs are assumed to be as sensitive and specific as conventional radiography. A secondary analysis is performed utilizing the sensitivity (93%) and specificity (97%) of 100 mm x 100 mm miniature chest radiography compared to conventional radiography.[103] The cost of screening with miniature chest radiography is obtained from a cost-effectiveness analysis

of miniature chest radiography for active case finding of tuberculosis in the United States.[41]

3.9.2.1.2 Number of sputum assessments

The sensitivity of sputum smear and microscopy to diagnosis active pulmonary tuberculosis increases with additional testing.[52-55] A scenario analysis is performed for a screening plan that includes the increased sensitivity of performing two sputum smears and cultures for individuals identified with an abnormal chest film as well as the increased cost of the additional samples.[87]

3.9.2.1.3 Tuberculin skin testing

A model is constructed examining the additional costs and benefits of performing a tuberculin skin test in individuals with abnormal chest x-rays consistent with inactive pulmonary tuberculosis and negative sputum assessments for active pulmonary tuberculosis (Figure 3). The TST is performed to confirm that individuals with chest x-ray findings consistent with inactive pulmonary tuberculosis have been infected with *M. tuberculosis*.[23]

One problem with the TST is that individuals must return 48 to 72 hours after the tuberculin antigen is injected in the skin to have the results of the skin reaction interpreted.[23] The compliance of completing tuberculin skin testing in individuals found to have evidence of inactive pulmonary tuberculosis on chest x-ray is modeled on the compliance results for tuberculin skin testing in the Lung Health Study (0.81).[48,49]

Individuals who are non-compliant with tuberculin skin testing are not offered treatment for inactive pulmonary tuberculosis and enter into the appropriate Markov state.

Another difficulty with the tuberculin skin test, as discussed in section 3.7.1.2, is the test may be both falsely positive and falsely negative.[22-24] Therefore, without a definitive gold standard for *M. tuberculosis* infection, it is difficult to know whether the chest x-ray or the tuberculin skin test is correct when the results differ. It is assumed in this scenario analysis that the TST test is the correct indicator of *M. tuberculosis* infection (and not the chest x-ray), and treatment of inactive pulmonary tuberculosis is not provided to individuals with an abnormal chest x-ray and a negative skin test. In the first analysis, the tuberculin skin test is assumed to be the gold standard and providing the correct diagnosis. In the second scenario analysis, the positive and negative predictive values of tuberculin skin testing are calculated using published values of the sensitivity and specificity of tuberculin skin testing in HIV negative individuals and the prevalence of *M. tuberculosis* infection in this cohort of individuals.[19,21,48,49] Both a five mm and a ten mm criteria for a positive tuberculin skin test criteria are modeled as described in section 3.7.1.2. The prevalence of positive TST in those with chest x-ray abnormalities consistent with inactive pulmonary tuberculosis and negative sputum assessments for active pulmonary tuberculosis is 0.89 when a five mm positive test criteria is used and 0.85 when a ten mm positive test criteria is used.[48,49]

The additional cost of performing tuberculin skin testing is included in the screening costs of those who had abnormal chest x-rays and had tuberculin skin tests performed.

3.9.2.2 Isoniazid-related hepatitis and liver enzyme monitoring

A scenario analysis is performed to assess the costs and effects of routine liver enzyme monitoring while on treatment for latent tuberculosis infection.[58-75] Given the risk of hepatitis while on treatment for latent tuberculosis infection, North American guidelines have suggested routine liver enzyme assessments.[22,23,58] Studies with routine monitoring of liver enzymes while on latent tuberculosis infection treatment tend to have higher incidences of hepatitis, defined by liver enzyme elevations, but lower hepatitis fatality rates.[50-64] Routine liver enzyme monitoring confers a significant cost to the health care system, thus best assessed in a scenario analysis.[90]

3.9.2.3 Tuberculosis outcomes

In the base case analysis, the incidence of the development of pulmonary tuberculosis is modeled as the majority of treatment studies on inactive pulmonary tuberculosis monitored for the development of pulmonary disease.[3-16] In a scenario analysis, the incidence of development of all forms of tuberculosis disease and the case-fatality rate for all forms of tuberculosis disease is assessed.[56] In addition, outcomes that are difficult to assess, specifically the outcomes of tuberculosis disease developing during isoniazid treatment and retreatment failure outcomes are modeled in an alternate way in scenario analyses.

Assuming a worst case scenario for inappropriately treating active pulmonary tuberculosis as inactive pulmonary tuberculosis, the case fatality rate of tuberculosis

disease is utilized and the presumptive diagnosis of resistant disease is modeled by transitioning this group to the retreatment branch after inappropriate LTBI treatment.

Individuals who fail retreatment tuberculosis treatment are all presumed to die (worst case scenario) or all to have received appropriate treatment and then enter the post TB treatment group (best case scenario).

3.9.2.4 Tuberculosis treatment costs

Given the incomplete data on hospital costing for tuberculosis patients, a scenario analysis is performed that examines the effect of assuming all of the low costs for tuberculosis care and another that examines the effect of assuming all of the high cost estimates for tuberculosis treatment.

3.9.2.5 Utility measurements

Given the variability of the reported utilities for tuberculosis disease and treatment for latent tuberculosis infection, and the significant effect of the utilities on single variable sensitivity analysis further assessment of uncertainty is performed with two scenario analyses of utility. [17,21,67,70,72,78-83] Given the difference in severity between individuals hospitalized for tuberculosis and those treated as an outpatient, expert opinion of the utility of tuberculosis disease suggests that the utility of a tuberculosis inpatient is significantly lower than the utility of a tuberculosis outpatient.[21] Therefore, a decision analysis was performed using these hospitalization-specific utility estimates for tuberculosis disease.

In addition, because of the variability in utility estimates, the analysis was reassessed with all of the low estimates of utility and all of the high utility estimates of tuberculosis disease, hepatitis, and treatment of inactive pulmonary tuberculosis. [17,21,67,70,72,78-83]

3.9.2.6 Societal Costing

A societal perspective is taken in a scenario analysis. Estimates of mean annual income will be further examined in a sensitivity analysis as unemployment rates and mean household income vary significantly in different communities in South Africa.[89,104] Costs accrued will include transportation costs and work time lost for screening assessment, clinic visits, and hospitalization. Transportation and income costs are obtained from a study on cost-effectiveness of outpatient tuberculosis care.[89]

3.9.2.7 Estimation of secondary cases

A scenario analysis is performed where the secondary cases of tuberculosis disease caused by the active pulmonary tuberculosis disease cases are included in the costs and outcome of this study. Individuals with pulmonary tuberculosis can infect others, and once infected these individuals can subsequently develop disease.[22-26] Infectiousness of the different cohort states in this model are estimated in the following fashion. Studies have demonstrated that individuals with smear positive disease can infect between 3 and 13 individuals and those with smear negative disease will infect 0.22 times that of smear positive individuals (0.6 to 3).[19,21-26,80,97-99] Further modeling in HIV negative patients estimated that each tuberculosis disease case will result in 0.55 secondary cases of

tuberculosis disease over 20 years, 0.963 cases per smear-positive case and 0.21 cases per smear-negative culture-positive case.[19,21,37,105-107] Individuals diagnosed with tuberculosis disease in a screening program (active case finding) are less likely to have smear-positive tuberculosis disease than individuals diagnosed with symptoms (passive case finding).[77] In the Lung Health Survey, 57% of individuals diagnosed with active pulmonary tuberculosis were sputum smear positive while 87% of individuals diagnosed in 2001 in Cape Town outside of a screening program were sputum smear positive.[48,49,56] These percentages of sputum smear-positivity were used to estimate the number of secondary cases that developed from pulmonary cases of tuberculosis diagnosed within a screening program (0.639 secondary cases) and pulmonary tuberculosis diagnosed without a screening program (0.865 secondary cases), shown in Table 7.

When estimating the costs of the secondary cases in the model, an additional cost of 0.639 times the total cost of tuberculosis disease was added to the cost of individuals diagnosed with pulmonary tuberculosis during the screening process. For subsequent cases of pulmonary tuberculosis in the screening programme, and in all cases in the non – screening arm of the model, individuals diagnosed with active pulmonary tuberculosis were assigned an additional cost of 0.865 times the total cost of tuberculosis disease. These costs therefore represent the costs of the secondary cases of tuberculosis that developed from the initial cases of pulmonary tuberculosis.

The outcome measure of secondary cases was estimated in a similar fashion. Individuals diagnosed with active pulmonary tuberculosis in the model will cause disease in others

resulting in a loss of QALYs for the secondary cases. The loss of QALYs of the secondary cases was estimated as the difference between the QALYs of perfect health for six months and the QALYs of tuberculosis disease for six months. Individuals diagnosed with active pulmonary tuberculosis during the screening process were estimated to cause 0.639 cases of tuberculosis. Therefore, the QALY loss assigned for the secondary cases of active pulmonary cases diagnosed during the screening process is expressed numerically below:

- 0.639 (QALY total health/2 – QALY TB disease/2) = -0.109

For subsequent cases of pulmonary tuberculosis in the screening programme, and in all cases in the non screening arm of the model, individuals diagnosed with active pulmonary tuberculosis caused 0.865 cases of secondary tuberculosis resulting in a loss of 0.148 QALYs.

The outcomes and costs of the secondary cases must be discounted as the outcomes and costs of the secondary cases of tuberculosis disease do not occur immediately.[23, 31] Fifty percent of individuals infected with *M. tuberculosis* who develop tuberculosis disease do so within two years of their infection. Thus, fifty percent of the secondary cases were discounted at the same stage as the active pulmonary case.[23] The other fifty percent of secondary cases may develop tuberculosis disease anytime during their lifetime after the infection with *M. tuberculosis*.[23] In this model, these cases were estimated to develop disease ten years after the index case. The costs and outcomes of the other fifty percent of

cases were therefore discounted at the stage of the index case plus ten years (20 cycles). Sensitivity analyses were performed varying the stage of discounting for these fifty percent of secondary cases.

3.9.2.7.1 Secondary cases and HIV infection

In this model, the effect of HIV on tuberculosis incidence has not been directly modeled. Individuals who are known to be HIV positive are screened with tuberculin skin testing and offered LTBI treatment if found to be infected with *M. tuberculosis,* as per the South African NTP guidelines.[26] Therefore, HIV positive individuals would not be offered chest x-ray screening to detect inactive pulmonary tuberculosis as they are already participating in another tuberculosis screening programme.

However, when modeling the development of secondary cases of tuberculosis disease the incidence of HIV in the population screened should be considered. HIV positive individuals who become infected with *M. tuberculosis* are much more likely to develop disease and become a secondary case of active tuberculosis than immunocompetent individuals. Untreated individuals with HIV and *M. tuberculosis* co-infection develop tuberculosis disease at a rate of 6.7% per annum until death compared to immunocompetent individuals who have a 10% life-time risk of disease development after infection with *M. tuberculosis*.[22-26,44] In this scenario analysis, it is assumed that the HIV prevalence in the population at risk of becoming infected from the pulmonary tuberculosis cases is 10%.[48,49] With this assumption, each case of pulmonary tuberculosis diagnosed during the screening process would cause 1.043 secondary cases of

tuberculosis (compared to 0.639 cases when all exposed individuals were assumed to be immunocompetent) and 1.45 cases per active tuberculosis disease case diagnosed outside of the screening programme (compared to 0.865 when all exposed individuals were assumed to be immunocompetent). This would be a worst case analysis of tuberculosis disease development in HIV positive individuals, assuming that none of the HIV positive individuals had been determined to be co-infected with *M. tuberculosis* and prescribed preventive isoniazid treatment.

The costs and outcomes for these secondary cases are accounted for as described in the previous section.

3.9.2.8 Subgroup analysis with age categorization

The cost-utility analysis is performed examining the utility of performing chest x-ray screening for inactive pulmonary tuberculosis for different age categories, ages 15-34, 35-54, and greater than 55 years of age. Younger individuals may benefit from screening and treatment more than older individuals as they may have a longer lifetime without developing tuberculosis disease if treated for LTBI and they have a lower incidence of hepatotoxicity with treatment for latent tuberculosis infection.[55-72] However, older individuals have a higher prevalence of fibrotic chest x-ray changes consistent with inactive pulmonary tuberculosis and thus more individuals may be identified with inactive pulmonary tuberculosis if an older cohort is selected for screening.[1-3] Thus, subgroup analyses with age categorization is performed to determine if the age of

individuals screened will alter the cost-utility of a chest x-ray screening programme for inactive pulmonary tuberculosis.[108]

3.10 Assumptions

In order to construct and perform a decision analysis assessing the cost and benefit of chest x-ray screening for inactive pulmonary tuberculosis in an African population several assumptions are considered and summarized in point form below:

1.) Compliance of a chest x-ray screening program to detect inactive pulmonary tuberculosis is similar to compliance in a tuberculosis prevalence survey

2.) Chest x-ray and sputum examination is adequate to assess for inactive pulmonary tuberculosis

3.) Incidence of development of tuberculosis disease in individuals with normal chest x-rays, untreated inactive pulmonary tuberculosis, and treated inactive pulmonary tuberculosis in South Africa can be adequately estimated from the available literature

4.) Treatment of inactive pulmonary tuberculosis is as effective in Africa as in populations studied in other countries

5.) Incidence of isoniazid-induced hepatitis is the same in a North American and European cohort as in an African cohort

6.) Tuberculosis outcomes and case fatality rates for Cape Town are applicable in the urban area studied in the Lung Health Survey

7.) Mortality rates for Cape Town are applicable in the urban area studied in the Lung Health Survey

8.) Age-specific tuberculosis incidence and outcomes is the same in the urban area studied in the Lung Health Survey as in Cape Town

9.) Utility of tuberculosis patients diagnosed in a screening program differs from the utility of tuberculosis patients diagnosed outside of a screening program based on complaints of symptoms

10.) Case fatality rates in undiagnosed and untreated tuberculosis patients are the same as the case fatality rates in diagnosed and treated patients

11.) The inclusion of multi-drug resistant tuberculosis cases (retreatment failures) in this model would not significantly affect the results of this analysis

3.11 Limitations

This study is limited by the above assumptions that are assessed in the sensitivity and scenario analyses outlined in section 3.9 and outlined in detail below.

3.11.1 Effectiveness of treatment of inactive pulmonary tuberculosis in Africa

The major clinical limitation of this decision analysis is that treatment of inactive pulmonary tuberculosis has not been documented to be effective in a large population cohort of individuals in South Africa.[3-16] There may be significant differences between this cohort of individuals and this tuberculosis epidemic in sub-Saharan Africa compared to the other studied populations treated for inactive pulmonary tuberculosis and thus the effectiveness of this intervention may be different than published previously.

3.11.2 Inactive pulmonary tuberculosis and HIV infection

HIV is one of the major reasons for the increasing epidemic of tuberculosis in South Africa and this was not modeled directly in the base case analysis.[25] HIV testing was not performed in the Lung Health Survey, thus the chest x-ray results and risk of developing tuberculosis disease could not be stratified by HIV status.[48,49] However, a chest x-ray screening programme to detect inactive pulmonary tuberculosis would likely occur in the absence of knowledge of an individuals HIV status, similar to the study cohort.[48,49] LTBI treatment has already been shown to be cost-effective in HIV individuals and this proposed chest x-ray screening program would not supplant that indication.[26,35,44-46] In addition, the incidence of HIV in this urban area is low, presumed to be 12.4% by prenatal screening surveys.[48,49] The use of LTBI treatment in HIV positive individuals does not infer a life-time protection to tuberculosis, thus the outcomes of the abnormal chest x-ray group may be over-estimated in this study if a large proportion of the screened individuals with abnormal chest x-rays were HIV positive.[26,44-46] In order to clarify the effect of HIV co-infection on treatment of patients identified with inactive pulmonary tuberculosis, further tuberculosis prevalence studies would need to include HIV prevalence information.

3.11.3 Geographic transferability

The prevalence results of inactive pulmonary tuberculosis are from a large sample of individuals in Cape Town, South Africa.[48,49] However, all individuals screened and assessed reside in one district in Cape Town, thus the results may not be directly applicable outside of this district. A secondary analysis will occur for individuals screened in cohort studies across South Africa.[50] However, this data predates the HIV

epidemic and federal South African tuberculosis programme and thus may not accurately reflect the current tuberculosis epidemiology in the country.

3.11.4 Limitations of costing information

Direct costing and hospitalization rates of tuberculosis patients in the urban area studied in the Lung Health Survey are not directly measured but presumed from published data.[91,97-101] If hospitalization rates are different in this urban area compared with other areas of South Africa, the analysis may not be accurate. Patient-specific hospitalization costs for the referral hospitals in this urban district of South Africa are known for HIV positive patients but not known for tuberculosis patients. If patient-specific costs are significantly different from the published HIV costs, this analysis may be incorrect.

3.11.5 Age categorization

Age-specific tuberculosis treatment outcome results are not currently available for this cohort of individuals. Therefore, incidence of tuberculosis disease in certain age groups is estimated from Cape Town and South Africa estimates. When these cohort-specific age-stratified outcomes are available, this sub-group analysis should be repeated to see if the results are sensitive to changes in this estimate.

3.11.6 Chest x-ray findings other than tuberculosis

The costs of assessing individuals with non-tuberculous chest x-ray abnormalities detected in the screening programme was not captured during the Lung Health

Survey.[48,49] Thus the cost (and benefits) of this screening programme may be underestimated or overestimated in this decision analysis.

Chapter 4: Results

4.1 Model Validity

4.1.1 Face Validity

Face validity is the assurance that the model makes sense at an intuitive level and the findings are reasonable to experts.[27-30] This model functioned appropriately over variations in sensitivity analysis and approximated the findings from other similar studies. It also made intuitive sense as a screening and treatment programme. If the screening costs increased the cost of the programme increased. If the prevalence of inactive pulmonary tuberculosis increased, the programme became more efficient. Therefore it was felt that this model had reasonable face validity.

One value that was difficult to model was the accuracy of chest radiography for the diagnosis of inactive pulmonary tuberculosis. In the base case analysis, it was assumed that chest x-ray was a perfectly accurate method of detecting inactive pulmonary tuberculosis. An attempt was made in sensitivity analysis to model the PPV of a chest x-ray consistent with inactive pulmonary tuberculosis for *M. tuberculosis* infection by assuming that the TST is the gold standard for determination of *M. tuberculosis* infection. Therefore, the sensitivity and specificity of chest x-ray assessment for *M. tuberculosis infection* was calculated by comparing the results of chest radiography to TST results prior to sputum assessment for active tuberculosis disease. A major problem with this

estimation of the PPV of chest x-ray for *M. tuberculosis* infection was the high rate of false negative TST results in patients with active pulmonary tuberculosis (28.6%).[48,49] The high false negative rate of the TST in the patients with active pulmonary tuberculosis inappropriately lowered the positive predictive rate of an abnormal chest x-ray for inactive pulmonary tuberculosis. Therefore, it is felt that attempting to model the PPV of chest x-ray assessment for inactive pulmonary tuberculosis using TST as a gold standard prior to sputum assessment is inappropriate and resulted in inaccurate estimates of the incremental cost utility ratio (ICUR) of the proposed screening and treatment programme.

In standard practice, some clinicians will perform a TST in individuals with chest x-rays consistent with inactive pulmonary tuberculosis after active tuberculosis is ruled out with sputum assessments to confirm that those with suspicious chest x-rays have been infected with *M. tuberculosis*.[23] Scenario analyses were modeled in this fashion and produced a more clinically feasible results than the above method.

4.1.2 Predictive Validity

Predictive validity is the ability of the model to make accurate predictions of future events. This model needed to make accurate predictions of tuberculosis incidence, retreatment tuberculosis incidence, and mortality over a twenty year period.

The estimated 20 year mortality in Cape Town was calculated from the average total mortality in Cape Town in 2002 (0.0092) and was estimated to be 0.1688 (Table 10). The mortality results of the model run over twenty years was similar to that predicted,

0.1622 in the unscreened cohort and 0.1616 in the screened cohort. The mortality results in both cohorts are slightly lower than that expected. This may be because the fatality risk of tuberculosis in the base case was assumed to be that of pulmonary tuberculosis (0.044) and not that of all cases of tuberculosis (0.074). If the case fatality of tuberculosis disease is assumed to be that for all cases of tuberculosis (0.074), the twenty year mortality in this model was 0.1644 in the unscreened cohort and 0.1635 in the screened cohort. This result more closely approximated the predicted twenty year mortality in Cape Town (0.1688).

The total incidence of tuberculosis cases that developed was determined for the screening and unscreened cohort over the twenty year cycle and compared to the estimated twenty year incidence of tuberculosis disease based on the incidence on new cases of active pulmonary tuberculosis shown in Table 10. Compared to the expected 20 year tuberculosis incidence, the model slightly over-estimated the 20 year tuberculosis incidence, 0.0561 expected incidence compared to 0.0735 predicted in the no screening cohort. This over-estimation is not due to problems with model prediction, but due to the method of estimating incidence of tuberculosis in the different Markov states explained in detail in section 3.7.2. Table 11 demonstrates the expected five year incidence of tuberculosis disease compared to the model-obtained incidence of tuberculosis disease and demonstrates that the model is accurately predicting the tuberculosis incidence in the normal chest radiography cohort, untreated inactive pulmonary tuberculosis cohort, and treated inactive pulmonary tuberculosis cohort. Given concerns with the methods of

estimating tuberculosis incidence, extensive sensitivity analyses were performed with this variable.

Retreatment tuberculosis incidence was also estimated in this model. The predicted 20 year incidence of retreatment tuberculosis in Cape Town is 0.0286. In the no screening group the 20 year incidence of retreatment tuberculosis was 0.0112. The incidence of re-treatment tuberculosis should be significantly lower in this model cohort than in the general Cape Town population as all individuals with previous tuberculosis were excluded from the model process as the screening programme was designed to detect individuals without previous treatment who would experience benefit from treatment of inactive pulmonary tuberculosis. Therefore, the twenty year incidence of retreatment tuberculosis in the model cohort is felt to be an accurate estimate.

4.2 Base Case Analysis

In the base case analysis, the screening and treatment programme for inactive pulmonary tuberculosis in South Africa was associated with additional clinical benefit at an additional cost compared to a do nothing comparator. The incremental cost utility ratio (ICUR) for a chest x-ray screening programme to detect and treat inactive pulmonary tuberculosis in South Africa was 31,043 Rand (5,131 Canadian dollars) per QALY gained (Table 12). The incremental cost-effectiveness ratio (ICER) of the proposed programme was 17,384 Rand (2,873 Canadian dollars) per case of tuberculosis prevented (Table 16).

4.3 Sensitivity analysis

Results of one-way sensitivity analyses are shown in Table 12 and Table 13. The model results were sensitive to clinically plausible variations in the prevalence of inactive pulmonary tuberculosis, the incidence of tuberculosis disease development, the costs of screening, and the discount rate of the utility measurements.

4.3.1 Screening

The model was sensitive to variations in the estimated compliance of the proposed screening programme. With a 50% compliance rate the incremental cost utility ratio was 39,015 Rand (6,448 Canadian dollars) per QALY gained. The best case of 100% compliance with this programme resulted in an incremental cost utility ratio of 26,900 Rand (4,446 Canadian dollars) per QALY gained. Individuals who were selected for screening but were not compliant with chest radiography still cost the proposed screening programme money due to the costs of identification and contacting of these individuals. However, these individuals did not obtain any of the benefit of the programme. Therefore, as compliance increased, the ICUR of the programme increased as well.

The model was sensitive to estimates of the prevalence of inactive pulmonary tuberculosis detected on chest x-ray. The incremental cost per QALY gained significantly decreases as the prevalence of inactive pulmonary tuberculosis increases. With a prevalence estimate for inactive pulmonary tuberculosis of 0.132, the ICUR decreases to 13,683 Rand (2,261 Canadian dollars) per QALY gained.

The result of this model was sensitive to the varying estimates of the diagnostic accuracy of chest x-ray for inactive pulmonary tuberculosis. When tuberculin skin test was used as the gold standard of including or excluding underlying tuberculosis infection, the incremental cost per QALY gained of the screening programme increased as the positive predictive value decreased to a high of 42,499 Rand (7,025 Canadian dollars).

The model was insensitive to published ranges of the sensitivity and specificity of a single sputum smear and culture results, the ICUR ranged from 30,611 to 31,493 Rand per QALY gained.[52-55]

The results of this model were sensitive to estimates of the cost of the chest x-ray screening programme to detect inactive pulmonary tuberculosis. Specifically, using costing information from a clinic performing assessments for commencement of isoniazid preventive treatment in HIV positive individuals decreased the ICUR of performing screening to 13,130 Rand (2,170 Canadian dollars) per QALY gained. Costing information used from the Lung Health Survey may have overestimated the costs of a screening programme even with the exclusion of direct research costs, as personnel costs were significant given the extensive questionnaire data that was completed in this survey.[48, 49]

4.3.2 Estimation of tuberculosis incidence

The ICUR result in this model was sensitive to estimates of tuberculosis incidence. Utilizing the high incidence estimate of tuberculosis disease development in those with

inactive pulmonary tuberculosis the ICUR of the screening and treatment programme for inactive pulmonary tuberculosis decreased to 16,182 Rand (2,785 Canadian dollars) per QALY gained. With the low incidence estimate of tuberculosis disease (excluding 50 % of patients with presumed HIV co-infection) the ICUR increases to 49,018 Rand (8,102 Canadian dollars) per QALY gained.

4.3.3 Treatment of inactive pulmonary tuberculosis

4.3.3.1 Effectiveness of treatment of inactive pulmonary tuberculosis

Varying the estimate of the effectiveness of treatment of inactive pulmonary tuberculosis from published results in the literature did not significantly affect the ICUR of chest x-ray screening, the ICUR ranged from 28,132 Rand to 32,646 Rand (4,650 Canadian dollars to 5,396 Canadian dollars) per QALY gained.[3-17] Adjusting effectiveness based on isoniazid resistance in the Western Cape in 2001 minimally impacted the results, the ICUR slightly increased to 33,345 Rand (5,512 Canadian dollars) per QALY gained.

However, if we consider the role of reactivation of previous disease compared to reinfection as discussed in section 3.9.1.2.2, the chest x-ray screening and treatment programme for inactive pulmonary tuberculosis becomes much less economically attractive.[95]Assuming that tuberculosis cases that develop in inactive pulmonary tuberculosis are due to reactivation only 25% of the time significantly increased the incremental cost per QALY gained to 51,821 Rand (8,566 Canadian dollars). However, studies performed in North America in very high tuberculosis incidence communities showed the same effectiveness of treatment of inactive pulmonary tuberculosis as those

performed in low tuberculosis incidence communities suggesting that reactivation is still the predominant cause of tuberculosis disease in inactive pulmonary tuberculosis even during times of high rates of reinfection.[11-13]

4.3.3.2 Cost of treatment of inactive pulmonary tuberculosis

The ICUR was minimally affected by the reported costs of isoniazid preventive treatment of inactive pulmonary tuberculosis ranging from 29,371 to 31,127 Rand (4,855 to 5,145 Canadian dollars) per QALY gained.[46]

4.3.3.3 Hepatitis Risks

Utilizing the published ranges of the risk of hepatitis and fatal hepatitis in individuals with inactive pulmonary tuberculosis treated with isoniazid without routine liver enzyme monitoring did not change the results of this model significantly. The ICUR ranged from 30,779 Rand (5,087 Canadian dollars) to 31,624 Rand (5,227 Canadian dollars) per QALY gained.

4.3.4 Treatment of active tuberculosis

4.3.4.1 Tuberculosis outcomes

In one way sensitivity analysis, the success rate of new pulmonary tuberculosis and retreatment tuberculosis in the reported ranges for Cape Town 2002 did not significantly affect the results of the cost-utility analysis (Table 12).

Tuberculosis case fatality estimates were shown in other cost effectiveness analyses on inactive pulmonary tuberculosis treatment to significantly impact the results of the model.[17-21] The higher the tuberculosis case fatality rates the more economically attractive the screening and treatment program for inactive pulmonary tuberculosis becomes. The fatality results provided in the Cape Town report are thought to represent an underestimate of fatality due to tuberculosis.[56] A large proportion of people (0.116) prescribed treatment for active tuberculosis disease in Cape Town in 2001 stopped their treatment (treatment interrupters) and outcomes are not known for this group of individuals.[56] In the base case analysis, treatment interrupters were excluded from the estimation of tuberculosis treatment failures, tuberculosis case fatalities, and successful outcome.[56] However, if it assumed that all treatment interrupters are lost to follow-up due to death, as suggested in the report, the tuberculosis case fatality rate increase from 0.044 to 0.179 in new cases and from 0.068 to 0.306 in retreatment cases. Utilizing these case fatality rates, the ICUR is significantly reduced to 9,511 Rand (1,572 Canadian dollars) per QALY gained.

4.3.4.2 Tuberculosis costs

The cost of outpatient and inpatient tuberculosis care was varied in the ranges reported in the literature for South Africa with minimal effect in the results (Table 13).[89,91,93,97-99,101] Given the lack of tuberculosis patient-specific costs in hospital, inpatient patient-specific costs were varied in the analysis by 50%. This large range of patient specific costs did not affect the findings of this analysis significantly, ICUR ranged from 30,599 Rand to 31,461 Rand per QALY gained. However, the model was sensitive to variations in

hospital admission rates. The higher the rate of hospital admission for treatment of tuberculosis disease, the more economically attractive the screening programme becomes.

4.3.5 Utility estimates

Estimates of the utility of isoniazid hepatitis within the reported ranges in the literature had minimal impact on ICUR calculated in this model.

The utility of tuberculosis disease detected through a screening programme was estimated as described in section 3.7.3.2. Using the estimated utility for tuberculosis disease detected in a screening programme and using the utility of tuberculosis disease without adjustment in the screening arm of the model did not impact the findings of this study.

The results of this model were sensitive to variation in the utility estimates of tuberculosis disease in the ranges reported in the literature and this is further discussed in section 4.4.5.

Higher utility estimates for individuals taking isoniazid treatment for inactive pulmonary tuberculosis (utility of 1 instead of 0.93) resulted in a decrease of the ICUR to 22,688 Rand (3,750 Canadian dollars) per QALY gained. Previous economic analyses on treatment of inactive pulmonary tuberculosis used a utility score of 1 for individuals on treatment for inactive pulmonary tuberculosis in the absence of the development of hepatitis. Therefore, when comparing the results of this study to the previous analyses,

an ICUR of 22,688 Rand (3,750 Canadian dollars) per QALY gained is the more appropriate comparator.

The model was very sensitive to the discounting of QALYs. A screening and treatment programme of inactive pulmonary tuberculosis results in an upfront decrease in QALYs due to the immediate treatment of inactive pulmonary tuberculosis and an increase in QALYs in the future as tuberculosis disease is prevented. Thus, it is not surprising if QALYs are not discounted the screening programme is more economically attractive. If no discounting is considered for QALYs, the ICUR of this programme is 11,737 Rand (1,940 Canadian dollars) per QALY gained.

Discounting of costs had a less significant effect on the ICUR in this model, 22,085 Rand (0%) to 33,010 Rand (8%). Most of the costs are the upfront costs of screening and treatment of inactive pulmonary tuberculosis, thus cost discounting did not affect the ICUR to the same magnitude as discounting the outcomes.

4.4 Scenario analysis

Results from scenario analysis are presented in Table 14 and Table 15. A tornado diagram of relevant scenario analyses is presented in Figure 4.

4.4.1 Screening

Screening costs in this model significantly impacted the economic attractiveness of the proposed screening and treatment programme for inactive pulmonary tuberculosis.

Assuming all of the high cost estimates for screening resulted in an increase in the ICUR to 41,476 Rand (6,856 Canadian dollars) per QALY gained. Assuming all of the low costs estimates for screening decreased the ICUR to 16,730 Rand (2,765 Canadian dollars) per QALY gained. Given the large impact of screening costs on the ICUR of this proposed programme, an alternative screening method, specifically miniature chest radiography, was considered.

4.4.1.1 Miniature chest radiography

Miniature chest radiography has been used in several tuberculosis prevalence studies and for active case finding in high risk groups due to its decreased cost and ease of use compared to conventional radiography.[41,103,109] If it is assumed that miniature chest radiography is as sensitive as conventional radiography, and that individuals with abnormal miniature chest films have a conventional chest x-ray performed to confirm the diagnosis of inactive pulmonary tuberculosis, the use of miniature chest x-rays in the initial screening process was found to decrease the ICUR to 9,337 Rand (1,543 Canadian dollars) per QALY gained. Utilizing the published sensitivity and specificity of miniature chest radiography to calculate the negative predictive value of a normal miniature chest radiograph minimally impacted the result.

4.4.1.2 Number of sputum assessments

The performance of two sputum smears and cultures compared to one sputum smear and culture increases the sensitivity of the test to detect active pulmonary tuberculosis from 87% to 94%.[52-55] In a scenario analysis, the use of two sputum smears and cultures in

individuals with abnormal chest x-rays improved the ICUR slightly to 30,990 Rand (5,123 Canadian dollars) per QALY gained.

4.4.1.3 Tuberculin skin testing

A scenario analysis was performed examining the effect of performing tuberculin skin testing (TST) on those individuals found to have chest x-rays consistent with inactive pulmonary tuberculosis and negative sputum assessments. If it is assumed that the TST test is the gold standard of *M. tuberculosis* infection (and not the chest x-ray), and treatment of inactive pulmonary tuberculosis is not provided to those with a negative tuberculin skin test, the ICUR of this proposed programme slightly increased to 33,613 Rand (5,556 Canadian dollars) per QALY gained with the five mm TST criteria and 33,946 Rand (5,610 Canadian dollars) per QALY gained with ten mm TST criteria. Using the calculated PPV and NPV of tuberculin skin testing minimally changed the above results, ICUR of 33,639 Rand per QALY in the five mm TST criteria and 34,775 Rand per QALY for the 10 mm criteria (Table 14).

4.4.2 Isoniazid hepatitis and routine liver enzyme monitoring

In North America, individuals prescribed preventive treatment with isoniazid are routinely monitored for the development of hepatitis with liver enzyme assessments.[23,24,58] Modeling routine liver enzyme monitoring in individuals treated for inactive pulmonary tuberculosis in this scenario analysis did not significantly affect the ICUR, 32,076 Rand (5,301 Canadian dollars) per QALY gained. Increased isoniazid treatment costs due to liver enzyme testing appeared to be offset by the decreased rate of

hepatitis case fatality in this model. Previous studies on isoniazid preventive therapy have shown that varying the risks of hepatitis and fatal hepatitis did impact the results of decision analysis models.[65] One possible difference between this analysis and previously performed analyses on treatment of latent tuberculosis infection is the relative number of people who develop isoniazid hepatitis compared to the number of individuals who are assessed in the model. In this model, many individuals are screened compared to much smaller numbers of individuals with inactive pulmonary tuberculosis starting on treatment and the very few developing hepatitis. In previous treatment studies that have not assessed the number needed to screen to detect an individual to start on treatment for latent tuberculosis, the relative number of individuals developing hepatitis is much higher and may be the reason for the significant effect of hepatitis and hepatitis fatality rates on the cost-effectiveness of the intervention.[65]

4.4.3 Tuberculosis outcomes

New pulmonary tuberculosis cases were modeled in the base case analysis as most studies monitored for pulmonary tuberculosis.[1-21] A scenario analyses examined the effect of development of all forms tuberculosis. If treatment for inactive tuberculosis is presumed to decrease the incidence of all forms of tuberculosis disease and the case fatality rate for all cases of tuberculosis disease is used (0.074) the ICUR for screening is significantly reduced to 15,330 Rand (2,533 Canadian dollars) per QALY gained.

Inappropriate isoniazid preventive treatment of active tuberculosis was reassessed in a worst case analysis assuming all these individuals had to be retreated for tuberculosis. This scenario analysis did not impact the ICUR.

Differing modeling scenarios for managing individuals who failed tuberculosis retreatment minimally impacted the ICUR. Assuming all retreatment failures died decreased the ICUR to 27,543 Rand (4,553 Canadian dollars) per QALY gained. Assuming all retreatment failures were eventually cured and returned to health increased the ICUR to 33,427 Rand (5,525 Canadian dollars) per QALY gained. Not surprisingly, the worse the outcome is for retreatment tuberculosis, the more economically attractive it is to prevent disease.

4.4.4 Tuberculosis treatment costs

An expensive tuberculosis treatment regimen and a low cost treatment regimen for treatment of tuberculosis were assessed using the range of reported South African costs for tuberculosis treatment and maintaining the hospitalization rate at 10%. The ICUR per QALY gained, ranged from 26,800 Rand (4,430 Canadian dollars) per QALY gained for the high treatment costs to 35,802 Rand (5,918 Canadian dollars) per QALY gained for the low treatment costs. The model is robust across a worst and best case scenario for tuberculosis treatment costs in Cape Town.

4.4.5 Utility measurement

Variations in the estimated utility of tuberculosis disease and treatment for inactive pulmonary tuberculosis impacted the ICUR of the proposed screening and treatment programme for inactive pulmonary tuberculosis significantly. The base case analysis utilized a utility of tuberculosis disease of 0.66, a utility obtained directly using the time trade off method and also reported from a physician survey.[78,79] A utility of 0.93 was utilized for individuals with inactive pulmonary tuberculosis on isoniazid preventive treatment.[78] In Table 13, the ICUR is shown to significantly vary in one way sensitivity analysis using the high and low estimates of utility in tuberculosis disease from the literature, from 24,073 Rand (3,979 Canadian dollars) per QALY gained to 46,392 Rand (7,668 Canadian dollars).[17,21,67,70,72,78-83] However, assuming all of the low utility measures reported in the literature or all of the high utility measures reported in the literature in scenario analyses resulted in improved economic attractiveness of the programme, 24,090 to 29,897 Rand per QALY gained.

The difference between the sensitivity and scenario analyses is likely due to the relative differences in utility measurements of individuals treated for inactive pulmonary tuberculosis versus those treated for tuberculosis. When the high estimates of tuberculosis disease were used in a sensitivity analyses, the utility of tuberculosis disease was 0.9 and the utility of those treated for inactive pulmonary tuberculosis was 0.93. However, in the scenario analyses when all high utilities were considered, the utility of tuberculosis disease was 0.9 and the utility of those on treatment for inactive pulmonary tuberculosis was 1. These analyses demonstrate that this model is sensitive to the relative utilities of tuberculosis disease and those treated for inactive pulmonary tuberculosis.

An additional scenario analysis examined the effect of using different utility estimates for patients with tuberculosis disease treated as an in-patient or as an out-patient.[17,21,67,70,72,78-83] The ICUR of the proposed screening and treatment programme increased with this method to 39,589 Rand (6,544 Canadian dollars) per QALY gained. When the inpatient and outpatient utility scores were varied based on utility ranges reported in the literature, the ICUR of the programme changed significantly from 29,532 Rand (4,881 Canadian dollars) to 50,089 Rand (8,279 Canadian dollars) per QALY gained.

4.4.6 Societal costing

A scenario analysis was performed that assessed the chest x-ray and screening programme for inactive tuberculosis from a societal perspective and is described in section 3.9.2.5. The inclusion of indirect costing had minimal impact on the ICUR ranging from 30,937 Rand (5,114 Canadian dollars) to 33,093 Rand (5,470 Canadian dollars) per QALY gained. The productivity gains from preventing cases of tuberculosis appeared to be offset by the productivity loses due to missed work in those who presented for chest x-ray screening.

4.4.7 Estimation of secondary tuberculosis cases

The inclusion of development of secondary cases of tuberculosis disease from infectious tuberculosis cases significantly impacted the findings of this decision analysis. When secondary case development is considered the incremental cost per QALY saved by the chest x-ray screening and treatment program is 11,870 Rand (1,962 Canadian dollars).

Discounting of secondary cases of tuberculosis disease influenced the ICUR. Individuals who develop tuberculosis disease after exposure to an infectious case may do so immediately or anytime during their lifetime. The original assumption in this scenario analyses is that fifty percent of secondary cases of tuberculosis disease will develop within two years and the rest of individuals will develop disease ten years after their exposure. If the time to development of secondary cases of tuberculosis disease is increased the ICUR also increases (Table 13). If fifty percent of cases occur 20 years after individuals are infected, the ICUR of the screening programme increases to 13,777 Rand (2,277 Canadian dollars) per QALY gained.

4.4.7.1 Secondary tuberculosis cases and HIV infection

HIV positive individuals develop tuberculosis disease at a rate of 6.7% per annum after infection with *M. tuberculosis* compared to the 10% lifetime risk of developing tuberculosis disease in immunocompetent individuals.[23] In this scenario analysis it was assumed that 10% of contacts of pulmonary cases of tuberculosis are infected with HIV with the secondary case rate for HIV positive individuals estimated as described in section 3.9.7.2.1. With the consideration of a 10% background prevalence of HIV in contacts, and calculating secondary tuberculosis case development, the ICUR decreases from 11,870 Rand (1,962 Canadian dollars) to 8,958 Rand (1,480 dollars) per QALY gained.

4.4.8 Subgroup analysis with age categorizations

A scenario analysis was performed with different age groups selected for chest x-ray screening and treatment of inactive pulmonary tuberculosis. Individuals were grouped into three age categories: 15-34 years of age, 35-54 years of age, and those greater than 55. Results of the subgroup analyses are shown in Table 15 and Figure 4. Age specific fatality rates are not currently available for pulmonary cases of tuberculosis so the base assessment utilized the incidence and case fatality for all forms of tuberculosis disease. Therefore, the ICUR reported in the subgroup analyses should be compared to the ICUR of all cases of tuberculosis disease 15,381 Rand (2,542 Canadian dollars) per QALY gained.

Individuals 15 to 34 years of age had an increased ICUR of 24,281 Rand (4,013 Canadian dollars) compared to the above described ICUR of 15,381 Rand per QALY gained. Individuals 15 to 34 years of age differed from individuals 35 years of age and older on several measures that have been shown in one way sensitivity analyses to impact the ICUR in this model. Individuals 15 to 34 years of age had lower compliance of chest x-ray screening (0.713), lower prevalence of abnormal chest x-rays (0.042), high rates of active pulmonary disease (0.303) and lower case fatality rates (0.043) than individuals 35 years and older.

The ICUR for a screening and treatment programme for individuals 35 to 54 years of age with inactive pulmonary tuberculosis was found to be 14,866 Rand (2,457 Canadian dollars) per QALY gained and in those over the age of 54 years was 13,070 Rand (2,160 Canadian dollars) per QALY gained.

Chapter 5: Discussion

5.1 Willingness-to-Pay

This study has shown that a chest x-ray screening programme designed to detect and treat individuals with inactive pulmonary tuberculosis would improve the quality-of-life of this cohort of individuals and prevent cases of tuberculosis but at an expense to the South African public health system. The proposed chest x-ray screening and treatment programme for inactive pulmonary tuberculosis for this cohort would cost 31,043 Rand (5,131 Canadian dollars) per QALY obtained and 17,384 Rand (2,873 Canadian dollars) per case of tuberculosis prevented. At the current time, the South African government does not have a policy on the maximum willingness-to-pay for a health intervention.[110] In Canada, it is suggested that the evidence for supporting a new health intervention is strong if the ICUR is less than 20,000 Canadian dollars per QALY gained.[111,112] Thus, the proposed chest x-ray and screening programme for inactive pulmonary tuberculosis would be considered a reasonable intervention to support in Canada at a cost of 31,043 Rand (5,131 Canadian dollars) per QALY gained.

However, the willingness-to-pay threshold for a public health system in a middle income country such as South African is likely to be lower than that of a high income country such as Canada. The World Health Organization has suggested a willingness-to-pay threshold for funding new health interventions in low income countries of three times the Gross Domestic Product (GDP) per capita per DALY gained.[113] Using this recommendation, a possible willingness-to-pay threshold for the South African public

health system would be 62,238 Rand (10,287 Canadian dollars) per DALY gained (based on a GDP per capita of 20,746 Rand in South Africa in 2004).[110,113] While this willingness-to-pay threshold uses a different quality of life measure (DALY) than this study (QALY), it would appear that the proposed screening programme would cost less under all sensitivity and scenario analyses than this willingness-to-pay threshold. However, it has been suggested that this method of determining willingness-to-pay thresholds may overestimate a reasonable willingness-to-pay threshold in middle and high income countries.[111] Using Canada as an example, the GDP per capita was 38,000 Canadian dollars in 2003 leading to a willingness-to-pay estimate of 114,000 Canadian dollars per DALY.[111-114] This willingness-to-pay threshold is higher than other estimates currently suggested as appropriate in Canada.[111,112]

Another way of estimating the South African Government's willingness-to-pay threshold for new health interventions would be to examine the incremental costs of new health programmes recently introduced in the public health system and assume that those costs are acceptable. Isoniazid preventive therapy for HIV positive individuals has recently been introduced as an economically feasible way of preventing tuberculosis in South Africa.[26] The upper estimate of the ICER of this programme in South Africa is 7,000 Rand (1,157 Canadian dollars) per case of tuberculosis prevented.[35,46] ARV treatment for HIV positive individuals has also been recently introduced in the public health system of South Africa. The cost of this programme is estimated to be 14,000 Rand (2,314 Canadian dollars) per QALY gained.[91] Therefore, a willingness-to-pay threshold of the South African government will be estimated to be 7,000 Rand (1,157 Canadian dollars)

per case of tuberculosis prevented and 14,000 Rand (2,314 Canadian dollars) per QALY gained. The incremental costs of this proposed chest x-ray screening and treatment programme for inactive pulmonary tuberculosis will be compared to these presumed willingness-to-pay thresholds of the South African public health system.

5.1.1 Screening costs

Screening costs were shown to significantly impact the incremental cost-utility and cost-effectiveness of the proposed chest x-ray screening and treatment of inactive pulmonary tuberculosis control programme in sensitivity and scenario analyses. In order to screen all individuals in this urban district in Cape Town for inactive pulmonary tuberculosis and meet the willingness-to-pay criteria outlined above, screening costs would have to be as low as 50 to 60 Rand (8 to 10 Canadian dollars) per person.

Using conventional chest radiography, the lowest cost estimate for the performance and interpretation of a chest film is 71 Rand (11.74 Canadian dollars) per person.[86] This cost is higher than the willingness-to-pay limit of 50 to 60 Rand for total screening costs. An alternative to conventional radiography is mass miniature chest radiography.[37,41,103] Mass miniature chest radiography has been used in several tuberculosis prevalence surveys and for active tuberculosis case finding.[23,37,41] Mass miniature chest radiography is less expensive than conventional radiography as more images are placed per cassette and is also quicker to perform as cassettes do not have to be reloaded between patients.[115] A recent study examined the cost-effectiveness of miniature chest x-ray screening for detection of active pulmonary tuberculosis in jails in the United States.[41] The cost of

screening with miniature chest radiography in this setting was 6.60 US dollars (50.57 Rand) per person screened.[41] Using miniature chest x-ray screening instead of conventional radiography was assessed in a scenario analysis. With miniature chest radiography the cost to prevent a case of tuberculosis was 4,446 Rand (734 Canadian dollars) and 8,013 Rand (1,324 Canadian dollars) per QALY gained. These estimates would fall within the proposed willingness-to-pay thresholds outlined above. However, the cost of miniature chest radiography in this US based prison study may not be the same in this South African community setting.[41] In addition, the cost per person for miniature chest x-ray screening was based on performing 150 chest films per day.[41] Miniature chest radiography also requires the purchase of new equipment as opposed to utilizing radiography equipment already available. This capital outlay would not be appropriate if a large population is not recurrently sampled or additional cohorts of individuals are not selected for screening.

5.1.2 Age restriction of screening

Sensitivity and scenario analyses suggest that certain populations in the study cohort would be more economically attractive to screen and treat for inactive pulmonary tuberculosis. A cohort with a high prevalence of inactive pulmonary tuberculosis, high hospitalization rates, and high case fatality rates would seem to be the best group for targeted screening. In this urban area of Cape Town, individuals over 54 years of age most closely met these characteristics and chest screening and treatment of inactive pulmonary tuberculosis was found to cost 13,070 Rand (2,160 Canadian dollars) per QALY in this cohort.

Screening individuals 35 to 54 years of age was also economically attractive with an ICUR of 14,866 Rand (2,457 Canadian dollars) per QALY, close to the proposed willingness-to pay threshold. Screening individuals aged 15 to 34 years of age with conventional radiography always exceeded the willingness to pay threshold, an ICUR of 24,281 Rand (4,013 Canadian dollars) per QALY gained. This group of individuals had low prevalence of chest x-ray abnormalities consistent with inactive pulmonary tuberculosis (0.0442) and high rates of active pulmonary disease (0.303). Thus, the screening programme in this cohort was behaving almost like an active case finding chest x-ray screening programme, detecting prevalent cases of active pulmonary tuberculosis.

Previous prevention studies for individuals with tuberculosis infection documented by positive tuberculin skin testing have shown that younger individuals should be targeted given their lower rates of hepatitis and fatal hepatitis.[57-72] However, as this study shows, it may be more cost-effective for preventive tuberculosis programmes to target an older population, with a higher prevalence of inactive pulmonary tuberculosis, and much higher tuberculosis case fatality rates. Age specific tuberculosis control programmes have been previously proposed in South Africa. A recent study has suggested that individuals over 50 years of age represent a key source of tuberculosis transmission and should be targeted for intensified case finding.[116,117]

5.1.3 Economic feasibility

If a new programme is instituted that involves a net cost to the public health system, it must be determined if there are funds available to pay for the programme. Even though the proposed screening and treatment programme of inactive pulmonary tuberculosis is economically attractive in some scenarios, if there are no funds available for new programmes in the South African NTP then the programme cannot be funded.

In order to assess the economic feasibility of a chest x-ray and screening programme for inactive pulmonary tuberculosis, it would be useful to understand the upfront costs of establishing this programme. With this screening programme, the costs to the system occur at the start of the programme (screening costs and treatment costs for inactive pulmonary tuberculosis) with the benefits (decreased incidence of tuberculosis disease) occurring in the future. If miniature chest radiography was used to screen the entire cohort sampled in the Lung Health study (36,334 individuals) and it costs 97 Rand per person in the first 6 months to screen, treat inactive pulmonary tuberculosis and treat active pulmonary tuberculosis, the total resources spent in the first 6 months would be 3,524,398 Rand (582,545 Canadian dollars).[48,49] This money would need to be diverted from other tuberculosis control programmes or additional funding would need to be obtained from the public health system. Alternatively, this money could be raised from outside funders if not thought feasible to provide within the health care budget. A programme that targeted those 55 years of age and older with conventional radiography would cost 195 Rand per person during the first 6 months of the programme initiation and would target approximately 5,332 individuals in this community, costing 1,039,736 Rand (171,857 Canadian dollars).[48,49,57] The most economically feasible programme

would be to screen those 55 years of age and older with miniature chest radiography, the 6 month initial cost to the system would be 517,304 Rand (85,488 Canadian dollars).

5.2 Comparison to CEAs for treatment of inactive pulmonary tuberculosis

This study found that the incremental cost effectiveness of introducing a chest x-ray screening and treatment programme to detect and treat individuals with inactive pulmonary tuberculosis was 31,043 Rand per QALY saved and 17,384 Rand per case of tuberculosis prevented. This proposed tuberculosis control programme in South Africa was not found to be cost-saving. Two previous studies in the United States had shown that treatment of inactive pulmonary tuberculosis was cost-saving.[18,21] The major differences between these studies and this cost-effectiveness analysis are the hospitalization rates and the cost of hospitalization for patients diagnosed with tuberculosis.[18,21] Sensitivity analysis in this study demonstrated that as hospitalization rates increased for tuberculosis patients, the incremental cost utility and cost-effectiveness of the screening intervention improved. The cost of hospitalization and treatment of patients with tuberculosis disease is ten times higher in the United States than the highest cost estimate in South Africa.[89,93,97,98,100] The hospitalization rates of tuberculosis patients in the above two studies ranged from 0.5 to 0.6 compared to an estimated hospitalization rate of 0.1 in South Africa.[18,21,92] If the same hospitalization costs and rates of hospitalization are assumed in this decision analysis model as in these two US studies, chest x-ray screening and treatment of inactive pulmonary tuberculosis is also shown to be cost saving (Table 12).

A cost-effectiveness analysis performed in Canada examined the costs and benefits of treating individuals with inactive pulmonary tuberculosis from sub-Saharan Africa identified through immigration chest x-ray screening.[19] The ICER of treating this cohort was 23,855 Rand (3,943 Canadian dollars) per case of tuberculosis prevented. This result is similar to the ICER found in this study of 17,384 Rand (2,873 Canadian dollars) per case of tuberculosis prevented. [19]

A significant difference of the studies mentioned above to this decision analysis was that the total cost of detecting individuals with inactive pulmonary tuberculosis was not included in the above analyses.[18,19,21] The Canadian study included the cost of chest x-ray assessments but did not include the cost of managing the immigration process to detect active cases of pulmonary disease. This analysis has demonstrated that the cost of screening was a major contributor to the relative cost-effectiveness of the proposed screening and treatment programme

The only study that examined the total screening costs and the cost of treating inactive pulmonary was a study performed in Canada that examined the incremental cost-effectiveness of three different programmes for prevention of tuberculosis disease in immigrants.[20] This study showed that the additional treatment of inactive pulmonary tuberculosis detected on the immigration chest x-ray screening was cost-saving when the immigration screening process was designed to detect active cases (marginal cost of providing preventive isoniazid treatment).[20] In other words, with active case finding already being performed with a chest x-ray screening programme the additional cost to

provide treatment for inactive pulmonary tuberculosis resulted in net cost savings to the tuberculosis programme.[20] This is a different question than the question posed in this study where the purpose of chest x-ray screening is to detect inactive pulmonary tuberculosis for preventive treatment as well as treating active cases found with screening.

5.3 Strengths and Weaknesses of this study

5.3.1 Strengths

One strength of this study is that it is specifically designed to assess the cost-effectiveness of a screening and treatment programme for individuals with inactive pulmonary tuberculosis in Africa. All the costs of screening, diagnosing, and treating inactive pulmonary tuberculosis are included in this decision analysis compared to other studies that did not include the screening costs to detect inactive pulmonary tuberculosis.[19,21]

Another strength of this study is that the prevalence of inactive and active pulmonary tuberculosis is obtained from a large epidemiologic survey of tuberculosis disease that has been recently been performed in Cape Town. This data provides current information on inactive pulmonary disease in this cohort.

This decision analysis followed the Canadian guidelines for the performance of economic evaluation.[31] A reasonable comparator was used in this assessment, current treatment of inactive pulmonary tuberculosis. The results are presented as incremental cost-utility and cost-effectiveness ratios.

The decision analysis model built to assess the costs and benefits of a chest x-ray screening and treatment programme for inactive pulmonary tuberculosis had reasonable face and predictive validity.

5.3.2 Weaknesses

One important weakness of this study was that the impact of HIV co-infection on inactive pulmonary tuberculosis could not be directly modeled as HIV incidence in those with inactive pulmonary tuberculosis was not assessed in the Lung Health Survey.[48,49]

Another important limitation in this decision analysis model are the estimations required for the incidence of tuberculosis disease development in individuals with inactive pulmonary tuberculosis disease in Africa. Multiple sensitivity analyses were performed with this variable to have an understanding of the impact of these estimations. Varying the incidence of tuberculosis disease development within reasonable estimates from the literature significantly impacted the reported ICUR from a low of 16,182 Rand (2,675 Canadian dollars) to high of 49,018 Rand (8,102 Canadian dollars) per QALY. A difference in the reported ICUR of this degree may impact decision makers in their willingness-to-pay for this intervention.

In addition, direct hospital costing data and hospital admission rates for patients with tuberculosis disease is currently unavailable in the cohort of individuals studied in the Lung Health Survey.[48,49] If hospital costs or admission rates in this cohort are

significantly different than the reported outcomes in Cape Town and South Africa, the results of this study may be incorrect.

Age-stratified cohort-specific tuberculosis outcomes are not currently available and as such estimations from Cape Town were used. If the outcomes differ significantly between the urban community studied and results for Cape Town, the results reported in this analysis may be inaccurate.

5.4 Uncertainty and further study

Some of the weakness in this economic analysis could be addressed by further study into key missing variables of interest and are discussed below.

5.4.1 Disease incidence in inactive pulmonary tuberculosis

Without long-term epidemiologic studies on the development of disease in individuals with inactive pulmonary tuberculosis in South Africa better incidence estimates than those calculated utilizing previous large studies outside of Africa will be unavailable.[1-16] With the increasing epidemic of tuberculosis in South Africa, and excellent large studies on inactive pulmonary tuberculosis in cohorts outside of Africa, do we need to repeat these epidemiologic and treatment studies in Africa before commencing a screening and treatment programme? During a previous epidemic in Alaska, with similar tuberculosis incidence rates as current rates in South Africa, research was performed in conjunction with active case finding and preventive treatment. Over nineteen years of follow-up a 60% reduction in tuberculosis disease development in those treated for inactive

pulmonary tuberculosis was demonstrated.[11-13] If a screening programme was commenced in different cohorts in South Africa, the budget should include money for operational research to help answer these questions.

5.4.2 Hospitalization Rates

Most cost-effectiveness analyses in tuberculosis have been shown to be sensitive to estimations of hospitalization rates of tuberculosis cases. Information regarding hospitalization of tuberculosis patients should be directly obtained in the cohorts considered for chest x-ray screening.

5.4.3 HIV incidence and effect on inactive pulmonary tuberculosis

HIV has a significant impact on the current tuberculosis epidemic in Africa.[25,26] It is estimated that 50% of the current tuberculosis cases in South Africa are HIV positive.[26,117] A limitation of this study was that HIV prevalence was not obtained in the Lung Health Survey.[48,49] If a significant proportion of individuals with abnormal chest x-rays consistent with inactive pulmonary tuberculosis are HIV positive they would be at very high risk of developing tuberculosis disease. Given their HIV positive status they would already be targeted for isoniazid preventive treatment thus decreasing the benefit obtained from this screening and treatment programme. However, if individuals with inactive pulmonary tuberculosis have low rates of HIV co-infection but there are high background rates of HIV disease in the community in which they reside, this cohort of individuals with inactive pulmonary tuberculosis may be the ideal group to target for screening. In this analysis, presuming an HIV prevalence of 10% in individuals exposed

to pulmonary cases of tuberculosis, and considering the development of secondary cases of tuberculosis, the ICUR decreased to 8,958 Rand (1,481 Canadian dollars) per QALY gained. Further chest x-ray prevalence studies in Africa should include HIV testing to determine the HIV status of individuals with inactive pulmonary tuberculosis.

5.4.4 Frequency of screening

This decision analysis was modeled on an immigration chest x-ray screening programme, as a one time intervention to detect all prevalent cases of inactive pulmonary tuberculosis in a population. In some countries, chest x-ray screening is performed yearly for active case screening to detect incident cases of disease. This study is unable to answer the question if repeat screening of a certain population is appropriate or how often that screening should take place as repeat radiography in this cohort was not performed.

Given the economic attractiveness of this programme in individuals 35 years of age and older, it may be most appropriate to consider screening a high risk group of individuals upon reaching a certain age. Further study of individuals 35 years of age and older may identity an optimal age to perform screening. The optimal age would have to have a high prevalence of inactive pulmonary tuberculosis, low rate of additional diagnosis on chest x-ray screening, and high hospitalization and case fatality rates due to tuberculosis disease to maximize the benefit of this programme.

In addition, the costs to investigate chest x-ray abnormalities other than tuberculous abnormalities should be assessed if age-specific screening is considered as the prevalence

of other lung conditions increase as people age. These costs were not determined in the Lung Health Survey and not included in this analysis.

5.4.5 Utility estimates

This study demonstrated that utility estimates for tuberculosis disease and treatment for latent tuberculosis infection impacts the cost-utility assessment of screening and treatment of inactive pulmonary tuberculosis. Utility estimates using time-trade off method of determining preference were used in the base case and estimate of treatment of latent infection was taken from a physician preference survey.[78,79] However, many other physician preference utility estimates have been utilized in cost-effectiveness analysis.[17,21,67,70,72,78-83] It would be useful to determine the preference of HIV-negative South Africans for tuberculosis disease and LTBI treatment to better estimate the economic attractiveness of treating inactive pulmonary tuberculosis in South Africa.

In addition, the utility score of individuals after treatment of tuberculosis has not been assessed in Africa. Individuals with tuberculosis disease can have long-term disability from their illness, such as bronchiectasis from pulmonary tuberculosis, cognitive impairment after tuberculous meningitis, and cardiac limitation after pericardial tuberculosis.[22] All individuals in this study are assumed to return to a baseline utility of one after their six months of acute treatment for tuberculosis. If a sensitivity analysis is performed using this model ranging the utility of individuals post tuberculosis disease treatment from 0.66 to 1, the ICUR changes significantly (Figure 5). Even within a narrow range of utilites post tuberculosis treatment of 0.9 to 1, the ICUR ranges from

22,454 Rand (3,711 Canadian dollars) to 31,043 Rand (5,131 Canadian dollars). Thus, if the long-term quality of life after tuberculosis treatment is over-estimated by assuming all people return to perfect health the full impact of tuberculosis control programmes may be underestimated. Therefore, it is suggested that utility estimates for individuals post tuberculosis treatment be assessed.

Chapter 6: Conclusion

The current tuberculosis programme in South Africa has not been effective at controlling the escalating tuberculosis epidemic in this country and additional tuberculosis control methods must be introduced. Decision makers in the South African public health system will need to decide which additional tuberculosis control programmes to introduce and fund. As the tuberculosis epidemic decreased in high income countries, certain tuberculosis control programmes, such as active case finding with mass miniature chest radiography, became less efficient given the lower prevalence of tuberculosis and thus were stopped.[118] With the increasing incidence of disease and high prevalence of inactive pulmonary tuberculosis in South Africa, chest x-ray screening and treatment of individuals with active and inactive pulmonary tuberculosis should be considered as one method of tuberculosis control. This study has demonstrated that population screening with conventional radiography would be too expensive for the South African NTP to fund for this entire South African cohort assuming willingness-to-pay thresholds of 7,000 Rand per case of tuberculosis prevented and 14,000 Rand per QALY saved. Using miniature chest radiography for screening and screening individuals greater than 35 years of age and older for inactive pulmonary tuberculosis was more economically attractive

and should be further assessed as a tuberculosis control method to decrease the significant morbidity and mortality of this disease in South Africa. Given the significant constraints in the health care budget of South Africa, the opportunity costs of funding this programme compared to other health care programmes must be considered.

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Appendix A: Tables

Table 1: Screening Assumptions

	Base-Case estimate	Range for Sensitivity Analysis		References
		Low Value	High Value	
Accept screen				Den Boon 2005 [48]
all ages >=15	0.745	0.5	1.0	Den Boon 2006 [49]
15-34	0.713			
35-54	0.761			
>=55	0.823			
Abnormal CXR consistent				Den Boon 2005 [48]
with inactive pulmonary TB				Den Boon 2006 [49]
all ages >=15	0.0679			Gatner 1980 [50]
15-34	0.0442	0.085	0.132	
35-54	0.0673			
>=55	0.1350			
Prevalence of TB infection in				Den Boon 2005 [48]
all people who performed				Den Boon 2006 [49]
chest x-rays				
TST>=5				
all ages >=15	0.788			
15-34	0.781			
35-54	0.863			
>=55	0.668			
TST>=10				
all ages	0.752			
15-34	0.746			
35-54	0.832			
>=55	0.620			
Sensitivity of CXR				Den Boon 2005 [48]
TST>=5mm				Den Boon 2006 [49]
all ages >=15	0.096		0.11	Swartzman 2000 [19]
15-34	0.050			
35-54	0.082			
>=55	0.157			
TST>=10mm				
all ages >=15	0.098		0.11	
15-34	0.051			
35-54	0.083			
>=55	0.155			
Specificity of CXR				Den Boon 2005 [48]
TST>=5mm				Den Boon 2006 [49]
all ages >=15	0.946			Swartzman 2000 [19]
15-34	0.984		0.975	
35-54	0.977			
>=55	0.919			
TST.>=10mm				
all ages >=15	0.942			
15-34	0.982		0.975	
35-54	0.972			
>=55	0.906			
PPV chest x-ray				Den Boon 2005 [48]
TST>=5mm				Den Boon 2006 [49]
all ages >=15	1	0.866	0.941	Swartzman 2000 [19]
15-34		0.918		
35-54		0.957		
>=55		0.796		
TST>=10mm				
all ages >=15	1	0.837	0.930	
15-34		0.892		
35-54		0.936		
>=55		0.729		

Prevalence of culture positive tuberculosis in those with abnormal chest x-rays				Den Boon 2005 [48] Den Boon 2006 [49] Gatner 1980 [50]
all ages >=15	0.153	0.128	0.138	
15-34	0.303			
35-54	0.132			
>=55	0.061			
Sensitivity of				Anderson 1995 [52]
1 sputum	0.87	0.84	0.9	Harvell 2000 [53]
2 sputum	0.94			Swartzman 2000 [19]
3 sputum	0.97			
Specificity of sputum culture	0.99	0.95	1	Anderson 1995 [52] Harvell 2000 [53] Swartzman 2000 [19]
NPV of				Anderson 1995 [52]
1 sputum	0.977	0.970	0.982	Harvell 2000 [53]
2 sputum	0.982			Swartzman 2000 [19]
3 sputum	0.995			Den Boon 2005 [48] Den Boon 2006 [49]
Compliance of TST testing in those with CXR consistent with inactive TB				Den Boon 2005 [48] Den Boon 2006 [49]
all ages >=15	0.81			
15-34	0.74			
35-54	0.87			
>=55	0.80			
Prevalence of tuberculosis infection in those with abnormal chest x-rays and negative sputum				Den Boon 2005 [48] Den Boon 2006 [49]
TST>=5mm		0.890		
15-34		0.937		
35-54		0.933		
>=55		0.826		
TST>=10mm		0.850		
15-34		0.875		
35-54		0.933		
>=55		0.783		
Sensitivity of TST testing				Swartzman 2000 [19] Porco 2006 [21]
5 mm	0.99	0.9	1	
10 mm	0.93	0.9	1	
Specificity of TST testing				Den Boon 2005 [48] Den Boon 2006 [49]
5 mm	0.750			
10 mm	0.875	0.5	1	

Table 2: Tuberculosis Incidence Cape Town 2001

	Base-Case estimate	**Range for Sensitivity Analysis** Low Value	High Value	**References**
Incidence of tuberculosis disease Cape Town 2001				City of Cape Town 2002[56]
all cases	0.00581			
all new cases	0.00451			
new pulmonary	0.00288			
re-treatment pulmonary	0.00145			
6 month incidence of tuberculosis				City of Cape Town 2002[56]
all cases	0.00291			
all new cases	0.00226			
new pulmonary	0.00144			
re-treatment pulmonary	0.00073			
% reduction in tuberculosis disease in those treated for LTBI at 5 years	65	60	75	IUAT 1982 [3]
Estimated incidence of new pulmonary TB 6 month assuming 6 times increase risk of TB disease in abnormal CXR and 65% effectiveness		Excluding HIV Cases	CXR stratification	City of Cape Town 2002[56] Canadian Tuberculosis Standards [23] IUAT 1982 [3]
normal CXR	0.00144	0.00054	0.00101	
inactive pulmonary TB	0.00869	0.00326	0.00660	
inactive pulmonary TB Rx	0.00296	0.00113	0.00227	
Estimated incidence of pulmonary TB disease 6 month assuming 13 times increase risk of TB disease in abnormal CXR and 65% effectiveness		Excluding HIV Cases	CXR stratification	City of Cape Town 2002[56] Canadian Tuberculosis Standards [23] IUAT 1982 [3]
normal CXR	0.00144	0.00040	0.00080	
inactive pulmonary TB	0.02039	0.00528	0.01080	
inactive pulmonary TB Rx	0.00672	0.00182	0.00367	
Estimated incidence of new tuberculosis 6 month assuming 6 times increase risk of TB disease in abnormal CXR and 65% effectiveness		Excluding HIV Cases	CXR stratification	City of Cape Town 2002[56] Canadian Tuberculosis Standards [23] IUAT 1982 [3]
normal CXR	0.00266	0.00084	0.00169	
inactive pulmonary TB	0.01349	0.00514	0.01053	
inactive pulmonary TB Rx	0.00479	0.00177	0.00357	
Isoniazid resistance rate	0.052			WHO resistance report 2004 [94]
Percentage of secondary case of tuberculosis due to re-activation	0.25			Van Rie 1999 [95]
Estimated incidence of TB disease 6 months, varying effectiveness of LTBI Rx				
from IUAT study	65%	60%	75%	IUAT 1982 [3]
inactive pulmonary TB Rx	0.00296	0.00339	0.00211	
utilizing resistance rates		0.052		WHO resistance report 2004 [94]
inactive pulmonary TB Rx		0.00357		
utilizing re-infection rates		0.25		Van Rie 1999 [95]
inactive pulmonary TB Rx		0.0071		

Estimated 6 month incidence of TB by age category CT 2001			City of Cape Town 2002[56] SA Health Survey 1998[108] WHO 2004 report [25]
All new cases			
15-34	0.00253		
35-54	0.00281		
>=55	0.00241		
Re-treatment cases			
15-34	0.00094		
35-54	0.00096		
>=55	0.00082		
Estimated incidence of new pulmonary TB 6 month assuming 6 times increase risk of TB disease in abnormal CXR and 65% effectiveness		CXR stratification	City of Cape Town 2002[56] SA Health Survey 1998[108] WHO 2004 report [25]
15-34			
normal CXR	0.0019 (0.00190)	0.00150	
inactive pulmonary TB	0.0119 (0.01210)	0.00929	
inactive pulmonary TB Rx	0.0040 (0.00409)	0.00316	
35-54			
normal CXR	0.00195 (0.0021)	0.00138	
inactive pulmonary TB	0.01220 (0.0132)	0.00857	
inactive pulmonary TB Rx	0.00412 (0.0045)	0.00292	
>=55			
normal CXR	0.00168 (0.0009)	0.00093	
inactive pulmonary TB	0.01050 (0.0056)	0.00567	
inactive pulmonary TB Rx	0.00360 (0.0019)	0.00196	

Table 3: Mortality Rates Cape Town 2001

	Base-Case estimate	**Range for Sensitivity Analysis** Low Value	High Value	**References**
Census in Cape Town 2001				Cape Town Mortality 2001[57]
all ages>=15	2,327,729			
15-24	600,437			
25-34	609,132			
35-44	469,235			
45-54	307,334			
55-64	184,964			
>=65	156,628			
Mortality in Cape Town				Cape Town Mortality 2001[57]
Total 12 month				
all ages>=15 (21341)	0.0092			
15-24 (1580)	0.0026			
25-34 (2696)	0.0044			
35-44 (2718)	0.0058			
45-54 (2804)	0.0091			
55-64 (3203)	0.0173			
>=65 (8340)	0.0532			
Total 6 month				
all ages>=15	0.0047			
15-24	0.0013			
25-34	0.0022			
35-44	0.0029			
45-54	0.0046			
55-64	0.0087			
>=65	0.0270			
Excluding TB 12 month				
all ages>=15 (20002)	0.0086			
15-24 (1480)	0.0025			
25-34 (2387)	0.0039			
35-44 (2371)	0.0051			
45-54 (2527)	0.0082			
55-64 (3017)	0.0163			
>=65 (8220)	0.0525			
Excluding TB 6 month				
all ages>=15	0.0043			
15-24	0.0013			
25-34	0.0020			
35-44	0.0026			
45-54	0.0041			
55-64	0.0082			
>=65	0.0266			

Table 4: Hepatitis Outcomes

	Base-Case estimate	**Range for Sensitivity Analysis** Low Value	High Value	**References**
Probability of hepatitis while on INH LTBI without liver enzyme monitoring				Kopanoff 1978 [61] Snider 1986 [17] Nolan 1999 [63]
all ages >=15	0.0048	0.0030	0.0067	Taylor 2000 [59]
15-34	0.0030	0.0008	0.0030	Swartzman 2000 [19]
34-54	0.0120	0.0021	0.0120	
>=55	0.0230	0.0028	0.0310	
Probability of hepatitis being fatal without enzyme monitoring				Kopanoff 1978 [61] Snider 1986 [17] Fitzgerald 1990 [68]
all ages >=15	0.031	0.01	0.076	Taylor 2000 [59]
15-34	0.010	0	0.038	Swartzman 2000 [19]
>=35	0.046	0.01	0.076	
Probability of hepatitis while on INH LTBI with liver enzyme monitoring				Salpeter 1993 [62] Taylor 2000 [59] Swartzman 2000 [19]
all ages >=15	0.0120	0.011	0.035	Fountain 2005 [64]
15-34	0.0044			Saukkonen 2006 [58]
34-54	0.0086			
>=55	0.0208			
Probability of hepatitis being fatal with enzyme monitoring				Salpeter 1993 [62] Kopanoff 1978 [61]
all ages >=15	0.0008	0	0.002	Snider 1986 [17]
<35	0	0	0.038	Fitzgerald 1990 [68]
>=35	0.0100	0.01	0.076	Taylor 2000 [59] Swartzman 2000 [19]

Table 5: Tuberculosis Outcomes Cape Town 2001

	Base-Case estimate	**Range for Sensitivity Analysis** Low Value	High Value	**References**
Fatality risk for new pulmonary tuberculosis	0.044			Cape Town Report 2002[56]
Case fatality for all cases of tuberculosis disease Cape Town 2001				Cape Town Report 2002[56] Cape Town Mortality 2001[57]
all ages >=15	0.074			WHO 2004 report [25]
15-34	0.043			SA Health Survey 1998[108]
35-54	0.099			
>=55	0.129			
Success rate of those treated for new pulmonary tuberculosis (excluding those who died)	0.808 (0.846)	0.731 (0.746)		Cape Town Report 2002[56]
Fatality risk for retreatment pulmonary tuberculosis	0.068			Cape Town Report 2002[56]
Success rate of those retreated for pulmonary TB (excluding those who died)	0.665 (0.714)	0.586 (0.629)		Cape Town Report 2002[56]
Fatality risk assuming all treatment interruptors died				Cape Town Report 2002[56]
New case	0.179			
Retreatment case	0.306			

Table 6: Health Utilities

Health Utility	**Base-Case estimate**	**Range for Sensitivity Analysis** Low Value	High Value	**References**
TB non-screening program	0.66	0.45	0.90	Nguyen 1999 [78] Teng 2000 [79]
Probability of symptoms in screening program	0.67			Snider 1986 [17] Diel 2006 [47] Den Boon 2005 [48]
TB screening program	0.78	0.63	0.93	Verver 2000 [77]
TB in hospital	0.6	0.45	0.87	Teng 2000 [79] Snider 1986 [17] Porco 2006 [21]
TB outpatient				Porco 2006 [21] Snider 1986 [17]
non-screening	0.89	0.735	0.960	Salpeter 1997 [72]
screening	0.93	0.822	0.973	
Rx inactive pulmonary tuberculosis	0.93	0.93	1	Nguyen 1999 [78] Diel 2006 [47]
Hepatitis	0.62	0.4	0.85	Nguyen 1999 [78] Snider 1986 [79] Porco 2006 [21]
Length of time symptomatic with hepatitis	4 weeks	1 week	4 weeks	Salpeter 1997 [72]

Table 7: Additional Model Assumptions

	Base-Case estimate	**Range for Sensitivity Analysis** Low Value	High Value	**References**
Length of treatment of isoniazid	6 months			Comstock 1999 [60]
Secondary cases of tuberculosis				Salpeter 1998 [107] Swartzman 2000 [19]
smear positive	0.963			Porco 2006 [21]
smear negative	0.210			
Sputum positivity				Cape Town Report 2002[56]
screening	0.57			Den Boon 2005 [48]
no screening	0.87			Den Boon 2006 [49]
Secondary cases of tuberculosis				Salpeter 1999 Swartzman 2000
screening	0.639		1.043	Porco 2006
no screening	0.865		1.450	Bell 1999
Discount rate outcome	0.05	0	0.03	Canadian guidelines [31]

Table 8: Basic Costs

All costs in 2005 Rand	Base-Case estimate	Range for Sensitivity Analysis Low Value	High Value	References
Screening cost	273 594	136 797	449100	Personal communication
Screening cost per person (n=4898), excluding testing	64.64	32.32	106.12	Personal communication
Screening cost, decline screening cohort	64.64	32.32	64.64	Personal communication
Screening cost HIV patients for LTBI including testing		75.18	128.46	Hausler 2006[46]
Cost of CXR	104	71	104	SA UPFS 2005 [86]
Miniature chest x-ray screening	50.57			Jones 2001[41]
Cost of tuberculin skin test	7.84	4.20		Sinanovic 2003 [89] Hausler 2006[46]
Cost of sputum smear	23.30			Albert 2004 [87]
Cost of sputum culture negative culture positive culture	 53.53 101.87			Albert 2004 [87]
Clinic visit, nurse complete	30.38	28.82	31.94	Sinanovic 2003 [89]
Clinic visit, physician	58.43	56.09	60.76	Sinanovic 2003 [89]
Clinic visit, patient	6.27	6.08	6.46	Sinanovic 2003 [89]
Cost of one dose isoniazid	0.14			Pharmaceutical price list South Africa 2002 [88]
Cost of 6 months of isoniazid	25.20			Pharmaceutical price list South Africa 2002 [88]
ALT	29.40			SAIMR tariff costs 2002[90]
bilirubin	29.40			SAIMR tariff costs 2002[90]
Number of clinic visits during LTBI Rx	6	2	6	South African Tuberculosis Guidelines 2004 [26]
Number of liver enzyme assessments during LTBI Rx	0	0	6	South African Tuberculosis Guidelines 2004 [26]
Number of liver enzyme assessments with hepatitis	2	2	10	Fitzgerald 1990 [68] Salpeter 1997 [72] Swartzman 2000 [19]
Number of physician visits with hepatitis	2		3	Fitzgerald 1990 [68] Salpeter 1997 [72] Swartzman 2000 [19]
Percent of individuals with hepatitis requiring hospital admission	0.05	0	0.1	Fitzgerald 1990 [68] Salpeter 1997 [72] Swartzman 2000 [19]
Length of stay for hospital admission for severe hepatitis	7 days	4 days	14 days	Fitzgerald 1990 [68] Salpeter 1997 [72] Swartzman 2000 [19]
Outpatient costs Health Provider new case retreatment case	 4182.66 6324.68	 3270.64 5490.35	 5094.67 7159.02	Sinanovic 2003 [89]
Daily cost of HIV patient in Regional hospital Patient Care Cost Overhead cost Capital cost Total cost	 223.74 936.29 106.50 1266.53	 111.87 1154.37	 342.61 1385.4	Cleary 2002 [91]

Daily cost of HIV patient in Tertiary hospital				Cleary 2002 [91]
Patient Care Cost	303.70	151.85	455.55	
Overhead cost	1057.34			
Capital cost	365.29			
Total cost	1726.33	1574.48	1878.18	
Daily cost of inpatient in				Burn 2004 [97]
District Hospital	768.86			
Regional Hospital	1022.38			
Tertiary Hospital	1700.84			
Daily drug costs new case	2.26	2.26	2.51	Sinanovic 2003 [89] City of Cape Town 2002[56]
Daily drug cost re-treatment case	3.19	2.88	3.19	Sinanovic 2003 [89] City of Cape Town 2002[56]
Average length of stay for hospitalized tuberculosis patient, new case	17.8	4	21	Floyd 1997 [93] Colvin 2001[101] Zaylor 2000 [100]
Average length of stay for hospitalized tuberculosis patient, retreatment case	17.8	4	60	Floyd 1997 [93] Colvin 2001[101] Cleary 2002 [91] Burn 2004 [97]
Probability new case hospitalized non-screening arm	0.1	0	0.5	WHO 2006 report on South Africa [92]
Probability new case hospitalized in screening arm	0.033	0	0.17	Verver 2001 [77]
Percentage of retreatment cases hospitalized	0.1	0	0.5	WHO 2006 report on South Africa [92]
Average hourly time cost for a patient clinic visit	6.62			Sinanovic 2003 [89]
Average hourly wage in Ravensmead/Uitsig	21.63			SA Demographic survey 1998 [108]
Unemployment rate in Ravenmead/Uitsig	0.14		0.20	SA Demographic survey 1998 [108]
Average hourly time cost in Ravensmead/Uitsig	18.60			SA Demographic survey 1998 [108]
Average hourly wage				Income Western Cape 2000 [104]
unskilled	11.79			
Semi-skilled	17.62			
skilled	23.83			
Time cost to come to clinic	0.83 hours	0.80 hours	0.86 hours	Sinanovic 2003 [89]
Cost of transportation	1.55	.77	2.33	Sinanovic 2003 [89]
Discount rate for costs	0.05	0.03	0.08	Canadian guidelines [89] WHO guidelines [32]

Table 9: Component Costs

All results in 2005 R	Components	Cost
Cost of patient clinic visit	Time to clinic visit 0.83 hour	
	14% unemployment	
	0.83*0.86*hourly wage (21.63)	15.44
	Transportation cost to clinic	1.56
	Total:	17.00
Cost of INH treatment,	Isoniazid for 6 months	25.20
Health provider (HP)	1 physician visit	58.43
	5 nurse visit	151.90
	Total:	235.53
Cost of INH treatment,	Isoniazid for 6 months	25.20
Societal (S)	1 physician visit	58.43
	5 nurse visits	151.90
	6 patient visits	101.00
	Total:	336.53
Cost of INH treatment HIV study[30]		80.50
Cost of INH hepatitis outpatient, HP	2 physician visits	116.60
	2 ALT	58.80
	2 bilirubin	58.80
	Total:	234.20
Cost of INH hepatitis outpatient, S	2 physician visits	116.60
	2 ALT	58.80
	2 bilirubin	58.80
	2 patient visits	34.00
	Total:	268.20
Cost of INH hepatitis inpatient, HP	7 hospital days	8865.71
	3 ALT	88.20
	3 bilirubin	88.20
	2 CBC	64.80
	Total:	9106.91
Cost of INH hepatitis inpatient, S	7 hospital days	8865.71
	3 ALT	88.20
	3 bilirubin	88.20
	2 CBC	64.80
	Time lost from work	744.00
	Total:	9850.91
Total cost of INH hepatitis, HP	Probability of hospitalization 0.05	
	0.05* INH hepatitis IP Costs	455.35
	0.95* INH hepatitis OP Costs	222.49
	Total:	677.84
Total cost of INH hepatitis, S	Probability of hospitalization 0.05	
	0.05* INH hepatitis IP Costs	492.54
	0.95* INH hepatitis OP Costs	254.79
	Total:	747.33
Cost of INH hepatitis[90]		1924.00
Cost of new case of TB during	17.8 hospital days	22544.23
hospitalization, HP	17.8 days of medication	40.23
	Total:	22584.46
Cost of treatment for new case of TB	Hospitalization costs	22584.46
hospitalized patients including inpatient	Outpatient treat	3769.04
and outpatient time, HP	(180-17.8/180) outpatient costs	
	Total:	26353.50
Total cost of new case of TB	Probability of hospitalization in screening arm 0.033	
Screening, HP	0.033* cost of new case of TB inpatient	869.67
	Probability of no hospitalization in screening arm 0.967	
	0.967* cost of new case of TB outpatient	4044.63
	Total :	4914.30
Total cost of new case of TB	Probability of hospitalization in NS arm 0.1	
No screening (NS), HP	0.1* cost of new case of TB inpatient	2635.35
	Probability of no hospitalization in NS arm 0.9	
	0.9* cost of new case of TB outpatient	3764.39
	Total :	6399.74

Cost of new case of TB Outpatient S	Outpatient cost of TB 120 patient visits Total:	4182.66 2040 6222.66
Cost of new case of TB during hospitalization, S	17.8 hospital days 17.8 days of medication Lost salary Total:	22544.23 40.23 1891.88 24476.34
Cost of treatment for hospitalized patients including inpatient and outpatient time,S	Hospitalization costs Outpatient treatment (180-17.8/180) outpatient costs Total:	24476.34 5607.30 30083.65
Total cost of new case of TB Screening, S	Probability of hospitalization in screening arm 0.033 0.033* cost of new case of TB inpatient Probability of no hospitalization in screening arm 0.967 0.967* cost of new case of TB outpatient Total:	 992.76 6017.31 7010.07
Total cost of new case of TB No screening (NS), S	Probability of hospitalization in NS arm 0.1 0.1* cost of new case of TB inpatient Probability of no hospitalization in NS arm 0.9 0.9* cost of new case of TB outpatient Total:	 3008.37 5600.39 8608.76
Cost of retreatment (reRx) case of TB during hospitalization, HP	17.8 hospital days 17.8 days of medication Total:	22544.23 56.78 22544.23
Total cost of treatment for re Rx hospitalized patients including inpatient and outpatient time, HP	Hospitalization costs 17.8 days of medication Outpatient treat (240 -17.8/240) outpatient costs Total:	22544.23 56.78 5855.60 28456.61
Total cost of reRx case of TB, HP	Probability of hospitalization 0.1 0.1* cost of reRx case of TB inpatient Probability of no hospitalization 0.9 0.9* cost of new case of TB outpatient Total:	 2845.61 5692.21 8537.87
Cost of reRx case of TB, Outpatient S	Outpatient HP costs 160 patient clinic visits Total:	6324.68 2720.00 9044.68
Cost of re Rx case of TB during hospitalization, S	17.8 hospital days 17.8 days of medication Lost salary Total:	22544.23 56.78 1891.88 24492.89
Total cost of treatment for hospitalized patients including inpatient and outpatient time,S	Hospitalization costs Outpatient treatment (240-17.8/240) outpatient costs Total:	24492.89 8373.87 32866.76
Total cost of reRx case of TB, S	Probability of hospitalization 0.1 0.1* cost of reRx case of TB inpatient Probability of no hospitalization arm 0.9 0.9* cost of new case of TB outpatient Total :	 3286.67 8140.21 11,426.88

Table 10: Outcomes of Strategies for Inactive Pulmonary Tuberculosis over 20 years

	Screening and treatment	**No screening**	**Estimate from literature**
Proportion of individual developing new cases of pulmonary TB	0.0664	0.0735	0.0561
Proportion of individuals developing retreatment cases of pulmonary TB	0.0103	0.0112	0.0286
Proportion of individuals dead at year 20 (fatality of pulmonary cases of TB)	0.1616	0.1622	0.1688
Proportion of patients dead at year 20 (fatality of all cases of TB)	0.1635	0.1644	0.1688

Table 11: Five year incidence of Tuberculosis for Markov States

	Expected five year incidence	**Observed five year incidence**
Normal chest radiograph	0.0143	0.0149
Inactive pulmonary tuberculosis, untreated	0.0859	0.0892
Inactive pulmonary tuberculosis, treated	0.0292	0.0287

Table 12: Sensitivity Analyses – Outcomes

	Cost-utility ratio base case R per QALY	**CU ratio low value R per QALY**	**CU ratio high value R per QALY**
Base Case	**31,043 R per QALY**		
Compliance with screening program	0.745	0.50 **39,015* R per QALY**	1.0 26,900 R per QALY
Prevalence of abnormal CXR suggesting inactive disease	0.0679	0.085 23,850 R per QALY	0.132 **13,682R R per QALY**
PPV CXR MTX 5mm	1	0.866 **39,969 R per QALY**	0.941 34,505 R per QALY
PPV CXR MTX 10 mm	1	0.837 **42,499 R per QALY**	0.930 35,223 R per QALY
Prevalence of culture positive tuberculosis	0.153	0.128 31,407 R per QALY	0.138 31,262 R per QALY
Sensitivity of one sputum	0.870	0.84 30,611 R per QALY	0.9 31,493 R per QALY
Specificity of one sputum	0.990	0.9 30,962 R per QALY	1 31,061 R per QALY
Estimated incidence of pulmonary TB 6 month assuming 6 times increase risk of TB disease in abnormal CXR and 65% effectiveness		Excluding HIV Cases	CXR stratification
normal CXR inactive pulmonary TB inactive pulmonary TB Rx	0.00144 0.00869 0.00296 31, 043	0.00054 0.00326 0.00113 **49, 018 R per QALY**	0.00101 0.00660 0.00227 36,371 R per QALY
Estimated incidence of pulmonary TB 6 month assuming 13 times increase risk of TB disease in abnormal CXR and 65% effectiveness		Excluding HIV Cases	CXR stratification
normal CXR inactive pulmonary TB inactive pulmonary TB Rx	0.00144 0.02039 0.00672 **16,182 R per QALY**	0.00040 0.00528 0.00182 **40,579 R per QALY**	0.00080 0.01080 0.00367 26,970 R per QALY
Estimated incidence of new TB 6 month assuming 6 times increase risk of TB disease in abnormal CXR, 65% effectiveness, case fatality .074		Excluding HIV Cases	CXR stratification
normal CXR inactive pulmonary TB inactive pulmonary TB Rx	0.00266 0.01349 0.00479 **15,381 R per QALY**	0.00084 0.00514 0.00177 25,269 R per QALY	0.00169 0.01053 0.00357 **17,689 R per QALY**
Effectiveness of LTBI Rx range from studies	0.65	0.60 32,646 R per QALY	0.75 28,132 R per QALY
resistance .052		0.58 33,345 R per QALY	
re-infection .25		0.25 **51,821 R per QALY**	
Risk of hepatitis without monitoring	0.0048	0.003 30,834 R per QALY	0.0067 31,265 R per QALY
Hepatitis case fatality without monitoring	0.031	0.01 30,779 R per QALY	0.076 31,624 R per QALY

Tuberculosis case fatality risk	0.044		0.074 **19,720 R per QALY**
Tuberculosis case fatality assuming all treatment interruptors died new case retreatment case	 0.044 0.068		 0.174 0.306 **9,510 R per QALY**
Tuberculosis case fatality risk in the untreated tuberculosis patients	0.044	0.1 30,135 R per QALY	0.7 24,226 R per QALY
New case tuberculosis success rate in those who survive	0.846	0.746 29,047 R per QALY	
Re-treatment success rate in those survive	0.714	0.626 30,679 R per QALY	
Utility LTBI treatment	0.93		1 **22,688 R per QALY**
Utility tuberculosis screening program	0.78	0.66 31,043 R per QALY	0.93 31,045 R per QALY
Utility tuberculosis disease screening screening no screening	 0.78 0.66	 0.63 0.45 24,073 R per QALY	 0.93 0.9 **46,392 R per QALY**
Utility isoniazid hepatitis	0.62	0.4 31,072 R per QALY	0.85 31,012 R per QALY
Discount rate for outcomes	5%	0% **11,737 R per QALY**	3% **21,747 R per QALY**

* results that vary more than 25% from the base analysis are bolded in the table

Table 13: Sensitivity Analyses - Costs

	Cost-utility ratio base case R per QALY	**CU ratio low value R per QALY**	**CU ratio high value R per QALY**
Base Case	**31,043 R per QALY**		
Cost of screening, lung health study	64.64	32.32 **22,914 * R per QALY**	106.12 **41,474 R per QALY**
Cost of screening in the decline screening group	64.64	0 26,901 R per QALY	32.32 28,882 R per QALY
Cost of screening, HIV LTBI study		75.18 **13,130 R per QALY**	128.46 26,530 R per QALY
Cost of chest x-ray	104	71 24,859 R per QALY	104 31,042 R per QALY
Cost of LTBI treatment components clinic costs	30.38	28.82 30,950 R per QALY	31.94 31,127 R per QALY
number of clinic visits	6	1 29,408 R per QALY	6 31,043 R per QALY
Cost of LTBI, HIV LTBI study		80.50 29,371 R per QALY	
Hospitalization costs for hepatitis probability of hospitalization	0.05	0 31,019 R per QALY	0.1 31,065 R per QALY
length of stay	7 days	7 days 31,042 R per QALY	14 days 31,066 R per QALY
Cost of INH hepatitis, HIV study	635	635 31,042 R per QALY	1924 31,107 R per QALY
Assume total LTBI costs for all individuals with hepatitis	67% 12 weeks LTBI costs 33% 24 weeks LTBI costs		100% 24 weeks LTBI 31,047 R per QALY
Cost of outpatient tuberculosis care	new case 4182.66 reRx case 6324.68	new case 3207.64 reRx case 5490.33 31,794 R per QALY	new case 5094.67 reRx case 7159.02 30,333 R per QALY
Cost of inpatient hospital care			
all care at regional hospital	1266.53	50% patient cost 1154.37 31,461 R per QALY	150% patient cost 1385.40 30,599 R per QALY
all care at district hospital		768 32,905 R per QALY	
all care at tertiary hospital		50% patient costs 1574.48 29,892 R per QALY	150% patient costs 1878.18 28,758 R per QALY
probability of hospitalization	0.1	0 35,718 R per QALY	**0.5** **12,342 R per QALY**
length of stay	17.8	4 34,668 R per QALY	21 30,202 R per QALY
both probability and length of stay		35,718 R per QALY	**8,139 per R QALY**
Costs assigned to those who die of tuberculosis	0		50% 30,643 R per QALY
Discount Costs	0 **22,805 R per QALY**	0.03 28, 731 R per QALY	0.08 33,301 R per QALY

* results that vary more than 25% from the base analysis are bolded in the table

Table 14: Scenario Analyses

Scenario	Adjustments made to base model	Changes	CU ratio Cost per QALY
High screening costs	Screening CXR	106 Rand 104 Rand	**41,476* R per QALY**
Low screening costs	Screening CXR	32 Rand 71 Rand	**16,730 R per QALY**
Miniature CXR screening	Cost of screening Cost of additional full size film in those with abnormal films CXR low CXR high	50.57 71 104	**8,013 R per QALY** **8,916 R per QALY** **9,337 R per QALY**
Screening – Willingness to Pay	Estimates of cost to determine how much could pay for screening with a willingness-to-pay estimate of 8,000 per QALY	50 Rand 60 Rand 70 Rand	**6,267 R per QALY** **8,462 R per QALY** **10,656 R per QALY**
Two sputum sample HP	sensitivity of two sputum assessment additional sputum smear additional sputum culture negative additional sputum culture positive	0.94 23.30 53.53 101.87	 30,170 R per QALY
TST testing HP	Compliance with TST testing Increased cost of performing TST testing TST >=5mm abnormal CXR and negative sputum PPV 5 mm TST NPV 5 mm TST TST>=10mm abnormal CXR and negative sputum PPV 10 mm TST NPV 10 mm TST Compliance TST Cost of TST	0.81 7.84 R 0.89 .969 .902 0.85 .983 .607 0.5 1.0 4.20R	 33,613 R per QALY 33,639 R per QALY 33,946 R per QALY 34,775 R per QALY 36,543 R per QALY 31,949 R per QALY 33,572 R per QALY
Liver enzyme monitoring for LTBI treatment for inactive pulmonary tuberculosis	Risk of hepatitis Hepatitis fatality ALT monthly x 6 months Risk of hepatitis Probability of fatal hepatitis	0.012 0.0008 176.40 0.011-0.035 0-0.002	 32,806 R per QALY 32,568 to 33,674 R per QALY 32,779 R to 32,845 R per QALY
Assessing for all new cases of tuberculosis and including fatality for all new cases of tuberculosis	Base Cases Normal CXR Inactive pulmonary TB no Rx Inactive pulmonary TB Rx CXR stratification Normal CXR Inactive pulmonary TB no Rx Inactive pulmonary TB Rx Excluding HIV cases Normal CXR Inactive pulmonary TB no Rx Inactive pulmonary TB Rx Case fatality rate	 0.00223 0.01349 0.00479 0.00169 0.01053 0.00357 0.00084 0.00514 0.00177 0.074	 **15,330 R per QALY** **17,628 R per QALY** 25,243 R per QALY

LTBI Rx for tuberculosis disease Worst case	Mortality the same of active tuberculosis disease Cases transition to retreatment arm	0.044	33,427 R per QALY
Re-treatment	all failures to post-treatment TB arm all failures to dead arm		33,427 R per QALY 27,543 R per QALY
Low tuberculosis treatment costs	Outpatient cost new Outpatient cost re-treatment Daily hospital costs Hospitalization for TB no screened Hospitalization for TB screened LOS for new cases LOS for re-treatment	3270.64 5490.35 768.88 0.1 0.03 4 4	 35,802 R per QALY
High tuberculosis treatment costs	Outpatient cost new Outpatient cost re-treatment Daily hospital costs Hospitalization for TB no screened Hospitalization for TB screened LOS for new cases LOS for re-treatment	5094.67 7159.02 1877.84 0.1 0.03 21 21	 26,800 R per QALY
Utility TB by hospitalization	utility TB inpatient utility TB outpatient non screening utility TB outpatient screening utility Rx TB infection	0.60 (0.450 -0.870) 0.89 (0.735 -0.960) 0.93 (0.822 -0 973) 0.93 (0.930 -1.000)	 **39,589 R per QALY** **29,532 to 50,089 R per QALY**
Low utility	utility TB non screening utility TB screening utility Rx TB infection utility hepatitis	0.45 0.63 0.93 0.42	 24,090 R per QALY
High utility	utility TB non screening utility TB screening utility Rx TB infection utility hepatitis	0.900 0.933 1.000 0.850	 29,897 R per QALY
Societal perspective of base case	See component costing, Table 3 Wage 12.63 Wage 6.62 All working smear positive TB cases lose 15 days of work		 33,093 R per QALY 31,873 R per QALY 30,937 R per QALY
Secondary tuberculosis cases	Smear positive disease Smear negative disease Sputum positivity screening arm Sputum positivity in non-screening arm Percent develop disease in two years Discount rate of secondary cases Sensitivity analysis All secondary cases discounted Discount rate changed Assuming background HIV 10%, Secondary cases in screening arm Secondary cases in non screening arm	0.963 secondary cases 0.21 secondary cases 0.57 0.87 0.5 stage + 10 years stage + 10 years stage stage + 15 years stage + 20 years 1.043 1.45	 **11,871 R per QALY** **16,597 R per QALY** **9,052 R per QALY** **12,922 R per QALY** **13,777 R per QALY** **8,958 R per QALY**
US costs	Hospital day 10,445 Rand Probability of hospitalization 0.5		**Cost-saving**

* results that vary more than 25% from the base analysis are bolded in the table

Table 15: Sub-Group Analysis with Age Categorization

	CE base case	CE ratio low value	CE ratio high value
Base Case	**15, 381 R per QALY**		
15-34	**24,281 R per QALY**		
35-54	**14,866 R per QALY**		
>=55	**13,070 R per QALY**		
PPV CXR MTX 5mm			
	1	0.918	
15-34		**24,706 R per QALY**	
	1	0.957	
35-54		**15,084 R per QALY**	
	1	0.796	
>=55		**18,768 R per QALY**	
PPV CXR MTX 10 mm			
	1	0.892	
15-34		**25,027 R per QALY**	
	1	0.936	
35-54		**15,190 R per QALY**	
	1	0.726	
>=55		**22,650 R per QALY**	
CXR stratification			
15-34		**24,997 R per QALY**	
35-54		**18,408 R per QALY**	
>=55		**24,378 R per QALY**	
Probability of hepatitis			
15-34	0.0003	0.0008	0.003
		24,268 R per QALY	**24,281 R per QALY**
35-54	0.012	0.0021	0.012
		13,148 R per QALY	**14,866 R per QALY**
>=55	0.023	0.0028	0.031
		11,522 R per QALY	**13,175 R per QALY**
Probability of fatal hepatitis			
15-34	0.01	0	0.038
		24,282 R per QALY	**24,280 R per QALY**
35-54	0.046	0.01	0.076
		13,217 R per QALY	**14,863 R per QALY**
>=55	0.046	0.01	0.076
		11,765 R per QALY	**13,061 R per QALY**
QALY 1 for inactive pulmonary tuberculosis Rx			
15-34			**24,281 R per QALY**
35-54			**11,893 R per QALY**
>=55			**9,048 R per QALY**
Discount effect	0.05	0	0.03
15-34		**10,117 R per QALY**	**17,344 R per QALY**
35-54		**4,955 R per QALY**	**9,911 R per QALY**
>=55		**4,201 R per QALY**	**8,401 R per QALY**
Miniature chest radiography		Cost of screening 50.57	
15-34		**5,185 R per QALY**	
35-54		**2,459 R per QALY**	
>=55		**1,498 R per QALY**	

Table 16: Cost Effectiveness Analysis

Model	Adjustments made to model	Cost-effectiveness
Base Case		17,384 R per case of TB prevented
Base Case	Included re-treatment case of TB disease	15,508 R per case of TB prevented
Miniature chest x-ray	Screening costs with miniature radiography	4,446 R per case of TB prevented

Appendix B: Figures

Figure 1: Decision Tree

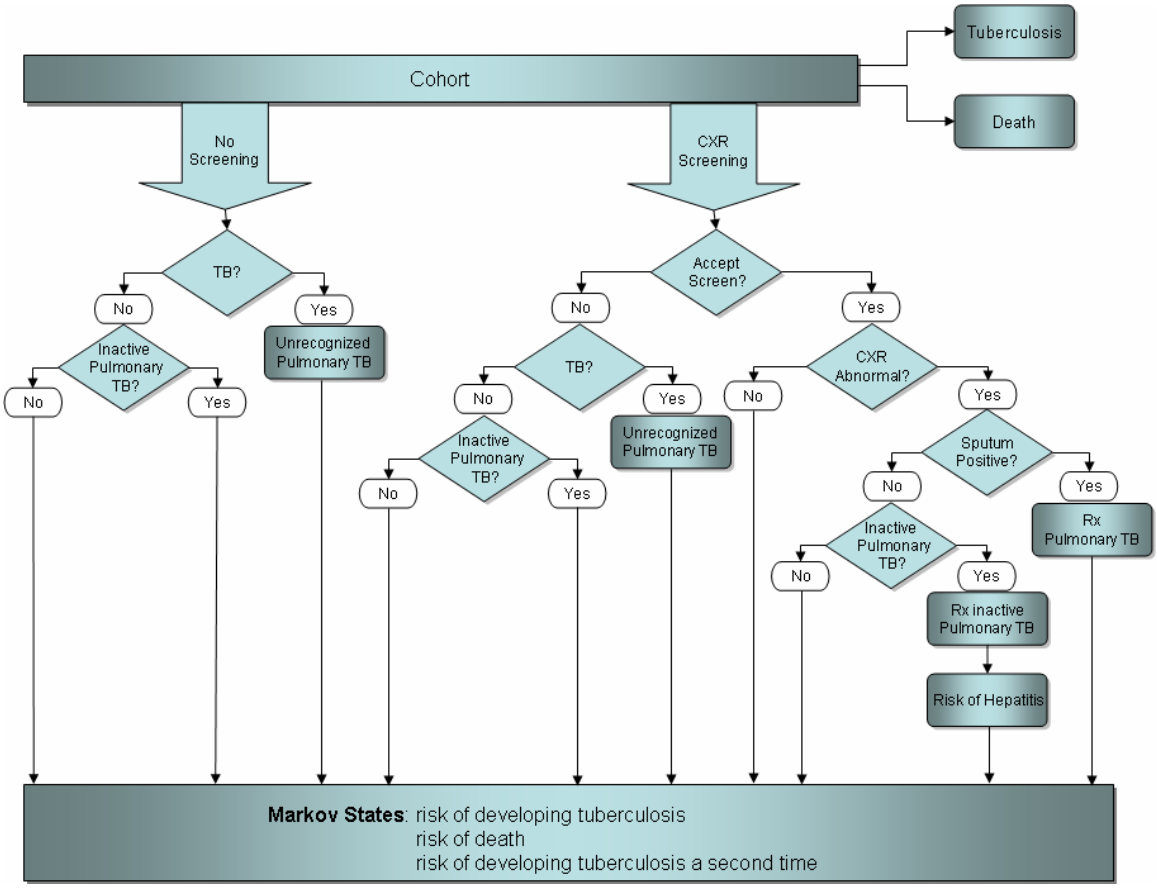


Figure 2: Transitioning Markov States

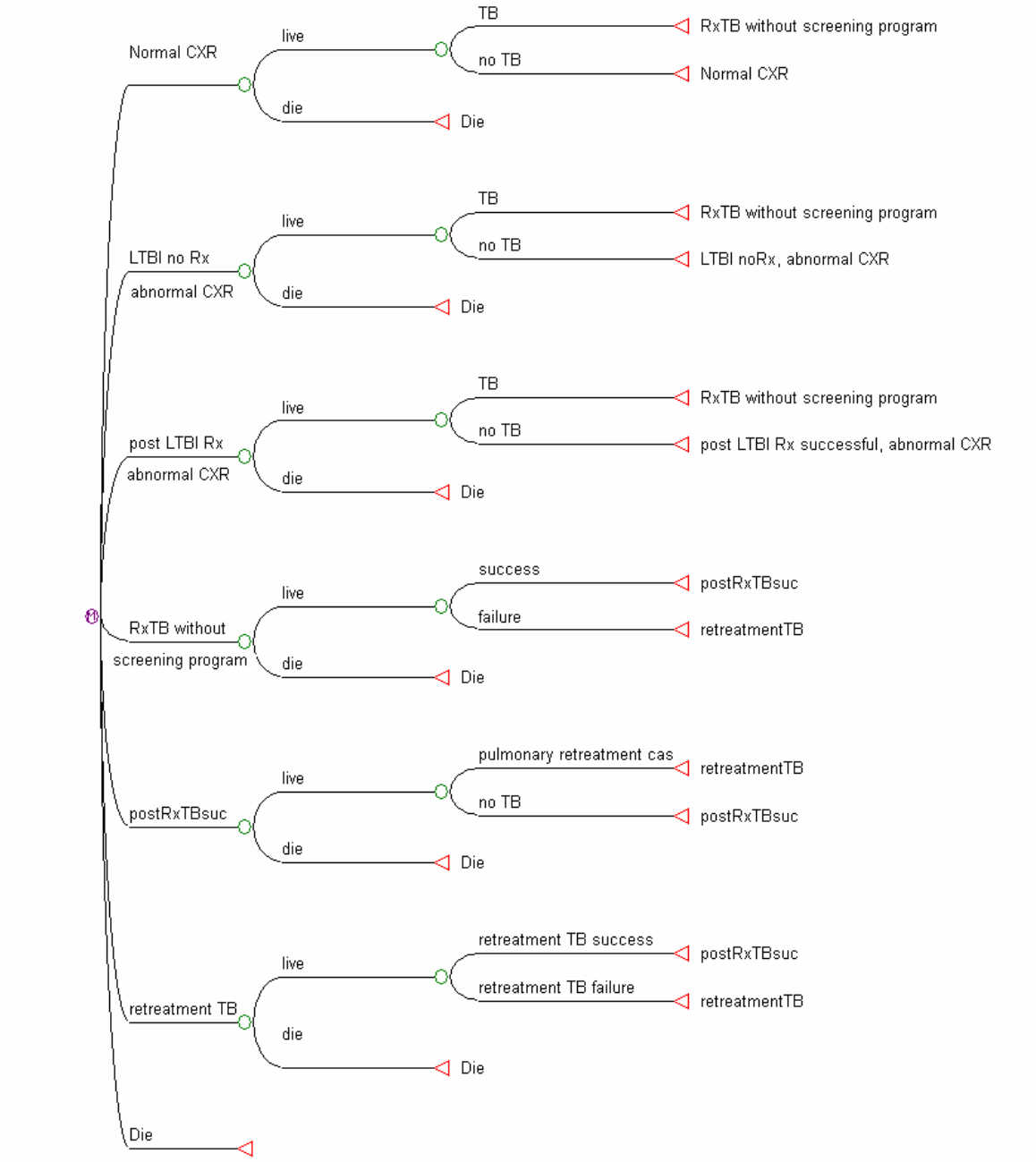


Figure 3: Tuberculin Skin Testing Scenario Analyses

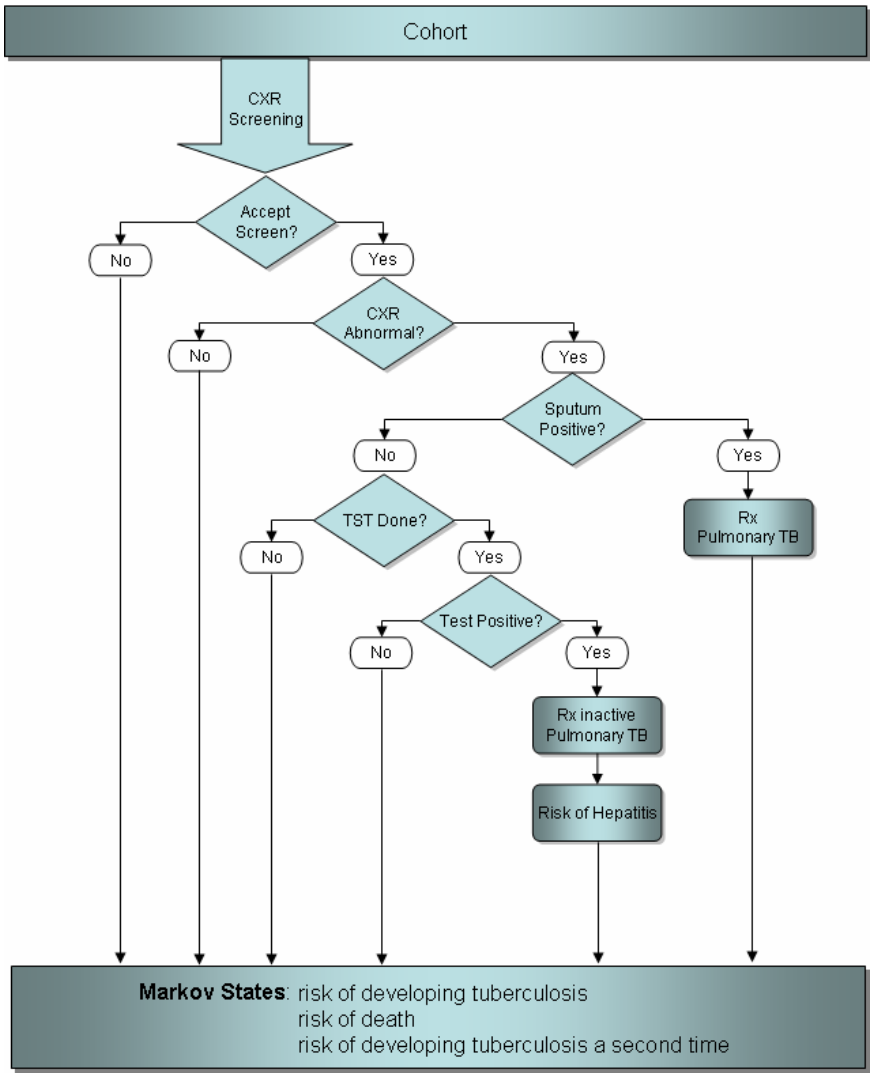


Figure 4: Scenario Analyses

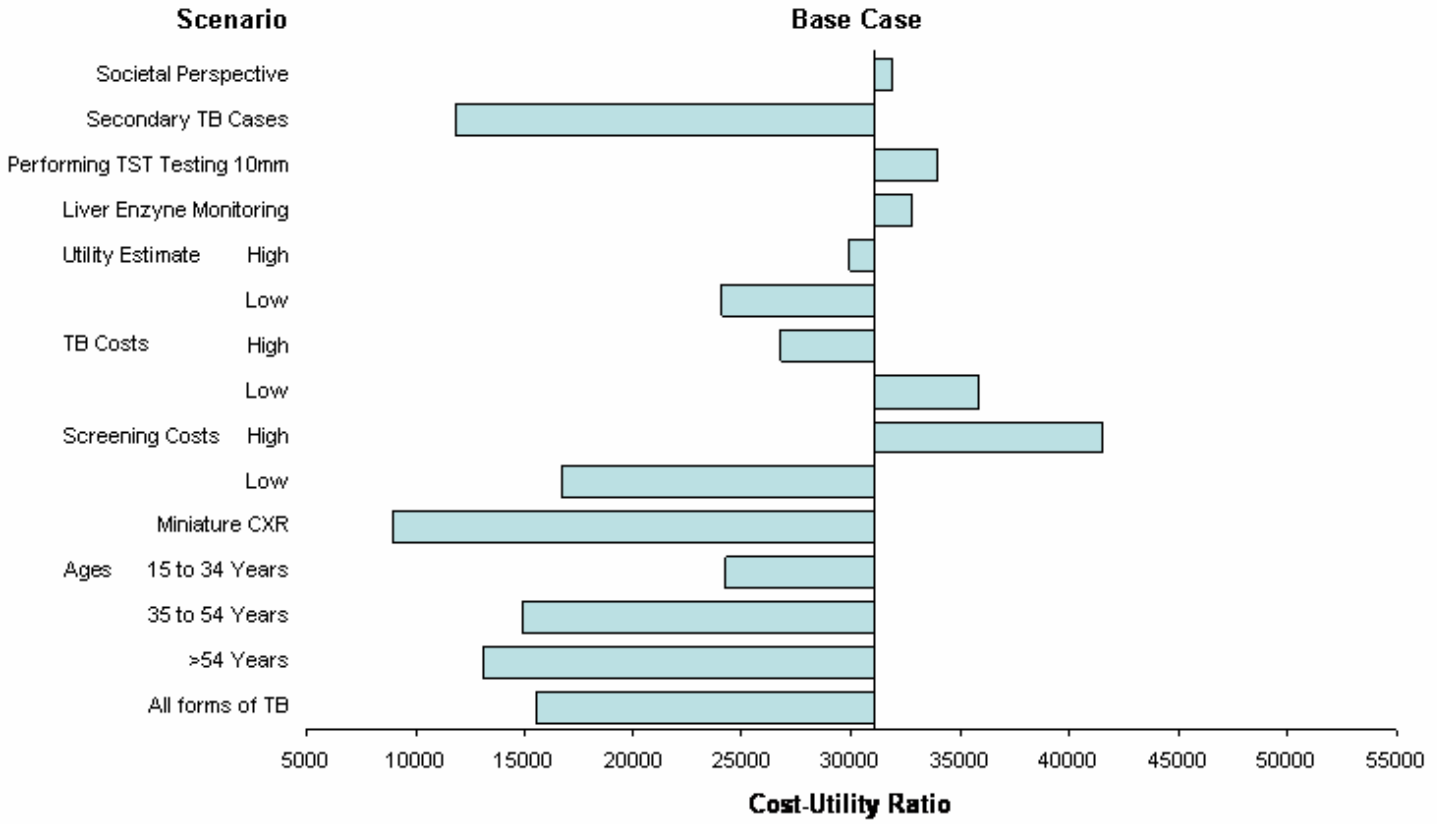
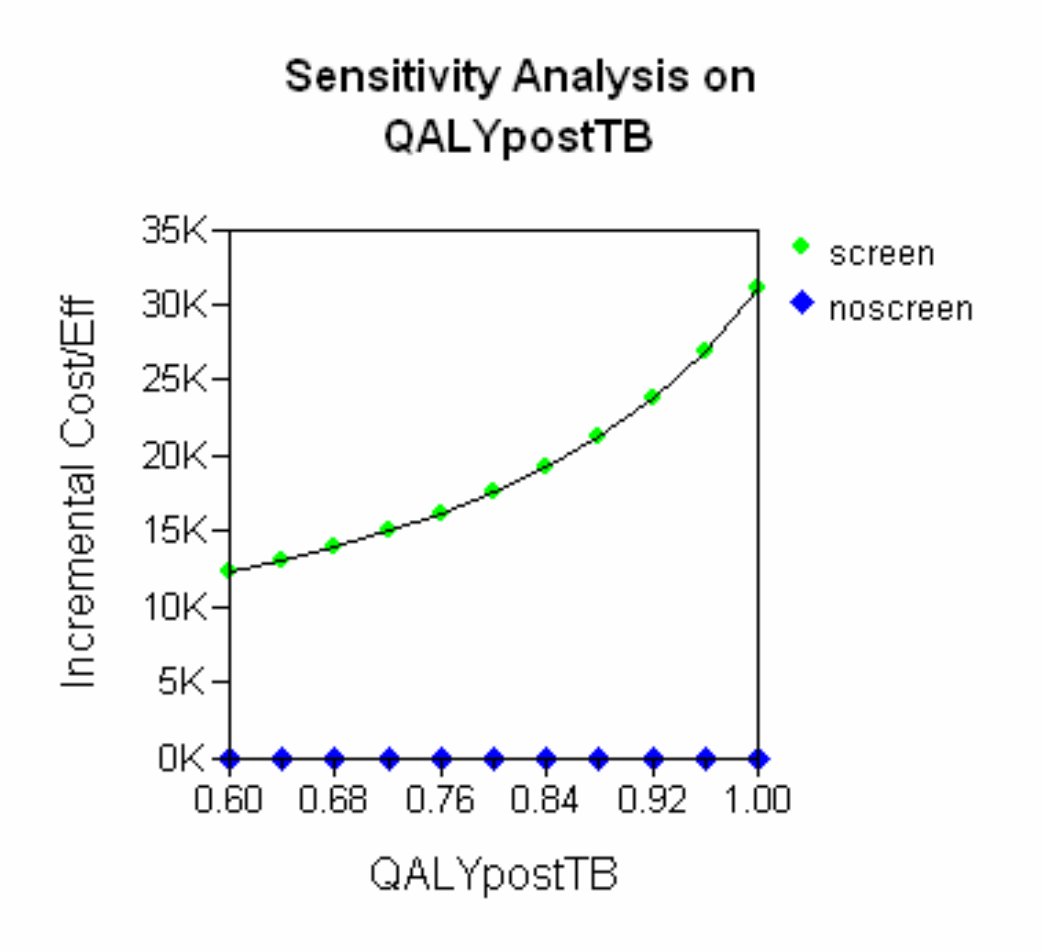


Figure 5: Sensitivity Analysis adjusting QALY post tuberculosis treatment



Appendix C: Ethics Approval

FACULTY OF MEDICINE | UNIVERSITY OF CALGARY

2006-03-09

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Dr. Braden Manns
Department of Medicine
Foothills Medical Centre
Calgary, Alberta

Dear Dr. Manns:

RE: Cost-effectiveness of chest x-ray screening for diagnosis and treatment of inactive pulmonary tuberculosis in a high-incidence country

Ethics ID: E-20061

Student: Ms. Dina Fisher

The above-noted proposal including the Thesis Proposal (Cost-Effectiveness of CXR Screening for Diagnosis and Treatment of Inactive Pulmonary Tuberculosis in a High-Incidence Country) has been submitted for Board review and found to be ethically acceptable.

Please note that this approval is subject to the following conditions:
(1) access to personal identifiable health information was not requested in this submission;
(2) a copy of the informed consent form must have been given to each research subject, if required for this study;
(3) a Progress Report must be submitted by March 09, 2007, containing the following information:

i) the number of subjects recruited;
ii) a description of any protocol modification;
iii) any unusual and/or severe complications, adverse events or unanticipated problems involving risks to subjects or others, withdrawal of subjects from the research, or complaints about the research;
iv) a summary of any recent literature, finding, or other relevant information, especially information about risks associated with the research;
v) a copy of the current informed consent form;
vi) the expected date of termination of this project.

4) a Final Report must be submitted at the termination of the project.

Please note that you have been named as the principal collaborator on this study because students are not permitted to serve as principal investigators. Please accept the Board's best wishes for success in your research.
Yours sincerely,

Glenys Godlovitch, BA(Hons), LLB, PhD
Chair, Conjoint Health Research Ethics Board

GG/gk
c.c. Dr.J.Conly (information)
Office of Information & Privacy Commissioner

Research Services

Ms. Dina Fisher (Student)