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DETERMINATION OF THE COST-EFFECTIVENESS OF A
TUBERCULOSIS PREVENTION PROGRAM ALONG THE U.S. / MEXICO
BORDER USING MARKOV PROCESS MODELING WITHIN A
PREVENTION EFFECTIVENESS FRAMEWORK

by
Matthew Elvin Borrego

A Dissertation Submitted to the Faculty of the
DEPARTMENT OF PHARMACY PRACTICE AND SCIENCE
In Partial Fulfillment of the Requirements
For the Degree of
DOCTOR OF PHILOSOPHY
WITH A MAJOR IN PHARMACEUTICAL SCIENCES
In the Graduate College
THE UNIVERSITY OF ARIZONA

1998
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Matthew Elvin Borrego entitled DETERMINATION OF THE COST-EFFECTIVENESS OF A TUBERCULOSIS PREVENTION PROGRAM ALONG THE U.S./MEXICO BORDER USING MARKOV PROCESS MODELING WITHIN A PREVENTION EFFECTIVENESS FRAMEWORK and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

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Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

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STATEMENT BY AUTHOR

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SIGNED: Matthew E. Barigo
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DEDICATION

Completion of this dissertation and doctoral program is dedicated to my parents, Severino Robert and Bertha Borrego. Thanks for instilling in me the value of education and ethic of hard work. Thanks for your unending support and encouragement. Most of all, thanks for believing in me.

Completion of this dissertation and doctoral program is especially dedicated to my son, Justin Bailey Borrego.
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ABSTRACT

A prevention effectiveness analysis framework was used to estimate the cost-effectiveness of a county administered tuberculosis prevention program along the U.S. / Mexico border. The tuberculosis prevention program under study used prophylactic isoniazid therapy in patients who have tested positive for tuberculosis infection. This analysis determined the cost-effectiveness of the current program versus no program from the perspective of the county government and was modeled for two time periods; five years and 15 years post preventive therapy initiation.

Costs were calculated using actual data from tuberculosis prevention and active tuberculosis treatment programs as well as hospital discharge data. The outcome of interest, cases of active tuberculosis averted, was calculated through a Monte Carlo simulated Markov process model. Average and incremental cost-effectiveness ratios were then calculated for the tuberculosis prevention program scenario. The cost-effectiveness ratios were calculated separately with the inclusion or exclusion of the tuberculosis contagion costs.

The results of the cost-effectiveness ratio calculations established that the prevention of active tuberculosis cases with the tuberculosis prevention program is considerably cost-effective. Every baseline incremental cost-effectiveness ratio, across the five and 15 year analysis periods (irrespective of contagion costs) determined in this prevention effectiveness study demonstrated cost savings. Additionally, the cost savings were substantial. The results indicate that rather than incurring costs to avert active
tuberculosis cases, the tuberculosis prevention program actually saves money.

One-way sensitivity analyses were performed for selected parameters used in the calculation of the cost-effectiveness ratios. The cost-effective results obtained in the baseline analysis became sensitive when the percentage of patients hospitalized for tuberculosis decreased and when the preventive therapy compliance rate decreased for the 5 years post preventive treatment scenario with tuberculosis contagion costs excluded. However, when the tuberculosis contagion consequences of not having the tuberculosis prevention program were considered; the cost effectiveness and cost savings were once again realized.
CHAPTER 1
INTRODUCTION

Tuberculosis is an airborne communicable disease caused by *Mycobacterium tuberculosis*, the tubercle bacillus. Tuberculosis is spread primarily through the inhalation of tiny airborne particles, droplet nuclei, which have been expelled by a person who has infectious tuberculosis [U.S. Department of Health and Human Services (USDHHS), 1994]. Tuberculosis infection occurs with the multiplication of the tubercle bacillus in the alveolar macrophages; however, the infected persons immune system response usually prevents the development of active disease.

Tuberculosis infected persons are asymptomatic, non-infectious, and do not have active tuberculosis. Tuberculosis infected persons usually have a positive reaction to the tuberculin skin test. Almost 10% of tuberculosis infected persons will develop active tuberculosis disease at some time in their lives, the risk increases for patients who are immunosuppressed (USDHHS, 1994). Although the majority of tuberculosis cases are pulmonary, tuberculosis can occur in almost any anatomical site or as disseminated disease.

Tuberculosis is a contagious disease. The number of new tuberculosis infections caused each year by one case of undiagnosed and untreated smear-positive tuberculosis has been estimated to be between 10 and 14 persons per year (Murray, Styblo, and Rouillon, 1990). Murray et al. (1990) estimate that these 10 to 14 tuberculosis infected persons will cause 0.6 to 1.2 cases of active tuberculosis over the next 1.5 years. For
untreated cases, the cycle of tuberculosis infection and re-infection continues.

Tuberculosis remains an important public health problem worldwide. There are an estimated eight to ten million new cases and two to three million deaths yearly due to tuberculosis (Kochi, 1991). Worldwide, tuberculosis is the leading cause of death from a single infectious disease, accounting for over one-fourth of avoidable deaths among adults (Nakajiima, 1993). The number of new tuberculosis cases occurring each year is predicted to increase from 7.5 million in 1990 to 10.2 million in the year 2000 (Raviglione, Snider Jr., and Kochi, 1995).

The United States had witnessed a significant decline in reported cases of tuberculosis from just over 84,000 in 1953 (when the national system of reporting tuberculosis began) to a low of about 22,000 cases in 1984 (Raviglione et al., 1995). However, from 1985 to 1993, the number of reported cases increased about 14%. This increase in cases accounted for an estimated 63,800 excess reported cases from the declining trend seen from 1980 through 1984 [Center for Disease Control (CDC), 1994]. Fortunately, in 1993, the tuberculosis case rate in the U.S. resumed its decline and had reached its lowest rate (8.0 per 100,000 persons in 1996) since tuberculosis surveillance was begun (Snider, 1997; CDC, 1997).

Causative factors used to explain this tuberculosis resurgence between 1985 and 1993 include: the HIV (human immunodeficiency virus) epidemic, immigration from foreign countries, an increasing homeless population and an increasing number of intravenous drug abusers with higher potential for transmission through adverse living
conditions. Additionally, many city and state governments were unable to maintain or improve their tuberculosis treatment programs when the need for tuberculosis control had increased (Bloom and Murray, 1992; Cantwell, Snider Jr., Cauthen and Onorato, 1994).

From 1985 to 1993, the number of cases among children four years of age or younger increased in all ethnic groups except Native Americans; foreign born cases among children increased at more than three times the rate of U.S.-born cases (Cantwell et al., 1994). This trend is particularly worrisome since tuberculosis in young children indicates recent infection and these rates in young children are an often used measure of tuberculosis transmission within a community (Rieder, Cauthen, Comstock, and Snider, 1989).

In the early 1990’s, the Centers for Disease Control and Prevention investigated seven outbreaks of multiple drug resistant-tuberculosis (MDR-TB). Organisms isolated from patients in these outbreaks were characterized by resistance to the most powerful anti-tuberculosis drugs, isoniazid and rifampin (Bloch, Cauthen, Onorato, Dansbury, Kelly, Driver, and Snider Jr., 1994). A recent nationwide survey of drug resistance in tuberculosis found: the overall resistance rate to one or more drugs was 14.2 %, resistance to isoniazid and/or rifampin was found in 10 % of tuberculosis cases, and the risk of MDR-TB in racial and ethnic minorities was 10 to 15 times that of non-Hispanic whites (Bloch et al., 1994).

The consequences associated with resistance to both isoniazid and rifampin are severe. The minimum duration of therapy must be extended, mortality among patients with
MDR-TB may be extraordinarily high and MDR-TB cases may be associated with rapid progression from diagnosis to death (Dooley, Jarvis, Martone, and Snider Jr., 1992).

Of particular concern in the recent resurgence of tuberculosis is the number of reported foreign-born cases. In 1993, 70% of the nearly 25,000 cases reported occurred in ethnic minorities, and almost 30% of cases occurred in persons born outside the United States (Cantwell et al., 1994). Although there was a 6.4% decrease in tuberculosis cases in the U.S. from 1994 to 1995, the percentage of reported cases occurring in foreign-born persons living in the U.S. increased four percent from 32% to 36% (CDC, 1996).

In 1995, 22% of all foreign-born persons with tuberculosis (eight percent of the national total) were born in Mexico; of these, 81% were reported by the four U.S. states bordering Mexico - Arizona, California, New Mexico and Texas (CDC, 1996a). The incidence of tuberculosis in foreign-born persons residing in the western United States was almost twice the rate among foreign born-persons in the rest of the county (McKenna et al., 1995). From 1986 to 1993, most foreign-born patients with tuberculosis were from Latin America, with Mexico accounting for over one-half of these patients.

A 1996 CDC study characterized patterns of immigration and migration by foreign-born Hispanic patients receiving treatment for tuberculosis from public health departments in eight United States counties in close proximity to urban areas bordering Mexico (CDC, 1996a). Results of this CDC study indicated that a majority of the patients were from one of the six Mexican states bordering the U.S. Up to 82% of patients reported migrating back and forth between their county of origin during the year.
preceding their tuberculosis diagnosis, 14% doing so weekly to monthly. Tuberculosis prevalence among foreign-born Hispanic patients was 1.7 to 5.0 times higher and the prevalence of multidrug resistance (isoniazid plus rifampin) was 6.8 times higher than those among U.S. born non-Hispanic patients.

Problems encountered in treating tuberculosis along the U.S. / Mexico border mirror those identified by the CDC in treating tuberculosis among foreign-born persons entering the United States (CDC, 1990). These problems range from immigrants arriving in the U.S. with inadequately treated or drug resistant tuberculosis due to limited resources within their country of origin, to many local health departments with insufficient numbers of culturally sensitive outreach workers who speak the immigrants language. An additional problem is the potential development of MDR-TB related to the availability of prescription drugs along the U.S. / Mexico border.

Shepherd, Sasane and McKeithan (1997) have documented the availability of pharmaceutical products to residents on both sides of the border. Most therapeutic categories, including antibiotics, are considered over the counter and are readily available without a prescription in Mexico. Gellert (1994) addressed the issue of pharmacy practice and the potential for abuse of anti-tuberculosis medications along the US-Mexico border. The abuse or overuse of anti-tuberculosis medication with little or no medical supervision has serious implications for the selection of drug resistant forms of tuberculosis.

Costs are another concern related to the resurgence of tuberculosis. Two recently published studies have examined expenditures related to the treatment of tuberculosis. One
analysis found that the average cost of care and length of stay for a hospitalized patient with pulmonary tuberculosis were $20,222 (1992 dollars) and 18.7 days per patient (Shulkin and Brennan, 1995).

Brown, Miller, Taylor, Palmer, Bosco, Nicola, Zelinger and Simpson (1995) provide an extensive evaluation of the health care expenditures for tuberculosis in the United States. Direct medical expenditures for tuberculosis in 1991 were estimated at $703.1 million. Inpatient treatment accounted for 60% of the total expenditures for tuberculosis treatment, outpatient treatment accounted for 26%. The remaining 14% was spent on public health activities such as screening, contact tracing, preventive therapy and surveillance.

A median charge of $18,588 and 19.9 days per patient were calculated for the 20,803 hospital discharges with a principal diagnosis of tuberculosis. Estimated expenditures for outpatient treatment were $182.3 million. Outpatient drug therapy to combat tuberculosis ranged from $2,300 per patient in drug susceptible tuberculosis to $8,000 per patient in multiple drug resistant tuberculosis. Total expenditures for preventive therapy were estimated at $17.9 million.

The diagnosis of active tuberculosis is preceded by tuberculosis infection which indicates that a person has been infected by the Mycobacterium tuberculosis organism but has not progressed to active disease. Epidemiologic changes and costs seen in the recent tuberculosis resurgence may have been prevented via detection of tuberculosis infection and completion of a prevention program that utilizes isoniazid prophylactic therapy.
Isoniazid chemoprophylaxis was first conceived over 40 years ago by a group of workers in the U.S. Public Health Service (Grzybowski, 1986). Preventive therapy with isoniazid (given daily for 6 to 12 months) effectively decreases the risk (up to 90 percent) of future active tuberculosis in patients with tuberculosis infection. However, whether to prophylactically treat all tuberculosis infected patients remains controversial. The treatment dilemma is in weighing the potential hepato-toxicity of isoniazid against the potential survival benefits. The American Thoracic Society-CDC guidelines recommend isoniazid prophylaxis in all adult tuberculosis reactors with additional risk factors for active tuberculosis (Reichman, 1994).

As a result of the resurgence of tuberculosis in the mid 1980's a surge of work for public health tuberculosis clinics emerged. Nolan (1997) provides an example of a county health clinic in which during a five year period (1989 to 1993), tuberculosis related services delivered by the clinic increased - doubled in most cases. These services included annual visits, skin tests, chest x-rays, and isoniazid preventive therapy. The resurgence also aided tuberculosis to reappear in the medical literature and became a fashionable subject for the lay press.

Today, tuberculosis control program (usually state or county administered) services are still enlisted in the battle against tuberculosis. These services include screening, prevention, and treatment of tuberculosis. However, Teustch and Harris (1996) report that for many years it was sufficient to show that the benefits of a technology exceed its hazards before using it. Now, in a world of limited resources for public health,
officials must use resources as efficiently as possible and must demonstrate that a technology delivers value for the resources expended.

Short course drug therapy for active tuberculosis has been identified as one of the most cost-effective of all health care interventions available, and has been included in the essential package of clinical interventions recommend by the World Bank (The World Bank, 1993; Murray et al., 1990). However, the cost-effectiveness of tuberculosis prevention programs which use isoniazid preventive therapy may still be in question.

Tsevat, Taylor, Wong, and Pauker's (1988) economic analysis favored withholding preventive isoniazid therapy for tuberculin reactors with no additional risk factors of five age categories (20, 35, 50, 65 and 80). Murray et al. (1990) have indicated that preventive therapy would not be cost effective in developing countries. In most developing countries, the number of tuberculin-positive subjects is very large. Since only six to eight percent of recent converters evolve into active tuberculosis, approximately 15 % of recent tuberculin positive patients would have to be given chemoprophylaxis to prevent one case of tuberculosis (assuming prophylaxis is 100 % effective). Murray et al. (1990) suggest it would be more cost-effective to focus efforts on case-finding and treatment of patients presenting with symptoms suspicious of tuberculosis.

A 1995 study found that for HIV-negative tuberculin reactors aged 20 to 34 and living in areas with high isoniazid resistance, there was a minimal net benefit of isoniazid preventive therapy (Sterling, Brehm, and Frieden, 1995).

There have been many economic analyses which have shown the cost-effectiveness
of isoniazid preventive therapy in various treatment situations. Snider Jr., Caras, and Koplan (1986) found that a prophylactic regimen of 24 weeks duration was more cost-effective than either 12 or 52 week regimens. Rose, Schechter, Fahs and Silver (1988) performed a cost-effectiveness analysis which found that high risk tuberculin reactors taking isoniazid incurred a net savings of $429 per person, a small gain in life expectancy and fewer deaths from tuberculosis and isoniazid hepatitis. Cost-effectiveness ratios in this population were calculated at $12,625 per year of life gained and $35,011 per death averted.

Fitzgerald and Gafni (1990) developed a cost-effectiveness model which evaluated the use of isoniazid for patients with a positive skin test compared with no use of prophylaxis from a societal perspective. They found that for most age groups, the costs per case of tuberculosis prevented were not exorbitant and implied that the cost of preventing cases in high risk groups would be more cost-effective.

Age, ethnicity and gender were the focus of a study which used decision analysis in determining whether or not to use isoniazid preventive therapy (Jordan, Lewit, and Reichman, 1991b). In low risk reactors, isoniazid was preferred for all 20 year-olds, all 35 year-olds except black women and no 50 year-olds. Life expectancy gains by prescribing isoniazid ranged from 3 to 19 days of life. In high risk reactors, isoniazid preventive therapy was favored for all groups except 50 year-old black females. The risk of isoniazid induced hepatitis was cited as the reason isoniazid was not preferred in low risk black women over 35 years old, all low risk 50 year-olds and high risk 50 year-old
black females.

As illustrated by the results of previous economic studies appearing in the literature, the cost-effectiveness of prevention programs which use isoniazid therapy is typified by conflicting results. A point of contention with these previous cost-effectiveness studies is related to the scope of the study. One aspect of scope concerns the groups of people to be considered in the cost-effectiveness analysis (Torrance, Siegel and Luce, 1996).

Torrance et al. (1996) liken the scope of a cost-effectiveness study to drawing a circle around the study to contain it, noting that any cost-effectiveness study can become a career in itself if the investigator chases down every ripple or linkage related to the study. They suggest that the analyst must attempt to balance all significant effects of the intervention that will be relevant to the decision maker with the need to contain the study to the form of a manageable and feasible project.

Infectious diseases such as tuberculosis are transmitted across populations and, over time, a single case (or case prevented) can ultimately affect very large numbers of individuals. Many previous cost-effectiveness studies or economic analyses related to the use of isoniazid in tuberculosis prevention programs have not considered the results or outcomes of "downstream" or future effects of prevention with isoniazid.

Many previous studies have neglected to take into account the epidemiologic progression of tuberculosis infection and the potential for development of active tuberculosis cases (second generation cases). Specifically, the effects of a tuberculosis
prevention program (which uses isoniazid) on these second generation tuberculosis related transmission outcomes (morbidity, mortality, new cases, resources consumed) within the community is not clear. Previous studies may have drawn the circle around their study too narrowly and thus have failed to take into account many downstream outcomes associated with a tuberculosis prevention program.

Additionally, the cost-effectiveness of a tuberculosis prevention program may be population specific. For example, it is reasonable to speculate that tuberculosis prevention programs which utilize isoniazid chemoprophylaxis in high incidence tuberculosis areas may be more cost-effective than programs where tuberculosis incidence is low.

There is nothing in the published literature related to the cost-effectiveness of tuberculosis prevention programs that use isoniazid preventive therapy in a predominantly Hispanic population. Likewise, no published economic analyses appear related to the cost-effectiveness of a tuberculosis prevention program in the population along the U.S. / Mexico border.

Given the resurgence of tuberculosis (especially among the foreign-born); the problems associated with the development of multiple drug resistant tuberculosis; the costs involved in treating tuberculosis; and the problems health departments face in combating tuberculosis along U.S. / Mexico border (primarily due to immigration); a comprehensive analysis is needed, focusing on the cost-effectiveness of a tuberculosis prevention program which employs isoniazid therapy in this unique and unstudied population. One such method is through the use of a prevention effectiveness analysis or
Prevention Effectiveness Framework

Prevention effectiveness assessment is the scientific approach to evaluating the effectiveness of prevention strategies (Teutsch, 1992). Prevention effectiveness studies involve the systematic assessment of the impact of public health policies, programs and practices on health outcomes. The roots of these studies lie in the assessment of medical technology and in research on health services and outcomes (Teutsch and Harris, 1996).

Prevention effectiveness studies seek to link directly the intervention with the health outcome of interest (e.g., mortality, quality of life) by pulling together information from epidemiology and public health surveillance, intervention studies and economic analyses. Prevention effectiveness analyses provide a systematic approach to organizing available information about prevention strategies so that decision and policy makers can have a scientific framework for making decisions.

Description of the Prevention Effectiveness Model

Figure 1 provides a conceptual model for the development and implementation of prevention strategies and the role of prevention effectiveness. The evolution of public health strategies range from basic scientific research to implementation into the general population. Basic research provides the foundation by identifying biological risk factors. Once risk factors are understood, strategies for potential intervention programs are developed.

After risk factors have been determined, applied research seeks to provide
Figure 1. Evolution of Prevention Strategies and the Role of Prevention Effectiveness

Basic Research → Applied Research → Community Demonstrations → Implementation


Prevention Effectiveness

Quantitative Methods
- Descriptive Epidemiology
- Decision Analysis
- Economic Analysis
- Meta-analysis

Qualitative Assessments
- Distributional Effects
- Legal Effects
- Ethical Effects
- Social effects

Source: Teutsch, SM. A framework for assessing the effectiveness of disease and injury prevention programs. MMWR 1992;41: (no. RR-3).

information on the efficacy of an intervention. Efficacy answers the question “Does it work?” The efficacy of a particular intervention or therapy is usually proved by experts under ideal conditions, with randomized controlled studies serving as the gold standard.

Community based demonstrations are then used to assess the real world effectiveness of the prevention strategy. Effectiveness answers the question “How well does it work in the real world?”, and is defined as the impact that an intervention achieves in the real world under practical resource constraints in an entire unselected population. Effectiveness will almost always be lower than efficacy, because of individual compliance, resource constraints and coverage of an intervention strategy.
Once the efficacy of the intervention has been established, the domain of prevention effectiveness begins. The prevention effectiveness process continues from the development of the technology to their application in real world settings. Epidemiologic, mathematical or economic models can be constructed to estimate the potential future impact of an intervention program (Teutsch, 1992). If the intervention or program already exists, data and results from actual program experience may be used to modify the programs and to provide more accurate estimates of changes in outcomes and associated costs and benefits.

Conducting a prevention effectiveness analysis involves three essential steps (Haddix, Teutsch, Shaffer and Dunet, 1996). The first, framing the question, addresses thirteen key points at the start and is one of the most important steps in the successful completion of the prevention effectiveness analysis (Farnham, Ackerman and Haddix, 1996). These key points range from defining the audience for the evaluation, specifying the perspective of the evaluation, determining the analytic method or economic model to employ, to performing sensitivity analyses. The second step in conducting a prevention effectiveness analysis involves structuring the decision model. The third requires analyzing the model and interpreting the results.

**Economic Models**

The economic models most often used in a prevention effectiveness study include cost-effectiveness, cost-benefit or cost-utility analysis. Cost-effectiveness analysis (CEA) involves the comparison of the net resource effect (costs) of an intervention with some
non-monetary measure of its net effect on health outcome (effectiveness) [Chrischilles, 1991]. Results of a cost-effectiveness analysis are presented in the form of cost-per-health outcome, such as, cost-per-life saved. Cost-effectiveness analysis is most useful when the interventions being compared have one clear and specific outcome.

Cost-benefit analysis (CBA) seeks to answer the question "Will the benefits of a program exceed the cost of implementing it?" It compares the value of all resources consumed (costs) in providing a program or intervention with the value of the outcome (benefit) from that program or intervention (Kitz, 1991). Costs and benefits are valued in the same units, usually dollars.

There are certain advantages to using cost-benefit analysis over cost-effectiveness analysis (Kitz, 1991). Cost-benefit analysis may be used to compare programs with different outcomes; cost-effectiveness analysis identifies the least costly approach for a single outcome. The disadvantage (to some) is that cost-benefit analysis requires that all the outcomes or benefits be assigned a dollar value. Some investigators not only find it distasteful, but difficult, to place a monetary value on something like a human life and opt for cost-effectiveness analysis instead.

Cost-utility analysis (CUA) is a specific kind of cost-effectiveness analysis that is appropriate when quality of life is an important outcome or the program being evaluated affects both morbidity and mortality (Dasbach and Teutsch, 1996). In CUA, the intervention outcome or consequence is measured in terms of patient preference or quality of the health outcome. The results of a cost-effectiveness analysis are usually expressed in
intervention cost–per-quality adjusted life year (QALY) gained or changes in quality of life (QOL) measurement for a given intervention cost (Bootman, Townsend, and McGhan, 1991).

**Decision Models**

The economic models used in prevention effectiveness analyses often utilize mathematical or simulation models in determining outcome probabilities and in incorporating costs for different outcomes for the prevention intervention under study. Most often, modeling is out of necessity since data for many of the economic models may be incomplete.

Models for estimating cost-effectiveness in a prevention effectiveness analysis may be characterized by several non-mutually exclusive characteristics (Mandelblatt, Fryback, Weinstein, Russell, Gold, and Hadorn, 1996). First, models must employ an analytic methodology to account for events over time. Decision-tree, state-transition and other types of dynamic models are different, but related, mathematical models that represent the unfolding of a process over time. Second, models may apply to cohorts longitudinally or to populations cross-sectionally. Third, models may be either deterministic or stochastic (probabilistic). In the deterministic models, the average number of events per population is used. In stochastic models, randomization is used to simulate the probability distributions that events might occur.

Mandelblatt et al. (1996) note, “no model is a perfect representation or reality; its validity rests on whether its assumptions are reasonable in light of the needs and purposes
of the decision maker and, importantly, in light of whether, after close examination, its implications make sense."

Decision analysis is an explicit, quantitative, and systematic approach to decision making under conditions of uncertainty (Barr and Schumacher, 1991; Weinstein et al., 1980; Snider, Holtgrave and Dunet, 1996). Decision analysis uses mathematical tools to help decision makers choose the option that maximizes utility for an individual, to society or a community. It can be used as a stand alone method for decision making or it can be used to calculate cost per unit of outcome in cost-effectiveness analyses and net present value in cost-benefit analyses.

One limitation of decision analysis models is that they are not well suited to representing recurrent events that repeat over time (Mandelblatt et al., 1996). In some diseases or cases, events and probabilities of events (such as complications from the disease or its treatment, recurrence of disease and mortality) are confronted and change repeatedly during a lifetime. Rather than model each event as a separate branch of a complex decision tree, more efficient representations of such events may be modeled by the use of state-transition models.

State-transition models allocate members of a population into one of several categories or health states. Health states are defined according to disease stage, treatment status, or a combination of the two. Transitions occur from one state to another at defined recurring time intervals according to transition probabilities. Through simulation, or mathematical calculation, the numbers of members of the population passing through each
state at each point in time can be estimated. State transition models can be used to
calculate life expectancy or quality adjusted life expectancy.

A Markov model is a special type of state-transition model in which the transition
probabilities depend only on the current state and not on the previous states or the path by
which the state was entered. Markov models are particularly useful when a problem
involves a risk that is ongoing over time (Sonnenberg and Beck, 1993).

Markov models are categorized by whether or not state-transition probabilities are
constant over time. A Markov chain model is characterized by the assumption that each of
the transition probabilities are fixed over time. A Markov process is characterized by time
dependent transition probabilities.

One method in which Markov processes can be represented is through the use of a
Monte Carlo simulation (Sonnenberg and Beck, 1993). A Monte Carlo simulation
determines the prognoses of a large number of individual patients which pass through the
model one at a time. A random number generator is used with the transition probabilities
to determine in which state the patient will begin the next cycle. A patient is given credit
for each cycle spent in a particular state depending on the incremental utility of that state.
When a patient reaches an absorbing state, the simulation ends.

This simulation is repeated for a large number of patients, usually on the order of
10,000. Once all patients have progressed through the simulation, the average number
of cycles in each non absorbing state can be calculated (equivalent to life expectancy)
and average number of cycles in each state may be estimated.
Distributional Effects

The final component of the prevention effectiveness framework is the consideration of social, legal, and distributional aspects of the prevention strategy in the decision making process (Teutsch and Harris, 1996). Many prevention interventions or strategies have much broader effects than health outcomes. Teutsch and Harris (1996) provide excellent examples of these aspects in a prevention strategy.

The social impact of an intervention is exemplified by condom distribution in schools which has raised concerns reflecting the conflicting social values involving students, parents, educators and public health officials. Prevention strategies can also have an influence on the legal system and procedures. The banning of smoking in public places and commercial airlines are examples where advances in public health required changes in legislation. Distributional effects refer to the population to whom prevention programs are directed. Alternate strategies (such as use in a high-risk population versus an entire population) may have very similar costs and benefits, yet the groups that benefit may differ significantly.

Statement of the Problem

Preventive therapy with isoniazid has been proven effective in preventing the development of active tuberculosis in patients who complete at least a six month course of therapy (IUAT-Committee on Prophylaxis, 1982; Snider et al., 1986; CDC, 1990a). In fact, preventive therapy with isoniazid has been utilized by tuberculosis prevention programs in the fight against tuberculosis for the last 40 years (Grzybowski, 1986).
Previous research has found prevention programs which use isoniazid therapy against tuberculosis (in various patient populations and settings) cost-effective in most cases, some studies however, have concluded the opposite.

The cost-effectiveness of a tuberculosis prevention program which utilizes isoniazid therapy in a predominantly Hispanic patient population along the U.S. / Mexico border has not been explored. Thus, a prevention-effectiveness study is needed in order to assess the cost-effectiveness of a tuberculosis prevention program comparing all relevant costs (incurred and prevented) and the intended health outcome (the number of tuberculosis cases averted or prevented).

**Statement of Purpose**

The purpose of this research was to compare the cost-effectiveness of a tuberculosis prevention program which utilized isoniazid preventive therapy along the U.S. / Mexico border against a no tuberculosis prevention program scenario. The prevention effectiveness framework was used to model the cost-effectiveness from a county government perspective.

The determination of cost-effectiveness required the estimation of cost and effectiveness components. Costs were calculated using actual data from tuberculosis prevention and active tuberculosis treatment programs as well as hospital discharge data related to hospital admissions for active tuberculosis. Monte Carlo simulated Markov process models were developed to estimate the effectiveness outcome of interest; number of tuberculosis cases averted. The cost-effectiveness ratio determined for this research was
the cost-per-case of active tuberculosis averted for the prevention program scenario.

Average and incremental cost-effectiveness ratios were calculated.

Research Objectives

The following were the proposed research objectives:

1. Determine the probability of the outcome (number of tuberculosis cases averted) associated between the prevention and no prevention program scenarios.

2. Determine direct costs incurred by the prevention program scenario.

3. Determine cost savings associated with the prevention of active tuberculosis by the prevention program scenario.

4. Determine cost savings associated with the prevention of future active tuberculosis cases that would occur due to the contagious nature of tuberculosis in the absence of the prevention program scenario.

5. Determine the average cost-effectiveness ratio for the prevention program scenario.

6. Determine the incremental cost-effectiveness ratio for the prevention program scenario.

Significance of the Problem

An extensive evaluation of health care expenditures for tuberculosis in the United States has documented the staggering costs related to tuberculosis treatment and prevention (Brown et al., 1995). Expenditures for prevention and surveillance composed only 14 % ($98.4 million) of the total direct medical tuberculosis expenditures (estimated
at $703.1 million in 1991). Of the 14% spent on prevention and surveillance, total expenditures for preventive therapy with isoniazid were estimated at $17.9 million. Brown et al. (1995) advocate that (from a public health perspective) cost-benefit analyses of the use of preventive tuberculosis therapy in high-risk populations could strengthen the argument for prevention strategies for tuberculosis, particularly when compared with the high costs of inpatient treatment.

Zuber, McKenna, Binkin, Onorato and Castro (1997) have recognized that the number of immigrants from countries with high prevalence of tuberculosis to the U.S. has continuously increased during the last 15 years. As a result, the number of long term residents with latent infection most likely will rise in the coming years. The rise in latent infection rates may be accompanied by an increased number of active tuberculosis cases.

Zuber et al. (1997) advocate that broader use of preventive therapy for persons at highest risk of reactivating a latent tuberculosis infection acquired before immigration is needed to strengthen the control of tuberculosis. McKenna, McCray, and Onorato (1995) add that tuberculosis control programs that minimize barriers to appropriate screening and preventive therapy must be available to foreign-born residents if progress is to be made in the control of tuberculosis.

A continual increase in the number of immigrants would significantly impact tuberculosis control programs along the U.S. / Mexico border. If immigration (both legal and illegal) continues to rise, county health departments will ultimately bear the full brunt of the new tuberculosis cases; financial, personnel and time wise. A prevention
effectiveness evaluation which potentially shows the cost-effectiveness of a tuberculosis prevention program in this border population could strengthen their position in the eyes of policy or decision makers. Additionally, the results of the prevention-effectiveness evaluation may be used as a tool for acquiring needed or additional resources.

Most importantly, if this prevention effectiveness analysis is successful in elucidating the cost-effectiveness of a tuberculosis prevention program in this population; guidelines related to screening and subsequent preventive therapy may be strengthened in this potentially high risk population. This would ultimately reap benefits by reducing the number and spread of active tuberculosis cases, not to mention costs associated with their treatment.

Definitions

alien - defined in the U.S. immigration and Nationality Act as any person not a citizen or national of the United States.

decision analysis - explicit, quantitative, systematic approach to decision making under conditions of uncertainty in which probabilities and consequences of each possible event are explicitly stated.

discharging - a method used to adjust the value of future costs and benefits to an equivalent value today (present value) that accounts for time preference and opportunity cost.

economic evaluation - comparative analysis of alternative courses of action in terms of both their costs and consequences.

incremental cost-effectiveness ratio - the ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives.

Markov model - a mathematical model containing a finite number of mutually exclusive and exhaustive health states, with time periods of uniform length, in which the probability of movement between states depends on the current state.
Markov process - a modeling technique that describes the transitions a cohort of patients make among a number of health states during a series of short intervals or cycles.

Monte Carlo simulation - a simulation modeling technique that utilizes random numbers to capture the effects of uncertainty. Multiple simulations are run and simulation results are compiled, providing a probability distribution for the overall result.

multiple-drug resistant tuberculosis (MDR-TB) - *mycobacterium tuberculosis* strains which are resistant to at least two anti tuberculosis drugs.

*mycobacterium tuberculosis* - the tuberculosis bacillus, the cause of the vast majority of tuberculosis cases.

sensitivity analysis - mathematical calculations that isolate or consider factors or parameters involved in a decision or economic analysis to indicate the degree of influence each factor or parameter has on the outcome of the entire analysis. Used to measure the uncertainty of the probability distributions.

state transition model - models which allocate, and subsequently reallocate, members of a population among health states. Transitions from one state to another occur at predetermined, recurring time intervals according to transition probabilities. The number of members of the population passing through each state at each point in time can be calculated or estimated through simulation or mathematical calculation.

stochastic model - health care process models that use computer generated random numbers to simulate the occurrence of events over time. Events are simulated to a cohort over time by modeling the time course for each individual as a series of random events controlled by specified probabilities in the simulation.

undocumented alien - any alien who entered the U.S. without inspection, or someone in the U.S. in violation of the Immigration and Nationality Act or any other law in the U.S.
CHAPTER 2
REVIEW OF THE RELATED LITERATURE

This chapter presents a review of the literature related to this research. The salient literature can be divided into nine major areas.

1. A review of the literature related to the incidence of tuberculosis worldwide and in the United States.


3. A review of the literature related to the incidence of tuberculosis and tuberculosis related treatment problems along the U.S. / Mexico border.


5. A review of the literature related to the costs of treating tuberculosis in the United States.


7. A review of the framework for economic evaluations in medicine.

8. A review of the role of decision analysis and Markov modeling in the economic evaluation process.

9. A review of the literature assessing the economic evaluation of tuberculosis prevention programs which utilize isoniazid preventive therapy.
Tuberculosis Incidence

Worldwide

Tuberculosis remains an important public health problem worldwide, resulting in an estimated eight to ten million new cases and two to three million deaths yearly (Kochi, 1991). An estimated 1.7 billion people, one third of the world's population, are infected with *Mycobacterium tuberculosis* and are at risk for developing the disease (Barnes and Barrows, 1993). Worldwide, tuberculosis is the leading cause of death from a single infectious disease, accounting for over one fourth of avoidable deaths among adults (Nakajiima, 1993).

Tuberculosis is out of control in many parts of the world. The majority of cases, and more than 95% of the deaths related to tuberculosis, occur in the developing world (Nakajiima, 1993). However, the number of cases in North America and Europe have risen dramatically from 1988 to 1993. Nakajiima warns that tuberculosis cannot be controlled in the industrialized countries unless it is sharply reduced as a health threat in the developing countries of Asia, Africa, and Latin America.

The global tuberculosis incidence and mortality rates for the years 1990-2000 have recently been estimated (Dolin, Raviglione, and Kochi, 1994; Raviglione et al., 1995). For the 10 year period 1990-99, it is estimated that 88.2 million people will develop tuberculosis, eight million of which will be secondary to HIV infection. During the same 10 year period, it is estimated that 30 million people will die of tuberculosis. Almost three million (10%) of these deaths will be in those suffering from HIV infection. The number
of new tuberculosis cases occurring each year is predicted to increase from 7.5 million in 1990, to 8.8 million in 1995, to 10.2 million in the year 2000.

United States

In the United States, a national system of reporting tuberculosis cases was started in 1953, at which time 84,304 cases were reported (Raviglione et al., 1995). Since 1953 the United States experienced a significant decline in cases to a low of 22,255 cases in 1984; an average decline in cases of approximately 5.3 % per year. However, from 1985 to 1993, the number of reported cases increased to about 14 %. This increase resulted in an estimated 63,800 excess cases from the declining trend seen from 1980 through 1984 (CDC, 1994).

Bloom and Murray (1992) have provided factors that help explain the resurgence of tuberculosis cases between 1985 and 1993. These factors include: (1) the HIV epidemic, (2) an increasing homeless population with a higher potential for transmission through adverse living conditions, (3) increasing number of intravenous drug users with similar adverse living conditions, (4) the concentration of all three of these risk factors in combination in these population subgroups, and (5) at a time when the need for tuberculosis control had increased, many city and state governments were unable to maintain or improve their tuberculosis treatment programs. Cantwell et al. (1994) reported that immigration into the U.S. from foreign countries also contributed to the excess tuberculosis mortality during this time period.

The HIV epidemic has greatly contributed to the trend in tuberculosis morbidity.
The largest increases in reported tuberculosis cases have occurred in age groups and geographic areas affected by the HIV epidemic. Raviglione et al. (1995) report that the matching of tuberculosis and AIDS registries by the CDC in 1990 has revealed that almost five percent of reported AIDS cases were also in the tuberculosis registry. Additionally, the CDC’s HIV seroprevalence surveys in tuberculosis clinics have demonstrated a high prevalence of HIV infection among tuberculosis patients.

From 1985 through 1993, all age groups under the age of 65 years experienced an increase in tuberculosis cases, the largest among persons 25 to 44 years old (Cantwell et al., 1994). Cases of tuberculosis in young children are the result of recent infection and are often used as measures of tuberculosis transmission within a community (Rieder et al., 1989). From 1985 through 1992, the number of cases among children four years of age or younger increased in all ethnic groups except Native Americans. The number of foreign-born cases in young children increased at more than three times the rate of U.S.-born cases. However, it could not be determined if these increases were the result of transmission before or after immigration (Cantwell et al., 1994).

Of the tuberculosis cases reported in 1993, 70% of the nearly 25,000 cases occurred in ethnic minorities, and almost 30% of cases occurred in persons born outside the United States (Cantwell et al., 1994). Case rates per 100,000 persons in 1992 were 4.0 in non-Hispanic whites, 16.3 in American Indians/Native Americans, 22.4 in Hispanics, 31.7 in non-Hispanic blacks, and 46.6 in Asians/Pacific Islanders. Non U.S.-born individuals accounted for 60% of the increase in cases from 1986 to 1992.
Since 1993, the tuberculosis case rate in the United States resumed its decline and had reached its lowest rate for tuberculosis cases reported (8.0 per 100,000 persons in 1996) since tuberculosis surveillance was begun in 1953 (Snider, 1997; CDC, 1997). Snider (1997) contends that the resumption of the decrease in the rate of new cases was largely due to a reinfusion of federal funds, the expansion of inner-city clinics and the institution of directly observed treatment. Interestingly, although there was a decrease of 6.4% in the number of reported cases of tuberculosis in the U.S. from 1994 to 1995, the percentage of reported cases occurring in foreign-born persons increased 4% from 32% to 36% (CDC, 1996).

**Multiple Drug Resistant Tuberculosis in the United States**

Cohen (1992) provides a useful perspective on the epidemiology of drug resistance and its implications. Cohen explains that the development and use of antimicrobial agents was one of the most important measures leading to the control of bacterial diseases in the twentieth century. Today, the concept of an untreatable disease is foreign to most physicians in the developed world. The introduction of a new drug was almost always followed by resistance; however, there were always newer drugs.

Recently, the continued general effectiveness of antimicrobial agents is in question. The emergence of multiple drug resistance not only in *Mycobacterium tuberculosis*, but in other microbes such as *Streptococcus pneumoniae* and *Staphylococcus aureus* have made many currently available antimicrobial drugs ineffective. In certain instances, the emergence of multiple drug resistance is already posing important public health problems.
Cohen further reports that fewer new antimicrobial drugs are under development.

One of the more important consequences of antimicrobial resistance is that resistance can lead to an increase in the incidence of disease (Cohen, 1992). An example of this would be a person infected with a multidrug-resistant strain of *Mycobacterium tuberculosis* who has not been effectively treated may continue to pose a risk of transmission. This is in contrast to the patient infected with a susceptible strain for whom treatment prevents transmission.

In 1990, the CDC investigated outbreaks of multiple drug resistant tuberculosis (MDR-TB) in two large U.S. cities (Bloch et al., 1994). In 1992, the trend continued with MDR-TB outbreaks reported in six hospitals in the eastern U.S. as well as a state correctional system. Organisms isolated from patients involved in these outbreaks were characterized by resistance to the most powerful anti-tuberculosis drugs, isoniazid and rifampin. Often, the outbreaks were accompanied by resistance to other first line anti-tuberculosis drugs (ethambutol, streptomycin, and pyrazinamide).

There are severe consequences of resistance to both isoniazid and rifampin (Dooley et al., 1992). The minimum duration of therapy must be extended from 18 to 24 months. Mortality among patients with MDR-TB in the outbreaks mentioned above was extraordinarily high (73 to 89 %) and was associated with rapid progression from diagnosis to death (with a median interval of 4 to 16 weeks). Health care workers at hospitals experiencing outbreaks of MDR-TB have shown positive tuberculin skin test results after exposure to patients with MDR-TB. At least eight health care workers
at these hospitals where the outbreaks occurred developed active MDR-TB.

The first attempt in assessing the incidence of drug resistance for all tuberculosis patients reported in the United States during a given time period was reported in 1994 (Bloch et al., 1994). Using 1991 first quarter data, the important findings of this survey included the following: overall rate of resistance to one or more drugs was 14.2 %, a resistance rate of 13.4 % in new cases with no history of tuberculosis and 26.6 % in cases with recurrent disease.

A disturbing finding was that nearly 10 % of tuberculosis cases were resistant to isoniazid and/or rifampin. In addition, the risk of MDR-TB in ethnic minorities was 10 to 15 times that of non-Hispanic whites. If the data from culture positive cases reported in the first quarter of 1991 were representative of the entire year; the authors estimate that for all of 1991, there may have been 2,500 patients nationwide with organisms resistant to one or more anti-tuberculosis drugs.

In 1993, an expanded tuberculosis surveillance program was implemented in response to the unprecedented upturn in tuberculosis morbidity and outbreaks of MDR-TB described above (Bloch, Onorato, Ihle, Hadler, Hayden and Snider Jr., 1996). The new surveillance system allows for a comparison of the quality of care of patients in both the public and private sectors. The new surveillance system will also allow for epidemiologic variables such as membership in high-risk groups, history of substance abuse, and HIV status. The new system will also capture initial drug susceptibility results on culture positive patients. This information will allow for monitoring of the
epidemiology of drug resistance and will assist in detecting outbreaks of MDR-TB so that appropriate interventions can be implemented.

Tuberculosis Incidence and Treatment Problems Along the U.S./Mexico Border

Published research regarding the true incidence of tuberculosis along the U.S./Mexico border is limited. A piece meal attempt will be performed to provide some evidence as to the incidence and treatment problems related to tuberculosis in this area.

Incidence

McKenna et al. (1995) recently published an epidemiologic study on the incidence rates of tuberculosis among foreign-born residents in the United States. The study used data from the national reporting system for tuberculosis and from U.S. Census Bureau surveys of the foreign-born population. They report that the proportion of patients reported to have tuberculosis who were classified as foreign-born increased from 21.6% in 1986 to almost 30% in 1993.

The CDC reported that by 1995, the percentage of tuberculosis cases among foreign-born persons in the United States had increased to 35% of the national total (CDC, 1996a). In 1995, 22% of all foreign-born persons with tuberculosis (eight percent of the national total) were born in Mexico. Of these 22%, 81% were reported by the four U.S. states bordering Mexico-Arizona, California, New Mexico, and Texas.

The incidence of tuberculosis in foreign-born persons residing in the western United States was almost twice the rate among foreign-born persons in the rest of the country (McKenna et al., 1995). Although the tuberculosis rate was highest among those
from Asia, there were more patients with tuberculosis from Latin America. Mexico represented the country of origin for almost 57% of the 21,115 patients from Latin America over the eight year period (1986 to 1993). The case rate for foreign born Hispanic persons over this eight year period was 32.2/100,000 person years. In U.S.-born Hispanics the case rate over this same time period was 22.1/100,000 person years, the total case rate for U.S.-born persons of all races was 8.1/100,000 person years.

McKenna et al. (1995) reported that between 1980 and 1990, the foreign-born population in the United States increased by over 40%. The top five countries of origin during this period were Mexico, the Philippines, Vietnam, China and Korea. The tuberculosis incidence rates in these countries are 10 to 30 times greater than that in the United States. McKenna et al. (1995) suggest that this increase in immigration has profoundly affected the recent epidemiology of tuberculosis in the United States.

In 1996, the CDC reported an epidemiologic study conducted in 1995 which sought to characterize patterns of immigration and migration among foreign-born Hispanic patients with tuberculosis and their health seeking behavior (CDC, 1996a). The study included foreign-born Hispanic patients receiving treatment for tuberculosis from public health departments in eight United States counties bordering Mexico. The study included one county each from Arizona and New Mexico, two from California and four from Texas. Counties represented in the study were selected because they included urban areas in close proximity to urban areas in Mexico.

The majority (94%) of the 169 patients interviewed were from Mexico, the other
6% were from Central America. Of the patients born in Mexico, 78% reported being born in one of the six states of Mexico bordering the United States. Eighty-two percent of the participants reported ever returning to their country of origin. Most (73%) had returned during the year preceding their tuberculosis diagnosis; 21% reported returning at least weekly, 14% weekly to monthly, and 25% monthly to yearly.

Prevalence of single-drug resistance among foreign-born Hispanics patients was compared with prevalence in U.S. born non-Hispanic patients and U.S. born Hispanic patients residing in the same eight counties for 1995. Prevalence among U.S. born Hispanic patients was 1.6 to 3.2 times higher than U.S. born non-Hispanics. Prevalence among foreign-born Hispanic patients were 1.7 to 5.0 times higher than those among U.S. born non-Hispanic patients. The prevalence of multidrug resistance (isoniazid plus rifampin) was 6.8 times higher among foreign born Hispanic patients than among U.S. born non-Hispanic patients. Multidrug resistance prevalence rates among U.S. born and foreign born Hispanic patients were similar (CDC, 1996a).

Tuberculosis Related Treatment Problems

Published data regarding the treatment of tuberculosis in populations along the U.S. / Mexico border are scarce. However, many of the problems encountered in treating this population are very similar to those identified by the CDC in treating tuberculosis among foreign-born persons entering the United States (CDC, 1990).

The CDC has identified the following problems associated with the screening and follow up of patients with tuberculosis:
1. Aliens enter the U.S. with active tuberculosis that was missed during the required medical examination. Misdiagnosis may occur due to reasons related to equipment or technical competence. Since a medical examination is valid for an entire year, a visa applicant who was free of tuberculosis at the time of the exam may have developed tuberculosis in the time period before arriving in the U.S.

2. Persons with tuberculosis may enter the U.S. under a waiver but fail to comply with the waiver provisions calling for further examinations and/or therapy. If an alien with tuberculosis is granted a waiver of excludability and is allowed to enter the U.S., there is a requirement that medical care be sought immediately upon arrival in the U.S. However, no federal mechanism exists for assuring that these aliens report for evaluation or comply with treatment recommendations.

3. Some aliens arrive in the U.S. with inadequately treated or drug resistant tuberculosis. Some applicants may have been diagnosed with tuberculosis prior to application for admission to the U.S. Due to limited resources in other countries, the treatment these aliens received may have been inadequate, delayed, or inappropriate and are at the risk of relapsing with drug-resistant disease.

4. Aliens in certain classifications may enter the U.S. for extended periods without being required to have a medical evaluation for tuberculosis. Aliens may enter the U.S. for protracted stays (greater than one year) without being required to undergo a medical examination before entry. This accounted for one million people in 1988 (CDC, 1990). College students pose a special problem because they often stay for greater than four
years, and transmission may occur in dormitory settings.

5. Aliens enter the U.S. infected with the tubercle bacilli but do not have current disease. A large portion of tuberculosis cases are the result of foreign-born persons who had asymptomatic infection and are from countries where, one-half or more of the adult population is infected and at risk for developing tuberculosis. Tuberculosis skin testing is the only available method for identifying these people.

A 1993 study found a 42% prevalence rate for tuberculosis infection (via a positive skin test) in 4,840 applicants applying for adjustment of immigration status with the Immigration and Naturalization service in Denver (Blum, Polish, Tapy, Catlin, and Cohn, 1993). The majority of patients (75%) were between the ages of 15 and 34 years, 91% were from Mexico.

6. Some undocumented aliens may have tuberculosis when they enter the U.S. or may develop it after entry. The problems presented by undocumented aliens with tuberculosis infection or active disease are much more difficult to address because: 1) no mechanism exits for identifying them when they enter, and 2) they tend to avoid official public agencies because of fear of deportation.

7. Foreign-born persons who enter the U.S. often have language, cultural, and financial adjustment problems that may serve as barriers to obtaining tuberculosis treatment and follow-up. Many local health departments do not have sufficient numbers of culturally sensitive outreach workers who speak the aliens’ language.

McKenna et al. (1995) report that there are more that 20 million non-immigrant
visitors and students and an estimated 200,000 undocumented immigrants who enter the U.S. every year. The impact of these visitors and undocumented workers (who do not undergo a prescribed medical evaluation before entry) on the tuberculosis rate is impossible to estimate given the current surveillance data. This may be due in part to the reluctance of local health departments to inquire about legal status, because illegal residents with infectious disease may delay seeking care if they suspect they will be reported to immigration authorities (Asch, Leake, and Gelberg, 1994).

Assessment of the magnitude of drug resistance to tuberculosis agents in this region is also very challenging. Cohn, Bustreo, and Raviglione (1997) report that there are several limitations to adequate assessment of the drug resistance problem, especially in developing countries. In many areas there are no or few facilities for laboratory cultures, and whenever they exist, antimicrobial susceptibility testing is often not performed.

The CDC supports five bi-national projects which involve the collaboration of paired cities on both sides of the U.S. / Mexico border. These projects were developed to direct resources to areas of need and to develop cooperative working relations between health professionals managing tuberculosis control and prevention programs along both sides of the U.S. / Mexico border (CDC, 1996a).

One additional problem related to the development or potential development of multiple drug resistant tuberculosis is the availability of prescription drugs along the U.S. / Mexico border. McKeithan and Shepherd (1996) and Shepherd et al. (1997) have documented the availability of pharmaceutical products to residents on both sides of the
border. McKeithan and Shepherd (1996) found that an average of 67 U.S. residents declared pharmaceutical products (purchased in Mexico) daily at one U.S. port of entry from Mexico.

Aside from being cheaper (by 35 % to 1,000 % in some cases), the sale of pharmaceutical products are less regulated in Mexico compared to the U.S. Therapeutic categories such as antibiotics, antihypertensives, antihistamines, anti-inflammatory agents, anti-ulcer medications and estrogen-containing products are considered over-the-counter and are readily available without a prescription.

Pharmacists in Mexico frequently play the role of a “quasi-physician”. They diagnose conditions, recommend treatment and sell drug products to patients. However, the Mexican pharmacist is not considered a member of the health care team. Many Mexican pharmacists are not college or university graduates, but rather, learned to practice pharmacy through an apprenticeship with another pharmacist. There are no licensing requirements or continuing education requirements for pharmacists in Mexico.

Pharmacy practice standards in Mexico are vastly inferior to those of the U.S. Few Mexican pharmacies are computerized and most do not maintain patient profiles. The concepts of drug screening and comprehensive pharmaceutical care are not well developed in Mexico, especially in the border towns (Shepherd et al., 1997).

Gellert (1994), in a letter to the editor of the *Journal of the American Medical Association* addressed the issue of pharmacy practice and antibiotic-resistant tuberculosis along the U.S. / Mexico border. Gellert describes a 1993 case in which a nurse practicing
in the U.S. city of Nogales, Arizona, encountered a mother who was treating her child for a month long history of cough with rifampin suspension. The mother had purchased the drug over the counter at a Nogales, Mexico pharmacy at the recommendation of a local pharmacist and was administering it without medical oversight.

Gellert then conducted a study to assess the scope of this case. The study, included 17 Nogales, Mexico pharmacies during a single four hour period. In response to the interviewer’s question of a recommendation for a five year old child with a “bad-cough” of one month duration, all pharmacists recommended an antibiotic. When asked what would be recommended if the child had tuberculosis, 82 % of pharmacists responded that the mother should see a physician; only one pharmacist produced a rifampin suspension before the interviewer inquired about tuberculosis. When the interviewer specifically requested the rifampin suspension, 11 of 12 pharmacists (92 %) produced the rifampin and stated that it could be purchased immediately.

Gellert reports that despite the fact that the product clearly indicated on the label that a medical prescription was required, only one pharmacist stated that the rifampin was controlled and refused to sell it. Gellert concludes that this data indicate a potential for abuse of anti-tuberculosis medications along the U.S. / Mexico border. The abuse or overuse of anti-tuberculosis medication with little or no medical supervision has serious implications for the selection of drug resistant forms of tuberculosis.
History and Guidelines of Preventive Tuberculosis Programs Utilizing Isoniazid Preventive Therapy

A sobering look at the reemergence and dramatic transformation in the epidemiology of tuberculosis has been presented. However, epidemiologic changes such as the proliferation of multiple drug resistant tuberculosis and the spread of active tuberculosis may have been prevented with detection of tuberculosis infection and completion of a prophylactic drug regimen of isoniazid.

History

Grzybowski (1986) has provided a concise history on the use of isoniazid chemoprophylaxis in tuberculosis prevention programs in the United States. Isoniazid chemoprophylaxis was first conceived over 40 years ago by a group of workers in the U.S. Public Health Service. A landmark study followed which found that isoniazid prophylaxis reduced morbidity from tuberculosis by 50 to 80% in individuals who took the drug for a period of 12 months.

Attempts were then made to tuberculin test large groups of the general population, such as employees of certain industries, and to place reactors on a course of preventive therapy. These attempts were generally unsuccessful because of the difficulty in securing compliance with regular and prolonged treatment. The emphasis then turned to certain groups of infected individuals at high risk, such as contacts of active cases of tuberculosis, those who were recently infected (tuberculin converters) and previously untreated, or poorly treated cases with inactive disease.
A tragedy in Baltimore in 1974 in which several people apparently died of isoniazid-induced hepatitis dealt another blow against the concept of widespread use of isoniazid chemoprophylaxis. This hepatotoxic risk was found to increase with age, and thus recommendations of limiting chemoprophylaxis to positive reactors younger than 35 years old or those over the age of 35 with known risk factors were developed.

With the decline of tuberculosis cases in the U.S. during the later part of the twentieth century; state and local public health agencies became the major sources of consultation and information on clinical issues relating to tuberculosis (Nolan, 1997). By the 1970’s, public health departments were actually discouraging medical practitioners from retaining supervision of newly diagnosed tuberculosis cases.

As a result of the resurgence of tuberculosis in the late 1980’s, a surge of work for public health tuberculosis clinics or programs emerged. This resurgence also aided tuberculosis to reappear in the medical literature and became a fashionable subject for the lay press. Nolan provides an example of a county health clinic in the Seattle area in which during a five year period (1989 to 1993), the number of annual visits almost doubled from 13,147 to 21,717. Other tuberculosis related services delivered by the clinic increased (doubled in most cases) during the same period. These services included skin tests, chest roentgenograms (x-rays), and isoniazid preventive therapy.

**Guidelines**

The diagnosis of active tuberculosis is preceded by tuberculosis infection. Tuberculosis infection indicates that a person has been infected by the *Mycobacterium*
tuberculosis organism but has not progressed to active disease. Ten to fifteen million people in the United States are infected with Mycobacterium tuberculosis (Barnes and Barrows, 1993).

Persons with tuberculosis infection, detected by a positive PPD (purified protein derivative) tuberculin skin test reading of greater than 10 mm, should be considered candidates for preventive therapy (Huebner and Castro, 1995). The American Thoracic Society-CDC guidelines recommend isoniazid prophylaxis in all adult tuberculosis reactors with additional risk factors for active tuberculosis including HIV positive serostatus, chronic conditions such as renal failure or diabetes mellitus, current treatment with immuno-suppressive medication, close contact with infectious tuberculosis source, and recent skin test conversion (Reichman, 1994).

Whether to prophylactically treat all tuberculosis infected patients regardless of risk factors remains controversial. The dilemma is in weighing the potential hepatotoxic side effects of isoniazid against the potential survival benefits. Equally controversial is the screening of the general public for tuberculosis infection. One suggestion, since we lack infinite resources, is to target those groups or communities in which likelihood of positivity is fairly high. These include immigrants from endemic tuberculosis areas, HIV infected patients and persons who lack access to regular health care (Reichman, 1994).

A preventive therapy program consisting of isoniazid (given daily for 6 to 12 months) effectively decreases the risk (up to 90 %) of future active tuberculosis in most adults and children with tuberculosis infection (American Thoracic Society, 1994; ACCP
Consensus Statement, 1995). A prophylactic therapy of six months was found to be the most cost-effective regimen, although 9 to 12 months may be slightly more effective in preventing the few organisms that are present from advancing to active tuberculosis (Snider Jr. et al., 1986). The usefulness of a prophylactic tuberculosis regimen in preventing the progression to active disease and in preventing the development of drug resistance to therapeutic agents can only be realized with strict adherence or medication taking compliance to an appropriately prescribed therapy.

**Tuberculosis Related Treatment Costs**

In 1996, Holger Sawert of the World Health Organization's - Global Tuberculosis Program wrote about the economic implications due to the re-emergence of tuberculosis. Sawert noted that three factors determined the economic impact of the recent resurgent tuberculosis epidemic: (1) the increasing number of patients who would require additional funding for regular care activities, (2) the emergence of multi-drug resistance that would substantially increase the cost of treatment for those affected patients, and (3) significant indirect costs from the morbidity and premature mortality caused by the disease which largely had not been described (Sawert, 1996).

Two recently published studies have examined the expenditures related to the treatment of tuberculosis in the United States. The first of these analyses looked at patients with a primary diagnosis of tuberculosis admitted to a university hospital during a one year period in 1992 (Shulkin and Brennan, 1995). Costs were examined separately for patients at initial admission and readmission. An average length of stay and total cost were
then calculated for each of the admission categories listed above. Costs (reported in 1992 dollars and not discounted) were calculated using the average mean charges of the institutions adjusted by the hospital wide 1992 cost-to-charge ratio from the university institution where the study was conducted.

Results from the study included a total of 32 patient admissions; 18 initial and 14 readmissions. The average length of stay was 22.7 days for initial admission and 13.5 days for readmission, for a total average length of stay of 18.7 days. Average costs of care were $27,109 for initial admission, $13,094 for readmission and $20,222 for the entire group of patients. Room costs made up the majority of the total cost of care, followed by lab costs, ancillary costs, other costs and pharmacy costs.

Shulkin and Brennan (1995) suggest that their analysis provided useful baseline data on resource use in the management of tuberculosis and that clinicians interested in determining more cost-effective methods of caring for tuberculosis patients should look at strategies to reduce length of stay and streamline laboratory testing, radiographs and the use of pharmaceuticals.

The second analysis (Brown et al., 1995), provided an extensive evaluation of the health care expenditures for tuberculosis in the United States. The analysis was the result of the National Multidrug - Resistant Tuberculosis Task Force’s (Subcommittee on the Cost of Tuberculosis) plan to assess the economic burden of tuberculosis in the United States. The retrospective cost-of-illness study estimated 1991 direct expenditures for tuberculosis treatment and public health activities related to tuberculosis.
Specifically, their analysis examined total expenditures for outpatient and inpatient diagnosis, screening of individuals for latent tuberculosis infection, identification and evaluation of contacts of patients with tuberculosis, preventive therapy for persons with latent tuberculosis infection, surveillance activities, and tuberculosis outbreak investigations.

The direct medical expenditures for tuberculosis in 1991 were estimated at $703.1 million. Inpatient treatment accounted for 60% ($423.8 million) of the total tuberculosis expenditures, outpatient treatment accounted for 26% ($182.3 million), and the remaining 14% was spent on screening and preventive therapy activities, contact investigation and surveillance.

There were an estimated 20,803 hospital discharges with a principal diagnosis of tuberculosis in 1991. The mean length of stay for patients with tuberculosis was 19.9 days and the median charge in 1991 dollars was $18,588. The total hospital charges were $386.7 million, and physician charges related to the hospital stay were estimated at $37.1 million.

The estimated expenditures for outpatient treatment were $182.3 million. It was estimated that out of the just over 23,000 cases of tuberculosis reported in 1991, 90% percent received outpatient treatment. Of these, 83% received standard treatment for drug susceptible tuberculosis (six months treatment), 10% for single drug resistant disease (9 to 12 months of therapy) and about 7% for multiple drug resistant tuberculosis (at least 24 month duration). The expenditures for outpatient tuberculosis drug therapy in
1991 ranged from $2,300 per patient in drug susceptible tuberculosis to $5,000 per patient in single drug resistant tuberculosis, to $8,000 per patient in multiple drug resistant tuberculosis.

The study estimated that approximately 140,000 individuals began preventive therapy through health departments in 1991. Almost 57% of these persons completed preventive therapy. The remainder were assumed to have completed half the therapy. The medical resources and costs incurred for preventive therapy used in the study were estimated by the tuberculosis control programs surveyed. These resources included a chest radiograph and interpretation ($25), six months of isoniazid therapy ($7.20) and a monthly nurse visit for monitoring ($20 per visit). Costs associated with adverse reactions were not included. Total expenditures for preventive therapy were estimated at $17.9 million.

The major finding of the study (i.e., 60% of total expenditures were attributable to inpatient treatment) was noteworthy since tuberculosis has been considered an ambulatory disease for the past 25 years. Also noteworthy was that expenditures for prevention and surveillance composed only a moderate 14% of the total tuberculosis expenditures, compared to the 86% spent on patients with active or suspected disease.

Brown et al. (1995) suggest that from a public health perspective, cost-benefit analyses of the use of preventive tuberculosis therapy in a variety of high risk populations could strengthen the argument for prevention strategies for tuberculosis; particularly when compared with the high costs of inpatient treatment.
Framework for Conducting a Prevention Effectiveness Study

Performing a prevention effectiveness study involves three essential steps (Haddix et al., 1996). The first step involves framing the question. The second requires the structuring of a decision model. Finally, analysis of the model and interpretation of the results is required.

Framing the Question

Farnham et al. (1996) advise that before beginning a prevention effectiveness study, a number of issues must be addressed. The process of framing the question is one of the most important steps in successful completion of the prevention effectiveness analysis. Framing the question in a prevention effectiveness study identifies thirteen key points that must be addressed before the analytical process begins.

1. Define the audience for the evaluation. This step identifies the users of the results of the study, and indicates how the results will be used. The audience is defined as the consumer of the results. This may include policy or program decisions makers or other interested parties (insurance companies, general public, etc...).

2. Operationally define the problem or question to be analyzed. The study question must address the policy or program issues that drive the analysis and must identify the target audience. The study question also provides the basis for the determination of other key elements in the economic analysis; elements such as perspective, time frame, analytical method, costs and outcomes of interest.

3. Clearly indicate the prevention strategies being evaluated. The list of alternative
prevention strategies in prevention effectiveness studies should include all reasonable options and a baseline comparator (usually either the current program or no program). The results of an analysis may show that the baseline comparator is the most cost-effective strategy, but it cannot be demonstrated unless it is explicitly included.

4. Specify the perspective of the analysis. The perspective identifies the viewpoint that the analysis will take. Single provider, insurer, health care system or society are representative perspectives that may be taken. The perspective taken will determine which costs and benefits are included in the analysis.

5. Define the relevant time frame and analytic horizon for the analysis. The time frame consists of the time period in which the interventions will be evaluated. The time period in which the cost and effects accrue from the interventions define the analytical horizon. An example of this is the lifetime (analytical horizon) effects of preventing chronic heart disease in persons who participated in a cholesterol screening and education program during a one year period (time frame).

6. Determine the analytic methods or method. This involves choosing an economic evaluation method such as cost-benefit or cost-effectiveness analyses. The choice will be based on the policy question, the outcomes of interest, and the availability of data.

7. Determine whether the analysis will be a marginal or incremental analysis. Marginal analyses examine the effect on health outcomes of making an additional investment in an intervention. An incremental analysis examines the relationship between making an investment in a different intervention and the health outcomes expected to be produced by
that strategy.

8. Identify the relevant costs. All relevant costs in the evaluation should be identified prior to construction of the model. The availability of cost data may influence decisions about the perspective of the analysis and the analytic methods used.

9. Identify the health outcome or outcomes of interest. In prevention effectiveness studies, outcomes are the result of implementing a prevention strategy and are usually considered in terms of health conditions; such as, cases prevented or quality adjusted life years. The number and nature of outcomes are useful in determining the appropriate analytical method to employ.

10. Specify the discount rate or time preference for costs and non monetary outcomes that occur in the future. Since most public health projects involve benefits that continue into the future, the present value of these benefits and costs must be calculated to make them comparable in terms of time dimension. The choice of a discount rate is a controversial issue that can have a significant impact on the results of the analysis.

11. Identify the sources of uncertainty and plan sensitivity analyses. It is important to list the assumptions upon which the values of variables (both outcomes or parameters of the model) are based. A sensitivity analysis is one way to harness uncertainty. Sensitivity analysis may be accomplished by varying one parameter or by simultaneously varying two or more probability or outcome estimates.

12. Determine the summary measures that will be reported. Examples of summary measures include the incremental net present value of benefits in a cost-benefit analysis
or the incremental cost-effectiveness ratio in a cost-effectiveness analysis.

13. If the distribution of the costs and benefits in the population will differ for the prevention intervention options including the baseline comparator, determine the feasibility of analyzing the distributional effects of prevention programs.

Structuring the Decision Model

Models are useful in conducting prevention-effectiveness studies especially when evidence of the effectiveness is indirect or uncertain (Teutsch and Harris, 1996). When direct effects of the prevention strategy cannot be measured, indirect evidence of the effectiveness of an intervention must be relied upon. Indirect evidence may be used with confidence if each link in the chain of causality can be clearly documented.

Modeling may also help in identifying the important issues for which data are needed and thus help to formulate a research agenda. Economic analyses are often based on such models. The use of models makes the decision process explicit and can help clarify the criteria upon which decisions are to be made (Mandelblatt et al., 1996).

Economic analyses often utilize mathematical or simulation models in determining outcome probabilities and in incorporating costs for different outcomes for the prevention intervention under study. Most often, modeling is out of necessity since data for many of the economic analyses may be incomplete. The analyst must rely on methods of extrapolation and imputation to estimate the magnitude of health outcomes in terms useful for the economic model employed (Mandelblatt et al., 1996).

Decision-tree or decision analysis, state-transition and other types of dynamic
models are different, but related, mathematical models that represent the unfolding of a process over time. A detailed discussion of decision-tree and state transition models will be presented in a following section.

Mandelblatt et al. (1996) note "no model is a perfect representation of reality; its validity rests on whether its assumptions are reasonable in light of the needs and purposes of the decision maker and, importantly, in light of whether, after close examination, its implications make sense."

Analysis of the Model and Interpretation of the Results

Once the model has been specified, the model is "run" or estimated to produce expected values for both the costs and/or outcomes of interest. In decision analysis this process is known as averaging-out-and folding-back the decision tree. In state transition models the expected values of interest are usually obtained through the use of simulation or mathematical calculations.

Summary measures or ratios (such as incremental cost-effectiveness ratios) are then calculated. Finally, a sensitivity analysis is performed in an attempt to isolate factors involved in the economic analysis (or modeling process) to indicate the degree of influence each factor has on the outcome of the entire analysis.

Framework for Economic Evaluations In Medicine

This section of the literature review will present the framework used in performing economic evaluations or analyses in medicine. Economic evaluations are highlighted here because of the key role they play in prevention effectiveness studies.
Two basic premises underlie an economic evaluation (Drummond, Stoddart, and Torrance, 1986; Bootman, Townsend and McGhan, 1991). First, economic evaluations assess the costs (or resources consumed) and consequences of activities or alternative therapies. Second, choices are required between alternative uses of resources due to resource scarcity. Economic analyses try to identify and make explicit one set of criteria which may be useful in deciding among different uses for scarce resources.

Drummond et al. (1986) indicate that the basic task of any economic evaluation is to identify, measure, value, and compare the cost and consequences of the alternatives being questioned. In order to be considered a full economic evaluation, the evaluation must contain (1) a comparison of two or more alternatives and (2) an examination of both the costs (inputs) and consequences (outputs) of the alternatives.

Three components have been deemed essential in conducting an economic evaluation (Bootman et al., 1991; Weinstein and Stason, 1977; Eisenberg, 1989). The first is the perspective from which to evaluate the various costs and benefits. Second, delineation of costs to be included in the evaluation (direct, indirect, and intangible) must be performed. The third required component is the identification of the economic methodology for the given activity or health program under question. These methodologies include cost-minimization, cost-effectiveness, cost-benefit, and cost-utility analyses.

**Perspective**

Economic evaluations may assume the viewpoint of a single provider, insurer,
health care system or society. Bootman et al. (1991) indicate that the perspective taken may influence the economic methodology used. It is important to state explicitly the perspective of an economic analysis, since the perspective determines which costs should be included in the analysis and what economic outcomes are considered as benefits (Petitti, 1994). Drummond et al. (1986) indicate that it is essential to specify the viewpoint since an item may be a cost from one point of view, but not a cost from another. An example of this is workmen's compensation payments which are a cost to the employer, a gain to the patient and neither a cost nor a gain to society.

Drummond et al. (1986) and Weinstein and Stason (1977) have advocated for a comprehensive, relevant, and broadly applicable societal point of view in economic evaluations. However, they have also recognized the importance that the particular objectives of the actual decision makers or commissioning body be considered.

**Costs**

Direct costs are made up of both medical and non-medical components (Larson, 1991). Direct medical costs include items such as amount spent on medical services to treat illness, hospital care, professional services, drugs, and supplies. Out-of-pocket expenses for items outside direct medical care sector (such as transportation and lodging for family during treatment) are examples of direct non-medical costs.

Drummond et al. (1986) define direct costs as those consisting of the costs of organizing and operating the program. These direct costs are further broken down into variable costs (supplies, hospital costs) and fixed or overhead costs (such as rent, heat, or
capital costs). Direct costs are usually measured by combining the direct medical cost and the direct non-medical costs for the given activity or alternative therapy.

Indirect costs are those such as earnings lost as a result of temporary or permanent disability because of the illness. Petitti (1994) defines indirect costs as the cost of lost productivity and monetary values, associated with the use of time, and that are neither production cost nor overhead. Petitti equates indirect costs with opportunity costs.

The opportunity cost of a resource is its total value in another use. Opportunity costs may consist of both production and indirect costs. An example would be a person going to the hospital to get a chest x-ray, who takes an hour off from their regular job. The total opportunity cost of the visit for the x-ray includes the production cost (labor, film, overhead) of the x-ray and the indirect cost (amount of lost wages for the hour the person took off). Petitti (1994) indicates that it is common to ignore costs due to lost productivity and lost wages in an economic-analyses. However, when information on these costs is available, they should be incorporated in the analysis.

Indirect costs or productivity losses attempt to measure the economic burden an illness places on an individual and are costs that should be included when undertaking a study from a societal perspective (Haddix and Schaffer, 1996). The human-capital method is used to assess productivity loses from illness or injury, as measured by income foregone because of morbidity or premature mortality. Labor force participation rates and earning of affected persons are used to calculated the value of productivity lost because of morbidity of premature mortality. Time lost from work to participate in an intervention
program or as the result of morbidity from side effects due to the intervention can also be calculated (Haddix and Schaffer, 1996).

Intangible costs, as the name implies, are very difficult to directly measure primarily because a monetary value cannot be easily assigned. These include costs such as pain, suffering and grief. Intangible costs are measured via the use of the willingness to pay method and are usually part of a cost-benefit analysis (Haddix and Schaffer, 1996). The willingness to pay method estimates the cost of an injury or disease by calculating what society would be willing to pay to avoid or reduce the likelihood of the injury or disease.

Methodology

Economic analyses that search for the least costly alternative given that the outcomes or consequences are identical are defined as cost-minimization or cost-analyses (Bootman et al., 1991; Drummond et al., 1986). The goal in cost-minimization analyses is finding the least expensive method of achieving the outcome.

Cost-effectiveness analysis (CEA) involves the comparison of the net resource effect (costs) of an intervention with some non monetary measure of its net effect on health outcome (effectiveness) [Chrischilles, 1991]. Cost-effectiveness analysis is most useful when the goal of the analysis is to identify the most cost-effective strategy from a set of options that produce a common effect (Haddix and Shaffer, 1996). Results of a cost-effectiveness analysis are presented in the form of cost-per-unit of effectiveness, such as cost-per-life saved. Cost-effectiveness analysis is most useful when the interventions
being compared have one clear and specific outcome.

Weinstein (1981) explains that the conceptual model for cost-effectiveness is one of constrained optimization. The objective being to maximize the expected aggregate health benefits, or effectiveness, in the population of interest; subject to an overarching constraint on expenditures or resources. Weinstein and Stason (1977) indicate that a cost-effectiveness analysis serves to place priorities on alternative expenditures without requiring that the dollar value of life and health be assessed (as in cost-benefit analysis).

Cost-benefit analysis (CBA) seeks to answer the question “Will the benefits of a program exceed the cost of implementing it?” Cost-benefit analyses compare the value of all resources consumed (costs) in providing a program or intervention with the value of the outcome (benefit) from that program or intervention (Kitz, 1991). Costs and benefits are valued in the same unit, usually dollars.

Clemmer and Haddix (1996) tout cost-benefit analysis as the “gold standard” of economic evaluations because it provides the most comprehensive consideration of the costs and benefits of intervention programs. Clemmer and Haddix also provide a simple, yet effective, definition of cost-benefit analysis. Cost-benefit analysis attempts to weigh all the impacts of a program to assess whether it is worthwhile, i.e., whether its benefits exceed its costs.

There are certain advantages to using cost-benefit analysis over cost-effectiveness analysis (Kitz, 1991). Cost-benefit analysis may be applied to single or multiple programs; cost-effectiveness analysis is applied to multiple programs. Cost-benefit analysis may be
used to compare programs with different outcomes; cost-effectiveness analysis identifies
the least costly approach for a single outcome. The disadvantage (to some) is that cost
benefit analysis requires that all the outcomes or benefits be assigned a dollar value. Some
investigators not only find it distasteful, but difficult, to place a monetary value on
something like a human life and opt for cost-effectiveness analysis instead.

Dasbach and Teutsch (1996) define cost-utility analysis (CUA) as a specific kind
of cost-effectiveness analysis that is appropriate when: (1) quality of life is the, or, an
important outcome, (2) the program being evaluated affects both morbidity and mortality,
(3) the programs being compared have a wide range of different outcomes and/or (4) the
comparator program has already been evaluated using cost-utility analysis.

In cost-utility analysis, the intervention outcome or consequence is measured in
terms of patient preference or quality of the health outcome. The results of a cost-utility
analysis are usually expressed as cost per quality adjusted life year (QALY) gained or
changes in quality of life (QOL) measurement for a given intervention cost (Bootman et
al., 1991)

Decision Analysis and Markov Modeling in the Economic Evaluation Process

Economic analyses often utilize mathematical or simulation models in determining
outcome probabilities and in incorporating costs of different outcomes for the prevention
intervention under study. One of the most often used estimation models is decision
analysis. Decision analysis is usually represented by decision-tree models which model the
sequence of chance events and decisions over time. State-transition models (such as
Markov models) are enlisted when events being modeled involve a risk that is ongoing over time. Markov models are also used when modeling recurrent events with a decision tree becomes difficult because decision trees may become "bushy" and unmanageable.

**Decision Analysis**

Decision analysis is an explicit, quantitative, and systematic approach to decision making under conditions of uncertainty (Barr and Schumacher, 1991; Weinstein et al., 1980, and Snider et al., 1996). Decision analysis can be used to assist the decision maker to identify the available options, predict the consequences and outcomes of each option, assess the probability of the identified possible outcomes, determine the value of each outcome and select the decision option that will provide the best pay-off.

Decision analysis uses mathematical tools to help decision makers chose the option that maximizes utility for an individual, to society or a community. It can also be used to calculate cost-effectiveness in cost-effectiveness analyses and net present value in cost-benefit analyses. Decision analysis can be used as a stand alone method for decision making or as a framework for conducting cost-effectiveness, cost-benefit or cost-utility analyses. In a prevention effectiveness study, decision analysis can help in structuring the problem (Snider et al., 1996).

The application of decision analysis involves four steps: structuring the problem, estimating probabilities, valuing outcomes and selecting option with highest expected value. Structuring the problem involves stating the major issues, defining the perspective, and developing the decision tree. The term decision-tree is used because options are
arranged to resemble a tree in appearance.

The decision tree is usually written from left to right, starting with the initial decision node on the extreme left and moving to the final outcomes on the extreme right (representing a temporal sequence of events). Estimating probabilities involves assigning a probability to each event (in the tree) controlled by chance. Estimates of probability may come from literature searches, previous research, or from expert opinion.

Valuing outcomes involves assigning a value to each outcome on the decision tree. Selection of the option with the highest expected value occurs after the process known as averaging-out and folding-back the decision tree. Expected value is the sum of the products of the estimates of the probability of events and their outcomes.

In a cost-effectiveness and cost-utility analyses, the process of averaging-out and folding-back is performed twice. The first iteration is for determination of costs. The second iteration is done for effectiveness data as the measure of the outcome. The result of these two calculations are then combined in summary ratios. These mathematical results must then be interpreted and sensitivity analysis must also be performed to test for the robustness of the expected-utility or expected value calculations.

Snider et al. (1996) have listed the benefits of using decision analysis in public health. The first benefit is the explicitness of the decision analysis process. Decision analysis requires that the options be clearly stated, consequences be clearly identified and uncertainties be recognized. Decision analysis is also useful in improving communication. The decision analysis process allows decision makers to understand and convey
information clearly about aspects of the problem.

Decision analysis may also relieve some of the stress brought on by decision making. Many people are uncomfortable about making decisions, especially complex decisions with far reaching consequences. The logical, rational process of decision analysis lends structure, organization and reason to a difficult process (Snider et al., 1996). Lastly, decision analysis encourages focus. This allows decision makers to focus on truly important issues rather than on issues that merely seem to be important.

One important limitation of decision analysis models, however, is that they are not well suited to representing recurrent events that repeat over time (Mandelblatt, et al., 1996). In some diseases or cases, events and probabilities of events (such as complications from the disease or its treatment, recurrence of disease, and mortality) are confronted and changing repeatedly during a lifetime. Rather than model each event as a separate branch of a complex decision tree, more efficient representations of such events may be modeled by the use of state-transition models.

State-transition models allocate members of a population into one of several categories or health states (Mandelblatt et al., 1996, Sonnenberg and Beck, 1993). Health states are defined according to disease stage, treatment status, or combination of the two. Transitions occur from one state to another at defined recurring time intervals according to transition probabilities. Through simulation, or mathematical calculation, the numbers of members of the population passing though each state at each point in time can be estimated. State transition models can be used to calculate life expectancy or quality
adjusted life expectancy.

**Markov Modeling**

A Markov model is a special type of state-transition model in which the transition probabilities depend only on the current state and not on the previous states or the path by which the state was entered. Markov models are particularly useful when a problem involves a risk that is ongoing over time (Sonnenberg and Beck, 1993; Beck and Pauker, 1983).

There are two important consequences of events that have ongoing risk. First, the times at which the events will occur are uncertain. The implications of this are important since the utility of an outcome often depends on when it occurs. Second, representing events that are repetitive is difficult using a simple decision tree model.

The Markov model assumes that member of the study population is always in one of a finite number of states of health known as Markov states. The events of interest are modeled as transitions from one state to another. Each state is assigned a utility, and the contribution of this utility to the overall prognosis depends on the length of time spent in each state. The time horizon of the analysis is divided into equal increments of time, called Markov cycles. The length of the cycle is chosen to represent a clinically meaningful time interval.

Evaluation of the Markov model yields the average number of cycles (or average amount of time) spent in each state. The utility that is associated with spending one cycle in a particular state is referred to as the incremental utility. Utility for the entire Markov
model is the total number of cycles spent in each state, each multiplied by the incremental utility for that state.

Calculation of cost-effectiveness analyses involves the specification of a separate incremental utility for each state representing the financial cost of being in that state. The model is then evaluated separately for cost and survival. Cost-effectiveness ratios are then calculated as for a standard decision tree (Sonnenberg and Beck, 1993).

Markov models are categorized by whether or not state-transition probabilities are constant over time. A Markov chain model is characterized by the assumption that each of the transition probabilities are fixed over time. A Markov process is characterized by time dependent transition probabilities.

Markov processes are best represented by the use of a Markov cohort simulation (Sonnenberg and Beck, 1993). The Markov cohort simulation considers a hypothetical cohort of patients beginning the process with some distribution among the starting states. At each cycle, the patients are redistributed to the health states defined by the transition probabilities. The number of patients in any given state and the total number of patient cycles in any given state are recorded. Cycle sums are then calculated for each cycle by taking the number of cohort members in each state and multiplying it by an incremental utility value. Life expectancy can also be calculated by adding times spent in each cycle (except the death stage) by each member of the cohort.

A Monte Carlo simulation is an alternative to simulating prognosis of a hypothetical cohort of patients (Sonnenberg and Beck, 1993). The Monte Carlo
simulation determines the prognoses of a large number of individual patients which pass through the model one at a time. A random number generator is used with the transition probabilities to determine in which state the patient will begin the next cycle. A patient is given credit for each cycle spent in a particular state depending on the incremental utility of that state. When all patients reach the absorbing state, the simulation ends.

This simulation is repeated for a large number of patients, usually on the order of 10,000. Once all patients have progressed throughout the simulation, the average number of cycles in each non-absorbing state can be calculated (equivalent to life expectancy) and average number of cycles in each state may be estimated.

The advantage of the Monte Carlo simulation over the Markov cohort simulation method is the generation of a distribution of the survival values and times spent by patients in any particular state. Statistical measures such as variance and standard deviation of the expected utility may also be determined from this distribution.

The construction of a Markov model requires four steps (Beck and Pauker, 1983). First, all distinct states of health or the problem of interest must be enumerated. The states must: (1) be distinguished by their prognosis or transition probabilities, (2) correspond to standard or literature based notions of disease and (3) be capable of being placed in a continuous scale of relative values.

Second, the allowable state transitions in the Markov model must be defined. Long term and temporary states are allowed in Markov modeling. Long term states are states in which it is possible to remain from cycle to cycle (i.e., a transition from a long term state
to itself is allowable). Temporary states reflect short-term events that force transition to another state in the model in the next cycle.

Third, probabilities must be assigned or associated with the state transitions. Probabilities may be obtained from the literature or may represent expert opinion. Many state transitions obtained from the literature appear as rates, which range from zero to infinity and are expressed per unit time. Probabilities vary from zero to one and have time built into them implicitly. Rates can be converted to probabilities by use of the following formula:

\[ P[t] = 1 - e^{rt} \]

where \( r \) = rate, and \( P \) = probability of an event occurring over a time interval of \( t \) time units.

Finally, outcomes of interest (such as life expectancy, utility, or costs of therapy) can be calculated. This may be accomplished by one of three ways: 1) Monte Carlo simulation, 2) cohort simulation, or 3) a matrix algebra solution when using a Markov chain.

For this prevention effectiveness study, the analytic method or economic model used was a cost-effectiveness analysis. The cost-effectiveness analysis was modeled by the use of a Monte Carlo simulated Markov process model.

**Review of Economic Evaluations of Preventive Therapy with Isoniazid in Tuberculosis Prevention Programs**

There have been many economic evaluations performed relative to the use of
isoniazid preventive therapy in tuberculosis prevention programs. This section summarizes
the published economic evaluations of tuberculosis prevention programs which have
utilized preventive therapy with isoniazid.

The criteria used to evaluate the economic evaluations found in the literature were:
the economic evaluation methodology used, outcome measures reported, and the inclusion
or consideration of the infectious nature of tuberculosis in the economic evaluations. This
last criterion is especially important since the contagious nature of tuberculosis has many
downstream impacts; both financial and societal (public health). The studies will be
presented in chronological order.

Snider Jr. et al. (1986) performed a cost-effectiveness analysis which compared
three alternative durations of preventive isoniazid therapy; 12, 24, and 52 weeks. Prior to
this study, 12 months (52 weeks) of daily isoniazid therapy was the recommended course
for the prevention of active tuberculosis.

Net health care costs were defined as expenditures for isoniazid preventive
therapy and for adverse drug reactions due to preventive therapy minus the savings from
tuberculosis cases prevented. The outcomes or net health effectiveness were defined in
two ways: (1) cases of tuberculosis averted and (2) quality adjusted life years gained.
Cost-effectiveness ratios in this study were expressed as "dollars spent in medical costs
per case of tuberculosis averted" and "dollars spent in medical costs per additional year of
full health achieved". The analysis involved a societal perspective and included direct costs
only.
The results indicated a regimen of 24 weeks duration was more cost-effective than either the 12 or 52 week regimens. The cost per case prevented for the 24 week regimen was approximately half of that for the 52-week regimen ($7,112 versus $16,024). Each additional case prevented cost $80,807 with a 52 week regimen. Expressed as cost per QALY gained, the 24 week regimen once again proved the most cost-effective ($4,353 versus greater than $9,000 for the other two regimens). The study concluded that a shorter course of isoniazid preventive therapy (24 weeks) was relatively more cost-effective compared to the existing policy (52 weeks).

The next published economic analysis related to preventive isoniazid therapy used decision analysis with a Markov model to examine whether adults, 20 to 80 years of age (with no risk factors), should take isoniazid to prevent the development of active tuberculosis disease (Tsevat et al., 1988). The study adopted the perspective of the individual patient. Life-expectancy was identified as the outcome of interest.

The results of their analysis favored withholding isoniazid for all groups. For 20 year olds, the model favored withholding isoniazid therapy by an additional four days of life expectancy. For 35 year old patients avoiding isoniazid provided an additional 13 days of life expectancy. The results indicated that as the patients became older, the decision to avoid isoniazid became clearer. The model indicated that 50 year old patients not taking isoniazid would result in an additional 17 days of life expectancy, in 65 year olds the gain in life expectancy by not taking isoniazid was 10 days.

Since their results reached different conclusions from previous studies, Tsevat et
al. (1988) suggest that the individual patient might decide if the results (a decreased life expectancy of 4 days for a 20 year old on preventive therapy or 17 days in a 50 year old patient) were meaningful. Additionally, since the analysis took a perspective of the individual patient and not society as a whole, Tsevat et al. concede (1988) that “what may be better for the individual may not maximize the public good, especially in the case of a contagious disease.”

Providing evidence that every two cases of active tuberculosis may generate one new one, they state that society would reap the dividends from all patients who take isoniazid. However, they pose the question, “Would it be ethical to ask patients more than 20 years of age to take isoniazid to their detriment but for the good of the public?”

In a critical rebuttal of the Tsevat et al. (1988) study, Snider (1988) asserts that the results of this particular analysis were not useful for influencing individual (or public) policy decisions because some of the input data and several of the assumptions were incorrect. This included a gross underestimation of deaths attributable to tuberculosis and the data used on the effectiveness of isoniazid preventive therapy. Snider (1988) states that “decision analysis can be a useful technique for making decision about medical interventions; however, the analysis must use data and assumptions which closely portray reality if the results are to be taken seriously and acted upon.”

Using decision analysis, Rose and colleagues (1988) performed a cost-effectiveness analysis of isoniazid chemoprophylaxis for two populations with positive skin tests: recent tuberculin converters, who were at high risk for activation, and older
tuberculin reactors (over the age of 35), who had a low risk for activation and for whom preventive treatment was at that time not recommended.

Costs included were the cost of isoniazid prophylaxis plus the cost to treat adverse effects of isoniazid plus the costs of treating active tuberculosis that occurred despite having taken isoniazid minus the cost of treating active tuberculosis in those who decline isoniazid. The outcomes or health effects studied included life expectancy and fatalities from tuberculosis or isoniazid hepatitis. The cost-effectiveness ratios for the study were: (1) cost per year of life extended by isoniazid prophylaxis, and (2) cost per death averted by isoniazid prophylaxis. The study included only direct medical care costs.

Using base case assumptions, Rose and colleagues reported that high risk tuberculin reactors taking isoniazid incurred a net savings of $429 per person, a small gain in life expectancy and fewer deaths from tuberculosis and isoniazid hepatitis. Low risk tuberculin reactors taking isoniazid could also expect small gains in life expectancy and fewer deaths from tuberculosis and isoniazid hepatitis, but a net cost of $126 per person. Cost-effectiveness ratios were calculated at $12,625 per year of life gained and $35,011 per death averted in the low risk tuberculin reactors.

The study concluded that isoniazid preventive therapy was effective for young, high risk infected persons, and that its use reduced medical care expenditures. For older, low-risk tuberculin reactors, the benefits of isoniazid chemoprophylaxis were positive but small.

This study was unique in that cost-effectiveness ratios were calculated for those
cases which resulted from the contagiousness of tuberculosis. Inclusion of contagious cases in the analysis resulted in smaller monetary costs and several more deaths averted. When contagious cases were included, high risk tuberculin reactors taking isoniazid incurred a net savings of $471 per person, similar gains in life expectancy and 17 fewer deaths from tuberculosis and isoniazid hepatitis as compared to the base case analysis.

The study further estimated that for a cohort of 100,000 high risk tuberculin reactors who did not take isoniazid, active disease would develop in 15,356 people. These active cases would, in turn, have 46,068 household contacts, among whom 10,289 will convert to a positive tuberculin test; 520 of these converters would eventually develop active disease and 25.6 would have fatal disease.

Fitzgerald and Gafni (1990) reported the results of a cost-effectiveness analysis which evaluated the use of isoniazid for patients with a positive Mantoux skin tests compared with no use of prophylaxis from a societal perspective. Cost effectiveness ratios, cost per case prevented, were calculated for 20, 50, and 70 year old low risk patients. Their analysis was the first analysis (related to preventive isoniazid therapy) which attempted to adopt a true societal perspective. They included the calculation of both direct (costs of preventive and active tuberculosis treatment) and indirect costs (loss of earnings).

The total cost for routine isoniazid prophylaxis over a twelve month period was $645 in 1987 Canadian dollars. Costs for treatment of tuberculosis over a nine-month period, including indirect costs, totaled $9,182. The authors found that for a 20-year-old
patient the base cost of preventing one case of tuberculosis was $8,586 when direct costs were included compared with $3,236 when direct and indirect costs were included. With a 50-year old patient, the total cost per case prevented ranged from $28,260 (direct costs) to $30,893 (direct and indirect costs). In 70 year old patients, the cost per case prevented would be $11,320 (direct and indirect costs) and $40,102 for direct cost alone.

Fitzgerald and Gafni (1990) explain their cost-effectiveness results as follows; the inclusion of indirect costs made isoniazid more cost-effective because in preventing tuberculosis, and in particular deaths from tuberculosis, there is a significant reduction in time lost from work and also projected lifetime loss of earnings, which was the main indirect cost included in their study. Their analysis attempted to take into account the contagious nature of tuberculosis by incorporating the costs related to contact tracing and the risk of infection and, ultimately, the occurrence of the tuberculosis disease.

Fitzgerald and Gafni (1990) conclude that for most age groups, the cost per case of tuberculosis prevented were not exorbitant. However, they did not provide a reference point of what they considered “exorbitant”. They reported that the costs generated in their study (a study which assumed low-risk for tuberculosis activation) implied that the cost of preventing cases in other high risk groups would be more cost-effective and highlighted the importance of pursuing active contact tracing of all index cases of tuberculosis with a view to completion of adequate chemoprophylaxis.

A study which provided subgroup-specific decision analysis for preventive isoniazid in low risk reactors that incorporated age, gender and ethnicity was reported by
Jordan et al. (1991b). For purposes of comparison, however, the decision was analyzed for both low-risk and high-risk reactors.

Analyses were performed for twelve subgroups of patients according to age, gender, and ethnic group. The subgroups for the analysis were comprised of the combinations of black, white, and gender for each of the age groups. The ages of 20, 35, and 50 years old were used to facilitate comparison with the previous analysis (Tsevat et al., 1988) that reported findings in these ages. Life expectancy was used as the primary outcome measure.

This study found that in low-risk reactors, isoniazid was preferred for all 20-year-olds, all 35 year-olds except black women and no 50-year olds. Life-expectancy gains by prescribing isoniazid in low-risk reactors ranged from 3 to 19 days of life. When the decision was not in favor of isoniazid (35-year-old black women and all 50-year-olds), withholding it provided advantages ranging from 2 to 33 days of life gained. In high-risk reactors, isoniazid was favored an advantage of 1 to 44 days of life expectancy for all groups except 50 year old black females. Withholding isoniazid for the high-risk 50 year-old black female resulted in an advantage of approximately 12 days of life gained.

The study purports that the major objective of the investigation was to show that it may be essential to consider ethnicity and gender as well as age when making the decision to prescribe or withhold preventive therapy for tuberculosis. Jordan et al. (1991b) acknowledge that some investigators consider a benefit of only a few days to a few weeks of expected life too close to call one way or the other (i.e., whether to use preventive
isoniazid or not). They further imply that if the small life expectancy benefits to the individual are considered in conjunction with the associated many fold reductions in the number of tuberculosis cases and in total deaths, the decision to prescribe isoniazid is strengthened considerably.

An economic evaluation related to the use of preventive isoniazid therapy examined its use in HIV-infected intravenous drug abusers (Jordan et al., 1991a). The study used a decision analysis to determine if and when isoniazid should be prescribed to prevent tuberculosis in patients who are serologically positive for the HIV-virus (given the high tuberculosis risk and high likelihood of false negative skin test in this patient population). The base case for the analysis was a hypothetical 35-year-old, HIV sero-positive patient with a history of intravenous drug abuse. Tuberculosis skin test status, race and gender were varied in the analyses.

Results of the decision analysis indicated that whether a high or low life expectancy was used, the decision favored (1) prescribing isoniazid as a preventive therapy for black men, white men, and white women regardless of tuberculin test status; (2) prescribing isoniazid as a preventive therapy for black women whose tuberculin test status was either positive or unknown and (3) withholding isoniazid as a preventive therapy for black women whose tuberculin test status was negative. When a high life expectancy was assigned to HIV sero-positive intravenous drug abusers, the magnitude of life expectancy benefits associated with isoniazid use ranged from a low of 7.3 days for tuberculosis-negative white men to a high of nearly 285 days for tuberculin positive black
Jordan et al. (1991a) conclude that the results of their study argue persuasively for prescribing isoniazid (even in the absence of tuberculin testing) for all HIV sero-positive patients with a history of intravenous drug abuse, except for tuberculin-negative black women. The apparent anomaly associated with black women in their analysis reflected repeated indications in the literature that these individuals are at increased risk for isoniazid induced mortality.

Sterling et al. (1995) reported the results of a decision analysis which examined the use of isoniazid preventive therapy, for low-risk tuberculin reactors and low-risk recent tuberculin converters, that considered the recently increased isoniazid resistance rate. Their decision analysis was performed by means of a Markov simulation modeled after the decision tree model of Tsevat et al., (1988). They used a Markov simulation to account for the annual variation in the development of active tuberculosis and all cause mortality.

The analysis took the perspective of the patient within one of two cohorts: 1) tuberculin reactors aged 20 to 34 with no risk factors for developing tuberculosis and 2) tuberculin converters (within two years) aged 20 to 64 years without any additional risk factors for activation.

The results of the study indicated that for 20 to 34 year-old tuberculin reactors, isoniazid preventive therapy increased life expectancy by two days in an area with 26 percent isoniazid resistance. For recent tuberculin converters living in an area with 26 percent isoniazid resistance, the increase in life expectancy provided by isoniazid
preventive therapy varied according to age. Those aged 20 to 34 years would experience a 17 day increase in survival. For those aged 35 to 49 years there would be a 15 day benefit, and recent converters aged 50 to 64 years would have a 14 day increase in survival.

A limitation of the study listed by the authors was that the net benefit of isoniazid as it would pertain to an individual in a cohort of tuberculin reactors or converters does not reflect either quality of life or societal benefits- i.e., that effective isoniazid prophylaxis prevents illness and further spread of tuberculosis.

Sterling et al. (1995) report that the net two day increase in survival for tuberculin reactors (aged 20-34 years) who receive isoniazid preventive therapy in areas of high isoniazid resistance should make physicians seriously consider withholding isoniazid, or at least discussing the potential risks and benefits of such therapy with their patients. Furthermore, the improvement in survival for recent tuberculin converters in areas of high isoniazid resistance is at most modest; approximately two weeks. Sterling et al. (1995), acknowledge that the improved life expectancy, as well as the societal benefits of isoniazid preventive therapy, argue for the continued use of isoniazid preventive therapy among all other recent tuberculin converters.

More recently, a Markov model was used to evaluate the risks and benefits to an individual patient and the public health benefit resulting from isoniazid prophylaxis in low risk tuberculin reactors older than 35 years of age (Salpeter, Sanders, Salpeter, and Owens, 1997). Specifically the study evaluated monitored isoniazid prophylaxis in persons who were 35, 50 and 70 years old. The population used in their study was low risk.
tuberculin reactors over the age of 35 years in the United States.

The study was conducted to update the previous conflicting studies surrounding the widespread use of isoniazid prophylaxis for tuberculin reactors of all ages. These previous studies had used data from the 1970's; data which was produced before the advent of routine monitoring for isoniazid-induced hepatotoxicity.

The results of their study indicated that isoniazid preventive therapy increased the probability of survival at one year and for all subsequent years. The life expectancy for the three subgroups increased (less than five days in each subgroup) and health care expenditures per person also decreased (less than $100 in each subgroup). Prevention of one tuberculosis related death required administering isoniazid prophylaxis to approximately 600 patients for each of the subgroups.

When the effect of the secondary transmission of tuberculosis to potential contacts was included, the benefits of isoniazid prophylaxis increased, as did cost savings. Giving isoniazid prophylaxis to all low-risk tuberculosis reactors older than 35 years of age averted 35,176 deaths and reduced medical expenditures by $2.11 billion dollars (for the population of low risk tuberculin reactors over the age of 35 years in the United States). A more realistic estimate provided by the authors was the assumption where isoniazid prophylaxis given to only 20 percent of the low-risk tuberculin reactors would avert 7035 deaths in the United States and save $422 million.

As illustrated by the results of previous economic studies appearing in the literature, the cost-effectiveness of isoniazid preventive therapy in tuberculosis prevention
programs is typified by conflicting results (i.e., some study results have shown cost-effectiveness, other studies have not). Some study results have advocated isoniazid prophylaxis, others have not.

Many of the economic evaluations were based on specific gender, age, or race subgroups. The results of the evaluations related to specific characteristics, such as race and age, are probably most useful for comparison in similar subgroup populations. However, the generalizability of the results to the larger or general population are limited.

Additionally, many of the outcome results may not provide useful information for decision makers; especially when life expectancy is the primary outcome reported. The finding that taking, or not taking, isoniazid preventive therapy will decrease life expectancy by four days raises the question related to the usefulness of this outcome measure. Studies based on life expectancy do not provide useful information to a person who is trying to decide whether to discontinue prophylactic therapy for tuberculosis. Life expectancy does not indicate the future costs or consequences of discontinuing preventive therapy.

Many (nearly half) of the previous studies reviewed neglected to take into account the epidemiologic progression of tuberculosis infection and the potential for development of active tuberculosis cases. Infectious diseases such as tuberculosis are transmitted across populations and, over time, a single case (or case prevented) can ultimately affect very large numbers of individuals. Additionally, costs consequences related to the epidemiologic progression of tuberculosis are important.
Finally, there have been no published economic evaluations related to the cost-effectiveness of a tuberculosis prevention program in a predominantly Hispanic population. Likewise, no published economic analyses appear related to the cost-effectiveness of a tuberculosis prevention program in the population along the U.S. / Mexico border; undoubtedly, a high incidence tuberculosis area.

Summary

This chapter provides the theoretical basis upon which this research was developed. A review of the literature related to the incidence of tuberculosis worldwide and in the United States was presented to illustrate that tuberculosis remains a serious public health problem. A review of the literature related to the incidence and implications of multiple drug resistant tuberculosis (MDR -TB) in the United States was included to illustrate that costs related to tuberculosis treatment are likely to increase. An overview of the literature related to the incidence of tuberculosis and tuberculosis related treatment problems along the U.S. / Mexico border was presented to demonstrate the added challenges faced in combating tuberculosis in this region.

A review of the history and guidelines related to use of preventive isoniazid therapy in tuberculosis treatment programs in the United States was presented to serve as baseline information related to the types of programs that are the subject of this research. A review of the literature related to the costs of treating tuberculosis in the United States was performed to report the economic burden to society that is the result of tuberculosis.

A review of the framework for economic evaluations in medicine and for
prevention effectiveness evaluation of health prevention programs was described to provide background information on the types of economic methods or analyses used in this prevention effectiveness study. A discussion of the role of decision analysis and Markov modeling in the economic evaluation process was provided to specify their role in the prevention effectiveness evaluation process. Finally, a review of the literature assessing the economic evaluation of isoniazid preventive therapy in the prevention of tuberculosis was presented to provide a synopsis of previous economic studies in this area of inquiry.
CHAPTER 3

METHODS

The overall purpose of this research was to perform a prevention effectiveness analysis that examined the cost-effectiveness of a county administered tuberculosis prevention program along the U.S. / Mexico border. Specifically, the tuberculosis prevention program under study used prophylactic isoniazid therapy in patients who have tested positive for tuberculosis infection. The analysis compares the cost-effectiveness of the current program versus no program from the perspective of the county government. The cost effectiveness of the program scenario was examined for two time periods; five years and 15 years post preventive therapy initiation.

The outcome of interest, cases of active tuberculosis averted, was calculated through a Monte Carlo simulated Markov process model. Costs were calculated using actual data from tuberculosis prevention and active tuberculosis treatment programs as well as hospital discharge data related to hospital admissions for active tuberculosis. Average and incremental cost-effectiveness ratios were calculated for the tuberculosis prevention program scenario. One-way sensitivity analyses were performed for selected parameters used in the calculation of the cost-effectiveness ratios.

Variables

**Independent Variable**

This research included two levels of the independent variable, the prevention of tuberculosis cases. One level of the independent variable was the prevention of
tuberculosis with a tuberculosis prevention program. The second level of the independent variable was the no tuberculosis prevention program option.

**Dependent Variables**

The first set of dependent variables to be estimated in this research were the outcomes used to establish the cost-effectiveness of the prevention program scenario. The outcome evaluated in this research was the number of active tuberculosis cases averted or prevented under each scenario.

The second set of dependent variables to be estimated were direct medical costs associated with the prevention program and no prevention program scenarios. This included direct intervention costs incurred by the tuberculosis prevention program for the screening and prevention of active tuberculosis with isoniazid therapy. Also calculated were the downstream cost savings associated with the tuberculosis prevention program scenario. These cost savings included obviating treatment of active tuberculosis, preventing future active tuberculosis cases, and contact tracing/follow-up that would occur from initial cases in the absence of the tuberculosis prevention program.

**Study Site**

A majority of the cost and probability data used in the development of the model used in this prevention effectiveness analysis were primary data from the Santa Cruz County Health Department-Tuberculosis Control Program (SCC-TCP). The SCC-TCP provides tuberculosis prevention and control services for the residents of Santa Cruz County, Arizona. The program clinic is located in Nogales, Arizona (a port of entry
between Mexico and the United States). Its sister city, Nogales, Sonora, Mexico is separated from Nogales, Arizona by a fence.

Although Santa Cruz County is, geographically, the smallest county in Arizona, it is larger than the state of Rhode Island. The population of Santa Cruz County in the 1990 census was 29,676 with 19,489 living in Nogales, Arizona. However, resident aliens typically are under reported in census data. Thus, this population estimate may be under representative of the true population of the county. The 1997 official estimated population of Nogales, Sonora, Mexico was just over 150,000 inhabitants; the unofficial population estimate was approximately 300,000 people (Ingram, Laney and Gillilan, 1995).

The SCC-TCP staff is comprised of one full-time registered nurse (who also serves as Program Director), one full-time secretary and one half-time licensed practical nurse. The SCC-TCP provides tuberculosis screening, a tuberculosis clinic which is conducted once a month by a physician, an active tuberculosis control program and a preventive tuberculosis control program. The tuberculosis control program has an annual budget of approximately $98,500 and is funded through Santa Cruz County. Medication for the tuberculosis control program during the study period was procured from a private vendor.

A recent study, related to compliance with preventive therapy, is useful in describing representative demographic information of patients enrolled in the tuberculosis prevention program (Borrego and Slack, 1996). The median age of patients enrolled in the program was 24.5 years, with a range of less than one year to 73 years old. Eighty-six percent of the study population was less than 35 years old. Females represented 62% of
the population, males 38%. The study population composition, by race, was 93% Hispanic, 3% white and 4% other. For the information available on birth status, 26% of patients were born in the United States, 74% were born outside the U.S. Of those patients born outside the United States, 95% were born in Mexico.

Patients are enrolled in the preventive tuberculosis program either through the detection of a positive skin test performed by the tuberculosis prevention program staff or via a documented positive tuberculin skin test result from a referring agency. Patients are referred by a variety of sources; self, other health care agencies, correctional facilities and immigration agencies. The preventive tuberculosis program follows the CDC guidelines related to skin test reading and risk factors in determining candidates for preventive therapy.

A patient chart with demographic and risk factor information is initiated and a chest x-ray is performed. Based on patient information and skin test/x-ray results, the physician initiates prophylactic therapy for all patients under the age of 35 and for patients over the age of 35 with additional risk factors. Patients over the age of 35 with no additional risk factors are not placed on preventive therapy because the side effects of isoniazid may outweigh the benefits. Baseline and follow-up liver enzyme tests are performed (every 3-4 weeks) on patients greater than 35 years of age who have been started on preventive therapy.

Preventive therapy consists of isoniazid 300mg daily for six months, in children and infants the dose is adjusted according to body weight. The goal of the preventive
program is six continuous months of therapy (or 180 total doses), however, the completion of six months of therapy in a 12 month period is considered therapeutic success.

Methodology

This research determined the cost-effectiveness of the preventive program scenario by using the prevention effectiveness evaluation methodology described by Haddix et al., 1996. This section will describe the procedures used for the determination of costs and outcomes used in the cost-effectiveness analysis portion of the evaluation.

Costs

Given the perspective of the analysis (county government), only direct costs were measured in this prevention effectiveness study. Direct costs measured for the analysis were as follows: 1) direct intervention costs incurred by the tuberculosis prevention program for the screening and prevention of active tuberculosis with preventive isoniazid therapy, 2) direct cost savings associated with the tuberculosis prevention program scenario, and 3) direct cost savings related to contact tracing and follow-up as well as prevention of future active tuberculosis cases that would occur from initial cases in the absence of the tuberculosis prevention program due to the contagious nature of tuberculosis.

_Tuberculosis Prevention Program Costs_

Average direct treatment costs for screening and preventive therapy were calculated through a survey of actual program costs for the Santa Cruz County
Tuberculosis Control Program for 1997. Tuberculosis prevention program cost components used in this analysis are presented in Table 1.

Costs related to the tuberculosis prevention program were comprised of fixed and variable costs. The fixed cost portion included personnel, facilities and supplies costs. The variable cost portion included costs related to skin testing, lab and x-ray charges, and drug therapy with isoniazid. The variable cost portion varied based upon the percent of patients skin tested, percentage of patients receiving liver function tests, and percentage of patients completing isoniazid therapy. Costs related to personnel time spent providing treatment (such as skin test interpretation and clinic visits) were assumed to be personnel duties and accounted for as fixed costs in the personnel cost section.

_Tuberculosis Prevention Program Cost Savings_

Average direct cost savings were calculated for treatment costs related to active tuberculosis that would occur in absence of the tuberculosis prevention program. The cost per case of active tuberculosis was comprised of an average hospitalization charge and subsequent average outpatient treatment cost component.

Direct costs for hospitalization due to active tuberculosis were obtained through a survey of all charges associated with a primary diagnosis of active tuberculosis reported for 1996 to the Arizona Department of Health Services, Office of Health Planning, Evaluation and Statistics, Hospital Discharge Database. Given the perspective of the analysis (county government), hospital charges were used to represent direct costs for hospitalization due to active tuberculosis since charges represent the true cost that would
Table 1. Tuberculosis Prevention Program Cost Components

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total (A x B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIXED COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrator</td>
<td>% of time</td>
<td>annual salary/benefit</td>
<td></td>
</tr>
<tr>
<td>LPN</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Secretary</td>
<td>1 year</td>
<td>contracted price</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>% use x 12 months</td>
<td>avg. monthly cost</td>
<td></td>
</tr>
<tr>
<td>Utilities (electric)</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Utilities (water/waste)</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Phone</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Mail</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Security</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Supplies</td>
<td></td>
<td>avg. monthly cost</td>
<td></td>
</tr>
<tr>
<td>Office Supplies</td>
<td>% use x 12 months</td>
<td>avg. monthly cost</td>
<td>cost</td>
</tr>
<tr>
<td>Compliance Incentives</td>
<td>1 year</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VARIABLE COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculin skin test materials</td>
<td>% tested x # pt.</td>
<td>cost</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 2 months isoniazid</td>
<td>%completed x #pt.</td>
<td>monthly cost x 2</td>
<td>Monthly cost x 2</td>
</tr>
<tr>
<td>3 to 4 months isoniazid</td>
<td>&quot;&quot;</td>
<td>monthly cost x 4</td>
<td>Monthly cost x 4</td>
</tr>
<tr>
<td>5 to 6 months isoniazid</td>
<td>&quot;&quot;</td>
<td>monthly cost x 6</td>
<td>Monthly cost x 6</td>
</tr>
<tr>
<td>Pyridoxine 50 mg (6 months)</td>
<td>% treated x # pt.</td>
<td>monthly cost x 6</td>
<td>Monthly cost x 6</td>
</tr>
<tr>
<td>Liver function test (6 months)</td>
<td>% treated x # pt.</td>
<td>monthly cost x 6</td>
<td>Monthly cost x 6</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL ANNUAL TB PREVENTION PROGRAM COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Participants per year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AVERAGE PREVENTIVE TREATMENT COST PER PATIENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Costs related to tuberculin skin test interpretation and monthly follow up clinic visits for monitoring while on preventive therapy are assumed personnel duties related to the program and accounted for in personnel section.
100

be borne by the county in providing hospital treatment for active tuberculosis.

The median hospital charges evaluated in this analysis were based on the primary
diagnosis of tuberculosis using the International Classification of Diseases, Ninth
Edition, Clinical Modification (ICD-9-CM) coding system (American Medical
Association, 1997). The ICD-9-CM codes used in this analysis are the same as those used
by Brown and colleagues (1995) in their determination of inpatient treatment costs related
to tuberculosis. The ICD-9-CM codes used in the survey are inclusive of all codes related
to the diagnosis of active tuberculosis and include the following:

010 - primary tuberculosis infection (excluding positive PPD or positive skin
test without active tuberculosis);

011 - pulmonary tuberculosis;

012 - other respiratory tuberculosis;

013 - tuberculosis of meninges and central nervous system;

014 - tuberculosis of intestines, peritoneum, and mesenteric glands;

015 - tuberculosis of bones and joints;

016 - tuberculosis of genitourinary system;

017 - tuberculosis of other organs;

and 018 - miliary tuberculosis.

The median charge for tuberculosis related hospital admissions was inflated to
1997 dollars using the Consumer Price Index (CPI) for medical care. Since the CPI for
medical care for 1997 was not yet published at the time of this analysis, hospital charges
were inflated using the CPI's for 1995 (index value for year in which cost was reported) and 1996 (base year index value) as a proxy (U.S. Bureau of the Census, 1997; Shaffer and Haddix, 1996).

Cost-data related to physician services per typical inpatient or hospital admission for active tuberculosis were estimated using the 1997 Medicare National Average Allowance Fee Schedule and the *Physician's Current Procedural Terminology, Fourth Edition* (CPT-4) code numbers 99222 and 99231 (Health Care Consultants of America, 1997; American Medical Association, 1996).

CPT-4 code 99222 represents a daily physician charge for initial hospital care for the management of a patient which requires a comprehensive history, a comprehensive exam and medical decision making of moderate complexity. CPT-4 code 99231 represents a physician charge for subsequent hospital care which includes a problem focused examination and medical decision making that is straightforward or of low complexity. In this analysis, it was assumed that the typical active tuberculosis inpatient would incur one charge for CPT-4 code 99222 and a charge for CPT-4 code 99231 times the average patient length of stay (in days) minus one.

Average direct costs for the treatment of active tuberculosis treated on an outpatient basis were calculated through a survey of actual program costs for the Pima County Tuberculosis Control Program, Tucson, Arizona. Data from the neighboring Pima County Program (which also shares borders with Mexico) was used because their data were more representative given their experience in treating a larger number of patients.
with active disease, as compared to the Santa Cruz County Tuberculosis Control Program.

Costs related to the outpatient treatment program were comprised of fixed and variable costs. The fixed cost portion included personnel, facilities and supplies costs. An overhead cost percentage value (set by the county and based on a percentage of salaries) was used to calculate the facilities and supplies cost portion.

The variable cost portion included costs related to lab and x-ray charges, drug therapy, side effects, program travel costs to provide therapy and compliance incentives. Costs related to personnel time spent providing treatment (such as clinic visits or the administration of directly observed therapy) were assumed to be personnel duties and accounted for as fixed costs in the personnel cost section. Active tuberculosis hospitalization and outpatient treatment program cost components are presented in Table 2.

*Tuberculosis Contagion Cost Savings*

Average direct cost savings were also calculated for the prevention of future active tuberculosis cases that would occur from initial cases in the absence of the tuberculosis prevention program alternative due to the contagious nature of tuberculosis. This was comprised of costs related to 1) contact tracing, identification, and follow-up of patients exposed to a person with untreated active tuberculosis, 2) preventive therapy of a portion of those contacts, and 3) treatment of subsequent active tuberculosis cases caused by one case of untreated active tuberculosis. Cost saving components related to tuberculosis contagion are presented in Table 3.
Table 2. Active Tuberculosis Hospitalization and Outpatient Program Cost Components

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total AxB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOSPITALIZATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median hospital charge based on ICD-9-CM codes for primary diagnosis of tuberculosis</td>
<td>% of patients hospitalized</td>
<td>median charge per patient</td>
<td></td>
</tr>
<tr>
<td>Physician costs based on CPT-4 codes for initial and subsequent hospital care</td>
<td>% of patients x % of patients x LOS</td>
<td>CPT-4 charge</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL Average Hospital Cost Per Patient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OUTPATIENT PROGRAM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FIXED COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrator</td>
<td>% of time</td>
<td>annual salary/benefits</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Licensed Practical Nurse</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Secretary</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Data Entry</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Social Worker</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>X-ray technician</td>
<td>&quot;</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>Facilities/Supplies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overhead</td>
<td>county %</td>
<td>total salaries/benefits</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 (cont.) Active Tuberculosis Hospitalization and Outpatient Program Cost Components

<table>
<thead>
<tr>
<th>VARIABLE COSTS*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>#/patient x # patients</td>
<td>cost</td>
</tr>
<tr>
<td>Sputum smear and culture</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Antibiotic sensitivity</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Liver function test</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td># months x # patients</td>
<td>monthly cost</td>
</tr>
<tr>
<td>Rifampin</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Function</td>
<td>%patients x #patients</td>
<td>cost</td>
</tr>
<tr>
<td>Program Travel Costs</td>
<td>#patients x avg. miles</td>
<td>cost/mile</td>
</tr>
<tr>
<td>Compliance Incentives</td>
<td># patients</td>
<td>cost / patient</td>
</tr>
</tbody>
</table>

Subtotal

TOTAL Annual Active Tuberculosis Outpatient Treatment Costs

Participants per year

TOTAL Average Cost Per Case for Active Tuberculosis on Outpatient Basis

TOTAL AVERAGE COST PER CASE FOR TREATMENT OF ACTIVE TUBERCULOSIS (Hospital + Outpatient Treatment)

* Costs related to monthly follow up clinic visits or for directly observed therapy (DOT) are assumed to be part of program personnel duties and accounted for in personnel section.
Table 3. Tuberculosis Contagion Cost Saving Components*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity</th>
<th>Cost / Unit</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(A)</td>
<td>(B)</td>
<td>(A x B)</td>
</tr>
<tr>
<td>Tuberculin skin test materials</td>
<td>10 patients</td>
<td>cost</td>
<td></td>
</tr>
<tr>
<td>Administration / interpretation of skin test</td>
<td>10 patients</td>
<td>(LPN/hr x 0.5 hr)</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray and reading</td>
<td>10 patients</td>
<td>cost</td>
<td></td>
</tr>
<tr>
<td>Initial consultation</td>
<td>10 patients</td>
<td>(LPN/hr x 0.5 hr)</td>
<td></td>
</tr>
<tr>
<td>6 months isoniazid (INH)</td>
<td>5 patients</td>
<td>cost/month x 6</td>
<td></td>
</tr>
<tr>
<td>Clinic visits for 6 months isoniazid therapy</td>
<td>30 visits</td>
<td>(LPN/hr x 0.25 hr)</td>
<td></td>
</tr>
<tr>
<td>Active case of tuberculosis</td>
<td>1 case</td>
<td>avg. cost per case</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(from Table 2)</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL Cost per Case Related to Tuberculosis Contagion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ x \] Number of active tuberculosis cases averted or prevented (from Markov process model)

**TOTAL COST SAVINGS RELATED TO TUBERCULOSIS CONTAGION**

* Quantity column provides estimated number of contact investigations, patients requiring preventive treatment and number of active tuberculosis cases expected to develop per one case of untreated active tuberculosis (Moore et al., 1996; Murray et al., 1990).
Outcomes

A Markov Process model was developed to estimate the outcome of interest, number of cases of active tuberculosis averted with the prevention program versus no prevention program scenario.

Markov Process Models

The construction of the Markov process models followed the four required steps outlined by Beck and Pauker (1983). These steps include: 1) description of model states, 2) definition of model state transitions, 3) probability assignment to model state transitions and 4) calculation of the outcome of interest.

Model State Descriptions

Figures 2 and 3 graphically represent the Markov process models developed to estimate the outcomes for the tuberculosis prevention program versus no prevention program scenarios, respectively. Eight model or health states were identified for the tuberculosis prevention program and three model states for the no program scenario. Markov process model states are identified by numbers within a bolded circle in Figures 2 and 3. Markov process model state descriptions are presented in Table 4 (preventive program scenario) and Table 5 (no preventive program scenario).

In the tuberculosis prevention program scenario Markov model (Figure 2), health state numbers 1 through 3 represent entry states into the model. A tuberculosis infected patient could enter the model in any one of these health states. The proportion of patients entering any one of these three entry states is based on compliance data from actual
Figure 2. Markov Process Model - Tuberculosis Prevention Program Scenario

- = state transition numbers
- = model state numbers
Table 4. Markov Process Model State Descriptions - Tuberculosis Prevention
Program Scenario

<table>
<thead>
<tr>
<th>State</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preventive Treatment</td>
<td>Patient enters preventive treatment with isoniazid for up to two months.</td>
</tr>
<tr>
<td></td>
<td>1-2 months</td>
<td>Entry state.</td>
</tr>
<tr>
<td>2</td>
<td>Preventive Treatment</td>
<td>Patient enters preventive treatment with isoniazid for greater than two and up to four months. Entry state.</td>
</tr>
<tr>
<td></td>
<td>3-4 months</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Preventive Treatment</td>
<td>Patient enters preventive treatment with isoniazid for greater than four and up to six months. Entry state.</td>
</tr>
<tr>
<td></td>
<td>5-6 months</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Post Preventive Treatment</td>
<td>Patient received preventive treatment with isoniazid for zero to two months.</td>
</tr>
<tr>
<td></td>
<td>1-2 months</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Post Preventive Treatment</td>
<td>Patient received preventive treatment with isoniazid for greater than two and up to four months.</td>
</tr>
<tr>
<td></td>
<td>3-4 months</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Post Preventive Treatment</td>
<td>Patient received preventive treatment with isoniazid for greater than four and up to six months</td>
</tr>
<tr>
<td></td>
<td>5-6 months</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Active Tuberculosis</td>
<td>Active tuberculosis disease.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absorbing state.</td>
</tr>
<tr>
<td>8</td>
<td>Death</td>
<td>Absorbing state.</td>
</tr>
</tbody>
</table>
Table 5. Markov Process Model State Descriptions - No Tuberculosis Prevention Program Scenario

<table>
<thead>
<tr>
<th>State</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tuberculosis Infection Positive</td>
<td>Tuberculosis infection positive patients who are candidates for preventive treatment with isoniazid. Entry state.</td>
</tr>
<tr>
<td>2</td>
<td>Active Tuberculosis</td>
<td>Active tuberculosis disease. Absorbing state.</td>
</tr>
<tr>
<td>3</td>
<td>Death</td>
<td>Absorbing state.</td>
</tr>
</tbody>
</table>
prevention program experience. For example, if a patient had only participated in the prevention program for three months, the patient would have entered the model in state number 2 (Preventive Treatment 3 - 4 months).

Model state numbers 4 through 6 represent Post Preventive Treatment States. In these states, patients would have completed a given number of months of preventive treatment (up to two, four or six months) based on the previous entry health state (states 1, 2, or 3). Model state number 7 is an absorbing state and represents the outcome of interest, development of active tuberculosis. The eighth and final model state, death, represents patients dying from any cause and is also an absorbing state.

The no tuberculosis program scenario Markov process model (Figure 3) is represented by three model states. Model state number 1, Tuberculosis Infection Positive, represents the state where a patient is tuberculosis infection positive (and at risk for developing active tuberculosis) and is the only entry state in the model. Model state numbers 2 (Active Tuberculosis) and 3 (Death) are absorbing states and are equivalent to state numbers 7 and 8 in the tuberculosis prevention program Markov process model. The assumptions for both the program and no program scenarios are that all model health states are discrete and the model description is exhaustive.

State Transitions

In the prevention program scenario Markov process model, a total of twelve transitions between model states are possible. The allowable state transitions for the prevention program scenario appear as numbers within square boxes in Figure 2. Based
upon the model, Preventive Treatment state patients can transition from state 1 to 3 only to their corresponding Post Preventive Treatment model state (states 4 through 6, respectively). Transitions to state number 7 (Active Tuberculosis) are allowed from each of the respective Post Preventive Treatment model states (states 4 through 6). Transition to state 8 (Death) are allowed from each state in the model except state 7 (Active Tuberculosis). The allowable transitions (transitions 7 through 12) to the Death state are represented by dashed lines in Figure 2.

In the no prevention program scenario Markov process model, a total of two transitions between model states are possible. The allowable Markov process model state transitions for the no program scenarios appear as numbers within square boxes in Figure 3. Patients are allowed to transition form state 1 to state 2 and state 3. The assumptions related to the state transitions for the program and no program scenario models are that only the model state transitions labeled are possible.

State Transition Probabilities

State transition probabilities for the program and no program scenarios were assigned using a combination of program experience and literature based data. Rates were converted to probabilities by use of the following formula:

\[ P[t] = 1 - e^{-rt} \]

where \( r \) = rate, and \( P \) = probability of an event occurring over a time interval of \( t \) time units (Beck and Pauker, 1983).

State transition probabilities for the preventive program scenario were comprised
of fixed and varying probabilities. State transition probability numbers 1 through 3 were varying probabilities. Since each of the Preventive Treatment model states (model state numbers 1 through 3) represent specific time periods, patients can exist in these entry states for a known period of time; up to two, four or six months. Thus, these state transition probabilities (numbers 1 through 3) were varied to reflect these known periods of time.

For example, a patient in the 3 - 4 month Preventive Treatment model state would be required to exit that model state no sooner than three months and no later than four months. In both models, it is assumed that each tick or clock period used in the model simulation represents one month. The probability for this model state would vary as follows: 1) for months or ticks number one and two, the probability of transitioning to model state number 5 (Post Preventive Treatment 3 - 4 months) would be equal to zero, 2) for month or tick three, the probability of transitioning was set to \( p = 0.5 \) (indicating that half of the patients entered state 5) and 3) for month or tick four, the probability of transitioning was set to \( p = 1.0 \) (indicating that all remaining patients must exit the entry state). Similar methods of varying probabilities were established for all three Preventive Treatment Entry states.

Transition probabilities 4 through 6 were also varying transition probabilities which represent the probability of developing active tuberculosis after having completed one of the three preventive treatment states (classified by number of months of isoniazid preventive treatment completed). These model state transition probabilities were varied
because the lifetime probability of developing active tuberculosis is greater during the first
two years (the first year being highest in risk) after converting to a tuberculosis infection
positive state.

Transition state number 4 represents the case where having two months or less of
preventive treatment is equivalent to the preventive isoniazid treatment having no
protective effect against developing active tuberculosis. Transition probability states 5 and
6 represent the probabilities of developing active tuberculosis after the protective effect of
preventive isoniazid treatment. The formula used to calculate the probabilities for these
state transitions is based on the previous work of Tsevat et al. (1988) and Sterling et al.
(1995). The formula is:

\[
p_{TB^{INH}} = p_{TB^{0INH}} - (\text{baseline effectiveness} \times p_{TB^{0INH}})
\]

where,

\[p_{TB^{INH}} = \text{probability of developing active tuberculosis given that the patient has taken preventive isoniazid therapy};\]

\[p_{TB^{0INH}} = \text{probability of developing active tuberculosis without preventive isoniazid therapy};\]

and \text{baseline effectiveness} = \text{effectiveness of preventive isoniazid therapy in preventing active tuberculosis, based on number of months of isoniazid taken.}

Transition probabilities 7 through 12 are fixed transition probabilities which
represent the probability of dying from any cause other than tuberculosis. This probability
was obtained from life tables and reflected the average age of a person in the study
population.

State transition probabilities for the no preventive program scenario were also a combination of fixed and varying probabilities. State transition probability number 1 was a varying probability which represented the probability of developing active tuberculosis from the Tuberculosis Infection Positive state.

This model state transition probability was varied because the lifetime probability of developing active tuberculosis is greater during the first two years (the first year being highest in risk) after converting to a tuberculosis infection positive state. This state transition probability value was obtained through program experience and literature based data. Model state transition probability number 2 represents the probability of Death from any cause and is the same probability as in the preventive program scenario Markov process model.

Calculation of the Outcome of Interest

The Markov process models for the preventive program and no preventive program scenarios were analyzed via a computer software program which used Monte Carlo simulation to determine the prognoses of the hypothetical cohort of patients. The data were analyzed using a computer software program developed by Gary Dooley, Ph.D. A separate evaluation was simulated for each of the respective program scenario models over two time periods (five year and 15 years post preventive therapy).

**Preventive Program Scenario Model**

As noted previously, in the tuberculosis prevention program scenario Markov
model (Figure 2), health state numbers 1 through 3 represent entry states into the model. A tuberculosis infected patient could enter the model in any one of these three health states. The proportion of patients entering any one of these three entry states is based on compliance data from actual prevention program experience. For example, if a patient had only participated in the prevention program for three months, the patient would have entered the model in model state number 2 (Preventive Treatment 3 - 4 months).

Since Monte Carlo simulation requires the simulation of a large number of patients (on the order of 10,000), the number of patients entering one of the three Preventive Treatment entry states in the model could have been calculated based on compliance proportions form actual program data. For example, compliance proportions for the three Preventive Treatment model entry states were 16%, 12% and 72%, respectively. The number of patients entering the respective states would be equal to 1,600 patients (state 1), 1,200 (state 2) and 7,200 patients (state 3) based on the 10,000 patients required for simulation.

A better estimate of the Markov process model for the preventive program scenario was obtained by developing and simulating 10,000 patients each through three smaller Markov process models, based on their initial Preventive Treatment model state. Use of the three smaller Preventive Treatment Specific Markov models provide a more accurate estimation of the model than in the former case where only 1600, 1200 or 7200 patients would be simulated through their respective model path.

More clearly stated, the process of splitting the original Markov process model
into three smaller Markov process models, simulating 10,000 patients through each of the three smaller models, and multiplying the results by their respective compliance proportions; models the experience of a total of 10,000 patients going through the original program scenario Markov process model (Figure 2).

Figure 4 presents a representative model structure for the three Preventive Treatment Specific Markov process models. Table 6 presents representative model state descriptions for the three Preventive Treatment Specific Markov process models. In the Preventive Treatment Specific Markov process models, patients enter the model in the Preventive Treatment model state (state 1) and progress to the Post Preventive Treatment model state (state 2) based on whether they completed up to two, four or six months of preventive therapy.

From the Post Preventive Treatment state, patients were allowed to transition to state 3, Active Tuberculosis, an absorbing state. Patients were also allowed to transition to the absorbing state of Death (state 4) from state 1 and 2.

Each of the three Preventive Treatment Specific models were evaluated until all patients entered one of two absorbing states, Active Tuberculosis or Death, or the clock period reached 60 cycles (5 years). The clock or tick period used in the evaluation was set to one month in duration.

A time period of five years was selected as baseline because it was assumed that the benefits of the prevention program (cases of active tuberculosis averted) would begin to accrue given that the probability of developing tuberculosis is greatest two years after
Preventive Treatment $x$ to $x^*$ months

Post Preventive Treatment $x$ to $x^*$ months

Active Tuberculosis

Death

\[ O \]

\[ O \leftarrow \text{model state numbers} \]

\[ \square \leftarrow \text{state transition numbers} \]

\[ x \text{ to } x^* \text{ months} = 1 \text{ to } 2 \text{ months, } 3 \text{ to } 4 \text{ months, or } 5 \text{ to } 6 \text{ months.} \]
Table 6. Representative Model State Descriptions for Preventive Treatment Specific Markov Process Models

<table>
<thead>
<tr>
<th>State</th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Preventive Treatment x to x* months</td>
<td>Patient enters preventive treatment with isoniazid for up to x* months. Entry state.</td>
</tr>
<tr>
<td>2</td>
<td>Post Preventive Treatment x to x* months</td>
<td>Patient received preventive treatment with isoniazid for x to x* months.</td>
</tr>
<tr>
<td>3</td>
<td>Active Tuberculosis</td>
<td>Active tuberculosis disease. Absorbing state.</td>
</tr>
<tr>
<td>4</td>
<td>Death</td>
<td>Absorbing state.</td>
</tr>
</tbody>
</table>

Where x to x* months = 1 to 2 months, 3 to 4 months, or 5 to 6 months.
acquiring the tuberculosis infection. The evaluation process was repeated for the 180 cycle (or 15 year) scenario. It was assumed that transitions from model state to model state occurred at the end of each clock period.

The outcome of interest, the number of entries per patient into the Active Tuberculosis model state from each of the three Preventive Treatment Specific Markov process models, were obtained from the evaluation output data. The outcome of interest was then multiplied by the following proportions based on actual preventive program compliance data:

Preventive Treatment 1-2 months = entries/patient × 0.161;
Preventive Treatment 3-4 months = entries/patient × 0.116;
Preventive Treatment 5-6 months = entries/patient × 0.723.

Multiplying each of the entries/patient outcome value by the compliance proportion value yields the proportion of active tuberculosis cases that would occur despite each of the Preventive Treatment states. Summing the proportion of active tuberculosis cases for each Preventive Treatment state indicates the total number of active tuberculosis cases that would occur despite the tuberculosis prevention program option.

No Prevention Program Scenario Model

Evaluation of the no prevention program scenario model was accomplished by entering 10,000 patients in the Tuberculosis Infection Positive entry model state (Figure 3). As in the three prevention program scenario Markov process model evaluations, the no preventive program scenario model was evaluated until all patients entered one of two
absorbing states, Active Tuberculosis or Death, or the clock period reached 60 cycles (5 years). The evaluation process was repeated for the 180 cycle (or 15 year) scenario. The clock or tick period used in the evaluation were set to one month in duration. It was assumed that transitions from state to state occurred at the end of each clock period.

The evaluation data output results provide the outcome of interest, the number of entries per patient into the Active Tuberculosis model state. This result provides the total number of active tuberculosis cases that would occur with the no prevention program scenario. The difference between the number of patients entering the Active Tuberculosis state in the prevention program and no prevention program scenarios estimates the number of cases averted or prevented.

**Data Analysis**

This section provides a discussion of the methodology used in: 1) discounting future costs and outcomes estimated in this analysis, 2) the calculation of average and incremental cost-effectiveness ratios for the for the preventive program scenario and 3) the performing of sensitivity analyses for the analysis.

**Discounting**

Since this study has costs and benefits occurring beyond one year, future costs and benefits were adjusted and translated to their present value (Shaffer and Haddix, 1996). Since there are advantages to incurring costs later or receiving benefits earlier, it is necessary to incorporate the concept of time preference into a cost-effective analysis. Discounting is the process of converting future costs and benefits into their present value.
The quantitative measure of time preference is the discount rate.

Future health outcomes must also be discounted in cost-effectiveness analyses. If health outcomes are not discounted but the costs are discounted, the alternative will always appear most cost-effective. Thus, discounting health outcomes at the same rate as monetary outcomes creates an "exchange rate" for dollars and health outcomes that is invariant (Haddix and Shaffer, 1996).

Haddix and Shaffer recommend using a 3% or 5% real discount rate for both costs and benefits, monetary and non-monetary, to increase the comparability of public health problems. In this analysis, a 3% discount rate for both costs and outcomes was used. The equation used for discounting the stream of future dollars and/or future outcomes into present value in this analysis was:

\[ PV = F_0 + \frac{F_1}{(1+r)^1} + \frac{F_2}{(1+r)^2} + \frac{F_3}{(1+r)^3} + \ldots + \frac{F_n}{(1+r)^n} \]

where

\( PV \) = present value;

\( F \) = future value;

\( r \) = discount rate

\( n \) = analytical horizon.
**Average Cost-Effectiveness Ratio Calculation**

The average cost-effectiveness (CE) ratio, evaluated against the baseline or reference option, is the net cost of a prevention strategy divided by the number of health outcomes averted (Haddix and Shaffer, 1996). The formula for the average cost-effectiveness ratio for an intervention is:

\[
\text{Average CE Ratio} = \frac{\text{Intervention Cost} - \text{Disease Cost Averted}}{\text{Total Health Outcomes Prevented}}
\]

where,
- **Intervention Cost** = Cost of intervention for which average CE ratio is calculated;
- **Disease Cost Averted** = Cost \(\text{Disease A} \text{ (baseline state)} - \text{Cost Disease A (disease cost after intervention)}\); 
- **Total Health Outcomes Prevented** = Outcome \(0 \text{ (# at baseline)} - \text{Outcomes A (# at intervention).}\)

**Incremental Cost-Effectiveness Ratio Calculation**

Incremental cost-effectiveness ratios are used to examine the efficiency of one intervention relative to another. The incremental cost-effectiveness ratio is generally reported as the additional cost per additional health outcome prevented. The formula for the incremental cost-effectiveness ratio for an intervention is:

\[
\text{Incremental CE Ratio} = \frac{\text{Additional Intervention Cost} - \text{Additional Cost Averted}}{\text{Additional Total Health Outcomes Prevented}}
\]

where,
Additional Intervention Cost = Cost_{Intervention B} - Cost_{Intervention A}

Additional Disease Cost Averted = Cost_{Disease A} - Cost_{Disease B}

Additional Health Outcomes Prevented = Outcomes_A - Outcomes_B

Petitti (1994) and Destsky and Naglie (1990), indicate that the average cost-effectiveness ratio and the incremental cost-effectiveness ratio are identical only in the highly unusual situation where the alternative treatment has a zero cost and no effectiveness. Because the no preventive program scenario has no cost and is not an effective method to prevent active tuberculosis, the average and incremental cost-effectiveness ratios are identical in this analysis.

In this analysis, the incremental (and average) cost-effectiveness ratio was calculated by use of the following formula:

$$\frac{\text{Net Direct Care Costs}}{\text{Net Health Effects}} = \frac{\text{Cost}}{\text{Case Averted}} = \frac{C_{tp} + C_{tb(p)} - C_{tb(np)} - C_{ctb}}{E_{no\ program} - E_{program}}$$

where:

- $C_{tp} =$ cost of tuberculosis prevention program;
- $C_{tb(p)} =$ cost of treating active tuberculosis that occurs despite program;
- $C_{tb(np)} =$ cost of treating active tuberculosis that occurs without program;
- $C_{ctb} =$ costs related to prevention and treatment of future tuberculosis related cases that would be due to the contagious nature of tuberculosis (i.e., contact tracing and identification, preventive therapy of contacts, and treatment of future active...
tuberculosis cases) and that would occur without the program;

\[ E_{\text{no program}} = \text{number of active tuberculosis cases that occur without program}; \]

\[ E_{\text{program}} = \text{number of active tuberculosis cases that occur in spite of program}. \]

**Sensitivity analyses**

Sensitivity analyses were conducted for selected parameters used to model the cost-effectiveness between the program and no program scenarios. A one-way sensitivity analysis was performed on the cost-effectiveness results of the program scenario for the parameter related to the percentage of patients requiring hospitalization for active tuberculosis. The second sensitivity analysis performed was a one-way sensitivity analysis which was used to predict the effect of increased or decreased compliance with preventive therapy on the cost-effectiveness between the prevention and no prevention program scenarios. The third one-way sensitivity analysis was performed for the discount rate used in discounting costs and outcomes calculated in the study.

The first one-way sensitivity analysis varied the percentage of patients hospitalized due to typical case of active tuberculosis. The percentage of patients hospitalized due to active tuberculosis was used in the calculation of average cost per case of active tuberculosis in the absence of the program alternative and in the calculation of tuberculosis contagion related costs. This cost parameter is significant for two reasons.

First, hospitalization costs comprise the majority of costs related to the treatment of active tuberculosis. Second, previous analyses have used hospitalization rates of 80 % to 90 % (Rose et al., 1988; Moore et al., 1996; Salpeter et al. 1997). The hospitalization
rates used in these previous analyses are based on the standard treatment protocol which advocate hospitalization for active tuberculosis. However, actual program data in this research has found the percentage of hospitalizations in the treatment of active tuberculosis closer to 70%. Thus, this parameter was varied from a low to high range of 50% to 90%, with 70% serving as baseline.

The second sensitivity analysis performed was a one way sensitivity analysis that varied the proportion of patients who started in any one of the three Preventive Treatment states in the three individual program scenario Markov process models. The proportion of patients in each of these Preventive treatment states represent compliance with preventive therapy of 0-2 months, 3 to 4 months, and 5 to 6 months.

The goal of the prevention program staff is to get as many patients as possible to complete six months of therapy. Thus, the proportion of patients in the preventive treatment states were varied between a low and high range to estimate the impact of increased or decreased compliance with preventive therapy. The range chosen for the analysis was 60% to 85%, with 72% serving as the baseline compliance rate (program data).

The upper range used in this sensitivity analysis corresponds to the Healthy People 2000, National Health Promotion and Disease Prevention objective number 20.18 (US Department of Health and Human Services, 1990). Prevention objective number 20.18 is to increase to at least 85% the proportion of people found to have tuberculosis infection who completed courses of preventive therapy. This sensitivity analysis was performed to
provide insights as to the effect of a targeted compliance program on costs, cases prevented and overall cost-effectiveness of the prevention program relative to the no prevention program scenario.

The third one-way sensitivity analysis varied the discount rate used in discounting costs and outcomes calculated in this study. Shaffer and Haddix (1996) recommend that to increase the comparability of public health programs a 3% or 5% discount rate for both costs and benefits (monetary and nonmonetary) should be used. In this study a baseline discount rate of 3% was used. In this one way sensitivity analysis, the discount rate for both costs and outcomes were varied to 5%.

An additional sensitivity analysis was performed related to the discount rate used in discounting costs and outcomes calculated in this study. In this one-way sensitivity analysis, a discount rate of 5% was used for costs and a discount rate of 3% was used for outcomes. Coyle and Tolley (1992) recommend that analysts conduct sensitivity analyses employing differential discount rates for health benefits as well as monetary costs and benefits. This recommendation is based on their contention that the social time preference rate for health benefits is unlikely to be the same as that for monetary costs and benefits.

Prevention Effectiveness Analysis Checklist

The prevention-effectiveness analysis methodology was used in conducting this research (Haddix et al., 1996). The prevention effectiveness analysis methodology includes: 1) framing the question, 2) structuring the decision model, and 3) analyzing the model and interpreting the results. The framing the question portion identifies thirteen key
points that must be addressed before the analytical process begins. Table 7 provides a summary of the key points addressed in this analysis.

Assumptions

1. The no prevention program alternative is an option.

2. The prevention alternatives (program versus no program) in this research are independent of each other.

3. The cost calculations performed in this research are appropriate and representative for the program, population and setting under study.

4. Estimated state transition probabilities are appropriate and representative to the program, population and setting under study.

5. Modeling assumptions are appropriate for the analysis in this study

Study Limitations

One limitation of this research is that only direct costs were used in the calculation of the cost-effectiveness ratio. While the use of direct costs was not incorrect, given the perspective of the analysis; the inclusion or exclusion of indirect costs would have undoubtedly affected the cost-effectiveness ratio between the program alternatives. The exclusion or inclusion of indirect costs, such as costs related to loss of productivity due to hospitalization in active tuberculosis cases or travel costs related to the prevention program, may underestimate or overestimate the cost-effectiveness of the prevention program alternative.

Another limitation of the study may be the alternatives chosen for this analysis; the
Table 7. Prevention Effectiveness Analysis Summary Checklist

<table>
<thead>
<tr>
<th>Point</th>
<th>Question</th>
<th>Analysis Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Define the audience for the evaluation</td>
<td>Policy and program decision makers at federal, state, and county levels.</td>
</tr>
<tr>
<td>2</td>
<td>Operationally define the problem or question to be analyzed.</td>
<td>Is a tuberculosis prevention program along the U.S. / Mexico border cost-effective compared to the no prevention program scenario?</td>
</tr>
<tr>
<td>3</td>
<td>Clearly indicate the prevention strategies being evaluated.</td>
<td>Tuberculosis prevention program versus no tuberculosis prevention program.</td>
</tr>
<tr>
<td>4</td>
<td>Specify the perspective of the analysis</td>
<td>County government.</td>
</tr>
<tr>
<td>5</td>
<td>Define the relevant time frame and analytical horizon for the analysis.</td>
<td>Time frame - 1 year Analytical horizon - 5 and 15 years</td>
</tr>
<tr>
<td>6</td>
<td>Determine the analytic methods.</td>
<td>Cost-effectiveness analysis.</td>
</tr>
<tr>
<td>7</td>
<td>Determine whether the analysis will be a marginal or incremental analysis.</td>
<td>Incremental analysis.</td>
</tr>
<tr>
<td>8</td>
<td>Identify the relevant costs.</td>
<td>1) Prevention program costs 2) Prevention program cost savings 3) Tuberculosis contagion cost savings</td>
</tr>
<tr>
<td>9</td>
<td>Identify the health outcome of interest</td>
<td>Number of cases of active tuberculosis averted.</td>
</tr>
<tr>
<td>10</td>
<td>Specify the discount rate or time preference for costs and non-monetary outcomes that occur in future.</td>
<td>Costs and non-monetary outcomes were discounted using a 3 percent discount rate.</td>
</tr>
<tr>
<td>11</td>
<td>Identify the sources of uncertainty and plan sensitivity analyses.</td>
<td>One-way and “what-if” analyses were performed for selected parameters used in the analysis.</td>
</tr>
<tr>
<td>12</td>
<td>Determine summary measures that will be reported.</td>
<td>Average and incremental cost-effectiveness ratios, sensitivity analyses results.</td>
</tr>
<tr>
<td>13</td>
<td>Assess distributional effects of prevention program.</td>
<td>Addressed in discussion and recommendation section.</td>
</tr>
</tbody>
</table>
program versus no program alternative. Some may argue, that, given the infectious nature of tuberculosis, the no program alternative would never be an option. However, the argument has been made that the most cost-effective tuberculosis prevention strategy would be to abandon preventive therapy programs (especially in developing countries) and concentrate on case finding, contact tracing and follow up of active tuberculosis cases (Murray et al., 1990).

Another limitation is that only a brief period or “snapshot” in time was represented in this analysis. The data from one program (in which average costs, number of patients enrolled in program and preventive treatment compliance rates for a one year time period) were used in the development of the model for this analysis. If average costs or compliance rates were spuriously high or low for the given year data were obtained, the resulting cost-effectiveness ratio modeled in this analysis may have been overstated or understated.

The external validity of this study applies to the characteristics of the study population, characteristics of the tuberculosis control programs and characteristics of the hospitalization data for the state of Arizona analyzed in this research. The parameters used and results obtained in this research are specific to this population and area. However, the methods used in the determination of cost-effectiveness for the study alternatives may be generalized to other tuberculosis prevention programs.
CHAPTER 4
RESULTS

A prevention effectiveness analysis framework was used to model the cost-effectiveness of a tuberculosis prevention program along the U.S. / Mexico border compared to a no prevention program scenario. The cost effectiveness of the prevention program scenario was examined for two time periods; five years and 15 years post preventive therapy initiation. Cost determination in this analysis was performed by using actual data from tuberculosis prevention and active tuberculosis treatment programs as well as hospital discharge data related to hospital admissions for active tuberculosis.

The outcome of interest, cases of active tuberculosis averted, was estimated through the development of Monte Carlo simulated Markov Process models. The Markov process models were estimated with a Markov model computer software program developed by Gary Dooley, Ph.D. This chapter presents the results from analyses of costs, state transition probabilities used in the Markov process modeling, outcome (effectiveness) data from the Markov process models, cost-effectiveness ratio calculations and sensitivity analyses.

Cost Determination

Given the perspective of the analysis (county government), only direct costs were measured in this prevention effectiveness study. Direct costs measured for the analysis were as follows: 1) direct intervention costs incurred by the tuberculosis prevention program for the screening and prevention of active tuberculosis with isoniazid therapy,
2) direct cost savings associated with the tuberculosis prevention program scenario, and
3) direct cost savings related to contact tracing and follow-up as well as prevention of
future active tuberculosis cases that would occur from initial cases in the absence of the
tuberculosis prevention program due to the contagious nature of tuberculosis.

**Tuberculosis Prevention Program Costs**

The total annual direct tuberculosis prevention program costs and average cost per
preventive patient managed were calculated through a survey of actual program costs for
the Santa Cruz County Tuberculosis Control Program for 1997.

The calculated total annual direct tuberculosis prevention program costs were
$45,232 (1997 dollars). An average of 250 patients per year have been enrolled in the
Santa Cruz County Tuberculosis prevention program for the last four years (1994-1997).
The calculated average cost per preventive patient managed for 1997 was $181. The
tuberculosis prevention program cost components and calculated program costs are
presented in Table 8.

**Direct Cost Savings Associated with the Tuberculosis Prevention Program**

Average direct cost savings were calculated for treatment costs related to
active tuberculosis cases that would occur in absence of the tuberculosis prevention
program. The cost per case of active tuberculosis was comprised of an average
hospitalization charge and subsequent average outpatient treatment cost component.

**Hospitalization Costs Related to Active Tuberculosis**

The average charge for hospitalization due to active tuberculosis was obtained
Table 8. Tuberculosis Prevention Program Costs*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total Cost (AxB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIXED COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administrator</td>
<td>0.10</td>
<td>$31,491</td>
<td>$3,149</td>
</tr>
<tr>
<td>LPN</td>
<td>0.50</td>
<td>21,040</td>
<td>10,520</td>
</tr>
<tr>
<td>Secretary</td>
<td>0.80</td>
<td>17,454</td>
<td>13,963</td>
</tr>
<tr>
<td>Physician</td>
<td>1.00</td>
<td>5,200</td>
<td>5,200</td>
</tr>
<tr>
<td>Facilities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>12 x 0.5</td>
<td>500</td>
<td>3,000</td>
</tr>
<tr>
<td>Utilities (electric)</td>
<td>12 x 0.5</td>
<td>265</td>
<td>1,590</td>
</tr>
<tr>
<td>Utilities (water/waste)</td>
<td>12 x 0.5</td>
<td>90</td>
<td>540</td>
</tr>
<tr>
<td>Phone</td>
<td>12 x 0.5</td>
<td>100</td>
<td>600</td>
</tr>
<tr>
<td>Mail</td>
<td>12 x 0.5</td>
<td>50</td>
<td>300</td>
</tr>
<tr>
<td>Security</td>
<td>12 x 0.5</td>
<td>40</td>
<td>240</td>
</tr>
<tr>
<td>Supplies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office Supplies</td>
<td>12 x 0.5</td>
<td>40</td>
<td>240</td>
</tr>
<tr>
<td>Compliance Incentives</td>
<td>1.00</td>
<td>175</td>
<td>175</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>$39,517</td>
</tr>
<tr>
<td><strong>VARIABLE COSTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculin skin test materials</td>
<td>0.35 x 250</td>
<td>$0.90</td>
<td>$79</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>250</td>
<td>15</td>
<td>3,750</td>
</tr>
<tr>
<td>Up to 2 months isoniazid</td>
<td>0.1614 x 250</td>
<td>2.34</td>
<td>94</td>
</tr>
<tr>
<td>3 to 4 months isoniazid</td>
<td>0.1165 x 250</td>
<td>4.68</td>
<td>136</td>
</tr>
<tr>
<td>5 to 6 months isoniazid</td>
<td>0.7219 x 250</td>
<td>7.02</td>
<td>1,267</td>
</tr>
<tr>
<td>Pyridoxine 50 mg (6 months)</td>
<td>0.02 x 250</td>
<td>2.70</td>
<td>14</td>
</tr>
<tr>
<td>Liver function test (6 months)</td>
<td>0.02 x 250</td>
<td>75</td>
<td>375</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>$5,715</td>
</tr>
<tr>
<td><strong>TOTAL ANNUAL TB PREVENTION PROGRAM COSTS</strong></td>
<td></td>
<td>$45,232</td>
<td></td>
</tr>
<tr>
<td><strong>Participants per year</strong></td>
<td>250</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL AVG. PREVENTIVE TREATMENT COST PER PATIENT</strong></td>
<td></td>
<td>$181</td>
<td></td>
</tr>
</tbody>
</table>

* Costs calculated in 1997 dollars.
** Costs related to tuberculin skin test interpretation and monthly follow up clinic visits for monitoring while on preventive therapy are assumed personnel duties related to the program and accounted for in personnel section.
through a survey of all charges associated with a primary diagnosis of active tuberculosis reported for 1996 to the State of Arizona, Department of Health, Hospital Discharge Database. The charges were based on the primary diagnosis of tuberculosis using the ICD-9-CM codes 010.1 to 016.9, 017.1 to 018.9.

Cost-data related to physician services per average inpatient admission for active tuberculosis were estimated using the 1997 Medicare Average Allowance Fee Schedule and CPT-4 code numbers related to hospital care. In this analysis, it was assumed that the typical active tuberculosis inpatient would incur one charge for CPT-4 code 99222 (initial hospital care) and a charge for CPT-4 code 99231 (subsequent hospital care) multiplied by the average patient length of stay, in days, minus one.

Seventy-two percent of the 144 tuberculosis related hospital admissions reported in 1996 were for the primary diagnosis of pulmonary tuberculosis. The remaining tuberculosis related hospital admissions, by primary diagnosis and their respective percentages, were as follows: tuberculosis of the meninges or central nervous system (9%), miliary tuberculosis (6.9%), tuberculosis of the bones and joints (6.3%), tuberculosis complex (2.7%), other respiratory tuberculosis (2.1%), and tuberculosis of the intestines, peritoneum and mesenteric glands (less than 1%).

The median hospital charge and average length of stay for a primary diagnosis of pulmonary tuberculosis in 1996 was $11,746 and 12.7, respectively. The median hospital charge and average length of stay for hospital admissions related to all primary diagnoses of tuberculosis was $14,086 and 14.3, respectively. In 1997 dollars, the median hospital
charge for a primary diagnosis of pulmonary tuberculosis was $12,156. For all primary
diagnoses of tuberculosis, the median hospital charge was $14,578.

The total hospital cost per patient was then calculated by multiplying the median
hospital charge per patient and the average physician charge for initial and subsequent
hospital care, by the percentage of patients who would be hospitalized for active
tuberculosis. In this analysis, a baseline value of 70%, was used. This percentage was
based on primary data from the Pima County Tuberculosis Control Program.

The total hospital cost (for all primary diagnoses of tuberculosis) per patient was
$10,618 (1997 dollars). The calculated value was comprised of the median hospital
charge per patient of $10,205 and the average physician charge for initial and subsequent
hospital care of $413 based on 70% of patients who would be hospitalized due to active
tuberculosis. The total hospital cost per patient with a primary diagnosis of pulmonary
tuberculosis was $8,922 (1997 dollars). The total hospital cost per patient and its related
cost components are presented in the upper portion of Table 9.

*Outpatient Program Treatment Costs Related to Active Tuberculosis*

The annual direct program costs and average cost per case for active tuberculosis
treatment on an outpatient basis were calculated through a survey of actual program
costs for the Pima County Tuberculosis Control Program for 1997.

The total annual direct outpatient tuberculosis treatment program costs were
estimate to be $191,078. A total of 35 patients were enrolled in the Pima County
Tuberculosis Control Program for 1997. The average cost per case for active tuberculosis
### Table 9. Active Tuberculosis Hospitalization and Outpatient Treatment Program Costs*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total (A x B)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HOSPITALIZATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median hospital charges based on ICD-9-CM codes for primary diagnosis of tuberculosis</td>
<td>.70</td>
<td>$14,578</td>
<td>$10,205</td>
</tr>
<tr>
<td>Physician charges based on CPT-4 codes for initial and subsequent hospital care</td>
<td>.70 x 1 (initial visit)</td>
<td>111</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>.70 x 13.3 days (subsequent visits)</td>
<td>36</td>
<td>335</td>
</tr>
<tr>
<td><strong>TOTAL Hospital Cost Per Patient</strong></td>
<td></td>
<td></td>
<td>$10,618</td>
</tr>
</tbody>
</table>

**OUTPATIENT PROGRAM**

**FIXED COSTS**

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total (A x B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrator</td>
<td>.20</td>
<td>$57,096</td>
<td>$11,419</td>
</tr>
<tr>
<td>Physician</td>
<td>.20</td>
<td>114,500</td>
<td>22,900</td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>.50</td>
<td>44,281</td>
<td>22,140</td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>.50</td>
<td>38,541</td>
<td>19,270</td>
</tr>
<tr>
<td>Public Health Nurse</td>
<td>.50</td>
<td>36,936</td>
<td>18,468</td>
</tr>
<tr>
<td>Licensed Practical Nurse</td>
<td>.05</td>
<td>26,389</td>
<td>1,319</td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>.10</td>
<td>20,302</td>
<td>2,030</td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>.10</td>
<td>20,302</td>
<td>2,030</td>
</tr>
<tr>
<td>Public Health Aide</td>
<td>.10</td>
<td>12,200</td>
<td>1,220</td>
</tr>
<tr>
<td>Secretary</td>
<td>.20</td>
<td>22,417</td>
<td>4,483</td>
</tr>
<tr>
<td>Data Entry</td>
<td>.20</td>
<td>22,417</td>
<td>4,483</td>
</tr>
<tr>
<td>Social Worker</td>
<td>.50</td>
<td>12,110</td>
<td>6,055</td>
</tr>
<tr>
<td>X-ray technician</td>
<td>.10</td>
<td>27,384</td>
<td>2,738</td>
</tr>
</tbody>
</table>

| Facilities/Supplies            |              |                 |               |
| Overhead                       |              | 22.3%           | 118,555       |

| Subtotal                      |              |                 | $144,993      |

*Note: The table provides a detailed breakdown of costs associated with hospitalization and outpatient treatment programs for active tuberculosis patients, including medians, quantities, costs per unit, and total costs. The data is used to illustrate the financial implications of managing such programs.*
Table 9 (cont.) Active Tuberculosis Hospitalization and Outpatient Treatment Program Costs

<table>
<thead>
<tr>
<th>VARIABLE COSTS**</th>
<th>3 x 35</th>
<th>$30</th>
<th>$3,150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>3 x 35</td>
<td>$30</td>
<td>$3,150</td>
</tr>
<tr>
<td>Sputum smear and culture</td>
<td>8 x 35</td>
<td>22</td>
<td>6,160</td>
</tr>
<tr>
<td>Antibiotic sensitivity</td>
<td>1 x 35</td>
<td>20</td>
<td>700</td>
</tr>
<tr>
<td>Liver function test</td>
<td>3 x 35</td>
<td>8</td>
<td>840</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 x 35</td>
<td>1.15</td>
<td>242</td>
</tr>
<tr>
<td>Rifampin</td>
<td>6 x 35</td>
<td>31.67</td>
<td>6,651</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2 x 35</td>
<td>142.84</td>
<td>9,999</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2 x 35</td>
<td>85.31</td>
<td>5,972</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>6 x 35</td>
<td>1.00</td>
<td>210</td>
</tr>
<tr>
<td>Side Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function test</td>
<td>3 x 2</td>
<td>8.00</td>
<td>48</td>
</tr>
<tr>
<td>Travel Costs</td>
<td>340 x 35</td>
<td>0.27</td>
<td>3,213</td>
</tr>
<tr>
<td>Compliance Incentives</td>
<td>35</td>
<td>254</td>
<td>8,900</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>$46,085</td>
</tr>
<tr>
<td><strong>TOTAL Annual Active Tuberculosis Outpatient Treatment Costs</strong></td>
<td></td>
<td></td>
<td>$191,078</td>
</tr>
<tr>
<td>Participants per year</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL Average Cost Per Case for Active Tuberculosis on Outpatient Basis</strong></td>
<td></td>
<td></td>
<td>$5,459</td>
</tr>
<tr>
<td><strong>TOTAL AVERAGE COST PER CASE FOR TREATMENT OF ACTIVE TUBERCULOSIS (Hospital + Outpatient Treatment)</strong></td>
<td></td>
<td></td>
<td>$16,077</td>
</tr>
</tbody>
</table>

* Costs calculated in 1997 dollars.
** Costs related to monthly follow up clinic visits or for directly observed therapy (DOT) are assumed to be part of program personnel duties and accounted for in personnel section.
treatment costs on an outpatient basis for 1997 was calculated at $5,459. The annual
direct outpatient active tuberculosis treatment program costs, average cost per case for
outpatient active tuberculosis treatment and their respective cost component calculations
are presented in Table 9.

Finally, the average cost per case for the treatment of active tuberculosis for all
primary diagnoses of tuberculosis, consisting of hospitalization and subsequent outpatient
therapy, was calculated at $16,077 in 1997 dollars. This figure was comprised of an
average per patient hospitalization charge of $10,618 and an average per patient
outpatient treatment cost of $5,459. The average cost per case for the treatment of active
tuberculosis for a primary diagnosis of pulmonary tuberculosis, consisting of
hospitalization and subsequent outpatient therapy, was calculated at $14,381 in 1997
dollars.

**Direct Cost Savings Related to the Tuberculosis Contagion**

Average direct cost savings were calculated for the prevention of future (second
generation) active tuberculosis cases that would occur from initial cases in the absence of
the tuberculosis prevention program alternative due to the contagious nature of
tuberculosis. Average direct cost savings related to the tuberculosis contagion were
calculated by multiplying the total cost per case related to the tuberculosis contagion by
the number of active cases averted by the tuberculosis prevention program.

The calculated average direct cost savings related to the tuberculosis contagion for
all primary diagnoses of tuberculosis were $49,938 (1997 dollars; discounted 3%
annually). This value was comprised of $16,646 (the average cost related to the contagious effects of one untreated case of active tuberculosis) times the 3.0 cases averted between the prevention program and no prevention program scenarios over a five year period. The cost savings and number of cases prevented were discounted at 3% annually based on time active case was prevented. Cost saving components related to tuberculosis contagion are presented in Table 10.

**Markov Process Models State Transition Probabilities**

Markov process model state transition probabilities for the program and no program scenarios were assigned using a combination of program experience and literature based data. Rates were converted to probabilities by use of the following formula:

\[ P(t) = 1 - e^{-rt} \]

where \( r \) = rate, and \( P \) = probability of an event occurring over a time interval of \( t \) time units (Beck and Pauker, 1983).

**Preventive Program Scenario State Transition Probabilities**

State transition probabilities for the preventive program scenario Markov process models were comprised of fixed and varying probabilities. State transition probabilities number 1 through 3 (Figure 5) were varying probabilities that represented specific time periods patients could stay in one of the three entry states; up to two, four or six months. Probability values for the three Preventive Treatment Entry level states are presented in Table 11 for the Preventive Program Scenario Model and in Tables 12 through 14 for the
Table 10. Tuberculosis Contagion Cost Savings Components*

<table>
<thead>
<tr>
<th>Resource</th>
<th>Quantity (A)</th>
<th>Cost / Unit (B)</th>
<th>Total Cost (A x B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test materials</td>
<td>10 patients</td>
<td>$0.90</td>
<td>9</td>
</tr>
<tr>
<td>Administration / interpretation of skin test</td>
<td>10 patients</td>
<td>0.5 hr x $10/hr</td>
<td>50</td>
</tr>
<tr>
<td>Chest x-ray and reading</td>
<td>10 patients</td>
<td>$35</td>
<td>350</td>
</tr>
<tr>
<td>Initial consultation</td>
<td>10 patients</td>
<td>0.5 hr x $10/hr</td>
<td>50</td>
</tr>
<tr>
<td>6 months isoniazid (INH)</td>
<td>5 patients</td>
<td>$1.17 x 6</td>
<td>35</td>
</tr>
<tr>
<td>Clinic visits for 6 months isoniazid therapy</td>
<td>30 visits</td>
<td>0.25 hr x $10/hr</td>
<td>75</td>
</tr>
<tr>
<td>Active case of tuberculosis (from Table 9)</td>
<td>1 case</td>
<td>avg. cost per case</td>
<td>16,077</td>
</tr>
</tbody>
</table>

** TOTAL Cost per Case Related to Tuberculosis Contagion ** = 16,646

\[ \text{x Number of active tuberculosis cases prevented} \]
\[ \text{(from Markov process model) *** = 3.0} \]

** TOTAL COST SAVINGS RELATED TO TUBERCULOSIS CONTAGION ** = 49,230

* Quantity column provides estimated number of contact investigations, patients requiring preventive treatment and number of active cases expected to develop per one case of untreated active tuberculosis (Moore et al., 1996; Murray et al., 1990).

** Costs in 1997 dollars.

*** Discounted 3% annually. Based on time tuberculosis case was prevented.
Table 11. Markov Process Model State Transition Probabilities - Tuberculosis Prevention Program Scenario

<table>
<thead>
<tr>
<th>Transition Number</th>
<th>From</th>
<th>To</th>
<th>Cycle or Tick</th>
<th>probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PT₁-₂</td>
<td>PPT₁-₂</td>
<td>Cycle 1</td>
<td>0.500</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 2</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PT₃-₄</td>
<td>PPT₃-₄</td>
<td>Cycle 1-2</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 3</td>
<td>0.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 4</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PT₅-₆</td>
<td>PPT₅-₆</td>
<td>Cycle 1-4</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 5</td>
<td>0.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 6</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PPT₁-₂</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000866</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000467</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000061</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>PPT₃-₄</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000727</td>
<td>4, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000392</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000051</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PPT₅-₆</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000217</td>
<td>4, 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000117</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000015</td>
<td></td>
</tr>
<tr>
<td>7-12</td>
<td>States₁-₆</td>
<td>Death</td>
<td>Cycle 1-60</td>
<td>0.000519</td>
<td>8</td>
</tr>
</tbody>
</table>

References: ¹model assumption; ²Brewer et al., 1996; ³Comstock and Edwards, 1975; ⁴Sterling et al., 1995; ⁵primary program data; ⁶Jordan et al., 1991; ⁷Salpeter et al., 1997; ⁸life tables.
Preventive Treatment $x$ to $x^*$ months

Active Tuberculosis

Death

$\text{Absorbing State}$

$1$ = model state numbers

$2$ = state transition numbers

$x$ to $x^*$ months = 1 to 2 months, 3 to 4 months, or 5 to 6 months.

Figure 6. Representative Model Structure for Preventive Treatment Specific Markov Process Models
Table 12. Markov Process Model State Transition Probabilities - Preventive Treatment Specific - 1 to 2 Months

<table>
<thead>
<tr>
<th>Transition Number</th>
<th>From</th>
<th>To</th>
<th>Cycle or Tick</th>
<th>probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PT₁₋₂</td>
<td>PPT₄₋₂</td>
<td>Cycle 1</td>
<td>0.500</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 2</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PPT₄₋₂</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000866</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000467</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000061</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>States₁₋₂</td>
<td>Death</td>
<td>Cycle 1-60</td>
<td>0.000519</td>
<td>8</td>
</tr>
</tbody>
</table>

References: ^1 model assumption; ^2 Brewer et al., 1996; ^3 Comstock and Edwards, 1975; ^4 Sterling et al., 1995; ^5 primary program data; ^6 life tables.

Table 13. Markov Process Model State Transition Probabilities - Preventive Treatment Specific - 3 to 4 Months

<table>
<thead>
<tr>
<th>Transition Number</th>
<th>From</th>
<th>To</th>
<th>Cycle or Tick</th>
<th>probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PT₃₋₄</td>
<td>PPT₃₋₄</td>
<td>Cycle 1-2</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 3</td>
<td>0.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 4</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PPT₃₋₄</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000727</td>
<td>2, 3, 4, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000392</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000051</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>States₁₋₂</td>
<td>Death</td>
<td>Cycle 1-60</td>
<td>0.000519</td>
<td>8</td>
</tr>
</tbody>
</table>

References: ^1 model assumption; ^2 Brewer et al., 1996; ^3 Comstock and Edwards, 1975; ^4 Sterling et al., 1995; ^5 primary program data; ^6 Jordan et al., 1991; ^8 life tables.
Table 14. Markov Process Model State Transition Probabilities - Preventive Treatment Specific - 5 to 6 Months

<table>
<thead>
<tr>
<th>Transition Number</th>
<th>From</th>
<th>To</th>
<th>Cycle or Tick</th>
<th>probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PT₅₋₆</td>
<td>PPT₅₋₆</td>
<td>Cycle 1-4</td>
<td>0.000</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 5</td>
<td>0.500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 6</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PPT₅₋₆</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000217</td>
<td>4, 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000117</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000015</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>States₁-₂</td>
<td>Death</td>
<td>Cycle 1-60</td>
<td>0.000519</td>
<td>8</td>
</tr>
</tbody>
</table>

References: ¹ model assumption; ⁴ Sterling et al., 1995; ⁷ Salpeter et al., 1997; ⁸ life tables.
Preventive Treatment Specific Models. All probabilities are reported as monthly or one cycle probabilities. Figures 5 and 6 were previously discussed and are replicated with their corresponding state transition probability table(s) to ease interpretation.

Model state transition probabilities numbers 4 through 6 are also varying transition probabilities which represent the probability of developing active tuberculosis after having completed one of the three preventive treatment states (classified by number of months of preventive treatment completed). Varying probabilities assigned to these model state transition probabilities represent the time dependent probability of developing active tuberculosis from a tuberculosis infected state without preventive therapy; after the effectiveness of preventive therapy is considered.

The probability of developing active tuberculosis is greater during the first two years (3.3% in year one; 1.7% in year two) after converting to a tuberculosis infection positive state (Sterling et al., 1995). After year two, the annual probability of developing active tuberculosis while in a tuberculosis infection positive state has been estimated at 0.072% (Brewer et al., 1996).

The probability value representing the development of active tuberculosis after becoming tuberculosis infected in the study population was a calculated value. The calculated probability value used in this analysis was based on the time dependent probabilities of developing active tuberculosis multiplied by (1) the estimated percentage of patients who were recent converters (tuberculosis infection positive for less than two years) and (2) the estimated percentage of patients who were tuberculosis infection
positive for greater than two years.

Data from the Santa Cruz County Tuberculosis Prevention Program estimates that 30% of patients fit the recent converter criteria. The annual probabilities of developing active tuberculosis from a tuberculosis infection positive state without preventive therapy in this population are: \( p = 0.0105 \) in year one, \( p = 0.0056 \) in year two, and \( p = 0.00073 \) yearly, after year two.

Transition state number 4 represents the case where two months or less of preventive isoniazid treatment has zero effectiveness against developing active tuberculosis. The calculated monthly probability for state transition number 4 in the Tuberculosis Prevention Model and for state transition number 2 in the Preventive Treatment Specific - 1 to 2 Months Model are presented in Tables 11 and 12, respectively.

Transition probability state numbers 5 and 6 represent the probabilities of developing active tuberculosis after the protective effect of preventive isoniazid treatment. The formula used to calculate the probabilities for these state transitions is:

\[
p_{TB_{INH}} = p_{TB_{no\,INH}} - (\text{baseline effectiveness} \times p_{TB_{no\,INH}})
\]

where,

\( p_{TB_{INH}} = \) probability of developing active tuberculosis given that the patient has taken preventive isoniazid therapy;

\[ p_{TB_{no\,INH}} = \] probability of developing active tuberculosis without preventive isoniazid therapy;
and baseline effectiveness = effectiveness of preventive isoniazid therapy in preventing active tuberculosis, based on number of months of isoniazid taken.

The effectiveness of a three month course of isoniazid has been estimated at 16%, with an effectiveness range of 12% to 21% (Sterling et al., 1995; Jordan et al., 1991). In this analysis, the effectiveness value of 16% was used in the calculation of the monthly probability value for state transition number 5 in the Tuberculosis Prevention Model (Table 11) and for transition state number 2 in the Preventive Treatment Specific - 3 to 4 Month Model (Table 13).

The effectiveness range for a six month course of isoniazid therapy has been estimated between 55% to 93% (IUAT, 1982; Kopanoff et al., 1978; Sterling et al., 1995; Jordan et al., 1991). A recent study used an effectiveness value of 85% for a full six month course of therapy (Salpeter et al., 1997). In this study, an effectiveness value of 75% was used in the calculation of the monthly probability value for state transition number 6 in the Tuberculosis Prevention Model (Table 11) and for transition state number 2 in the Preventive Treatment Specific - 5 to 6 Month Model (Table 14).

Transition probabilities number 7 through 12 are fixed transition probabilities which represent the average probability of dying from any cause during the modeling time period. This probability value was obtained from life tables and reflects the average probability of dying, from any cause, for the median age of the study population (25 years). These probability values are presented as probabilities number 7 through 12 in the Tuberculosis Prevention Model (Table 11) and as probabilities number 3 and 4 in each of
the respective Preventive Treatment Specific models (Tables 12 through 14).

**No Preventive Program Scenario State Transition Probabilities**

State transition probabilities for the no preventive program scenario Markov process model were a combination of fixed and varying probabilities. State transition probability number 1 represents the varying probability of developing active tuberculosis from the Tuberculosis Infection Positive state. This state transition probability value was estimated through program experience and literature based data.

The estimation of this state transition probability was previously discussed and is equivalent to the monthly probability value for state transition number 4 in the Tuberculosis Prevention Model (Table 11) and for state transition number 2 in the Preventive Treatment Specific - 1 to 2 Month Model (Table 12).

Model state transition probability number 2 represents the probability of Death from any cause and is the same probability as in the preventive program scenario Markov process model. Monthly state transition probability values and the state transition model for the no preventive program scenario are presented in Figure 7 and Table 15, respectively.

**Calculation of the Outcome of Interest**

The outcome of interest, cases of active tuberculosis averted, were estimated via the Markov process models. The Markov process models for the preventive program and no preventive program scenarios were analyzed via a computer software program which used Monte Carlo simulation to determine the prognoses of the hypothetical cohort of
Tuberculosis Infection Positive

Active Tuberculosis

Death

Absorbing State

Absorbing State

• = model transition numbers
1 = model state numbers
Table 15. Markov Process Model State Transition Probabilities - No Tuberculosis Prevention Program Scenario

<table>
<thead>
<tr>
<th>Transition Number</th>
<th>From</th>
<th>To</th>
<th>Cycle or Tick</th>
<th>probability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TIP</td>
<td>ATB</td>
<td>Cycle 1-12</td>
<td>0.000866</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 13-24</td>
<td>0.000467</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 25-60</td>
<td>0.000061</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TIP</td>
<td>Death</td>
<td>Cycle 1-60</td>
<td>0.000519</td>
<td>8</td>
</tr>
</tbody>
</table>

References: ^Brewer et al., 1996; ^Comstock and Edwards, 1975; ^Sterling et al., 1995; ^primary program data; ^life tables.
patients. A separate evaluation was simulated for the respective program scenario models over two time periods (five years and 15 years).

**Prevention Program Scenario Model Outcome**

Evaluation of the preventive program scenario Markov process models was accomplished by entering 10,000 patients in each of the three Preventive Treatment Specific models. The three Preventive Treatment Specific models were evaluated until all patients entered one of two absorbing states, Active Tuberculosis or Death, or the clock period reached 60 cycles (five years). The evaluation process was repeated for the 180 cycle (or 15 year) analysis. It was assumed that transitions from model state to model state occurred at the end of each one month clock period.

The number of entries per patient into the Active Tuberculosis model state from each of the three Preventive Treatment Specific Markov process models, were obtained from the computer simulation output data. The number of patient entries into the Active Tuberculosis model state were then multiplied by a respective proportion which represented actual preventive program compliance data. The calculations for the five year post preventive therapy initiation analysis are as follows:

Preventive Treatment 1-2 months = 0.014 entries/patient \times 0.161 = 0.00225;

Preventive Treatment 3-4 months = 0.009 entries/patient \times 0.116 = 0.00104;

Preventive Treatment 5-6 months = 0.002 entries/patient \times 0.723 = 0.00145;

Multiplying each of the entries/patient value by the compliance proportion provided the proportion of active tuberculosis cases that would occur despite each of the
Preventive Treatment states. Summing the proportion of cases for each Preventive Treatment state reveals that an estimated 0.00474 or (0.474 per 100) active tuberculosis cases would occur over a five year time period despite the tuberculosis prevention program option. Translated to our study population of 250 patients; an estimated 1.2 cases of active tuberculosis would occur in five years despite the tuberculosis prevention option.

**No Preventive Program Scenario Model Outcome**

Evaluation of the no preventive program scenario Markov process model was accomplished by entering 10,000 patients in the Tuberculosis Infection Positive entry state. The no preventive program scenario Markov process model was evaluated until all patients entered one of two absorbing states, Active Tuberculosis or Death or the clock period reached 60 cycles (five years). The evaluation process was repeated for the 180 cycle (or 15 year) analysis. It was assumed that transitions from state to state occurred at the end of each clock period.

The computer simulation output data provided the estimated number of entries per patient into the Active Tuberculosis model state. The Markov process output data revealed that an estimated 0.017 or (1.7 per 100) active tuberculosis cases would occur over a five year time period in the absence of the tuberculosis prevention program. Translated to our study population of 250 patients; an estimated 4.25 cases of active tuberculosis would occur in five years without the tuberculosis prevention program.
Cases Averted Between Prevention and No Prevention Program Scenarios

The difference between the number of patients entering the Active Tuberculosis state in the prevention program and no prevention program scenarios estimates the outcome of interest, the number of cases of active tuberculosis averted or prevented. The estimated number of cases of active tuberculosis averted five years after the initiation of preventive therapy intervention was 3.1 cases. This number was then used as our denominator value, or effectiveness measure, in the calculation of the cost-effectiveness ratios for this study.

Cost-Effectiveness Ratio Calculations

Average and incremental cost-effectiveness ratios (cost per case of active tuberculosis averted) were calculated for the prevention program scenario. The average cost-effectiveness ratio, evaluated against the baseline or reference option, is the net cost of a prevention strategy divided by the number of health outcomes averted (Haddix and Shaffer, 1996). Incremental cost-effectiveness ratios are used to examine the efficiency of one intervention relative to another. The incremental cost-effectiveness ratio is generally reported as the additional cost per additional health outcome prevented.

Petitti (1994) and Destsky and Naglie (1990), indicate that the average cost-effectiveness ratio and the incremental cost-effectiveness ratio are identical only in the highly unusual situation where the alternative treatment has a zero cost and no effectiveness. Because the no prevention program scenario has no cost and is not an effective method to prevent active tuberculosis, the average and incremental cost-
effectiveness ratios are identical in this analysis.

The average and incremental cost-effectiveness ratio for the five year and 15 year post preventive therapy initiation analyses was calculated by use of the following formula:

\[
\frac{\text{Net Direct Care Costs}}{\text{Net Health Effects}} = \frac{\text{Cost}}{\text{Case Averted}} = \frac{C_{\text{tpp}} + C_{\text{tb(p)}} - C_{\text{tb(np)}} - C_{\text{tb}}}{E_{\text{no program}} - E_{\text{program}}}
\]

where:

- \( C_{\text{tpp}} \) = cost of tuberculosis prevention program;
- \( C_{\text{tb(p)}} \) = cost of treating active tuberculosis that occurs despite program;
- \( C_{\text{tb(np)}} \) = cost of treating active tuberculosis that occurs without the program;
- \( C_{\text{tb}} \) = costs related to prevention and treatment of future tuberculosis related cases that would be due to the contagious nature of tuberculosis (i.e., contact tracing and identification, preventive therapy of contacts, and treatment of future active tuberculosis cases) and that would occur without program;
- \( E_{\text{no program}} \) = number of active tuberculosis cases that occur without program, and
- \( E_{\text{program}} \) = number of active tuberculosis cases that occur despite the program.

Average and incremental cost effectiveness ratios were calculated for five and 15 years post preventive therapy initiation time periods. In the cost-effectiveness ratio calculation, costs related to the treatment of active tuberculosis that would occur without the program were for all primary diagnoses of active tuberculosis. The cost-effectiveness ratios were calculated separately with the inclusion or exclusion of the tuberculosis contagion costs. Costs and outcomes used in the respective cost-effectiveness ratio calculations were discounted at 3 % annually prior to calculating the cost-effectiveness
ratios. All costs are reported in 1997 dollars. Appendix A presents the results of a representative cost-effectiveness ratio calculation. The results presented in Appendix A are for the (5 year post preventive therapy initiation, contagion costs excluded, costs and outcomes discounted at 3 %) scenario.

Table 16 presents a summary of the average and incremental cost-effectiveness ratio calculations for the tuberculosis prevention program scenario for the five year post preventive therapy initiation time period and the respective tuberculosis contagion scenarios.

The calculated average and incremental cost-effectiveness ratio for the tuberculosis prevention program scenario five years after the initiation of preventive therapy and without the inclusion of tuberculosis contagion costs was -$1,023 per case averted. This indicates that the tuberculosis prevention program is cost-effective in averting active tuberculosis cases compared to the no tuberculosis prevention program scenario five years after patients are enrolled in the program. If further indicates that having the tuberculosis prevention program potentially saves Santa Cruz County (taxpayers) $1,023 for each case of active tuberculosis that is prevented five years after patients enter the program, even without the inclusion of tuberculosis contagion costs.

When the costs related to the contagious nature of tuberculosis were included, the calculated average and incremental cost-effectiveness ratio for the prevention program scenario five years after the initiation of preventive therapy was -$17,692 per case of active tuberculosis averted. This indicates that when the costs related to spread of
### Table 16. Average and Incremental Cost Effectiveness Ratios for Tuberculosis Prevention Program Scenario - 5 Years Post Preventive Therapy Initiation

<table>
<thead>
<tr>
<th></th>
<th>Average and Incremental Cost Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Cost (Savings)</td>
</tr>
<tr>
<td>No Prevention Program</td>
<td>$0</td>
</tr>
<tr>
<td>Prevention Program - Contagion Costs Excluded (^{c})</td>
<td>$(3,068)</td>
</tr>
<tr>
<td>Prevention Program - Contagion Costs Included (^{c})</td>
<td>$(53,075)</td>
</tr>
</tbody>
</table>

\(^{a}\) Discounted at 3% annually.

\(^{b}\) Compared with no prevention program.

\(^{c}\) Contagion costs are costs related to contact tracing and follow-up as well as prevention of future (second generation) active tuberculosis cases that would occur from initial cases in the absence of the tuberculosis prevention program due to the contagious nature of tuberculosis.
tuberculosis are considered, the tuberculosis prevention program becomes considerably
more cost-effective. Given that three cases of active tuberculosis would be prevented over
the five year post preventive therapy period, a potential cost savings of $53,075 could be
realized by the prevention program option.

The calculated average and incremental cost-effectiveness ratio for the tuberculosis
prevention program scenario 15 years after the initiation of preventive therapy without the
inclusion of tuberculosis contagion costs was -$4,971 per case averted. This indicates
that as time increases, the cost-effectiveness of the tuberculosis prevention program
relative to a no prevention program alternative also increases. Having the tuberculosis
prevention program potentially saves Santa Cruz County (taxpayers) $4,971 for each case
of active tuberculosis that is prevented 15 years after patients enter the program.

When consideration of costs related to the contagious nature of tuberculosis were
included in the 15 year post preventive therapy initiation analysis, the calculated average
and incremental cost-effectiveness ratio for the prevention program scenario was
-$21,825 per case averted. This indicates that when the costs related to spread of
tuberculosis are included, having the tuberculosis prevention program potentially saves
Santa Cruz County $21,825 for each case of active tuberculosis averted 15 years after
patients entered the program. Table 17 presents a summary of the average and incremental
cost-effectiveness ratio calculations for the tuberculosis prevention program for the 15
years post preventive therapy initiation time period and the respective tuberculosis
contagion scenarios.
Table 17. Average and Incremental Cost Effectiveness Ratios for Tuberculosis Prevention Program Scenario - 15 Years Post Preventive Therapy Initiation

<table>
<thead>
<tr>
<th>Prevention Program</th>
<th>Total Cost (Savings)</th>
<th>Cases of Disease</th>
<th>Net Cost (Savings) (^{a,b})</th>
<th>Total Cases Averted (^{a,b})</th>
<th>Average and Incremental Cost (Savings) Per Case Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prevention Program</td>
<td>$0</td>
<td>5.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention Program - TB Contagion Costs Excluded(^{c})</td>
<td>$ (19,884)</td>
<td>1.4</td>
<td>$ (19,884)</td>
<td>4.0</td>
<td>$ (4,971)</td>
</tr>
<tr>
<td>Prevention Program - TB Contagion Costs Included(^{c})</td>
<td>$(87,300)</td>
<td>1.5</td>
<td>$(87,300)</td>
<td>4.0</td>
<td>$(21,825)</td>
</tr>
</tbody>
</table>

\(^{a}\)Discounted at 3% annually.
\(^{b}\)Compared with no prevention program.
\(^{c}\)Contagion costs are costs related to contact tracing and follow-up as well as prevention of future (second generation) active tuberculosis cases that would occur from initial cases in the absence of the tuberculosis prevention program due to the contagious nature of tuberculosis.
Sensitivity Analyses

Sensitivity analyses were conducted for selected parameters used to model the cost-effectiveness of the prevention program scenario. This section presents the results of the sensitivity analyses conducted in this research.

A one-way sensitivity analysis was performed on the program cost-effectiveness results for the cost parameter related to the percentage of patients requiring hospitalization for a typical or average case of active tuberculosis. The percentage of patients hospitalized is important because hospitalization costs comprise the majority of costs related to the treatment of active tuberculosis. The percentage of patients hospitalized cost parameter was varied from a low to high range of 50 % to 90 %, from the 70 % baseline percentage.

The results of the one-way sensitivity analysis are presented in Table 18. When the percentage of patients hospitalized are varied from the 50 % to 90 %, the incremental cost per case averted becomes sensitive to the 50 % hospitalization rate. At the 50 % hospitalization rate, the cost savings related to the tuberculosis prevention program alternative seen in the base-case scenario becomes a cost of $2,015.

This indicates that if only 50 % of patients are hospitalized for tuberculosis and the costs related to the tuberculosis contagion are not included, it would cost the prevention program $2,015 to prevent one case of active tuberculosis during the five year time period after the initiation of therapy. While it may make the cost per case prevented in this analysis less cost-effective, a 50 % hospitalization rate would in itself indicate a cost savings since the treatment of tuberculosis on an outpatient basis is much less expensive
Table 18. One-Way Sensitivity Analysis Results: Average and Incremental Cost Effectiveness Ratios for Tuberculosis Prevention Program Scenario - Percentage of Patients Hospitalized for Active Tuberculosis*

<table>
<thead>
<tr>
<th>Year Post Preventive Therapy</th>
<th>Sensitivity Analysis: Incremental Cost Effectiveness ratios**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevention Program Scenario 50% Hospitalization Rate 70% Hospitalization Rate 90% Hospitalization Rate</td>
</tr>
<tr>
<td></td>
<td>50% Hospitalization Rate</td>
</tr>
<tr>
<td></td>
<td>$2,015</td>
</tr>
<tr>
<td></td>
<td>$(14,655)</td>
</tr>
<tr>
<td></td>
<td><strong>TB</strong>* contagion costs excluded</td>
</tr>
<tr>
<td>5 Year Post Preventive Therapy</td>
<td><strong>TB</strong>* contagion costs excluded</td>
</tr>
<tr>
<td></td>
<td>$(1,900)</td>
</tr>
<tr>
<td>15 Year Post Preventive therapy</td>
<td><strong>TB</strong>* contagion costs excluded</td>
</tr>
<tr>
<td></td>
<td>$(18,754)</td>
</tr>
</tbody>
</table>

* Percentage of patients hospitalized for active tuberculosis represents the percentage of patients who would be hospitalized for a typical diagnosis of active tuberculosis.
** Cost-effectiveness ratios reported in 1997 dollars; discounted at 3 percent annually.
*** TB = tuberculosis
than in an inpatient setting.

Additionally, paying $2,015 to prevent one case of active tuberculosis is still cost-effective if one considers the tuberculosis contagion consequences of not having the prevention program. If contagion costs are included with the 50% hospitalization scenario; the cost savings (and cost-effectiveness), of the prevention program relative to the no prevention program alternatives, are never in question (a cost savings of $14,655 per case prevented).

The results of this sensitivity analysis further indicate that as the percentage of patients hospitalized increases, the prevention program scenario becomes substantially more cost effective. For example, if 90% of patients were hospitalized for active tuberculosis in this study, the cost savings related to the prevention program option would be approximately four times greater per case prevented than that seen in the 70% hospitalized baseline analysis over the five year period with contagion costs excluded.

The second sensitivity analysis was a, one-way sensitivity analysis which was used to predict the effect of increased or decreased compliance with isoniazid preventive therapy on the cost-effectiveness of the prevention program scenario. The range chosen for the analysis was 60% to 85%, around the baseline compliance percentage of 72%.

The upper range used in this sensitivity analysis corresponds to the Healthy People 2000, National Health Promotion and Disease Prevention objective number 20.18 (US Department of Health and Human Services, 1990). Objective number 20.18 is to increase to at least 85% the proportion of people found to have tuberculosis infection who
completed courses of preventive therapy.

The results of the sensitivity analysis related to compliance with preventive therapy are presented in Table 19. When the preventive therapy compliance rate is varied from the 60% to 85%, the incremental cost per case averted becomes sensitive to 60% compliance rate. At the 60% compliance rate, the cost savings seen in the base-case scenario becomes a cost of $877.

This indicates that if only 60% of patients complete the six months of prescribed therapy and the costs related to the tuberculosis contagion are not included; it would cost the program $877 to avert one case of active tuberculosis five years after the initiation of therapy. The cost savings realized in the 72% compliance rate baseline analysis would be lost.

If contagion costs are included with the 60% compliance rate scenario; the cost savings (and cost-effectiveness), of the prevention program relative to the no prevention program alternative, are never in question (a cost savings of $15,813).

The results of this sensitivity analysis also indicate an added cost savings per case prevented if the prevention program were to meet its 85% compliance with preventive therapy goal. For example, if 85% of patients were to complete the six-month prescribed course of therapy, the cost savings would be almost 2.5 times greater per case prevented over the five-year post preventive therapy initiation period.

The third one-way sensitivity analysis varied the discount rate used in discounting costs and outcomes calculated in this study. In this one-way sensitivity analysis two
Table 19. One-Way Sensitivity Analysis Results: Average and Incremental Cost Effectiveness Ratios for Tuberculosis Prevention Program Scenario - Percentage of Compliance With Preventive Therapy*

<table>
<thead>
<tr>
<th>Scenario</th>
<th>60% Compliance Rate</th>
<th>72% Compliance Rate</th>
<th>85% Compliance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Year Post Preventive Therapy</td>
<td>TB contagion costs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>excluded</td>
<td>$ 877</td>
<td>$ (1,023)</td>
<td>$ (2,577)</td>
</tr>
<tr>
<td>included</td>
<td>$(15,813)</td>
<td>$(17,692)</td>
<td>$(19,880)</td>
</tr>
<tr>
<td>15 Year Post Preventive therapy</td>
<td>TB contagion cost</td>
<td></td>
<td></td>
</tr>
<tr>
<td>excluded</td>
<td>$(3,429)</td>
<td>$(4,971)</td>
<td>$(6,304)</td>
</tr>
</tbody>
</table>

* Compliance is based on a 6 month prescribed course of preventive isoniazid therapy.
scenarios were analyzed: (1) the discount rate for both costs and outcomes were varied to 5% and (2) a discount rate of 5% was used for costs and a discount rate of 3% was used for outcomes.

The results of the sensitivity analysis related to varying the discount rate used in discounting costs and outcomes calculated in this study are presented in Table 20. When the discount rate for both costs and outcomes are varied from 3% to 5%, the incremental cost-effectiveness ratio results are not sensitive. The cost per case prevented remains a cost saving, however, the magnitude of the cost savings per case is decreased ( - $1023 versus - $847 ). Similarly, when the discount rate for costs are varied to 5% and 3% for outcomes, the incremental cost-effectiveness results are not sensitive. The cost-per-case prevented remains a cost saving.

Summary

The results of the analyses presented in this chapter illustrate that the tuberculosis prevention program in this study is considerably more cost-effective in averting active tuberculosis cases than not having a program. In all baseline cases, the cost per case averted by the prevention program scenarios yielded potential cost savings. When the costs related to the tuberculosis contagion were included, the cost effectiveness of the prevention program yielded additional potential cost savings.

The prevention program’s cost-effectiveness results become sensitive as the percentage of patients hospitalized for active tuberculosis decreases from 70 % to 50 % or as the percentage of compliance with prescribed preventive therapy decreases from 72%
Table 20. One-Way Sensitivity Analysis Results: Average and Incremental Cost Effectiveness Ratios for Tuberculosis Prevention Program Scenario - Discount Rates Varied

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Sensitivity Analysis: Incremental Cost Effectiveness ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discount Rates Costs: 3% Outcomes: 3%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>5 Year Post Preventive Therapy</td>
<td></td>
</tr>
<tr>
<td>TB contagion costs excluded</td>
<td>$ (1,023)</td>
</tr>
<tr>
<td>TB contagion costs included</td>
<td>$ (17,692)</td>
</tr>
<tr>
<td>15 Year Post Preventive therapy</td>
<td></td>
</tr>
<tr>
<td>TB contagion cost excluded</td>
<td>$ (4,971)</td>
</tr>
<tr>
<td>TB contagion cost included</td>
<td>$ (21,825)</td>
</tr>
</tbody>
</table>
to 60%. The prevention program’s cost effectiveness results are only sensitive for the “five year post preventive therapy initiation period and exclusion of contagion costs” scenario. When the costs related to the tuberculosis contagion are considered for all scenarios, the cost-effectiveness results are not sensitive; there will always be a cost savings.
CHAPTER 5

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

This research used Markov process modeling and cost data to model the prevention effectiveness of a tuberculosis prevention program along the U.S. / Mexico border compared to a no prevention program scenario. Average and incremental cost-effectiveness ratios were calculated for the prevention program scenario at five years and 15 years post preventive therapy initiation time periods. Sensitivity analyses were performed to determine whether the analysis results were sensitive to components used in the estimation process. This chapter presents a discussion of the results determined in this analysis, conclusions drawn from the results, and recommendations based on the results of this research.

Discussion

Cost Determination

All the cost data used in this prevention effectiveness study were primary data from actual program experience from two county tuberculosis control programs in southern Arizona and from hospital discharge data reported to the State of Arizona, Department of Health. This was important since the use of primary data in this analysis provided a true reflection of the actual costs involved in providing tuberculosis prevention services and in treating active tuberculosis in an outpatient and hospital setting in this area.

The calculated average cost per preventive treatment case managed was $181 (1997 dollars). The calculated average cost per active tuberculosis case treated on an
outpatient basis was $5,459. The costs calculated for this study were greater than those from a recent study which used calculated costs of $105 for preventive cases and $3,113 (1996 dollars) for active tuberculosis cases treated on an outpatient basis (Salpeter et al., 1997). The discrepancy between the studies results may be the inclusion of all program costs, such as facilities, overhead and administration, in this study. Inclusion of all program costs may have provided a better representation of true costs.

The average cost per case for the treatment of active tuberculosis for a primary diagnosis of tuberculosis consisting of hospitalization and subsequent outpatient therapy was calculated at $16,077. The average direct costs related to the prevention of future (second generation) tuberculosis cases that would occur in the absence of the tuberculosis prevention due to the contagious nature of tuberculosis were calculated at $49,938 over the five year post preventive therapy initiation time period. The calculated active tuberculosis treatment costs determined in this study are presented to reiterate the financial burden that tuberculosis still is, and to illustrate the potential impact that the tuberculosis prevention program can have related to costs.

State Transition Probabilities

Markov model state transition probabilities were assigned using program experience and literature based data. A combination of fixed and varying state transition probabilities were used in the Markov process models to estimate the outcome of interest used in the determination of cost-effectiveness.

One probability determination of note was the determination of the varying
The probabilities related to developing active tuberculosis from a tuberculosis infected state. Studies related to these probabilities in a predominately Hispanic population, or in populations located near the U.S./Mexico border do not exist in the literature. Existing data related to the activation of tuberculosis from a tuberculosis infected state are from clinical trials conducted between 1950 and 1970 in populations of black and white individuals (Comstock et al., 1975).

These varying probability values used in this study were, out of necessity, calculated through a combination of available literature and prevention program data. The calculated probability values used in this analysis were based on the sum of the annual time dependent probabilities of developing active tuberculosis multiplied by (1) the estimated percentage of program patients who were recent converters (tuberculosis infection positive for less than two years) and (2) by the estimated percentage of program patients who were tuberculosis infection positive for greater than two years.

The calculated value of these probabilities and the estimation of subsequent analyses related to these probability values are limited to the accuracy of the assumptions of equivalence between the population groups (Hispanic population versus literature value of other populations) and of the estimated percentage of recent converters in the study population.

**Outcome Data and Cost-Effectiveness Determination**

The outcome of interest, cases of active tuberculosis averted, was determined through the development and estimation of Markov process models. The Markov process
models for the preventive program and no preventive program scenarios were estimated via a computer software program which utilized Monte Carlo simulation. The respective program scenario models were modeled over two time periods (5 and 15 years).

The estimated number of cases of active tuberculosis averted five years after the initiation of preventive therapy intervention was three cases. For the 15 year post preventive therapy initiation time period, the estimated number of cases of active tuberculosis cases averted by having the tuberculosis prevention program was 3.9 cases.

At first glance, three cases averted in five years and 3.9 cases averted in 15 years do not appear significant given the resources expended ($45,232) by the tuberculosis prevention program for 250 patients. However, when one considers the cost of treating one case of active tuberculosis ($16,077) and the potential costs related to the subsequent second generation of cases due to the contagious nature of tuberculosis ($49,938 if the initial three cases were not averted); the significant impact of having the prevention program becomes apparent. Quantification of this significant impact was accomplished though the determination of the cost-effectiveness of the tuberculosis prevention program scenario.

Average and incremental cost-effectiveness ratios (cost per case of active tuberculosis averted) were calculated for the prevention program scenario for five and 15 year post preventive therapy initiation time periods. The cost-effectiveness ratios were calculated separately with the inclusion or exclusion of the tuberculosis contagion costs.

The results of the cost-effectiveness ratio calculations established that the
prevention of active tuberculosis cases with the tuberculosis prevention program is considerably more cost effective than not having a tuberculosis prevention program. Every baseline incremental cost-effectiveness ratio, across the five and 15 year analysis periods and with the inclusion and exclusion of contagion costs, determined in this prevention effectiveness study demonstrated cost savings.

Additionally, the cost savings were substantial. The cost savings ranged from a low of $1,023 per case prevented in the five year-contagion costs excluded analysis, to a high of $21,825 per case prevented in the 15 year-contagion cost included analysis. The results indicate that instead of incurring costs to avert active tuberculosis cases, having the tuberculosis prevention program actually saves Santa Cruz County (taxpayers) money.

The results of this analysis were somewhat surprising given the results of previous analyses. Fitzgerald and Gafni (1990) found that it cost a low of $9,182 (in 20 year old low risk patients with positive skin tests) to a high of $28,260 (in 50 year old low risk patients) per case of tuberculosis prevented. Snider Jr. et al. (1986) reported a cost per case prevented of $7,112 for a 24 week preventive treatment regimen; also in a low risk patient population.

In their analysis, Fitzgerald and Gafni (1990) indicate that “the cost of preventing cases in other high risk groups would be even more cost-effective and highlights the importance of pursuing active contact tracing of all index cases of tuberculosis with a view to completion of adequate chemoprophylaxis”. Brown et al. (1995) advocated that (from a public health perspective) cost-benefit analyses of the use of preventive tuberculosis
therapy in high-risk populations could strengthen the argument for prevention strategies for tuberculosis, particularly when compared with the high costs of inpatient treatment.

This results of this study may be used to strengthen the argument as to the worth of a tuberculosis prevention program in a high risk, predominately Hispanic, U.S. / Mexico border population. The cost-effectiveness and cost savings related to the tuberculosis prevention program found in this study may most likely be attributed to higher risk of developing tuberculosis in our study population. The estimated 30 % of recent tuberculin converters in our study population indicates that the threat of tuberculosis in our study population is a real one. It also indicates that the risk of developing tuberculosis is this geographical area may be greater than in the general U.S. population.

**Sensitivity Analyses**

Sensitivity analyses were conducted for selected parameters used to model the cost-effectiveness of the prevention program scenario in this study. This section presents a discussion related to the results of the sensitivity analyses conducted in this research.

A one-way sensitivity analysis was performed on the cost-effectiveness results between program scenarios for the cost parameter related to the percentage of patients requiring hospitalization for a typical case of active tuberculosis. The percentage of patients hospitalized is important because hospitalization costs comprise the majority of costs related to the treatment of active tuberculosis. The percentage of patients hospitalized cost parameter was varied from a low to high range of 50 % to 90 %, with 70 % serving as baseline.
The results of the one-way sensitivity analysis indicated that as the percentage of patients hospitalized is decreased to 50%, the incremental cost per case averted results become sensitive. At the 50% hospitalization rate, the cost savings related to the tuberculosis prevention program alternative seen in the base-case scenario become a cost. The cost savings seen at baseline (70% hospitalization rate) are no longer realized.

However, cost savings may still be realized if the percentage of patients requiring hospitalization for active tuberculosis decreases. A decrease in the number of patients hospitalized will mean a corresponding increase in the number of patients treated on an outpatient basis. Treatment on an outpatient basis is a much less expensive option. Additionally, the prevention program remains a cost-effective alternative when the tuberculosis contagion consequences of not having the prevention program are considered.

The second one-way sensitivity analysis was used to predict the effect of increased or decreased compliance with isoniazid preventive therapy on the cost-effectiveness between the prevention and no prevention program scenarios. The results of this sensitivity analysis should provide valuable information to the potential audience of this study; policy and program decision makers associated with tuberculosis treatment programs.

This sensitivity analysis was useful in predicting the benefits to be gained by the prevention program’s effort in improving the rate of completion with preventive therapy. Likewise, the sensitivity analysis may illustrate what benefits may be lost if preventive
therapy compliance rates decrease due to lack of adequate funding or complacency.

The range chosen for this sensitivity analysis was 60 % to 85 %, with 72 % serving as the baseline compliance rate from our study population. If only 60 % of patients complete the six months of prescribed therapy and the costs related to the tuberculosis contagion are not included; it would cost the program $ 877 to avert one case of active tuberculosis five years after the initiation of therapy. The cost savings of $1,023 per case averted realized in the 72 % compliance rate (current program) analysis would be lost. However, the prevention program alternative is still cost-effective when the tuberculosis contagion consequences of not having the prevention program are considered.

The upper range used in this sensitivity analysis corresponds to the Healthy People 2000 prevention objective (# 20.18): “to increase to at least 85 percent the proportion of people found to have tuberculosis infection who completed courses of preventive therapy” (US Department of Health and Human Services, 1990).

The results of this sensitivity analysis indicate an added cost savings per case prevented if the prevention program were to meet their 85 % compliance with preventive therapy goal. For example, if 85 % of patients were to complete the six month prescribed course of therapy, the cost savings would be almost 2.5 times greater per case prevented over the five year post preventive therapy initiation period. In 1997 dollars, this would represent a cost savings of $ 5,179 for the 0.34 additional cases that would be averted (over five years post preventive therapy initiation and contagion costs excluded) by increasing patient compliance from 72 % to 85 %.
Distributional effects

Given limited resources and, undoubtedly, the large number of county funded services competing for these resources, the distributional aspects related to the findings of this prevention effectiveness study will now be addressed.

In this study, the costs and benefits of the tuberculosis prevention program were considered relative to the do nothing option (no program). Having a prevention program costs money. Not having a program, theoretically, costs nothing. In providing funding for the tuberculosis prevention program, we are allocating resources that could be used elsewhere. Additionally, in providing tuberculosis preventive treatment services (free of charge), we are focusing resources towards a small, high risk segment of the population. This may raise the question of equity in the distribution of public resources.

Given the results of this study, the benefits realized by having the tuberculosis prevention program may silence this question of equity. First, the results of this study have shown that the potential return on the investment by having the tuberculosis prevention program are substantial. The results of this study established that the prevention of active tuberculosis cases with the tuberculosis prevention program is considerably more cost effective (and cost saving) than not having a tuberculosis prevention program.

Second, and most importantly, is the role that the tuberculosis prevention program plays relative to the spread of tuberculosis. Given that one undiagnosed and untreated smear positive tuberculosis case can infect 10 to 14 persons a year and cause the development of an additional case of active tuberculosis; the case for having the
tuberculosis prevention is obvious. The public health benefits that result from infection control programs such as the tuberculosis prevention program are important. One only needs to look to developing countries where infection control programs are non-existent or poorly funded to realize the ramifications of not having these type of public health programs.

Limitations

One limitation of this study was that only a brief period or “snapshot” in time was represented in this analysis. The experience of one program (in which average costs, number of patients enrolled in program and preventive treatment compliance rates for a one year time period) were used in the development of the model for this analysis. If average costs or compliance rates were spuriously high or low for the given year data was obtained, the resulting cost-effectiveness ratio modeled in this analysis may have been overstated or understated.

This research was also limited by the lack of empirical data related to the study population. Specifically, the tuberculosis activation rate from a tuberculosis infected state in a Hispanic population were unknown. These data were essential in determining probability values used in modeling the outcomes of interest. Additional studies in this population are needed to provide accurate data.

A limitation of this study may be the alternatives chosen for this analysis; the program versus no program alternative. Some may argue, that, given the infectious nature of tuberculosis, the no program alternative would never be an option. However, the
argument has been made that the most cost-effective tuberculosis prevention strategy would be to abandon preventive therapy programs (especially in developing countries) and concentrate on case finding, contact tracing and follow up of active tuberculosis cases (Murray et al., 1990).

The results of this study established that the prevention of active tuberculosis cases with the tuberculosis prevention program is considerably more cost effective (and cost saving) than not having a tuberculosis prevention program. Thus, the comparison of the the program versus no program alternative in this study appear to be justified.

Finally, the external validity and findings of this study apply only to the characteristics of the study population, characteristics of the tuberculosis control programs and characteristics of the hospitalization data for the state of Arizona analyzed in this research. The parameters used and results obtained in this research are specific to this population and area. However, the methods used in the determination of cost-effectiveness for the study alternatives may be generalized to other tuberculosis prevention programs.

Conclusions

The overall purpose of this research was to use a prevention effectiveness analysis framework to estimate the cost-effectiveness of a county administered tuberculosis prevention program along the U.S. / Mexico border. Specifically, the tuberculosis prevention program under study used prophylactic isoniazid therapy in patients who have tested positive for tuberculosis infection. This analysis determined the cost-effectiveness of
the current program versus no program from the perspective of the county government.
The cost effectiveness of the program scenario was examined for two time periods; five
years and 15 years post preventive therapy initiation.

Costs were calculated using actual data from tuberculosis prevention and active
tuberculosis treatment programs as well as hospital discharge data related to hospital
admissions for active tuberculosis. The outcome of interest, cases of active tuberculosis
averted, was calculated through a Monte Carlo simulated Markov process model.
Average and incremental cost-effectiveness ratios were then calculated for the
tuberculosis prevention program scenario. The cost-effectiveness ratios were calculated
separately with the inclusion or exclusion of the tuberculosis contagion costs.

The results of the cost-effectiveness ratio calculations established that the
prevention of active tuberculosis cases with the tuberculosis prevention program is
considerably more cost effective than not having a tuberculosis prevention program. Every
baseline incremental cost-effectiveness ratio, across the five and 15 year analysis periods
and with the inclusion and exclusion of contagion costs, determined in this prevention
effectiveness study demonstrated cost savings. Additionally, the cost savings were
substantial. The results indicate that instead of incurring costs to avert active tuberculosis
cases, having the tuberculosis prevention program saves Santa Cruz County (taxpayers)
money.

One-way sensitivity analyses were performed for selected parameters used in the
calculation of the cost-effectiveness ratios. The cost effective (and cost-saving) results
obtained in the baseline analysis became sensitive when: (1) the percentage of patients hospitalized for tuberculosis was decreased from 70% to 50% and (2) the preventive therapy compliance rate was decreased from 72% to 60%; both for the 5 years post preventive treatment scenario with tuberculosis contagion costs excluded. However, when the tuberculosis contagion consequences of not having the tuberculosis prevention program were considered; the cost effectiveness and cost savings were once again realized.

Recommendations

The results of this prevention effectiveness study provide direct evidence of the cost-effectiveness of a tuberculosis prevention program versus the no tuberculosis prevention program option in this previously unstudied population and geographical area. This study was unique in that it may be the first cost-effectiveness study related to a tuberculosis prevention program in (1) a predominately Hispanic population and (2) a U.S./Mexico border population.

The findings of this study should prove useful to public health policy makers as to the value and cost-effectiveness of tuberculosis prevention programs in high risk (of acquiring tuberculosis) populations. At a minimum, the results of this research illustrate the worth of the tuberculosis prevention program, as it currently exists, in preventing the spread of tuberculosis and in saving money relative to the no prevention program option.

Undoubtedly, the high risk of developing tuberculosis in this study population may be attributed to its geographical location. The boundary between the United States and
Mexico in this study setting is, in reality, imaginary. Travel and interaction between both sides of the border is relatively easy. In Mexico, U.S. citizens (and their money) are warmly welcomed. Mexican citizens are allowed in the U.S. given that an individual has appropriate documentation or proof that a family member lives within 60 miles of the international boundary on the U.S. side.

Unfortunately, infectious diseases, such as tuberculosis, are not left at the immigration check point upon crossing the border. Herein lies the battle that many, if not most, public health programs along the U.S./Mexico border face. A battle to control infectious diseases brought upon, in part, by both legal and illegal immigration.

Zuber et al. (1997) indicate that "the first priority for tuberculosis control among foreign born persons in the United States is to treat active disease among recent arrivals. The screening system is of no utility, however, for those that do not enter the U.S. as legal immigrants or refugees. In areas where a substantial portion of newly arrived persons are not entering as legal permanent residents, selective screening programs could be organized to reach the highest risk groups identified in their analysis. To assure optimal control of tuberculosis, treatment and diagnostic services need to be readily available regardless of immigration status."

Given that a large portion of the study population were born in Mexico and the previously discussed proximity to Mexico; the results of this study may be used by public health policy makers to advocate for increased selective screening programs and continued funding of tuberculosis prevention programs, regardless of immigration status. While the
current political debate centered around illegal immigration and provision of resources to
illegal immigrants is highly contentious; from purely a public health perspective, the
benefits of preventing tuberculosis cases with the tuberculosis prevention program may
clearly outweigh any political controversy.

An interesting finding, as a limitation, of this research was the lack of published empirical data related to tuberculosis treatment in: (1) predominantly Hispanic populations, (2) the U.S./Mexico border region, and (3) foreign born individuals (Mexico specifically). This was surprising given (1) the recent emphasis on eliminating tuberculosis in the U.S. through identification and treatment of tuberculosis in high risk groups such as foreign born persons and (2) that from 1986 to 1993, most foreign born patients with tuberculosis were from Latin America, with Mexico accounting for over half of these patients (Cantwell et al., 1994; McKenna et al., 1995).

Additional empirical research is needed in these population groups and this geographical area. Specifically, research related to the percentage of recent tuberculin converters and an estimation of the rate of activation to active tuberculosis from a tuberculosis infection state in a predominately Hispanic population is needed. Additional studies related to birth origin of individuals enrolled in both preventive and active tuberculosis program in this geographical area may help to identify and track trends related to foreign born transmission.

A final research need to be addressed is the immigration status of foreign born individuals enrolled in both preventive and active tuberculosis programs. Research in this
area would be useful in identifying if the transmission of tuberculosis within the community is primarily due (or not due) to legal or illegal immigration. Additionally, research in this area would serve to ascertain whether or not the legal immigration tuberculosis screening and follow up process is working.

Finally, additional research is warranted to confirm the results of this prevention effectiveness study. Replication of this research is encouraged in other tuberculosis prevention programs.
APPENDIX A

REPRESENTATIVE COST EFFECTIVENESS RATIO CALCULATION
Incremental and Average Cost-Effectiveness Ratio Formulas:

\[
\frac{\text{Net Direct Care Costs}}{\text{Net Health Effects}} = \frac{\text{Cost}}{\text{Case Averted}} = \frac{C_{\text{pp}} + C_{tb(p)} - C_{tb(np)} - C_{tb}}{E_{\text{no program}} - E_{\text{program}}}
\]

where:

- \(C_{\text{pp}}\) = cost of tuberculosis prevention program;
- \(C_{tb(p)}\) = cost of treating active tuberculosis that occurs despite program;
- \(C_{tb(np)}\) = cost of treating active tuberculosis that occurs without program;
- \(C_{tb}\) = costs related to prevention and treatment of future tuberculosis related cases that would be due to the contagious nature of tuberculosis (i.e., contact tracing and identification, preventive therapy of contacts, and treatment of future active tuberculosis cases) and that would occur without program;
- \(E_{\text{no program}}\) = number of active tuberculosis cases that occur without program;
- \(E_{\text{program}}\) = number of active tuberculosis cases that occur in spite of program.

Incremental and Average Cost-Effectiveness Ratio Calculation: 5 Year Post Therapy Initiation - Contagion Costs Excluded - Costs and Outcomes Not Discounted

\[
\frac{C_{\text{pp}} + C_{tb(p)} - C_{tb(np)} - C_{tb}}{E_{\text{no program}} - E_{\text{program}}} = \frac{45,232 + 19,132 - 68,327 - 0}{4.25 - 1.19} = - 1,295
\]
Cost-Effectiveness Ratio Calculation: 5 year Post Preventive Therapy Initiation - Contagion Costs Excluded - Costs and Outcomes Discounted at 3%

Costs:

\[ PV_{\text{costs}} = F_0 + \frac{F_1}{(1+r)^1} + \frac{F_2}{(1+r)^2} + \frac{F_3}{(1+r)^3} + \ldots + \frac{F_n}{(1+r)^n} \]

\[ PV_{\text{costs}} = 14,846 + \frac{-12,540}{(1+0.03)^1} + \frac{-2,090}{(1+0.03)^2} + \frac{-2,090}{(1+0.03)^3} + \frac{-2,090}{(1+0.03)^4} \]

\[ PV_{\text{costs}} = -3,068 \]

Outcomes:

\[ PV_{\text{outcomes}} = F_0 + \frac{F_1}{(1+r)^1} + \frac{F_2}{(1+r)^2} + \frac{F_3}{(1+r)^3} + \ldots + \frac{F_n}{(1+r)^n} \]

\[ PV_{\text{outcomes}} = 1.89 + \frac{0.78}{(1+0.03)^1} + \frac{0.13}{(1+0.03)^2} + \frac{0.13}{(1+0.03)^3} + \frac{0.13}{(1+0.03)^4} \]

\[ PV_{\text{outcomes}} = 3.0 \]

Incremental and Average Cost Effectiveness Ratio Calculation:

\[ \frac{Cost \text{ effectiveness ratio}}{PV_{\text{outcomes}}} = \frac{PV_{\text{costs}}}{PV_{\text{outcomes}}} = \frac{-3,068}{3.0} = -1,023 \]
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