Prospects for Elimination: An Individual-based Model to Assess TB Control Strategies in California

By

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A thesis submitted in partial satisfaction of the

Requirements for the degree of

Joint Master of Science with the University of California San Francisco

In

Health and Medical Sciences

In the

Graduate Division

Of the

University of California, Berkeley

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Spring 2016

Part I: Literature review for a multi-disease model: HIV/AIDS, Tuberculosis, and Diabetes in South Africa

INTRODUCTION

Despite available therapeutics, tuberculosis (TB) remains an eminent global killer. The World Health Organization (WHO) estimates that in 2012, there were 8.6 million people that developed active TB disease, and 1.3 million who died from the disease (1). Although there has been an average of 2% decline in incidence of active disease over the past decade, 22 nations continue to struggle with controlling the disease. These 22 nations (the so-called high burden countries, or HBCs), represent 80% of the active TB cases, and only half are on track to meet the Millennium Development Goals (MDG) targets of reduction in incidence, mortality, and prevalence. This has become even more challenging as new drug-resistant stains of TB have developed.

A large reason for the surge in TB deaths over the past two decades has been the emergence of the human immunodeficiency virus (HIV), especially in sub-Saharan Africa. In 2012, 320,000 HIV-infected individuals were estimated to have died from tuberculosis, while 1.1 million HIV-positive individuals had active disease. Fortunately, significant efforts have been made worldwide to control the HIV/AIDS epidemic, including massive rollout of anti-retroviral therapy (ART), resulting in significant less risk of HIV-associated TB (1).

Many of these nations are now increasingly experiencing a *double burden* of communicable and non-communicable disease. As less-developed economies become more globalized, some low-income and middle-income nations have found themselves with quickly rising GDPs and a concomitant rise in life-expectancy. Additionally, global populations are becoming more urbanized, adopting Western diets, and increasingly following a sedentary lifestyle. This has caused a shocking increase in prevalence of non-communicable disease traditionally faced by exclusively wealthy nations, such as cardiovascular disease and diabetes. Although there has been a noted linked between diabetes and tuberculosis since antiquity, it is now understood that diabetes mellitus (DM) may become comparable to HIV in terms of a population-level risk factor for TB (2). Although the mechanisms are not well understood, individuals with diabetes have a 3-fold increased risk to progress to active TB, and an increased TB-associated mortality (2,3).

A nation with a very high burden of these converging epidemics is South Africa. South Africa has one of the highest prevalence of HIV world wide (17.9% in 14 to 54-year-olds), and the second-highest incidence of TB per capita in the globe (1,4). Additionally, it has a high burden of diabetes: 3.9-8.8% of the population is diabetic (5), and an estimated 8.3% of the population is pre-diabetic as defined with impaired glucose tolerance (6). Diabetes prevalence is projected to rise by 2-fold in Africa within the next 15 years (6). Unfortunately, there is little understanding of the potential impact of the increasing burden of DM in South Africa, and how it will affect TB and/or HIV burdens.

One way to predict the effects of changing disease dynamics is through mathematical modeling. Modeling diseases allows policy-makers to collect relevant data, analyze potential future projected scenarios, compare policy options, and decide how to allocate resources. They are particularly helpful with more complicated conditions, where predicting the effects of policies or

interventions is difficult to ascertain *a priori*. Models can also help bring stakeholders together to determine where key data needed to understand a disease are missing.

In order to understand the trajectory of TB in South Africa, an understanding of the trajectories of HIV/AIDS and diabetes must also be understood, as well as the interaction between these diseases. Unfortunately, there is a lack of precedent of evaluating more than two diseases and their interactions in a single model. Although there are a few examples of models with different diseases in them (in particular, WHO's SPECTRUM), we have been unable to identify any which evaluate more than two diseases and their *interactions*, as opposed to separately-operating models which are only synchronized through population size.

Modeling two diseases—however—is more common, and is often used to model TB and HIV in sub-Saharan Africa. Additionally, many well-developed models of DM exist.

Given the approaching convergences of these epidemics, a population-level mathematical model of TB, HIV/AIDS, and diabetes mellitus is desperately needed, especially in a setting such as South Africa. Unfortunately, no investigation has yet been completed, potentially due to a lack of a precedent of multi-disease modeling approaches, or the fact that these interactions were elucidated relatively recently. Therefore, this paper attempts to review a variety of topics necessary to build such a model, namely: modeling theory required to an understanding of multi-disease modeling approaches, the relevant physiology of each of the diseases (as to aid in the understanding of potential disease interactions), the epidemiology and economics of each of the disease in South Africa, recent modeling attempts of the individual diseases, and the characterized interactions between the diseases.

DISEASE MODELING METHODOLOGY

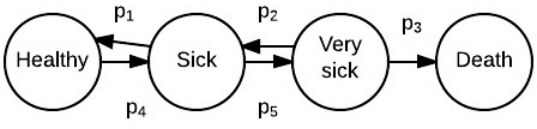
Introduction

Throughout human history, epidemics of many varieties had destroyed populations in wanton and unpredictable manners. Due to a lack of understanding of many of the environmental, physiological, and pathophysiological processes at play, it was difficult for researchers to understand or in any way predict patterns of health. However, as medicine matured, researchers began applying methods borrowed from other disciplines to help understand these dynamics.

One of the first individuals to do so was Anderson Gray McKendrick, a Scottish physician. Working with Ronald Ross and William Ogilvy Kermack, he wrote the first treatise on modeling disease, entitled *Application of Mathematics to Medical Problems* in 1926 (7). Since then, the field has matured significantly, pulling in methodologies from operations research, industrial engineering, mathematics, and computational biology.

One of the core methodologies used in disease modeling is the *Markov method*, proposed by Andrey Markov in 1906. What Markov suggested is conceptually simple. He proposed that populations could be broken into *compartments*, or *states*. In the case of disease modeling, these represents disease progression, such as "healthy," "sick," "very sick," and "death." He suggested that from any one state there was a probability (*p*) associated with moving to another state within one *discrete* time interval (or *cycle*). For example, if one is "very sick" there is a *probability* of 0.9 of dying within one year. These transitions are assumed to take no time. This has been called a *discrete-time Markov chain,* or simply a *Markov chain*. It is helpful to imagine a physical chain, where each link of the chain represents some time period.

These can be represented visually using a *state transition diagram.* In state transition diagrams, circles (also called *nodes*) are used to represent the disease states, while directional arrows (also called *edges* or *arches*) represent the potential transitions, and their probability per cycle (*p*) is written next to them. Impossible transitions, such as moving out of the "death" state, are not draw. In this example, an individual can become more ill, but can also recover.



Although it is common to make these models using discrete time intervals, it is also possible to model these events in a continuous manner. These are referred to as *continuous-time Markov processes*, or simply *Markov processes*. Instead of looking at probabilities of transfer during a segment of time, such as a year, Markov processes use *rates* of transfer from one state to another, such as 1000 people per year. The first models of disease, by McKendrick *et al*, used continuous-time Markov processes. We turn to those now, and will then return to the discrete-time method.

Continuous-time models

The classic model is one developed by McKendrick, looking at an infectious disease, whereby individuals could be categorized into one of three states: susceptible (*S*), infected (*I*), and removed (*R*), the so-called *SIR* model. In these *SIR* models, individuals in the removed compartment are either immune to infection or have died from the infection.

These models are deterministic, meaning they produce only a single mean value of transitions or occupants in states. One can represent the number of individuals in each state as functions of time *t*, i.e. *S(t)* is the number of susceptible individuals at time *t*. If we assume a constant total population of *N*, and a rate of recovery to full-immune status of α, we can express these functions are differential equations (note that epidemiology uses a prime notation, *X'*, to signify derivatives, not the traditional *dx/dt*). For example, the rate of change in susceptible population (*S'*) can be estimated at time *t* to be the negative number of contacts sufficient for infection (*β*) multiplied by the proportion of the population that is susceptible, multiplied by the number of infected individuals.

$$S' = -\beta\frac{S}{N}I$$

To make this more concrete, let us imagine a pandemic of influenza in a small city of 50,000 individuals. This specific type of fanciful influenza is only transmitted by shaking hands, which people do at random in the population, and causes infection 100% of the time. Imagine that each person shakes 5 hands per day, and by the third day there are 200 individuals infected, and 10 have recovered. What is the rate of change in the susceptible population?

$$S' = -\frac{5}{day}\times\frac{49\,790}{50\,000}\times 200$$

$$S' = -\frac{995.8}{day}$$

This means that the susceptible population will shrink by approximately 996 people on the third day – this makes sense as the 200 people will shake in total 1000 hands but some of these individuals will potentially already be infected, meaning no infection could occur. What if we wanted to find the derivative of the infected compartment? It is not just the negative of the susceptible derivative, because people are recovering from infection in this model (at the rate of α). Therefore, it can be expressed as such:

$$I' = \beta\frac{S}{N}I - \alpha I$$

If we assumed that 10% of the infected population recovers per day, we could find the solution with our example:

$$I' = \frac{5}{day}\times\frac{49\,790}{50\,000}\times 200 - \frac{0.1}{day}\times 200$$

$$I' = \frac{995.8}{day} - \frac{20}{day}$$

$$I' = \frac{975.8}{day}$$

996 people will become newly infected on the third day, and 20 will recover. Therefore the rate of change is approximately 976 people per day. It is also easy to see that:

$$R' = \alpha I$$

and

$$N = S + I + R$$

and

$$S' + I' + R' = 0$$

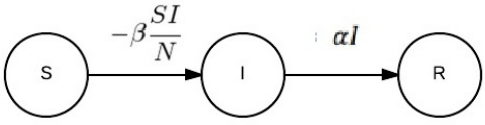
Because the *SIR* model assumes no changes in population, it is best suited for modeling short amounts of time, such as immediate infections.

Another useful statistic is R_0, pronounced "R-not," defined as the *basic reproductive number*. This represents the average number of infections caused by one person over the length of one infection and is defined as β divided by α. If it is larger than one, the infection will spread; if it is less than one, the infection will not spread. It can also be broken down into constitute parts:

$$R_0 = \frac{\beta}{\alpha} = \left(\begin{matrix}\text{contacts per} \\ \text{unit time}\end{matrix}\right)\left(\begin{matrix}\text{probability of transmission} \\ \text{per contact}\end{matrix}\right)\left(\begin{matrix}\text{length of time person} \\ \text{is infectious}\end{matrix}\right)$$

Even with our outlandish scenario of hand-shaking influenza, one can imagine how these methods could be very useful to predict the patterns of epidemics. More complicated models are made with these methods, including treatment stages, screening, detailed pathologies, or even age-structuring.

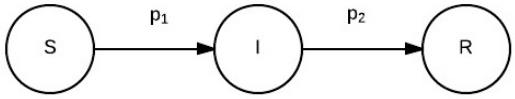
Now that we have a more full understanding of McKendrick's model, we can see a state transition diagram could look something like this (note that instead of probabilities per cycle, we are using rates to signify the transitions):



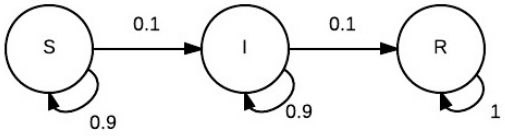
Sometimes, however, it is much more simple to model these processes using discrete time cycles, with the previously-described Markov chain.

Discrete-time models

The discrete-time models are also conceptually simple. For example, one could create a similar example to the influenza-handshake one above:



In our above discrete-time *SIR* model, instead of using the rate of transfer to the infected state, we would instead have two probabilities for one year: the probability of becoming infected in one year (p_1, let's imagine 0.1) and the probability of staying in the susceptible state (which, since they can go no where else, would be 0.9). Let's imagine that the probability of infected people recovering per year, p_2, is 0.1. Transitions which are impossible in the model's framework (such as R to I) are assigned probabilities of zero. The transitions probabilities of staying in the same state can be added to our diagram, shown as recursive arrows:



In addition, one can display these transition probabilities in the form of a *transition matrix*, which shows the estimated transition probabilities. The transition matrix can be represented as a traditional table or a mathematic matrix, classically labeled *P*. All *rows* (but not necessarily columns) should add to one, since an individual in a state must either transfer or remain in their state during a cycle.

		Transition to state:		
		S	**I**	**R**
Transition from state:	**S**	0.9	0.1	0
	I	0	0.9	0.1
	R	0	0	1

$$P = \begin{pmatrix} 0.9 & 0.1 & 0 \\ 0 & 0.9 & 0.1 \\ 0 & 0 & 1 \end{pmatrix}$$

Using these probabilities, it is easy to calculate the progress of an epidemic given initial conditions, or *initial state*. Imagine an group with 90% of individuals in the susceptible category, 10% in the infected category and none in the recovered category. This can be represented as a vector, traditionally called p^0, of our threes states (p^0_1, p^0_2 and p^0_3).

$$p^0 = (p_1^0, p_2^0 . p_3^0) = (0.9, 0.1, 0)$$

At the beginning of the first year, we would have 90% of individuals in *S* and 10% in *I*. After the first year passes, we can find the new distribution of individuals, p^1, through a simple matrix multiplication:

$$p^1 = p^0 \times P = (0.9, 0.1, 0) \times \begin{pmatrix} 0.9 & 0 & 0 \\ 0.1 & 0.9 & 0 \\ 0 & 0.1 & 1 \end{pmatrix} = (0.81, 0.18, 0.01)$$

Therefore, by the beginning of the second year, 81% of our population is susceptible, 18% is infected, and 1% has recovered. To find the next year's matrix, p^2, we would multiple p^1 by P. This can be continued for as many years as one desires to investigate. Put another way, any cycle's results can be found by multiplying the last vector by the transition matrix:

$$p^1 = p^0 \times P$$
$$p^2 = p^1 \times P$$
$$p^3 = p^2 \times P$$
$$p^n = p^{n-1} \times P$$

Or, even more simply, just the power of the transition matrix can be used. This is called the *power method*.

$$p^n = p^0 \times P^n$$

Unfortunately, such methods are only useful due to the simplicity of our model; we assumed that transition probabilities would be constant, whereas this is obviously not true: in the context of infectious disease, the probability of becoming infected is dependent on the number of other infected individuals. Therefore we would need to re-calculate our transition matrix before calculating any new vectors.

Additionally, though the power method is useful, it only provides us with the distribution of the population at cycle *n.* This is called a *direct solution* to a Markov chain. However, as epidemic modelers, we are interested in the whole path – what did the population looks like at cycles *n-1* and *n-2*? These broader solutions are termed *transient solutions*.

The Markov property

Both the continuous and discrete-time Markov methods have what is termed the *Markov property*: each transition probability is based on the state of current affairs, regardless of past events. In order words, to calculate the distribution of the population in states at cycle *n*, we only need to know the distribution at cycle *n*-1. In many cases this is a simplification; for example, individuals who were infected 10 years ago might be more susceptible to a re-infection than individuals who recently recovered for immunological reasons. The Markov property asserts that each individual in a state is treated homogenously without history. The above example shows the Markov property well: in order to calculate p^3, for example, we only need to know the state of the model at p^2: p^1 and p^0 are irrelevant. This can be called a *first-order Markov chain*. However, there are variations of the Markov methodology that allow for some "memory." If we require data from two previous steps (i.e. we would need p^1 and p^2 to calculate p^3), this is called *a second-order Markov*, and so on.

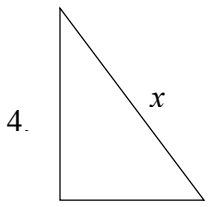
If a state can only receive individuals, but they are unable to transfer out (e.g. death), this is referred to as an *absorbing* state. States that allow individuals to return are called *recurrent*; whereas if there is zero probability of returning to that state, it is referred to as *transient* (8).

There are many assumptions in classic discrete-time Markov modeling as above. One of the problematic assumptions is the constant nature of the transition probabilities. In the context of infectious disease, the transition probabilities are obviously not constant; as the infection becomes more common in a population, the probability of a susceptible person becoming infected rises. Therefore, it the context of infectious diseases, the transition probabilities (or rates in continuous-time models) would be represented by functions of the number of individuals in other states, similarly to the example from McKendrick *et al*. This is termed *load-dependence*.

One can hopefully see how useful both the discrete-time and continuous-time Markov methods can be in modeling disease processes. However, these techniques have shown us how to model these conditions if the transition probabilities/rates are either functions such as those defining *S'*, or single digits, such as 0.9. These models have given us good rough deterministic estimates of the average pathways through diseases. However, what if we wanted to know the average path through a chain, as well as the variance or standard deviations? In order to do this, we need to introduce some randomness to our model. A method for doing this is the Monte Carlo method.

Monte Carlo methods

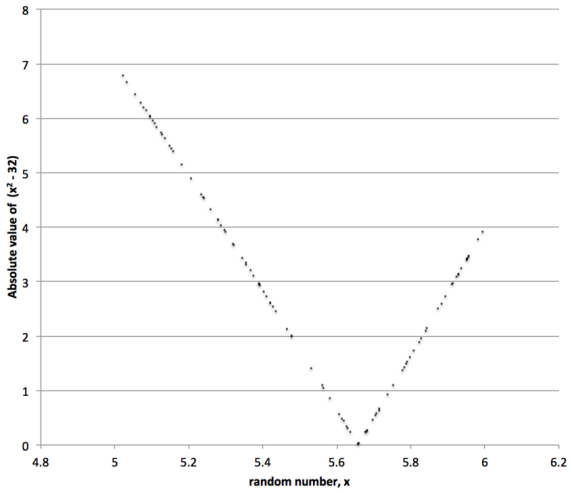
Scientists working on the development of nuclear weapons in the 1940s at Los Alamos Labs developed a set of methods, which they named after the Monte Carlo, a popular Las Vegas casino. In essence, they are defined as methods that *involve deliberate use of random numbers in a calculation*. This may seem too simple a definition, but let us explore a very basic example. Imagine we were presented with the following simple geometric problem and asked to solve for x:



Using the Pythagorean theorem, we could derive:

$$x^2 = 4^2 + 3^2$$
$$x^2 = 32.5$$

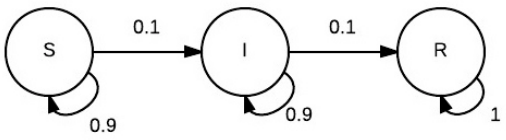
Now imagine we had not developed a mathematical method for finding the square route of 32.5; or perhaps the mathematical computation was too difficult. Since 5^2 is 25 and 6^2 is 36, we know that *x* lies between 5 and 6. Let us sample 100 random numbers between 5 and 6, plotted against the distance of the square from 32.



We can see that our evaluation of the square root of 32.5 lies somewhere between 5.6 and 5.8. Even with only 100 sampled numbers, one sample of *x* came within 99.1% of the true answer. Although this is a very simple example, one can hopefully imagine how as equations become more and more complex and difficult to solve analytically, these random methods can become useful.

How can this be applied to disease modeling? Monte Carlo methods have been applied in the context of Markov processes. Note that the term *Monte Carlo Markov Chains (MCMC)* is not relevant here – this is a separate entity that is not as relevant to disease modeling.

One method of incorporating Monte Carlo methods in Markov chains is by creating a series of *random walks* or *sample paths* to model at an individual level. If we model more than one individual at a time, this is referred to *simultaneous simulation*. This is a method commonly used in *individual-based* or *agent-based modeling*. Whereas in our previous example we estimated at the percent of a cohort that would transfer to one state based on their probability, in a sample path we analyze the pathway of a specific individual. For example, let us look at our simple discrete-time *SIR* model once again.



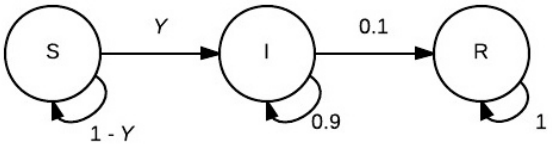
Let us imagine that we have 1000 individuals, 90% of whom are susceptible, 10% of whom are infected, and 0% of whom are recovered. In this case, we would have 900 susceptible individuals, 100 infected, and none dead. We complete the analysis by analyzing each

individual's movement, one individual at a time. So, first, we look at out first individual in the susceptible category – s/he has a 0.90 probability of staying in the susceptible state and a 0.1 probability of becoming infected. We can therefore generate a pseudorandom number between 0 and 1 with a computer program, and use this number to determine which state the individual will transition to; perhaps we can say that if the number is between 0 – 0.1, they will become infected, whereas if it is above 0.1 they will stay susceptible. Let's imagine we generate 0.54 – therefore they stay. We then move on to the second individual in the susceptible category, and generate a random number of 0.03; they transition and become infected. This process continues until each individual has been assigned a new state, then you continue to the next cycle. A full simulation to the end of the model is called a *simulation run*. An example is shown of five individuals over five cycles.

Cycle	State					
	Individual 1	Individual 2	Individual 3	Individual 4	Individual 5	…
0	S	S	S	S	S	…
1	S	I	S	S	S	…
2	S	I	I	S	S	…
3	S	R	I	S	S	…
4	S	R	I	S	I	…
…	…	…	…	…	…	…

This sample path method should produce similar results to a traditional Markov chain model given a very large number of runs. However, it is useful because it will provide not only an estimate of the average path, but the distribution of paths, allowing for the calculation of variance/standard deviation and hypothesis testing between two models.

Another commonly used Monte Carlo method, called *Probabilistic Sensitivity Analysis* (PSA), does not rely on individual-level modeling, but instead incorporates Monte Carlo methods to the transition probabilities themselves. For example, let us imagine the simple discrete-time *SIR* model once again. However, let's imagine that instead of the transition from *S* to *I* being a known probability of 0.9, let us imagine there is some uncertainty, and that its probability is best represented by a normal distribution *Y*, with a mean of 0.4 and a standard deviation of 0.05. We can then visualize this on our state diagram and transition matrix:



$$P = \begin{pmatrix} Y-1 & 0 & 0 \\ Y & 0.9 & 0 \\ 0 & 0.1 & 1 \end{pmatrix}$$

Let's look at how this would look if we ran the model with 1000 iterations. For first iteration, we would take a random sample from Y – let's imagine we sampled 0.45. We would then complete the calculations in a similar manner as the above example, using this as our transition matrix:

$$P = \begin{pmatrix} 0.55 & 0 & 0 \\ 0.45 & 0.9 & 0 \\ 0 & 0.1 & 1 \end{pmatrix}$$

Once the calculations for the request number of cycles were completed, we would start the calculation over and require a new sample from the Y distribution. In this manner, we would be able to develop a set of results that are more representative of the known distributions of transition probabilities.

Modeling multiple diseases

Modeling multiple diseases with Markov models presents some interesting issues. Consider a simple example of modeling two unrelated diseases, for example influenza and malaria. Let us imagine there is no interaction, and that each disease has only two states: susceptible (*S*) and infected (*I*). We can represent these two diseases with their two transition matrices, using subscript *f* ("flu") to represent influenza and *m* to represent malaria:

$$P_m = \begin{pmatrix} a_{SS} & a_{SI} \\ a_{IS} & a_{II} \end{pmatrix}$$

		Transition to malaria state:	
		S	**I**
Transition from malaria state:	**S**	a_{SS}	a_{SI}
	I	a_{IS}	a_{II}

Where a_{ij} is the probability of transferring from state i to state j in one cycle.

$$P_f = \begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix}$$

		Transition to malaria state:	
		S	**I**
Transition from malaria state:	**S**	b_{SS}	b_{SI}
	I	b_{IS}	b_{II}

Where b_{ij} is the probability of transferring from state i to state j in one cycle.

Imagine we wanted to create a master, or *global*, transition matrix, which could represent the probabilities of transferring from, for example, susceptible to both diseases to infected with both. To do so, we would find the tensor product of each of the matrices. For a review of matrix algebra, see Searle.(9)

$$P_m \otimes P_f = \begin{pmatrix} a_{SS} & a_{SI} \\ a_{IS} & a_{II} \end{pmatrix} \otimes \begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix} = \begin{pmatrix} a_{SS}\begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix} & a_{SI}\begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix} \\ a_{IS}\begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix} & a_{II}\begin{pmatrix} b_{SS} & b_{SI} \\ b_{IS} & b_{II} \end{pmatrix} \end{pmatrix} = \begin{pmatrix} a_{SS}b_{SS} & a_{SS}b_{SI} & a_{SI}b_{SS} & a_{SI}b_{SI} \\ a_{SS}b_{IS} & a_{SS}b_{II} & a_{SI}b_{IS} & a_{SI}b_{II} \\ a_{IS}b_{SS} & a_{IS}b_{SI} & a_{II}b_{SS} & a_{II}b_{SI} \\ a_{IS}b_{IS} & a_{IS}b_{II} & a_{II}b_{IS} & a_{II}b_{II} \end{pmatrix}$$

In table form, it could resemble something like this:

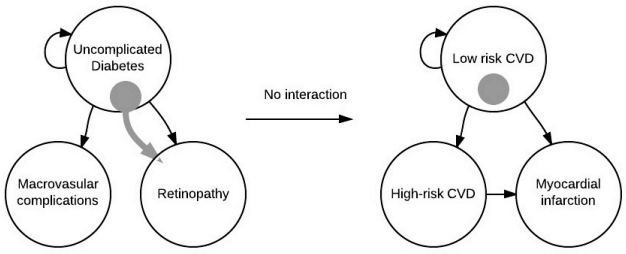
				Transition to: Malaria			
				S		I	
				Influenza			
				S	I	S	I
Transition from:	malaria S	influenza	S	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$
			I	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$
	malaria I	influenza	S	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$
			I	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$	$a_{ss}b_{ss}$

This seems to work for a small number of diseases with a small number of states. However, as these numbers increase, investigators face an exponentially increasing number of states, the so-called *state-space explosion* (10). Imagine we were modeling ten diseases, each with ten potential disease states. This would make the total number of potential states 10^{10}, or 10 billion. The number of elements in the transition matrix would need to be the square of ten billion, or 1 x 10^{18}, 100 sextillion. Even the fastest computers would be unable to handle this amount of data or calculation.

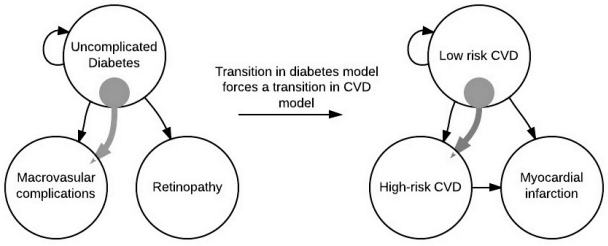
One method to manage the state-space explosion is the idea of *decomposition*. Decomposition allows a large Markov matrix, the *global* matrix, be broken into smaller *local* matrices – in essence, the reverse of what we've show above. Some models might be *completely decomposable*, broken into two completely separate models with no interaction. In this case, the solutions to the Markov chains can be solved separately. If the global chain is not fully decomposable, relying on only a few interactions between the chains, it can be referred to as *nearly completely decomposable* (NCDE). Most disease processes will need a NCDE methodology, since if an individual dies of diabetes, they should be moved to the "death" state in all of the Markov chains, not only in the diabetes chain.

One method for the solution of NCDEs is the creation of locally-interacting Markov chains, also called *stochastic automata networks* (SANs). Imagine we were attempting to model cardiovascular disease (CVD) and diabetes. Consider that we wanted to analyze a cohort of 1000 people, and we can represent one individual, *person X*, with a grey dot, showing which state they occupy. In this case they have uncomplicated diabetes and a low CVD risk.

Now imagine that during the first cycle, this person advances to have diabetes-related eye damage, or retinopathy. This has no effect on cardiovascular disease, as the eyes to not affect your cardiovascular health. This event can be referred to as a *local event*, because it has no effect on any other local chains.



On the other hand, if someone with diabetes advanced to having macrovascular disease, they would have an increased chance of having a myocardial infarction – this means that a transition in the diabetes model has now interacted with the CVD model, and can force a transition to "high risk CVD." This type of event is called a *synchronizing event* or *synchronized transition* because it requires a local chain to become synchronized with other local chains (10).

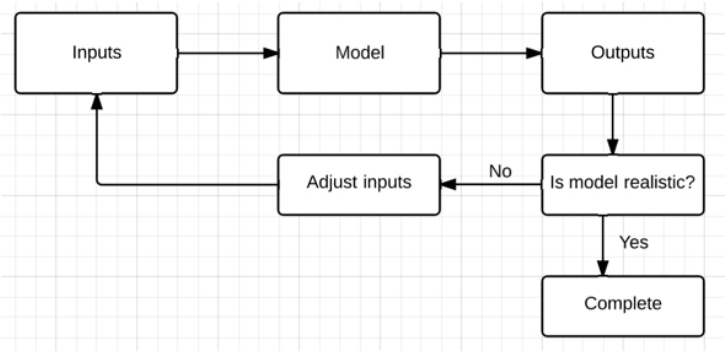


Another way to represent this interaction would be to use *functional probabilities* – ie, the probability of having a myocardial infarction could be represented with a function of the state of the diabetes chain.

Hopefully, one can see that it may be possible to represent the interaction of many diseases with a combination of Markov chain, Monte Carlo, and stochastic automaton network methods. However, once a model is built, how does an investigator know how realistic the performance of that model is? Even with seemingly realistic model inputs, it is possible to develop wildly unbelievable models. To address this issue, we now turn to the topic of model validation and calibration.

Calibration, validation, and bench-marking

Creating models of disease often requires adaptation of data from a wide variety of sources, many with different research goals. One or two poor estimated parameters could result in model predictions that are unpredictable and, at times, quite unreasonable. In order to prevent the use of unverifiable models for policy decisions, investigators are required to analyze their model outputs and assess their reliability. If the models are judged to be unrealistic, investigators should adjust their parameters with the highest degree of uncertainty to improve goodness-of-fit with other available reliable data. This process can iterate, as shown below.



In the context of multiple diseases, modelers need to show that each individual disease model works well on its own, and that the interaction between the diseases occurs in a way that would be expected.

One newer methodology for calibration called *Bayesian melding* allows the use of distributions for both inputs and outputs, and attempting to find the parameters that fit both inputs and outputs best. It has been used in the context of HIV modeling in South Africa and elsewhere (11,12) Its specific methods are discussed by Poole *et al* (13).

REVIEW OF DISEASES & THEIR MODELS

In this section, I review the relevant physiology of each of the three diseases, as well as explain two to three recent modeling approaches to them.

HIV/AIDS

Pathogenesis & pathophysiology of HIV/AIDS

Overview

The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). It is a small retrovirus of the lentivirus family, which infects and destroys CD4+ "helper" T-lymphocytes, causing serve immunosuppression. There are two forms, HIV-1 and HIV-2, which HIV-2 being primarily constrained to West Africa (14).

Viral transmission occurs through sexual contact (especially receptive anal sex), blood transfusions, sharing of intravenous drug equipment, breastfeeding, and childbirth (14).

Once HIV has entered the host's body, it is able to bind CD4+ cells, primarily lymphocytes, macrophages and dendritic cells. It initiates a program of membrane fusion, which allows the HIV genome to enter the cytoplasm of the cell. Once inside the cytoplasm, the virus undergoes reverse transcription (via *reverse transcriptase*), modifies its proteins to be functional enzymes (via *protease*) and is able to incorporate itself into the host's genome (via *integrase*). Integrated into the host genome, the provirus may enter a latent infection state, whereby it is not transcribed for weeks or years. Alternatively, it may undergo transcription, form complete viruses and reach the surface of the cell, forming small "buds" that are able to leave the cell cytoplasm. If this budding program continues for some time, cell death will occur. Note that viral DNA is only transcribed in activated T-lymphocytes, meaning that an active infection will produce the cascade of viral transcription, budding, and cell death (14).

Acute disease

Early in infection, patients can be described as having *acute disease*. The first cells to be infected are mucosal lymphocytes, resulting in a significant decline in the number of lymphocytes. Once dendritic cells are infected, the dendritic cells begin migrating to lymph nodes in order to present the HIV antigens. Once in the lymph nodes, HIV is able to infect other lymphocytes and replicate heavily. The host mounts an immune response (both humoral and cell-mediated), which lowers detectible virus levels. Flu-like symptoms develop in 50 to 70% of patients, which cell resolve upon control of the virus by the immune system, resulting in conversion from sero-negative to seropositive. Although symptoms are minimal or flu-like during this period, transmissibility is at a maximum level due to heavy viremia. Once this decline in viremia occurs (after approximately 12 weeks), patients return to a relatively healthy state, and can be characterized as having *chronic disease* during this *clinical latency period* (14).

Chronic disease

Patients in the clinical latency period have no or very few symptoms (such as mild opportunistic infections and lymphadenopathy). HIV replication and destruction continues in the lymph organs, which contain 90% of the body's lymphocytes. This allows total CD4+ T-cell counts to drop gradually with minimal symptoms, since the majority of peripheral T-cells are uninfected. In addition to the gradual decline in CD4+ T-cells from direct virus-mediated cell lysis, HIV also: disrupts CD+ T-cell precursors, induces apoptosis in non-infected CD4+ T-cells, dysregulation cytokine production, disruption of lymphoid tissue structure, immune-mediated killing on CD4+ infected cells, and improper function of CD4+ infected T-cells. These events cause complete dysregulation of the immune system. During the chronic phase, as CD4+ T-cell lymphocyte level continue to decline, HIV-related symptoms may become more common. Fever, fatigue, or rashes may present.

Severe disease

Once CD4+ T-cells drop below 500 cells/μL of blood, more severe symptoms develop as the immune system is unable to fight off infections. This can be seen as a crisis phase. Fatigue, fever, weight loss and diarrhea are common. Other severe conditions, such as secondary neoplasms (eg, Kaposi's sarcoma) and opportunistic infections can develop. There is a large number of common HIV-associated opportunistic infection, fungal, parasitic, bacterial and viral. These secondary manifestations of disease or a reading of 200 CD4+ T-cells/μL of blood places a patient into the category of AIDS, as opposed to chronic HIV infection. Without treatment, most patients will progress to AIDS in 7-10 years after infection, although there is a high range of variability. Untreated, AIDS is invariable fatal.

Screening, prevention, and treatment of HIV/AIDS

HIV prevention is a well-studied topic with a variety of potential interventions, including the distribution of condoms, educational campaigns, reduction in needle-sharing among injection drug users (IDUs), male circumcision, and prophylactic therapy among at-risk individuals (15).

Voluntary HIV testing and counseling has been a strategy long recommended by public health officials. Diagnosis can be suspected from symptoms or sexual relations history, and is determined with an *enzyme immunoassay* (EIA) and confirmed with a Western blot (16). These test confirm the presence of an antibody response to HIV. Therefore, individuals in the acute phase, pre-seroconversion, will not be detected by this test. There is also a PCR-based test.

Clinical monitoring of HIV patients is done through two primary mechanisms: the concentration of CD4+ T-cells in the blood, and an estimate of viral load. CD4 is better than viral load, due to lower costs (17).

Treatment is accomplished with a drug cocktail targeting specific proteins necessary for the HIV lifecycle, so-called *anti-retroviral therapy* or ART.

Protease enzymes (such as those encoded by the *pol* gene) are used by HIV to clip non-functional proenzyme into functional enzymes. Protease inhibitors (PI), such as indinavir and ritonavir, are used to disrupt this process. Unfortunately, there is a high level of P450 interaction, and they cause a metabolic-syndrome-like disease process, with dyslipidemia and insulin resistance, though less so in newer PIs like atazanavir (18).

Nucleoside reverse-transcriptase inhibitors (NRTI), such as zidovudine/azidothymidine (AZT) and didanosine (DDI), prevent the production of DNA from the RNA virus by introducing a non-functional nucleoside that is preferentially taken up by HIV's reverse transcriptase, ending reverse transcription. Unfortunately, there is a high amount of resistance to AZT. When used with protease inhibitors, is referred to as highly active antiretroviral therapy (HAART). Non-nucleoside reverse transcriptase inhibitors, such as nevirapine and efavirenz, disrupt the same pathway through a different mechanism (18).

Fusion inhibitors (FIs), such as enfuvirtide or maraviroc, block entry of the HI virus into host cells by disturbing membrane machinery (such as gp41 or CCR5). Integrase inhibitors, such as ratelgravir, block the entry of the DNA provirus in the host genome (18).

Currently, most patients receive a drug cocktail with medications of different mechanisms. Successful treatment can expand lifespan extensively, and reduce infectiousness by 96% (19).

Epidemiology & economics in South Africa

Over 22 million individuals have died from AIDS (hereafter referred to as HIV/AIDS) since it was recognized in 1981. Of the 33 million individuals living with HIV/AIDS in 2009, 70% were in Africa and 20% were in Asia.

South Africa has had one of the highest prevalence's of HIV/AIDS since the beginning of the early 1990s. There have been a few factors proposed for the disease's continued persistence: the common age difference between sexual partners, multiple concurrent partnerships, widespread extreme poverty, and large amounts of migration and population mixing because of extractive industries (20,21).

Although the epidemic was somewhat concentrated in the 1980's among men who have sex with men (MSM), it became a generalized epidemic in the 1990's. Between 1990 and 1994, prevalence among pregnant women rose from 0.8% to 7.6%, mostly through heterosexual contact (20). Prevalence in pregnant women rose to over 20% by 2000, and peaked in 2004 at 30.2% (22). Mortality surged reducing the life expectancy by approximately 20 years (23). Prevalence of infection was much higher in black South Africans than white south Africans.

Unfortunately, according to Karim *et al*, the South African response to the epidemic has been characterized by "denialism, ineptitude, obtuseness, and deliberate efforts to undermine scientific evidence as the basis for action." Nevertheless ART was introduced in the public sector in 2004, and has made significant gains in reducing morbidity and mortality. From 2003 to 2011, life

expectancy in the KwaZulu-Natal province for adults rose 11.3 years, to 60.5, largely due to ART scale-up (24).

Currently, HIV remains an enormous problem, with 17.9% of the 14-54yo population infected and 240,000 yearly AIDS-related deaths estimated for 2012 (4).

Previous modeling attempts

Unlike DM, HIV/AIDS has a long history of being modeled with another disease – tuberculosis. In addition, HIV models have been well-developed over the last decade. Here, I will review one HIV-only model, which utilizes methodology common to many HIV models. More detailed models of HIV with TB are discussed below, in the TB section.

Granich *et al* built a deterministic model to predict the outcomes of immediate antiretroviral therapy on population-level epidemic in South Africa (25). This model was used later with other analyses (26). They did not include homosexual transmission, as most transmission is confined to heterosexual interactions in South Africa. They created four HIV/AIDS "progression of disease" states, defined by CD4+ T-cell counts, as well as a separate "acute" and "final" state, both with marked increases in transmissibility. The model was calibrated by fitting it to 2005 national data. They included a screening rate (and subsequent migration to treatment states), treatment drop-outs from refusal, treatment failure, second-line treatment states, and an aggregate reduction in HIV transmissibility due to various prevention interventions (e.g. condom distribution). Transmission was calculated with a stochastic model calibrated to South African national statistics, and accounted for population HIV/AIDS prevalence as well as treatment status (25).

Diabetes mellitus

Pathogenesis & pathophysiology

Type 1 diabetes mellitus

Insulin is normally produced by pancreatic Beta cells. In *type 1 diabetes mellitus* (T1DM, or insulin-dependent DM), an agent on the surface of beta cells becomes identified as an antigen (limited evidence suggest that a beta-cell enzyme or insulin itself may be these antigens). It is unclear how this component losses its ability to be recognized as normal. Regardless, the islet cells are invaded by T lymphocytes and are necrotized. This process is called insulitis. Additional pathways for beta cell destruction include locally produced cytokines, as well as antibodies. It is unclear whether antibodies are produced directly to beta cell antigens, or if it is a byproduct of beta cell destruction by T lymphocytes. Classic manifestations of DM show up after ~90% of beta cells have been destroyed.

A lack of insulin creates a condition where blood glucose is unable to enter cells and is retained in the plasma of the blood, forming a hyperglycemic mixture of blood. The insulin deficiency causes metabolic imbalance by essentially promoting a starving state: muscle degradation, gluconeogenesis, lipolysis are all activated. Ketoacidosis becomes a primary complication.

Buildup of glucose in blood increases its osmolality. This creates a large osmotic gradient; passing blood extracts water from the cells and interstitial space. Thus patients present with polyruria, polydipsia, polyphagia and glycosuria, and are normally identified at a young age.

In summary, T1DM results in a lack of insulin secondary to immune-modulated beta-cell destruction.

Type 2 diabetes mellitus

Type 2 diabetes is a far more common occurrence, and has a different pathogenesis. T2DM is often found in older, obese individuals and is characterized by a loss of sensitivity to insulin.
Macrovascular disease
The hyperglycemic state of diabetes results in glycosylation of many proteins that are not normally glycosylated. A notable one is hemoglobin, where long exposure to large amounts of blood glucose causes a glycosylation of HbA to HbA1C. The process is called *non-enzymatic glycosylation* (NEG), and produces *advanced glycation end products*, or AGEs.

Another common target of glycosylation are extracellular matrix proteins (such as collagen) and vessel endothelial basement membrane. This sets off a cascade of pathways: lipids get stuck in the matrix, plasma proteins bind to it, a coagulation cascade starts, macrophages are attracted the site, and even more extra-cellular matrix is produced. This leads to atherosclerosis, or the formation of plaques in the vessel. Atherosclerosis is an artery wall thickening as a result of the accumulation of fatty materials. It is characterized by a chronic inflammatory response in the walls of arteries, caused largely by the accumulation of macrophages and white blood cells and promoted by low-density lipoproteins (LDLs).

This increase in atherosclerosis puts individuals at risk for myocardial infraction, which is the largest cause of deaths in diabetics.

Microvascular disease

Thickening of the vascular wall with a non-cellular protein substance (referred to as *hyaline arteriolosclerosis*) reduces the size of the artery's lumen, thereby increasing blood pressure. Therefore, hypertension is a common complication of diabetes. Additionally, many endothelial cells, such as those forming the basement membranes of different tissues, are not insulin-dependent and therefore absorb much of the glucose with which they are bathed in. This creates huge concentrations of intracellular glucose, and cells respond by creating more membrane glycoproteins. This overproduction of membrane glycoproteins thickens the membranes significantly. Although thicker, the membranes become more permeable to protein.

This "microangiopathy" (microvascular disease) is responsible for the other major complications of diabetes: diabetic nephropathy, retinopathy, and neuropathy, among others.

Diabetic nephropathy

Diabetic nephropathy includes diffuse glomerulosclerosis (hardening of the glomerulus in the kidney) and nodular glomerulosclerosis (development of hyaline lesions in glomerulus loops). These are also called Kimmelstiel-Wilson lesions.

Diabetic retinopathy

Diabetic retinopathy has two stages: non-proliferative and proliferative: Non-proliferative retinopathy is characterized by damage to vasculature of retina. Some vision problems may develop. Proliferative retinopathy occurs as body attempts to build new vasculature. This causes problems, and can lead to blindness.

Diabetic neuropathy

Diabetic neuropathy is caused by damage to the vessels which supply the nerves. Damage can be within the autonomic or voluntary pathways; pain, sensation and afferent.

Diabetic foot

Although not well understood, DM slows the healing process. Along with a loss of sensation in the feet, it is common for diabetics to develop foot ulcers that are resistant to healing.

Screening, prevention, and treatment

Since the exact etiology of type 1 diabetes is poorly characterized, there are no known preventative options. On the other hand, prevention of type 2 diabetes is a well-studied topic that includes many behavioral interventions aimed at reducing the amount of simple carbohydrate intake and the promotion of active lifestyles (27).

Treatment of DM is aimed at reducing the symptoms of active hyperglycemia and reducing the risk of macro and microvascular complications.

Similarly to prevention, nutrition is one of the main treatment strategies (so-called medical nutrition therapy, or MNT). DM patients are encouraged to eat a diet low in carbohydrates and pursue an active lifestyle.

Pharmacological treatment for type 1 and type 2 diabetes can involve the use of insulin (sort or long-acting), to replace or supplement endogenously produced insulin. One class of medications relies on increasing the amount of insulin released by the pancreas, the insulin secretagogues. These drugs (such as glyburide, glipizide, and repaglinide) imitate glucose in the beta cell, causing a cascade that results in the release of insulin (18).

The most common non-insulin treatment for DM is metformin, a biguanide. Metformin's mechanism is still not fully understood, but is believed to increase peripheral intake of glucose, as well as reduce hepatic and renal gluconeogenesis (18).

The thiazolidinediones (such as rosiglitazone) bypass traditional pharmacologic targets, and activate a glucose-absorbing program in peripheral tissue on the DNA itself (18). Many other treatments for DM exist, and are continually in development, but those described above are core to the management of DM in the developing world.

Screening DM patients for TB could also advanced detection and treatment (28). Screening is currently not standard practice in some settings, and finding ideal cost-effective strategy has not been studied. Screening is suggested by some guidelines (eg ATS & CDC 2000).

Epidemiology & economics in South Africa

Globally, in 2013, it was estimated that there was 382 million individuals living with diabetes, estimated to rise to 592 million by 2035, and 5.1 million diabetes-related deaths (6). More than 80% of adults with diabetes live in low and middle-income nations and is often found in younger individuals in these nations (29).

Diabetes prevalence in South Africa has been steadily rising due to increased urbanization, Western-style diets, and sedentary lifestyle (30,31). This is especially important considering South Africa's already-burdened health system and the high costs of diabetes complications and treatment, estimated to be approximately 11,400 international dollars per diabetes case per year, in similar nations (32). Prevalence of diabetes is estimated to be 8.3% in South Africa (2.7 million people), 57% of which are undiagnosed (6). Betram *et al* attempted to use multiple studies to estimate the age-adjusted prevalence within South Africa, showing that prevalence increased as patients aged (33).

Berta *et al* also estimated the incidence of diabetic to be 126 per 100,000 population across all ages, but were unable to provide estimates for neuropathy or diabetic foot. There were 83,114 estimated diabetes-related deaths in 2011. Type I diabetes is rare, with an incidence of 0.8 cases in 0-14yo per 100,000 people per year (29).

Previous modeling attempts

Since the majority of DM incurred worldwide is type 2, the majority of modeling efforts undertaken have been focused on T2DM.

Type 2 diabetes modeling is complex, and involves an understanding of demographic shifts, as well as shifts in risk factors, such as obesity, nutrition, and physical activity. Additionally, the complexity and variety of diabetic complications makes modeling more challenging. Also, due to the relative novelty of diabetes epidemics in Africa, diabetes-specific models are lacking for many African nations, including South Africa.

One oft-cited article by Huang *et al*, attempts to predict trends of DMT2 in the United States. They created a Markov-based model that accounted for the variables of diabetes status and BMI. They did not account for age, gender, or race/ethnicity. Individuals "progress" towards diabetes with a variable that was determined through calibration to estimates from the National Health Interview Survey (NHIS). Once theoretical individuals become diabetic, they can develop various complications: retinopathy, nephropathy, neuropathy, coronary heart disease, and CVAs. Each of these complications can contribute to the risk of mortality.

In 2010, Boyle *et al* continued modeling DMT2 in the US, placing non-diabetics into two states of risk, based on national estimates of glucose control and obesity. Previously, Honeycutt & Boyel *et al* completed a similar analysis, and stratified states by age (in one-year intervals from 0-99), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), and sex (male, female)– this allowed them to predict the effect of the demographic shifts occurring in the United States to an older and more ethnically diverse population. A logistic regression model was made using NHIS data to estimate the risk of diabetes for a patient based on these demographic characteristics. Changes in national demographics was accomplished through different age distributions for ethnicities and immigration data. Race, age, and sex did not contribute to diabetes-specific mortality risk. (34) This method of modeling could be very useful in a South African context, considering that some South African ethnicities (black, colored/bruinmense) are at a higher risk of developing HIV, TB, and DM compared to white South Africans (21,35).

One of the largest and most comprehensive diabetes models to date is the CORE diabetes model, created by the Center for Outcomes Research, a division of the for-profit ISM Health. The CORE model is not designed to evaluate changing prevalence or incidence within a population, but is mean as a tool to predict the clinical outcomes and costs incurred of a specific cohort of T1 or T2 diabetic patients. There is a high level of detail in modeling the specific diabetic complications, such as neuropathy or retinopathy. They used a Markov chain to specify specific essential states, but found that the "memory-less" quality of them did not allow for calculation of interaction between different complications (i.e. how does dyslipidemia affect CVD and

neuropathy?). In order to do so, since Markov states are mutually exclusive, they would need to create a new state for every *combination* of potential disease state, which is computationally intensive and difficult to manage, as previously described. To include this feature, they developed a novel method – they broke each complication into separate sub-models and incorporated a stochastic Monte Carlo method, whereby individuals progress through each model in parallel. This allowed interaction between conditions to be accounted for in a computationally feasible manner. In total, they modeled 15 complications: "angina, cataract, congestive heart failure, foot ulcer and amputation, hypoglycemia, ketoacidosis, lactic acidosis, macular edema, myocardial infarction, nephropathy, neuropathy, peripheral vascular disease, retinopathy, stroke and non-specific mortality." (36) This approach could be potentially useful to account for the specific interactions understood in our approach to HIV, TB and DM in South Africa.

Tuberculosis

Pathogenesis & pathophysiology

Overview

TB is one of the oldest diseases in human history, and may have even infected hominids, and is characterized by an infection of the lung parenchyma (pulmonary TB), which can migrate to other organs (extra-pulmonary TB) (16).

The etiologic agent of TB is a mycobacterium of the order *Actinomycetales*. The most common specific agent is *M. tuberculosis hominis*, a rod-shaped, thin bacterium, which is an obligate aerobe. The specific structure of the waxy cell wall (high concentration of long-chain fatty acids called mycolic acids) makes them particularly good at avoiding common antibiotic therapy. They are gram negative and cannot be decolorized by acid alcohol, classifying them as acid-fast bacilli (AFB). The infection of TB is unique among bacteria, as there are no endotoxins or exotoxins; all of the damage done to patients occurs through aggressive attack by the host immune system.

Infection almost always occurs through inhalation of infectious nuclei. Transmissibility of TB is modified by a variety of factors, including: the infectiousness of the individual with TB, the duration of exposure, and environment of the contact (i.e. crowded rooms). Historically, and today, poverty has been recognized as a risk factor.

After inhalation, the majority of the bacilli are captured by the upper airways and removed via ciliated mucosal cells. A small portion, make it to the alveoli where they are engulfed by inactivated alveolar macrophages. A portion of patients clear the infection at this point, before cell-mediated immunity is activated. These patients will not test positive on the skin-diagnostic ("PPD") test.

The macrophages begin a program designed to auto-phagocytize the bacilli, but TB is able to block this pathway and prevent autophagy. If completed, the bacilli begin replication, filling the macrophage until it lyses. This recruits other phagocytic cells, which engulf the bacilli and the remaining contents of the original macrophage, facilitating the spread of infection throughout the host. These recruited macrophage create the initial granuloma in TB (*tubercle*), called a *Ghon focus*. Eventually, dendritic cells become infected with bacilli, where they migrate to lymph nodes and begin the antigen presentation process. This creates granulomas in the lymph nodes, known as *Ghon complexes*.

Primary disease

Once a host has activated cell-mediated immunity (and is thus positive by PPD), they can be classified as having primary TB disease. Patients with primary disease often present with no symptoms or fever and some pleuritic chest pain, and are minimally infectious. In most instances, the disease resolves itself (leading to a latent infection) leaving only a small, telltale calcified nodule. Primary disease may progress to clinical manifestations in young children and those that are immune-compromised. The site of the lesion increases in size and can results in a

pleural effusion in two-thirds of patients. In children, may develop hilar or paratracheal lymphadenopathy.

Pathophysiologically, there are two emerging responses that begin after two to four weeks of infection: the macrophage-activating response, and the tissue-damaging response.

Macrophage-activating response concerns the activation of macrophages to kill bacilli. It is a T-cell mediated process, whereby APCs present antigen fragments to T-cells, which produce lymphokines. These lymphokines then allow macrophages to begin neutralizing the tubercle, causing necrosis. This necrosis grossly appears like soft cheese, and is thus referred to as *caseous necrosis*.

Often the macrophage-activating response is weak and not sufficient to remove all bacilli, so the immune system relies on this more intense system of destruction, called the tissue-damaging response. Through a delayed-type hypersensitivity (type IV), infected un-activated macrophages are killed, along with tissue around them. As tubercles grow, more peripheral tissue is destroyed and the necrotic caseous core liquefies. This creates cavities in the lungs, where high-concentration bacilli liquid is free to drain into the airways to be transmitted to an additional host.

Additionally, the bacilli that were transported back to regional lymph nodes are able to enter the venous system ("Occult hematogenous dissemination"), where they are able to develop lesions at other regions of the lungs or outside of the lungs (extra-pulmonary).

Latent tuberculosis infection

Most patients that undergo the process of primary TB disease will contain their infection and return to an asymptomatic state. However, there are often live bacilli contained with the granulomas of the lungs or other tissue. This condition is referred to as latent TB infection (LTBI). Contained LTBI is associated with a 79% decreased risk of reinfection (37).

Adult-type

Originally it was thought that this variant of TB was exclusively due to reactivation, whereby dormant bacilli in granulomas would escape after an immunosuppressive event, but new evidence exists which suggest that it may be mostly re-infections. Although not well understood, re-infection is associated with a more severe disease state. Regardless, this variant of TB it is often referred to as secondary or post-primary TB, or active TB as opposed to the aforementioned latent TB. Developing active TB after infection is mostly determined by immunological factors. Approximately 10% of individuals with dormant TB will develop active disease over the course of their life; approximately 50% of these diseases will develop with the first year and a half after infection (37).

In general adult-type TB consists of an area of cavitation, often near the apex of the lungs, with liquefied necrosis that spills into the airway allowing passage to other areas of the lungs. Clinical manifestations vary widely. Some patients present with massive cavitation and pneumonia, some enter a chronic state, others spontaneously heal. Early symptoms include night sweats from spiking fever, weight loss, anorexia, and weakness. Cough develops in 90% of patients,

sometimes leading to a productive cough with blood. Most will respond to treatment within a few weeks.

Having active disease is associated with a three to four-fold risk of progressing to active disease upon reinfection (38,39).

Extrapulmonary TB

Once TB has access to the systemic circulation, it is able to disseminate itself to various organs of the host. It is more common in HIV-associated TB (40,41). Common sites of colonization include: lymph nodes, pleura, upper airways, genitourinary system, skeletal system (including the vertebrae – so-called Pott's disease), the CNS, and gastrointestinal system, among others.

Miliary TB

A specific type of extrapulmonary TB is characterized by widespread infection into many organs and small (1-5mm) granulomas. It occurs in less than 2% of TB cases, but accounts of up to 20% of extrapulmonary cases (42).

Drug resistance

Particular concerning is the continued development of resistant strains by tuberculosis bacilli. Two commonly-used medications, isoniazid and rifampicin have lost effectiveness against strains of bacilli, referred to as isoniazid-resistant TB (IR-TB) and rifampicin-resistant TB (RR-TB). Strains that have developed resistance to both of these medications are referred to as multi-drugs resistant TB (MDR-TB), and if resistant to an additional second-line therapy referred to as extensively drug-resistant TB (XDR-TB) (1).

Transmission

Transmissibility has been noted to be high in patients whose sputum contains AFB visible by microscopy. Patients with extrapulmonary disease without concomitant pulmonary TB have much lower rates of transmissibility, as pulmonary TB is needed to produced aerosolized disease. The highest category of infectious patients are those with cavitary pulmonary TB and laryngeal TB, whose sputum contain 10^5-10^7 AFB/mL. Smear-negative/culture-positive TB patients have lower risk of transmission.

Screening, prevention, and treatment of TB

Prevention

Bacille-Calmette-Guerin (BCG) vaccine contains live organisms, and confers an approximately 50% prevention against TB (43). Obviously, prevention can also entail reducing indoor contact between infected and susceptible individuals.

Screening

For latent TB, purified protein derivative (PPD) is used to test for exposure. A small sample of tuberculin protein is inserted into the epidermis, and will trigger a type IV hypersensitivity reaction if an individual has been previously exposed. There are different grades for different risk levels. This test confirms exposure, not active disease (16). Screening for latent TB is appropriate depending on risk group, and is completed with PPD and/or interferon-gamma release assay (44).

For active TB, sputum microscopy and drug-susceptibility testing are standardly used to diagnose active TB, as well as Interferon-gamma release assays. Additionally, histopathological inspection of a biopsy, radiography, and PCR methods can be used to assist in diagnosis. Xpert MTB/RIF is a new diagnostic tool that utilizes DNA amplification techniques to test for the presence of *M. tuberculosis*, as well as drug resistance to rifampicin.

Treatment

Latent infections are treated with isoniazid for 9 months. Patients with HIV in nations with high TB prevalence may be treated for longer. Prophylactic treatment is 6-9 months of isoniazid, which can prevent TB in persons with infection but no clinical symptoms.

Active disease is treated differently. Standard treatment for uncomplicated pulmonary TB generally includes a combination therapy of isoniazid, rifampin, and pyrazinamide for two months, followed by four months of isoniazid and rifampin. For areas where MDR-TB is more common (>4%), ethambutol or streptomycin can be added.

Epidemiology & economics in South Africa

The WHO estimated that were 9.4 million (8.9–9.9 million) new cases of TB in 2009, 95% in developing nations. Additionally, the WHO estimated there were 1.7 million deaths (1.5–1.9 million) due to TB, 96% of which are from developing nations (16). Overall, TB incidence has been falling at less than 1% per year since 2004 (45).

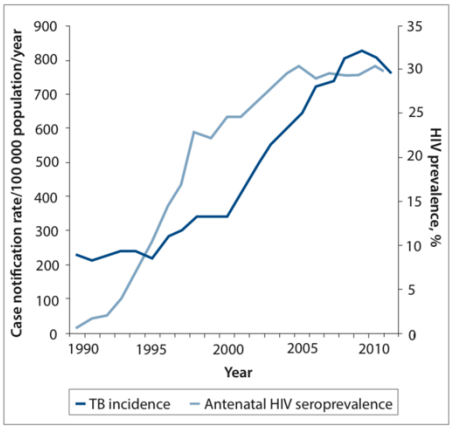


Fig. 1. Trends in tuberculosis case notification rates and HIV prevalence in South Africa.

In South Africa, it is estimated that there are 500,000 active TB cases per year, representing 1% of the general population. This number has increased five-fold from 1990 to 2011, and continues to rise, according to the WHO (46). Currently, SA has the highest number of incident TB cases per capita and highest TB prevalence of all 22 nations with high TB burdens (45). This continual rise can be largely attributed to the high burden of HIV/AIDS, a large risk factor for TB in SA (47). Indeed, SA has the highest number of HIV-associated cases of TB worldwide, and the second-highest number of diagnosed MDR-TB cases (45).

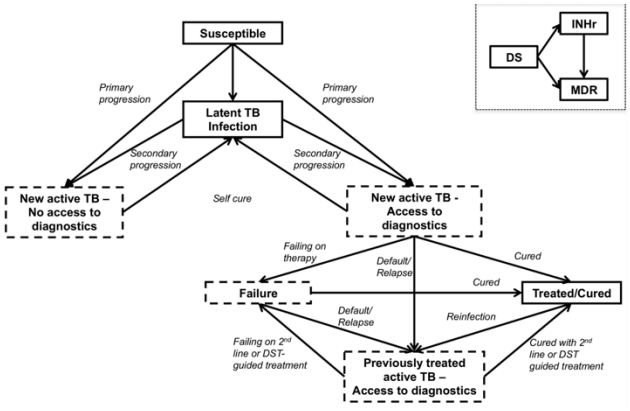
Beyond being driven by the HIV/AIDS epidemic, economic and social conditions in SA, largely created by years of apartheid, have predisposed many individuals to TB (21). Additionally, the large workforce in extractive industries such as mining have exposed many workers to risk factors, such as overcrowding, air pollution, and poor nutition (21). However, in 1996, two years after the formation of the current South African government, the National TB Control Program was created, utilizing a directly-observed therapy (DOTS) approach. In 2011, SA developed the integrated Nation Strategic Plan for HIV, STIs, and TB (2012-2016), which aims to halve TB incidence and mortality by 2016, as well as reduce the number of incident TB cases and deaths to zero by 2032 (48).

Previous TB and HIV modeling attempts

Although attempts to model more than two diseases are sparse, HIV and TB have been modeled together extensively, as it is difficult to model TB alone in a setting of high HIV prevalence. A review by Houben *et al* identified 69 different manuscripts published before September 2012 which describe attempts to model TB epidemics (49). They argue that TB models so far have contributed to scientific understanding in four general areas: the natural history of TB in a high HIV prevalence setting, antiretroviral therapy and isoniazid preventive therapy, impact of additional interventions for TB-HIV, and implementations of interventions for TB. These models have used a variety of methodologies, as reviewed by Houben. Methodologies utilized included: population-based compartmental models with a dynamic transmission consideration, population-based models without the dynamic transmission component, cost-effectiveness decision tree models, Markov chain simulations, and compartmental models that evaluate intra-host disease dynamics. Some investigations have mixed methods, such as decision trees and Markov chains.

Regardless of the exact model type, most of the past models have developed compartments to represent the various states of disease, pathogenesis, and transmission. In order to better understand these commonly-used methods for TB, we will review a series of investigations.

In 2014, Denkinger and colleagues created a compartmental model with a dynamic transmissibility to evaluate the usefulness in detection of isoniazid-resistant strains of TB (50). The model evaluated 100,000 individuals distributed into a total of 20 states. One state represented uninfected susceptible individuals, one represented all-cause mortality, and there were 6 states representing disease: latent TB infection, new active TB – No access to diagnostics, new active TB – access to diagnostics, failure, treated/cured, and previously treated active TB – no access to diagnostics. These six disease states were then tripled, representing three drug sensitivity types: sensitive, isoniazid-resistant, and MDR. When susceptible individuals are infected, they were moved to a latent of active TB state. Latent states incorporated the risk of re-activation to active TB. The risk of becoming infected was based on the number of infectious individuals and the infectivity of their strain. Individuals were then moved into a "diagnosed" state at a rate of diagnostic events. Once in active disease, individuals were categorized into three clinical categories: cured/recovered, active, and failed. If an individual is re-infected, they move to a state of active TB that was previously treated. All states had a baseline mortality, and active TB states included a TB mortality. HIV or DM status was not evaluated.



In 2014, Pretorius *et al* used three different epidemiological models to predict the effects of HIV treatment policies on tuberculosis in South Africa: (1) the Menzies model, a specific and detailed HIV-TB model (51) (2) the PopART model, a individual-based model which includes a patient history of infections and (3) the Goals model, which used another model (Spectrum) to produce HIV estimates, and used these estimates to form a regression model. For HIV, all of the models defined a CD4 count for individuals; the Menzies uses a continuous variable, while the other two used categories.

Modeling of TB varied between the two models (Menzies and PopART) with detailed modeling. In the Menzies, there were eight states of TB: susceptible, latent/recovered, Active smear-positive untreated, Active smear-negative untreated, Active smear-positive DOTS, Active smear-negative DOTS, Active smear-positive non-DOTS treatment, Active smear-negative non-DOTS treatment. Subdivisions were created for the different resistance: (1) sensitive (2) isoniazid

resistant (INH) (3) rifampicin resistant (RIF), (4) isoniazid and rifampicin resistant (MDR), and (5) resistance to isoniazid and rifampicin plus one other drug (XDR). These subcategories, combined with HIV statuses, produced a total of 580 potential states. The PopART model simplified the TB modeling by excluding drug resistance, and having only one level of treatment. Therefore only susceptible, latent, active smear negative treated and active smear positive untreated were modeled. In both of the models, transition to active was possible through primary progressive disease, re-activation of latent disease, or re-infection. Recovery was possible through self-cure or treatment. Diagnostics were handled wither through a detailed algorithm (Menzies) or a simplified case-detection variable (PopART and Goals). Treatment was approximately DOTS in all three models, and non-DOTS in one (Menzies). Collectively, risk factors for TB included infection history, treatment history, HIV status, CD4 count, and ART status.

INTERACTIONS

HIV-related and ARV-related diabetes

The incidence of onset diabetes in HIV patients has been contested. Many of the large, multi-center trials (mostly in European, or European-descendant populations) earlier in the epidemic pointed to an increasing likelihood of becoming diabetic with comorbid HIV infection. For example, the Multicenter AIDS Cohort Study found a more than 4-fold increases in DM incidence in HIV patients. However, other studies have found no association, (52,53) or even a reduction in risk (54).

In a 2014 article, Nix and Tien argue that much of this heterogeneity can be attributed to the metabolic toxicity of older-generation protease inhibitors and thymidine analogs. These older drugs have a well-documented effect on insulin resistance, and are rarely used in ART today. They also suggest that some of the older findings from large-cohort studies would not be valid using a newer definition of diabetes (55).

Additionally, a systematic review of HIV metabolic issues in sub-Saharan Africa found no association between HIV and DM (56). They attributed this to either differences in sub-Saharan population from those studied in the large multi-center cohorts, or from small study size in African studies.

Regardless of the direct effect of ART on DM incidence, ART promotes an extended lifespan – putting individuals at risk of developing diabetes. One modeling exercise in South Africa, by Levitt and Bradshaw, looked at this relationship (57).

HIV- and ART-related vascular disease

HIV is associated with a large shift in immunological function. One of the emerging discoveries is the amount of inflammation patients with HIV experience. This so-called HIV-associated inflammation has been observed in association with metabolic derangements, such as metabolic syndrome, lipodystrophy, and atherosclerosis.

Metabolic syndrome has been of particular interest. Unfortunately, the evidence is unclear whether HIV is associated with metabolic syndrome – many studies, particularly in Latin America or those with patients on the older generation of ART, suggest a strong association. Other large cohort studies have shown a decreased incidence, according to Nix and Tien (55).

Regardless of the relationship with metabolic syndrome, it does appear that HIV is associated with an increased risk of cardiovascular disease and stroke, likely through poorly-understood inflammatory pathways. One prospective study of 23,468 patients with HIV infection found a 26% increase in risk of myocardial infarction for each year of exposure to ART (58). A 2012 meta-analysis found a relative risk of 1.61 for CVD in HIV-infected, untreated individuals compared to HIV-negative individuals, and a 2-fold increase risk of CVD for HIV-infected,

treated individuals compared to HIV-negative indivudals (59). Though there have been some criticism of this study not taking into account potential confounders and inadequate controls (60). A 2013 meta-analysis of African HIV-related CVD predictors found an elevated level of CVD risk factors compared to the uninfected population, but did not provide relative risk estimates for specific health outcomes or events (56).

TB in HIV patients

Low CD4 counts have been associated with a higher susceptibility to TB. In a 1997 study in South African miners, HIV prevalence was associated with a 2.9 increased relative-risk (2.5–3.4) of TB seroconversion for untreated individuals in their first year of infection, and an RR of 2.0 (1.4–3.1) afterward. A study in Mwanza, Tanzania found a 8.3 RR (6.4-11.0) (61).

Similarly to HIV-negative individuals, HIV-positive patients are more likely to have symptoms of pulmonary tuberculosis that extra-pulmonary TB. They present with similar signs and symptoms, but have more severe disease as their CD4 count decreases. One notable exception is the cavitations formed by the tissue-damaging response; in patients with extremely low CD4 counts, cavitations are more rare (because there is no immune function able to destroy the lung tissue via the tissue-damaging response).

That being said, extra-pulmonary TB is much more common in HIV-infected individuals. A 2013 meta-analysis found an RR of 1.3 (1.05-1.6) (62). This extra-pulmonary TB is more likely to be concomitant pulmonary TB as well (63).

HIV is associated with a more severe TB progression (64–66). Additionally, HIV has been shown to cause and increased likelihood of death due to TB (46,67,68). A twelve-year study in San Francisco found a 2-fold difference in TB mortality between HIV-positive and HIV-negative groups. A 1995 study in Côte d'Ivoire found an increasing risk of TB mortality associated with declining CD4 counts, resulting in risks of death 12-28 times higher than HIV-negative populations (69). This association goes both ways – HIV-positive individuals infected with TB are at a higher risk of death than HIV-positive individuals with no TB. A 2010 meta-analysis found a RR of 1.8 (1.4-2.3) (70). though there were noted methodological concerns with the meta-analysis (71).

People living with HIV are also at a higher risk of recurrence, either through re-activation or re-infection (72). However, there is evidence that people living with HIV are no more intrinsically infectious than those without HIV (73).

ARVs in HIV + TB patients

A 2012 meta-analysis suggested that ARVs were effective in reducing the rate at which patients progressed to active TB disease. Suthar *et al* found a reduction in TB incidence of 16% (7-36%) in individuals with CD4 counts below 200 cells/ml, 34% (19-60%) for between 200 to 350 cells/ml, and 43% (30-63%) for those with greater than 350 cells/ml (74). Modelers, particularly Williams BG, have used this data to predict that ART would have positive effects on reducing overall TB incidence (75,76). However, model estimates have varied widely – from predicting a

98% reduction in HIV-associated TB, to relatively minor impacts in other models (77–79). One key parameter is the acute phase of infection, where HIV infectiousness is highest although relatively few individuals will be on treatment.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) is a condition whereby a patient with immunosuppression, such as an individual with HIV/AIDS, is unable to fight off a opportunistic infection (commonly *Cryptococcus neoformans* or *M. tuberculosis*). Without immune system, there are no symptoms. When individuals are started on ARVs, however, their infections become symptomatic.

A 2010 meta-analysis found that 16.7% (2.3-50.7) of individuals with TB starting ART experienced IRIS, and 3.2% (0.7-9.2%) died from the condition. They additionally found a relationship between CD4-count and IRIS; individuals with lower CD4 counts upon ART initiation were more at risk of developing IRIS (80).

In this way, ART may decrease overall TB transmission or risk of acquisition, but may accelerate active TB disease. Other related condition names include *unmasking tuberculosis-associated IRIS*, *ART-associated tuberculosis*, and *tuberculosis-associated IRIS*.

DM-related tuberculosis

Increased susceptibility

Much of the DM epidemic is happening in quickly-developing countries, where TB is endemic. A 2010 systematic review of 18 studies on screening for DM in patients with TB found a 1.9% to 35% prevalence of DM in patients with TB (81).

A 2008 meta-analysis found a 3-fold increase in TB cases in DM patients (RR = 3.11, 95% CI 2.27–4.26) compare to non-diabetic individuals (2). They also found that the RR increased in nations with higher TB incidence and young people were particularly at risk. It has been well-established that HIV/AIDS constitutes a large risk at an individual level, but the emerging DM epidemic may be more of a risk-factor than HIV at a population level (2).

In HIV-infected individuals, it is unclear whether having comorbid DM increases the chance of TB. In one study of Asian men on ART, blood glucose was associated with risk of TB (82). However, one study in Tanzania found no additional risk of TB from co-morbid DM (83). Only one other study has evaluated individuals with the "triple burden" of HIV, TB and DM (84).

There are various potential physiological explanations for increased susceptibility. There are a few specific phagocytic cells that are responsible for controlling our response to TB, mainly alveolar macrophages. Diabetes is known to affect chemotaxis, macrophage activation, phagocytosis, and antigen presentation in these cells (85). Another potential explanation

concerns diabetic derangement of interferon-gamma production in T-cells, which is a cytokine essential to cell-mediated immunity (85,86).

Other studies have indicated that glucose control is one of the important predictors of TB susceptibility.

New diagnosis

Type 2 DM is commonly not diagnosed in patients with TB. A study Indonesia found diabetes is newly-diagnosed in 61% of TB patients (87).

Primary vs reactivated

Some have hypothesized that there is a unique presentation of TB associated with diabetes – such as an association with primary or reactivation TB. However, a study in Mexico by Ponce-de-Leon *et al* in 2004 suggests that this association cannot be found (88).

Sputum-smear

There is conflicting evidence that DM is associated with smear-positive or smear-negative tuberculosis (89).

Radiologic findings

Studies about radiological findings of tuberculosis in diabetes patients have found conflicting results (89).

Extra-pulmonary TB

Extra-pulmonary TB is less common in DM patients than in those without DM (89). This was confirmed by two studies in India, which showed that DM increased risk of pulmonary TB but not extra-pulmonary TB, in contrast with HIV where extra-pulmonary effects are more common (84, 90).

Body weight and age

Overall, TB patients with DM are more likely to be older, obese, have a sedentary lifestyle, and a previous family history of diabetes, all of which are related to DM (91).

Culture conversion

There is conflicting evidence about the impact of DM on time of TB culture conversion (89). Overall, evidence suggests that sputum conversion takes a modestly longer time but is similar to non-diabetics by 2-3 months of treatment (85).

TB bacterial treatment outcomes

There is conflicting evidence about the impact of DM on TB treatment outcomes from a bacteriology standpoint (89).

TB treatment failure and death

Evidence points to an increased risk of treatment failure and mortality among TB patients with diabetes, but it is unclear whether this is due to a more aggressive DM-related tuberculosis or comorbidities related to diabetes alone (85). A 2011 meta-analysis found a RR of 1.69 (1.36 – 2.12) for the combined outcome of treatment failure or death, and an RR of 3.89 (2.43-6.23) for relapse (3). Potential reasons for higher death include: adherence issues, higher MDR-TB, and lower plasma concentration of TB drugs.

MDR TB

There is conflicting evidence that DM is associated more with MDR-TB (89).

Pre-diabetes and TB

There is evidence that pre-diabetes is also associated with TB. One study in India found that 24.5% of TB patients had prediabetes by the WHO criteria – but it is unclear whether TB was a cause or an effect of prediabetes in these patients (90).

Severity of DM linked to TB

Screening patients with TB for DM could improve detection and improve the timeliness of treatment, and may play a role in preventing DM (28). Screening is currently not standard practice in some settings, and finding ideal cost-effective strategy has not been studied. In a 2010 systematic review of twelve studies on screening for TB in people with DM, researchers found a 1.7% to 36% prevalence of TB in DM patients (81). Prophylactic TB medication for patients with DM was reported in two studies cited in the 2010 systematic review; unfortunately neither study was methodologically rigorous enough to warrant a recommendation for prophylaxis.

Other concerns

One additional interaction between the three diseases is a concern about sepsis, which is a potential complication of HIV and DM. Unfortunately, the evidence seems inconclusive (92).

HIV replication is increased by tuberculosis infections, resulting in an increased mortality. TB patients are therefore placed on ARV medication earlier than TB-negative HIV patients (44). Tuberculosis infection leads to higher HIV-related deaths, as noted above.

TB effects on DM

Tuberculosis can cause transient hyperglycemia, potentially increasing the risk of acute diabetic complications (93).

TB medication effects on DM

Tuberculosis and tuberculosis drugs disrupt glycemic control (89).

Rifampicin

Rifampicin, a common bactericidal antibiotic used to treat TB, interacts with many of the anti-diabetic medications through P450-related inhibitions and inductions, such as the sulfonylureas, glinides, and thiazolidinediones (89).

Other first-line TB dugs

Other first-line medication is unlikely to interact (89).

Other potential interacting drugs

There is no evidence that insulin or metformin interact with Rifampicin, and might be good choices for less-developed settings.

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Part II: Prospects for Elimination: An Individual-based Model to Assess TB Control Strategies in California

INTRODUCTION

Tuberculosis (TB) remains an imminent threat to global public health, killing 1.2 million individuals in 2014 (1). The World Health Organization's post-2015 global TB strategy aims to reduce the number of deaths due to TB by 95% and the incidence of TB by 90% by 2035 as compared to 2015 (2).

Although the majority of TB cases occur in high-burden nations, global goals may be compromised by a plateau in TB prevention and treatment in low-burden nations. Therefore, the WHO has published a framework to guide TB control in low-incidence nations. The framework outlines two ambitious goals. Firstly, they mandate that *pre-elimination* (less than 10 cases per million) should be met in low-incidence nations by 2035. Secondly, *elimination* (less than 1 case per million) should be reached by 2050 (2).

In the low-incidence nation of the United States, the State of California has the largest share of TB cases, comprising 23% of the US TB burden in 2014 (3). In 2014, there were 2,147 cases of active TB, or a rate of 55 annual cases per million population (4). California has a unique TB epidemiology. Of the 2,147 cases in 2014, 1,667 (78%) occurred in foreign-born (FB) as opposed to the US-born (USB) individuals. Immigrants from Mexico (446 cases), the Philippines (354), Vietnam (205), China (145), and India (96) comprised 58% of all cases. High-risk groups include the undocumented (396) and the unhoused (102) (4). Of all cases, 7.5% occurred within one year of immigration and presumably represent imported active cases. Seventeen percent are estimated to be recent infections that were transmitted within California (5). The remaining 75.5% are thought to be from reactivation of latent TB infection (LTBI).

Given that most cases were due to LTBI reactivation, the epidemiology of TB in California is highly sensitive to medical risk factors for progression from LTBI to active disease, including cigarette smoking, diabetes, HIV, uw3 or tumor necrosis factor (TNF)-alpha inhibitor or post-transplant immunosuppressive drugs, and end-stage renal disease (ESRD). Individuals with any of these medical risk factors accounted for 1,031 cases in 2014 (4).

In light of goals proposed by the WHO, the California Department of Public Health (CDPH) has set a goal of TB pre-elimination by 2035 and elimination by 2050. Between 2001 and 2014, there was a decline in the cases of TB by 44% and 33% in the US- and foreign-born, respectively. Although this represents a 3.1% overall decline per year (4% in USB and 2.8% in FB), it is insufficient to achieve elimination by 2050 (5).

Past models of TB in the US suggest that preventive therapy (treating those with LTBI) can play a crucial role in reducing active disease (6). However, given the heterogeneity of TB risk in California, and the cost of LTBI programs, testing and treating every individual in California is impractical. Targeted testing and treatment of LTBI (TTT) in particular at-risk groups offers a more cost-effective option (7). Yet no study to date has assessed the impact, costs, and cost-effectiveness of different TTT strategies in California, including which test choice, treatment choice, or the different at-risk groups to target. In addition, the effect that TTT strategies would have on the prospects of elimination is unknown. Thus, in this paper, we evaluate the costs,

impact, and cost-effectiveness of scaling-up TTT in California and assess the likelihood that these strategies would reach elimination targets.

METHODS

Overview

Our investigation contained three major steps, in which we determined: (1) the most cost-effective combination of specific technical options for testing and treating LTBI, (2) the most cost-effective at-risk groups to target, and (3) the likelihood of elimination by scaling-up the use of TTT in these subpopulations.

Testing and treatment options

We assessed three testing options and four treatment options, for a total of 12 testing/treatment combinations. Testing options included: tuberculin skin test (TST) and the two CDC-approved interferon-gamma release assays (IGRA), QuantiFERON-TB Gold (QFT) and TSPOT-TB. LTBI treatment options included: nine months of isoniazid (9H), six months of isoniazid (6H), four months of rifampin (4R), and three months of isoniazid and rifapentine (3HP).

Costs, sensitivity, and specificity of the tests were estimated from empirical data (Table 1, Table 2). TST and QFT/TSPOT sensitivity was estimated to be 0.83 (0.71-0.87) and 0.85 (0.7-0.97), respectively, for both US-born and foreign-born. Specificity of QFT was estimated at 0.99 0.98 1.00 in both the US-born and foreign-born. Specificity of TST was estimated at 0.95 (0.82-0.99) in the US-born and 0.82 (0.47-0.9) in the foreign-born, respectively. This lower TST specificity in the FB population due to the Bacillus Calmette–Guérin (BCG) vaccine, and that the immunosuppressive effects of HIV and ESRD had a negative impact on both TST and IGRA test performance. We used the ERSD test performance for individuals with both HIV and ESRD. We assumed no effect on test performance for the other medical risk factors modeled. Testing costs included the test reagents and labor. LTBI treatment costs included drugs, physician fees, and a diagnostic x-ray, for a total cost of $38.91 and $65.53 for TST and QFT/TSPOT, respectively. Scales of economy were not considered.

Model development

We developed an individual-based, discrete-time model of 300,000 individuals, representing the population and demographics of California. We modeled only those 15 years of age or older, which comprise more than 90% of TB cases in California (4). A one-month time step was utilized, and simulations were run from 2001 to 2085. The model was implemented as a stochastic locally-interacting Markov chain structure, with TB and each medical and demographic factor represented with a separate chain. Each individual progresses through chains in parallel. State transitions are based on specified probabilities, with a stochastic determination at each cycle (random walk). The chains interact as suggested by empirical data, similarly to the CORE diabetes model (8). One chain accounts for LTBI acquisition within the last three years (recent), and thus heightened risk of progression to active disease. An additional chain accounted for natural deaths not due to TB or the medical risk factors, using life expectancies from the 2011 US Social Security Actuarial Life Tables (9). Costs were assessed from a societal perspective in 2014 dollars.

Demographic information was obtained for the State of California for 2001-2014 from the American Community Survey via the IPUMS database (10). Relevant variables included: sex,

race/ethnicity, age, years in the US, citizenship status, and birthplace. Ethnicities included Asian, Black/African-American, Hispanic, non-Hispanic white, and other. Age was grouped by 5-year intervals starting at 15 and capped at 80 or older. Birthplace information was consolidated to include only the United States, Mexico, Central America, and the WHO 22 high burden countries in 2014 (11). The remaining birthplaces were grouped by their WHO region.

At the beginning of the simulation, a random sample of 300,000 individuals was selected from the 2001 demographics dataset. For each subsequent time step, the cohort was updated with a sample of individuals representing those maturing into age range and those immigrating to California. For each year from 2001-2014, these incoming individuals were sampled from their respective ACS sample. For each year after 2014, we sampled from the 2014 dataset. We assumed no change in the birthrate or immigration rate from 2014 forward.

Medical risk factors

We assessed six medical risk factors for progression from LTBI to active disease: cigarette smoking, diabetes, HIV, TNF-alpha inhibitor use, post-transplant immunosuppressive drugs, and ESRD. We estimated the prevalence of each risk factor in California using California-specific data if possible, and national-level estimates otherwise (Table 3). No data source was available for TNF-alpha use, so we estimated its use from the prevalence of the use of these drugs in rheumatoid arthritis and IBD (Table 3). Since we used an individual-based simulation, individuals could have more than one risk factor. Thus, prevalence of each medical risk factor was stratified by sex, age, race/ethnicity and nativity where available. To estimate the relative risk (RR) of progression to active disease, we conducted a literature review and arrived at expert consensus among team members as to which estimates were most suitable for the at-risk Californian population (Table 3). Each medical risk factor's independent risk of mortality was incorporated as a standardized mortality ratio, which yielded a life expectancy once the conditions were distributed within the population (Table 3).

LTBI prevalence

To estimate LTBI prevalence, we derived estimates of LTBI prevalence stratified by sex, age, race/ethnicity, and nativity (FB and USB) from the 2011-2012 NHANES TST results, using 10 mm of induration as our preliminary indicator of TST positivity (see below). The 1999-2000 data set, although a more appropriate timeframe, was not used because this survey lacked appropriate Hispanic and Asian designations; additionally, there have been no significant differences noted in the older and more recent survey results (12). TST positivity was adjusted to estimate true LTBI prevalence with a method described previously (13). To estimate differences in LTBI prevalence by foreign birthplaces, we adjusted using LTBI prevalence estimates in the country of origin or WHO region (14) while holding nativity- and race-specific estimates constant (Table 4). LTBI prevalence in FB was assumed to decline by 1.9% annually as an approximation of global TB control efforts (15). Approximately 25% of LTBI from USB and FB was assumed to be from recent transmission (5).

TB chain structure

Individuals were placed into a state in the chain based on the presence of LTBI, treatment, or active disease. Risk of progression from LTBI to active disease was set at a static base level, and was increased by the presence of a recent infection (Table 1) or medical risk factor (Table 3). We assumed no decline in LTBI progression rate apart from the drop-off after the initial three years. Relative risks for progression were assumed to be multiplicative.

The cost of case-finding was not included. Treatment costs, efficacy, and dropout-rates were estimated from available data (Table 1). We assumed that individuals completing treatment achieved lifetime protection, were not susceptible to reinfection, and would not undergo future testing or treatment; those dropping out before treatment completion garnered no benefit. Dropout rates were assumed to be constant throughout treatment. We assumed that 1.5% of individuals found to have LTBI had completed prior treatment, as suggested by the most recent NHANES (12). We assumed the treatment was daily self-administered isoniazid 300 mg for 9 months (9H). The effects of multidrug-resistant TB were not incorporated, since rare in the U.S. Costs were discounted 3% (1-5%) per year as suggested by the U.S. Panel on Cost-effectiveness in Health and Medicine (16).

Transmission of TB infection was captured using a semi-random mixing model. Each case of active TB was assumed to propagate additional cases of LTBI, with 80% of that risk accounted for within an individual's race/ethnicity and birthplace group, and 20% within the general population (Table 1). This is consistent with evidence that recent transmission occurs more commonly within race/ethnic minority and immigrant populations within California (17). We included active case finding, assuming that each active case investigation identified 2.5 infections, 75% of which were recent transmissions (5).

Interventions and Cost-Effectiveness

We created a base-case scenario that represents current testing and treatment, with 4.5% of individuals tested annually, as supported by internal California (5) and national data (18). We assumed 50% of those tested were with QFT and 50% with TST and that individuals electing treatment would undergo therapy with 9H.

We assessed potential strategies for TB elimination by increasing the rate of testing in specific populations by 2-fold, 4-fold, and 10-fold. The populations are: (1) FB Californians, (2) Californians with medical risk factors, (3) FB Californians with medical risk factors and (4) all Californians.

We evaluated the cost-effectiveness of interventions with two methods. First, with the goal of TB elimination, we evaluated the cost per TB case averted. Secondly, with the goal of maximizing overall health utility, we used a traditional cost-utility analysis framework and evaluated the cost per added quality-adjusted life-year (QALY), using standard methods described elsewhere (19).

Health State Utilities

QALYs lost per active case of TB was estimated at 1.4 QALYs from a cohort analysis of cases in Texas (20). Acute and chronic morbidity accounted for 0.046 and 0.96 QALYs, respectively,

while mortality accounted for 0.22 QALYs (20). Utilities were discounted 3% (1-5%) per year as suggested by the US Preventive Health Task Force (16).

Calibration

To calibrate the model, we employed a step-wise, non-algorithmic approach. We first adjusted the death rate to match known populations from the ACS from 2001-2014. Secondly, we calibrated the risk factors to match known trends in their prevalence from 2001 to 2014 by adjusting the initial prevalence and/or incidence. We calibrated HIV prevalence from 2008 to 2012 from CDC data (21). Diabetes and smoking prevalence were derived from CDC's Behavioral Risk Factor Surveillance System from 2001 to 2014 (22). ESRD prevalence in the years 2001-2014 was estimated from the United States Renal Data System (23). Estimates for the California prevalence of transplant recipients or TNF-alpha inhibitor users was not available, so we calibrated them to remain constant as a proportion of the population using incidences gathered from the literature (Table 2). TNF-alpha usage was calibrated to fall within the 95% confidence interval of TNF-alpha usage in four waves of NHANES data reported by Yeats *et al.* (24).

Lastly, we matched our estimates of active TB cases from 2001-2014 with reported cases, assuming a 100% case detection rate. We obtained data from the CDPH Report of Verified Case of Tuberculosis (RVCT) database from 2001 to 2014, stratified by sex, nativity, race/ethnicity, and medical risk factors. To calibrate, we first adjusted the respective relative risks of reactivation associated with each risk factor to match the reported number of cases in those with a medical risk factor (Table 2). As noted elsewhere, there is a significant amount of unexplained heterogeneity in risks of reactivation amongst race and nativity groups, presumably due to unmeasured risk factors (25). To account for this difference, we assigned race- and nativity-specific risks of reactivation. US-born Asians, Blacks, Hispanics, Whites, and individuals of other ethnicities required a 1.2, 2.2, 1.5, 2.0 and 0.5 relative increase in risk of progression rates, respectively. FB Asians, Blacks, Hispanics, Whites, and individuals of other ethnicities required a 1.48, 1.5, 0.83, 0.5, and 2.0 relative adjustment.

The number of active cases reported in FB diabetics was 1.6-fold higher in historical data than estimated by our model (26). We thus included a FB diabetes-specific reactivation rate to account for this difference. After matching the 2001 cases by risk group, nativity, and ethnicity, our results did not align with the historical decline in the following 15 years. Only after a reduction of the transmission coefficient by 33% did the results fit the historical trend. The resulting predictions aligned well with historical data (Figure 1).

Sensitivity analysis

Sensitivity analyses were used to account for uncertainty in results. One-way sensitivity analysis was conducted to isolate highest impact inputs while probabilistic sensitivity analysis (PSA) was used to determine uncertainty and range for outputs. A triangular distribution was utilized for all PSA parameters.

Technical specifications

The model was encoded using Python (Python Software Foundation, Beaverton, OR) and Go (Google Inc, Mountain View, CA). Go is a fast, compiled, statically-typed language designed for concurrency, and has been used previously in computational biology (27). To our knowledge, this is the first published use of Go in public health research. The model's source code is available online (28) and is entirely reproducible using a Virtual Machine (29), in accordance with the best practices of reproducible informatics research (30).

RESULTS

Cost-effectiveness of TTT interventions

Of the 12 testing and treatment options assessed for LTBI, the combination of QFT testing with three months of once-weekly rifapentine plus isoniazid (3HP) treatment was most cost-effective in both the USB and the FB (Figure 2, Table 4). It was estimated to cost $17,000 per QALY and $24,000 per active case averted in FB, and $110,000 per QALY and $152,000 per active case averted in USB. TST with 9H was found to be the least cost-effective approach for both USB and FB populations, with a cost-per-QALY over $50,000 in FB and USB. TST performed poorly largely because of its low specificity in the FB population: 0.82 compared to QFT's 0.99. This means that significant costs were incurred treating false-positive individuals.

The cost per case averted varied based on the target risk group (Figure 3). The groups with the most favorable cost-effectiveness measures were foreign-born individuals from India, identifying as Black or Asian, smokers, and those who have recently arrived. The least favorable group to target was USB with ESRD, where averting one case of active TB cost $350,000. These results are a function of LTBI prevalence, risk of progression, test performance, and life expectancy. Groups with lower life expectancies (such as those with ESRD) and those conditions which negatively effect test performance (HIV and ESRD) suffered a loss in cost-effectiveness.

To illustrate this, the model predicts that in 1000 randomly-selected Asian foreign-born individuals, there would be 238 individuals with LTBI; 10 of whom would develop active disease within their lifetime. If they were all screened, a QFT would identify 172 of those individuals for a cost of $67,000. Offered 3HP, 117 LTBI-positive individuals and 4 false-positives would complete therapy, costing $133,000. This would reduce the risk of reactivation in those treated by 92%, averting 5.3 cases of active TB on average. Averting these cases would save $167,887 in active TB treatment costs, and would gain 7.2 QALYs, with an ICER of $6,030 per QALY gained. Conversely, in the white USB, in 1000 individuals, we would expect 14 individuals with LTBI. Screening with QFT would identify 11 of those individuals for $67,000; 9 LTBI-positive people would complete treatment, as well as 4 false-positives for a cost of $11,000. Without LTBI therapy, less than one individual (0.4) would have an active case of TB. Preventive therapy would halve that risk, gaining 0.3 QALYs with an ICER of $433,088.

Sensitivity analysis

Using the ranges specified in table 1, the cost-effectiveness of TTT with the QFT 3HP combination was most sensitive to the risk of progression to active disease, according to the one-way sensitivity analysis (Fig 3). A base-case risk of progression of 6.09 per 100,000 person-years was used; if the risk of progression is assumed to be 3.0 or 9.1 per 100,000 person-years, the cost per case averted becomes $11,000 or $94,700, respectively.

Elimination

The results of the elimination model suggested that scaling-up testing and treatment rates averts significant number of infections by targeting FB and those with medical risk factors (Figure 4). However, elimination was not met by 2050 even with 10-fold increases in testing and treating in the overall population. Increasing the rate of testing for the entire state of California lead to a total of 64 cases per year in 2050, whereas elimination would be classified as under 59 cases per year. Sensitivity analysis was not completed for the elimination projections.

DISCUSSION

Tuberculosis remains a significant challenge for California health policy makers. In order to determine the likelihood of reaching elimination, we built a comprehensive transmission model that assessed the cost-effectiveness of varied testing, treatment, and subpopulation options. We found that targeting foreign-born individuals and certain US-born individuals with medical risk factors for LTBI screening with QFT and 3HP is cost-effective below the threshold of $50,000 per QALY, but that reaching TB elimination by 2050 would only occur with an unprecedented scale-up of testing and treatment services within the general population.

Calibrating the model revealed that there is significant heterogeneity in the risk of progression to active disease among race and nativity groups in California. This is consistent with past evidence. Shea *et al.*, comparing 1999/2000 NHANES TST data to CDC reported cases of active disease, found that rates of reactivation in varied by as much as 8.8-fold (USB whites compared to FB blacks). They found that rates of reactivation were higher amongst foreign-born individuals, attributing this to unmeasured risk factors (25). Interestingly, our calibration revealed the opposite finding in California: rates of reactivation were higher amongst USB, with the exception of whites, who had a lower risk of progression. This may be due to different levels of recently transmitted disease which we could not explicitly account for, or may reflect a different risk landscape for Californian immigrants.

The calibration process also confirmed a poorly-understood phenomenon of high levels of active TB in foreign-born diabetics in California (31). To account for this difference, we adjusted the risk of progression by 1.6-fold. There are a few potential explanations for this finding. First, Yeats suggests that diabetes is not only a risk factor for active disease, but LTBI (24), as it serves

as a proxy for social status. This seems less likely in our population since US-born diabetics did not require an increased risk of progression beyond that supported in the evidence. The alternative explanation, offered by Demlow *et al.* is that FB in California, particularly those from South East Asia, are prone to type 2 diabetes without being overweight, which may put them at additional risk of TB since overweight seems to confer a protective effect (ref).

Once the model was calibrated, we assessed the best strategies to target, test and treat those with LTBI. We found that the use of QFT in combination with the 3HP regimen was the most cost-effective testing and treatment option. Testing and treating FB was cost-effective below the level of $50,000 per QALY, while testing and treating USB was only cost-effective below $50,000 per QALY for certain risk groups. This suggests a risk assessment considering multiple factors would ensure the most efficient use of public health resources.

The model also suggests a rapid decline in the number of annual cases; this is due largely to the all-cause mortality of individuals with LTBI, the entrance of individuals into the model with a lower LTBI prevalence, and the baseline level of preventive LTBI therapy. Although the decline is rapid, the model suggests that elimination is impossible before 2050 without an unprecedented level of screening.

This study has limitations. First, our elimination projections are severely hampered by our lack of sensitivity analysis. As with any model, inputs are estimated, and are often triangulated from other data where directly measured data is not available. Without sufficient sensitivity analysis, we are unable to estimate the reliability of our forecasts.

Second, we did not account for economy of scale in testing and treatment interventions. It would be reasonable to assume that with a 2- to 10-fold increase in the number of tests being administered, there may be economies of scale. Many of the clinics that target high-risk TB groups are state-run. A large scale up in testing may allow drugs to be purchased in greater bulk and for specialization to occur decreasing personnel costs. On the other hand, this large scale-up in testing and treatment may require additional overhead expenses (new clinics, buildings) that were not accounted for by the model, as well as higher costs to reach more populations. Additionally, we did not account for the overhead costs of testing or treatment, as well as the cost of liver-function test monitoring, or adverse events from the LTBI treatment.

Third, we utilized a non-geographic transmission model, focusing on non-random mixing by nativity and race/ethnicity. Although there is evidence that these are important determining factors (17), we would expect transmission to be geographically clustered, and based on social and economic networks not captured by our representation. Improved understanding of the geography of TB in California may allow for the design of geographically-focused interventions.

Additionally, our use of two different levels of reactivation rates (recent vs. remote transmission) is a simplification. It is thought that the rate of reactivation decays over time in a non-linear function (32), although the dynamics are poorly understood.

Another limitation is the lack of explicit portrayal of undocumented immigrants or unhoused individuals. In 2014, 18% of TB cases in California were in undocumented immigrants. Since

our demographic data was sourced from the American Community Survey, these individuals are supposedly included in the sampling adjustments, however, there is no explicit field for documentation status. For this reason, we were unable to include them as a high-risk group to target. Undocumented immigrants may be less likely to seek LTBI therapy, more likely to live in unhealthy housing, and be more at risk for TB from these and other social determinates of health (33). In addition, 5% of TB cases in 2014 were in unhoused individuals. This population is particularly at-risk because of intra-population transmission as well as a higher prevalence of risk factors, such as HIV and smoking. Other important risk factors for this population, such as injection drug use and alcohol abuse were not included, although there is evidence that these increase the risk of progression (34). It is difficult to imagine TB elimination occurring in California without a concerted effort to reach and treat the undocumented and unhoused populations.

Additionally, we do not model children, since the natural history of pediatric TB is significantly different than that in adults (35). It would be expected that as incidence of active disease fell, transmission within California, and thus the risk to children, would become negligible.

The changing demographics of California will affect the number of future TB cases. However, we did not account for changes in the number or types of immigrants, instead assuming that the recent California immigrants in the 2013 American Community Survey represent the next 50 years of immigration. This is a gross simplification, and may have a large effect on the model. Unpredictable global economic shifts will impact the flow of immigrants and may hasten or retard California's path to elimination. This is also true of TB control measures in countries of origin for California immigrants.

Many of our estimates for the prevalence of risk factors were from national-level data. If there are significant differences in the levels of medical risk factors in California compared to the US as a whole, our results would be less credible. Additionally, there is no available estimate for the prevalence of TNF-alpha inhibitor use in the US. We estimated the prevalence of use based on the prevalence of rheumatoid arthritis and inflammatory bowel disease, and the prevalence of TNF-alpha inhibitors in these conditions. This may play a more important role that it has in the past as TNF-alpha inhibitors are being approved for more conditions are quickly becoming more widely used. Overall, this group should contribute few cases since testing for TB with an IGRA test is standard clinical practice.

Our results differ from those found in other works. In 2015, Zamarchi et al. completed a systematic review of the cost-effectiveness of LTBI screening, and identified nine studies, eight of which found LTBI screening to be cost-effective (<$50,000 per QALY), three of which found it to be cost-saving (36). The most thorough study of LTBI screening cost-effectiveness in various subgroups was completed by Linas et al. in 2011 (13). In this study, they assessed the cost-effectiveness of IGRA and TST-based tests, assuming a 9H treatment option. They found vastly different cost-effectiveness ratios for different groups, from $23,700 to over $2 million per QALY. Yeats *et al.* published a PhD dissertation assessing the cost-effectiveness of screening for LTBI in FB in the US, using QFT as the test and 4R as the treatment. They estimated that this would cost $58,334 per QALY, from a societal perspective (24) – this is higher than our finding

of $23,000, but within our 95% confidence interval (3,000 - 63,000). This study is one of the first evaluating 3HP.

In summary, our analysis found that targeting foreign-born individuals and certain US-born individuals with medical risk factors for LTBI screening with QFT and 3HP is cost-effective below the threshold of $50,000 per QALY, but that reaching TB elimination by 2050 would require a heroic scale-up of testing and treatment services within the general population. These results suggest that while elimination is a noble goal, a strategy focused on scaling-up testing and treating in the FB and those with medical risk factors will avert more morbidity and mortality for a reasonable expenditure than a strategy focused on elimination alone.

TABLES

Table 1. Estimated single parameters

Name	Base	Low	High	Reference
Proportion of individuals that enroll in treatment after a positive TST LTBI test	0.76	0.72	0.80	(37,38)
Proportion of individuals that enroll in treatment after a positive QFT/TSPOT test	0.83	0.76	0.89	(37,38)
Number of LTBI cases caused by one active case*	4.00	3.95	15.00	Calibration, (39)
Base risk of progression	0.0000609	0.00	0.00	Calibration, (25)
Proportion of LTBI treated	0.02	0.01	0.10	(12)
Fast latent progression	0.0008097	0.00	0.00	Derived, (26)
QALYs gained averting one case of active TB	1.39	0.5	1.74	(20)
Proportion of started who complete treatment				
9H	0.50	0.38	0.63	(43,44)
6H	0.50	0.38	0.63	(43,44)
4R	0.78	0.59	0.98	(43)
3HP	0.82	0.62	1.00	(45)
Total cost				
TST	38.91	29.18	48.64	(46)
QFT	65.53	49.15	81.91	(46)
TSPOT	65.53	49.15	81.91	Assumed
TST+QFT	104.44	78.33	130.55	(46)
TST+TSPOT	104.44	78.33	130.55	(46)
Cost of active TB case	31400.00	13377.16	39250.00	(47)
9H	592.50	444.38	740.63	(41,42)
6H	431.47	323.60	539.34	(41,42)
4R	542.32	406.74	677.90	(41,42)
3HP	840.64	630.48	1050.80	(41,42)
Efficacy of therapy				
9H	0.92	0.90	0.93	(40)
6H	0.69	0.52	0.86	(40)
4R	0.65	0.49	0.81	(40)
3HP	0.92	0.69	1.00	Set equal to 9H

Table 2. Estimates of test performance

	Sensitivity				*Specificity*			
Name	***Base***	***Low***	***High***	***Reference***	***Base***	***Low***	***High***	***Reference***
USB TST	0.83	0.71	0.87	(48–61)	0.95	0.82	0.99	(48–61)
USB QFT	0.85	0.70	0.97	(48–61)	0.99	0.98	1.00	(48–61)
USB TSPOT	0.85	0.70	0.97	(48–61)	0.98	0.97	1.00	(48–61)
FB TST	0.83	0.71	0.87	(48–61)	0.82	0.47	0.92	(48–61)
FB QFT	0.85	0.70	0.97	(48–61)	0.99	0.98	1.00	(48–61)
FB TSPOT	0.85	0.70	0.97	(48–61)	0.98	0.97	1.00	(48–61)
HIV TST	0.75	0.68	0.83	(62)	0.64	0.58	0.70	*Assumed*
HIV QFT	0.59	0.53	0.65	(62)	0.89	0.80	0.98	(62)
HIV TSPOT	0.59	0.53	0.65	Assumed	0.89	0.80	0.98	Assumed
ESRD TST	0.51	0.46	0.56	(63)	0.64	0.58	0.70	(63)
ESRD QFT	0.53	0.48	0.58	(63)	0.69	0.62	0.76	(63)
ESRD TSPOT	0.53	0.48	0.58	Assumed	0.69	0.62	0.76	Assumed

Table 3. RR for progression, prevalence, and life expectancies for medical risk factors

Risk group	Stratified by	Modeled prevalence, 2014	Reference	Relative Risk of Progression (pre- calibration)	Relative Risk of Progression (post-calibration)	Reference	Life Expectancy
Diabetes	Age, sex, race/ethnicity, nativity	8.92%	(64)	1.6 (1.3-3.60)	1.6	(65)	16.05
Smoking	Age, sex, race/ethnicity, nativity	12.70%	(64)	2.5 (1-4)	2.5	(66)	24.84
HIV	Age, sex, race/ethnicity	0.41%	CA Dept of AIDS	12 (2.9-22)	5.4	(67)	15.83
TNF-alpha	Age, sex	0.80%	Expert opinion. Derived from (68–73)	4.7 (2.5-5.3)	4.7	(24)	24.81
Solid-organ transplants	Age, sex,	0.17%	Organ Procurement and Transplantation Network	2.4 (1.7-18)	2.4	(74)	27.53
ESRD	Diabetes, age, sex, race/ethnicity	0.30%	(23)	11 (2-20)	10.4	(75)	3.74

Table 4. LTBI prevalence in selected demographic groups

	US born	FB
Total	2.4%	19.4%
Sex		
Male	3.1%	24.4%
Female	1.7%	14.8%
Race/Ethnicity		
Asian	5.1%	30.1%
Hispanic	2.7%	13.8%
Black	7.1%	21.7%
White	1.4%	15.1%
Other	2.2%	25.5%
Age		
Age 15-19	0.4%	11.1%
Age 20-24	0.7%	12.5%
Age 25-29	3.3%	19.6%
Age 30-34	3.2%	18.4%
Age 35-39	2.9%	20.2%
Age 40-44	2.1%	18.6%
Age 45-49	4.4%	23.1%
Age 50-54	3.6%	26.1%
Age 55-59	3.7%	24.2%
Age 60-64	3.7%	27.3%
Age 65-69	1.7%	13.4%
Age 70-74	0.5%	9.4%
Age 75-79	0.8%	13.0%
Age 80+	1.5%	9.1%

Table 5. Cost effectiveness of testing and treatment combinations

	Cost per case averted (2014 USD)		Cost per QALY gained (2014 USD)	
Testing and treatment combination	FB	US	FB	USB
QFT with 3HP	24,000 (9870 - 48,000)	152,000 (112,000 - 187,000)	17,000 (16,000 - 29,000)	110,000 (95,000 - 145,000)
QFT with 6H	26,000 (8840 - 55,000)	167,000 (105,000 - 236,000)	19,000 (13,000 - 36,000)	120,000 (97,000 - 176,000)
QFT with 4R	33,000 (25,000 - 43,000)	226,000 (112,000 - 315,000)	24,000 (7855 - 49,000)	162,000 (8776 - 354,000)
TSPOT with 3HP	35,000 (24,000 - 49,000)	239,000 (140,000 - 325,000)	25,000 (11,000 - 50,000)	172,000 (40,000 - 350,000)
QFT with 9H	37,000 (31,000 - 46,000)	249,000 (176,000 - 292,000)	27,000 (12,000 - 51,000)	179,000 (58,000 - 330,000)
TSPOT with 6H	39,000 (38,000 - 44,000)	263,000 (219,000 - 289,000)	28,000 (17,000 - 50,000)	189,000 (92,000 - 326,000)
TSPOT with 4R	48,000 (33,000 - 81,000)	161,000 (118,000 - 228,000)	35,000 (33,000 - 58,000)	116,000 (92,000 - 185,000)
TSPOT with 9H	48,000 (10,000 - 107,000)	333,000 (189,000 - 512,000)	35,000 (23,000 - 66,000)	239,000 (265,000 - 287,000)
TST with 3HP	50,000 (5869 - 120,000)	346,000 (161,000 - 601,000)	36,000 (16,000 - 79,000)	249,000 (198,000 - 400,000)
TST with 6H	52,000 (35,000 - 74,000)	338,000 (183,000 - 557,000)	78,000 (60,000 - 98,000)	243,000 (192,000 - 314,000)
TST with 9H	55,000 (46,000 - 72,000)	358,000 (152,000 - 692,000)	81,000 (43,000 - 130,000)	257,000 (165,000 - 412,000)
TST with 4R	61,000 (16,000 - 140,000)	413,000 (315,000 - 725,000)	85,000 (99,000 - 111,000)	297,000 (306,000 - 409,000)

Figure 1. Results of calibration. Number of cases predicted by model and those reported to CDPH in the RVCT database by nativity, 2001-2014. CAPE represents our model, RVCT represents historical data. (A) Total (B) Asian (C) Black (D) Hispanic (E) Other ethnicity (F) White.

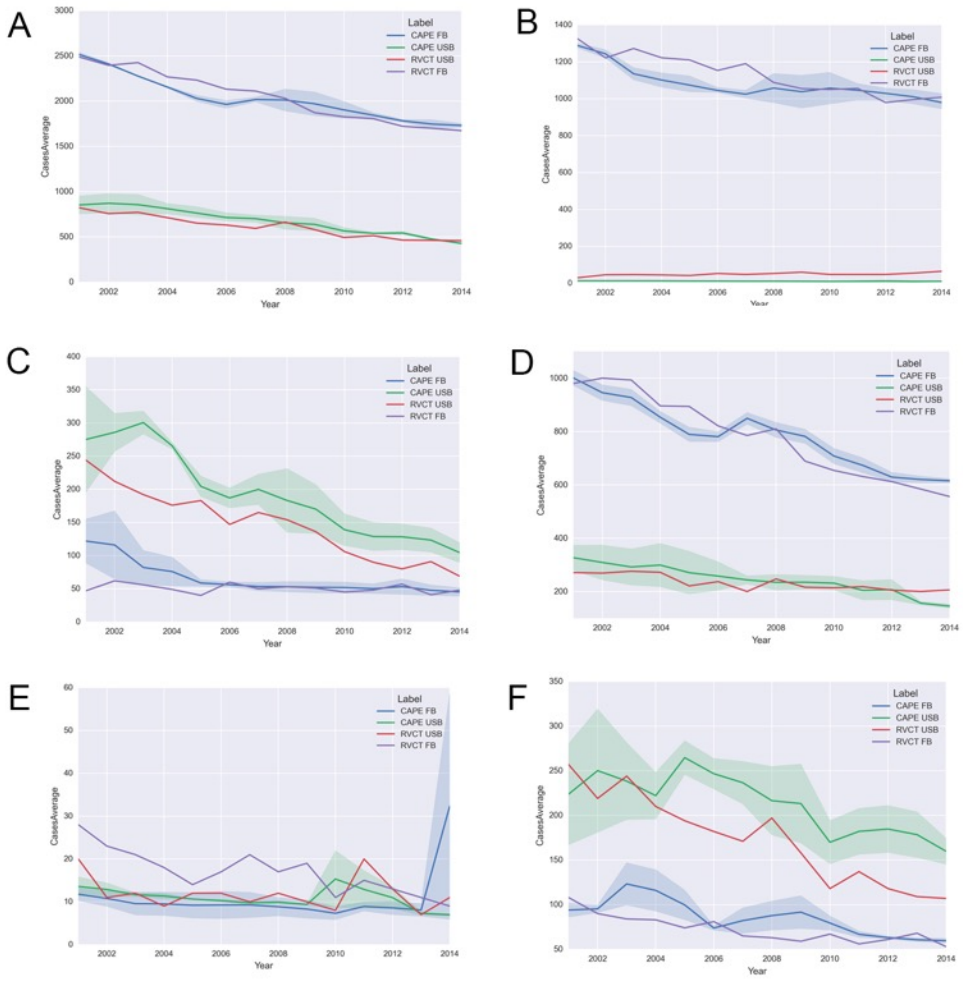


Figure 2. Net cost of averting one case of active tuberculosis in the foreign-born

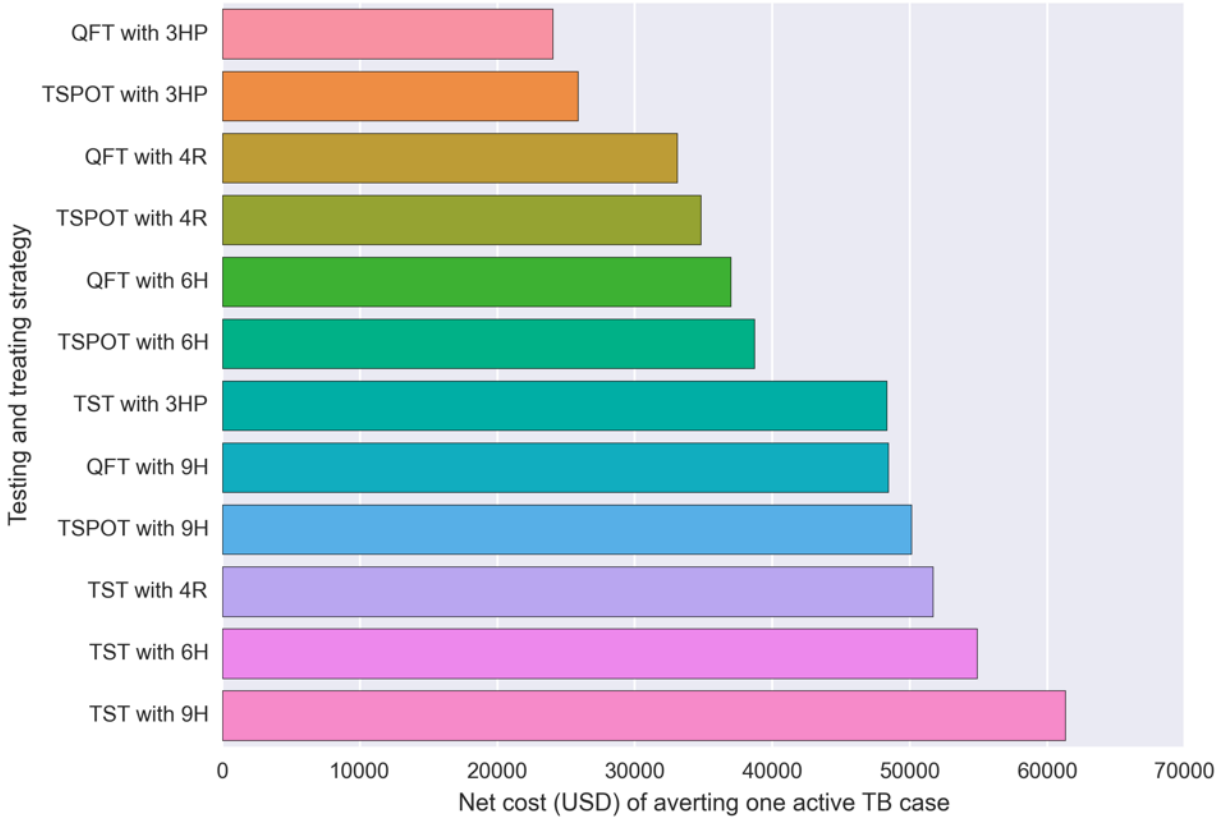


Figure 3. Net cost of averting one case of active tuberculosis in various risk groups

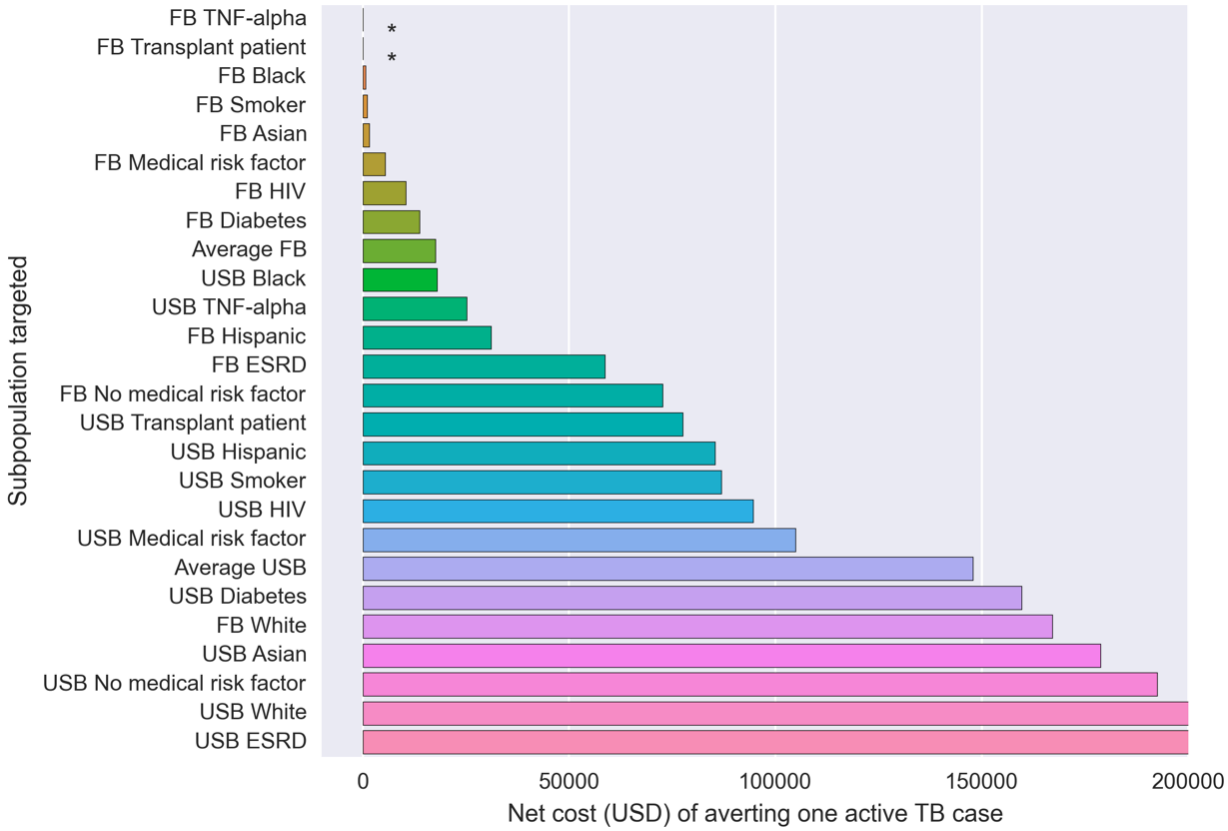


Figure 4. Tornado diagram showing one-way sensitivity analysis of selected variables, QFT and 3HP.

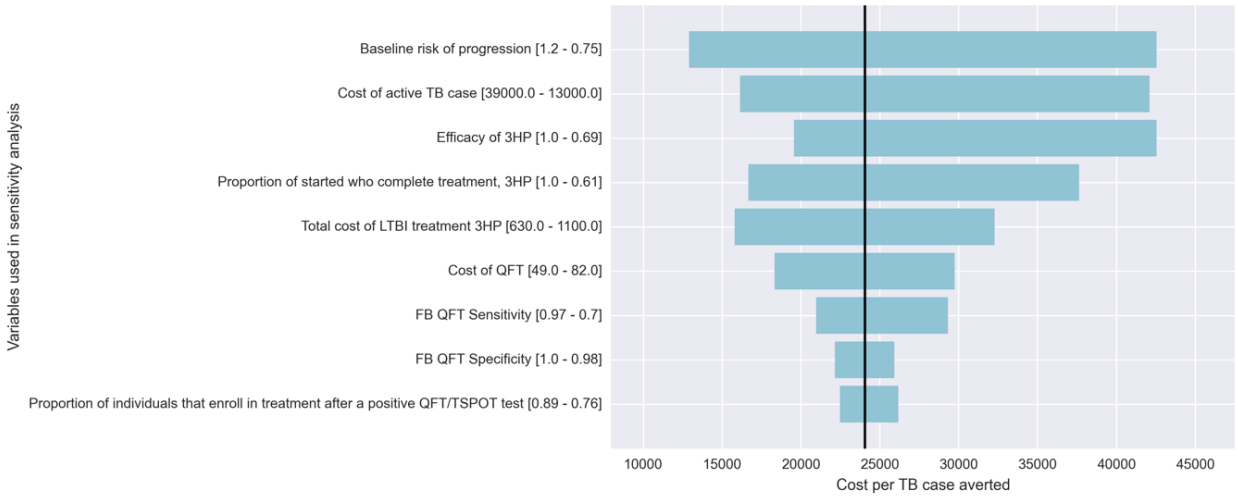
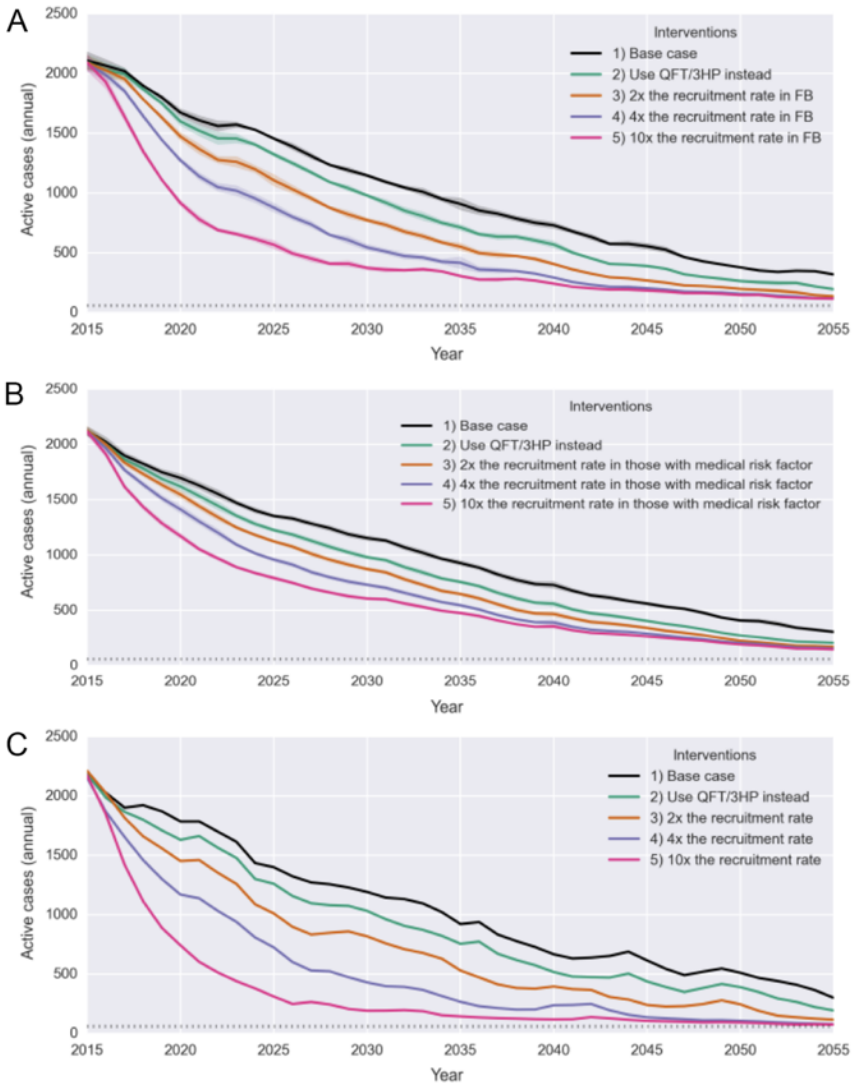


Figure 5. Schematics showing annual active cases and effect of interventions projected from 2015-2055. (A) Scaling up TTT in FB (B) Scaling up TTT in those with medical risk factors (C) Scaling up TTT in overall population



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