SPECIFIC AIMS

Overview: The goal of the proposed research is to create, evaluate, and disseminate a combined epidemic-economic model of tuberculosis (TB) diagnosis for use by TB experts and public-health decision-makers as they decide how best to scale up novel TB diagnostic tests and strategies.

Despite the availability of curative treatment, TB kills an estimated 1.7 million people per year,[1] due in part to the lack of effective diagnostic testing.[2] Sputum smear microscopy – the most widely-used diagnostic test worldwide – has a sensitivity near 50%,[3] and an estimated 37% of TB cases worldwide go undiagnosed.[1] Since 2007, the World Health Organization (WHO) has approved an unprecedented number of new diagnostic tests and strategies for TB,[4, 5] including the widely-publicized Xpert MTB/RIF polymerase chain reaction (PCR) test.[6, 7] Many additional diagnostic tests are in development and may enter the market in the next 5-10 years.[8]

If improved diagnostics are to impact the global TB epidemic, they must be scaled up across a wide spectrum of local conditions.[9] Factors important to scale-up in one setting may be less relevant to another. Mathematical models are important tools for projecting the likely costs and impact of alternative diagnostic strategies when complete information is lacking.[10, 11] Models translate existing knowledge and assumptions (e.g., local epidemiology, scale-up strategies, and test accuracy in the field) into projected outcomes, with estimates of uncertainty. However, most existing TB models study pre-specified interventions in either large regions or single locations; customized results for a diversity of local situations are not available. Furthermore, these models cannot be replicated without specific expertise in TB modeling. As a result, most decisions regarding scale-up of TB diagnostics currently occur without the benefit of supporting models. Since many countries will face questions related to scaling up TB diagnostics, it is essential that a widely-available model be produced urgently. We see two specific needs: (1) a simple Web-based model providing decision-makers rapid access to basic, evidence-based estimates of impact and cost-effectiveness for policy decisions, and (2) a moderately-advanced model that teams of in-country expert consultants could use as a standardized and transparent framework to answer specific questions related to scaling up TB diagnostics under local conditions.

Thus, we propose to develop, evaluate, and disseminate a standardized, publicly-accessible mathematical model to evaluate TB diagnostics. This model would represent the first step toward a global standard in TB diagnostic modeling, which as an open-source project could be refined and adapted by TB epidemiologists and modeling experts around the world. The guiding principles of this modeling project are (1) accessibility and ease of use, (2) flexibility to adapt to local conditions, (3) simplicity of interpretation, and (4) speed of dissemination. Once developed, this model will enable decision-makers to adapt a transparent modeling methodology to local conditions, providing customized estimates of the likely impact of alternative scale-up strategies. TB decision-makers need a modeling platform to help answer questions of scale-up as soon as possible to ensure maximum possible benefit from scale-up decisions. We believe that rapid development and wide dissemination of an open-source model will help to achieve this objective most rapidly.

The specific aims of this project are:

1. To develop a combined epidemic-economic model of TB diagnosis.

a) To enumerate and review the key parameters needed for a useful model of TB diagnosis.

b) To create a dynamic transmission model of a generalized TB epidemic, with a focus on the TB diagnostic process, incorporating operational realities.

c) To create an iterative framework whereby descriptions of local TB epidemiology (e.g., incidence and mortality) and operational processes (e.g., access to care) are translated into model inputs.

d) To incorporate formal economic outcomes into a dynamic modeling framework of TB.

2. To project the impact and cost-effectiveness of strategies for scaling up TB diagnostics.

a) To estimate 10-year TB incidence and mortality after scale-up of existing TB diagnostics, Xpert MTB/RIF, novel diagnostic tests with different target product profiles, and empiric treatment algorithms.

b) To estimate discounted costs and incremental cost-effectiveness of different scale-up strategies.

c) To evaluate the relationship of scale-up speed versus cost, cost-effectiveness, and impact.

d) To validate model results against other models of Xpert MTB/RIF in Tanzania, South Africa, and India.

3. To broadly disseminate the structure and findings of a TB diagnostic model for use, adaptation, and improvement by the global TB control community.

a) To develop a web-based platform through which end-users can input local parameters and receive locally-relevant modeling results and estimates of goodness-of-fit.

b) To distribute open-source modeling code through a monitored public forum.

c) To develop and deliver a training workshop by which TB experts (e.g., graduate students and public health consultants) can learn model structure and utilize model results.

RESEARCH STRATEGY

1. SIGNIFICANCE

1.1. Importance of New Diagnostics for Tuberculosis Control

Tuberculosis (TB) is a curable disease, yet it remains a leading infectious killer, causing an estimated 1.7 million deaths globally in 2009.[1] The Stop TB Partnership has set global targets of halving TB prevalence and mortality by 2015.[2] However, despite optimistic initial projections,[12] global TB incidence rates are only falling at about 1% per year, with declines in prevalence even slower.[1] This disappointing situation is due in large part to poor TB case detection using inadequate diagnostic tests, with the result that over one-third of all TB cases worldwide go undiagnosed.[1] If global targets for TB control are to be met, improved TB diagnostics must be scaled up rapidly.[13] It has been estimated that wide implementation of improved TB diagnostics could prevent 20% of all TB deaths – nearly 400,000 lives saved per year – with exponential benefits in future years from reduced transmission.[13-15] However, it is also essential that the scale-up process be evidence-based.[16] For example, scaling up suboptimal diagnostics (i.e., serological tests) to 20% of India's TB suspects could expend India's entire national TB control budget and produce no meaningful benefit to the population.[9, 17]

Since 2007, the World Health Organization has approved nine new diagnostic tests for detection of TB or TB drug resistance.[5] Many additional tests are in the development pipeline and may come to market in the next 5 years.[8] Most recently, the Xpert MTB/RIF system (Cepheid, Inc.; Sunnyvale, CA), a PCR-based test capable of providing results in 2 hours with minimal technical requirements,[6] was shown to have sensitivity for *M. tuberculosis* (relative to multiple cultures) of 98.2% for sputum smear-positive TB and 72.5% for smear-negative TB, as implemented in six developing-country settings.[7] This novel technology has been described as potentially effecting a "game change" in TB diagnosis.[18] Global concessionary prices have been negotiated,[19] and country-wide scale-up (e.g., in South Africa[20]) has already begun. To date, these decisions have been made without published projections of their long-term implications.

1.2. Scaling Up TB Diagnostics: The Need for Mathematical Models

The optimal strategy for improving TB diagnosis in high-burden countries is not clear. For example, although Xpert MTB/RIF is accurate and easy to use, it carries an estimated cost of over $40 per test in South Africa (C. Hanrahan, unpublished data) and over $100 in the Indian private sector. Cheaper tests, including light-emitting diode (LED) microscopy,[21] may free up resources to improve TB case-detection in other ways (e.g., intensified case finding[22]). Alternatively, high-quality diagnostics that use existing infrastructure (e.g., TB culture[23]) may have similar impact to a new test.[15] Changing national guidelines for diagnostic algorithms is complex, expensive, and time-consuming;[24] decision-makers must determine whether to implement the new test centrally versus peripherally, immediately versus phased-in over time, and in the context of existing diagnostic routines and supplies.[11] For example, an excellent test for drug-resistant TB may not be scalable in areas with unreliable stocks of second-line drugs or no infrastructure for communicating results from labs to clinicians. Thus, in deciding how to scale-up new TB diagnostics, it is essential to carefully consider the implications of alternative policies, in terms of projected epidemic impact and cost-effectiveness.

Mathematical models are important tools for projecting the likely impact of health policies before they are enacted.[10, 11] Dynamic transmission (i.e., epidemic) models use series of mathematical equations to represent the processes of infectious disease transmission, progression, and treatment response to translate existing knowledge into projections of effect over time.[25] In modeling other diseases (e.g., HIV[26]), economic parameters have also been successfully linked to epidemic models to evaluate the effect of reductions in transmission on long-term cost-effectiveness of prevention and control strategies. If effects on transmission are ignored, the effect of improved diagnostics may be underestimated relative to other interventions,[9, 14] leading to inappropriate decisions about which scale-up strategies will have greatest impact.

1.3 Lessons from Models of Other Infectious Diseases

For many other major infectious diseases, specific mathematical models have been tailored for broad use by decision-makers in a variety of local circumstances. Examples include the SPECTRUM model of AIDS impact,[27] the MIDAS models of pandemic influenza,[28] and the ONCHOSIM model of onchocerciasis.[29] Most recently, Maude and colleagues developed an internet-based dynamic model of malaria that allows end-users to input local parameters (e.g., malaria endemicity, bednet coverage) and receive tailored estimates of epidemic progression under different disease-control strategies.[30] To date, no mathematical model of TB has been developed for flexible use by end-users in different circumstances. Given the rapidity with which TB diagnostics are being scaled up globally, the need for such a model – particularly a model with a focus on the diagnostic process – has never been more acute. The present study would fill this critical knowledge gap.

2 INNOVATION

The proposed project is innovative in many ways:

- **A flexible dynamic model of TB:** Prior TB epidemic models have focused either on global impact (e.g.,[12, 31]) or specific local situations (e.g.,[15, 32]). No published dynamic transmission model of TB has, to date, allowed users in different locations to adapt a standardized modeling platform to obtain results customized to local epidemiologic and operational conditions. We will use an iterative programming algorithm[15] to provide locally-relevant results using a simple, standardized model structure.
- **Modeling the diagnostic process for TB:** It is increasingly recognized that the process of TB diagnosis is complex, and that models of TB diagnostics must account for operational realities.[11] The present model will be among the first to account for repeat diagnostic attempts, patient dropout, different levels of access/diagnostic sophistication, and age differences[33] in a dynamic modeling framework of TB diagnosis.
- **Dynamic modeling of economic outcomes in TB diagnosis:** While dynamic epidemic-economic models have been successfully developed for other infectious diseases, only one published attempt has been made in the TB literature.[34] The proposed model would be among the first to evaluate the cost-effectiveness of alternative TB diagnostic strategies in a dynamic modeling framework.
- **Open-source modeling:** Although open-source publication of model code is commonplace in biophysics and the biological sciences,[35] it is not prevalent in infectious disease modeling. Given the urgency of developing an accessible and widely-accepted dynamic model of TB diagnostics, we believe there is no faster or more effective way to arrive at consensus than to make our modeling code transparent and adaptable. Not only will we make our modeling code available, we will also advertise it on widely-trafficked websites such as www.tbevidence.org, hosted by the Stop TB Partnership's New Diagnostics Working Group.
- **Dissemination research:** Other models currently in preparation aim to evaluate Xpert MTB/RIF scale-up both globally and in a select handful of countries (T. Cohen and C. Dye, personal communications). However, none of these efforts includes a plan to provide locally-tailored results via public interface, or to disseminate the modeling tool itself. Through these mechanisms, we aim to empower country-level decision makers (with reasonable in-country technical support) to generate meaningful epidemic estimates without relying on mathematical modelers of TB. Our dissemination plan – including both an open-source modeling framework and simultaneous development of a training course targeted at in-country experts – is thus unique in the world of TB research, and is indeed rare in any field of infectious disease modeling.

3. APPROACH

3.1. Investigative Team

Our study team combines expertise in mathematical modeling (including economic modeling) with TB epidemiology, diagnostics, and operational research. **Dr. David Dowdy** is an Assistant Professor in Epidemiology at the Johns Hopkins Bloomberg School of Public Health. He has widely published both epidemic[14, 15, 36] and economic[37-39] models of TB, with a particular focus on TB diagnostics. He has served as a consultant/panelist for the WHO, Bill and Melinda Gates Foundation, academic institutions (e.g., University of California, San Francisco), and non-governmental organizations (e.g., Population Services International) as an expert in mathematical and economic modeling of TB and HIV. **Dr. Madhukar Pai** is an Associate Professor of Epidemiology at McGill University. He is an international expert on TB diagnostics and serves as the co-chair of the Stop TB Partnership's New Diagnostics Working Group. He has conducted field evaluations of several TB diagnostics,[21, 40-44] holds particular expertise in data synthesis,[4, 8, 16, 45, 46] and has helped craft several policies related to TB diagnostics.[4, 16, 17] **Dr. Richard Chaisson** is a Professor of Medicine, Epidemiology, and International Health at Johns Hopkins School of Medicine and Director of the Johns Hopkins Center for TB Research. He is the PI of the Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE), a multinational consortium of cluster-randomized trials and operational studies of TB/HIV interventions in Brazil, South Africa, and Zambia,[47, 48] and is an international expert on TB control interventions in HIV-endemic regions.[49, 50] **Dr. Adithya Cattamanchi** is an Assistant Professor of Medicine at the University of California, San Francisco, and brings expertise in TB diagnostics and implementation research to the research team.[51-53] He has served as a member of multiple WHO expert panels on TB diagnostics and is actively evaluating operational impact of scaling-up new TB diagnostics (i.e., Xpert MTB/RIF) in Uganda and Viet Nam. **Dr. Peter Dodd** is a Research Fellow in mathematical modeling at the London School of Hygiene and Tropical Medicine, with a specific focus on modeling TB and HIV.[54] We have a broad array of expertise, bringing epidemiologists, modelers, implementation experts, and thought leaders together early in the process of model-building, to ensure that our model is both computationally sound and relevant to decision-makers in a variety of situations.

3.2. Preliminary Studies and Experience

3.2.1 Mathematical and Operational Modeling of TB Diagnosis

Our team has extensive experience in mathematical modeling of TB diagnostics, including operational aspects of the diagnostic process. In a model of TB diagnosis in HIV-endemic regions, Drs. Dowdy and Chaisson found that clinic-based rapid molecular testing (with 50% sensitivity for smear-negative TB) could reduce TB mortality rates by 20%.[14] We subsequently modeled the potential impact of TB culture in South Africa, finding a similar potential reduction of 17% in 10-year TB mortality (Fig. 1, blue triangles).[15] A new test with 100% sensitivity and no diagnostic delay could cut TB mortality by 38% within 5 years (Fig. 1, purple circles), [15] but delayed implementation of any test attenuated its potential impact. This model incorporated operational realities such as empiric diagnosis, loss to follow-up, and delayed diagnosis. Our team has also evaluated the operational impact of TB diagnostics in the field. For example, Drs. Dowdy and Chaisson found that expanded TB culture in Rio de Janeiro, Brazil, would avert only 8 TB deaths per 1,000 TB suspects because diagnosed patients were difficult to locate,[38] and Dr. Cattamanchi discovered that diagnostic suspicion and linkage to treatment were so low in Ugandan primary health centers that only 11% of patients with smear-positive TB could expect to receive therapy.[55] Our investigative team has the combined expertise in modeling and operational research needed to model TB diagnostics as implemented in the field.

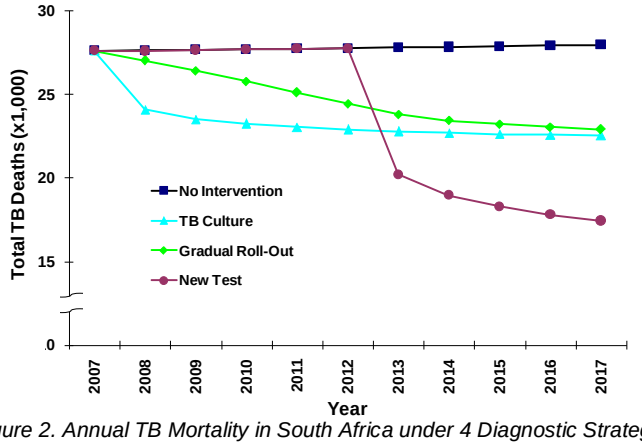

Figure 2. Annual TB Mortality in South Africa under 4 Diagnostic Strategies

The South African model described above also incorporates two unique elements that we intend to leverage during the proposed project. First, it uses a recursive algorithm to simultaneously translate nine user-defined epidemiological inputs (e.g., TB incidence, HIV prevalence) into model parameters (e.g., transmissibility of TB, HIV infection rates). Thus, the model can be adapted to other epidemics; Dr. Dowdy used the same model structure (with different inputs) to evaluate the impact of TB diagnostics in China for the WHO, creating projections of TB incidence to within 5% of published WHO estimates. Second, the model includes economic parameters, as described below. Thus, we have demonstrated our ability to create flexible epidemic-economic models of TB diagnostics and will apply this expertise to the present proposal.

3.2.2. Economic Evaluation

Using the model described above, we found that rapid scale-up of TB culture in South Africa would cost 20% of the National TB Program budget in year 1, but would generate cost savings by year 10 (unpublished). Similar findings could be used by National TB Control Programs to develop long-term strategies for scaling up diagnostics, and to secure up-front funding for such efforts. Dr. Dowdy has modeled (using a static decision-analytic framework) the cost-effectiveness of novel point-of-care diagnostic tests for TB in Brazil, Kenya, and South Africa,[39] finding that, because of its low cost, high specificity, and ability to identify the most infectious patients, sputum smear microscopy would be more efficient than even a point-of-care test with a sensitivity of 90%, specificity of 95%, and price of $1/test. However, a new test with 70% sensitivity and a price of $20/test would be highly cost-effective and avert 46-49% more disability-adjusted life years (DALYs) than sputum smear microscopy alone.[41] Drs. Dowdy, Pai, and Cattamanchi recently described the unique challenges of economic analyses evaluating scale-up of TB diagnostics, as well as methods for overcoming those barriers.[9] Our cost-effectiveness work on serological tests for active TB[17] was recently used by WHO to make its first "negative" policy in TB control, against their use. Our team understands the importance of conducting economic analyses that are meaningful to decision-makers and will create a model that has operational utility.

3.2.3. Dissemination Research

Essential to the success of the proposed research is dissemination of findings. In concert with the economic analysis of novel TB diagnostics above, we developed a simple Web-based interface (www.tbtools.org) allowing end-users to specify test characteristics and receive customized cost-effectiveness estimates (Fig. 3). This software can also create more detailed interfaces and link to dynamic modeling platforms. Our team members have also developed and disseminated other open-access resources, including World BCG Atlas (www.bcgatlas.org), TST/IGRA interpreter (www.tstin3d.com) and Evidence-based TB

Diagnosis (www.tbevidence.org). Our team is strategically placed at institutions capable of supporting and publicizing the proposed training course, with extensive international partnerships that will enable us to bring in trainees from around the globe.

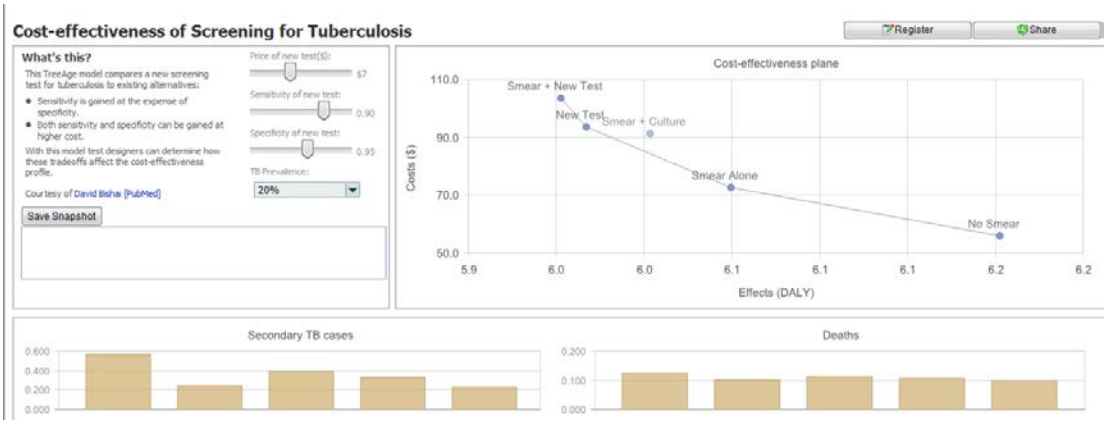

Figure 3. Screen Shot of User-Friendly TB Economic Model

Dr. Chaisson brings years of experience in dissemination of findings through the CREATE Policy and Advocacy Core. We have the experience and institutional infrastructure to create the first globally-available, user-friendly epidemic model of TB, and to ensure that decision-makers across the world are trained in its use.

3.3. Research Design and Methods

3.3.1. Specific Aim 1: Developing an Epidemic-Economic Model of TB Diagnosis

Taking our model of TB culture in South Africa[15] as an initial guide, we will construct a dynamic compartmental difference-equation model of TB diagnosis. The model will incorporate TB transmission dynamics as well as operational aspects of TB diagnosis and economic factors (through a separate, linked operational/economic modeling framework) to project TB incidence, TB mortality, costs, quality-adjusted life years (QALYs), and multiple other outcomes over timeframes of 5, 10, and 25 years. We will construct the model in Python, a programming language that is free (open-source), downloadable from a public website, designed to be learned quickly, and easily linked to other programs (e.g., R, Excel). The model will incorporate the following elements, allowing end-users to customize them to local conditions:

- **Access to care:** Three different levels of access and diagnostic sophistication (local, district, region)
- **Operational accuracy:** Sensitivity and specificity of novel diagnostics as utilized in the field, in combination with existing diagnostic techniques and clinician judgment
- **Scale-up over time:** Modeling the impact of different time courses and delays in scale-up
- **Drug resistance and drug sensitivity testing:** Including the speed of DST and emergence of resistance during episodes of inappropriate treatment
- **TB diagnostic algorithms:** Use of different diagnostics, repeat testing, referral to higher level of care
- **Local TB epidemiology:** TB transmissibility, drug-resistance patterns, treatment success rates, and patient delays in diagnosis will be defined based on the local TB epidemic using recursive algorithms[15]
- **Dynamic cost and cost-effectiveness analysis:** Incorporating effects of diagnosis on transmission
- **Key covariates:** Different outcomes according to HIV status, age, gender, and infectivity/smear status
- **Uncertainty and goodness of fit:** Sensitivity analyses incorporated, and if users are willing to allow additional computational time, estimates of probabilistic uncertainty and fit to user-supplied data

The model will be constructed in modular format, allowing for model complexity to be "turned off." Thus, users with little modeling expertise hoping to obtain rough projections can access an appropriately simple model, allowing standardized outcomes that can be calculated quickly. By contrast, decision-making teams with more expertise can "turn on" model complexity, allowing them to investigate the impacts of nuanced interventions more closely. The model code will be made available on a public website through an open-source license, thus allowing for rapid improvements to the model, adaptations to different locations, discussion of appropriate parameter values, evaluation with primary data from ongoing studies, and ascertainment/correction of any errors. We have a small seed grant to begin development of this model in early 2012; the present proposal would enable us to complete and validate the model rapidly. This project has the potential to serve as a paradigm for open scientific collaboration to rapidly create flexible models of disease when data to inform decision-making is urgently needed, by users with different levels of expertise, in a short time frame.

3.3.2. Specific Aim 2: Projecting Impact and Cost-Effectiveness of TB Diagnostic Scale-Up Strategies

3.3.2.1. Model Validation

The primary goal of the present proposal is to develop and rapidly disseminate a broadly-useful modeling tool for TB diagnostics. While the generation of specific estimates is not our primary aim, it is

essential for model calibration and validation, and to ensure that the model can generate locally-relevant results. We will validate our model through comparison against existing modeling projects evaluating the impact of Xpert MTB/RIF in India, South Africa, and Tanzania. By the time our model is complete, we anticipate that results from these models – each of which uses local data – will be published (C. Dye, T. Cohen, personal communication). Thus, we will be able to demonstrate that our model generates similar results, and to describe important differences between the various modeling approaches. We will then engage decision-makers (e.g. National TB Program managers) in urban Brazil, urban India, rural Malawi and Uganda, and rural Viet Nam – settings in which our study team has direct experience – to ensure that the model produces useful results for their local situations. We will document this process of local engagement and disseminate lessons learned. During this process, we also anticipate that the model will be used to answer specific questions of local interest that will not be addressed by other published models. These include: deployment of Xpert MTB/RIF centrally vs. peripherally, informing a "target product profile" for future TB diagnostics in various locations, and the potential impact of empiric TB treatment. If successful in creating a flexible model capable of answering locally-relevant questions, we intend to apply for additional funding to use the model for a variety of analyses based on end-user feedback.

3.3.2.2. Analyses and Outcomes

Outcomes	Analytic Strategy
Primary: 10-year TB incidence, prevalence, and mortality	Difference-equation modeling
Secondary: Incremental cost-effectiveness, accounting for transmission	Dynamic cost-effectiveness analysis
Secondary: Relationship between scale-up speed and TB epidemiology	Difference-equation modeling
Secondary: Key parameters in projections of impact/cost-effectiveness	Sensitivity analysis

As stated above, we will perform these analyses first in already-studied populations for model validation, then apply them to local scenarios in areas in which we have ongoing collaborations. We hypothesize that the impact of scaling-up TB diagnostics on incidence and mortality will depend heavily on local operational realities, particularly access to care and quality of existing diagnosis. We hypothesize that cost-effectiveness of scale-up will fall under standard thresholds (e.g., gross domestic product per capita[56]) but will exceed the capacity of many national TB control programs in terms of affordability. Thus, while we will produce numerical estimates of impact and cost-effectiveness, our primary analytic focus is to explore the operational and epidemiological factors having greatest influence over these estimates at the local level, not to create a global estimate of the impact of TB diagnostic (e.g., Xpert MTB/RIF) scale-up.

Regarding cost-effectiveness analysis, we will initially take the perspective of the healthcare system (with capacity to incorporate a societal perspective, as recommended[57]), since existing data on patient and societal costs of TB diagnosis and treatment are sparse. Although we will report 10-year outcomes in terms of averted incidence and mortality, we will discount future costs and QALYs for the purpose of cost-effectiveness analysis. Costs will be enumerated using a "modified ingredients" approach[58] that will incorporate local product costs and existing diagnostic algorithms. Costs associated with diagnosing patients with conditions other than TB will be incorporated, including treatment costs for false-positives, as we have done before.[17] This model will be among the first to incorporate dynamic cost-effectiveness analysis for a TB diagnostic intervention.

3.3.3. Specific Aim 3: Dissemination Research

If a flexible mathematical model is truly to have global impact on decision-making, it must be made not just publicly available, but usable and widely known – both in simple form to decision-makers without modeling expertise, and in well-documented form (i.e., user manual and training videos), with technical support, to teams of experts. We plan for this project to serve as an exemplar of rapid model dissemination; decisions about scaling up TB diagnostics are actively being made across the globe, such that a delay in dissemination is equivalent to a reduction in impact.

We will adopt a two-pronged dissemination strategy. First, using the example of a recently-developed internet malaria model,[30] we will create a simplified (and thus rapidly-calculable) epidemic model of TB with a public user interface. Unlike the malaria model, neither our model code nor the equation compiler will remain proprietary. The interface will be constructed using BaseCase, a widely-used cloud-computing software solution for building web interfaces to economic and mathematical models.[59] This software will enable us to create and maintain a public user interface at low initial cost, with an option to expand (e.g., web development, and permanent hosting) if successful. We will publicize this model broadly, including through open-source scientific publication (e.g., PLoS or BMC), posting on widely-trafficked websites (e.g., tbevidence.org, videos

on YouTube and SciVee), at scientific meetings, and through word of mouth. We will track utilization of the model and ask users to complete a survey regarding dissemination practices while their results are computed.

Although a simplified model with public interface is helpful for individual practitioners and local leaders with few resources, we hope also to make our model useful to groups making larger-scale decisions about scaling up TB diagnostics. These teams will generally include technical experts with sufficient background to utilize additional model complexity, and also to adapt or improve the existing model structure to answer new questions. For these individuals, the major barrier to utilization of the model will be a lack of technical support – understanding the model code and learning from its developers how to adapt it. Thus, our second major dissemination strategy will be the development of a three-day workshop, held in a high-burden country (e.g., India or South Africa), that will include background on TB diagnostics modeling, detailed description of the model, hands-on exercises requiring participants to add prototypical elements to the model, and one-on-one question/answer sessions with our study team. We will aggressively recruit participants from high-burden areas who are likely to best understand the operational aspects of TB diagnosis in their locales, post all educational materials publicly on the Web, and provide ongoing support to participants as they adapt the model to questions of greatest local interest. We will also study the process of dissemination, asking participants to complete surveys and participate in focus groups that aim to improve practices in disseminating results from mathematical models to decision-makers in the field. By emphasizing and studying the process of dissemination, targeting different dissemination techniques to stakeholders with different levels of expertise, this project will serve as an example of "best practices" in translating results from theoretical models into meaningful decisions "on the ground."

3.3.4 Study Timeline

		Year of Study			
		1		2	
		0-6 m	6-12 m	0-6 m	6-12 m
Activities Planned	Aim 1: Model Development	X			
	Aim 1: Model Checking/Parameterization		X		
	Aim 2: Model Validation		X		
	Aim 2: Consultation with Local Experts			X	
	Aim 3: Web Interface		Development	Goes Live	Support
	Aim 3: Expert Workshop			Recruitment & Development	Workshop
	Dissemination of Results/Best Practices			X	X

3.3.5. Limitations and Strengths

Timing is a particular challenge for this study. On one hand, decisions about scaling up TB diagnostics are already being made, such that any delay in development or dissemination is likely to reduce impact. As a result, we have targeted an aggressive timeline and adopted innovative practices (e.g., open-source model) aimed at disseminating model findings as rapidly as possible. These considerations must be balanced against the need to develop a high-quality model with rigorous checks of performance (internal validity) and faithfulness to the diagnostic process as actually implemented in various locales (external validity). Thus, this project runs simultaneous risks of being developed and disseminated too late to have the desired impact, and of being made available before the implications of its findings can be fully explored. However, the only alternative to grappling with these time constraints is to forego modeling and allow policy decisions to be made in the absence of a comprehensive evidence base. We do not believe this is an acceptable option.

We are also keenly aware of the challenge of creating a model that appropriately balances simplicity of use for end-users against the need for complexity to faithfully represent the TB diagnostic process. This is the basis of our two-pronged dissemination strategy, with simultaneous development of a simple public model and a complex and well-documented model (with a dissemination plan) for experts.

As described above, strengths of this project include: (a) innovative approach, (b) unique expertise of the study team, (c) use of dynamic modeling to evaluate the operational and economic implications of TB diagnosis, (d) policy relevance and potential to be used by those without modeling expertise, (e) emphasis on transparency and engagement of the scientific community, (f) focus on dissemination, and (g) potential impact on the TB epidemic across a wide array of local experiences. As a scientific community, we must take an active role in translating the advances of science into the hands of decision-makers, both local and global. This project takes a significant step in that direction, aiming to save the lives of TB patients worldwide by determining how best to deliver effective diagnosis to their doorstep.