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A modelling framework to support the selection and implementation of new tuberculosis diagnostic tools

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SUMMARY

Efforts to stimulate technological innovation in the diagnosis of tuberculosis (TB) have resulted in the recent introduction of several novel diagnostic tools. As these products come to market, policy makers must make difficult decisions about which of the available tools to implement. This choice should depend not only on the test characteristics (e.g., sensitivity and specificity) of the tools, but also on how they will be used within the existing health care infrastructure. Accordingly, policy makers choosing between diagnostic strategies must decide: 1) What is the best combination of tools to select? 2) Who should be tested with the new tools? and 3) Will these tools complement or replace existing diagnostics? The best choice of diagnostic strategy will likely vary between settings with different epidemiology (e.g., levels of TB incidence, human immunodeficiency virus co-infection and drug-resistant TB) and structural and resource constraints (e.g., existing diagnostic pathways, human resources and laboratory capacity). We propose a joint modelling framework that includes a tuberculosis (TB) transmission component (a dynamic epidemiological model) and a health system component (an operational systems model) to support diagnostic strategy decisions. This modelling approach captures the complex feedback loops in this system: new diagnostic strategies alter the demands on and performance of health systems that impact TB transmission dynamics which, in turn, result in further changes to demands on the health system. We demonstrate the use of a simplified model to support the rational choice of a diagnostic strategy based on health systems requirements, patient outcomes and population-level TB impact.

KEY WORDS: modelling; TB diagnostics; simulation; transmission

HHL and IL contributed equally in the writing of this article.

Previous articles in this series **Editorial:** Enarson D A. Operational research, a State of the Art series in the *Journal.* Int J Tuberc Lung Dis 2011; 15(1): 3. **No 1:** Lienhardt C, Cobelens F G J. Operational research for improved tuberculosis control: the scope, the needs and the way forward. Int J Tuberc Lung Dis 2011; 15(1): 6–13. **No 2:** Harries A D, Rusen I D, Reid T, et al. The Union and Médecins Sans Frontières approach to operational research. Int J Tuberc Lung Dis 2011; 15(2): 144–154. **No 3:** Rieder H L, Lauritsen J M. Quality assurance of data: ensuring that numbers reflect operational definitions and contain real measurements. Int J Tuberc Lung Dis 2011; 15(3): 296–304. **No 4**: Bratton D J, Nunn A J. Alternative approaches to tuberculosis treatment evaluation: the role of pragmatic trials. Int J Tuberc Lung Dis 2011; 15(4): 440–446. **No 5**: Menzies D. Systematic reviews and meta-analyses. Int J Tuberc Lung Dis 2011; 15(5): 582–593. **No 6**: Mann G H, Thomson R, Jin C, et al. The role of health economics research in implementation research for health systems strengthening. Int J Tuberc Lung Dis 2011; 15(6): 715–721. **No 7**: Squire S B, Ramsay A R C, van den Hof S, et al. Making innovations accessible to the poor through implementation research. Int J Tuberc Lung Dis 2011; 15(7): 862–870.

INVESTMENT IN and coordination of efforts to develop new diagnostic tests for TB have resulted in promising new tools (e.g., polymerase chain reaction-based DNA amplification tests) and modifications of existing approaches (e.g., light-emitting diode microscopy, front-loading and sputum processing with bleach or by centrifugation).[1–6] Faced with this growing arsenal of diagnostic options, policy makers must make difficult choices about which new technology or combination of technologies to implement, and how to incorporate them into diagnostic algorithms. These choices are further complicated by the rapidly changing policy environment, where investments made based on current recommendations might need to be modified in response to subsequent recommendations.[7] Ideally, policy makers would select the

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most cost-effective tools that best improve patient outcomes and, by reducing the expected duration of undetected infectious disease, limit transmission in the community. In reality, understanding the health system requirements and population-level impact of diagnostic tools is challenging, as the long-term dynamics of TB epidemics make it difficult to measure the epidemiological impact of interventions, and the wide array of tools (and potential combinations of these tools) makes testing and comparing all options impossible.

While most previous studies of the potential impact of new TB diagnostics have focused on the test characteristics of the tools (i.e., sensitivity and specificity),[8,9] we suggest that a more complete understanding of impact also requires consideration of how these tools will be used within diagnostic pathways. Accordingly, these decisions require the comparison of different diagnostic strategies that incorporate consideration of both the technical characteristics of the tools and how these tools will actually be implemented within a health system, and at what cost. Different diagnostic strategies may prove superior in settings with different levels of human immunodeficiency virus (HIV) associated or drug-resistant TB, or in areas with a different existing health care infrastructure.

Traditionally, separate modelling approaches have been used to project the impact of new interventions on disease dynamics (i.e., dynamic epidemiological modelling) and to understand the impact of new technologies on the performance of health systems (i.e., operational modelling). While several previous studies have discussed the importance of the health system context for TB diagnostics,[8,10–13] a practical methodology for bringing this context into rational policy decision making has not been suggested. We therefore propose a new type of linked model to assess the potential impact of new diagnostic strategies on health system costs and infrastructure, patient access and outcomes, and the TB epidemic. As there is feedback between the dynamic epidemiological and operational aspects of the system (Figure 1), this linked modelling approach provides a natural framework for these comparisons.

In the present study, we illustrate the development and use of a linked modelling approach for assessing effects using a simplified example of a new diagnostic tool that requires less processing time, fewer patient visits and has increased test sensitivity in comparison to smear microscopy. We first introduce each modelling component separately; we then describe how they can be linked to compare different diagnostic strategies.

DEFINING THE POTENTIAL IMPACT OF A NEW DIAGNOSTIC TOOL

Standard approaches for the diagnosis of pulmonary TB rely on microscopic examination of sputum samples collected from TB suspects over at least 2 days. This approach has several clear limitations: it requires that a patient return to a health care facility more than once, resulting in higher costs to patients[14] and more opportunity for losses to follow-up,[15–17] it cannot differentiate between *M. tuberculosis* and other non-tuberculosis mycobacteria and it does not detect drug resistance.

There are several different potential levels of effect from a new diagnostic tool that overcomes these limitations (Table 1). First, the new diagnostic may have a beneficial effect for patients who receive an early diagnosis because of a test with increased sensitivity. A test that does not require multiple visits will reduce patient costs and limit losses to follow-up,[4] and individuals detected at earlier disease stages may have improved treatment outcomes.[15] Second, the new diagnostic will have effects at the health systems level; in particular, there may be initial, or ongoing, investment in equipment, training and personnel requirements associated with the new tool. Third, new diagnostics may also positively impact the epidemiology of TB in a community. In particular, if the new tool is associated with increased case detection and treatment, it will likely reduce the prevalence of infectious source cases and thus reduce TB transmission.

Understanding the overall impact of a new diagnos-

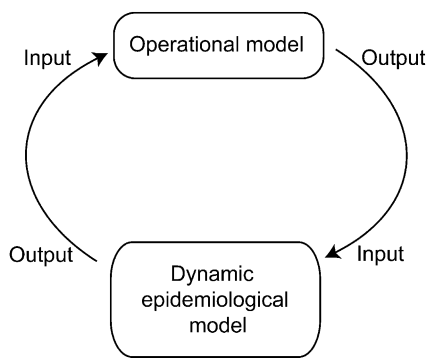

Figure 1 Feedback loop between operational and dynamic epidemiological models.

Table 1 Potential effects of a new diagnostic tool

Effect level	Metrics
Patient	Diagnosis outcomes and time to diagnosis Treatment outcomes and time to cure/fail Number of visits to health system required Cost per health facility visit
Health system	Staff requirements by skill type and shift pattern Equipment requirements Health system investment and ongoing costs Treatment requirements and costs Capacity of the health system and bottlenecks
Population	Tuberculosis prevalence Tuberculosis incidence

tic is challenging not only because it is necessary to consider several levels of effect, but also because there is complicated feedback among these levels. While some health system effects are easy to anticipate (e.g., the upfront costs of new equipment and training requirements), there are also other, less obvious consequences of the introduction of new diagnostic tools. A new tool may reduce one source of delay in the laboratory, only to result in the appearance of a new downstream bottleneck that prevents the full effects of the new tool from being appreciated. Conversely, a new tool may reduce the need for alternative testing among those not diagnosed by the less sensitive existing diagnostic (i.e., smear-negative TB suspects), thereby unexpectedly freeing up additional resources. Changing patterns of patient diagnosis can also change demand in other areas of the health system. For example, a more sensitive TB diagnostic may initially produce increases in the number of TB patients that are detected and thus require treatment. This initially adds to the burden on health care providers and requires additional investment to support treatment, but over time, it may actually reduce transmission in the population and relieve these burdens.

METHODS

Assessing the total effect of a new diagnostic tool requires attention not only to individual benefits, but also to the impact of interventions at the health system and population levels. As field testing of all possible uses and combinations of interventions is not feasible and the effects will likely differ between settings, we propose a modelling framework to help inform local decision making. The interrelated nature of the patient-, heath system- and population-level effects suggests the benefit of developing a linked operational and transmission model that can simulate feedback in the system and expand our ability to compare the total effect of diagnostic strategies. Before presenting our linked model, we briefly describe the general approaches typically used for operational and dynamic epidemiological modelling.

Operational models

Operational models have been widely used to plan and assess the performance and efficiency of processes in industrial and commercial settings,[18–20] and have been increasingly used to help improve the performance of the health sector.[21,22] Some previous applications include models of automotive manufacturing facilities[23,24] and retail operations.[25] While there are many examples of operational modelling of health systems in high-income countries, to our knowledge there are few applied to model health systems in low- or middle-income countries.[26,27]

Many operational models use a discrete event simulation approach where the system modelled is first defined in terms of its most important elements, including the items or people processed through the facility, resources, activities, rules and the process flow. The required outputs of the model are defined (e.g., productivity, costs, identification of bottlenecks, capacity and sensitivity to changes), along with the key input parameters to be investigated. Once the system is defined and appropriate parameter inputs are assigned (e.g., the number of items entering the system, the quantity of resources and the time for completing particular activities), then simulations can be run to assess the relative effect of different assumptions about the values of input parameters on model output.

Dynamic epidemiological models

Mathematical models that describe the within-host natural history of infection and allow for the simple representation of transmission have offered many insights into the dynamics of infectious diseases in communities and approaches for disease control.[28]

Many of these models are formulated as differential equation models that specify how a population is divided into mutually exclusive health states (e.g., susceptible to infection, infectious, recovered) and how the flow of individuals between states depends on the current state of the system (e.g., how the incidence of infection depends on the prevalence of disease in the population). Outputs of these models are most naturally shown as trends in the proportion of population in each state over time (e.g., the prevalence of disease), but they can also provide insight into more complex considerations of cost-effectiveness associated with interventions.[29,30] While some insight from simple models can be gained through analytical approaches, more complicated models usually require numerical simulation. Once the model equations and input parameters (e.g., rate of recovery from infectiousness, treatment coverage levels, disease-associated mortality) are defined, simulation permits the rapid comparison of the relative impact of different modelled interventions.

A linked operational and dynamic epidemiological model for a new TB diagnostic

The operational model component is structured to reflect diagnostic pathways for TB suspects, specimen collection and laboratory procedures, and treatment algorithms for TB patients based on the current World Health Organization (WHO) guidelines.[31] The model structure includes entities (e.g., patients, sputum, samples and vehicles), activities (e.g., sputum collection, microscopy and diagnosis), queues (e.g., patient waiting areas and samples waiting to be processed) and resources (e.g., microscopy technicians and clinicians). A simplified diagram of the process for suspects seeking TB diagnosis and then subsequent treatment as appropriate is shown in Figure 2. All activities from TB suspects arriving at the diagnostic centre, through reception, sputum collection, consultation, diagnosis and treatment, are modelled. This includes patients

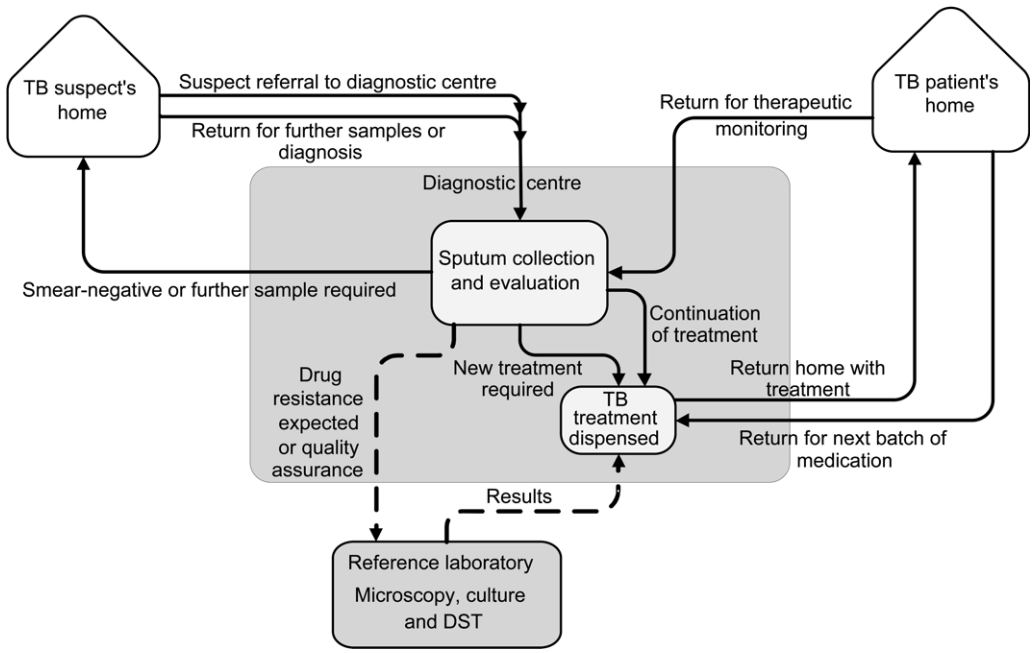

Figure 2 Simplified diagram of TB diagnostic and treatment process. The figure shows the flow for patients and samples through a single diagnostic centre, with samples being transported to a central reference laboratory for DST if necessary. TB suspects are referred to the diagnostic centre for testing, where they provide a sputum sample which is examined using microscopy. In the base case, a second sample is required so suspects return home, returning the next day to provide a second sample. Some suspects will receive a diagnosis the same day, while others may have to return home and return a subsequent day to receive diagnosis. If diagnosed with TB, they will receive treatment and return home (icon in top right). TB patients are required to return to the diagnostic centre every 2 weeks to receive subsequent medication. Therapeutic monitoring requires TB patients to return to the diagnostic centre for further sputum examination at three points during treatment: at the end of the intensive phase (Month 2 for new patients, Month 3 for retreatment patients), at Month 5 for all patients and at treatment completion (Month 6 for new patients and Month 8 for retreatment patients). If smears are positive during these follow-up assessments, further specimens are required for microscopy, culture and DST at the reference laboratory in accordance with current World Health Organization guidelines.[31] Every time a patient returns home, there is a probability that he/she will not return to the diagnostic centre and therefore will be lost to follow-up or treatment. TB = tuberculosis; DST = drug susceptibility testing.

Table 2 List of inputs into and outputs from the operational and transmission models. The linkage between the two models results from using model outputs from one model as inputs for the other

Operational model	
Input	**Output**
Average number of tuberculosis suspects coming for diagnosis per diagnostic centre per day	Average time to receive diagnosis
Proportion of smear-positive tests	Loss to follow-up (diagnostic default)
Treatment times	Number of visits to diagnostic centre
Number of microscopy staff at diagnostic centre	Diagnosis outcomes
Laboratory time per sample	Treatment outcomes
Staff shift patterns	Time to complete treatment
Physician availability	Default in treatment
Probability of default during diagnostic and treatment pathways	Number of samples processed
Transport availability for samples	Health system costs
Unit costs	Patient costs
Transmission model	
Output	**Input**
Tuberculosis incidence	Transmission rate
Tuberculosis prevalence	Primary progression rate
	Reactivation rate
	Natural cure rate
	Tuberculosis-specific mortality
	Diagnostic test performance—sensitivity
	Loss to follow-up (diagnostic default)
	Duration parameters (e.g., from symptom onset to health centre visit, from seeking diagnosis to receiving diagnosis)
	Tuberculosis treatment parameters (e.g., fraction of initial defaulters, treatment success rate, treatment failure and death rate)

returning home between sputum sample collections and before diagnosis is received. Diagnostic algorithms for new TB suspects and retreatment patients are represented in the model. Sample collection and sputum examination by microscopy are also modelled in detail at the diagnostic centre and in the reference laboratory. At the reference laboratory, culture and drug susceptibility testing are performed consistent with current diagnostic and treatment algorithms.[31]

Necessary input data for and output from the operational model are provided in Table 2. We use the WITNESS modelling tool (WITNESS PwE 2.0 Service and Process Performance Edition, Lanner, Redditch, UK, http://www.lanner.com/en/witness.cfm), a discrete event simulation software, to produce the simulation results. The WITNESS software utilises a graphic-based approach that allows for a simple visual representation of model processes; these graphic features facilitate communication between model developers and decision makers and allow for rapid development, validation and simulation.

The dynamic epidemiological component is based on a differential equation model that captures the most important features of the natural history of TB (Figure 3, top panel).[32] As with many TB transmission models, we include states that include individuals who are susceptible (S), latently infected (Lf and Ls), infectious (Isp and Isn), and recovered (R). Several previous assessments of the potential impact of new diagnostics on transmission dynamics of TB have simply reduced the average infectious period for those with TB by increasing the rate at which individuals recover; however, this approach cannot account for how the diagnostic will operate within existing diagnostic pathways.[33,34] To incorporate the health system context where the diagnostic tool will be employed, we further expand the active disease states of the model to include the details of the pathway from

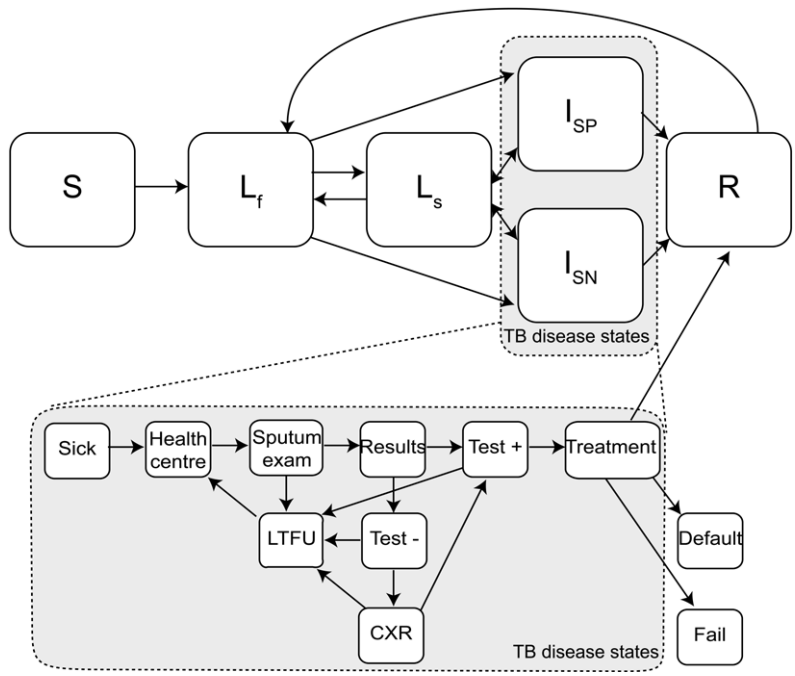

Figure 3 Graphic representation of the compartmental transmission dynamic model. The upper part of the figure shows a structure that is similar to many TB transmission models: the susceptible population (S), once exposed to infectious cases, may be infected and enter the latent infection states (Lf for early latent stage and Ls for late latent stage). Latently infected people can progress (from Lf) or reactivate (Ls) to the active disease state. Patients with active disease have either smear-positive pulmonary (Isp) or smear-negative pulmonary (Isn) disease (those with extra-pulmonary TB do not contribute to the transmission dynamics of TB and therefore are not accounted for in this model). Those with TB may recover from disease through case detection and treatment (R), self-cure and return to the latent infection state, or die from TB.

The lower part of the figure shows how this simple standard TB transmission model is further expanded to investigate the effect of diagnostic tools within health systems. This requires additional representations of patient diagnostic pathways within the model. Here we include an early TB disease state ('sick') that prompts a person to visit a local health centre for medical attention ('health centre'). After some delay, a clinician might suspect TB and refer the patient to a diagnostic centre for sputum examination ('sputum exam'). The TB suspect may be lost to follow-up during this process (LTFU). Among those receiving a diagnostic test, there is a delay before the results become available (Results). Some of these tested suspects will test positive ('test+') and this fraction represents the sensitivity of sputum smear microscopy (true-positive). Those who test negative (test–) will either receive CXR if it is available (CXR), or be lost to follow-up with the false impression of not having TB (LTFU). A fraction of patients who receive CXR will test positive ('test+'). For those who test positive (from either sputum examination or CXR), a proportion will never initiate treatment due to loss to follow-up (LTFU, also known as initial defaulters). The rest of those testing positive will be treated (treatment) after some delay and may then have different treatment outcomes ('R', 'default', 'fail'). TB = tuberculosis; CXR = chest X-ray.

disease onset to TB diagnosis and initiation of treatment. Figure 3 (top and bottom panels together) illustrates an expanded transmission model using a diagnostic algorithm for a pulmonary TB suspect that is based on sputum smear microscopy and chest X-ray for smear-negative cases. By incorporating the patient pathway and mechanisms of action of diagnostic tools within the health system context, the expanded transmission model provides a platform to systematically understand how the improved test characteristics of new tools can be translated into population impact on transmission and epidemiology of TB. Necessary input data for and output from the transmission model are provided in Table 2. We use Berkeley Madonna (Berkeley Madonna 8.3.18, University of California, Berkeley, CA, USA) as our numerical solver for this differential equation model.

The operational and dynamic epidemiological model components are linked by using selected outputs of one model to serve as the inputs into the other. For example, the incidence of TB is an output of the transmission model; this informs the input into the operational model through the number of TB suspects coming for diagnosis in the health system (Table 2).

Model scenarios

While several novel diagnostic tools that address one or more limitations of standard smear microscopy are now available,[8] for illustrative purposes we consider the potential impact of a new generic diagnostic that has improved sensitivity, requires shorter laboratory processing times and may reduce the number of patient visits compared with standard smear microscopy. We use information that we collected from Tanzania and Malawi to demonstrate the development and application of a linked modelling approach. We compare a base case where sputum smear examination using Ziehl Neelsen and light microscopy is used as the diagnostic to an alternative scenario with an improved diagnostic requiring fewer sputum samples, shorter laboratory processing times and increased diagnostic sensitivity (Table 3). The inputs and outputs of the operational and dynamic epidemiological models are exchanged annually; we present results over 10 years to illustrate short-term and longer-term effects of these two diagnostic strategies.

Table 3 Test scenarios

Test scenarios	Sputum samples *n*	Laboratory time needed per sample min	Sensitivity of diagnostic among new pulmonary tuberculosis cases %
Base case	2 (spot–morning)	15	50
Alternative	1 (spot)	5	65

RESULTS

To illustrate the need for a combined modelling approach to evaluate the impact of new diagnostics, and to demonstrate the feasibility of such an approach through actual development and linkage of the models, we present selected results from our linked models (Table 4). The results from the operational component

Table 4 Selected inputs for and outputs from the illustrative linked model

	Operational model: Input			Operational model: Output		
	Year 1	Year 5	Year 10	Year 1	Year 5	Year 10
	Tuberculosis suspects coming for diagnosis per day*			Average time to diagnosis, days		
Base case	15.0	13.5	12.2	4.32	4.12	4.16
Alternative†	15.0 (0.0%)	13.0 (–3.7%)	11.5 (–5.7%)	1.72 (–60.2%)	1.68 (–59.0%)	1.63 (–60.8%)
	Proportion of smear-positive tests, %			Loss to follow-up, % (diagnostic default)		
Base case	15	15	15	6.0	6.3	6.2
Alternative†	19 (+26.7%)	19 (+26.7%)	19 (+26.7%)	0.1 (–98%)	0.0 (–100%)	0.0 (–100%)
	Laboratory time per sample, min			Patients requiring treatment per diagnostic centre*		
Base case	15	15	15	874	734	716
Alternative†	5 (–66.7%)	5 (–66.7%)	5 (–66.7%)	1021 (+16.8%)	891 (+21.4%)	857 (+19.7%)
	Transmission model: Output			Transmission model: Input		
	Year 1	Year 5	Year 10	Year 1	Year 5	Year 10
	Annual tuberculosis incidence (per 100 000)			Loss to follow-up, % (diagnostic default)		
Base case	113	103	93	6.0	6.3	6.2
Alternative†	112 (–0.9%)	100 (–2.9%)	87 (–6.4%)	0.1 (–98%)	0.0 (–100%)	0.0 (–100%)
	TB prevalence (per 100 000)			Average time to diagnosis, days		
Base case	172	143	118	4.32	4.12	4.16
Alternative†	160 (–7.0%)	122 (–14.7%)	99 (–16.1%)	1.72 (–60.2%)	1.68 (–59.0%)	1.63 (–60.8%)

*Numbers given are for a sample diagnostic centre.
†Percentages indicate relative difference when comparing alternative to base cases.

of the linked model illustrates that the alternative diagnostic strategy can substantially reduce the average time to diagnosis (~60%), nearly eliminate the fraction of suspects lost to follow-up (~100%) and increase the number of patients accessing treatment at a diagnostic centre (~20%). The linked model was fit to country settings in which TB incidence and prevalence are in decline when smear microscopy (base case) is in use. The transmission model component projects that the alternative diagnostic scenario may result in a more rapid decline in TB incidence and that the proportional reduction in incidence (compared to the base case) will increase over time (~1% in Year 1, ~3% in Year 5 and ~6% in Year 10). These results demonstrate some of the effects different diagnostic tools may have on key outcomes, and are only intended to illustrate the feasibility of a linked modelling approach. Further calibration and analysis are required before more detailed results from such an approach can be presented.

DISCUSSION

The Stop TB Partnership's New Diagnostics Working Group has described a pathway from need assessment to delivery for evidence-based policies for TB diagnosis; this includes concept formation, development, evaluation, demonstration, scale-up and epidemiological impact.[35] Most existing research on TB diagnostics has taken the form of studies to measure the sensitivity and specificity of new tools,[1,3] systematic reviews of these types of studies,[2,36] and demonstration projects.[37] While accurate and efficient diagnostic tools are essential, technological advances alone will not ensure better TB control. The overall effect of these diagnostic tools depends on whether the tools improve the timeliness of administration of effective treatment. Accordingly, understanding the potential effects of diagnostic tools requires consideration of how these tools may modify access to diagnostic services, the loss of patients during the diagnostic (and treatment) processes and the burdens on and performance of the health system itself.[10]

Projecting the overall effects of scaled-up use of a diagnostic tool with improved test characteristics is not easy. First, the design of field studies to evaluate the epidemiological impacts of a new tool presents a major challenge: the impact on transmission cannot be easily observed because of the slow intrinsic dynamics of TB. Incomplete case notification in most areas further complicates the interpretation of trend data for TB incidence. Second, understanding how the adoption of a new diagnostic tool affects overall flow of patients and specimens (and resultant burdens on personnel and equipment) is not easy to predict and requires detailed understanding of diagnostic pathways and health systems infrastructure. In the present study, we discuss the role of operational and dynamic epidemiological models for comparing the potential overall effects of different diagnostic tools and strategies.

We have provided a rationale for linking operational and dynamic epidemiological models; the simple results included here show how the test characteristics of diagnostic tools (e.g., sensitivity and number of specimens required for diagnosis) have an effect on important epidemiological parameters (e.g., initial default during diagnosis and thus the average duration of infectiousness). Similarly, changing epidemiological parameters (e.g., TB incidence) affect the demand on health systems (e.g., TB suspects requiring diagnostic services). However, we also believe that operational models and dynamic epidemiological models can also be of tremendous use when used independently of one another. For example, analysis of the operational model developed here shows the non-trivial impact of a new, more sensitive diagnostic tool on the number of patients requiring treatment services (Table 4). This type of effect is important to anticipate in advance of adopting a new diagnostic strategy. Similarly, the dynamic epidemiological model can itself provide important insight into how improved diagnostic performances (e.g., test sensitivity) translate into reduced TB incidence and how external factors (e.g., patient delay in seeking medical attention and loss to follow-up along the patient pathway) could undermine their effects. Further research is required to identify the circumstances in which linked models result in substantially different insight than models used in parallel.

This modelling framework identifies several types of input that are important to project the impact of diagnostic tools. In many settings, detailed knowledge of flows (of patients, specimens and information) and related bottlenecks in the health system may not be available. Models that include operational components demonstrate why these logistical issues are important for predicting the effectiveness of diagnostic tools, and sensitivity and uncertainty analysis can be used to identify which unknown operational components are most important to measure.

The goal of this model development activity is to demonstrate the feasibility of the linked modelling approach. An essential consideration that we have not included in the model results presented here is the costs and comparative cost-effectiveness of different diagnostic strategies. As noted above, modelling provides an opportunity for attaching health system and patient costs to the different elements of a diagnostic process and weighting them by the probability of each element taking place, including accounting for the impact of bottlenecks and economies of scale. The operational model can be run for multiple years, enabling longer-term cost projections to be considered.

Health economic modelling has typically used static decision models, with a focus on health system costs.[38] Such models do not allow us to assess the

longer-term impacts on epidemiology. In our linked model, the long-term impact of a new diagnostic on TB epidemiology can be projected from the dynamic epidemiological component of the model. Linked modelling therefore allows a broader range of outcomes to be assessed against cost, such as infections or deaths averted over longer time frames. Models can also be structured to allow for outcomes and costs faced by groups of patients disaggregated by factors such as HIV status, poverty and sex. Thus, the likely effects of new diagnostic strategies on health equity can also be assessed.

We have also not included drug-resistant TB in the transmission component of the current model, but plan to expand this work to consider diagnostics that detect drug-resistant TB. Models that include drug resistance and costs will be used in future work that addresses more realistic decisions faced by country-level decision makers. For example, many questions are currently related to the potential impact of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA)[3] as a replacement for (or in addition to) microscopy as specified in the WHO-recommended algorithms that would be amenable for study with these models.[39,40]

In conclusion, we suggest that operational and dynamic epidemiological models can serve to support inference on the overall effects of diagnostic strategies. In this study, we developed a simple example to demonstrate the structure and use of a linked model that can be used to compare the projected individual-, health system- and population-level effects of diagnostic strategies that incorporate the use of new diagnostic technologies. The proposed models are flexible and can be used to assess different diagnostic options (e.g., different tools and different ways of using those tools within the health system), and can be adjusted to reflect specific epidemiological situations and health system infrastructures. Accordingly, this linked modelling approach can serve as an appropriate method for comparing strategies and helping policy makers who must simultaneously consider their existing infrastructure and capabilities, their local epidemiology and what future tools may be in the pipeline, before committing to a particular decision. This assistance is particularly important as local policy makers grapple with a rapidly expanding list of diagnostic recommendations from the WHO.[7]

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References

1 Marais B J, Brittle W, Painczyk K, et al. Use of light-emitting diode fluorescence microscopy to detect acid-fast bacilli in sputum. Clin Infect Dis 2008; 47: 203–207.
2 Morgan M, Kalantri S, Flores L, Pai M. A commercial line probe assay for the rapid detection of rifampicin resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. BMC Infect Dis 2005; 5: 62.
3 Boehme C C, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010; 363: 1005–1015.
4 Ramsay A, Yassin M A, Cambanis A, et al. Front-loading sputum microscopy services: an opportunity to optimise smear-based case detection of tuberculosis in high prevalence countries. J Trop Med 2009; 2009: 398767.
5 Mase S R, Ramsay A, Ng V, et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review. Int J Tuberc Lung Dis 2007; 11: 485–495.
6 Angeby K A, Hoffner S E, Diwan V K. Should the 'bleach microscopy method' be recommended for improved case detection of tuberculosis? Literature review and key person analysis. Int J Tuberc Lung Dis 2004; 8: 806–815.
7 van Kampen S C, Ramsay A R, Anthony R M, Klatser P R. Retooling national TB control programmes (NTPs) with new diagnostics: the NTP perspective. PLoS One 2010; 5: e11649.
8 Wallis R S, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. Lancet 2010; 375: 1920–1937.
9 Pai M, Ramsay A, O'Brien R. Evidence-based tuberculosis diagnosis. PLoS Med 2008; 5: e156.
10 Mann G, Squire S B, Bissell K, et al. Beyond accuracy: creating a comprehensive evidence base for TB diagnostic tools. Int J Tuberc Lung Dis 2010; 14: 1518–1524.
11 Small P M, Pai M. Tuberculosis diagnosis—time for a game change. N Engl J Med 2010; 363: 1070–1071.
12 Small P M. Strengthening laboratory services for today and tomorrow. Int J Tuberc Lung Dis 2008; 12: 1105–1109.
13 Perkins M D, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis 2007; 196 (Suppl 1): S15–S27.
14 Kemp J R, Mann G, Simwaka B N, Salaniponi F M, Squire S B. Can Malawi's poor afford free tuberculosis services? Patient and household costs associated with a tuberculosis diagnosis in Lilongwe. Bull World Health Organ 2007; 85: 580–585.
15 Squire S B, Belaye A K, Kashoti A, et al. 'Lost' smear-positive pulmonary tuberculosis cases: where are they and why did we lose them? Int J Tuberc Lung Dis 2005; 9: 25–31.
16 Creek T L, Lockman S, Kenyon T A, et al. Completeness and timeliness of treatment initiation after laboratory diagnosis of tuberculosis in Gaborone, Botswana. Int J Tuberc Lung Dis 2000; 4: 956–961.
17 Nyirenda T, Harries A D, Banerjee A, Salaniponi F M. Registration and treatment of patients with smear-positive pulmonary tuberculosis. Int J Tuberc Lung Dis 1998; 2: 944–945.
18 Robinson S. Simulation: the practice of model development and use. Warwick, UK: Warwick Business School, University of Warwick: John Wiley & Sons, 2003.
19 Lanner. Case studies. Redditch, UK: Lanner, 2008–2011. http://www.lanner.com/en/case-studies.cfm?offset=6 Accessed May 2011.
20 SIMUL8 Corporation. Case studies. Boston, MA, USA: SIMUL8 Corporation, 2011. http://www.simul8.com/solutions/case_studies/ Accessed May 2011.

21 Günal M, Pidd M. Discrete event simulation for performance modelling in health care: a review of the literature. J Simulation 2010; 4: 42–51.
22 Brailsford S, Harper P, Patel B, Pitt M. An analysis of the academic literature on simulation and modelling in health care. J Simulation 2009; 3: 130–140.
23 Williams E J, VanBelle R. Exploring alternatives in an automotive industry job shop using simulation. Simulation 2005; 81: 637.
24 Mayer G, Spieckermann S. Life-cycle of simulation models: requirements and case studies in the automotive industry. J Simulation 2010; 4: 255–259.
25 Siebers P, Aickelin U, Celia H, Clegg C. Towards the development of a simulator for investigating the impact of people management practices on retail performance. J Simulation 2010; http://dx.doi.org/10.1057/jos.2010.20.
26 Katsaliaki K, Mustafee N. Applications of simulation research within the healthcare context. J Oper Research Society 2011; 62: 1431–1451.
27 Rauner M S, Brailsford S C, Flessa S. Use of discrete-event simulation to evaluate strategies for the prevention of mother-to-child transmission of HIV in developing countries. J Oper Research Society 2005; 56: 222–233.
28 Anderson R M, May R M. Infectious diseases of humans: dynamics and control. Oxford, UK: Oxford University Press, 1991.
29 Murray C J, Salomon J A. Modeling the impact of global tuberculosis control strategies. Proc Natl Acad Sci USA 1998; 95: 13881–13886.
30 Baltussen R, Floyd K, Dye C. Cost effectiveness analysis of strategies for tuberculosis control in developing countries. BMJ 2005; 331: 1364.
31 World Health Organization. Treatment of tuberculosis: guidelines. 4th ed. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO, 2009.
32 Blower S M, McLean A R, Porco T C, et al. The intrinsic transmission dynamics of tuberculosis epidemics. Nat Med 1995; 1: 815–821.
33 Abu-Raddad L J, Sabatelli L, Achterberg J T, et al. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. Proc Natl Acad Sci USA 2009; 106: 13980–13985.
34 Dowdy D W, Chaisson R E, Maartens G, Corbett E L, Dorman S E. Impact of enhanced tuberculosis diagnosis in South Africa: a mathematical model of expanded culture and drug susceptibility testing. Proc Natl Acad Sci USA 2008; 105: 11293–11298.
35 Stop TB Partnership's New Diagnostics Working Group WHO. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics. Geneva, Switzerland: WHO, 2009.
36 Steingart K R, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006; 6: 570–581.
37 Barnard M, Albert H, Coetzee G, O'Brien R, Bosman M E. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med 2008; 177: 787–792.
38 Soares-Weiser K, Bravo Vergel Y, Beynon S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. Health Technol Assess 2007; 11: iii–iv, ix–206.
39 World Health Organization. WHO endorses new rapid tuberculosis test. Geneva, Switzerland: WHO, 2011. http://www.who.int/tb/laboratory/new_rapid_test/en/index.html Accessed May 2011.
40 World Health Organization. Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB. Geneva, Switzerland: WHO, 2010. http://www.who.int/tb/laboratory/roadmap_xpert_mtb_rif_rev23dec2010.pdf Accessed May 2011.

RÉSUMÉ

Les efforts visant à stimuler des innovations technologiques pour le diagnostic de la tuberculose (TB) ont entraîné l'introduction récente de divers nouveaux outils de diagnostic. Au fur et à mesure de l'apparition de ces produits sur le marché, les décideurs de politique doivent prendre des décisions difficiles au sujet du choix des outils disponibles à mettre en application. Ces choix ne devraient pas dépendre seulement des caractéristiques des tests (par exemple leur sensibilité et leur spécificité, mais aussi de la façon dont ils seraient utilisés au sein de l'infrastructure existante des soins de santé. Par voie de conséquence, les élaborateurs de politique choisissant entre diverses stratégies de diagnostic doivent décider : 1) quelle est la meilleure combinaison d'outils devant être sélectionnée? 2) qui devrait bénéficier d'un test avec les nouveaux outils? et 3) ces outils vont-ils être un complément ou remplacer les outils de diagnostic existants? Le meilleur choix de la stratégie de diagnostic va probablement être différent en fonction des différences de contexte épidémiologique (par exemple, niveaux d'incidence de la TB, co-infection virus de l'immunodéficience humaine et TB à germes résistants) et des contraintes structurelles et financières (par exemple, parcours de diagnostic existants, ressources humaines et compétences du laboratoire). Nous proposons un canevas conjoint de modélisation qui comporte une composante pour la transmission de la TB (un modèle épidémiologique dynamique) et une composante système de santé (un modèle opérationnel de système) afin de servir de support aux décisions de stratégie de diagnostic. Cette approche de modélisation capture les boucles complexes de rétroaction du système : les nouvelles stratégies de diagnostic modifient en effet les demandes imposées aux systèmes de santé et à leurs performances, ce qui a un impact sur la dynamique de transmission de la TB qui, de son côté, entraîne des modifications ultérieures en matière de demandes à l'égard du système de santé. Nous faisons une démonstration de l'utilisation d'un modèle simplifié qui facilite le choix rationnel d'une stratégie de diagnostic basée à la fois sur les exigences des systèmes de santé, les résultats pour le patient et l'impact sur la TB au niveau de la population.

RESUMEN

Las iniciativas encaminadas a fomentar la innovación tecnológica en el diagnóstico de la tuberculosis (TB) han dado lugar a la introducción reciente de instrumentos diagnósticos nuevos. A medida que se comercializan estos productos, los responsables de las políticas sanitarias deben tomar la delicada decisión de elegir los métodos que se pondrán en ejecución. Esta elección debe ser función no solo de las características de las pruebas (es decir su sensibilidad y especificidad), sino también de la manera de aplicarlas en la infraestructura existente de atención sanitaria. En consecuencia, las autoridades que escogerán las estrategias diagnósticas tendrán que decidir: 1) la combinación de instrumentos elegidos; 2) ¿a quién se deben realizar estas pruebas? y 3) ¿complementan o reemplazan estos instrumentos los métodos diagnósticos existentes? Es probable que la mejor estrategia diagnóstica difiera en los entornos que presentan características epidemiológicas diferentes (como los niveles de incidencia de TB, la coinfección por el virus de la inmunodeficiencia humana y la TB farmacorresistente) y limitaciones variables de estructuras y recursos (como las secuencias diagnósticas, los recursos humanos y las capacidades de laboratorio existentes). En el presente artículo se propone un marco mixto de modelización, que comporta un componente relacionado con la transmisión de la TB (un modelo epidemiológico dinámico) y un componente del sistema de salud (un modelo de sistemas operativos), cuyo propósito es respaldar las decisiones estratégicas en materia de diagnóstico. La estrategia de modelización captura los circuitos complejos de retroalimentación en este sistema: las nuevas estrategias diagnósticas modifican las demandas al sistema de salud y el desempeño del mismo, lo cual tiene repercusiones en la dinámica de transmisión de la TB y esta a su vez genera nuevas exigencias a la estructura sanitaria. Se demuestra además la aplicación de un modelo simplificado que respalda la elección racional de una estrategia diagnóstica con base en las necesidades de los sistemas de salud, los desenlaces clínicos de los pacientes y la repercusión sobre la situación de la TB a escala de la población.