Practice of Epidemiology

Modeling the Impact of Alternative Strategies for Rapid Molecular Diagnosis of Tuberculosis in Southeast Asia

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Initially submitted January 21, 2013; accepted for publication August 6, 2013.

Novel diagnostic tests hold promise for improving tuberculosis (TB) control, but their epidemiologic impact remains uncertain. Using data from the World Health Organization (2011–2012), we developed a transmission model to evaluate the deployment of 3 hypothetical TB diagnostic tests in Southeast Asia under idealized scenarios of implementation. We defined diagnostics by their sensitivity for smear-negative TB and proportion of patients testing positive who initiate therapy (“point-of-care amenability”), with tests of increasing point-of-care amenability having lower sensitivity. Implemented in the public sector (35% of care-seeking attempts), each novel test reduced TB incidence by 7%–9% (95% uncertainty range: 4%–13%) and mortality by 20%–22% (95% uncertainty range: 14%–27%) after 10 years. If also deployed in the private sector (65% of attempts), these tests reduced incidence by 13%–16%, whereas a perfect test (100% sensitivity and treatment initiation) reduced incidence by 20%. Annually detecting 20% of prevalent TB cases through targeted screening (70% smear-negative sensitivity, 85% treatment initiation) also reduced incidence by 19%. Sensitivity and point-of-care amenability are equally important considerations when developing novel diagnostic tests for TB. Novel diagnostics can substantially reduce TB incidence and mortality in Southeast Asia but are unlikely to transform TB control unless they are deployed actively and in the private sector.

diagnostic techniques and procedures; epidemiologic methods; Southeast Asia; theoretical models; tuberculosis

Abbreviations: HIV, human immunodeficiency virus; NAAT, nucleic acid amplification test; POC, point-of-care; SEAR, Southeast Asia Region; TB, tuberculosis; UR, uncertainty range; WHO, World Health Organization.

Globally, 8.7 million people develop active tuberculosis (TB) every year, and 1.4 million die (1). Many of those transmission events and deaths could be averted with timely and accurate diagnosis, followed by rapid initiation of treatment. Thus, novel TB diagnostic tests have been prioritized in modern TB research and control efforts (2). Novel tests could fill many important niches for TB diagnosis, including tests for monitoring response to treatment and for detecting extrapulmonary TB (3). One of the greatest needs remains a test for active, pulmonary TB that is more sensitive than sputum-smear microscopy and can be performed in closer proximity to the patient or deployed for active case detection, thereby facilitating rapid treatment decisions.

Xpert MTB/RIF (“Xpert”; Cepheid, Sunnyvale, California), an automated rapid molecular diagnostic test, was released in 2010 (4), and its price has been reduced below $10 per cartridge. However, Xpert requires temperature regulation and a stable electrical supply, which (along with price) potentially limits its utility as a fully decentralized, point-of-care (POC) test in high-burden countries (5). As a result, novel diagnostic tests for active pulmonary TB remain a key priority for development (6, 7). The first such tests are likely to be molecular tests that are more compact, are battery-operated, function under a wider range of temperatures, require minimal laboratory infrastructure, and provide results within 45–90 minutes (7, 8). At least 4 such “fast-follower” nucleic acid
amplification tests (NAATs) are now on the market and may be more deployable than Xpert, though their performance characteristics are not yet well-characterized (8). Ultimately, advances may lead to rapid, cheap, equipment-free tests, such as dipstick tests using biomarkers placed on a lateral flow platform. These advances may potentially come at the expense of reduced sensitivity but might allow deployment at the lowest levels of the health-care delivery system (e.g., health outposts and primary-care clinics without peripheral laboratories). Other tests (e.g., immunological or radiological tests) might be more sensitive for subclinical or incipient TB, thereby facilitating active case detection with higher sensitivity than is possible with tests that depend on a high sputum bacillary load (e.g., sputum smear).

Over 40% of all new TB cases and almost half of all TB deaths occur in the World Health Organization (WHO) Southeast Asia Region (SEAR); India alone bears 25% of the world’s TB burden (1). The region is unique in having widespread private-sector TB care; thus, engaging the vast private sector to improve the quality of TB diagnosis and treatment is critical to regional

Figure 1. Model of a tuberculosis (TB) epidemic in Southeast Asia. A) Structure of the deterministic model. Each compartment is further stratified by human immunodeficiency virus status (positive or negative) and location of residence (urban or rural), assuming no migration (not shown). Mortality from each compartment is not shown. B) Diagnostic process underlying the rate at which populations progress from active disease to treatment/recovery. The success of each diagnostic attempt depends on the diagnostic test used and the sector (public vs. private) in which both diagnosis is attempted and treatment is initiated. Each person with diagnosis-seeking active TB has a 35% probability of seeking care in the public sector. Dotted lines denote rates or proportions that can be modified through interventions.
TB control. Developing simple diagnostic tests that could improve case-finding of active, pulmonary TB in both the public and private sectors might therefore have a substantial population-level impact on TB incidence and mortality. To compare the impact of diagnostic tests meeting different profiles of sensitivity and deployability, we constructed an epidemic model of TB in the SEAR.

**MATERIALS AND METHODS**

Using ordinary differential equations, we developed a compartmental transmission model of adult TB in Southeast Asia, with an estimated TB incidence of 193 cases per 100,000 people per year (9). We aimed to construct a simple, transparent model in order to assess the relative impact of novel diagnostic tools in a generic fashion that is easily compared with similar existing models of other TB interventions (10). Our primary outcomes were the reductions in TB incidence and mortality relative to the existing diagnostic standard of care after gradual implementation of a novel diagnostic test to the point of full intended coverage after 10 years in the public sector.

The model categorizes subpopulations based on urban/rural residence, human immunodeficiency virus (HIV) status, and TB status (Figure 1). People enter the population at age 15

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### Table 1. Parameter Values Used in a Transmission Model Evaluating the Deployment of 3 Hypothetical Diagnostic Tests for Tuberculosis in Southeast Asia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No.</th>
<th>Proportion</th>
<th>Sensitivity Range</th>
<th>Published Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TB Transmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual secondary TB infections per active smear-positive case&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of 10 years</td>
<td>9.76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative probability of rapid progression (reinfection vs. initial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>0.50</td>
<td></td>
<td>0.28–0.84</td>
<td>Vynnycky, 1997 (33); Sutherland, 1982 (34)</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>1.00</td>
<td></td>
<td>0.90–1.00</td>
<td></td>
</tr>
<tr>
<td>Relative infectiousness of smear-negative cases</td>
<td>0.22</td>
<td></td>
<td>0.16–0.29</td>
<td>Behr, 1999 (35)</td>
</tr>
<tr>
<td><strong>TB Progression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections resulting in rapid (“primary”) progression&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>0.14</td>
<td></td>
<td>0.10–0.18</td>
<td>Vynnycky, 1997 (33)</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>0.37</td>
<td></td>
<td>0.25–0.67</td>
<td>Sergeev, 2012 (36)</td>
</tr>
<tr>
<td>Annual reactivation rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>0.001</td>
<td></td>
<td>0.4 × 10⁻³–1.8 × 10⁻³</td>
<td>Horsburgh, 2010 (37)</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>0.06</td>
<td></td>
<td>0.03–0.10</td>
<td>Sergeev, 2012 (36)</td>
</tr>
<tr>
<td>Incident TB that is smear-positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>0.53</td>
<td></td>
<td>0.40–0.66</td>
<td>WHO, 2011 (9)</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>0.44</td>
<td></td>
<td>0.16–0.53</td>
<td>Getahun, 2007 (38)</td>
</tr>
<tr>
<td>Duration of “prediagnostic” period, years&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.75</td>
<td></td>
<td>0.60–1.00</td>
<td>Dowdy, 2013 (11)</td>
</tr>
<tr>
<td><strong>TB Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life expectancy, years</td>
<td>70.10</td>
<td></td>
<td>67.10–73.80</td>
<td>World Bank, 2012 (39)</td>
</tr>
<tr>
<td>Annual mortality rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative, smear-positive TB</td>
<td>0.42</td>
<td></td>
<td>0.32–0.53</td>
<td>Tiemersma, 2011 (40)</td>
</tr>
<tr>
<td>HIV-negative, smear-negative TB</td>
<td>0.10</td>
<td></td>
<td>0.08–0.13</td>
<td>Tiemersma, 2011 (40)</td>
</tr>
<tr>
<td>HIV-positive, without TB</td>
<td>0.06</td>
<td></td>
<td>0.05–0.11</td>
<td>Sergeev, 2012 (36)</td>
</tr>
<tr>
<td>HIV-positive, active TB (any form)</td>
<td>0.82</td>
<td></td>
<td>0.62–1.00</td>
<td>Sergeev, 2012 (36)</td>
</tr>
<tr>
<td><strong>Spontaneous Cure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual rate of spontaneous cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>0.21</td>
<td></td>
<td>0.16–0.28</td>
<td>Tiemersma, 2011 (40)</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>0.00</td>
<td></td>
<td>0.00–0.50</td>
<td>Sergeev, 2012 (36)</td>
</tr>
</tbody>
</table>

Table continues
years and leave at death. For simplicity, we assumed a constant population with no immigration or emigration. Since the TB transmission rate cannot be directly measured, we calibrated this parameter using an iterative process to achieve a steady state at baseline that reflects the ratio of infectious persons to susceptible persons in the population. We assumed that the TB transmission rate is 9.9 infections per infectious person-year, which is similar to that of other models (11, 12).

We modeled care-seeking as having a constant rate after an initial infectious period in which people do not seek care (Figure 1B); we calibrated the duration of this period to approximate the estimated duration of TB disease (i.e., prevalence/incidence) (1) in the SEAR and the rate of care-seeking to reflect diagnostic delays reported in the literature (14, 15). In our model, care-seeking occurs more quickly in urban settings, reflecting greater access to health-care providers. The success of each care-seeking attempt is determined by the sensitivity of the diagnostic test, the proportion of persons lost to follow-up between initial contact and initiation of treatment, and the proportion of cases that are empirically treated (adjusted to the region’s baseline “case detection rate” (1), the proportion of all incident cases that are detected), and the probability of successful treatment. We assumed that a positive test leads to a decision to treat, that successful treatment renders a person immediately noninfectious, and that unsuccessful treatment results in return to the active (infectious), diagnosis-seeking compartment.

We assumed that people with suspected TB have a 35% probability of seeking care in the public sector and a treatment success of 70% (Figure 1B). We calibrated the duration of this period to approximate the estimated duration of TB disease (i.e., prevalence/incidence) (1) in the SEAR and the rate of care-seeking to reflect diagnostic delays reported in the literature (14, 15). In our model, care-seeking occurs more quickly in urban settings, reflecting greater access to health-care providers. The success of each care-seeking attempt is determined by the sensitivity of the diagnostic test, the proportion of persons lost to follow-up between initial contact and initiation of treatment, and the proportion of cases that are empirically treated (adjusted to the region’s baseline “case detection rate” (1), the proportion of all incident cases that are detected), and the probability of successful treatment. We assumed that a positive test leads to a decision to treat, that successful treatment renders a person immediately noninfectious, and that unsuccessful treatment results in return to the active (infectious), diagnosis-seeking compartment.

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cess rate of 0.89 in the public sector (where directly observed therapy is widely practiced and patients are aggressively tracked after missed visits) (9, 16, 17), as opposed to 0.5 in the private sector (where such mechanisms are not in place) (18). These parameter values were estimated on the basis of limited literature on the scale of private-sector TB management in SEAR countries and tests that are commonly used in this sector (chest radiography and serology) (19–22).

We calibrated the model at steady-state to 2010 WHO estimates of TB incidence, prevalence, mortality, and case detection for Southeast Asia (9). We fitted annual HIV incidence to the estimated HIV prevalence of the region (23).

We assumed that the baseline population would start at a steady state reflective of the 2010 WHO estimated population for the region, and that TB incidence would fall at the currently estimated rate of 2% per year thereafter (1). We examined the implications of 5 idealized novel diagnostic tests, to reflect technologies already available, technologies that will soon reach the market, and those that are in early development. These tests were defined in terms of their sensitivity for smear-negative cases (reasoning that any test with suboptimal sensitivity for smear-positive TB would be combined with sputum-smear microscopy) and their amenability to POC testing, realized as the proportion of people with a positive test who actually initiate treatment (i.e., the inverse of those lost to follow-up due to diagnostic delay). For simplicity, we did not explicitly model false-positive results (i.e., specificity), drug-resistant TB, or costs (since a future test’s negotiated price might depend on its projected impact, and deployment costs are uncertain). The 5 tests were as follows.

- The current standard of care in most SEAR countries, in which sputum smears are done exclusively (including the current mix of spot-morning/spot-spot/3-sample collection) in peripheral microscopy centers and are generally batched, such that same-day treatment initiation is logistically infeasible. This standard has an 85% treatment initiation proportion (i.e., 15% of persons who produce 1 or more sputum samples for evaluation either do not receive their results or do not start treatment based on those results) (24, 25).
- “District-level molecular test”: 70% sensitivity for smear-negative TB but no improvement in the 85% treatment initiation proportion (e.g., Xpert, implemented in a fashion that provides results at the same speed as is currently available with smear).
- “Peripheral-level NAAT”: 50% sensitivity for smear-negative TB and 95% treatment initiation (e.g., NAAT that is deployable at the microscopy center level and requires 1–2 hours for amplification and detection, thereby potentially facilitating same-day treatment).
- “POC dipstick”: 40% sensitivity for smear-negative TB (and 100% sensitivity for smear-positive TB) with 100% treatment initiation (e.g., lateral-flow assay with no infrastructure requirements that can be used in the most peripheral settings, producing results and treatment decisions within minutes).
- “Systematic TB screening”: includes passive detection of TB cases with the district-level molecular test as above, plus systematic screening of people at high risk of active TB (e.g., household contacts of infectious TB cases), as recommended by current guidelines (26), under the assumption that 20% of all prevalent TB cases could be identified in this fashion (27). We assume that a novel test is available (“triage test,” e.g., a new serological test) with imperfect specificity but 90% sensitivity for all prevalent symptomatic or asymptomatic smear-negative TB (including subclinical TB) (11). Patients testing positive on this test then receive a confirmatory test (e.g., smear plus culture, or NAAT) with high specificity and 70% sensitivity for all prevalent (including subclinical TB), assuming 85% treatment initiation of those testing positive on both evaluations (high treatment initiation reflecting more active efforts to retain people who test positive).

To inform the potential limit of passive case detection, we evaluated a “perfect” POC test with 100% sensitivity for both smear-positive and smear-negative cases and no loss to follow-up. We also evaluated implementation across both public and private sectors. Additional scenario analyses evaluating different levels of access to care, prediagnostic delay, treatment success, and gradual implementation of the diagnostic tests are described in the Web Appendix.

We performed 1-way sensitivity analyses to assess the change in the primary outcome as a result of varying all model parameters across a range of uncertainties reported in the literature or, if not specified, ±25% of the parameter value. We also performed a 2-way sensitivity analysis to examine the reduction in TB incidence based on the 2 key parameters that specify the impact of novel diagnostic tests: treatment initiation (range, 0.75–1.0) and sensitivity for smear-negative TB (range, 0.0–1.0).

Lastly, we conducted a multivariate uncertainty analysis to quantify uncertainty in the model outputs. For this analysis, we first brought the model to steady-state as described above. We then selected a time point from a uniform distribution at which all parameters were simultaneously varied using Latin hypercube sampling over the ranges shown in Table 1, assuming a beta distribution with α = 4. We then allowed the model to run (using these new parameters) until the year 2010 and selected only those simulations with a TB incidence within ±25% of the target 2010 incidence (53% of 15,000 simulations). We calculated 95% uncertainty ranges as bounded by the 2.5th and 97.5th percentiles of accepted simulations.

We used Python, version 2.7 (Python Software Foundation, Beaverton, Oregon), to construct the model and solve the differential equations, using a time step of 0.01 years, and R (R Foundation for Statistical Computing, Vienna, Austria), version 3.0.0, for uncertainty analyses.

RESULTS

Impact of novel diagnostics by sector of deployment

Under the parameter values listed in Table 1 and the assumption of a 2% decline in incidence per year, TB incidence (per 100,000 population per year) fell from 193 to 158 over the 10-year analysis period, and TB mortality fell from 22.3 to 19.1; starting values were representative of the WHO SEAR in 2010 (9). Under the standard of care, 34% of diagnoses
and 48% of successful treatment courses were achieved in the public sector. Public-sector implementation of the district-level molecular test, peripheral-level NAAT, or POC dipstick increased these proportions to 47%–48% of diagnoses and 61%–62% of successful treatments. The initial duration of disease (from onset of infectiousness to treatment initiation, spontaneous recovery, or death) was 1.21 years, falling to 1.05–1.07 years after passive deployment of any of these 3 diagnostic interventions (due to having fewer unsuccessful care-seeking attempts).

The projected impact of the 3 diagnostic tests was similar, demonstrating a tradeoff between sensitivity and POC amenability. Figure 2 shows TB incidence over a period of 10 years following immediate deployment of the novel diagnostic tests; Table 2 describes the final TB incidence and mortality under each scenario, and Web Figure I shows the corresponding uncertainty ranges for each scenario over time. The introduction of a diagnostic test with 70% smear-negative sensitivity and 85% treatment initiation (“district-level molecular test”) reduced TB incidence at the end of 10 years by 7.5% (95% uncertainty range (UR): 4.2%–12.0%), to 146 per 100,000 per year. Assuming the current TB incidence in the region under the standard of care (and a population size equal to that in 2010), this corresponds to 1.1 million cases averted over a period of 10 years. Similarly, deployment of a test with 50% smear-negative sensitivity and 95% treatment initiation (“peripheral-level NAAT”) reduced TB incidence by 8.3% (95% UR: 4.9%–12.8%), or 1.2 million cases prevented, and a test with 40% sensitivity and 100% treatment initiation (“POC dipstick”) achieved an 8.4% reduction (95% UR: 5.1%–12.8%), or 1.2 million cases averted. The corresponding reductions in 10-year TB mortality were greater: 20.1% (95% UR: 14.7%–26.4%; 360,000 lives saved), 21.7% (95% UR: 16.8%–27.3%; 370,000 lives saved), and 21.9% (95% UR: 17.3%–27.2%; 360,000 lives saved), respectively. Systematic TB screening using a 2-step strategy incorporating a novel test (“active triage test”) with 70% sensitivity for smear-negative TB reduced incidence by 18.8% (95% UR: 11.5%–26.0%) and mortality by 37.0% (90% UR: 29.9%–43.2%). The impact of each diagnostic strategy remained similar under different scenarios of access in urban and rural areas (Web Table 2).

The impact of novel diagnostics was enhanced by deployment in the private sector. By the end of 10 years, the 3 passive diagnostic interventions, if deployed in the private sector alone, reduced TB incidence by an estimated 10.0%–10.3% (95% URs: 6.0%–15.2%). Deployment in both sectors reduced incidence by 13.7%–15.4% after 10 years—an 82%–83% relative increase in impact compared with public-sector deployment alone. The impact of diagnostic strategies in the public sector alone was increasingly eroded in scenarios that assumed a larger private sector size (Web Figure 2), whereas improved treatment success in the private sector enhanced the impact of deploying novel diagnostic tests (Web Figure 3). In the “best-possible-case” scenario, we estimated that a hypothetical,

Figure 2. Ten-year incidence of tuberculosis (TB) following gradual implementation of novel diagnostic tests. The modeled population was calibrated, using data from the World Health Organization’s Southeast Asia Region (2011–2012), to a steady-state TB incidence of 193 per 100,000 population (solid black line) and compared with scenarios in which hypothetical new diagnostic tests with different specifications were implemented gradually (linear increase from 0% to 100% coverage) over a period of 10 years. The graph shows the projected trajectories of TB incidence for tests with different sensitivities and treatment initiation proportions in the public sector, as well as for the “ideal point-of-care test” implemented in both the public and private sectors (long-dashed black line) and systematic TB screening involving deployment of the “district-level molecular test” in the public sector combined with an “active triage test” with 70% smear-negative sensitivity and 85% treatment initiation (short-dashed black line) that detects 20% of prevalent TB cases every year.
optimal passive diagnostic test (100% sensitivity, 100% treatment initiation, implemented in both sectors) could reduce incidence by 20.0% (95% UR: 12.5%–27.6%) at the end of 10 years, nearly equivalent to the systematic TB screening strategy using a more realistic test.

Immediate scale-up of diagnostic testing strategies achieved similar impact by the end of 10 years, as did gradual scale-up (Web Table 3), but averted over twice as many cases and deaths during the 10-year scale-up period (Web Table 4). Partial scale-up (20% of the population) had much smaller effects, and a study completed after 2 years of even immediate scale-up would greatly underestimate long-term impact (Web Figure 4).

Sensitivity analysis

The projected impact of novel diagnostic tests on TB incidence was sensitive to the proportion of TB resulting from recent infection. Specifically, diagnostics had greater impact when more TB resulted from recent transmission (i.e., high transmission rate, high probability of primary progression, low degree of protection against reinfection, poor treatment success, and high infectiousness of smear-negative TB; Figure 3A). Although the duration of the “prediagnostic” period is unknown, wide variation in this parameter did not substantially affect results; when varied from 2 months to 1.5 years, the relative impact of the POC dipstick on TB incidence (e.g., Figure 3A) varied only from 7.0% to 11.4%.

Figure 3B shows the projected 10-year reduction in TB incidence, as a function of a novel diagnostic test’s sensitivity for smear-negative TB and treatment initiation proportion (“POC amenability”). Incremental changes in treatment initiation (horizontal movement in Figure 3B) are more important than equivalent changes in sensitivity (vertical movement in Figure 3B). Furthermore, as sensitivity increases, incremental decreases in the proportion lost to follow-up have a greater impact (i.e., wider variation on horizontal movement at the top of Figure 3B than at the bottom).

DISCUSSION

When deployed passively in the public sector, novel diagnostic tests have the potential to reduce TB incidence and improve patient outcomes; we projected reductions in TB incidence of 7%–9%, and reductions in mortality of 20%–22%, 10 years after deployment of diagnostic tests with realistic specifications. For novel tests to realize their full potential for TB control, they must be deployed in the private sector or used for active case detection—either of which might double diagnostics’ impact on TB incidence. If novel diagnostic tests are to dramatically alter the population-level epidemiology of TB, they must be deployed outside the strict setting of public-sector symptomatic presentation and must generate results that can facilitate same-day treatment decisions.

Previous modeling analyses have suggested that currently available TB diagnostics could reduce incidence by 20% or
more (28, 29), with one analysis suggesting that a dipstick could achieve a 39% reduction (10). Our projections, like those of other recent models (30, 31), are more modest. Specifically, we found that a POC dipstick—even with 100% treatment initiation of positive testers—only reduced TB incidence by 8.4% after 10 years, versus 7.5% achievable with a district-level molecular test similar to an existing platform (Xpert MTB/RIF). Unlike many earlier models, our model incorporates certain key elements of TB diagnosis, namely: 1) loss to follow-up between diagnosis and treatment due to diagnostic delays, 2) diagnosis that generally occurs late in the infectious period, 3) involvement of the private sector, and 4) realistic incorporation of repeated attempts at diagnosis. Thus, despite the simplicity of our analysis, there is reason to believe that our more modest projections may be more realistic.

Our analysis suggests that novel diagnostic tests can indeed have an impact on TB incidence; however, their effectiveness depends not only on sensitivity but also on the manner in which they are deployed. Specifically, tests that can be deployed closer to the point of care, for active screening, or in the private sector can have a markedly greater impact than those deployed passively in the public sector alone; however, uptake of novel diagnostic tests in the private sector may be heterogeneous and dependent on patient and provider satisfaction with the new test. Furthermore, achieving same-day results (with the potential for same-day treatment) with closer proximity to...
patients can compensate for lower sensitivity. All of these gains could be achieved more rapidly with immediate implementation, as shown in Web Figure 4.

As with any model-based analysis, there were a number of limitations to this study. First, in order to provide a transparent, generalizable analysis, our model structure assumed a homogeneous population with no population growth or migration in the large world region of Southeast Asia, and it greatly simplified the TB epidemic. While our results reflect the epidemiology and health-care setting of Southeast Asia, further analyses may be justified to extend these results to other regions with different epidemiologic and systemic considerations (e.g., high HIV prevalence in Africa, declining incidence and migration in low-burden countries). For example, while private-sector provision of health care in India is very high, it is less prominent in other SEAR countries, such that public-sector deployment of novel tests may have a greater impact in those settings (see Web Figure 1). Nonetheless, our findings support the approach of the Indian Revised National TB Control Programme, as outlined in its National Strategic Plan (2012–2017) emphasizing private sector engagement, intensified case detection, and novel diagnostics with an aim of universal access to quality-assured TB diagnosis and treatment (32). Second, we treated HIV in a superficial fashion, and we did not incorporate drug-resistant TB. Drug susceptibility testing is an important consideration for any TB diagnostic algorithm and is included in many technologies (e.g., Xpert); our model thus provides only partial guidance regarding the role of any real-world diagnostic test. Third, certain source data were limited, such as those pertaining to the private sector, the duration of "prediagnostic" infectious TB, and the specifications of any new technology. As such, broad sensitivity analyses around these parameters were required, and our estimates should be interpreted with caution. Finally, while we conducted a broad array of uncertainty analyses, certain combinations of parameter values (i.e., those falling outside of the 95% uncertainty ranges or outside our selected ranges for parameter variation) may nevertheless fit the data well and predict substantially greater or less impact than that presented here.

In conclusion, passively deployed novel diagnostic technologies will likely have an important but not transformative impact on the TB epidemic in Southeast Asia. The full potential of new diagnostic tests for TB can only be realized by deploying them in a way that leverages improved sensitivity, amenability to POC testing, linkages to rapid treatment, engagement with private-sector providers, and active case detection. Ultimately, if we are to use novel diagnostics to transform the fight against TB, we must develop tests that are not only sensitive and rapid but also deployable in a broad and active fashion.

ACKNOWLEDGMENTS

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This research was supported in part by grants from the Bill & Melinda Gates Foundation (grant OPP1061487), the Canadian Institutes of Health Research (MOP grant 123291), and the US National Institutes of Health (grant R21AI101152).

Conflict of interest: none declared.

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