EXPLORING THE EPIDEMIOLOGICAL IMPACT OF UNIVERSAL ACCESS TO RAPID TUBERCULOSIS DIAGNOSIS USING AGENT-BASED SIMULATION

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ABSTRACT

Many high-burden countries have committed to providing universal access to rapid diagnosis of tuberculosis (TB), but the corresponding impact on population-wide incidence is unknown. We designed an agent-based simulation of drug-susceptible (DS) and drug–resistant (DR) TB in a representative Indian setting and compared the impact of Xpert testing via a decentralized (Xpert available at each local-population) versus centralized (Xpert available at the district-level serving multiple local-populations) strategy. Decentralized testing resulted in a 36% reduction in DR-TB incidence at 10 years compared to no Xpert. Depending on assumptions regarding pre-treatment loss to follow-up (ranging from 5 to 50%), the impact of centralized testing ranged from a 35% to 22% reduction in DR-TB incidence. Implementation of Xpert by either approach had a negligible impact (<5%) on DS-TB incidence. Decisions regarding choice of centralized vs. decentralized Xpert will heavily depend on operational aspects of centralized Xpert and loss to follow-up.

1   INTRODUCTION

Tuberculosis (TB) has existed for millennia and remains a major global health problem. TB infects millions of people each year, and in 2015 was named as one of the top 10 causes of death worldwide, ranking above HIV/AIDS as the leading cause of death from an infectious disease. This trend is despite the fact that TB disease can be cured in most cases if a timely diagnosis and correct treatment are made available.

Although TB control has been effective in some regions of the world and incidence has declined marginally over the past decade, these gains are threatened by the emergence of resistance to anti-TB drugs. The increasing burden of multi-drug resistant (MDR) and extensively drug resistant (XDR) TB – associated with high rates of mortality and high cost of treatment – poses a serious threat to global health. Worldwide, approximately 5% of patients with TB are estimated to have either MDR or XDR types, but the distribution of cases is not uniform (World Health Organization 2016). Despite availability and

provision of effective drugs for DS-TB, the primary transmission of MDR and XDR tuberculosis is now driving the spread of resistance in high-burden countries such as China, India, and South Africa, which is mainly attributed to delays in DR-TB diagnosis, failure to provide effective drugs for DR-TB, and poor management of DR-TB patients in these settings.

Global targets and milestones for reductions in the burden of TB disease in the period 2016–2035 have been set as part of the Sustainable Development Goals and World Health Organization's (WHO) End TB Strategy. The first milestones set for 2020 are a 35% reduction in TB deaths and a 20% reduction in the TB incidence rate. To reach these milestones, effective strategies are needed to facilitate the diagnosis and treatment of drug-susceptible and -resistant TB, especially in high-burden settings.

Isolation of *Mycobacterium tuberculosis* using conventional solid culture is the gold standard for TB diagnosis worldwide, and may be followed by culture-based, phenotypic drug susceptibility testing (DST). However these methods, as well as newer and slightly faster approaches such as liquid culture and molecular line probe assays, require long turnaround time, expensive laboratory infrastructure, extensive biosafety precautions, and specialized laboratory personnel seldom found in primary health care facilities in developing countries (World Health Organization 2015). The only WHO-recommended rapid diagnostic test for detection of TB and rifampicin resistance currently available, the Xpert MTB/RIF® assay, overcomes many of these operational difficulties in TB diagnosis (Boehme et al. 2011). WHO recommends Xpert as an initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB, and as a follow-on test to smear microscopy in settings where MDR-TB or HIV are of lesser concern. Of the 48 countries classified by WHO as "high burden" based on one or more criteria, 15 had adopted national algorithms by the end of 2015 positioning Xpert MTB/RIF as the initial diagnostic test for all people suspected of having pulmonary TB (World Health Organization 2016). These countries accounted for only 10% of the estimated global number of incident TB cases in 2015, suggesting a persistent gap in global TB diagnosis.

Many studies have evaluated performance characteristics of the Xpert MTB/RIF assay and cost-effectiveness of various strategies for implementing Xpert in different countries including India (Chang et al. 2012; Dorman et al. 2012; Vassall et al. 2011). A traditional model for implementation of Xpert in developing countries is via a "centralized" facility that provides services to several communities transporting clinical specimens (e.g., patients' sputum samples) to that facility (World Health Organization 2014). This strategy enables cost-sharing across multiple different entities, consolidates maintenance of high-level infrastructure in a small number of facilities, and ensures high testing volume. However, the time required for transporting samples and conveying results back to the local level turns a two-hour test into a several day process, requiring patients to return another day for their test result – and thus leading to increased loss to follow-up. The forthcoming GeneXpert Omni device – a simpler, cheaper, and more portable testing platform for performing the Xpert assay – provides an unprecedented opportunity to "decentralize" molecular TB testing to the primary care level and to provide equal access to quality TB diagnosis (Alland et al. 2015). A decentralized strategy could help reduce pre-treatment losses to follow-up, while also improving sensitivity of TB detection over smear microscopy in settings where Xpert has not yet been made available.

India, which shoulders approximately 26% of the global TB burden, has recently announced a commitment to eliminate TB by 2025, with an ambitious new National Strategy Plan (2017-2025) which includes universal testing for drug-resistant TB among other interventions. Given the complexity of the Indian health care system and resource constraints, it is imperative to evaluate the likely impact and cost-effectiveness of centralized versus decentralized Xpert implementation with regard to variation in the resulting rate of loss to follow-up. We therefore constructed a suite of economic and epidemiological models to explore the implications of these testing strategies within the Indian public sector. In this paper, we discuss our approach for development of the underlying agent-based simulation model of TB transmission in a representative Indian setting, and present preliminarily and descriptive results on the epidemiological impact of centralized vs. decentralized Xpert implementation.

2   METHODS

In order to compare the implementation of centralized versus decentralized Xpert, we modeled two different levels of the public health system, which are based on the number of people served and reflect the organizational structure of India's national TB control program. Our baseline model simulates a self-contained population of 100,000 individuals corresponding to the catchment area of a single designated microscopy center (DMC), a local health clinic with capacity for sputum smear microscopy (Figure 1). We represent the central level – a District TB Center (DTC) referral facility with more advanced laboratory capacity, designed to serve at least one million people – as composed of several DMCs.
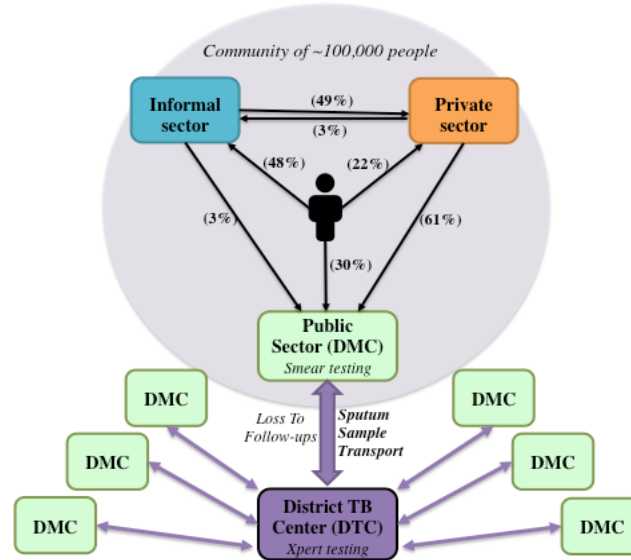

Figure 1: Schematic representation of TB diagnostic system in India. Each simulation models a community of 100,000 individuals, served by three types of providers: informal, private and public sector (DMC). The upper panel represents the network of providers and the patients' likelihood of presentation to each provider after a visit. Depending on availability of Xpert at a central location (DTC) versus a decentralized location (DMC), TB testing can result in various levels of pre-treatment loss to follow-up.

In the centralized scenario, Xpert testing is available only at the DTC, which operates a transport system to bring patients' sputum samples from each DMC and takes up to a week to report results back to the DMC level. In contrast, the decentralized scenario places Xpert testing capacity at the DMC level – eliminating potential delays in returning diagnostic results and allowing patients to receive a test result the same day that they provide a sputum sample. We assume that the primary epidemiological difference between centralized and decentralized Xpert testing is that centralized testing will incur an additional probability of pre-treatment loss to follow-up[14]. As such, our primary goal is to evaluate impact of the Xpert testing at various levels of pre-treatment loss to follow-up ranging from 0% to 50%.

2.1   Population demography and network of contacts

Population demographics including age and gender distributions are calibrated to national census information from India (World Health Organization 2017). Assuming a steady population size, the annual birth rate is tuned to balance the number of deaths over time. To capture the heterogeneous pattern of TB transmission within a community, we implement a simplified household structure and define two types of contacts: 1) "close" contacts between household members, and 2) "casual" contacts among all community members. Close contacts are assumed to occur frequently between any two housemates and are modeled

at each time step (week) between all members of a household; casual contacts are assumed to occur less frequently among random pairs throughout the community. Households (ranging between 1 to 10 members) are generated randomly at the beginning of the simulation according to a normal distribution of household size. During the simulation, newborns are randomly assigned to existing households, without controlling for the household age distribution over time. Individuals' weekly frequency of casual contact is calibrated to reported levels from a synthetic network analysis of social contacts in Delhi, India (Xia et al. 2015).

2.2 TB natural history

The natural history of TB is modeled at an individual level as shown in Figure 2. We model circulation of both drug-susceptible (DS) and rifampin-resistant (DR) TB strains in the population. Each person is born in full health and susceptible (SUS) to TB disease. When successful transmission of TB infection occurs, the infected person enters the Early Latent TB (DS-/DR-ELTB) state for a period of five years, during which the per-time-step probability of active TB development (Fast Progression Rate) is high but decreasing over time. At the end of this five-year period, the person enters the Late Latent TB (DS-/DR-LLTB) state, which can last for many years and is associated with a lower, constant probability per time step (Slow Progression Rate) of developing active TB. Individuals with Active TB (DS-/DR-ATB) are symptomatic, infectious, and subject to increased mortality. The infectiousness and mortality of ATB is modeled as increasing linearly with time as disease progresses during the first months of infection, from zero to a peak level, and then staying constant until treatment initiation (DS-/DR-Trt) or death occurs (Kasaie et al. 2014). The peak infectiousness of DR-TB is allowed to be lower than that of DS-TB.
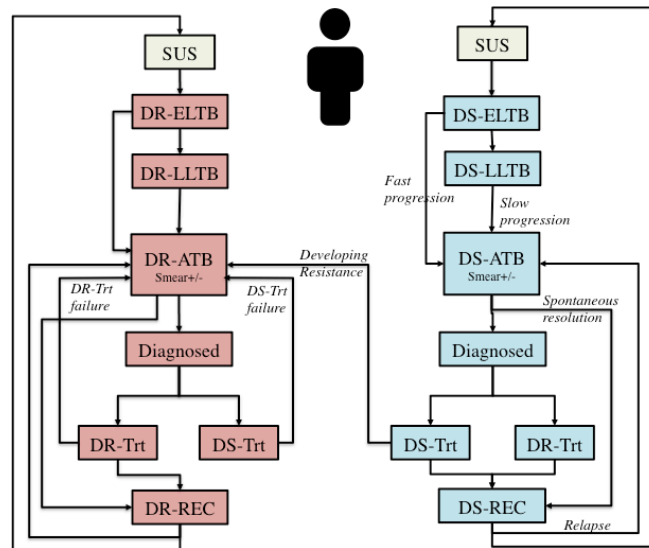

Figure 2: TB natural history outline. Individuals are born susceptible to the disease and upon infection with DS-TB or DR-TB, they move through several stages over time. Individuals with active disease (DS-ATB & DR-ATB) are subject to increased mortality risk (not shown). Latently infected or recovered individuals can get reinfected with either strain, at which time they move to the early latent stage (not shown).

2.3 Care seeking behavior

We model care-seeking behavior as a function of time since development of active TB disease, with the per-time step probability of seeking care (and probability of sputum smear positivity) increasing linearly

over the first months of infectiousness and staying at a constant level thereafter (Dowdy, Basu, and Andrews, 2013). Considering a representative care structure in a typical Indian setting, care for TB symptoms may be sought in one of three sectors: 1) the informal sector, comprising providers with no formal medical training; 2) the qualified private sector, including providers with formal allopathic or non-allopathic medical training but no access to microscopic labs; or 3) the public sector (DMC), namely a local health clinic with capacity for sputum smear microscopy. Following prior studies (Salje et al. 2014; Kapoor et al. 2012; Mistry et al. 2016), individuals may initially seek care in any of these sectors, each with a specified probability, and if they remain untreated, their probability of visiting each sector during a subsequent care-seeking attempt is modeled as a function of where they sought care during their previous attempt, as shown in Figure 1. We assume that an informal-sector diagnosis never leads to appropriate treatment of TB, while a proportion of patients visiting the private sector will receive diagnosis for DS-TB – though the diagnosis never leads to appropriate treatment of DR-TB. As such, a definitive bacteriologic diagnosis (using smear and/or Xpert) only occurs in the public sector.

Given the focus of our study on implementation of Xpert within the public sector, we modeled informal- and private-sector encounters as simple events, with a given probability of DS-TB treatment in the private sector and no other impact on the course of disease. Upon accessing the public sector, however, individuals with symptoms of TB will undergo a series of "clinical encounters" as shown in Figure 3. An encounter is defined as all activities occurring from initial suspicion of active TB to arriving at a presumptive diagnosis. As such, each encounter may encompass multiple clinic visits; for example, a patient may undergo an initial smear or Xpert test, return for bacteriologic results, undergo additional ancillary tests (e.g., chest X-ray, basic laboratory testing), and initiate empiric treatment – all as part of the same clinical encounter.
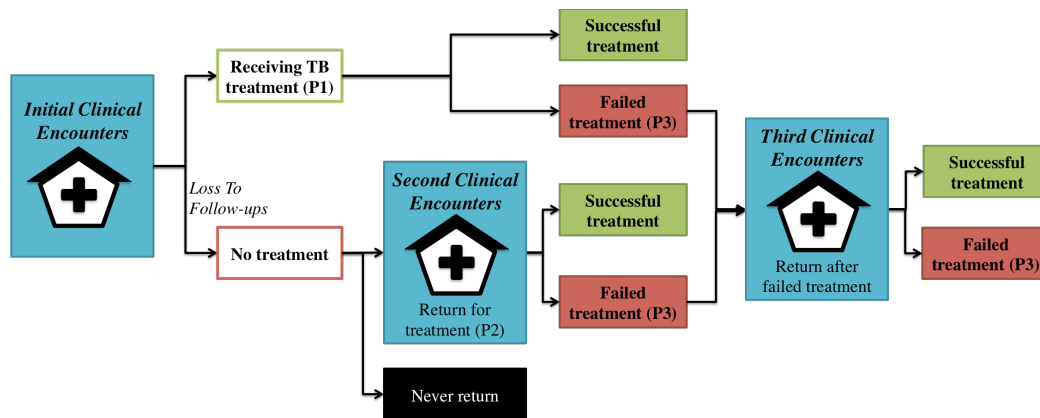

Figure 3: A simplified model of TB diagnosis attempts at the public sector. Each clinical encounter is defined as a collection of activities (e.g., visits, labs, etc.) occurring from initial suspicion of active TB to arriving at a presumptive diagnosis (positive or negative). As such, an encounter does not correspond to a single visit but rather a collection of visits (and other activities) before arriving at a clinical decision.

At the initial encounter (encounter 1), we assumed all patients with presumptive TB will receive a bacteriologic test by definition (i.e., if such a test was not performed during an encounter, that encounter would not be considered a public-sector attempt at TB diagnosis). At the end of this encounter, patients will either initiate TB treatment (P1 in Figure 3) or will remain untreated due to a false-negative test (with no empiric treatment decision) or pre-treatment loss to follow-up (i.e., those testing smear-positive, as well as a proportion of patients with smear-negative results who receive an empiric diagnosis based on high suspicion of TB, will be treated). We assume that a proportion of patients who are not started on TB treatment during the initial encounter will never be successfully diagnosed in the future (P2 in Figure 3);

these individuals either die from TB or will spontaneously resolve. The remainder of patients are successfully diagnosed and treated, which we model as occurring at a second clinical encounter that will include a repeated bacteriological test (smear or, if available, Xpert) for TB. All patients who initiate TB treatment may be cured (through treatment or spontaneously), die of TB, or fail treatment (P3 in Figure 3). Those who fail treatment (still infectious) are assumed to undergo a third clinical encounter in which culture and drug susceptibility testing are performed, in addition to Xpert where available. These patients will subsequently receive a new round of TB treatment (assuming correct diagnosis of DS/DR-TB among all retreated patients), but if they fail that treatment again, they are no longer eligible for a new encounter.

2.4   TB Treatment and Role of Xpert

We assume that all individuals initiating treatment for active TB are initiated on a four-drug treatment regimen for DS-TB unless they receive an Xpert test result indicating resistance to rifampin – in which case we assume that they are initiated appropriately on treatment for DR-TB. We assume that DR-TB treatment lasts for 20 months and is equally effective for individuals with DS-TB (clearing any active or latent DS-TB infection) and DR-TB.

2.5   Evolution of drug-resistance

DS-TB patients receiving DS-TB treatment are subject to a probability of treatment failure and acquiring drug resistance, upon which they will develop active DR-TB disease and will continue to transmit the DR-strain to other susceptible individuals until treated. We calibrate this probability, along with the maximum infectiousness of DR-TB, to provide the expected levels of DR-TB infections among new and previously-treated TB patients at baseline (Table 1).

2.6   TB transmission

TB transmission is modeled at the end of each month over all active household and community contacts. The probability of transmission (*ptrans*) from an infectious individual (*p*) to his/her contact (*q*) at time *t* is calculated as follows:

$$Ptran(p,q,t) = Inf(p,t) \times Imm(q,t) \times cx$$

$$Inf(p,t) = \begin{cases} \dfrac{t-t_0}{d} \times MaxInf & if \ (t-t_0) \leq d \\ MaxInf & o.w. \end{cases}$$

where *Inf(p,t)* estimates the infectivity of person *p* at time *t,* computed via a step function with linear increase over the first *d* months after original infection (time t_0) before reaching the maximum level of infectiousness (*MaxInf*) and staying at that level afterward. In addition, *Imm(q,t)* denotes immunity of person *q* toward infection (1 if actively infected, 0.5 if latently infected or recovered, and 0 otherwise), and *cx* is a simulation coefficient used to tune the overall probability of transmission for calibration purposes. In the event of multiple transmissions to a single individual over a timestep, the resulted infection is chosen from successful transmissions at random.

2.7   Mixed infection

All individuals in latent or recovered states are subject to reinfection with either strain. Latent infections offer a degree of immunity against additional infection with either strain. In order to preserve a record of DR-TB risk when a person with latent DR-TB also becomes infected with and then treated for latent DS-TB, we allow mixed latent infections with both DS-TB and DR-TB; for each strain type (DS and DR), we track only an individual's most recent infection, but an individual may simultaneously, for example, have ELTB for one strain and LLTB for the other strain. Once active TB occurs with any strain, however, the

active infection and its subsequent multiple-drug treatment are assumed to eradicate the other latently-infecting strain, such that dual active infections do not occur and such that future reactivation will only occur with the strain that caused the active disease.

Table 1: List of key model parameters.

Parameter	Value	Reference
Annual risk of progression from early latent state by age	[0 – 2] years: 20% (2 – 10] years: 2% (10 – 15] years: 6% (15 – 104] years: 9%	(Vynnycky and Fine 1997; Marais, Gie, and Schaaf 2004)
Annual risk of LLTB progression	0.5%	(Horsburgh 2004)
Annual risk of mortality, active TB	12%	(Tiemersma et al. 2011)
Reduction in reinfection probability if latently infected	0.5	(Andrews et al. 2012; Sutherland, Švandová, and Radhakrishna 1982)
Risk of relapse within 2 years of resolution	2%/year (DS-TB) 4%/year (DR-TB)	(Marx, Dunbar, and Enarson 2014; D. Menzies et al. 2009) (Palmero, Ambroggi, and Brea 2004)
Individual's likelihood of acquiring resistance during DS-TB treatment	0.001	Calibrated to DR-TB proportion among new-/ retreated-TB patients
Coefficient of TB transmission upon each infectious contact	0.022	Calibrated to provide target incidence of DS-TB
Coefficient of DR-TB maximum infectiousness (relative to DS-TB)	0.57	Calibrated to provide target incidence of DR-TB
pTrans	0.0208	Calibrated to provide the DS-TB incidence at baseline
Maximum weekly probability of seeking care	0.17	Calibrated to provide the DS-TB prevalence at baseline
Probability of empiric treatment at encounter 1 (smear-negative)	0.25	Assumption
Probability of loss to follow up at encounter 1 in public sector	0.13	(MacPherson and Houben 2014)
Maximum probability of returning for encounter 2 in public sector	0.52	Corresponding to an average duration of one month
Probability of MDR-TB treatment failure (among those completing treatment)	17%	(World Health Organization 2016)
Sensitivity of Xpert for TB (smear-positive)	smear-pos = 1 smear-neg = 0.67	(Steingart et al. 2014)
Sensitivity of Xpert for rifampin resistance	95%	(Steingart et al. 2014)
Specificity of Xpert	1	(Steingart et al. 2014)
Probability treatment private sector	0.5	Calibrated to DS-TB incidence/prevalence

2.8   Pediatric TB

In order to capture the impacts of household contact interventions on TB morbidity and mortality in young children, the TB natural history described above is age-dependent. Young children (infected at age 0-2 years) have a higher risk than adults of fast progression from early latent to active TB (Marais 1997), while older children (infected at age 2-10 years) have lower risk of fast progression than adults. Children who do progress to active TB before 10 years of age are considered non-infectious (Marais et al. 2006) and do not contribute to household or community transmission, although they face the same mortality risk as other ATB. In late latent infection, children are assumed to have the same risk of slow progression as adults. Infections acquired during childhood that progress to active TB after age >10 years are as infectious as other adult TB.

2.9   Calibration and Intervention Scenarios

After selecting the fixed model parameters from available literature (Table 1), we calibrated simulations in a multi-step procedure. We first brought the model to a steady-state equilibrium reflecting the prevalence of DS-TB in India. As a validation procedure, we evaluated the fit of the model against the TB incidence and mortality in India as estimated by the World Health Organization (Figure 4). We then introduced drug resistance at a time point of 40 years prior to the present day, assuming a relatively lower infectiousness of DR-TB (versus DS-TB) such that the incidence of DR-TB at present would match current estimates from the WHO (10 per 100,000/year), and the associated breakdown of DR-TB prevalence in new versus previously-treated cases (2.5% and 16%, respectively). During this time, we assumed that TB diagnosis was entirely by smear microscopy, except for evaluation of patients failing treatment.

At the end of the calibration period ("baseline"), we modeled the introduction of Xpert as an immediate up-front addition to sputum smear microscopy, and evaluated TB epidemiological outcomes over the following 20 years in terms of reduction in TB incidence and mortality. Each scenario was consequently replicated through 100 independent runs and outcomes were reported in terms of mean and 95% uncertainty range of observations. Given the preliminarily status of this analysis, no statistical test of significance was performed.

3   RESULTS

At baseline, the simulation models a community of 100,527 individuals (half men) between the ages of 0 to 104 (median age of 43 years), distributed among random households with a median size of 6 individuals per household. Prior to the introduction of Xpert, DS-TB incidence in our simulated population was 167 [95% Uncertainty Range: 135 – 202], corresponding to a prevalence of 189 [151 – 229] per 100,000 person years. At baseline (40 years after introduction of drug resistance), DR-TB incidence was 9.5 [0 – 61] per 100,000 person years, with 2% [0 – 15%] of new (pDR-new) and 19% [0 – 75%] of previously-treated (pDR-treated) TB patients having DR-TB infection. This corresponds to an overall TB mortality of 14 [7 – 23] cases per 100,000 person-years at baseline (Figure 4).

Implementation of Xpert: Decentralized implementation of Xpert testing (providing no loss to follow-up) resulted in a 36% [-6% – 60%] reduction in DR-TB incidence at 10 years compared to no Xpert. The rate of improvement was greater at the beginning of program, showing a 24% [-16% – 50%] reduction in incidence by the end of 5 years compared to 52% [27% – 66%] by the end of 20 years. Universal access to Xpert testing reduced the proportion of misdiagnosed DR-TB patients to 0.39 [0 – 1] from 0.63 [0 – 1] at baseline, corresponding to a 2-month reduction in the duration of untreated DR-TB infection at the 10th years of implementation (changing from 37.7 [10 – 69] months in the absence of Xpert to 35.8 [10 – 64] months after Xpert).

The impact of centralized testing was sensitive to assumptions regarding the associated pre-treatment loss to follow-up, and ranged from a 35% [3% – 62%] reduction in DR- TB incidence after 10 years to 22% [-7% – 46%] when assuming 5% versus 50% loss to follow-up during the sputum transport process (Figure 5- Panel B).
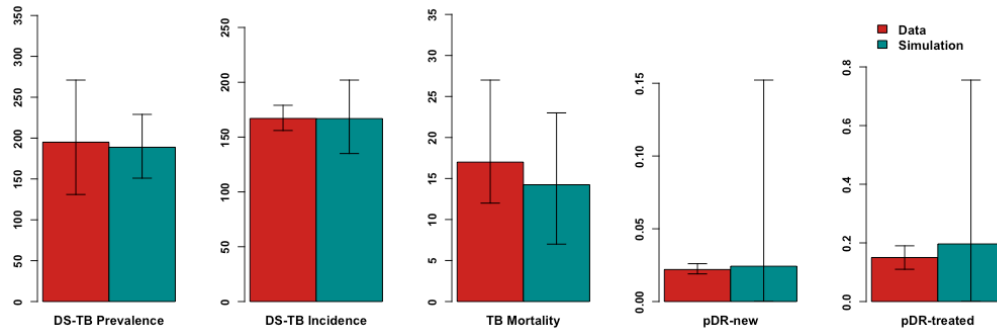

Figure 4: Overview of simulation calibration targets. Each panel compares the simulated means (green bars) versus data estimates (red bars). The black lines represent the 95% uncertainty ranges.
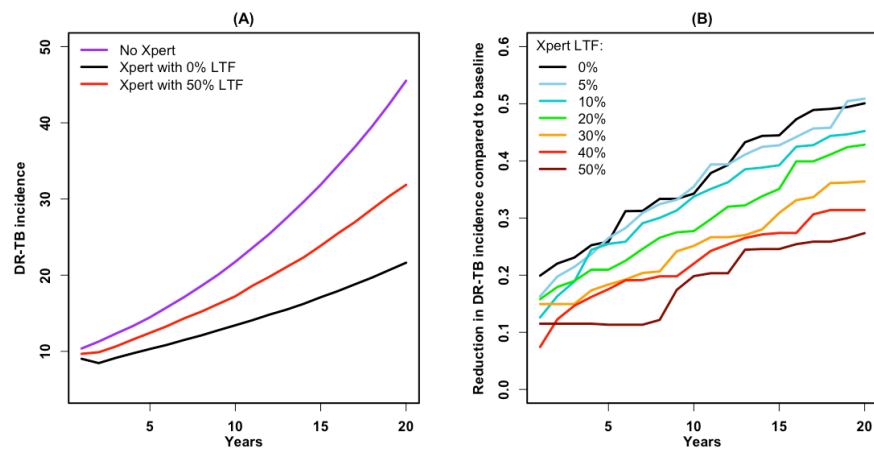

Figure 5: Epidemiologic impact of Xpert implementation on DR-TB incidence. Panel A compares DR-TB incidence in the absence of Xpert (purple) to decentralized Xpert (black) and centralized Xpert with 40% loss to follow-ups (LTF) (red). Panel B compares programs at various levels of LTF for reduction in DR-TB incidence. Each line presents the mean value across 100 independent simulation replications.

Implementation of Xpert by either approach had a negligible impact (<5%) on DS-TB incidence and TB mortality, partly due to the role of empiric treatment for DS-TB in the absence of Xpert as well as the long duration of TB disease before diagnosis (18.5 [16.5 – 20.7] months). Moreover, despite implementation of Xpert, the incidence of DR-TB continued to rise over time, reflecting the underlying increasing trend in DR-TB incidence assumed at baseline (Figure 5- Panel A).

4   DISCUSSION

Implementation of Xpert for diagnosis of TB can have an immediate and significant impact on the population-level incidence of DR-TB in India (resulting in up to 36% reduction in 10 years). This impact,

however, can be diminished by pre-treatment losses to follow-up associated with delays in returning diagnostic results to patients under various models of Xpert implementation.

Our modeling results for population-level impact of Xpert on DR-TB incidence and prevalence are in line with previous cost-effectiveness studies (Cohen et al. 2012). However, the projected small impact of Xpert on DS-TB incidence and mortality in our model differs from those previously suggested. These results are partially driven by the long duration of untreated DS-TB disease (18 months) among patients at baseline (driven by calibration targets for incidence and prevalence of DS-TB in India), which – when combined with our assumption of increasing smear positivity over time -- increased the efficacy of smear microscopy testing alone for detection of DS-TB. Moreover, this observation is consistent with emerging evidence that empiric treatment practices may greatly attenuate the impact of Xpert at the population level (Menzies et al. 2015).

As with any modeling exercise, our analysis is limited by simplifying assumptions used in design and analysis of a simulation model, including simplified household structure and dynamics, homogeneous contact networks within households and community, a simplified model of the Indian TB diagnostic system as three provider tiers, and the discrete representation of the patient diagnostic process at the public sector via three clinical encounters. To the extent that these simplifications depart from the complex reality of TB transmission and diagnosis in the Indian healthcare system, our estimates of epidemiological impact may be affected.

In conclusion, this epidemiological model illustrates the potential impact of Xpert testing to facilitate faster detection of drug-resistant TB, and highlights the important role of pre-treatment loss to follow-up in determining the population-level impact of Xpert on TB incidence. The projected health benefits of implementing and scaling up Xpert involve a significant increase in demand for healthcare resources. While the global TB control community is moving to embrace new diagnostic technologies, several studies have highlighted the important issues concerning the cost of programs and additional demands that they place on the existing healthcare infrastructure (Dowdy et al. 2011; Trébucq, Enarson, and Chiang 2011). As such, any decisions regarding the choice of centralized versus decentralized Xpert would require additional evidence on cost-effectiveness of each alternative and further considerations regarding the affordability of each program at the country level.

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