Estimating the Impact of Tuberculosis Case Detection in Constrained Health Systems: An Example of Case Finding in South Africa

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Abbreviations: HR, human resources; PHC, public health clinics; TB, tuberculosis; HIV, human immunodeficiency virus; ICF, intensified case finding; ART, anti-retroviral therapy

Abstract

Mathematical models are increasingly used to compare strategies for tuberculosis control and inform policy decisions. Models often do not consider financial and other constraints on implementation and may overestimate the impact that can be achieved. We developed a pragmatic approach for incorporating resource constraints into mathematical models of tuberculosis. Using a transmission model calibrated for South Africa, we estimated the epidemiological impact and resource requirements (financial, human resource (HR) and diagnostic) of nine case finding interventions. We compared the model-estimated resources to scenarios of future resource availability and estimated the impact of interventions under these constraints. Without constraints, symptom screening in public health clinics or in those attending HIV care was predicted to lead to larger reductions in tuberculosis incidence (9.5% (95% range (8.6-12.2%)) and 14.5 (12.2-16.3)) than improved adherence to diagnostic guidelines (2.7% (1.6-4.1%)). However, symptom screening required large increases in resources, exceeding future HR capacity. Even under our most optimistic HR scenario, the reduction in tuberculosis incidence from clinic symptom screening was 0.2-0.9%, less than that of improved adherence to diagnostic guidelines. Ignoring resource constraints may result in incorrect conclusions about intervention impact, and to suboptimal policy decisions. Models used for decision making should consider resource constraints.

Keywords: Tuberculosis, South Africa , Mathematical model , Health Resources

While South Africa has experienced a decline in tuberculosis (TB) notifications from a peak in 2011,[1] TB remains a major public health problem. In 2017, there were an estimated 322,000 incident cases[2] and TB was the leading infectious cause of death.[3] Of the estimated incident cases in 2017, less than 70% were notified highlighting the need for improved TB case finding.

Diagnosis of TB in South Africa has traditionally relied on passive presentation to health services leading to delays in diagnosis, especially among HIV uninfected individuals,[4] suggesting that new approaches are required to identify people with TB sooner. Several studies have identified missed opportunities for TB screening in those already attending public health clinics (PHC),[5, 6] and recent initiatives in South Africa have led to increases in screening of PHC attendees with approximately 36 million persons screened for TB in 2015. Mathematical modelling[7] has suggested increased clinic-based screening, a form of intensified case finding (ICF), could result in significant reductions in TB. However, economic analysis suggest ICF, while cost-effective, is likely to require large financial commitments.[8, 9]

Traditionally estimates of impact and cost-effectiveness of TB case detection (and other interventions) have assumed that the only constraint on scale-up was the health sector budget. However, 'within' sector budgets, (e.g. the TB programme budget), may also be constrained if policy makers are unwilling to disinvest in other areas. It is also important to consider constraints on human resources (HR) and other health system requirements. Even if funding is available it may take time to produce the necessary staffing and infrastructure to deliver

services. Financial and health systems constraints may limit the impact of proposed interventions, either because the desired coverage cannot be achieved in the anticipated time-scale or because resources must be reallocated from elsewhere to achieve it.

While mathematical models are increasingly used to predict the impact of strategies for TB control and to inform policy making, few models include resource constraints. Instead, models assume some intervention coverage and estimate the costs and impact of achieving this coverage, assuming sufficient health system capacity. This issue has recently been highlighted in HIV modelling with Mikkelsen et al[10] calling for new approaches to dynamically incorporate constraints into mathematical models of anti-retroviral therapy (ART) scale up. Lin and Langley[11, 12] addressed the issue of health system capacity in TB modelling using an approach that links detailed epidemiological and operational models. However, this approach requires a detailed understanding of the flow of patients through the health system, and linking the two models has proven technically challenging.[12]

We propose an alternative pragmatic approach for incorporating resource constraints, illustrated via application to ICF for TB in South Africa. The approach was developed and applied in the context of informing the South African National Tuberculosis Plan,[13] and was conducted within the tight timeframe that country planning processes allow.[14]

Using a dynamic transmission model, secondary data from costing studies and national data on health sector HR we estimate the potential epidemiological impact and financial and non-financial resource requirements of achieving pre-specified coverage targets for nine intensified

case finding interventions. We then estimated the coverage and impact that could be achieved if resource use were to remain with estimates of future capacity.

METHODS

Transmission model

The model used is similar to a number of published TB models[15, 16] with additional refinements to describe screening and diagnosis in South Africa. Full details are given in Web Appendix 1, Web Tables 1-14 and Web Figures 1-4. The model was used to project the impact of ICF strategies from 2016 to 2035.

The population is divided into 3 "TB" states: susceptible, latently infected, and active disease (stratified into smear positive and smear negative states). Susceptible individuals are infected at a rate that depends on the prevalence of active disease. Following infection, some proportion progress directly to active disease, the remainder enter latent state. Latently infected individuals may remain infected, progress to disease (reactivation) or be re-infected. Individuals with active disease can self-cure, die or be diagnosed and treated for TB. Each of the infection and disease states is further stratified by treatment history (previously treated or treatment naïve) and drug resistance status (susceptible or multidrug resistant).

The model includes human immunodeficiency virus (HIV) and the association of co-infection with the risk of developing and dying from TB. Age-specific HIV incidence and ART coverage are external inputs to the model. The HIV infected population is stratified by CD4 count and time on ART. ART is assumed to reduce the risk of TB and of HIV and TB associated mortality.

Screening, diagnosis and treatment are a simplification of the national TB diagnostic guidelines in South Africa[17] (Web Figures 2-3). These are not included as explicit states in the model. Instead we calculate the rate at which individuals start treatment based on the steps of the diagnostic pathway (see Web Appendix 1 for details).

Base-case and interventions

The base-case describes continuation of current TB care in South Africa. We assume that individuals self-present (passively) with symptoms suggestive of TB at rates estimated by fitting to incidence and notification data prior to the introduction of ICF. Current rates of ICF (among clinic attendees and HIV infected individuals enrolled in care) are estimated by fitting to the total reported number of persons screened for TB in recent years. Amongst those not in HIV care we assume that those presenting with prolonged cough (of more than 2 weeks) are referred for sputum testing[17] while those in HIV care are evaluated based on the presence of any TB symptoms (WHO screening tool). Based on data reported to WHO we assumed that 40% of those enrolled in HIV care were asked about TB symptoms at their last visit.[18] National guidelines also recommend that household contacts of TB cases are screened for TB. We assume that attendance of contacts at clinics for TB screening is captured in the baseline passive screening rate. Active contact investigations, involving household visits, are not widely implemented in South Africa and were not included in the model. Eighty percent of initial diagnostic tests are assumed to be via Xpert MTB/RIF with the remainder via smear microscopy.[13] Xpert is a nucleic acid amplification test, endorsed by WHO in 2013, and subsequently adopted as the initial test for TB diagnosis in South Africa. HIV infected individuals

with an Xpert negative result should have further sputum samples collected for culture and drug susceptibility testing in line with national guidelines.[17] However, based on data from the Xtend study we assumed that only 14% of individuals receive appropriate follow-up.[19] Based on a systematic review published in 2014[20] and data from the Xtend study,[21] we assumed pre-treatment loss to follow up of 17%. Historical values of treatment success are based on national treatment outcome data:[22] 78% for drug susceptible TB and 50% for multidrug resistant TB in 2015. Full details of the base-case assumptions can be found in the appendix.

In a secondary analysis, we adapted the base-case to include the following activities planned in South Africa as part of the National Strategic Plan:[13] reducing pre-treatment loss to follow up by 80% (from 17% to 4%) by 2021; the introduction of short-course multidrug resistant TB treatment[23] alongside continued use of bedaquiline for pre-extensively drug resistant and extensively drug resistant TB.[24] This analysis allowed us to explore how the impact and resource use of the ICF strategies may be altered by other future improvements in the TB program.

We considered nine interventions representing increased adherence to current diagnostic guidelines and various strategies for ICF. These were defined in collaboration with policy makers as part of the TB Think Tank Project[14] and are shown in Table 1. For all interventions, we assumed linear scale up to the target values between 2017 and 2021.

Resource requirements and constraints

To illustrate our approach, we considered three types of resources and their future constraints: budget (total costs of TB programme), HR (nurse time spent on TB activities) and diagnostic

(ratio of Xpert tests to TB notifications). These were identified through discussions with local stakeholders that took place as part of the South African TB Think Tank.[14] During these discussions, stakeholders from the Department of Health highlighted financial, human resource and diagnostic supplies constraints as critical areas to be addressed in this analysis. Full details of the methods used to estimate unit costs and nurse time and the derivation of the future constraints can be found in Bozzani et al.[25]

Three future scenarios for the budget and total nurse time were considered (Table 2). We refer to these as the low (most restrictive), medium and high (least restrictive) scenarios; further details are provided below. For the diagnostic constraint we considered a single scenario in which the ratio of Xpert tests to notifications was capped at 20:1. This constraint reflects a limit on diagnostic supplies (Xpert cartridges) purchased annually in South Africa. In previous years the budget for purchasing Xpert cartridges has been set based on a ratio of 20 Xpert tests for every case of TB diagnosed (South African NDoH, personal communication).

The low budget (most restrictive) scenario was based on predicted GDP growth of 1.7% per year,[26] the medium scenario additionally assumed that a proportion of the current budget was reallocated to TB in line with the proportion of deaths in South Africa attributable to TB (approximately 10-15%) and the high scenario that a proportion of a health budget that achieves its full fiscal space growth was similarly reallocated.

In the low HR scenario, the nurse minutes spent on TB were adjusted in future years based on population growth only; the medium constraint incorporated a reallocation of the current workforce to TB based on disease burden as above; and the high scenario similarly reallocated a

proportion of the nursing workforce that achieved its maximum growth based on historical growth rates.

The budget and nurse time required in the base-case and each intervention were calculated by multiplying unit costs and nurse minutes per activity by the outputs of the transmission model (Table 3). Xpert use was calculated by dividing the number of tests (an output of the model) by the model estimated notifications.

The total costs, nurse time and Xpert ratio required by each intervention were compared to the constraint scenarios to identify interventions that exceed the constraints. These interventions were then re-simulated to estimate the epidemiological impact under the constrained scenarios. For the budget and HR constraints we iteratively reduced the maximum intervention coverage achieved in 2021 (assuming linear scale up from 2017 as in the unconstrained scenario) such that the projected cost or nurse time remained below the constraint over the entire time horizon (2017-2035). When implementing the constraint on the Xpert to notification ratio we assumed an intervention would be stopped (coverage reduced to zero) when the 20:1 ratio suggested by the Department of Health was exceeded.

Model calibration

The model was fitted to TB notification data (total and multidrug resistant),[18] number of screens reported to the Department of Health, number of laboratory tests conducted[27] and estimated TB incidence and mortality.[1] Details can be found in the Web Appendix 2 and Web Table 15. In summary, values for parameters were sampled from prior specified ranges. The model was then calibrated in a two-step process by varying selected model parameters to

minimise the weighted sum of square differences between the model and the observed data. First, the contact rate and passive screening rate were varied to match the incidence and notifications in 1990 (before the increase in HIV associated TB). Secondly, the increase in passive screening, rate of ICF, rate of acquisition of drug resistance, a multiplier for the impact of ART on TB risk in people living with HIV and a multiplier of the TB mortality rate in HIV infected individuals were varied to fit to all calibration data from 1990-2015. This process was repeated *N*=1000 times to incorporate the uncertainty in the unfitted parameters.

RESULTS

Baseline fit and base-case projection

The model reproduces the trends in incidence, mortality and notifications and predicts continued declines in incidence and mortality to 2020 (figure 1). Future notifications remained largely constant, although with large uncertainty. Short term increases in notifications result from an increase in the number of true positive TB cases diagnosed. However, over time, as TB incidence falls there will be an increasing number of false positive notifications due to the imperfect specificity of the diagnostic process. Reported testing volumes were within the model uncertainty. Baseline estimates of the total cost and nurse minutes spent on TB activities (see figure 2) in 2015/16 were consistent with previous estimates.[25]

Total costs, nurse minutes and the ratio of Xpert to notifications are predicted to increase over time. The increase in costs and nurse time this is driven by population growth and increases access to HIV care, both of which result in increased numbers of people being screened for TB.

The increase in the ratio of Xpert tests to notification is driven by the fall in the prevalence of TB; as TB becomes rarer the number needed to test to find one TB case will increase.

Impact of interventions – unconstrained scenario

In the base-case (which includes current levels of ICF), the predicted reduction in TB incidence from 2016 to 2035 is 18.9% (95% central range (3.5-29.4)). Figure 3 and table 4 show the additional percentage change in the incidence rate in 2035 compared to the base-case (intervention 1) for each intervention. When not accounting for constraints (black bars) the largest reductions in incidence are predicted for interventions which include increased coverage of screening using the WHO symptoms tool (interventions 8 (9.5% (8.6-12.2)), 10 (12.6% (9.8-14.9)) and 7 (14.5% (12.2-16.3)) in order of increasing impact). A smaller but significant reduction (5.0% (3.8-7.1)) is also predicted for increased use of cough-based screening in PHC clinic attendees when combined with improved adherence to the diagnostic algorithm (intervention 9).

Increased Xpert utilisation (intervention 2) and improved adherence to Xpert negative algorithms (intervention 3) result in small reductions in incidence. However, the combination of these two strategies (intervention 4) produces a similar impact to increases in PHC screening (intervention 6). The change to cough-based screening in those in HIV care (intervention 5), which is not recommended in national or WHO guidelines, results in an increase in incidence compared to the base-case. This is because cough-based screening has a lower sensitivity compared to the WHO screening algorithm which is included in the base-case. As a result,

despite the assumed increase in coverage this intervention strategy is inferior to continuation of current practice.

Resource requirements

Figure 2 shows the predicted resources required for the base-case and each intervention from 2015 to 2035.

All interventions, including the base-case, exceed the Low budget and Low nurse time constraints (most restrictive scenarios); these scenarios were not considered further. In contrast, the Medium and High budget constraints are not exceeded by any intervention. For interventions 6-10, which include increases in ICF, the model predicts increases in nurse time which exceed the proposed constraints. This is particularly the case for interventions based on WHO symptom screening (interventions 7, 8 and 10) because of the increased time taken to carry out the screening and the lower specificity compared to cough screening which results in an increased number of tests in individuals without TB. The Xpert constraint is exceeded by interventions that include increased use of symptom screening (interventions 7, 8 and 10) and strategies that include increased use of Xpert as the first line test (interventions 2, 4, and 9). The most ambitious intervention (intervention 10) required more than 45 Xpert tests per notification.

Impact of interventions – constrained scenarios

Including medium budget constraints in the model (figure 3, dark grey bars) does not change the predicted impact, because the future budget predictions do not exceed these constraints. The high budget constraint is also not exceeded (not shown). Similarly, the impact in the base-case (intervention 1), strategies focused on improved adherence to guidelines (interventions 2-4) and the use of cough screening in HIV infected individuals (intervention 5) is not affected by the nurse time constraint.

Both high (figure 3, mid grey bars) and medium HR constraints (figure 3, light grey bars) reduce the impact of increased ICF (interventions 6-10) as the previously assumed coverage (see table 1) cannot be reached. Under the high HR constraint, the largest median impact is still observed for increased symptom screening of HIV infected individuals (intervention 7). However, for the medium HR constraint the ranking of the interventions is changed with the largest impacts predicted for increased adherence to guidelines (intervention 4) and the combination with increased cough screening in clinic attendees (intervention 9). The additional effect of the Xpert constraint on top of the medium HR constraint (figure 3, white bars) is small partly because much of the impact in each intervention has been achieved by the point at which the Xpert to Notification ratio exceeds 20:1.

Secondary analysis

The results for the secondary analysis including the NTP strategy are qualitatively the same. In the base-case the model predicts a greater reduction in incidence due to the additional impact of improved linkage to care. However, the incremental benefit of each intervention, when combined with reduced pre-treatment loss to follow up, is smaller as the impacts are not

additive. The overall costs and nurse time are lower in the NTP scenario than for the corresponding interventions in the primary analysis however, the same interventions exceed the constraints. Web Appendix 3 and Web Figures 5-7 provide further details of the results of the secondary analysis.

DISCUSSION

Our results show that ICF may result in significant reductions in TB incidence, but with large increases in financial and HR requirements. While the costs may remain below the assumed budget projections, ICF strategies may exceed HR capacity, even under optimistic scenarios of reallocation of nurse time to TB, and normative limits around Xpert numbers. When the HR constraint is included in the model, the ranking of interventions by impact is changed. In particular, the impact of ICF strategies is greatly reduced and may, in rare cases, be less effective than continuation of current practice.

Our approach was developed and implemented in the context of supporting the use of modelling to inform policy in South Africa.[14] Our aim was to demonstrate the feasibility of a simple approach to highlight the potential importance of constraints. In this light, several simplifying assumptions were made. When incorporating constraints, we have assumed that other TB control activities continue at their current levels, and that the coverage of the new intervention is reduced to satisfy the constraint. An alternative would be to consider that the full intervention coverage is reached, and that the capacity for other activities must be reduced

to compensate. This approach could be considered in the framework used here but would require rules for prioritisation of activities.

Our illustrative approach also assumed a single change to intervention coverage to satisfy the constraints over the entire time-period considered. In reality, the mix and coverage of interventions may change over time as capacity varies. In our example, the HR constraint is typically exceeded in the short term as HR capacity is still increasing. As such it is possible that coverage could subsequently be increased in future. Our results are therefore likely a conservative estimate of the impact that could be achieved under these constraints. Yaesoubi and Cohen[28] modelled dynamic case finding policies and showed that they were preferable to static policies. However, they only considered the financial requirements of those policies. Combining these two approaches may be a useful way to identify strategies that account for the timescales of staff recruitment.

Several studies have addressed the issue of resource constraints in infectious disease models. Lin and colleagues[11] have proposed an alternative approach to incorporate health system capacity in models by combining a discrete event simulation of the health system with a compartmental model of TB transmission. This approach has been used successfully to explore the impact of new diagnostics in Tanzania,[12] however it requires a detailed understanding of the whole health system in the country and presents computational demands in linking the models. Hontelez et al [29] incorporated constraints into their analysis of changes to HIV treatment eligibility by defining a-priori a set of treatment scale-up scenarios that represented potential supply and demand side constraints. In contrast, our approach is similar to the

AsiaFluCap simulator used in planning pandemic influenza control;[30] the outputs of the model are used to dynamically estimate the resource needs of different interventions and compare these to constraints defined using a combination of secondary data and policy maker consultation.

While we have attempted to include the key aspects of TB control in South Africa, there are several important limitations. We relied on routine data that may be subject to inaccuracy and bias. We assume ICF occurs independently of true TB status, and hence may underestimate the TB prevalence in the population screened and the ICF impact. We also assume that linkage and completion of treatment is equal in those identified passively and via ICF. If those identified via ICF are less likely to start treatment[31] we may overestimate the impact and resource use. It is also possible that linkage to TB treatment may be greater for people in HIV care than for people not engaged with the health system. If this was the case it may increase the relative impact of screening in people living with HIV compared to other forms of ICF.

In this work we have considered South Africa as a whole. The resource requirements of ICF could be reduced by targeting interventions to geographic regions with the highest burden. The preferred strategies may differ between areas due to differences in factors such as the prevalence of HIV co-infection.

The model includes the association between of HIV and risk of TB but does not currently include other known risk factors for TB such as diabetes or smoking. Strategies to detect and prevent TB in these risk groups may form an important part of future efforts to control TB in South

Africa. Strategies that target these and other risk groups may reduce the resource requirements of case finding interventions.

Our results can be used to illustrate to policy makers the need to define policies that expand TB services at the same time as addressing constraints to expansion. For example, in this work we have assumed that all activities are conducted by nurses, the main cadre of staff that have historically been responsible for delivering TB services in South Africa. Our findings show that policies which aim to increases TB screening must be accompanied by strategies to address human resource constraints. This may be via investment in training, or through task-shifting activities like contact tracing or symptom screening to other staff such as lay-workers. While none of the interventions exceeded the medium and high budget constraints, these assume a substantial reallocation of the health budget. Without this reallocation none of the interventions are feasible. Limiting Xpert use based on the number needed to test to diagnose one TB case may also restrict the reduction in incidence that can be achieved. As TB burden declines this ratio will need to increase to ensure that cases are not missed.

It is also important to consider how these resource constraints may affect the cost-effectiveness of different strategies. Strategies that are deemed cost-effective in the absence of constraints may not be cost-effective if the potential impact is limited by constraints or the costs of relaxing constraints are included in the analysis. This is the focus of ongoing research.

Conclusion

This work highlights the importance of including resource constraints in models used to evaluate TB control strategies. Ignoring these constraints may result in overestimation of the achievable impact of interventions in the absence of other actions to increase health system capacity, and ultimately lead to inappropriate or unwarranted policy decisions.

Table 1. Summary of interventions modelled.

Intervention	Description
1. Base-case	Continuation of current practice
2. Xpert	Use of Xpert as first line test is increased from 80% to 100%
3. Guidelines	Adherence to Xpert negative guidelines increased from 14% to 90% in known HIV infected individuals
4. 2 + 3	Combination of 2 and 3
5. Cough HIV+	Cough based screening (cf. WHO symptom screen in base-case) in 100% (cf. 40% in the base-case) of HIV infected individuals enrolled in care
6. Cough PHC	Cough based screening in 90% (cf. 50% in the base-case) of PHC attendees
7. Symptom HIV+	WHO symptom screen in 100% (cf. 40% in the base-case) of HIV infected individuals enrolled in care
8. Symptom PHC	WHO symptom screen (cf. cough based screening in the base-case) in 90% (cf. 50% in the base-case) of PHC clinic attendees
9. 4 + 6	Combination of 2, 3 and 6
10. 4 + 8	Combination of 2, 3 and 8

Abbreviations: cf., compared to; HIV, human immunodeficiency virus; PHC, public health clinic; WHO, World Health Organisation.

Table 2. Description of Constraints

	Constraint Scenario		
Type	**Low**[a]	**Medium**[a]	**High**[a]
Budget[b] **(total cost of TB programme)**	GDCP growth	As low plus reprioritisation based on disease burden from 2017-2021	As medium plus earmarked taxes from 2017-2021
HR[c] **(nurse time spent on TB activities)**	Population growth	As low plus reprioritisation based on disease burden from 2017-2021	As medium plus historic nursing workforce growth
Diagnostic[d] **(ratio of Xpert tests to TB notifications)**	Ratio of Xpert tests to notifications does not exceed 20:1	Ratio of Xpert tests to notifications does not exceed 20:1	Ratio of Xpert tests to notifications does not exceed 20:1

Abbreviations: HR, human resources; TB, tuberculosis.

[a]Low scenarios are the most restrictive, high scenarios the least restrictive.

[b]Total cost of TB programme.

[c]Nurse time spent on TB activities.

[d]Ratio of Xpert tests to TB notifications (a single diagnostic constraint scenario was considered).

Table 3. Minutes and costs per unit activity.

Activity	Nurse time (minutes)	Cost (USD)	
Passive screening	2.63	0.68	per screen
Cough screening	1.26	0.68	per screen
WHO symptom screen	4.0	1.36	per screen
Sputum smear microscopy	3.16	10.87	per screen
Xpert	3.16	32.24	per screen
Follow up of Xpert negative	8.61	24.00	per screen
First line treatment (initiation phase, 2 months)	35.72	21.43	per month[a]
First line treatment (continuation phase, 4 months)	7.57	21.43	per month[a]
MDR treatment, DOT (initiation phase, 6 months)	237.04	359.1	per month[a,b]
MDR treatment, non-DOT (initiation phase, 6 months)	84.47	359.1	per month[a,b]
MDR treatment, DOT (continuation phase, 18 months)	159.83	359.1	per month[a]
MDR treatment, non-DOT (continuation phase, 18 months)	84.47	359.1	per month[a]
IPT	5.54	7.81	per month

Abbreviations: DOT, directly observed therapy; IPT, isoniazid preventive therapy; MDR, multidrug resistant; WHO, World Health Organisation.

[a]20% of drug susceptibe DS patients and 20% of decentralised MDR patients receive treatment via directly observed therapy (DOT), the remainder only attended monthly for drug collection (personal communication, National Department of Health).

[b]60% of MDR patients are hospitalised during the intensive phase. This activity is not included in our estimates of PHC nurse time.

Table 4. Predicted reductions in incidence in the unconstrained scenario.

Intervention[a]	% Reduction in incidence in 2035 compared to base-case (median (95% central range))[b]
1. Base-case	0 (0-0)
2. Xpert	1.6 (0.9-2.4)
3. Guidelines	1.1 (0.6-1.6)
4. 2 + 3	2.7 (1.6-4.1)
5. Cough HIV+	-0.7 (-2.0-0.76)
6. Cough PHC	2.6 (2.1-3.2)
7. Symptom HIV+	14.5 (12.2-16.3)
8. Symptom PHC	9.5 (8.6-12.2)
9. 4 + 6	5.0 (3.8-7.1)
10. 4 + 8	12.6 (9.8-14.9)

Abbreviations: HIV, human immunodeficiency virus; PHC, public health clinic.

[a]Rows refer to the interventions listed in table 1.

[b]Values indicate the reduction in incidence in 2035 in the intervention compared to the base-case (intervention 1). Values in parentheses give the 95% central range (2.5-97.5th percentile).

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Figure captions

Figure 1. **Baseline fit of the model.** A) TB incidence per 100,000 population, overall (dark grey) and in people living with HIV (light grey). The dotted line shows the point value and the shaded area the range of the WHO estimate. The dashed line shows the median and the solid lines the range of the model output. B) TB mortality per 100,000 population in HIV uninfected individuals (dark grey) and PLHIV (light grey). Other details as for panel A. C) No. of TB notifications (in thousands), all forms (circles) and multidrug resistant (triangles). Points show the reported data. The dashed line shows the median and the solid lines the range of the model output. D) Rate of laboratory testing for TB per 100,000 population. Other details as for panel C.

Figure 2. **Projection of future costs, HR requirements and Xpert to Notification ratio**. Symbols show the median model prediction for each intervention from 2015 to 2035. A) Total costs of TB control activities (in millions of US dollars). B) Nurse time spent on TB activities (in millions of minutes). C) Number of Xpert tests per TB notification. Solid black lines show the low, dotted black lines the medium and dashed black lines the high constraints for total cost and nurse minutes. In the Xpert panel (C) only the single constraint (a ratio of 20:1) is shown (dashed line).

Figure 3. Impact on incidence. Percentage reduction in incidence rate in 2035 compared to the baseline (intervention 1). Shading indicates the constraints applied to the model. Boxes show the 25^{th}-75^{th} percentile, whiskers indicate 1.5 times the interquartile range and black circles show outliers. The high budget constraint is not shown as results are the same as for the medium budget constraint. Values above 0 (dashed horizontal line) indicate a larger reduction in incidence compared to the baseline.