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Trade-offs between cost and accuracy in active case-finding for tuberculosis: a dynamic modelling analysis

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Abstract

Background

Active case-finding (ACF) may be valuable in tuberculosis (TB) control, but questions remain about its optimum implementation in different settings. For example, smear microscopy misses up to half of TB cases, yet is cheap, and detects the most infectious TB cases. What, then, is the incremental value of using more sensitive and specific, yet more costly, tests such as Xpert MTB/RIF, in ACF in a high burden setting?

Methods and Findings

We constructed a dynamic transmission model of TB, calibrated to be consistent with an urban slum population in India. We applied this model to compare the potential cost and impact of two hypothetical approaches, following initial symptom screening: (i) 'moderate accuracy' testing employing a microscopy-like test (that is, lower cost but also lower accuracy) for bacteriological confirmation and (ii) 'high accuracy' testing employing an Xpert-like test (higher-cost but also higher accuracy, while also detecting rifampicin resistance).

Results suggest that ACF using a moderate-accuracy test could in fact cost more overall than using a high-accuracy test. Under an illustrative budget of USD 20 million in a slum population of 2 million, high-accuracy testing would avert 1·14 (95% Bayesian credible intervals 0·75 – 1·99, with p = 0.28) cases relative to each case averted by moderate-accuracy testing. Test specificity is a key driver: high-accuracy testing would be significantly more impactful at the 5% significance level, as long as the high-accuracy test has specificity at least 3 percentage points greater than the moderate-accuracy test. Additional factors promoting the impact of a

high-accuracy are that: its ability to detect rifampicin resistance can lead to long-term cost savings in second-line treatment; and its higher sensitivity contributes to the overall cases averted by ACF.

Amongst limitations of this study, our cost model has a narrow focus on the commodity costs of testing and treatment; our estimates should not be taken as indicative of the overall cost of ACF. There remains uncertainty about the true specificity of tests such as smear and Xpert-like tests in ACF, including variations in the accuracy of the reference standard under such conditions.

Conclusions

Our results suggest that cheaper diagnostics do not necessarily translate to less costly ACF, as any savings from the test cost can be strongly outweighed by factors including false-positive TB treatment, reduced sensitivity, and foregone savings in second-line treatment. In resource-limited settings, it is therefore important to take all of these factors into account, when designing cost-effective strategies for ACF.

Authors' Summary

Why was this study done?
> Active case-finding (ACF) is a strategy for reducing the burden of tuberculosis (TB), which aims to identify and treat TB cases in the community, as rapidly as possible.
> However, because ACF can be very resource-intensive, it is important to understand how best to conduct it, in the most cost-efficient way.
> Concentrating on the tests used to diagnose TB, we hypothesised that cheaper tests, although less accurate than more costly tests, would be important in bringing down the overall cost of ACF.

What did the researchers do and find?
> Using a mathematical model of TB in urban slums in India, we simulated the cost and impact of an ACF intervention over the next 15 years.
> Contrary to our initial hypothesis, we found that the use of cheaper diagnostic tests with lower accuracy can in fact increase, not decrease, the overall cost of ACF.
> The reason is that the cost of a test can be outweighed by the costs of treatment: specifically, false-positive (unnecessary) TB treatment, and second-line treatment for drug-resistant TB; cheaper tests would also have lower impact overall, as a result of their lower sensitivity.

What do these findings mean?
> Our findings show how cheaper diagnostic tests may represent a false economy in active case-finding, i.e. leading to larger intervention costs overall, if they are also associated with reduced performance in ruling out TB.
> Those implementing ACF in resource-limited, high-burden settings should consider all of these factors in their planning, and not just the cost of the test.

Introduction

Tuberculosis (TB) remains a major concern for global health, with 10.4 million incident cases globally in 2017 and approximately 1·3 million deaths (1). The End TB strategy calls for a reduction in incidence of 90% by 2035 (2); to reach these targets, it will be necessary to accelerate the rate at which TB cases are diagnosed and initiated on treatment (2). Active case-finding (ACF) is one way of doing so: modelling suggests that ACF could be cost-effective under certain cost thresholds, particularly over longer (>10 years) time horizons (3) However, direct evidence for the potential impact of such measures in practice is limited (4), including in settings like India, the country with the world's largest TB burden, which alone has an estimated 26% of the 3·6 million estimated 'missing cases' (1).

In response to these challenges, a key component in India's 2017 National Strategic Plan for TB elimination is the need to perform intensive, sustained ACF in specific populations such as urban slums, which are known to have a greater TB burden than the general population (5). In general, ACF in these and other settings employs screening for symptoms suggestive of TB, followed by bacteriological testing. The latter is often performed using molecular tools such as Xpert MTB/RIF (hereafter referred to as 'Xpert') a cartridge-based nucleic acid amplification test. More recently, the 'Ultra' diagnostic platform offers higher sensitivity than Xpert, but at the expense of lower specificity (6). In the present work, we concentrate on the deployment of Xpert. Key advantages of Xpert are that (i) it is more sensitive than the conventionally used smear microscopy, which can miss up to half of pulmonary TB cases (7), and (ii) offers faster recognition of rifampicin resistance at the point of TB diagnosis (1,8), thus allowing the timely initiation of second-line treatment. However, those cases detectable through smear microscopy tend to be the most infectious (9), and this approach is considerably cheaper than Xpert. Therefore, the use of smear may achieve substantial epidemiological impact, at a lower cost.

Could smear-based ACF be more cost-effective than Xpert-based ACF, in settings such as India? What are the benefits of using Xpert in comparison to smear, and vice-versa? Our scope is not simply on yield (defined as the proportion of positive cases identified), a major focus of operational research, but also on potential epidemiological impact, taking into account the potential transmission implications of ACF. In line with India's National Strategic Plan, we model case-finding efforts in conditions typical of urban slums using a transmission model combined with a simple costing approach. Building on previous modelling analyses of ACF (10,11), in this work we focus on both the specificity and sensitivity of the diagnostic strategy employed in ACF.

Methods

Transmission model

We developed a dynamic transmission model of TB, illustrated in Fig 1, and described in further technical detail in S1 Text. The model captures key features in the natural history of TB, including asymptomatic but infectious disease; smear status; and TB mortality and spontaneous cure. The model focuses on pulmonary TB and neglects extrapulmonary TB, assuming ACF to focus on the former. Amongst those with TB (indicated by the orange box in the figure), we assumed that smear-negative pulmonary TB cases are, on average, 20% as infectious as smear-positive ones (9) (see Table 1 for model parameters). We incorporated 'passive' TB service delivery, including the split between public and private sectors that is a major feature of the health system in India (12). Additionally, the model also distinguishes drug-susceptible (DS) and drug-resistant (DR) TB, the latter including both rifampicin-resistant and multi-drug-resistant forms of TB. Although DR-TB only accounts for approximately 5% of the TB burden in India, it also consumes a disproportionate amount of the TB budget due to the high cost of second-line treatment (1). In the model, we account for the delay in recognition of DR-TB as a result of missed opportunities for drug sensitivity testing, as well as the potential impact of Xpert-based ACF in reducing this delay.

We separately simulated the dynamics of a 'Non-TB Symptomatic' (NTS) population, i.e. individuals who would be eligible for a TB diagnosis based on the presence of TB-like symptoms, but who do not have TB. This population is necessary for tracking the overall number of diagnostic tests being conducted during the case-finding intervention, as well as the unnecessary treatment of false-positive TB (13).
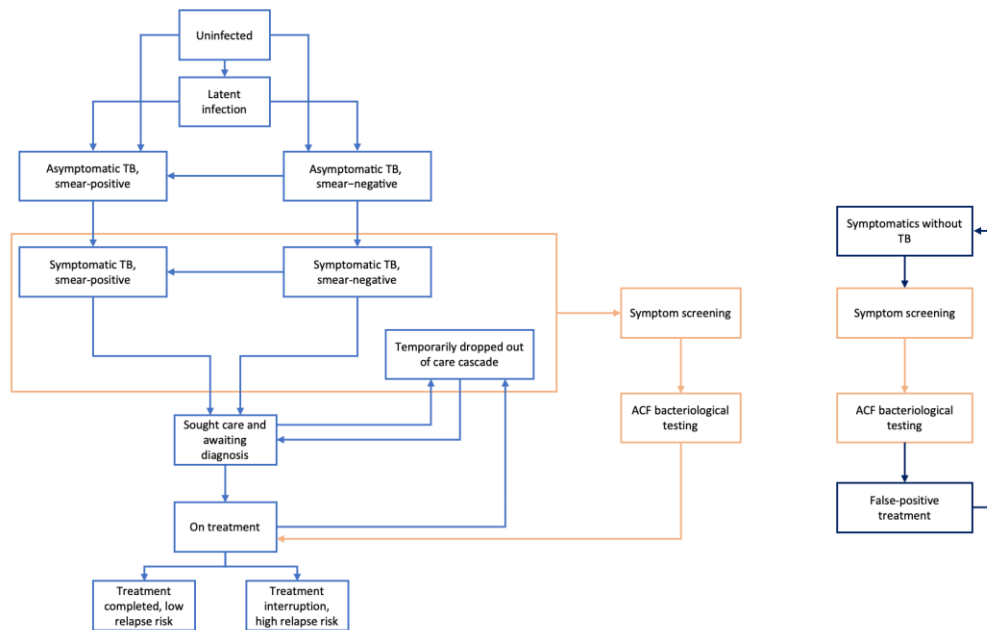
Fig 1. Schematic illustration of the model. The TB transmission model (left) distinguishes TB by smear status, and by symptom status. Upon developing symptoms, symptomatic individuals seek care through either the private or public sectors ('passive' TB services) after a certain delay, estimated to match data in Table 2. Although not shown here for clarity, the model captures these sectors separately, including the lower standard of TB care in the private sector (see S1 Text for full model details). Those successfully diagnosed initiate TB treatment; we assume that 15% of diagnoses in the public sector are conducted with Xpert, the remainder by microscopy. All those lost from the TB care cascade, whether because of missed diagnosis, pre-treatment loss-to-follow-up, or failed treatment, temporarily disengage from care-seeking, before once again seeking care after a given delay. Compartments shown in orange denote the effect of an active case finding (ACF) intervention on this 'passive' system; we assume that ACF consists of initial symptom screening, followed by microbiological confirmation. Meanwhile, the dark blue compartments on the right represent a subset of the general population that may be detected by the ACF intervention (orange compartments) because they have TB-like symptoms, but without TB: these may include, for example, individuals with COPD, bronchitis, and other lung conditions. They incur a cost in diagnosis and – if they are mistakenly diagnosed with TB – a cost in false-positive treatment. The number incorrectly identified as having TB is dependent on the specificity of both the screening and confirmatory stages. Finally, at any stage individuals may die of natural causes or of TB (in the diseased compartments) or recover spontaneously. For simplicity, these transitions are not shown in the figure (see S1 Text for full model details).

Model calibration

The model described above was calibrated to annual risk of *Mycobacterium tuberculosis* (*M.tb*) infection (ARTI) and prevalence estimates representative of urban slums in India (Table 2). To inform model parameters for symptom onset from asymptomatic stages, and for progression of smear status with developing disease, we drew from a prevalence survey in Chennai (5). In particular, we calibrated the model to the proportion of TB prevalent cases that are symptomatic and the proportion smear-positive amongst those who had not yet presented for care, stratified by symptom status (Table 2). We adjusted the size of the NTS population to capture an overall 3% prevalence of TB amongst symptomatic individuals, as indicated by the Chennai prevalence survey (5).

Uncertainty was estimated using Latin hypercube sampling to sample model parameters from their respective ranges (10,000 samples) and simulating the model to 2018, as described in S1 Text. Parameter sets were accepted in the sampling if they provided model projections that fell within the calibration target ranges, while the rest were rejected.

Intervention

Using the calibrated model, we simulated an ACF algorithm using symptom screening followed by a confirmatory microbiological test. We assumed that all TB diagnoses through ACF would be microbiologically confirmed, that is, assuming that there is no role for presumptive clinical diagnosis in ACF. For the screening stage, we modelled the use of symptom screening, with individuals reporting any symptom suggestive of TB to be deemed eligible for microbiological confirmation. For the sensitivity and specificity of this approach for TB, we drew from a recent meta-analysis of screening approaches (14). We also performed sensitivity analyses (described below) under an alternative screening approach identifying those with prolonged cough, rather than any TB symptom (prolonged cough screening having higher specificity but lower sensitivity than 'any TB symptom').

For the confirmatory test, we distinguished two types of strategy: a 'moderate-accuracy' strategy, using a confirmatory test with performance and cost consistent with smear microscopy, and a 'high-accuracy' strategy, with performance and cost consistent with Xpert (see Table 1 for parameters). The reason for these designations is that – although there exists data from clinical trials on the performance of smear and Xpert – there is currently little evidence for characteristics such as the specificity of either test in real-world conditions. In particular, test specificity is often assessed against culture as a reference standard, and thus do not address how to interpret smear-positive, culture-negative results that nonetheless show clear signs of having TB (15,16). We do not address the important question of how reference standards might be improved, to meet these challenges. Instead, our analysis casts light on

which types of uncertainty are most critical for future studies to address, in strategic planning for ACF activities. Consistent with the capabilities of smear and molecular tests such as Xpert, we assumed that the high-accuracy test can detect rifampicin resistance at the same time as detecting TB, while the moderate-accuracy test cannot. We assumed that all those recognised as having rifampicin resistance are immediately initiated on second-line therapy, while those with unrecognised rifampicin resistance are only switched to second-line therapy after failing first-line treatment.

We considered 'sensitivity' as the proportion of TB cases that would yield a positive microbiological result under a given test, and likewise 'specificity' as the proportion of those without TB that would yield a negative microbiological result. Moreover, we assumed that all smear-positive cases test positive through a smear-like test, and that no smear-negative cases do (i.e. sensitivities of 1, 0 respectively). This is a simplification for model purposes: we also performed a sensitivity analysis under alternative assumptions, where smear-status is associated with a given probability of diagnosis.

We simulated the intervention at different levels of coverage to run from 2020 to 2035, scaled up linearly over the first four years (2020-2024), ultimately to screen a given proportion of the population per year. We assumed for simplicity that this proportion is selected at random from the slum population each year. The impact of ACF was measured as the percentage reduction in cumulative incidence between 2020 and 2035. Finally, we calculated the incremental costs of the intervention relative to a baseline of status quo, i.e. current standards of TB care continued indefinitely, and without ACF.

Economic evaluation

We focus on the programmatic perspective, i.e. considering only costs borne by the TB programme, and ignoring broader societal costs. The model accounts for 'passive' TB services, i.e. those routine services (diagnosis and treatment, both first and second-line), independent of ACF, and contingent on patients presenting for care. Since these services could be lowered by the rollout of ACF, this will impact the overall incremental costs. Concentrating on programmatic costs, we counted only the costs of diagnosis and treatment in the public sector, and not the private sector. Moreover, new second-line regimens introduced in 2017 present a range of possible costs for DR-TB treatment. However, as the focus of the current study is on ACF, for simplicity we assumed costs and outcomes consistent with currently used regimens (Tables 1 and 3), while performing sensitivity analyses to this assumption. For all unit costs, for simplicity we assumed uncertainty intervals of +/-20%.

For the ACF costs, we assumed that all patients identified through ACF are linked to treatment in the public sector. We focused for simplicity on service costs, related to the numbers of confirmatory tests and patient-months of first- and second-line treatment incurred by the intervention. In doing so, we are neglecting the 'intervention costs' needed to facilitate the delivery of these interventions (for example, human resources). As discussed below, these are important cost components in any exercise aiming to estimate the full costs of ACF (17). For the purpose of the present study, however, if these intervention costs are similar for moderate- and high-accuracy testing, they may not substantially impact a comparison in cost between the two.

Finally, we tracked the costs of treating false-positive TB diagnoses, as driven by the imperfect specificity of the screening and diagnostic tools involved, and the low prevalence of TB (<5% amongst those with symptoms, even in urban slums). Unnecessary TB treatment carries heavy societal costs, including avoidable stigma (13), as well as the monetary costs to patients and households (e.g. travel costs) involved in completing a regimen of TB treatment (18). Such factors are outside the scope of our current study: here we focus on the unnecessary programmatic spending on the treatment of false-positive TB, recognising (as discussed below) that this approach represents only one narrow part of the overall adverse effects of false-positive treatment (13). All unit costs are provided in Table 3. Overall, we caution that our estimates should not be interpreted as representing the overall cost of any ACF intervention, given that it misses these cost components, as well as the implementation costs described above.

Sensitivity analysis

To test model sensitivity to alternative screening strategies, we first simulated impact on incidence and incremental costs when using 'prolonged cough' as a symptom screening strategy, with higher specificity and lower sensitivity than an approach using any symptom suggestive to TB that we use as a baseline. For additional sensitivity analyses, as a focal model output, we calculated the cumulative cases averted between 2020 and 2035 under an assumed budget of USD 20 million, taking a ratio of cases averted between the 'high-accuracy' and 'moderate accuracy' scenarios. This ratio offers an estimate of the relative cost-efficiency of the two approaches. We examined model sensitivity to individual parameters by conducting a partial rank correlation between this model output and each of the model inputs listed in Table 1. We additionally evaluated the focal model output under different scenarios: (i) Assuming that smear microscopy can detect 25% and 75% of smear-negative and -positive cases, respectively (as opposed to 0% and 100% in the main analysis). (ii) Alternative scenarios for the burden and management of DR-TB, which can consume a disproportionate

share of programmatic spending. We modelled a scenario consistent with Mumbai, having a substantially higher DR-TB burden than the national average. We also modelled a scenario with the adoption of new, more effective and less costly second-line regimens.

Planning and execution of Methods

At the outset of this analysis, the modelling plan focused on the confirmatory test, assuming the use of 'any symptoms suggestive of TB' as a screening strategy. Subsequently, our main adjustment to this initial plan was in response to constructive reviewer comments, on the need to better understand the influence of the screening algorithm. In response, we incorporated the additional analysis as described above, on the alternative use of 'prolonged cough' as a screening strategy. Also in response to reviewer comments, we incorporated the additional sensitivity analyses described above, for the alternative scenarios for the burden and management of DR-TB. Our initial modelling plan otherwise underwent no data-driven changes.

Results

Results of model calibration are shown in S1 Text Fig A. Simulating the ACF interventions, Fig 2 shows model projections for how epidemiological impact varies with coverage (proportion of the slum population screened per year). The higher the proportion of the slum population being screened each year, the greater the reduction in the prevalent pool of infectious TB; the impact shown in Fig 2 is the result of reducing opportunities for transmission in this way, measuring impact as the percentage reduction in cumulative incidence between 2020 and 2035. The figure illustrates that high-accuracy testing would have a greater impact than a moderate-accuracy strategy, at a given level of coverage, as a result of its higher sensitivity. Even with the latter diagnosing the most infectious cases, this difference in impact is robust to parameter uncertainty. Taking the example of 50% coverage, the relative impact of high- vs moderate-accuracy strategies is 1·16 (95% credible interval 1·11-1·22).

Next, Fig 3 illustrates how impact varies with incremental spending between 2020 and 2035, under the two ACF strategies. Here we assume an illustrative slum population of 2 million people, motivated by a mean population of major cities in India of ~10m, of whom roughly a third are slum-dwellers (19) (for smaller or larger cities, incremental spending will be proportional to population size). The vertical dashed line shows the number of cases that could be averted under an illustrative spend of USD 20 million. As noted above, this spend relates only to service costs of ACF, and does not reflect the full implementation costs of ACF. Under this budget, the impact of high-accuracy testing, relative to that of moderate-accuracy testing, is 1·14 (95% simulation intervals 0·75 – 1·99). Overall, therefore, results suggest that high-accuracy testing would not only be more impactful at a given level of coverage (Fig 2), it could – under certain circumstances – also be more cost-efficient.
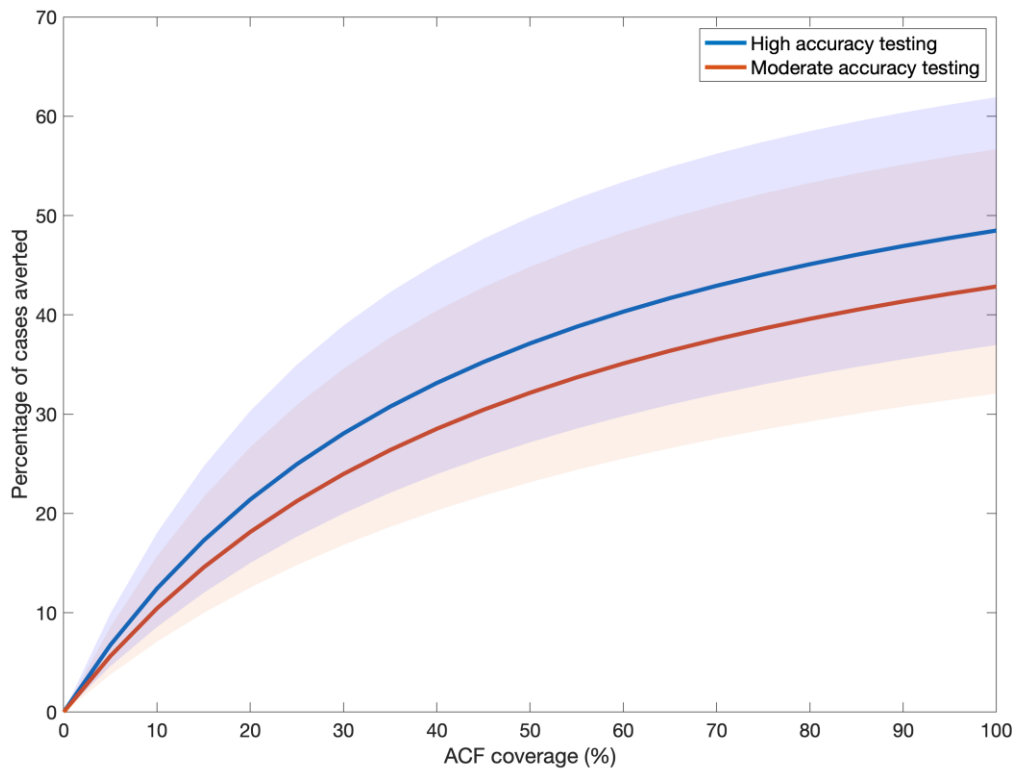
Fig 2. ACF impact as a function of coverage. Here we measure 'impact' as the percentage reduction in cumulative incidence between 2020 and 2035, and 'coverage' as the proportion of the slum population being screened per year. We assume for simplicity that a randomly selected proportion of the slum population is selected for screening each year, independent of screening in previous years. An ACF intervention with symptom screening is followed by bacteriological confirmation, using either a smear-like test (red curve) or an Xpert-like test (blue curve). The shaded areas represent the 95% uncertainty intervals. Each of the curves is generated by taking a range of annual screening from 0 (no ACF) to 1 (whole slum population screened for symptoms once a year): the upper endpoints of each curve occur at the upper limit of this range. Shaded areas represent the 95% credible intervals. Overlap between these areas does not imply a lack of significant difference between the interventions, as points in the red and blue areas are correlated. Indeed, the relative impact of the two strategies is robust to this parameter uncertainty (see main text).
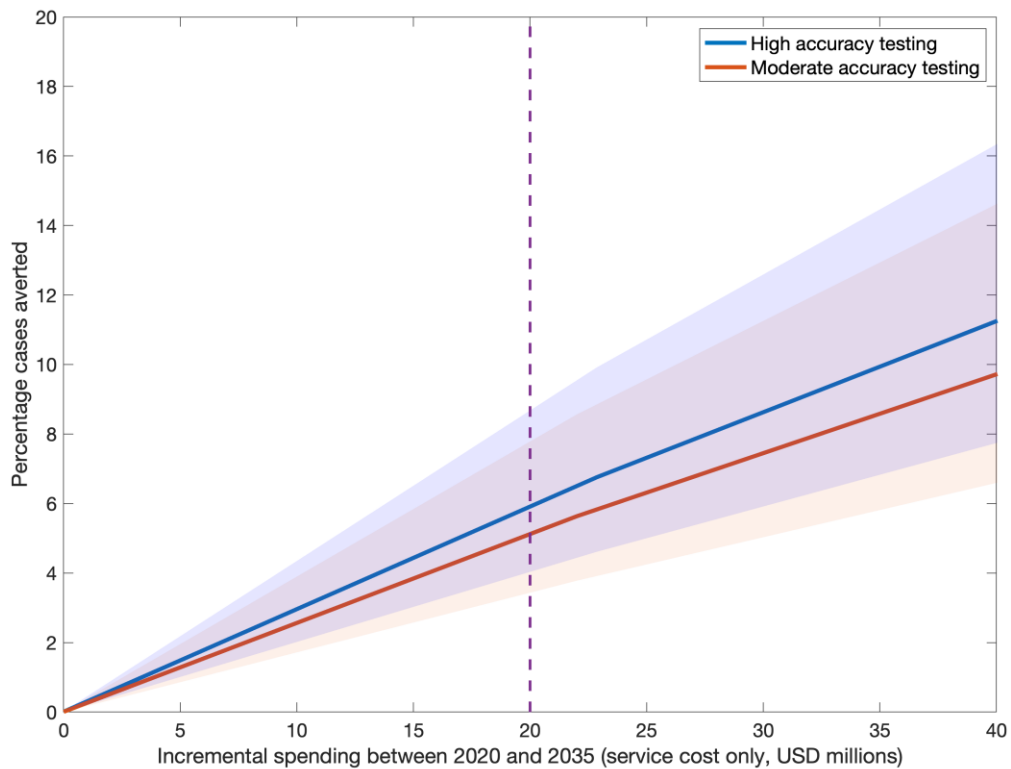
Fig 3. ACF impact as a function of incremental programmatic spending, in an assumed slum population of 2 million people. As in Fig 2, we measure 'impact' as the percent cases averted by ACF. Incremental spending is the overall service cost of diagnostics and treatment, relative to a baseline scenario of no ACF, and assuming current conditions continue indefinitely. The vertical, dashed line shows an illustrative budget of USD 20 million; in spite of using a lower-cost test, a moderate-accuracy strategy is overall less cost-efficient than a high-accuracy one. The shaded areas represent the 95% credible intervals. As in Fig 2, overlapping regions does not imply similar cost-efficiency, and indeed the cost-per-case averted for a high-accuracy strategy is robustly greater (see main text).

Fig 4 shows analysis to better resolve these circumstances. Fig 4A shows the most influential model parameters in the relative impact of a high- vs moderate-accuracy test at a budget of USD 20 million, highlighting the respective specificities of the two tests as the most influential parameters. In particular, the difference in specificity between the two tests is an important driver: Fig 4B shows the absolute difference, plotted against relative impact, highlighting that a high-accuracy test would be robustly more cost-efficient than a moderate-accuracy one, as long as it has specificity that is at least 3 percentage points greater.
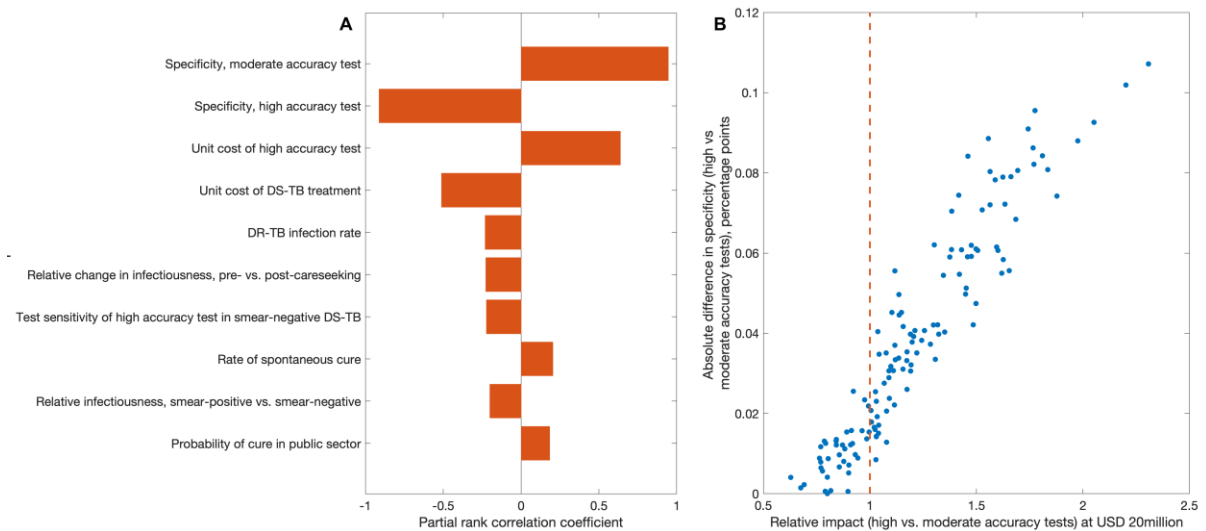
Fig 4. Sensitivity analysis to identify key model parameters in the relative impact of high- vs moderate-accuracy strategies, under a given budget of USD 20million between 2020 and 2035. Here, we denote 'relative impact' as the cases averted over this period, by a high-accuracy testing strategy, relative to a moderate-accuracy one. In Fig 3, this focal model output is estimated to be 1·14 (95% simulation intervals 0·75 – 1·99). (A) Partial rank correlation coefficients of model parameters against relative impact, showing only the 10 highest correlations, and highlighting the test specificities as being the most influential two parameters. (B) Association between relative impact and test specificity, showing that rather than individual specificities, it is their absolute difference that matters most for relative impact. All points to the right of the vertical, dashed line correspond to a high-accuracy test being more impactful than a moderate-accuracy one; these results suggest that an absolute specificity difference of at least 3 percentage points is sufficient to ensure that a high-accuracy test is more impactful than a moderate-accuracy one.

Fig 5 illustrates why specificity is a driving factor, as well as identifying additional drivers in the impact of a high-accuracy test. Taking the example of 50% coverage, the figure shows the separate components of incremental cost through time, for both diagnostic tests. Fig 5A illustrates that false-positive treatment is by far the largest cost driver of a moderate-accuracy ACF intervention, followed by the cost of second-line treatment. For a high-accuracy test (Fig 5B), major cost drivers are the cost of the test itself; the cost of treating false-positive diagnoses; and the cost of second-line treatment. Two comparisons bear mention. First, false-positive TB is strongly affected by the specificity of the confirmatory test, with a moderate-accuracy test being associated with 350k false-positive treatment initiations (95% CI 100k – 710k), compared to 180k for high accuracy testing (95% CI 30k – 560k). Second, the effects of each test on DR-TB plays an important role in cost dynamics: by identifying DR-TB cases early, high-accuracy testing tends to have a stronger impact on reducing DR-TB incidence, thus leading to cost-savings in second-line treatment costs, over 15 years.
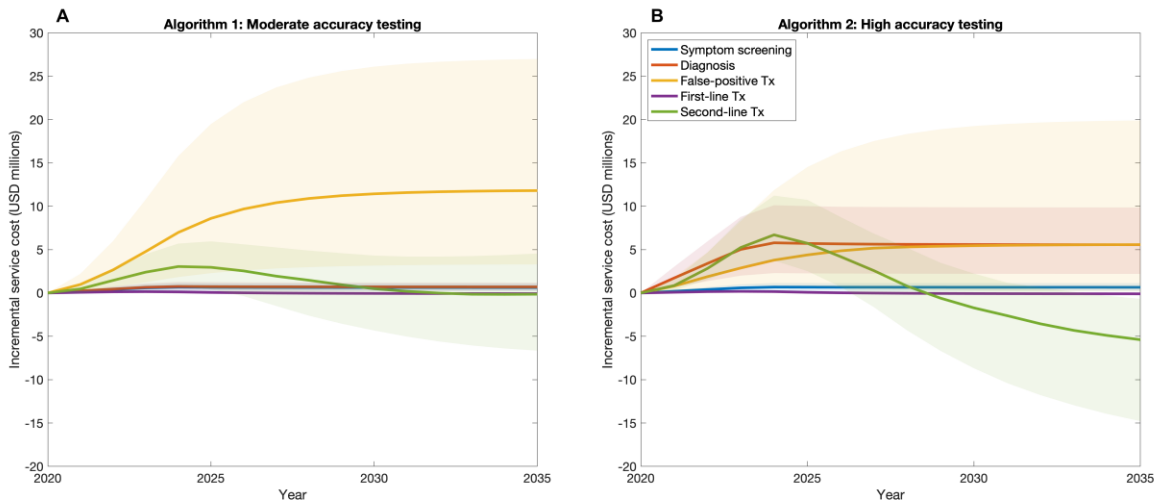
Fig 5. Breakdown of the incremental ACF service cost, shown here at 50% screening coverage for the two ACF algorithms. In the left-hand panel, the major driver of the incremental cost of moderate-accuracy testing is the treatment of false-positive TB, from the NTS population (green dashed line). Notably, the cost of treatment of false-positive individuals is nearly halved when using an Xpert-like test for diagnosis (solid orange line, right-hand panel) and alongside diagnosis (red solid line) the two components are the main cost drivers for high-accuracy testing. The shaded areas represent the 95% simulation intervals.

Both cost drivers are further explored in Fig 6. The role of false-positive TB treatment is illustrated in Fig 6A, which shows how the positive predictive value (PPV) of the whole diagnostic algorithm (including symptom screening) changes over time under both algorithms. For both scenarios, this value substantially decreases over time as a result of decreasing TB prevalence in the community but remains considerably lower for smear than for Xpert. Likewise, the role of DR-TB is further illustrated in Fig 6B, which shows the strong incidence reductions that would be brought about by a high-accuracy testing strategy, on DR-TB burden over time.

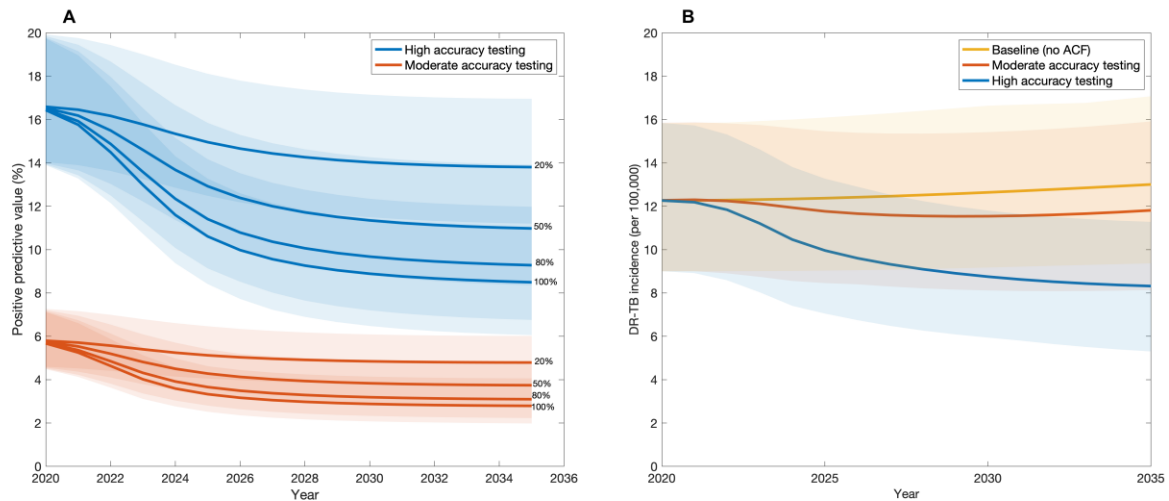**Fig 6. Additional comparisons between testing strategies** (A) Comparison of the positive predictive value (PPV) of ACF strategies. Plots show the positive predictive value (PPV) of the entire diagnostic algorithm (including symptom screening), and not just that of the confirmatory test. Percentages on the right-hand of the figure (20%, 50% etc) show ACF coverage scenarios, for the proportion of the slum population being screened per year. The shaded areas represent the 95% simulation intervals. Overall, as TB prevalence is reduced over time by ACF, the PPV also decreases. Improved diagnostic algorithms, with improved specificity, may be needed in these advanced stages. (B) Comparison of both testing strategies shown in Fig 3, by their impact on the incidence of DR-TB over time, at fixed 50% coverage. Because a high-accuracy test is able to diagnose rifampicin resistance at the point of TB diagnosis, it can contribute strongly to long-term reductions in DR-TB incidence, thus also averting future costs of second-line treatment (Fig 5B). A moderate-accuracy strategy also leads to a decline in DR-TB incidence, although to a lesser extent, as individuals with DR-TB are only switched to second-line therapy after failing first-line therapy.

The cost-efficiency of the overall ACF algorithm can be shaped as much by the choice of screening algorithm as by the choice of confirmatory test. S1 Text Fig B shows results for incidence and impact under an alternative screening algorithm, using 'prolonged cough' as an eligibility criterion for confirmatory testing, an approach having lower sensitivity and higher specificity (25% and 96% respectively (14)). At a given level of coverage, such a screening approach would reduce the overall impact of both high- and moderate-accuracy strategies, owing to its lowered sensitivity. As a result of its higher specificity, such an approach also substantially reduces the number of false-positive treatments overall, narrowing this specific advantage of a high-accuracy test. However, under a given budget of USD 20 million (as used in Fig 4), a prolonged-cough screening algorithm could allow many more people to be screened over time, potentially leading to a greater impact overall (S1 Text Table A and Fig B), than that shown in Fig 3. In turn, this enhanced impact promotes the long-term effect of the high-accuracy test in averting second-line costs. The overall effect is for the relative impact, of the two testing strategies at a budget of USD 20 million, to remain qualitatively

similar to that estimated from Fig 3 above, and indeed shifted in favour of the high-accuracy test.

Finally, we conducted sensitivity analyses. Focusing on the relative impact of the high- vs moderate-accuracy strategies shown in Fig 3, S1 Text Fig D shows how this focal model output varies under a range of scenarios. The figure illustrates that the essential qualitative results remain, under alternative scenarios for the sensitivity of smear microscopy; the burden and management of DR-TB; and the size of the NTS population.

Discussion

Active case-finding is potentially highly impactful, but also highly resource-intensive: our analysis therefore addresses the critical need to optimise its cost-effectiveness. We used mathematical modelling to examine strategies for microbiological testing in ACF for TB, aiming to identify the type of confirmatory test that would yield greatest epidemiological impact at lowest cost.

Findings

We hypothesised that a moderate-accuracy testing strategy, using a relatively cheap test that can nonetheless detect the most infectious cases, may be more cost-efficient (achieving incidence reductions at lower cost) than a high-accuracy strategy. However, our results suggest that the converse is true (Fig 3), wherever lower test cost is associated with reduced specificity. The reasons are threefold: (i) small improvements in test specificity can translate to large reductions in unnecessary (false-positive) TB treatments, that outweigh the cost of the test, (ii) a high-accuracy test that can also identify rifampicin resistance can offer long-term savings by reducing the burden of rifampicin resistant TB (and thus need for costly second-line treatment), and (iii) a high-accuracy test has greater impact than a moderate-accuracy test, as a result of its higher sensitivity (Figs 2 - 4).

We have conservatively designated the confirmatory tests as 'smear-like' and 'Xpert-like', in recognition that performance data drawn from meta-analyses of clinical trials (Table 1) do not necessarily reflect the numbers of appropriate or erroneous TB treatment that would arise in real-world ACF implementation. In light of this uncertainty, the key conclusion of our analysis is not that one test should be preferred over another, but rather that specificity in field ACF conditions – for any diagnostic test – is a critical data gap to address, for future ACF planning. In recent years the availability of molecular diagnostics has rapidly expanded for routine TB services in India (20–22); our findings support the use of similar tests, with equal or higher specificity and the ability to detect rifampicin resistance, in active case-finding.

Quantifying specificity

We note that quantifying 'true' specificity is a complex challenge, partly as the culture reference standard (against which specificity is judged) also has imperfect sensitivity, raising the question of how to interpret smear positive, culture negative results, particularly amongst those with strong clinical signs of TB. As initial steps in this direction, future ACF implementation research could aim, for example, to supplement microbiological reference standards with 'composite' reference standards, that additionally incorporate clinical diagnosis and patient assessment on follow-up, including response to anti-TB treatment. Our results

also have implications beyond the particular diagnostic tests being examined here. For example, a new generation of molecular diagnostic tests, Xpert Ultra, has higher sensitivity than Xpert, but also lower specificity (6). Its use in ACF would lead to similarly unacceptable numbers of false positive TB treatment, as those illustrated in Fig 4 (left-hand panel).

Role of screening

Our sensitivity analysis shows that the performance of the screening stage can also play an influential role, although whether this widens or narrows the gap between the two diagnostic tests (at a given budget) depends on the relative magnitudes of: (i) the reduction in false-positive TB treatments arising from a higher-specificity screening algorithm, and (ii) the long-term second-line TB treatment costs that can be averted by a high-accuracy test (S1 Text Fig C and Table A). In our current work, the overall effect is for our qualitative findings to remain unchanged. Strategies such as X-ray screening (not modelled in the current study) can show greater sensitivity and specificity than symptom screening alone (23), while allowing TB detection amongst those not reporting symptoms. Implementation of X-ray screening is more resource-intensive than symptom screening, but could be facilitated by the use of mobile radiography units (24,25), along with newly emerging technology for automated X-ray reads (26,27). While the present analysis has focused on confirmatory tests, a more systematic exploration of these and other screening strategies will be an important area for future work.

The patient perspective

Focusing on programmatic costs, our analysis does not address the important issue of patient costs associated with TB (28–30). In the context of routine TB services, the costs of care-seeking and TB treatment can have a substantial impact on productivity and household income, and is an important cause of catastrophic health expenditure (29). Previous work in India has shown that ACF can bring about substantial reductions in these patient costs (18), essentially by bringing TB services to those in need in a timely way. By neglecting patient costs, our analysis therefore does not capture the societal cost-savings that would result, from higher-sensitivity testing strategies. Our analysis also does not address the societal costs of false-positive TB diagnosis, including the potentially life-changing impact of stigma (13), and the potential side effects of TB treatment. Our analysis thus does not capture the societal cost-savings that would result, from higher-specificity ACF approaches. Overall, therefore, we expect that inclusion of societal costs would act to widen the gap between the strategies shown in Fig 3. The extension of our analysis, to incorporate these important costs to the patient, is an important area for future work.

Key considerations in intervention costs

Our study has focused on the performance of confirmatory tests in ACF but has not addressed the implementation of these tests. For example, the overall cost of an Xpert test will depend on whether Xpert units are readily accessible for use in ACF, or whether they are only available in central laboratories, requiring the additional expense of sample transport and relaying test results to the patient. Previous work has addressed these considerations in the context of routine TB services (31). Although such considerations are outside the scope of our current analysis, we note that access to Xpert facilities is likely to be more pressing in peripheral health facilities in rural India than in urban slums. India's current National Strategic Plan includes measures to improve the capacity for Xpert testing nationwide (32). Moreover, recent developments offer prospects for reduced reliance on laboratory infrastructure, for example with the development of new, more mobile molecular diagnostics such as Xpert Omni (33) and Truenat (34), as well as the deployment of Xpert MTB/Rif through mobile diagnostic vans (35). All of these developments would tend to reduce the per-test cost of high-accuracy diagnostic tools, through allowing closer proximity to the ACF intervention. For any study aiming systematically to estimate the full cost of ACF, these and other implementation factors will be important to take into account (for example, as demonstrated in refs. (17,31)). Nonetheless, our findings illustrate an important consideration in any such study: i.e. in addition to these important cost components, that the specificity of the confirmatory test, along with that of the whole ACF cascade, is likely to be a key driver of the cost/impact ratio of any ACF intervention.

Our analysis has ignored intervention costs directly associated with the roll-out of the intervention, such as human resources and costs associated with the purchase of equipment. We also take a simple approach of assuming unit costs that are unaffected by the scale of the intervention, thus ignoring the potential for economies of scale, especially at high levels of population coverage. If human resource costs are similar under the two strategies, they would have little effect on the relative costs of these strategies. Overall, however, we emphasise that our estimates should not be interpreted as estimates of the actual cost of ACF. An important area for future work would be to incorporate these important elements (17,36), for more comprehensive estimates of the full cost of ACF.

Model limitations

For simplicity, we ignored pre-treatment loss-to-follow-up. Although commonly observed in practical implementations of ACF (37), we do not expect this simplification to alter our essential findings, as long as it affects the two testing strategies roughly equally. Again, for simplicity, we assume that all false-positive TB diagnoses have the same rates of treatment completion as true positive diagnoses; if their completion rates are substantially lower, this would tend to reduce the treatment cost associated with false-positive TB diagnosis. Finally, we note that

there is considerable uncertainty about the potential transmission impact of ACF interventions, owing partly to a lack of direct evidence, particularly in South-Asian settings (4). In the present analysis, our impact projections are based on a series of assumptions, including perfect implementation of symptom screening and diagnosis; high-quality engagement with and participation by the community; effective linkage to treatment; immediate rapid bacteriological suppression upon treatment (thus interrupting transmission); and the degree to which ACF is able to identify TB cases while they still have substantial potential for passing on infection.(4) Lessons from current and future ACF initiatives will be invaluable in identifying which of these assumptions needs most attention.

Conclusion

As ACF efforts are scaled up in India and other high-burden settings, implementation planning could benefit from a population perspective of potential costs and benefits. Such a perspective, complementing other approaches such as operational research, takes into account both the epidemiological impact and unintended consequences (such as false-positive diagnosis) of large-scale deployment. Addressing important questions about the optimum implementation of ACF could open the way for considerable impact on TB burden, in India and elsewhere.

Parameter		Symbol	Value	Source / Notes
Natural History				
Infection rate, smear-positive DS-TB		β_{DS}	9·10 yr⁻¹ [7·35 – 10·70]	Fitted to epidemiological data (Table 2)
Infection rate, smear-positive DR-TB		β_{MDR}	5·19 yr⁻¹ [4·12 – 6·26]	
Relative infectiousness, smear negative vs. smear positive		ε	0·2 [0·1 – 0·3]	(9)
Rate of progression to active disease from latency		a	[0·0005 – 0·0015]	(38)
Proportion of infections being 'fast' progressors to active disease		p_{Fast}	[0·05 – 0·15]	(39)
Per-capita rate of initial care-seeking upon first developing symptoms		r_{CS}	0·73 yr⁻¹ [0·57 – 0·91]	Fitted: corresponds to a mean initial delay of over a year
Per-capita rate of repeat care-seeking		$r_{cs}^{(2)}$	12 yr⁻¹ [9 - 15]	Assumption: corresponds to a mean delay of 1 – 6 weeks
Per-capita rate of smear conversion	Symptomatic TB	m_0	0·71 yr⁻¹ [0·40 - 1·04]	Fitted to prevalence survey data (Table 2)
	Asymptomatic TB	m_1	0·63 yr⁻¹ [0·62 - 0·64]	
Per-capita rate of symptom development	Smear-positive TB	e_0	1·24 yr⁻¹ [1·02 - 1·65]	
	Smear-negative TB	e_1	2·37 yr⁻¹ [1·90 - 3·05]	
Proportion of prevalent TB cases that are smear positive		ω_+	0·6 [0·5 – 0·7]	(1)
Per-capita rate of relapse	Post treatment completion	r_1	0·032 yr⁻¹ [0·024 – 0·04]	(38)
	Post treatment default	r_2	0·14 yr⁻¹ [0·105 – 0·175]	
	Long-term (>2 years) relapse risk	r_3	0·002 yr⁻¹ [0·0011 – 0·0019]	
Per-capita rate of spontaneous recovery		γ	0·1667 yr⁻¹ [0·1250 – 0·2083]	(38) Together, yielding a 50% case fatality rate over 3 years of untreated TB
Per-capita rate of mortality, untreated TB		μ_{TB}	0·1667 yr⁻¹ [0·1250 – 0·2083]	

Proportion reduction in susceptibility to reinfection owing to previous infection		ρ	0·21 [0·15 − 0·25]	(40)
Per-capita background mortality rate		μ	0·0152 yr^{-1}	(38) Corresponding to mean life expectancy of 66 years
Per capita birth rate		b	0.0682	(41) Adjusted to yield 2.4% annual population growth from 1970
Diagnosis (routine TB services, in absence of ACF)				
Proportion seeking care from private sector		p_1	0·5 [0·4 − 0·6]	Assumption, consistent with (12)
Proportion correctly diagnosed per provider visit	Public sector	$p_0^{(Dx)}$	0·83 [0·81 − 0·85]	(42)
	Private sector	$p_1^{(Dx)}$	0·7 [0·6 − 0·8]	Assumption
Proportion of diagnoses successfully initiating treatment	First-line, public sector	$p_0^{(Tx)}$	0·88 [0·85 − 0·91]	Aggregated for first- and second-line (42)
	First-line, private sector	$p_1^{(Tx)}$	0·7 [0·6 − 0·8]	Assumption
	Second-line, public only	$p_0^{(Tx2)}$	0·88 [0·85 − 0·91]	Aggregated for first- and second-line (42)
Proportion of TB recognized as DR-TB at point of diagnosis (public only*)		p_{DST}	0.12 [0.08 − 0.20]	(22)
Treatment				
Per-capita rate of regimen completion	First-line	d_{TxFL}	2 yr^{-1}	(1,3) Corresponds to a duration of 6 months
	Second-line	d_{TxSL}	0·5 yr^{-1}	(1) Corresponds to a duration of 2 years
Proportion first-line treatment success	Public sector	c_0^1	0·85 [0·83 − 0·87]	(1,3)
	Private sector	c_1^1	0·6 [0·5 − 0·7]	Assumption
Proportion second-line treatment success (public only*)		c_2	0·46 [0·44 − 0·5]	(1,3)

Amongst DR-TB cases failing first-line treatment, proportion successfully transferred onto second-line treatment (public only*)		p_{SL}	0·88 [0·85 − 0·92]	Assumption
Rate of DR-TB acquisition amongst DS-TB cases on first-line treatment		r_{MDR}	0·01 yr^{-1}	(1,38)
Active case-finding				
High-accuracy test performance (consistent with available data for Xpert)	Sensitivity (smear-positive TB)	s_1	1	Assumption (at least as sensitive as smear)
	Sensitivity (smear-negative TB)	s_0	0·7 [0·6 − 0·8]	(43,44)
	Specificity	σ	0·99 [0·90 - 1·0]	(45) (see footnote **)
	Per-capita rate for performing diagnostic test	d_{Dx}	52 yr^{-1}	We assume 1 week for sample collection, transportation and analysis
	Proportion of TB recognized as DR-TB at point of diagnosis	p_{DSTA}	0·95 [0·90 − 0·97]	(8)
Moderate-accuracy test performance (consistent with available data for smear)	Sensitivity (smear-positive TB)	s_1	1	Simplifying model assumptions
	Sensitivity (smear-negative TB)	s_0	0	
	Specificity	σ	0·98 [0·93 − 1·0]	(45) (see footnote **)
	Per-capita rate for performing diagnostic test	d_{Dx}	52 yr^{-1}	We assume 1 week for sample collection, transportation and analysis
Symptom screening (any TB symptom)	Sensitivity	s	0·70 [0·58− 0·82]	(14)
	Specificity (***)	σ	0·61 [0·35 − 0·87]	(14)
	Per-capita rate for performing symptom screening	d_{sx}	365 yr^{-1}	Assumption, corresponds to 1 day

Table 1. List of model parameters. Footnotes: (*) We assume that all DR-TB management occurs in the public, not private, sector. (**) In the parameter sampling, we adopt only those joint parameter sets in which Xpert specificity is greater than that of smear. (***) The size of

the non-TB symptomatic (NTS) population was calculated using the specificity of the symptom screening method used (see S1 Text for full model specifications). For a strategy screening for 'any TB symptom', the size of the NTS population would therefore be 39% of the size of the population in which TB dynamics are modelled.

Data		Calibration target (95%CI)	Source/Notes
Slum prevalence (per 100,000 population) of culture-positive TB, as of 2012		432 (341 - 527)	Drawn from ref (5), using prevalence of culture-positive TB (259 per 100,000), and inferring the slum prevalence from the univariate odds ratio of culture-positive TB in slum vs non-slum settings (2.3), together with an assumed slum size of 20% of the urban population
Slum ARTI, as of 2006		2.5% (1.9 – 3.1%)	(46) and V.K. Chadha, personal communication
Proportion of TB incidence that is DR-TB as of 2018		5% (4 – 6%)	(47)
Proportion of prevalent TB having any TB symptoms		70% (58 – 82%)	By definition, same as assumed value of sensitivity of symptom screening (Table 1)
Proportion prevalent TB that is smear-positive as of 2012	In symptomatic individuals	67% (60 – 74%)	(5)
	In asymptomatic individuals	66% (56 – 77%)	(5)

Table 2. Data used to calibrate the compartmental model. ARTI denotes 'Annual Risk of TB Infection'. 'DR-TB' denotes 'drug-resistant' TB, including both rifampicin-resistant and multi-drug-resistant forms of TB. Although largely drawn from a prevalence survey in Chennai, South India (5), these data are broadly consistent with prevalence surveys in urban settings elsewhere in India (48).

Unit cost	Cost (USD)	Source
Active case-finding		
Symptom screening	2 (1.60 – 2.40)	Table S15 from (49) supplementary information – unit cost of symptom screening in South Africa.
Sputum smear-microscopy	2.26 (1.81 – 2.71)	Table 2 from (50) reports unit cost of USD 1.13 for a single AFB smear in India. With a minimum of two smears required for diagnosis, we double this cost.
GeneXpert MTB/RIF	17.53 (14.02 – 21.04)	Table S12 from (49) supplementary information – difference between unit cost of Xpert and microscopy is given to be 16.4.
Treatment (cost per patient-month)		
First-line treatment	2.42 (1.93 – 2.90)	For an average cost of USD14.5 (11.6 – 17.4). Electronic Supplementary Material, Annex 4, provider drug costs for DS-TB in India (28).
Second-line treatment	100 (80 – 120)	For an average cost of USD2,400 (1,920-2,880) for the full regimen (28,51).

Table 3. Unit (service) costs used in the analysis. For simplicity we ignore the 'new' second-line regimens, as it is unclear what proportions of patients will be eligible for the different treatment options. However, in S1 Text we provide a sensitivity analysis to the potential future uptake of these regimens. To capture uncertainty in costs, we allowed variation by +/- 20% for each of these cost components.

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S1 Text. Supporting information.

S1 CHEERS Checklist.

Table A in S1 Text. Comparison of different screening algorithms and testing strategies.

Table B in S1 Text. Proportion contribution of each cost component to the total incremental service cost.

Figure A in S1 Text. Results of the model calibration.

Figure B in S1 Text. Simulated impact and cost-effectiveness under alternative symptom screening strategies.

Figure C in S1 Text. Breakdown of the ACF incremental service cost under the prolonged cough screening strategy.

Figure D in S1 Text. Sensitivity analysis to different scenarios.