# Importance of confirmatory test characteristics in optimizing community-based screening for tuberculosis: An epidemiological modeling analysis

Short Title: Confirmatory test priorities for tuberculosis screening

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## ABSTRACT

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### Background

Current active case-finding (ACF) efforts for tuberculosis (TB) are limited by the costs, operational barriers, and sensitivity of available tools to confirm a TB diagnosis. However, it is not well understood which of these limitations has the greatest epidemiological relevance and might therefore warrant prioritization in test development.

### Methods

We developed a state-transition model of a one-time, community-based ACF intervention, with a fixed budget of one million United States dollars for screening and confirmatory testing. Assuming an adult population with four time the national prevalence of Uganda, we compared the impact of this intervention on TB diagnoses, mortality, and transmission when using a currently available confirmatory test (mirroring sputum-based Xpert Ultra) versus an improved confirmatory test. We considered the following test improvements: (1) increased sensitivity (from 69% to 80%), (2) non-sputum specimen type (increasing specimen availability from 93% to 100%), (3) immediate turn-around of test results (increasing delivery of positive results from 91% to 100%), (4) reduced costs (from $20 to $9 per confirmatory test). For those individuals not included in ACF efforts, TB outcomes under routine care were informed by recent natural history models.

### Results

In a simulated target population of 400,000 adults, 6,421 (1.6%; 95% uncertainty range [UR] 5,316-7,531) had TB disease, and 873 (612-1,182) were projected to die of TB in the absence of ACF. Assuming current tests, ACF efforts could reach 83,808 (59,388-118,601; 21% of the target population) people under the allotted budget, connecting 651 (429-983) individuals with TB to treatment and averting 76 (39-132) deaths. Of all hypothetical confirmatory test improvements modeled, higher diagnostic sensitivity most increased the number of people with TB who received treatment as a result of ACF (by 14% [4-26%]). However, considering mortality or transmission as a metric, the largest reductions resulted from tests that provided immediate turn-around of results (by 11% [5-18%]).

### Conclusion

Making confirmatory tests for community-based TB screening more accessible and rapid may lead to greater population health benefits than further increasing sensitivity.

Nonetheless, achieving large (>20%) increases in the health impact of ACF will require improvements to components of ACF other than the confirmatory diagnostic test.

## INTRODUCTION

Every year, an estimated four million people with new tuberculosis (TB) are not notified to public health authorities and many of these people are never diagnosed or treated [1]. Community-based screening or active case-finding (ACF) can potentially reduce TB mortality and transmission potential, by detecting and linking people with TB to treatment that would have otherwise been missed or only diagnosed after they have transmitted TB to others [2]. The uptake and epidemiological impact of ACF, however, is limited by deficiencies of currently available diagnostic tests [3].

Most ACF algorithms begin with a low-cost screening test or symptom survey, and thus require a second, more specific test to confirm positive screening results [4]. Currently, advanced tools for confirmatory testing include molecular sputum tests such as Xpert Ultra MTB / RIF (Cepheid, Sunnyvale, CA, United States; “Xpert Ultra”) [5-7], but even the best tools available are subject to several shortcomings. First, high testing costs [8] may limit the number of people who can be tested under a given budget. In addition, the need for a sputum specimen hampers testing reach and the long turn-around times associated with off-site and high-volume testing can inhibit people from receiving their test results [6]. Furthermore, even molecular tests designed for high sensitivity leave some individuals with low bacillary load undetected [9]. While many of the TB diagnostics development efforts that are underway could lead to tools that would overcome these shortcomings, it is not clear which test characteristics could provide the largest benefit when used for the confirmatory step in ACF algorithms – and might therefore warrant higher prioritization during test development.

To guide researchers and public health decision makers in developing valuable diagnostics for ACF, we developed a model exploring the importance of confirmatory test characteristics in the context of community-based screening for TB. We consider an illustrative community-

based ACF intervention that begins with chest x-ray screening in a high-TB-risk population in a setting similar to Uganda. We then estimate the impact of ACF on TB mortality, transmission potential and treatment initiation, when using Xpert Ultra versus various enhanced, hypothetical assays as the confirmatory test.

## METHODS

### Model design and TB disease course

We construct a model of an ACF intervention for adults, conducted on a background of routine TB care, to estimate the epidemiological impact of improving different characteristics of the confirmatory test used in ACF (Table 1). The results of ACF (detected and linked to treatment, or not) are estimated using a compartmental model (Figure 1A), which we place in a larger decision tree to project the individual-level clinical outcomes as well as the cumulative duration of TB disease under routine care and with the addition of ACF (Figure 1B). We differentiate prevalent TB by three characteristics: (i) high- or low-bacillary load (corresponding to positive or negative smear-microscopy status), (ii) presence of chronic cough ("cough positive" if a person with TB would report cough for more than two weeks, or "cough negative" otherwise), and (iii) HIV infection status ("HIV positive" or "HIV negative"). We assume that people with high bacillary loads are both more (i.e., fourfold [10]) infectious and more likely to test positive with any given confirmatory test [4, 9]. As an illustrative setting, we consider a hypothetical high-prevalence population of 400,000 adults in Uganda who are targeted for screening. They are modeled as having a TB prevalence of 1.6%, four times the national average [11], and a joint distribution of TB bacillary load, HIV status, and chronic cough reflecting nationwide patterns [11-14] (Table 2).

### Active case-finding

We model an ACF intervention consisting of community-based screening for TB, followed by confirmatory testing for those who screen positive. To reflect the current best available tools, we assume that the ACF intervention uses mobile chest X-ray to screen adults for TB, with immediate artificial intelligence-based reporting of results [4, 11, 15]. For people screening positive, we assume confirmatory testing to be immediately attempted, using sputum-based Xpert Ultra as the diagnostic test [5-7]. Individuals unable to produce sputum are excluded from confirmatory testing; sputum production is estimated based on systematic TB screening

efforts modeling people with chronic cough as more likely to produce sputum than those without chronic cough [16]. We assume that referral to treatment services is attempted for all participants with positive confirmatory test results, but that some losses are incurred in notifying participants (for confirmatory tests not completed at the point of care) and in linkage to treatment. For participants who initiate treatment as a result of ACF, outcomes following treatment are allocated such that they are not worse (i.e., increased TB mortality or longer disease duration) than under routine care (Table 2 and Appendix, Text S1) [17-21].

Costs of active case-finding and budget constraint

In order to compare various confirmatory test improvements, we consider an arbitrary limited budget of one million USD for the ACF effort, assuming that some of the target population will not be screened due to budget constraints. This budget includes screening and confirmatory testing costs, but we assume treatment costs for people diagnosed with TB to be budgeted separately; the latter assumption is modified in sensitivity analysis. For each modeled confirmatory test, we estimate the number of people who could be screened under the available screening and testing budget, based on the per-participant cost of the screening step (including staff, transport, and screening test costs), the proportion of participants who require confirmatory testing, and the per-person cost of confirmatory testing (Table 2 and Appendix, Text S2 and Table S3) [8, 22-28]. All costs are presented in 2023 USD (inflated using World Bank consumer price indices where applicable [29]) and from the healthcare system perspective.

Confirmatory test improvements

Our primary comparison is between ACF utilizing Xpert Ultra on an expectorated sputum specimen (“baseline confirmatory testing”) [4, 9] and a series of ACF interventions with hypothetical improved confirmatory tests, each of which improves on the background of Xpert Ultra in one aspect (further details in Figure 1 and Table 1): (A) reduced test cost, (B) non-sputum specimen, (C) immediate turnaround, and (D) increased test sensitivity.

Oral-swab based testing

One diagnostic testing strategy currently in development is oral-swab based testing. Oral swabs might be a more readily available specimen but result in reduced sensitivity (existing prototypes been have estimated to have sensitivities between 52% and 97% relative to sputum molecular testing [30, 31]). To reflect the potential impact of this testing method, we also project the minimal sensitivity required for oral-swab-based confirmatory testing to achieve at least the same epidemiological impact as the baseline confirmatory test. We assume that incremental false negatives occur in individuals with low bacillary load first [31] and that oral-swab sensitivity is independent of ability to expectorate except as mediated by the presence of chronic cough. To account for uncertainty in the proportion of people able to expectorate sputum for confirmatory testing, we perform these analyses at values of 93% (as in the primary analysis), 83%, and 73% for the proportion of people able to submit sputum (Appendix, Text S5).

TB diagnosis and treatment under background routine care

For people with TB not included in ACF efforts – due to either budget constraints or losses along the ACF care cascade – outcomes of routine care are determined by our model. Under routine care, an episode of TB can end before any treatment, either through death or through spontaneous resolution, or treatment can be initiated – in which case the disease course can end in either eventual cure or (for some whose treatment is unsuccessful) TB death after treatment (Figure 1).

For HIV-negative people, we estimate the competing probabilities of receiving treatment under routine care, or of dying or experiencing spontaneous TB resolution before any treatment, based on results from a published smear- and symptom-stratified model of TB natural history [32]. We use the same model's estimates of disease duration to estimate the time that each person spends with untreated TB, separately estimating the cumulative

191 amounts of time with high and with low bacillary loads (Appendix, Text S3 and Table S5).
192 For HIV-positive individuals, we adjust these estimates using results from another model of
193 TB disease courses that incorporated HIV-stratified estimates of TB notification and
194 mortality; in the absence of data for Uganda, we apply estimates for Kenya [33-35]
195 (Appendix, Text S3 and Table S5). Of note, the models underlying our work estimate a high
196 proportion of smear-negative TB to spontaneously resolve prior to receiving treatment. Given
197 that approximately 60% of people with prevalent TB in our modeled setting have a low
198 bacillary load, our model also projects 48% (95% uncertainty range [UR]: 40-55%) of
199 individuals with prevalent TB to spontaneously resolve prior to receiving treatment.
200
201 For people with TB who start treatment through routine care, the probability of an eventual
202 outcome of cure versus TB death is projected based on a combination of treatment
203 outcomes as reported to the World Health Organization plus clinical trial results to estimate
204 relapse risk (Appendix, Text S3, Table S4, and Table S6). Estimates are of the eventual
205 outcome of a TB episode, after any retreatments that may be required due to failure or
206 relapse [18-21, 36, 37]. In estimating how relapse and failure contribute to the cumulative
207 duration of TB, we assume that the average time spent with TB after an initial recurrence is
208 equal to the average duration of TB prior to any treatment, after stratification by HIV status.
209
210 Outcome measures and reporting
211 Our primary comparisons are of the health benefit of ACF, comparing ACF with the baseline
212 confirmatory test to ACF that uses the improved confirmatory tests described above, when
213 both are evaluated under the same constrained budget (Figure 1). We estimate the health
214 benefit of ACF using the following measures:
215
216 1. the total number of people linked to treatment through ACF,
217 2. the number of TB-related deaths averted through ACF, and

3. the TB transmission potential averted through ACF (estimated as a difference in total high bacillary-load-equivalent person-months, adjusting for an estimated fourfold lower infectivity during time spent with low bacillary load [10]).

We then estimate the incremental change in each of these measures when the confirmatory test is improved, on absolute scales and relative to the impact achieved with the baseline test.

Analysis and reporting

To capture uncertainty, we first simulate 10,000 iterations of the targeted community-based cohort of 400,000 adults and their disease courses under routine care; within each cohort, we then simulate all modeled diagnostic tests and perform pairwise comparisons. All parameters are independently sampled from beta (if bounded above by one) or gamma (if no upper bound) distributions reflecting the uncertainty in available primary data or published estimates (Table 2 and Appendix, Tables S1-6, with further details in Text S4). For each outcome, we report the median value across these simulated cohorts as the point estimate, with a 95% uncertainty range (UR) based on the $2.5^{th}$ and $97.5^{th}$ percentiles across all simulations. All analyses use R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). Ethical approval was not sought for this study as there was no human subject participation.

Sensitivity and scenario analyses

We analyze one-way sensitivity of model results to setting-dependent variation in TB and HIV prevalence and diagnostic testing costs [15, 38-45] (Appendix Text S5 and Table S7). We also evaluate how results change in scenario analyses that (1) include treatment costs as part of the ACF budget (to assess the potential impact of improved confirmatory test specificity) [46], (2) assume that prevalent TB does not spontaneously resolve (while assuming that treatment initiations and deaths prior to treatment occur in the same ratio as

246 in the base model), or (3) model costs [47] and accuracy of screening by chronic cough

247 rather than by chest X-ray (Appendix Text S5 and Table S8).

## RESULTS

### Population estimates

Our model projected 6,421 (95% uncertainty range: 5,316-7,531) people with TB in the target population of 400,000 adults, reflecting the assumed 1.6% (1.3-1.9%) prevalence of TB. Of the people with TB in the target population, 2,716 (2,089-3,420; 42% [35-50%]) people were projected to receive treatment through routine care in absence of any ACF, and 2,466 (1,897-3,105; 91% [90-92%]) of those were projected to be cured. An estimated 873 (612-1,182; 14% [10-17%]) individuals were projected to die from TB in absence of ACF: 625 (377-915) before receiving treatment and 249 (183-328) afterwards. The cumulative duration of culture-positive and potentially infectious TB among this population in absence of ACF was 42,604 (31,409-56,519) infectivity adjusted person-months (Figure 2).

### Community-based screening using Xpert Ultra

Accounting for a constrained budget of $1 million, and estimating costs of $10 ($7-14) per person for chest X-ray screening and $20 ($16-25) for confirmatory testing (Table 2 and Appendix Text S2), we estimated that the ACF budget would allow 83,808 (59,388-118,601; 21% [15-30%] of the target population) to undergo one-time TB screening. During this ACF intervention, TB would be detected in 718 (474-1,085) people, with 651 (429-983) of those started on treatment and 611 (403-924) eventually cured.

Of the people treated and cured as a result of ACF efforts with the baseline confirmatory test, 76 (39-132) were individuals who would have died had they not been detected through ACF. Thus, ACF reduced projected TB deaths in the target population to 796 (565-1,069), an 9% (6-13%) reduction compared to no ACF intervention. Furthermore, community-based ACF was projected to prevent 13% (9-18%) of future TB transmission potential from the people with prevalent TB in the target population: a reduction of 5,512 (3,402-8,818) infectivity-adjusted person-months (Figure 2).

Impact of confirmatory test improvements

Of the test improvements modeled, increased sensitivity led to the largest incremental increase in TB treatment initiations (14% [4-26%] more people than through ACF with baseline confirmatory testing, 93 (29-180) additional people among the 83,808 individuals screened]). Other confirmatory test improvements increased the number of people linked to treatment through ACF by 11% (5-18%; immediate turn-around), 8% (5-12%; non-sputum specimen), and 6% (2-22%; reduced test costs).

By contrast, when considering mortality outcomes, the largest impact was found with immediate turn-around (11% [5-18%] more deaths averted than through ACF with baseline confirmatory testing; 8 [3-17] incremental deaths averted), followed by using a non-sputum specimen (8% [4-12%] increase), reduced test costs (6% [2-22%] increase), and increased test sensitivity (5% [2-11%] increase). Relative results for averted transmission potential were similar to those for deaths averted (Figure 3 and Table 3).

Oral-swab based testing

For an oral-swab based test with reduced sensitivity to match the mortality impact of baseline sputum confirmatory testing (assuming 93% of the study population to be able to produce sputum), we estimated that oral-swab based testing would need to be at least 78% [77-82%] as sensitive as the sputum-based confirmatory test. This sensitivity requirement fell to 63% [62-67%] and 52% [51-56%] when assuming lower (83% and 73%, respectively) sputum production. Results were similar when considering transmission potential averted as a metric (Figure S1).

Sensitivity and scenario analysis

Neither variation of TB or HIV burden or tests costs in one-way sensitivity analyses (Text S6 and Figure S2) nor consideration of treatment costs as part of the ACF budget (Text S6 and

Figure S4) materially affected the relative importance of different confirmatory test improvements. When including treatment costs, specificity also remained less influential than other confirmatory test characteristics (Figure S4). However, when spontaneous TB resolution was eliminated from the model, increased sensitivity became the confirmatory test characteristic leading to the greatest reductions in TB mortality and transmission potential (Text S6 and Figure S3). Assuming chronic-cough-based rather than radiographic screening (i.e., screening at lower cost, sensitivity and specificity), the reach of screening increased to 279,271 individuals (129,894-414,818; baseline scenario: 83,808 [59,388-118,601]), thereby tripling the number of deaths averted to 238 (95-468; baseline scenario: 76 [39-132]) and infectivity-adjusted person-months averted to 17,871 (7,949-31,033; baseline scenario: 5,512 [3,402-8,818]). When screening by chronic cough, test costs became the most relevant confirmatory test improvement, with reduced confirmatory test costs leading to a 23% (9-56%) increase in incremental TB deaths and incremental TB transmission potential averted (Figure S5).

## DISCUSSION

This modeling analysis evaluates the potential epidemiological impact of improvements to current tools for confirmatory testing in community-based screening (i.e., ACF) for TB. Although accuracy is often prioritized in development of TB diagnostic tests, we predict the use of a highly-available specimen type and immediacy of turn-around to have greater impact on mortality and transmission potential, when considering a confirmatory testing use case during TB screening of high-TB-prevalence community. However, none of these improvements in isolation increased the mortality or transmission impact of ACF by more than 11%; thus, a greater variety of enhancements to feasibility and effectiveness are needed if ACF is to play a major role in meeting WHO End TB targets [48].

Our results indicate that an increase in confirmatory test sensitivity (from 69% to 80%) would result in the largest increase in the number of people diagnosed and treated through ACF, but would yield only small benefit in terms of reducing TB mortality and transmission. This discrepancy occurs because the people incrementally diagnosed by a more sensitive test would have lower bacillary loads; besides having lower current infectivity [10, 49], survival data from the pre-antibiotic data suggest such individuals have lower TB mortality risk [50], and models also translate this into less cumulative future transmission [32]. By contrast, reducing operational barriers to confirmatory testing, e.g., with a point-of-care test or a non-sputum sample type, would enable detection of additional people with high bacillary load (i.e., more fatal and more transmissible) TB. Hence, focusing efforts on reducing operational barriers in confirmatory testing might achieve greater population health benefits than further increasing test sensitivity. This is consistent with recent modeling showing that greater accessibility may be more impactful than high sensitivity in clinical diagnostic settings [51] – strengthening the case for focusing diagnostics development efforts on improving cost and ease of use.

The relative importance of sensitivity or cost characteristics could change under certain circumstances. Our primary analyses assume that community-based active case-finding would use some of the most accurate screening tools currently available, i.e., chest X-ray. However, if a less specific screening tool, such as symptom screening [11], is used, more people will require confirmatory testing, and confirmatory testing will comprise a greater proportion of the overall ACF budget. As seen in our scenario analysis, this increases the importance of confirmatory test costs relative to operational improvements in determining intervention reach and impact. In addition, certain test improvements, such as non-sputum-based testing, might require counterbalancing reductions in sensitivity. For example, we estimate that oral-swab-based testing – the currently most promising technique for complementing sputum testing – would require at least 63-78% the sensitivity of sputum-based testing to achieve a similar population health benefit in a setting where 83-93% of individuals are able to produce sputum. Most recent studies of tongue swab testing among symptomatic individuals presenting for care suggest sensitivities at least this high [31, 52]. If sensitivity at this level can be achieved in the context of community-based screening, oral-swab samples might provide a valuable addition to sputum-based testing for confirmatory testing in ACF interventions.

We estimated that isolated improvements to confirmatory tests were likely to increase the overall mortality and transmission impact of ACF by no more than 11%. In the context of population-wide systematic screening, this incremental benefit could be comparable to, for example, the estimated benefit of hypothetically improved TB treatment regimens (assuming 99% efficacy and 2 months treatment duration) [19]. Given expected synergies between different test improvements (e.g., if a non-sputum specimen were available, more individuals could complete confirmatory testing, further increasing the benefit of immediate results turn-around), the combined effect of improving multiple test characteristics could exceed the sum of their individual effects. Nonetheless, to optimally enhance the impact and cost-effectiveness of community-based active case-finding, other improvements than

confirmatory testing should be pursued as well; possibilities include better tools for identifying high-risk populations, simpler and more affordable screening tests, or efforts to combine ACF for TB with other health screening activities [53]. Thus, while changes through improved confirmatory testing would not be transformative, they could meaningfully increase the effectiveness and cost-effectiveness of ACF, especially if multiple improvements could be combined.

Our results are limited by simplifying assumptions in our model's representation of TB disease states, case-finding interventions, and treatment outcomes. Because it is not ethical to perform observational studies of the untreated TB disease course, disease durations and outcomes must be inferred from cross-sectional and historical data. Thus, our estimates of the outcomes of prevalent TB under routine care, which we based on prior modeling analyses, are subject to those models' uncertainties, including data limitations (e.g., on HIV-associated TB), reliance on historical microbiological classifications, and uncertain accuracy of country-level TB notification and mortality tabulations [32, 33]. Moreover, we have focused on how improvements to diagnostic tests would affect the outcomes of community-wide screening, but it is likely that those improvements would also enhance other TB interventions (e.g., contact screening and prevention) in ways we have not modelled. Furthermore, we dichotomize more nuanced population characteristics such as HIV severity, presence of chronic cough, and bacillary load. Lastly, our modeling of treatment outcomes is simplified by not explicitly modeling re-treatments, drug resistance, or relationships between the timing of diagnosis and treatment outcomes.

In conclusion, we found that reducing operational barriers for confirmatory TB testing – such as changing to a non-sputum specimen or facilitating immediate turn-around of test results – is likely to lead to greater impact on TB transmission and mortality in the context of community-based ACF than increasing sensitivity. Since improvements in confirmatory tests

400 are likely to have modest epidemiological impact in isolation, other measures to improve

401 ACF should be explored as well.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

## COMPETING INTERESTS

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## AUTHORS' CONTRIBUTIONS

S. S., F. M. M., C. M. D., D. W. D., and E. A. K. conceived the study. L. E. B. and E.A.K. performed the analysis, wrote a first draft of the manuscript, and finalized the manuscript based on co-authors comments. T.S.R. provided simulation-model results as inputs to the TB outcomes decision-tree model, and advised on the modeling approach. W.W., D.J.C., G.T., and A.C. provided substantial comments to a first draft of the analyses. All authors reviewed the manuscript and analyses and approved the final version for submission.

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| Confirmatory test characteristic | Mechanism of benefit | Model parameter affected | Baseline value (95% uncertainty range) | Improved value (95% uncertainty range) |
|---|---|---|---|---|
| A) Reduced test costs | Reduced test costs (including cartridge-costs, labor, equipment, consumables) allow more people to be screened under the same budget. | Test costs | 20 (16 to 25) USD, 2023 [8] | 50% of the baseline value [54][a] |
| B) Non-sputum specimen | Using a universally available non-sputum specimen increases completion of testing by including those who cannot produce sputum. | Proportion of prevalent TB with abnormal CXR completing confirmatory testing | 93% (89 to 96%)[b] | 100% (100 to 100%) |
| C) Immediate turn-around of test results | Reducing the time to result, as with a point-of-care test completed in 15 minutes or less, reduces loss to follow up among people not receiving their test result. | Proportion of prevalent TB that has completed confirmatory testing receiving the confirmatory test result | 91% (81 to 97%) [6] | 100% (100 to 100%) |
| D) Increased sensitivity | Fewer false-negative test results means that more people with TB receive a positive confirmatory test result. | Sensitivity for prevalent culture-positive TB among people with abnormal CXR | 69%[c] (48 to 86%) [4] | 80%[d] (80 to 80%) [54] |
| | | Sensitivity for prevalent culture-positive TB among people with abnormal CXR and a high bacillary load | 99% (98 to 100%) [9] | 100% (100 to 100%) |

ACF, active case-finding; CXR, chest X-ray; TB, tuberculosis; USD, United States dollar.

**Table 1. Hypothetical improvements of a test to confirm TB during active case-finding efforts.**

[a] Assumes consumables costs to be reduced from $8 to $4 (similar to the optimal target for a rapid, sputum-based test in the 2014 World Health Organization Target Product Profile [54]), with proportional reduction in labor / equipment costs.

[b] These proportions are based on data from Klinkenberg et al. [16] and an ongoing clinical trial (Clinic-based Versus Hotspot-focused Active TB Case Finding [CHASE-TB], ClinicalTrail.gov ID: NCT05285202; personal communication Emily A. Kendall). Results from both studies were pooled using the *metaprop* function (package "meta") in R version 4.0.2.

[c] Corresponds to sensitivity estimates for molecular diagnostic tests in a screening context [4].

[d] Corresponds to the minimal sensitivity requirement for a rapid, non-sputum-based test to diagnose TB at the microscopy center level as per the 2014 World Health Organization Target Product Profile [54].

| Parameter | Estimate (95% uncertainty range) | Distribution | Source |
|---|---|---|---|
| **Baseline population estimates, assuming a population of 400,000 individuals** [a] | | | |
| Number of individuals with bacillary load (↑) TB, HIV (+), chronic cough (+) | 323 (168 to 554) | See Appendix, Table S1, for underlying assumptions | |
| Number of individuals with bacillary load (↑) TB, HIV (+), chronic cough (-) | 199 (62 to 404) | | |
| Number of individuals with bacillary load (↑) TB, HIV (-), chronic cough (+) | 1,105 (766 to 1,510) | | |
| Number of individuals with bacillary load (↑) TB, HIV (-), chronic cough (-) | 987 (535 to 1,489) | | |
| Number of individuals with bacillary load (↓) TB, HIV (+), chronic cough (+) | 719 (468 to 1,057) | | |
| Number of individuals with bacillary load (↓) TB, HIV (+), chronic cough (-) | 450 (157 to 810) | | |
| Number of individuals with bacillary load (↓) TB, HIV (-), chronic cough (+) | 985 (620 to 1,409) | | |
| Number of individuals with bacillary load (↓) TB, HIV (-), chronic cough (-) | 1,575 (1,038 to 2,193) | | |
| Number of individuals without TB, HIV (+), chronic cough (+) | 6,773 (2,536 to 12,203) | | |
| Number of individuals without TB, HIV (+), chronic cough (-) | 14,687 (9,149 to 19,189) | | |
| Number of individuals without TB, HIV (-), chronic cough (+) | 17,390 (6,894 to 30,243) | | |
| Number of individuals without TB, HIV (-), chronic cough (-) | 354,676 (341,839 to 365,256) | | |
| | | | |
| **TB disease outcomes under routine care (average across all prevalent TB)** [b] | | | |
| Proportion of prevalent TB ending in death | 14% (10 to 17%) | See Appendix, Table S10, for further details, including differences in outcomes by individual characteristics, and Appendix, Text S3 for underlying assumptions | |
| Proportion of prevalent TB ending in cure following treatment | 39% (32 to 45%) | | |
| Proportion of prevalent TB resolving spontaneously | 48% (41 to 55%) | | |
| | | | |
| **Accuracy of chest X-ray and sputum-based Xpert Ultra (average across all prevalent TB)** [c] | | | |
| Chest X-ray – sensitivity | 90.0% (84.9%* to 94.1%*) | Beta | [11] |
| Chest X-ray – specificity | 96.0% (93.0% to 97.0%) | Beta | [4] |
| Sputum-based Xpert Ultra – sensitivity | 69.0% (48.0% to 86.0%) | Beta | [4] |
| Sputum-based Xpert Ultra – specificity | 98.8% (97.2% to 99.5%) | Beta | [4] |
| | | | |
| **Gaps in the TB care-cascade** | | | |

| | | | |
|---|---|---|---|
| Proportion of individuals with chronic cough unable to produce sputum | 8.0%[d] (3.7%[d] to 16.6%[d]) | Beta | [16, 55][d] |
| Proportion of individuals without chronic cough unable to produce sputum | 4.8%[d] (1.5%[d] to 14.2%[d]) | Beta | [16, 55][d] |
| Proportion of ACF target population not receiving confirmatory test result | 9.4% (4.2% to 15.8%) | Beta | [6] |
| Proportion not offered treatment despite having received a positive confirmatory test result | 9.3% (9.2% to 9.4%) | Beta | [17] |
| | | | |
| **Costs estimates (2023 USD)** | | | |
| Total costs to screen one person (using chest X-ray) | 10 (7 to 14) | See Appendix, Text S2 and Table S3 for underlying assumptions | |
| Total costs to perform confirmatory testing on one person (using sputum-based Xpert Ultra) | 20 (16 to 25) | | |
| Total costs to treat one person for TB [e] | 159 (76 to 243) | Gamma | [46] |

**Table 2. Key model parameters.**

* Lower and upper bounds were estimated from the published point estimate and sample size, using the qbeta function from the R base packages

[a] The sum of all people with smear positive TB, all people with smear negative TB, and all people without TB does not equal the size of the total population, due to uncertainties in values introduced through the Monte Carlo simulation.

[b] Values stratified by individual characteristics are provided in appendix, Table S10

[c] Values stratified by individual characteristics are provided in appendix, Table S2

[d] These proportions are based on data from Klinkenberg et al. [16] and an ongoing clinical trial (Clinic-based Versus Hotspot-focused Active TB Case Finding [CHASE-TB], ClinicalTrail.gov ID: NCT05285202; personal communication Emily A. Kendall). Results from both studies were pooled using the *metaprop* function (package "meta") in R version 4.0.2.

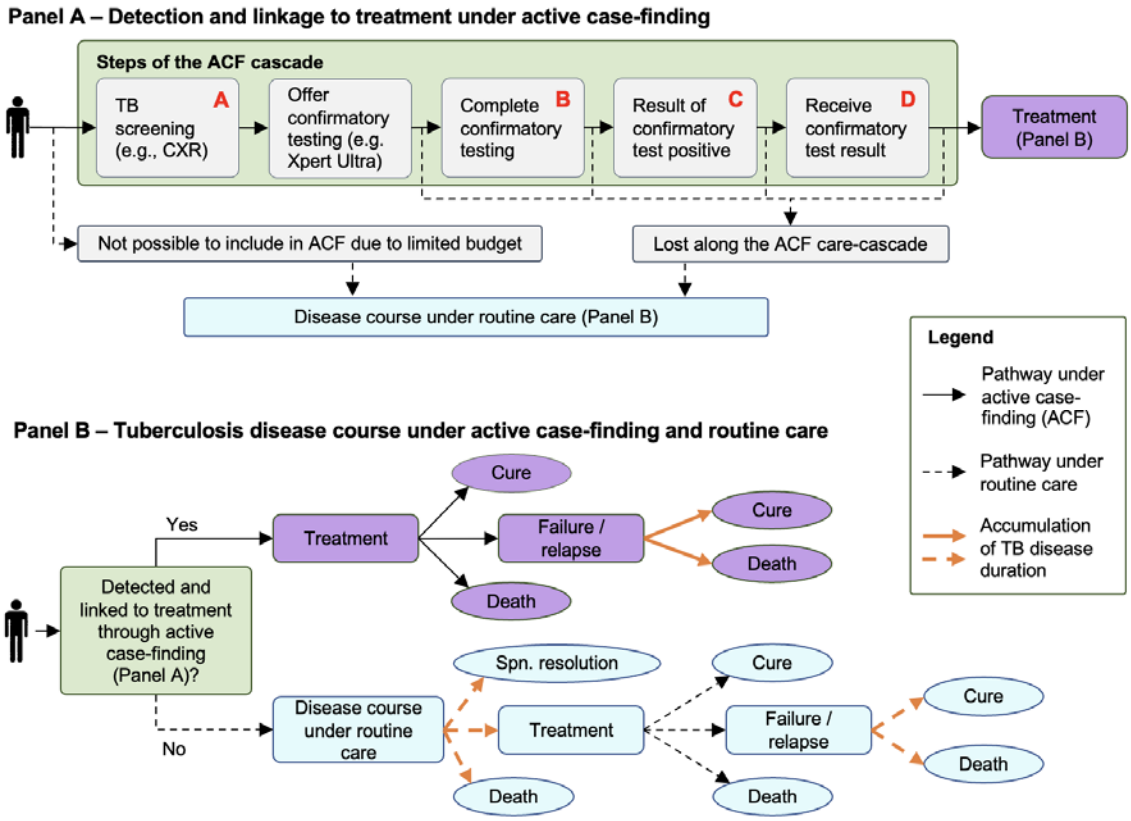
[e] Only relevant in the scenario analysis including TB treatment costs as part of the active case-finding budget

| Strategy | Routine care alone | Baseline active case-finding efforts | Active case-finding using an improved confirmatory test | | | |
|---|---|---|---|---|---|---|
| | | | Increased test sensitivity[a] | Non-sputum specimen[a] | Immediate turn-around of results[a] | Reduced test costs[a] |
| **Total population** | | | | | | |
| Total number of people modeled | 400,000 | 400,000 | 400,000 | 400,000 | 400,000 | 400,000 |
| People with TB | 6,421 (5,316; 7,531) | 6,421 (5,316; 7,531) | 6,421 (5,316; 7,531) | 6,421 (5,316; 7,531) | 6,421 (5,316; 7,531) | 6,421 (5,316; 7,531) |
| People with TB receiving treatment | 2,716 (2,089; 3,420) | 3,025 (2,372; 3,749) | 3,097 (2,441; 3,833) | 3,050 (2,395; 3,778) | 3,060 (2,399; 3,789) | 3,048 (2,393; 3,772) |
| People with TB cured following treatment | 2,466 (1,897; 3,105) | 2,766 (2,175; 3,424) | 2,838 (2,241; 3,510) | 2,790 (2,195; 3,452) | 2,799 (2,202; 3,465) | 2,790 (2,196; 3,449) |
| People who die due to TB | 873 (612; 1,182) | 796 (565; 1,069) | 792 (563; 1,064) | 790 (562; 1,061) | 788 (560; 1,058) | 790 (562; 1,060) |
| People who die due to TB without receiving treatment | 625 (377; 915) | 539 (326; 791) | 534 (323; 785) | 532 (322; 782) | 530 (322; 778) | 533 (322; 781) |
| People in whom TB spontaneously resolves | 3,047 (2,384; 3,790) | 2,829 (2,206; 3,521) | 2,764 (2,151; 3,445) | 2,811 (2,193; 3,501) | 2,805 (2,190; 3,496) | 2,812 (2,196; 3,502) |
| | | | | | | |
| **People included in active-case finding (ACF) efforts** | | | | | | |
| People screened as part of ACF | n/a | 83,808 (59,388; 118,601) | 83,808 (59,388; 118,601) | 83,808 (59,388; 118,601) | 83,808 (59,388; 118,601) | 90,262 (66,657; 124,404) |
| People with TB screened as part of ACF | n/a | 1,341 (909; 1,979) | 1,341 (909; 1,979) | 1,341 (909; 1,979) | 1,341 (909; 1,979) | 1,444 (1,015; 2,079) |
| People with TB receiving treatment following ACF | n/a | 651 (429; 983) | 743 (495; 1,119) | 701 (462; 1,061) | 721 (479; 1,083) | 700 (477; 1,038) |
| People with TB cured following treatment under ACF | n/a | 611 (403; 924) | 701 (466; 1,057) | 658 (434; 998) | 677 (449; 1,019) | 658 (447; 976) |
| People cured under ACF who would have died under routine care | n/a | 76 (39; 132) | 80 (42; 137) | 81 (42; 141) | 84 (44; 145) | 82 (43; 140) |
| | | | | | | |
| **Total transmission potential** | | | | | | |
| Cumulative infectivity-weighted person-months | 42,604 (31,409; 56519) | 36,968 (27,227; 49,211) | 36,704 (27,007; 48,887) | 36,540 (26,916; 48,672) | 36,361 (26,738; 48,421) | 36,556 (26,869; 48,699) |

**Table 3. Epidemiological outcomes under active case finding for tuberculosis, using alternative tests to confirm positive screening results.**

[a] See Table 1 for details on each confirmatory test improvement's mechanism of benefit.

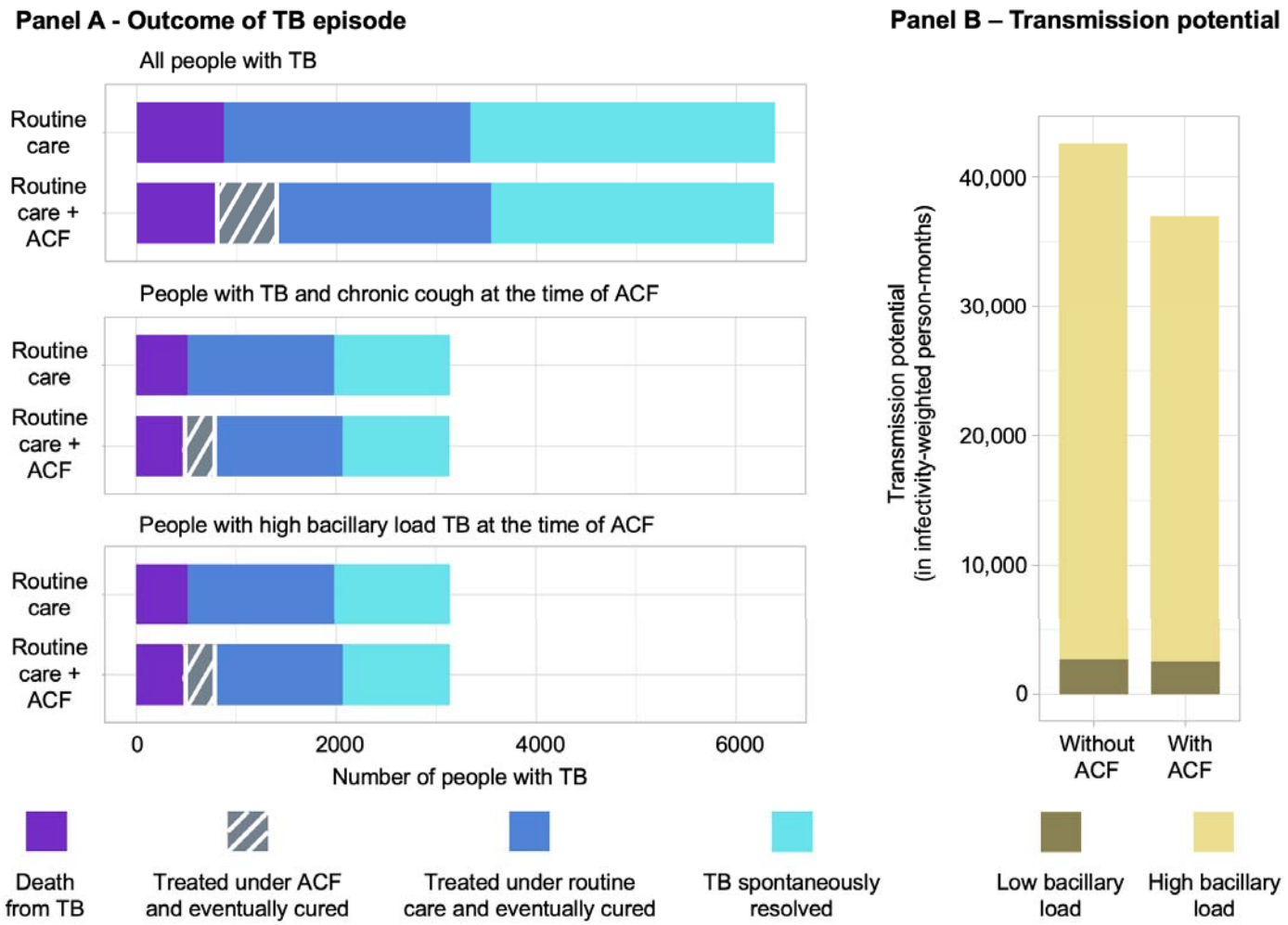
**Figure 1. Model structure.**




*Caption:* We model a one-time active case finding (ACF) intervention, consisting of one-time screening (modeled as chest X-ray) plus confirmatory testing for those who screen positive (Panel A). We consider four different improvements to the confirmatory test that could increase the number of people successfully diagnosed and treated under ACF efforts: (A) reduced testing costs from $20 to $10 per test; (B) a non-sputum specimen type, increasing confirmatory specimen availability from 93% to 100%; (C) a point-of-care format, increasing receipt of confirmatory test results from 91% to 100%; (D) increased test sensitivity from 69% to 80%. Improvement A increases the number of people that can be included in the ACF efforts under a budget constraint, while improvements B, C, and D directly enhance the confirmatory testing process (Table 1). We estimate TB disease outcomes under

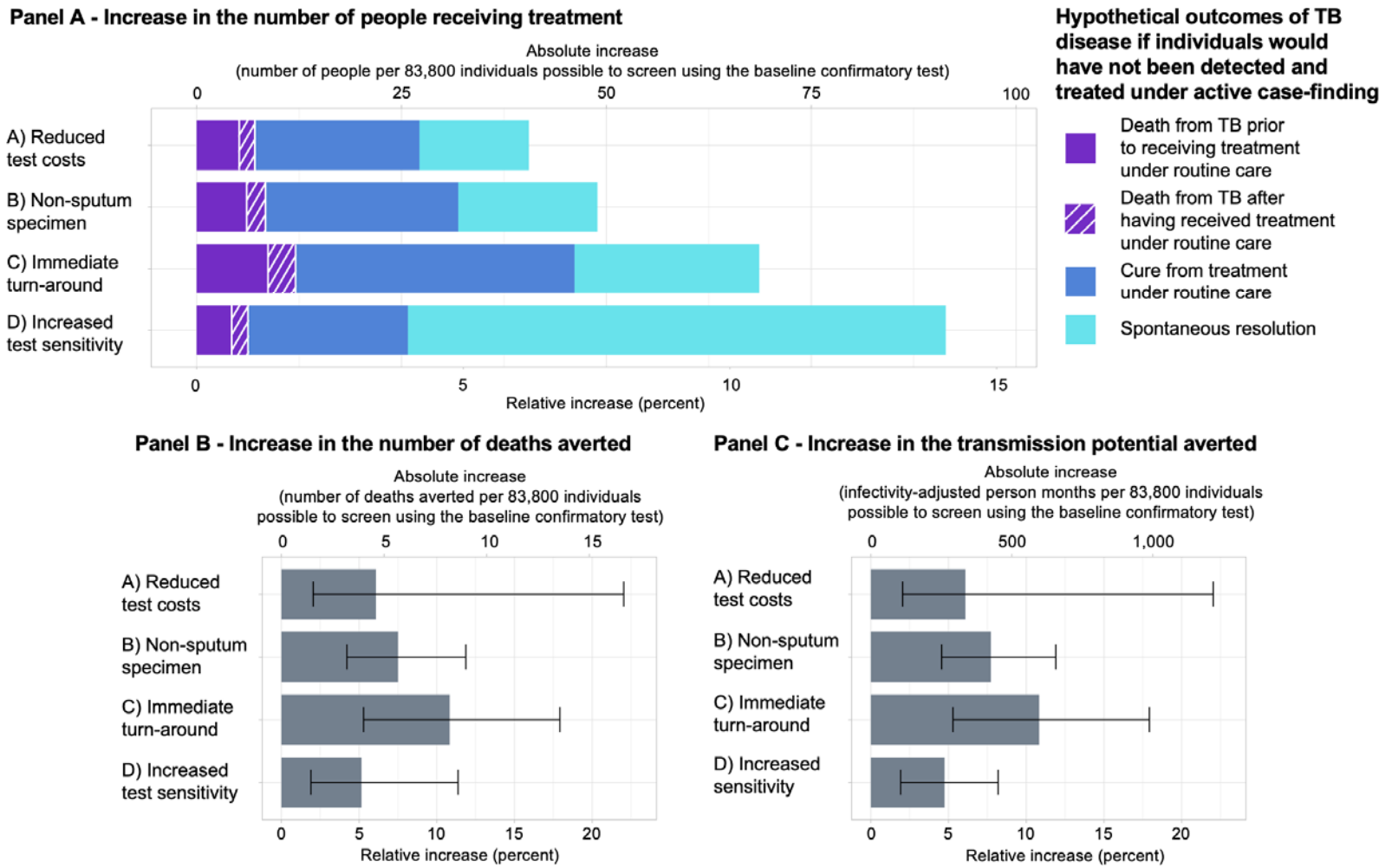
ACF or – for people with TB who are not screened or not detected through ACF – under routine care using a decision-tree model, projecting TB to eventually end in cure, spontaneous resolution, or death (Panel B). In addition, we project smear-negative and smear-positive disease duration until any of these endpoints are reached (depicted through the bold, orange arrows in Panel B).

**Figure 2. Projected epidemiological impact of a one-time active case-finding effort for tuberculosis in a high-burden population of 400,000 adults**



*Caption:* Bars depict the estimated epidemiological impact of active case-finding (ACF) for tuberculosis (TB) among adults using Xpert Ultra as confirmatory test, compared to a situation where no community-based screening is in place (assuming a setting similar to Uganda). Panel A shows the number of adults with TB (top), with TB and chronic cough (middle), and with high TB bacillary load (bottom) that are projected to die from TB (purple), be treated and cured from TB (grey or dark blue) and in whom TB might spontaneously resolve or be cured in subsequent treatment attempts (light blue). The dark blue refers to the number of people that are linked to treatment through routine care efforts, i.e., symptom-based passive case-finding, and grey to those receiving treatment under ACF efforts. Panel B shows the future transmission potential (in infectivity-weighted person months) resulting from people with prevalent TB with high bacillary load (i.e., where smear microscopy would be positive; light yellow) and low bacillary load (i.e., where smear microscopy would be negative; dark yellow) TB, when ACF is not in place (left) versus when community-based ACF is conducted (right).

**Figure 3. Epidemiological effect of an improved test to confirm tuberculosis, when used in an active case-finding campaign with a budget of 1 million US dollars**



*Caption:* Bars show the potential epidemiological benefit of ACF using hypothetical improved confirmatory tests when screening a target population of 400,000 people for tuberculosis (TB) compared to conducting the same ACF efforts using Xpert Ultra to confirm a positive screening test result. An estimated 82,400 individuals could be screened under the allocated budget in the baseline comparator scenario. Test improvements considered are: (1) Increase in test sensitivity (from 69.0% to 80.0%; purple bar), using a non-sputum respiratory specimen type (increasing confirmatory specimen production from 93% to 100% for those eligible), (3) point-of-care testing (increasing the proportion of receiving the confirmatory test result from 91% to 100%), and (4) reduced costs (from $20 to $10 per confirmatory test). Panel A depicts the increase in the number of people with TB diagnosed and treated under ACF efforts when each of the named confirmatory test improvements is used compared to ACF utilizing the baseline confirmatory test. Herein, the purple area of the bars refers to people with TB who would have died in the absence of community-based screening, the dark blue area to people with TB who would have received treatment and been eventually cured even in the absence of ACF, and the light blue area to people in whom TB would have spontaneously resolved prior to receiving any treatment. Panel B shows the estimated reduction in TB mortality (number of TB-related deaths) and Panel C the projected reduction in TB transmission (infectivity-adjusted person-months) resulting from each of the test improvements.