**Main text**

To understand the potential burden reductions that could arise from new diagnostic tools, it is useful first to understand the distribution of infectious TB in a population, across different stages of the TB care cascade. The upper row of Figure 1 shows results from recent, national prevalence surveys in India and South Africa, highlighting patients with TB that did not report symptoms; patients suffering symptoms who had not sought care; and those that that had sought care, but remained undiagnosed. New diagnostic tools could benefit patients at all stages of this cascade.

First, at the facility level, oral swabs coupled with molecular diagnostics, or future urine-LAM tests, will be more feasible to conduct in decentralised settings, than current sputum-based tests. Such diagnostic strategies could therefore offer new opportunities to expand timely testing for TB at the primary care level. The blue curve shows the potential impact arising from this scenario, averting 10.1% and 14.9% of cumulative TB deaths in India and South Africa, respectively (see table S3, supporting information, for a summary of impacts under all intervention scenarios). In India, the expansion of public-private mix initiatives would have an important role in amplifying this impact, by allowing it to reach more providers, and thus patients: such measures would increase incidence and mortality impact almost twofold.

Next, to reach symptomatics who have not sought care, oral swabs or urine samples could be collected at the household level, for example facilitated by community healthcare workers who encourage symptomatic individuals to collect self samples. The red curve in both figures shows the potential impact of twice-yearly screening amongst all symptomatics in the community, averting 17% and 12.1% of cumulative TB deaths in India and South Africa, respectively.

Finally, to reach those without symptoms, it is likely there will be a need to concentrate on vulnerable populations with a high prevalence of TB. Highly portable screening tools will be required, for example hand-held X-ray combined with artificial intelligence for X-ray reads. The pink curves suggest that screening those with leading risk factors (undernutrition in India, and HIV in South Africa) to identify 10% of asymptomatic TB would avert 1.8% and 1.7% of cumulative TB deaths in India and South Africa, respectively.

A combination of all of these interventions (green curves) would avert 25.5% and 25.2% of cumulative TB deaths in India and South Africa, respectively. Although substantial, these reductions alone are not sufficient to meet the SDG TB goals. Indeed, previous work has shown that, while diagnostics will play a critical role in reducing TB incidence and mortality, meeting the SDG goals will ultimately require the mass prevention of TB (refs).

**Figure caption**

Potential future impact of new diagnostic tools in high-burden countries. Shown are examples of India (left-hand column) and South Africa (right-hand column). The top row shows results from recent prevalence surveys in both countries (refs), highlighting the proportion of prevalence TB that had sought care yet remained undiagnosed (red); that had symptoms but had not sought care (green); and that did not report symptoms, despite being sputum bacteriologically positive (blue). Depending on their characteristics, new diagnostic tools could benefit patients at each stage of this sequence. The lower two rows show cumulative cases and deaths averted under different scenarios for the deployment of new diagnostic tools (see supporting information for incidence and mortality curves relating to each of these scenarios). In these plots, the green curve shows the impact of all interventions implemented in combination, while remaining curves show impacts of interventions implemented individually.

Starting at the right-hand side of the prevalence survey diagram and moving upstream, these interventions are as follows: (i) the blue curve shows a scenario where the probability of diagnosis and treatment initiation per care seeking visit is increased to 90%. Such effects could be achieved, for example, with the use of new tools based on oral swab or urine samples, both of which are easier to collect than sputum. Such tools could help expand the diagnosis of TB in decentralised primary care settings, facilitating early recognition of TB without need for multiple provider visits. (ii) In India, the impact of new diagnostic tools could be amplified if they are made available to all providers managing TB, not just the public sector. The red curve shows a scenario where new diagnostics are implemented as described above, at the same time as 90% of private healthcare providers being successfully engaged with the public programme. This combination increases the cases and deaths averted by xx and yy%, respectively. (iii) For both countries, the purple curves correspond to targeting symptomatics who have not sought care: shown is a scenario where people with symptoms in the general population are tested twice a year for TB, either through programme activities, or by self-testing, similar to COVID-19. Although infeasible with current tools, again the ease-of-implementation of oral swabs and urine samples may facilitate these levels of testing in future. (Iv) In both countries, the pink curves correspond to a scenario where vulnerable populations are tested without symptoms screening, assuming that 10% of subclinical TB in these populations is detected and initiated on treatment each year. Such levels of screening could be achieved with highly-portable screening tools currently in development, such as handheld X-ray combined with AI reads. In India, we assumed the vulnerable population to consist of those with undernutrition while in South Africa, we assumed this group to consist of those with HIV.

See table S1 for calibration data and table S2 for estimated baseline parameters, relevant to these interventions. See also table S3 for overall estimates for cumulative cases and deaths averted by 2030.

**Supporting information text on the model**

The model focused on pulmonary TB and simply assumed all TB are pulmonary TB. The model features the natural history of TB according to the needs of the active case-finding algorithms of interest. Before healthcare, the model divides active TB by asymptomatic/symptomatic stage. The active TB states provide the force of infection to drive the transmission process. A group of latent TB infection states (LTBIs) captures those who do not progress active TB directly after infection and those who recovered from active TB. The LTBIs still have the risk of TB infection but with a lower susceptibility and TB reactivation/relapse among them are possible. We also considered the development of TB as a reversible process. That is, the active TB can be spontaneously cured and the LTBIs has a chance of self-clearance, which reverts the LTBIs to an uninfected state. Governing equations for India and South Africa are given in the next section, with calibration targets shown in Table S1.

In India, the model distinguishes public and private sectors. We modelled the ‘vulnerable’ population as consistent with undernutrition, the TB risk factor with the greatest population attributable risk in India (ref). Consistent with data from the Food and Agriculture Organisation (ref), we assumed that 16% of the population suffers undernutrition, and further that this population has three times the prevalence of TB as the general population. In South Africa, the model takes account of HIV status, stratified into HIV-negative; those with HIV but not on ART; and those on ART. We did not aim to model the transmission dynamics of HIV, instead treating this as an exogenous input. We drew data from UNAIDS for HIV incidence, and ART coverage, over time (ref) and assumed the declining in HIV infection and increasing in ART initiation following the five year trend between 2015-2019.

To capture the state of the TB epidemic in the pre-COVID period, we calibrated the model to each of the calibration targets shown in Table S1. To propagate uncertainty systematically from model inputs to model projections, we used a Sequential Monte Carlo for approximate Bayesian computation (ABC-SMC). We used an adaptive ABC-SMC which harmonised the metropolis hastings to effectively exploring sample spaces into SMC and enhanced the stability of sampling process. For calibration targets shown in Table S1 we constructed a distance function capturing the Euclidean distance between data and the simulation, scaling by uncertainty intervals of the calibration targets. Upon the convergence of the sampling, we collected 1,000 effective posterior samples for presentation. We computed all model projections on the basis of these samples, estimating central values as the median estimate, and the 95% Bayesian credible interval as the range between 2.5th and 97.5th percentiles.

Next, to capture the effects of COVID disruptions, we used the same approach to that currently employed by WHO, for estimates of TB burden in the wake of these disruptions: we adjusted the care seeking rate in order to match the quarterly notifications in each country, assuming that any drop in notifications, relative to 2019, were attributable to inaccessibility of TB services. Finally, we simulated all interventions assuming that they are initiated in 2023, scaled up over the subsequent three years, and sustained thereafter. Figure S1 shows the resulting trajectories for incidence and mortality, under each intervention scenario.

***Equations***

Uninfected

, where deaths include all types of causes (all terms with ).

Latent TB infection and the recovered TB

Active TB

Notes: for the South Africa model, PLHIV without ART has an incidence rate ratio () applicable to all activation rates ().

**Table S1. Calibration targets for each country,** used forcalibration to pre-COVID conditions.

|  |  |  |
| --- | --- | --- |
| **Indicator** | **India** | **South Africa** |
| Prevalence of untreated TB, all types and all ages | Asymptomatic: 182  Symptomatic, pre-care seeking: 54.9  Symptomatic, sought care: 60.2  \* per 100k population  (ref) | Asymptomatic: 351  Symptomatic, pre-care seeking: 147  Symptomatic, sought care: 85.2  \* per 100k population  (ref) |
| TB case notification | TB case notification, 2017-2019 (after Nikshay launched) by public and private sectors | WHO TB case notification data, 2014-2019 |
| TB incidence and mortality | WHO TB burden estimates 2014-2019 | WHO TB burden estimates 2014-2019 |
| HIV and ART | Not applicable | UNAIDS data   * People living with HIV * HIV on ART * TB incidence in PLHIV * TB mortality in PLHIV |

**Table S2. Baseline model parameters relevant to modelled interventions**

|  |  |  |
| --- | --- | --- |
| **Parameter** | **India** | **South Africa** |
| Probability of diagnosis and treatment initiation, per patient careseeking visit | 60% for public sector  27% for private sector | 45% |
| Average duration of symptomatic TB before first careseeking | 3.8 (3.3 - 4.4) months | 3.2 (2.5 - 4.0) months |
| Average duration of subclinical TB before symptom onset | 4.5 (3.9 - 5.1) months | 2.6 (1.9 - 3.5) months |

**Table S3. Summary of impacts for each intervention scenario in 2030**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Intervention scenario** | **India** | **South Africa** |
| **Cumulative TB incidence averted, 2023 - 2030** | Increased diagnostic uptake in healthcare settings | 8.5% (6.4% - 10.3%)  with PPM | 7.7% (5.7% - 9.5%) |
| Proactive case-finding, symptomatic TB | 8.8% (6.6% - 10.8%) | 6.4% (4.8% - 8.0%) |
| ACF, 10% of asymptomatic TB in vulnerable population | 1.3% (1.0% - 1.5%) | 1.3% (0.7% - 1.7%) |
| All measure combined | 13.9% (10.5% - 16.5%) | 14.0% (11.4% - 16.6%) |
| **Cumulative TB mortality averted, 2023 - 2030** | Increased diagnostic uptake in healthcare settings | 16.3% (13.8% - 19.1%) | 14.9% (11.3% - 18.1%) |
| Proactive case-finding, symptomatic TB | 17.0% (14.3% - 19.8%) | 12.1% (9.7% - 15.2%) |
| ACF, 10% of asymptomatic TB in vulnerable population | 1.8% (1.5% - 2.0%) | 1.7% (1.0% - 2.2%) |
| All measure combined | 25.5% (22.2% - 28.8%) | 25.2% (22.1% - 29.8%) |

Chart

Description automatically generated

**Figure S1. Incidence and mortality curves under each intervention scenario.** These projections underlie the results for averted incidence and mortality, shown in Figure 1 in the main text. All interventions are as described in Figure 1.