What is the health impact of identifying a person with tuberculosis through systematic screening?

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Summary

Screening high-risk populations for tuberculosis may improve clinical outcomes and reduce transmission, but the value and cost-effectiveness of population-based screening depends on the uncertain health impact of early tuberculosis detection. In this Personal View, we propose a framework for estimating the incremental health impact of systematic screening, including effects on tuberculosis morbidity, mortality, sequelae, and transmission. Our framework accounts for the timing of screening, relative to when routine diagnosis might occur and when health effects become inevitable. We also account for the heterogeneous duration of tuberculosis, in that people with longer disease courses (associated with lower mortality but more transmission) are more likely to be detected by screening. Finally, we use this framework to estimate that population-based chest X-ray screening interventions might avert 2·4 (95% uncertainty interval 0·8-7·4) disability-adjusted life years per person found to have tuberculosis through screening – well within cost-effectiveness thresholds for many programs with published costs.

Introduction: The uncertain value of early TB detection

Population-based screening for tuberculosis (TB) is increasingly cited as a public health priority in high-burden countries, but wide-scale adoption is hindered by a lack of convincing evidence on effectiveness and cost-effectiveness at the population level. In the past decade, the scientific knowledge base underpinning the potential value of TB screening has grown. Specifically, population-based studies have shown that a large proportion of people with TB lack symptoms that would lead to routine diagnosis[1] and that mass screening for TB can lower disease prevalence and potentially reduce transmission.[2,3] Meanwhile, tools such as mobile chest X-ray with computer-aided detection are making mass screening more feasible and affordable.[4] Cheaper and more accessible molecular tests for TB could soon lower the overall cost of screening even further.[5,6] The World Health Organization (WHO) has recommended systematic screening of high-prevalence populations since 2021,[7] and increasing numbers of programs and countries have implemented some version of active case-finding. TB screening is very resource-intensive, however, and to date, the epidemiological evidence base has not allowed for systematic estimates of population-level impact to evaluate the return on this investment.

In estimating cost-effectivenesspopulation-based screening for TB, a major gap in our knowledge is a unified estimate of health utility – for example, the number of disability-adjusted life years (DALYs) averted or quality-adjusted life years (QALYs) gained – per person with TB detected through screening and subsequently treated. Whereas the costs and yield (i.e., number of people detected) for any given screening program can be directly measured by the program itself, the corresponding health impact – which includes reductions in transmission and post-TB morbidity – can only be indirectly estimated. As a result, most economic evaluations of mass screening have not attempted to assign a health utility value to early case detection, and have instead estimated only the cost per case detected or treated.[8–11] When the long-term health impact associated with active case-finding has been estimated, those estimates have been prone to substantial bias. For example, it is often assumed that infectiousness, symptom burden, detectability, and mortality risk are consistent over time and among all people with TB,[12–14] thereby implicitly suggesting that the people found to have TB during screening are representative of people with TB in the population as a whole. Furthermore, analyses of the impact of early case detection often consider counterfactual outcomes under passive case detection in only limited fashion.[15–17] Attempts to estimate post-TB sequelae averted by early detection have been extrapolated from published estimates that were not designed for that purpose.[18] Finally, the amount of Mtb transmission that is averted through early detection is difficult to quantify.

For all of these reasons, there is currently no consensus estimate of the number of incremental DALYs averted (or QALYs gained) per person with TB detected early through population-based screening. Partially as a result of this evidence gap, a WHO-convened evidence review in 2020 found no studies that could adequately inform assessment of the cost-effectiveness of systematic screening for TB.[9] We therefore sought to develop such an estimate through a novel conceptual approach, supported by quantitative modeling and evidence from the scientific literature.

A Conceptual Framework

Our conceptual framework is illustrated in **Figure 1**. We first estimate the total health consequences of the average episode of incident TB when only routine passive detection is available – accounting for morbidity, mortality, post-TB sequelae, and *Mtb* transmission. We then consider differences between people with longer TB disease trajectories (who are thus more likely to be detected through screening) and those with shorter disease trajectories. Third, we consider the degree to which early detection is likely to prevent each component of TB-related health consequences, by considering when those consequences become unavoidable relative to the timing of potential screening activities and the timing of routine diagnosis. Collectively, this framework allows us to estimate the incremental number of DALYs averted for each person with TB that is detected through population-based screening.

Estimating health consequences of developing tuberculosis

In the first step, we quantify TB-related health effects across four categories (**Figure 2**): (1) morbidity (reductions in quality of life during TB illness) among index individuals with TB; (2) TB mortality among index individuals; (3) long-term TB-related sequelae (disability or premature mortality that occur after cure[19,20]) among index individuals; and (4) TB-related morbidity, mortality, and sequelae among individuals who develop TB through secondary transmission.

In estimating TB morbidity, disability is matched to the duration of illness of the corresponding severity. The disability weight conferred by severe TB symptoms[21] is applied only to the estimated duration of severe symptoms,[22] rather than the full duration of microbiologically positive TB[23] (**Figure S1**). To estimate TB mortality, we combine the estimated case fatality ratio for incident TB[24] with an estimate of the average years of life lost per TB-related death, accounting for the older age of those who die of TB[19,25,26] and for predisposing conditions (e.g., smoking, undernutrition) that reduce life expectancy and are more prevalent among people with TB. For post-TB sequelae, we apply an average disability weight[19] to the calculated life expectancy of TB survivors,[25,27] and we multiply the estimated proportion of TB survivors who die prematurely from TB sequelae by an estimate of their remaining healthy life expectancy (in the absence of TB), with a discount rate for the delayed timing of those post-TB deaths.[19,28]

Finally, to estimate the adverse health consequences of transmission, we estimate the number of people who will develop incident TB as a result of transmission from the average index person with (incident) TB. To generate these estimates, we used a previously published population-dynamic model[29] to simulate the cumulative reduction in future incidence if one present-day case were prevented. We then assume the same TB-related adverse health consequences among these secondary cases as amiong index individuals (with discounting applied). Combining estimated health impacts across these four categories allows us to estimate the average total DALYs associated with one person developing incident TB.

Certain TB episodes are more likely to be detected through screening

We then consider that people with longer TB disease courses are more likely to be detected by a population-based screening intervention, and that certain health consequences of TB are therefore disproportionately experienced in people with higher probability of detection (**Figure 1, Estimate 2**). Specifically, people with longer disease courses, who are therefore more likely to be detected through screening (**Figure 3B**), may generate more cumulative transmission because they have longer opportunity for spread. But they may also have lower mortality risk, because there is a longer window of time during which routine diagnosis and treatment can prevent death (**Figure 3A**).

The probability that TB will be detected through screening is proportional to the time that it would (in absence of screening) spend in an undiagnosed but screen-detectable state. For example, for a screening intervention that screens for symptoms followed sputum molecular-test confirmation, this "screen-detectable window" begins when TB becomes both symptomatic and sputum-molecular-test-positive, and ends at the time when it would be diagnosed through routine care in the absence of screening. The risks of transmission and mortality, which also vary between indivduals, may be modeled as correlated with this duration of detectable disease (see Supplemental Text 1, Step 2, for further details).

Timing of health consequences relative to early and routine detection

Finally, for any TB episode that is detected early through a screening intervention, we estimate the proportion of adverse health consequences likely to be incrementally averted, based on the relative timing of screening, health effect accrual, and routine diagnosis (**Figure 1, Estimate 3**). In making these estimates, we consider health consequences to "accrue" when disease processes occur that will inevitably lead to death or disability, even if that death/disability is not yet experienced. For example, DALYs (or other measures of adverse health impact) accrue when TB causes debility that will eventually result in TB death, when lung inflammation develops that will eventually result in COPD, or when transmission occurs that will eventually lead to a secondary episode of symptomatic and/or infectious TB. We discount these future DALYs to account for their delayed timing, but consider them to accrue when they become inevitable.

Therefore, to estimate the potential benefits of early detection, we first estimate the proportion of TB-associated health effects that accrue during the "screen-detectable window" described above; this excludes any effects that accrue while the person would be classified as TB-negative by a given screening algorithm or after diagnosis would otherwise occur through routine care (e.g. due to loss to follow-up or ineffective treatment) (**Figure 4**). We then estimate the proportion of "screening-avertable" effects that early detection would actually avert, by considering the timing of health consequence accrual relative to the timing of potential detection through screening (assumed to occur at a random time during the screen-detectable window). Because TB severity tends to increase over time, health effects are more likely to accrue during later portions of the screen-detectable window; we have represented this an exponential increase in the DALY accrual rate over time (Table S1). The proportion avertable through screening may be different for personal versus transmission-related health consequences, as mechanisms of transmission may be less correlated with care-seeking and the

timing of routine diagnosis. Since health effects accrue more rapidly near the end of the screen-detectable window, whereas the timing of screening is independent of an individual's disease course, early detection tends to avert more than half of the negative health effects of TB that would have accrued during the screen-detectable window (**Figure 4**).

Combining to estimate DALYs averted

By combining these three considerations – the average total health consequences associated with TB, differences in those consequences based on duration of disease course, and the proportion of those consequences likely to be averted if detected early through screening – we can estimate health impact per TB case detected (and treated) early through screening.
We use DALYs to quantify TB-related health consequences, with temporal discounting where relevant., because despite their limitations,[30] DALYs facilitates summation across different mechanisms of benefit, comparison to other health interventions that have been evaluated similarly, and benchmarking against willingness-to-pay thresholds.[31,32]

Quantitative Application of the Framework

Drawing on this conceptual framework, we developed a corresponding mathematical model to provide quantitative estimates of this incremental health impact of TB screening. Parameter estimates and full details of our quantitative model are provided in **Text S1** and **Table S1**. Our parameter estimates, informed by literature review and sampled from probabilistic uncertainty ranges, are chosen to represent a population-based intervention such as mass chest x-ray screening that detects both symptomatic and asymptomatic TB disease, added to a background of routine diagnosis in a high-TB-burden setting (**Table S1**). Results are reported as medians and inner 95% quantile ranges across 1000 parameter samples.

Using the model described above, we estimated that a CXR-based mass screening intervention in a high-TB-burden setting averts 2·4 (95% CI 0·8-7·4) DALYs per person with TB detected (**Table 1**). Personal health benefits comprise 40% of this impact: 0·04 (0·01 - 0·10) DALYs from averted TB morbidity, 0·3 (0·0 - 1·2) from averted TB mortality, and 0·4 (0·1 - 1·3) from averted post-TB sequelae in the people whose TB was detected early. The remaining 60% of averted DALYs – 1·5 (0·4 – 5·8) – are due to averted transmission. The importance of transmission-related effects reflects the relatively large estimated percentage (38%) of all TB-related DALYs due to transmission in high-burden settings ("assuming uniformity"), augmented by the fact that screening is more likely to detect people with longer TB disease courses ("accounting for heterogeneity") (**Table 1**).

In sensitivity analyses (**Figure S2**), estimates of DALYs averted per case detected through screening were strongly correlated with parameters that determined the total DALYs per average TB episode, including the number of downstream transmission-related cases (range 1·8—5·2 DALYs averted when varying only this parameter), the case-fatility ratios for TB (range 2·0—3·8) and post-TB (2·5—3·8) and the corresponding years of life lost (1·9—3·5 for TB deaths, 2·6—3·5 for post-TB deaths), and the average severity of post-TB disability across all TB survivors (2·3—4·2). The associations of disease duration

(and, thus, probability of detection through screening) with transmission and mortality were also influential. Parameters that determined which DALYs were avertable by early detection were also important; these included the proportions of morbidity/mortality and transmission that accrued after routine diagnosis, and that accrued early versus late within the detectable period. Finally, because many TB-associated DALYs were realized years after accrual, the discount rate applied to future years was also influential (range 1·7—3·2 DALys averted when varying only this rate).

We also published the model as a Shiny app (https://eakendall.shinyapps.io/acf-impact-rshiny/) that allows readers to explore different numerical assumptions.

Implications for cost-effectiveness

Our estimation of health impact on a per-case-detected basis facilitates straightforward estimates of cost per DALY averted, through linkage with programmatic cost data. For example, mass CXR screening programs have been estimated to cost $180 per case detected in Zimbabwe,[33] $963 per case detected among elderly people in China;[34] and $435 per person diagnosed and initiated on treatment in Zambia.[35] Applying our estimate of 2·4 DALYs per case detected to these screening interventions (i.e., dividing each of these costs by 2·4 to estimate cost per DALY averted), these interventions would be classified as highly cost-effective compared to published country-specific cost-effectiveness threshholds.[36] When considering similar interventions in other settings, cost-effectiveness would depend on both costs and the underlying prevalence of TB, and would be most certain when screening subpopulations with above-average TB burden.

Importantly, these cost-effectiveness estimates would ideally also account for the incremental cost of treatment, comparing screening to no screening. This incremental cost should include the cost of treating TT that is detected through screening and would otherwise have resolved without treatment. It should also account for the possibility that routine diagnosis and treatment might be more expensive, being done at a more advanced stage of disease. People with TB who, if not screened, would be diagnosed and treated in exactly the same way under routine care would have an incremental treatment cost of near-zero. Another consideration is that our estimates assume the sensitivity of CXR. Symptom-based screening interventions often have lower costs per case detected,[37] but their shorter and later screen-detectable window (owing to reduced sensitivity) would result in a lower estimate of DALYs per TB case detected

Despite the importance of understanding DALYs averted per case detected when evaluating population-based TB screening programs, few published economic evaluations of TB case-finding have reported this quantity, and those that do tend to rely on simple, unsupported assumptions.[38] Other cost-effectiveness analyses, which have used transmission or Markov models to estimate DALYs averted by screening, either do not report the number of cases detected or quantify them only incremental to routine care.[12,39,40] In addition, most models of TB screening do not account for differences in TB duration, transmission, or clinical outcomes between the people whose TB is and is not detected through screening – effects that we found to be important when estimating the health impact of early case detection.[12,17,41]

Although our objective was not to estimate total DALYs per incident TB case (irrespective of screening), we estimated 3·9 (1·6-10·1) total DALYs per average TB episode as an intermediate outcome – considerably lower than another recent published estimate of 12·1 (10·0-14·9) DALYs.[19] This discrepancy reflects a number of differences in methodology. Specifically, we considered all TB episodes (rather than only those associated with major symptoms), and we assumed a lower prevalence, shorter duration, and lower mortality risk (with shorter life expectancy lost) of post-TB symptoms that were causally mediated by TB itself. Had we used those larger estimates of total TB and post-TB morbidity and mortality, our estimates of DALYs averted per case detected would be greater – particularly if we also assumed that most post-TB lung disease is avertible prior to routine diagnosis and that people with a lengthy duration of milder disease are as likely to experience severe TB sequelae as those who quickly develop signs of clinical illness.

Future directions

This work highlights several uncertainties in our current knowledge that, if reduced, could further improve our ability to estimate the health impact and cost-effectiveness of population-based screening. Future work should prioritize: understanding the causal burden of post-TB morbidity and mortality, estimating the transmission impact of TB screening, evaluating the timing at which TB-associated DALYs accrue and are avertable by screening, and understanding variability in the TB disease course and associated outcomes.

Given our estimates that averted transmission accounts for more than half of the health impact of TB screening, improving estimates of the transmission burden averted through screening (in areas with differing TB prevalence) is of particular importance. Unfortunately, the number of downstream cases attributable to each index case is not straightforward to estimate. Steady rates of TB incidence (estimated 0-4% per year decline in most high-TB-burden countries[25]) suggest a reproduction number close to one,[42] but epidemics also have equilibrium tendencies that limit the durability of transmission-reducing effects. In most transmission models of mass TB screening, prevalence returns to near baseline within a few years of intervention.[29,43] These estimates depend, however, on uncertain infection rates and probability of clearance,[44–48] and models that attribute a higher proportion of TB to recent transmission tend also to project greater transmission impact from active case-finding interventions.[49] To provide empirical data on this question, there would be great value in conducting long-term follow-up in communities where intensive screening interventions have reduced prevalence and transmission in the short term.[50]

Another key area of uncertainty is identifying when in the TB disease course future harms become inevitable. The timing of DALY accrual is difficult to directly measure, and evidence about the direct health effects of TB screening is scarce,[51] so estimates must extrapolate from knowledge of the relevant disease mechanisms. We presume that the processes leading to long-term morbidity and mortality increase exponentially when approaching symptom-driven diagnosis; however, quantifying exactly when in the disease course these changes become irreversible is difficult.[52] For example, TB-related inflammation[53] and radiographic burden[54,55] are associated with care-seeking, but the proportion of TB

sequelae that remain avertable at routine diagnosis is an open question.[56,57] Although we speculate that detecting TB before it causes severe symptoms is likely to avert most mortality and causally mediated sequelae, there is a need for well-designed empiric studies. Measuring effects of screening interventions or more-accessible tests on mortality and long-term health (including all participants, not just those notified with TB) could provide insight on the timing of these biological changes.

Finally, our results highlight the importance of quantifying differences between people with TB who are more versus less likely to be detected through screening. For transmission, the relationship between disease duration and cumulative transmission could be weaker than we assumed if those with a higher pathogen burden also tend to experience faster clinical progression (as some modeling suggests[58]), or stronger if those who are slow to seek care also have a particularly high contact rate with other people in their community. For TB mortality, it is known that some risk factors also increase the pace of disease progression, causing them to be under-represented in a cross-sectional screening sample. In particular, HIV co-infection is associated with a twofold lower TB prevalence-to-notification ratio (i.e., with half as much time spent with TB per notification)[59] and a twofold higher TB case-fatality ratio,[25] but additional data are needed to understand variability in the pace of TB progression between individuals (accounting for additional comorbidities, immunological differences, and other unmeasured effects) and associated variation in transmission, morbidity (including post-TB morbidity), and mortality in the absence of early diagnosis. In the absence of strong evidence, we assumed that prolonged but milder illness accrues a similar amount of cumulative morbidity and tissue injury as more severe disease that is routinely diagnosed after a shorter interval. If longer disease durations are associated with greater cumulative disability or pathologic change, then we may have underestimated the impact of early detection in this regard as well.

Conclusion

In summary, estimating the health impact of early TB detection requires quantifying the current and future health consequences of TB, including the morbidity and mortality of TB itself, the causally mediated impact on post-TB quality of life and survival, and the downstream health consequences that transmission causes for other individuals. It also requires understanding how health outcomes may differ between people with TB who are more versus less likely to be detected through screening, and the extent to which detection through screening averts long-term health effects.

Applying this framework to a non-symptom-gated TB screening intervention, we estimated that screening could avert 2·4 (uncertainty range 1 to 7) DALYs per case detected, and that screening might avert more transmission-related DALYs than are generated by the average TB case. This suggests that estimates of the impact of TB screening should account for transmission-related effects, and that they may also need to consider differences between those more and less likely to be detected by such an intervention. These estimates provide a basis for evaluating the cost-effectiveness of TB screening interventions, and they suggest that existing screening interventions may be cost-effective in high-prevalence settings, while also highlighting priority areas for future research.

Acknowledgements

This work was supported by the US National Institutes of Health, R01HL138728 to EAK and R01AI147681 to DWD. Funders had no role in the writing of the manuscript or the decision to submit it for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declaration of Interests

In addition to the above, EAK also discloses research funding from the Gates Foundation.

Author Contributions

EAK conceived the framework for estimating impact of early tuberculosis detection, developed the quantitative model, and drafted the manuscript. DWD extensively advised on the presentation of concepts and results and critically revised the manuscript.

Figure 1: A framework for estimating the health benefit per person with tuberculosis detected through screening. We estimate the health impact (i.e., disability-adjusted life years [DALYs] averted) of detecting an individual with TB through population-based systematic screening, relative to ongoing routine diagnosis. A first step is to estimate the total DALYs attributable to the average TB episode, categorized into TB morbidity, TB mortality, long-term post-TB sequelae, and *M. tuberculosis* transmission. Then, by considering how TB disease episodes that are more likely to be detected by screening differ in health effects from the average TB episode (because of longer duration, correlated also with lower mortality), we transform our first estimate into an estimate of the average total DALYs per average person with TB detected though a screening intervention. In the third and final step, we estimate what proportion of DALYs are likely to be averted when a TB episode is detected early, by considering what proportion of health effects remain avertable at different points in the disease course and how likely screening is to have occurred before each time point. The result is an estimate of total health impact in DALYs, per case detected through screening.

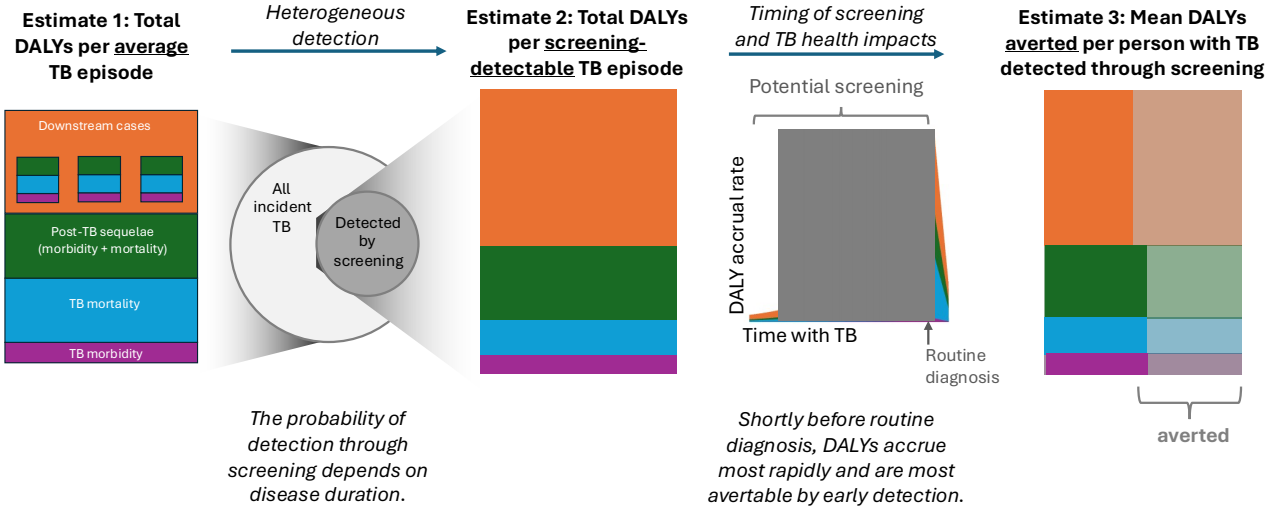

Figure 2: The total health consequences of the average TB episode. We estimate these consequences as a sum of morbidity (disability) experienced during TB, mortality directly related to TB, post-TB sequelae (including both disability and premature mortality), and transmission-related effects (i.e., similar disability and early mortality experienced by others who will develop TB as a result of the index case). All estimates are limited to causally attributable effects and include temporal discounting.

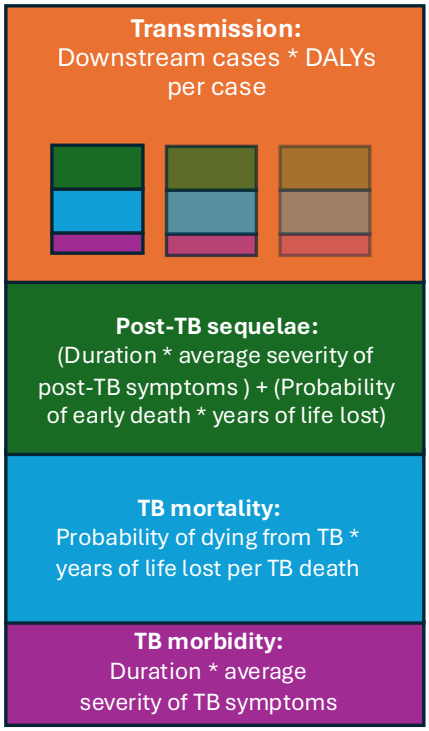

Figure 3: The probability and impact of early detection reflect heterogeneity in the tuberculosis disease course. Because people detected with TB through screening differ from those who go undetected, ignoring this heterogeneity can lead to biased estimates of screening impact. As shown in Panel A, people with longer disease courses (orange arrow) tend to have lower mortality (because of a longer window for treatment to achieve cure between routine diagnosis and death, depicted by dotted lines) but longer periods of transmission that could be averted by screening (depicted by shaded areas). As shown in Panel B, people with longer TB disease courses (orange lines) are also more likely to be detected by a population-based screening intervention (vertical dashed line). In this illustrative example, the orange lines represent only 50% of people with incident TB in the population, but they account for 75% of people diagnosed by the screening interventions; conversely, they account for only 15% of TB deaths. Since screening interventions are more likely to detect those with longer disease courses, such interventions may avert a disproportionately small fraction of total TB mortality but a disproportionately large fraction of total transmission.

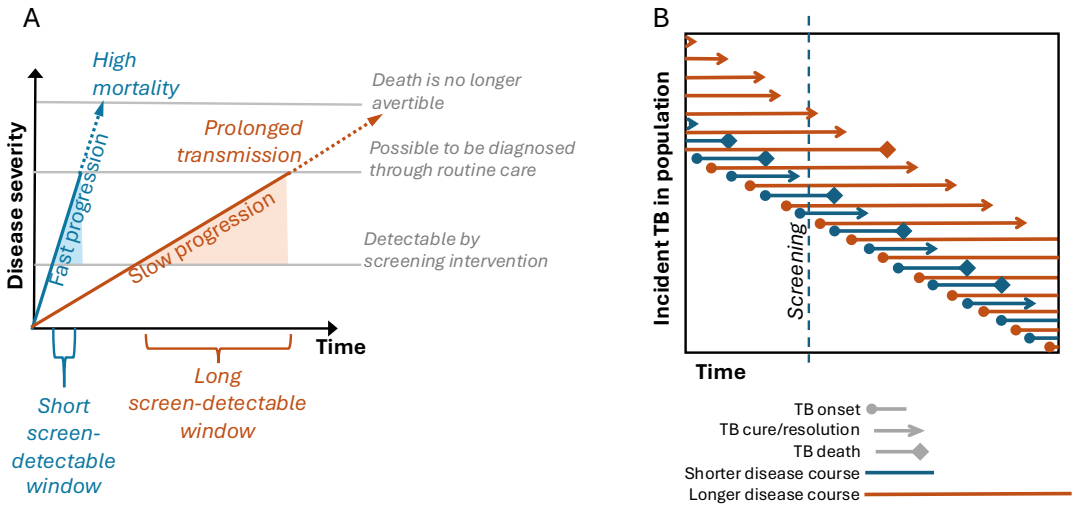

Figure 4: Relationship between timing of tuberculosis detection and accrual of health impact. A given screening program will detect individuals with TB only during the "screen-detectable window," which we define as the period between the time that those individuals become detectable by that program's screening algorithm and the time that those people will be routinely diagnosed in the absence of screening. Disability-adjusted life years (DALYs) will be averted by screening only if they accrue (i.e., become inevitable) between the time of detection through screening and the time of counterfactual routine diagnosis. An infrequent, cross-sectional screening intervention is equally likely to detect people with TB at any point during the screen-detectable window. However, the disease severity, and thus the DALY accrual rate, tends to increase over time as people approach routine diagnosis. In this figure, small arrows illustrate possible screening time points, and translucent gray rectangles to the right of each small arrow illustrate that detection will avert all subsequent DALY accrual (to the right of the screening time point) within the screen-detectable window. Thus, the DALYs that accrue latest (farthest to the right) within the screen-detectable window are most likely to be averted, as indicated by the greater opacity of the superimposed gray rectangles. Since DALYs accrue more quickly in the latter part of that window (i.e. the colored area is greater during later, more opacified time intervals), more than half of all avertable DALYs are, on average, averted by early detection.

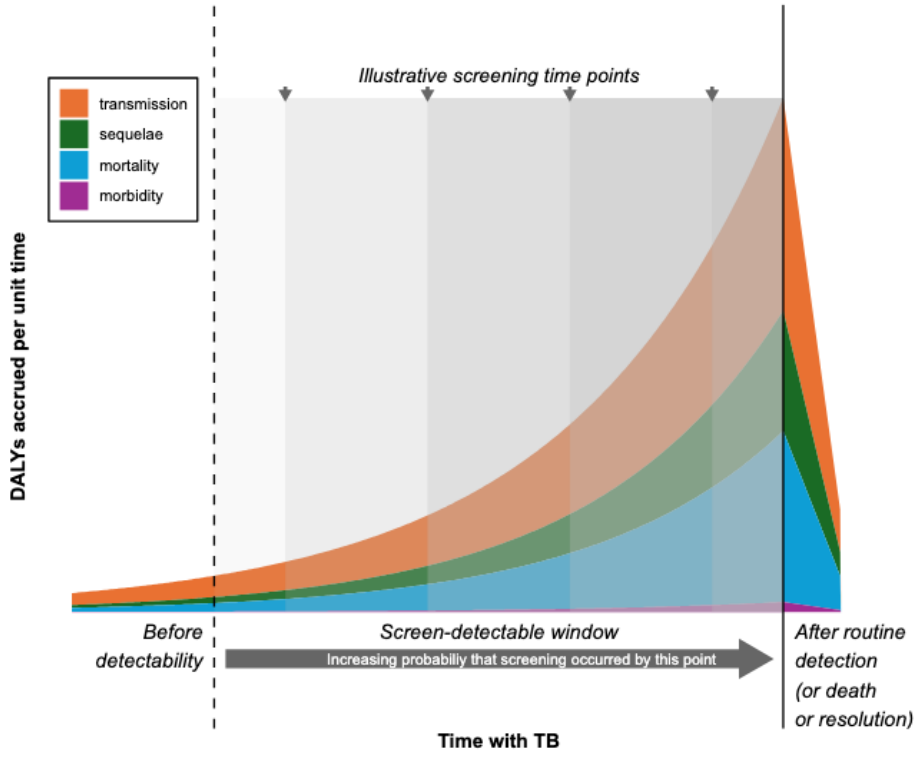

Table 1: Tuberculosis-associated disability-adjusted life years averted through population-based screening

	Average DALYs per TB episode		DALYs averted through screening	
Source of DALYs	**All TB***	**Screening-detectable TB****	**Assuming uniformity***	**Accounting for heterogeneity****
Morbidity	0·08 [0·03 - 0·20]	0·08 [0·03 - 0·20]	0·04 [0·01 - 0·10]	0·04 [0·01 - 0·10]
Mortality	1·2 [0·4 - 3·2]	0·7 [0·1 - 2·4]	0·6 [0·2 - 1·7]	0·3 [0·0 - 1·2]
Sequelae	0·9 [0·3 - 2·4]	0·9 [0·3 - 2·4]	0·4 [0·1 - 1·3]	0·4 [0·1 - 1·3]
Transmission	1·5 [0·4 - 5·0]	2·9 [0·8 - 10·4]	0·8 [0·2 – 2·8]	1·5 [0·4 – 5·8]
Total	**4·0 [1·6 - 9·0]**	**4·7 [1·7 - 13·6]**	**1·9 [0·7 – 4·8]**	**2·4 [0·8 - 7·4]**

DALYs = disability-adjusted life years; TB = tuberculosis

* Ignoring the increased probability of detection among people with longer TB disease courses

** Weighted by likelihood that each TB episode would be detected early through a population-based screening intervention. Accounts for higher transmission potential and lower mortality risk among those with longer disease courses who are more likely to be detected through screening (Figure 3).

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