**Post-tuberculosis mortality and morbidity: Valuing the hidden epidemic**

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Case fatality rates for tuberculosis disease (TB) have fallen progressively over the past 20 years, and an estimated 54 million people have survived TB since 2000.[1] More recently there have been increasing efforts to understand the long-term implications of morbidity and mortality *post-tuberculosis,* and a growing body of evidence describes how successful completion of treatment is unlikely to represent the end of ill health.[2]

A recent meta-analysis estimated all-cause mortality to be 2.91 (95%CI: 2.21–3.84) times greater among individuals *post-tuberculosis* compared to age- and sex-matched controls.[3] While these estimates may be inflated by coalescing factors predisposing to both TB and early mortality, separate lines of research have described the causal pathways through which TB impacts future health. These long-term *post-tuberculosis* sequelae include substantial morbidity from residual tissue damage, despite microbiologic cure. Evidence from meta-analysis suggests that pulmonary TB is an independent risk factor for airflow obstruction and spirometric restriction[4], alongside chronic obstructive pulmonary disease (COPD)[5]. TB meningitis and musculoskeletal TB also cause substantial long-term morbidity, and individuals *post-tuberculosis* face elevated risks of recurrent TB.[6]

However, chronic impairments are not yet reflected in conventional measures of TB burden[7], or in analyses comparing TB policy options.[8, 9] Here we describe how the burden of *post-tuberculosis* mortality and morbidity can be quantified using the disability-adjusted life year (DALY) framework. We provide an example of how this can change TB burden estimates in a high-incidence setting and consider the consequences for TB interventions, programming, and future research.

DALYs are a composite measure of health loss widely used to evaluate the impact and cost-effectiveness of health programmes. Interventions seek to avert DALYs, which are the sum of years of life lost due to premature death and years lived with disability.[7] In a typical analysis, DALYs averted by TB interventions only account for the mortality and morbidity accruing during treatment of TB disease, assuming that survivors return to full health *post-tuberculosis*.[9] Although some conditions have disability weights representing chronic disability following resolution of acute disease (e.g. long term consequences of stroke), TB does not.[1]

As an example, we considered pulmonary TB in India and calculated conservative estimates based only on *post-tuberculosis* changes in COPD prevalence only (Figure 1). For active TB DALYs, we assumed a 2-year duration of disability and case fatality estimates reported by WHO.[10] To calculate *post-tuberculosis* years of life lost, we estimated a lower-bound mortality rate ratio (MRR) of 1.22 based on elevated COPD prevalence and mortality among *post-tuberculosis* individuals.[5] For post-TB morbidity we estimated a *post-tuberculosis* disability weight of 0.053 based on elevated *post-tuberculosis* COPD prevalence and published disability weights for COPD and other chronic respiratory diseases.

We find that if *post-tuberculosis* mortality and morbidity is considered, the estimated burden of TB in India due to incident TB in 2018 increases by an additional 6.1 million DALYs, a 54% increase on estimates that assume a return to full health at the end of TB treatment. This burden would further increase, if post-tuberculosis conditions other than COPD were considered. We estimate an additional 20.1m DALYS (a 174% increase) as upper-bound, assuming that all excess mortality was attributable to past TB (MRR of 2.91)[3].

One implication of accounting for *post-tuberculosis* ill-health is a change in the prioritisation of TB programming. For example, the impact and cost-effectiveness of preventative interventions will increase due to greater DALYs averted per TB episode prevented – particularly relevant in the context of recent vaccine trials, and high-level political commitments to provide preventative

therapy to 30 million individuals by 2022.[11, 12] Interventions that limit lung damage from TB disease should also receive increased attention, including tools allowing earlier TB diagnosis [13], and new regimens that protect lung function during TB treatment.[14]

Given this potentially large burden of disease associated with *post-tuberculosis*, several lines of future research are important. First, clinical evidence on *post-tuberculosis* points to a highly heterogeneous set of symptoms and conditions, which need to be understood to enable more tailored *post-tuberculosis* care. Second, there is little evidence on how mortality and morbidity exacerbate household and macro-economic consequences of TB, since current estimates assume no costs are incurred and no productivity is diminished after treatment. Third, consistent measurement of lung damage could be used to quantify whether case finding is diagnosing cases earlier in their disease, which in turn relates to preventing transmission.[15] Fourth, estimates of mortality and morbidity from meta-analyses remain subject to bias due to confounding, and work is needed to confirm the causal impact of *post-tuberculosis* on long-term morbidity and mortality.

While much remains unknown, *post-tuberculosis* morbidity and mortality are a significant part of TB natural history, which deserve greater integration into the END TB strategy. As TB policies focus on both care and prevention, research and policy makers cannot ignore the impact and needs of individuals after resolution of TB disease.[12]

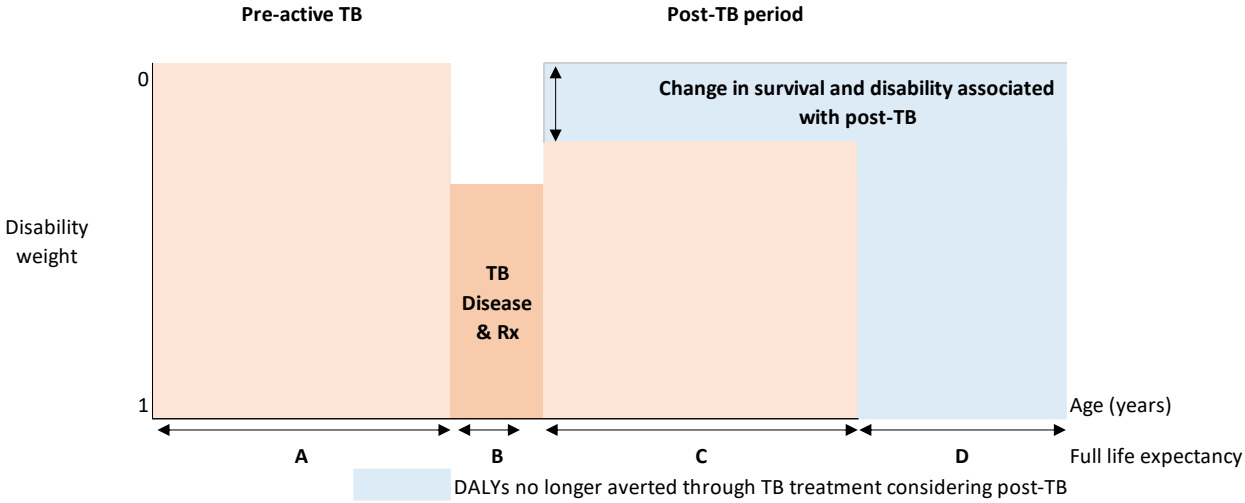


**Figure 1: Demonstration of *post-tuberculosis* DALY loss for a typical survivor of pulmonary tuberculosis treatment in India without HIV infection. Shaded blue area does not consider mortality or morbidity from conditions which share common causes with tuberculosis, thus this figure refers to a lower-bound scenario of post-tuberculosis.**

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