Post-tuberculosis mortality and morbidity: valuing the hidden epidemic

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Case fatality rates for tuberculosis disease have fallen progressively over the past 20 years, and an estimated 54 million people have survived tuberculosis 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 times (95% CI 2·21–3·84) greater among individuals post tuberculosis compared with age-matched and sex-matched controls.[3] Although these estimates might be inflated by coalescing factors predisposing to both tuberculosis and early mortality, separate lines of research have described the causal pathways through which tuberculosis affects future health. These long-term post-tuberculosis sequelae include substantial morbidity from residual tissue damage, despite microbiological cure. Evidence from meta-analysis suggests that pulmonary tuberculosis is an independent risk factor for airflow obstruction and spirometric restriction,[4] alongside chronic obstructive pulmonary disease (COPD).[5] Tuberculosis meningitis and musculoskeletal tuberculosis also cause substantial long-term morbidity, and individuals post tuberculosis face elevated risks of recurrent tuberculosis.[6]

However, chronic impairments post tuberculosis are not yet reflected in conventional measures of tuberculosis burden,[7] or in analyses comparing tuberculosis policy options.[8] 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 framework can change tuberculosis burden estimates in a high-incidence setting and consider the consequences for tuberculosis 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 tuberculosis interventions only account for the mortality and morbidity accruing during treatment of tuberculosis disease, assuming that survivors return to full health post tuberculosis.[8] Although some conditions have disability weights representing chronic disability following resolution of acute disease (eg, long-term consequences of stroke), tuberculosis does not.[1]

As an example, we considered pulmonary tuberculosis in India and calculated conservative estimates based only on post-tuberculosis changes in COPD prevalence (figure). For active tuberculosis DALYs, we assumed a 2-year duration of disability and case-fatality estimates as reported by WHO. 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 individuals post tuberculosis.[5] For post-tuberculosis 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

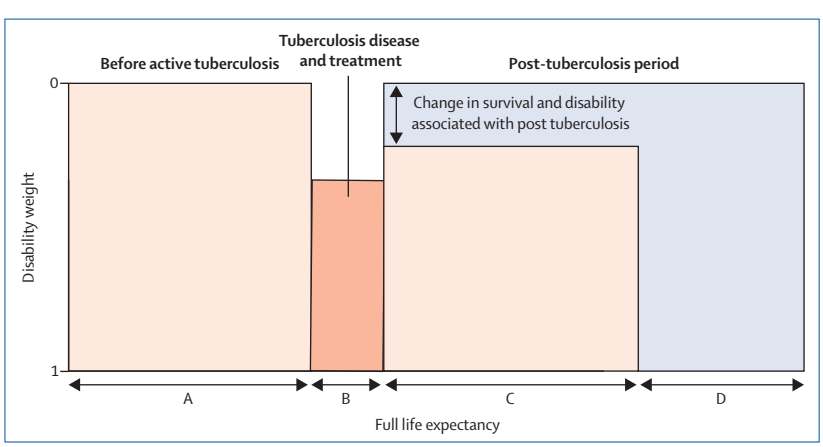

Figure: **Illustration of post-tuberculosis DALY loss for a typical survivor of pulmonary tuberculosis treatment in India without HIV infection**

Period A represents time before active tuberculosis disease. Period B represents tuberculosis disease and treatment. Period C represents life expectancy post tuberculosis, which is reduced by D years due to early mortality attributable to post-tuberculosis sequelae from COPD. The shaded blue area shows DALYs no longer averted through tuberculosis treatment considering post tuberculosis. This area does not consider mortality or morbidity from conditions that share common causes with tuberculosis; thus, this figure refers to a lower-bound scenario of post tuberculosis. DALY=disability-adjusted life-year. COPD=chronic obstructive pulmonary disease.

tuberculosis in India due to incident tuberculosis in 2018 increases by 6·1 million DALYs—a 54% increase on estimates that assume a return to full health at the end of tuberculosis treatment. This burden would further increase if post-tuberculosis conditions other than COPD were considered. We estimate an additional 20·1 million DALYS—a 174% increase—as an upper bound, assuming that all excess mortality was attributable to past tuberculosis (MRR 2·91).[3]

One implication of accounting for post-tuberculosis ill health is a change in the prioritisation of tuberculosis programming. For example, the impact and cost-effectiveness of preventative interventions will increase due to greater DALYs averted per tuberculosis 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.[9,10] Interventions that limit lung damage from tuberculosis disease should also receive increased attention, including tools allowing earlier diagnosis of tuberculosis[11] and new regimens that protect lung function during tuberculosis treatment.[12]

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 macroeconomic consequences of tuberculosis, 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.[13] 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 an important part of tuberculosis natural history, which deserve greater integration into the WHO End TB strategy. As tuberculosis policies focus on both care and prevention, research and policy makers cannot ignore the impact on and needs of individuals after resolution of tuberculosis disease.[10]

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