Invited Comment for Lancet Infectious Diseases (World TB Day)

Title:

Tackling long-term morbidity and mortality after successful tuberculosis treatment

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Tuberculosis (TB) is a curable disease, but the number of cases with difficult to cure drug resistant disease is rising (1). Even among patients in whom bacteriological cure is achieved, long-term functional impairment is common.(2) This is especially true for cases with a late diagnosis, in whom the initiation of appropriate treatment is delayed and in young children or immunocompromised individuals in whom disease progression can be rapid and early symptoms maybe non-specific.

Post-TB morbidity

Pulmonary TB, the commonest form of the disease, is an important, but under-appreciated, cause of chronic lung disease that is associated with substantial global morbidity and mortality.(3) Post-TB pulmonary morbidity includes functional disability due to reduced lung function, bronchiectasis with recurrent bacterial infections, and extensive cavitation with opportunistic infections such as *Aspergillus*.(3) A survey done in the United States identified lung function impairment in more than 50% of cured TB patients, with 10% suffering severe compromise.(2) A systematic review found a significant association between a history of TB and the presence of chronic obstructive lung disease (COPD) in older adults (pooled odds ratio 3.05; 95% confidence interval 2.42-3.85).(4) Among individual studies the strongest association between TB and chronic lung disease was found in high TB-incidence countries, especially in younger people not smoking cigarettes, since it is difficult to untangle confounding effect of cigarette smoking.

The TB treatment period provides an important opportunity to promote strategies that will optimise long-term lung health, including smoking cessation and general lung health education. This is even more important in patients with drug resistant-TB, who frequently experience increased adverse lung health impacts due to delays in commencing effective treatment.(5) Given that the treatment of drug resistant-TB is complex, costly and often toxic, an important lung health strategy is to prevent disease progression among close contacts of drug resistant-TB cases. The outcome of on-going prevention trials are eagerly awaited.(6) The prolonged engagement of patients with the health care system during TB treatment also offers an opportunity to consider other interventions that may improve their long-term health outcome, such as screening for common non-communicable diseases.(7) Person-centred care that includes pragmatic screening for diseases such as diabetes, hypertension and renal disease is feasible in TB patients and provides an opportunity to link those detected on initial screening to appropriate care pathways.(8)

Although children usually respond very well to TB treatment, young children (under 2-3 years of age) are particularly vulnerable to develop severe disseminated forms of the disease.(9) By the time TB meningitis becomes clinically apparent, it is often associated with permanent neurological sequellae, which emphasizes the need for better protection strategies and earlier diagnosis. Clinical deterioration due to hydrocephalus, stroke or tuberculoma formation is common following the initiation of effective TB meningitis treatment, highlighting the need for novel immune modulatory approaches to reduce the steroid-resistant inflammatory cascade that underlies these adverse outcomes.(10)

Post-TB mortality

TB is the leading infectious killer on the planet, despite the fact that current death estimates do not consider post-TB mortality. Accurate mortality estimates following discharge from TB care are not available, but a prospective cohort study among adults treated for pulmonary TB in Vietnam found that TB patients had a markedly elevated risk of death, particularly in the post-treatment period. In total, 9% of patients died within 2-3 years of treatment initiation; 3.1% during treatment and 5.8% after discharge. The standardized mortality ratio compared to population controls, in a setting with a low prevalence of human immunodeficiency virus (HIV) infection, was 4.0 (95% CI 3.7-4.2).(11)

A systematic review of 6922 deaths in 40 781 TB cases and community controls calculated a pooled standardised mortality ratio of 2·91 (95% CI 2·21–3·84), which increased to 3.76 (95% CI 3·04–4·66) when restricted to TB cases with confirmed treatment completion or cure.(12) Study heterogeneity was pronounced, and few confounding factors could be considered. However, the direction of the effect and effect estimates were similar when stratified by tuberculosis type, sex, age, and country-income category. Cardiovascular disease was the most common cause of death among those in whom this could be assessed, and mechanisms linking the TB and cardiovascular disease epidemics have been considered.(13) TB is not only pro-inflammatory but it also induces thrombophilia. However, studies exploring potential interventions to reduce post-TB cardiac mortality, such as the use of low-dose aspirin or statins during and after TB treatment have not been performed.

Other co-morbidities influencing health outcomes following TB treatment include alcohol and drug misuse, HIV co-infection, diabetes, malnutrition, the detrimental effects of stigma and social exclusion, as well socio-economic disadvantage, which has a bi-directional effect.(14) While these challenges have no easy solutions, it is essential that health systems recognise the continuing morbidity following TB. A greater focus upon the biomedical and

social interventions to reduce post-treatment morbidity and mortality will be essential if the long-term prognosis of patients with TB is to be improved (15).

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