TB, you're a long time cured

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Quantifying and comparing rates of chronic pulmonary aspergillosis, disease recurrence and other complications in treated TB patients are important to assess the true global impact of TB. International guidance on managing such patients would be valuable. http://ow.ly/ahQ730nHsLO

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Despite official country-level estimates having been produced for nearly three decades, much remains uncertain about the true global burden of tuberculosis (TB). Official statistics focus on incidence and mortality, while health systems concentrate on supporting patients through treatment, such that less is known about the longer term damage inflicted by disease episodes.

Although its epidemiology is changing, TB remains predominantly a disease of young adulthood in many high burden countries and the organism is now the world's leading infectious killer [1]. Deaths in early adulthood often remove primary carers and main income earners from struggling households in such countries, with devastating effects for affected families. In this context, the World Health Organization's focus on avoidance of catastrophic costs and universal health coverage in the End TB era is a welcome development and should draw greater attention to TB's devastating toll [2]. However, the persisting burden of disease and debility in TB survivors is also important and under-recognised, with evidence of significant physiological impairment resulting from past TB episodes [3, 4].

Despite this, international standards do not typically provide guidance on the optimal approach to care after treatment completion [5, 6], such that practice is likely to vary considerably. In low to moderate burden settings, recurrent TB is largely attributable to relapse and is most frequent in the 2–3 years following treatment [7, 8], so active follow-up may be most beneficial for this period [9]. However, even during this time, rates of disease are moderate and whether active follow-up reduces diagnostic delays is unknown. Monitoring for recurrent disease is not the only rationale for considering post-treatment follow-up; post-infectious complications, such as bronchiectasis, airflow obstruction, chronic pulmonary aspergillosis (CPA) and complications of extrapulmonary disease, are all potentially important. Post-treatment follow-up provides an opportunity to target specific patient groups for tailored interventions, as well as maintaining a link between TB control services and affected communities. Patients with extensive pulmonary damage may benefit from smoking cessation interventions, pulmonary function testing and vaccination against other respiratory infections, although evidence and recommendations are again sparse.

In developing countries, recurrent TB is likely to occur more often because of a greater frequency of reinfection, with rates of reinfection being influenced by HIV status [10] and rates of relapse likely to vary with programmatic quality. Therefore, although the value from post-treatment follow-up is higher, resource constraints often mean that only the most effective and efficient interventions are funded. In the high burden setting of Vietnam, a recent randomised controlled trial of contact investigation found considerably higher all-cause mortality in the control arm, despite most deaths not appearing to result

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directly from TB disease itself [11]. Findings such as these are a reminder of how great the unrecognised burden of TB may be in such countries, particularly given that around one-third of all TB cases worldwide are never identified by health systems.

CPA is an important contributor to excess morbidity and mortality in TB survivors in Uganda, as described by Page *et al.* [12] in this issue of the *European Respiratory Journal*. Despite the logistical challenges in diagnosing a condition that has clinical, immunological, microbiological and radiological features in a resource-limited setting, the authors were successful in tracing and reassessing more than 70% of around 400 enrolled patients 2 years after completing treatment for pulmonary TB. The main findings of around 5% and 26% prevalence of CPA in all reassessed patients and those with cavitation, respectively, are alarmingly high, although even these figures may be under-estimates due to attrition bias. These rates are higher than my personal clinical experience in a low burden setting, where we have historically followed pulmonary patients for 2–3 years post-treatment completion [13], although they are broadly consistent with previous studies. As the authors note, the largest previous post-TB treatment cohort was described in Britain before the advent of computed tomography [14, 15], while no other study has provided such a comprehensive assessment of a cohort of this size. New diagnostic criteria for CPA were published by European Society of Clinical Microbiology and Infectious Diseases and the European Respiratory Society in 2015 [16] and by Infectious Diseases Society of America in 2016 [17], both favouring 3 months for symptom duration. The study of Page *et al.* [12] was already underway at this time, so their shorter symptom duration requirement was unavoidable, but should have little effect on their main conclusions.

Post-pulmonary TB CPA has several features that make it important clinically: it is common, treatable and has a high case fatality rate. The global prevalence of the condition can be estimated by combining data on 1) pulmonary TB case numbers, 2) the frequency of cavitation in surviving patients and 3) the frequency of CPA in survivors with cavitation [18]. The third quantity is probably the weakest link in this modelling approach, and has previously been estimated from the single older British study mentioned above. The data presented by Page *et al.* [12] are consistent with this historical estimate, lending weight to the previous estimates. However, the rate of CPA in the large number of patients whose TB is never diagnosed may never be known and could be systematically higher or lower than that of a post-treatment cohort.

Even when recurrent disease is diagnosed, genotypic confirmation of relapsed disease is not possible for all cases and TB recurrence rates are broadly comparable [19–21] to the rates of CPA observed by Page *et al.* [12]. Therefore, post-treatment CPA misdiagnosed as recurrent smear-negative disease could conceivably contribute a substantial proportion of reported recurrence, with implications for assessing programme performance, as well as individual patients.

Given the often severe organ damage inflicted by TB, a greater focus on patient outcomes after they have achieved satisfactory treatment outcomes is desirable in both high and low burden settings. At a minimum, further research to quantify and compare rates and predictors of post-treatment complications would help to improve the accuracy of TB burden estimates. Evidence-based guidance on which investigations and interventions are appropriate to which post-treatment patient groups could mitigate TB's enormous global burden, while synergies could arise from greater integration of TB care with the broader health system.

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