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Benefit of treatment of latent tuberculosis infection in individual patients

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To the Editor

In their recent article, DOBLER *et al.* [1] described a decision aid that estimates a net benefit of treatment for latent tuberculosis infection (LTBI) in a low tuberculosis incidence environment. While the aid probably confers some clinical utility as described, its dynamic robustness could be strengthened in some important respects. In a series of previous articles [2–4] using primary longitudinal data from an urban American tuberculosis clinic that would be likely to benefit from use in some form of these authors' decision aid, I showed empirically a number of outcomes relevant to LTBI treatment in a low-incidence, mostly immigrant setting. First, nonadherent patients are likely to experience more adverse and expensive LTBI treatment outcomes (had they completed therapy) [2, 4], and potentially, greater likelihood of TB re-activation [3]; second, a transitional approach to treatment improves the net benefit received over any isoniazid (H) monotherapy (6 months (6H) or 9H) [4]; and third, ethnic heterogeneity in an immigrant clinic population may provide clinicians with guidance on tolerability to isoniazid [4].

Adapting the aid to include more flexible treatment options, such as a transitional therapy (*e.g.* isoniazid with transition to rifampicin (R) for adverse events), is needed. With regard to the decision tree presented by the authors for the complications of isoniazid treatment (figure 1 in their article), it is suggested that the “survive, incomplete treatment” outcomes given for adverse events from LTBI treatment (“adverse event other than hepatitis” and “drug-induced hepatitis”) is premature. Instead, an alternative regimen, including 4R, may be given to facilitate completion of the prophylaxis. Both 6H and 4R have quantified and reported efficacy and effectiveness outcomes, making the inclusion of 4R as a secondary treatment protocol a feasible option.

Additionally, more robustly accounting for ethnic identifiers, given what we now know about the genetics of isoniazid metabolism [5–7], will improve its utility. This is particularly important because of the emphasis placed by the authors on the low-incidence setting to

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which this aid would ideally apply. These environments, including the case study given by the authors themselves (page 1403 of their article), comprise large immigrant populations such that population stratification by ethnicity would elicit an important revision to the decision aid (see figure 7 in [4]).

A final note regards the authors' model assumption that patients are not reinfected with tuberculosis. This assumption may not be a biologically sound model component. ANDREWS *et al.* [8] calculated incidence rate ratios for progression to active tuberculosis among persons already identified as having LTBI *versus* people who were uninfected. They concluded that individuals with LTBI had 79% lower risk of progression to active disease after reinfection than uninfected individuals. This type of acquired "immunity" is not directly observable or recordable, but should be accounted for as best as possible in the aid, especially if the authors consider incorporating a transitional therapy as described above. However, for a clinic population of largely immigrants who come from nations with high tuberculosis burdens, this assumption dismisses potentially relevant information that might very well be useful to public health clinics with staff shortages and funding reductions in deciding who to treat and whether a transitional therapy is indeed desirable if the initial regimen fails.

Given the management of LTBI is a core intervention for any tuberculosis elimination strategy [9, 10], careful cumulative consideration of these points (*i.e.* better clarifying who is at high risk of progression to active disease and devising treatment protocols that maximise LTBI adherence potential for these individuals and acknowledging how ethnic heterogeneity in a low-incidence, largely immigrant population is likely to influence the net benefits received from treatment) is appropriate for inclusion in any clinical aid designed to promote a successful TB elimination goal.

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