Benefit of treatment of latent tuberculosis infection in individual patients

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].

References
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 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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References
variations in K. Fluegge further suggests including information on ethnicity in the decision model to account for (see discussion of inclusion of variables influenced by human behaviour above).

fast and intermediate acetylators when a standard dose of isoniazid was administered (OR 3.08, 95% CI NAT2 with an increased risk of isoniazid-induced hepatitis. A recent meta-analysis of 27 studies confirmed that NAT2 gene polymorphism testing is, however, not (yet) implemented in routine clinical care for patients with tuberculosis and/or LTBI. We believe that there is a role for NAT2 gene polymorphism testing in specific situations, especially when a patient has experienced an episode of severe drug-induced hepatitis, but continuation of treatment is considered essential. Test results can then be used to guide dosing of isoniazid. A randomised controlled trial found that NAT2 genotype-guided dosing of isoniazid improves the tolerability and efficacy of the 6-month, four-drug standard regimen for newly diagnosed tuberculosis [5]. While we support the clinical application of NAT2 gene polymorphism testing as described above, we do not think that inclusion in the model of a probability estimate for NAT2 slow acetylator status based on ethnicity is helpful. This is because: 1) slow acetylator status in an individual does not require a probability estimate, but can be determined with certainty; and 2) patients should not be excluded from LTBI treatment based on NAT2 slow acetylator status, as adjustment of the isoniazid dose will reduce the risk of drug-induced hepatitis.

The decision to restart treatment of LTBI with an alternative drug regimen will mainly depend on the perceived risk of developing tuberculosis. We believe that our decision not to include estimates of the probability of restarting treatment for LTBI after a serious adverse event is justified for two reasons: 1) sensitivity analysis of the decision model showed that varying completion rates for LTBI treatment after a serious adverse event had no significant effect on the overall treatment recommendation, and 2) these probabilities are not chance based but depend on physicians’ and patients’ willingness to restart treatment (see discussion of inclusion of variables influenced by human behaviour above).

K. Fluegge further suggests including information on ethnicity in the decision model to account for variations in N-acetyltransferase 2 (NAT2) gene polymorphism (slow acetylator status), which is associated with an increased risk of isoniazid-induced hepatitis. A recent meta-analysis of 27 studies confirmed that NAT2 slow acetylators had an increased risk of antituberculosis drug-induced liver injury compared with fast and intermediate acetylators when a standard dose of isoniazid was administered (OR 3.08, 95% CI 2.29–4.15) [4]. NAT2 gene polymorphism testing is, however, not (yet) implemented in routine clinical care for patients with tuberculosis and/or LTBI. We believe that there is a role for NAT2 gene polymorphism testing in specific situations, especially when a patient has experienced an episode of severe drug-induced hepatitis, but continuation of treatment is considered essential. Test results can then be used to guide dosing of isoniazid. A randomised controlled trial found that NAT2 genotype-guided dosing of isoniazid improves the tolerability and efficacy of the 6-month, four-drug standard regimen for newly diagnosed tuberculosis [5]. While we support the clinical application of NAT2 gene polymorphism testing as described above, we do not think that inclusion in the model of a probability estimate for NAT2 slow acetylator status based on ethnicity is helpful. This is because: 1) slow acetylator status in an individual does not require a probability estimate, but can be determined with certainty; and 2) patients should not be excluded from LTBI treatment based on NAT2 slow acetylator status, as adjustment of the isoniazid dose will reduce the risk of drug-induced hepatitis.

From the authors:

We read with interest the correspondence by K. Fluegge, which discusses inclusion of additional information in our recently published decision aid for treatment of latent tuberculosis infection (LTBI) [1]. K. Fluegge suggests that the dynamic robustness of the decision aid could be strengthened by including information on 1) treatment adherence, 2) transitional alternative treatment regimens (e.g. transition from isoniazid to rifampicin after adverse events) and 3) ethnicity (as an indicator of tolerability to isoniazid based on genetics of isoniazid metabolism).

The question of how to incorporate probabilities into the decision model that are not chance based (influenced by epidemiological and clinical characteristics only), but depend on human behaviour, was considered by us in-depth when we constructed the model. The use of tailored estimates of nonadherence to LTBI treatment in a decision aid for individual patients to determine their benefit from LTBI treatment seems unethical to us. Individual patients can consciously decide to adhere (or not adhere) to LTBI treatment. We agree with K. Fluegge that measures should be implemented to increase treatment adherence, especially in vulnerable population groups who have been identified to be at risk of nonadherence. However, we do not support the inclusion of an adherence variable into our decision analysis, as it is impossible to predict human behaviour at an individual person level. Information obtained from our decision aid should be used to inform discussions between clinicians and patients to arrive at shared decision making and is thus a means to an end, not an end in itself [2]. Treatment adherence and its impact on treatment outcomes should be discussed during the clinical encounter. We have acknowledged the general importance of treatment adherence on outcomes in our analysis, by using estimates of (mean) treatment effectiveness rather than efficacy for isoniazid preventive treatment [3].

In our model, we made the simplifying assumption that patients who developed an adverse event severe enough to require hospitalisation would not recommence isoniazid treatment and this would, in turn, reduce the effectiveness of treatment in preventing tuberculosis. We agree with K. Fluegge that it may be a reasonable option to change preventive treatment after a serious adverse event with isoniazid to rifampicin. The decision to restart treatment of LTBI with an alternative drug regimen will mainly depend on the perceived risk of developing tuberculosis. We believe that our decision not to include estimates of the probability of restarting treatment for LTBI after a serious adverse effect is justified for two reasons: 1) sensitivity analysis of the decision model showed that varying completion rates for LTBI treatment after a serious adverse event had no significant effect on the overall treatment recommendation, and 2) these probabilities are not chance based but depend on physicians’ and patients’ willingness to restart treatment (see discussion of inclusion of variables influenced by human behaviour above).