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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).

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.

The simplifying model assumption that patients are not re-infected with tuberculosis was based on our own study data that showed that the risk of recurrent tuberculosis due to re-infection was only 0.1% in a population in a setting with a low tuberculosis incidence [6]. In patients with significant re-exposure to tuberculosis after completed LTBI treatment (*e.g.* household contact of smear-positive patient with tuberculosis), we would recommend repeating a course of preventive tuberculosis treatment [7].

Finally, we would like to point out that increasing model complexity by adding more and more variables can result in overfitting. In this situation, variance becomes the primary problem, while bias falls. Optimal model complexity, however, will have the smallest possible overall error (combination of bias and variance) [8]. We would also like to re-emphasise that information provided by the decision aid should be used to assist the discussion between patients and physicians, and cannot replace the clinical encounter.

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High model complexity of a decision analysis for preventive tuberculosis treatment may result in overfitting http://ow.ly/Y8erf

Claudia C. Dobler[1,2], Andrew Martin[3] and Guy B. Marks[1,2]
[1]Woolcock Institute of Medical Research, University of Sydney, Sydney, Australia. [2]South Western Sydney Clinical School, UNSW Australia, Sydney, Australia. [3]Clinical Trials Centre, University of Sydney, Sydney, Australia.

Correspondence: Claudia C. Dobler, Dept of Respiratory Medicine, Liverpool Hospital, Liverpool, NSW 2170, Australia. E-mail: cdobler@med.usyd.edu.au

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