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Reply to Hong-min et al

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To the Editor

We thank Hong-min et al for their interest in our study [1, 2]. They request clarification of the exclusion criteria of studies with fewer than 5 household contacts. We set this minimum a priori in order to avoid bias from very small studies that are likely to have poor accuracy and precision in measuring the outcomes of interest, namely, prevalence of tuberculosis disease and latent tuberculosis infection among household contacts. Our rationale was to prevent such small studies from having undue influence on estimation of overall prevalence based on random effects models. Although there may be a concern for bias in excluding small studies, this criterion applied to only 2 otherwise eligible studies [3, 4] that reported evaluation of 2 and 3 contacts of index patients with drug-resistant tuberculosis. Hong-min et al also suggest that including studies with a single source case could introduce significant heterogeneity and publication bias. While we agree such studies could introduce heterogeneity, we considered that including them reduces bias because studies from low-burden multidrug-resistant tuberculosis settings could be included without affecting the precision of outcome measures.

A formal evaluation of the quality of the included studies using the suggested scales was not conducted. However, each study was eligible for inclusion only if there were data of

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sufficient quality and completeness to measure the outcomes of interest, as noted above, prevalence of tuberculosis disease and latent tuberculosis infection among household contacts. The studies we included in our analysis were predominantly cross-sectional. Hong-min et al suggest use of the Newcastle-Ottawa scale or Downs and Black instrument, which are intended for evaluating case-control or cohort designs. One alternative might have been to devise our own quality index (eg, assigning quality "points" to studies that use a standard evaluation protocol). Such a scale would not be considered a validated tool but, nonetheless, might have helped readers interpret our results.

The issue of heterogeneity was, in part, addressed through use of a random effects model. An analysis of the sources of heterogeneity was beyond the scope of our article. We did, nevertheless, conduct various subgroup analyses and failed to identify a subgroup in which prevalence was not significantly heterogeneous (data not shown). However, we are aware of at least 1 study in which researchers are currently evaluating exactly this question (K Velen, personal communication).

Any systematic review of published literature is inherently subject to publication bias, as unpublished results cannot be systematically searched. The tests suggested by Hong-min et al offer a formal measure of publication bias but are more appropriate for use in meta analyses that measure an "effect," for which null findings (or negative studies) may go unpublished. Tests of publication bias are therefore less relevant for our study where we measured the prevalence of a disease rather than the effect of an intervention. Furthermore, 24% (6/25) of included studies reported zero secondary tuberculosis cases, suggesting that publication bias against null results was not as much of a problem for our study as for treatment studies.

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