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Title

Confounding undermines inferences of preventive therapy effectiveness among subgroups of tuberculosis contacts

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Close contacts of individuals with pulmonary tuberculosis (TB) have an increased risk of developing TB disease, however it is not known whether the effectiveness of preventive therapy varies between subgroups. We read with interest the individual-participant data (IPD) meta-analysis of observational studies by Martinez and colleagues[1], to infer preventive therapy effectiveness stratified by age, transmission rates and tuberculin skin test (TST) or interferon-γ release assay (IGRA) status. We congratulate the authors on this comprehensive undertaking, including 439,644 participants from 32 studies across diverse settings. Preventive therapy was highly effective to prevent incident TB in TST/IGRA-positive individuals and remained effective even if administered unrestricted by test status, supporting the 'treat all' strategy of TB control programmes where resource constraints limit TST/IGRA testing.

Surprisingly, the analysis found no treatment effect in the TST/IGRA negative sub-group. At face value, this suggests that treatment effectiveness is conditional on immunosensitisation. However, the authors raise the limitation of confounding by indication in observational studies, where the prescription of treatment is independently associated with the outcome. We wish to underline the substantial impact of this limitation, especially as the degree of confounding by indication may differ in each subgroup analysis. Notably, the authors do not discuss the potential magnitude of the resulting bias due to confounding, or that it is likely to be differential between subgroups. Differential confounding by subgroup undermines comparisons of treatment effectiveness between groups, which is the primary aim of the current study.

Whilst confounding by indication can be mitigated, to some extent, by confounder adjustment guided by a causal inference framework, the authors used propensity score matching but did not adjust for comorbidities, country, and index exposure risk (e.g. infectiousness of index case, proximity of contact). Moreover, preventive treatment is rarely offered to people with a negative TST/IGRA programmatically, unless they are considered to be at very high *a priori* TB risk. Numbers of participants, and reasons for, receiving preventive treatment despite a negative TST/IGRA are not provided and are not discussed by the authors, but it is likely that individuals with higher *a priori* risk received treatment. Higher baseline risk in treated, compared to untreated groups can reduce or even reverse the apparent treatment effect (figure 1).

In the overall analysis, without stratification by *M. tuberculosis* infection test, there was also no adjustment for TST/IGRA status. The smaller treatment effect seen in low (versus high) burden settings, when unrestricted by TST/IGRA status, may therefore be due to greater enrichment of the treatment group with high-risk individuals in low burden settings where better prognostic ability of TST/IGRA allows for more precise stratification of treatment[2]. Furthermore, this observed treatment effect may be driven predominantly by the larger TST/IGRA-negative subgroup in low burden settings (due to lower prevalence of test positivity). Notably, this pattern is reversed with higher effectiveness in low (versus high) burden settings among TST/IGRA-positive participants, further questioning the plausibility of the opposite observation when unrestricted by TST/IGRA status. We also note that simple subgroup comparisons in IPD meta-analyses are subject to bias due to amalgamation of within-study and across-study information[3].

Additionally, caution must be taken when interpreting the number-needed-to-treat (NNT) estimates. As the reciprocal of absolute risk reduction, the pattern of higher NNTs in low (versus high) burden settings, when unrestricted by test status, may be partially explained by lower baseline risk in low burden settings, rather than true treatment effect differences. However, the lower baseline risk in untreated groups because of confounding by indication may have led to underestimated treatment effects and inflated NNTs, particularly among children <5 years where the NNT presented (>450) lacks plausibility given this is the highest risk age group.

Ultimately, we caution that residual confounding precludes definitive conclusions regarding differential treatment effects between subgroups in this observational analysis and the results presented should not be used to inform policy decisions.

Declaration of interests

We declare no competing interests.

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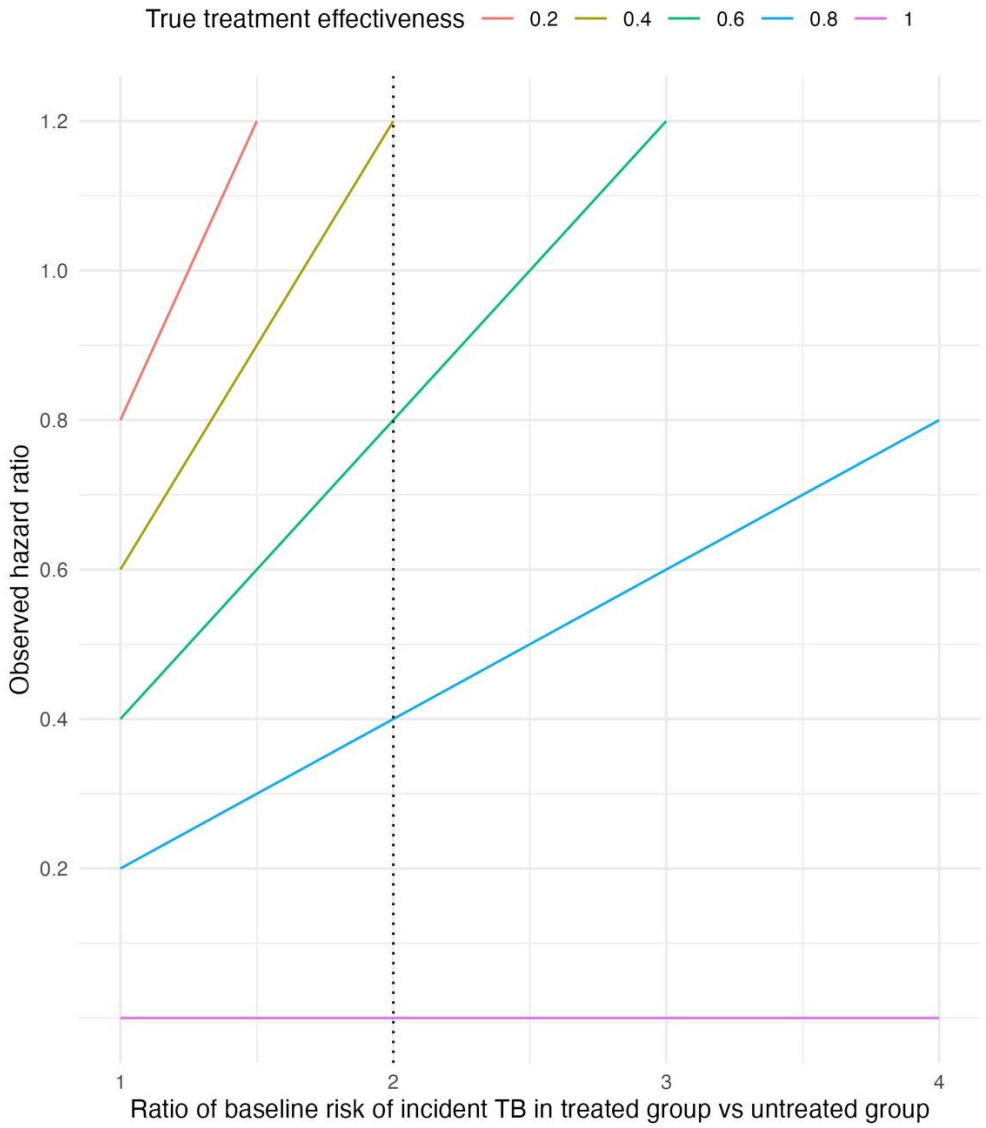

Figure 1: The effect of confounding by indication on the observed treatment hazard ratio

Confounding by indication is where the indication for treatment is independently associated with the outcome, resulting in individuals with higher baseline risk being more likely to be offered preventive treatment. We demonstrate that increasing the baseline risk of incident TB in the treated group relative to the untreated group (x-axis) increases the observed hazard ratio associated with treatment (y-axis). Doubling the baseline disease risk in the treated group versus untreated group results in an observed hazard ratio that is two times greater (dotted line).

References

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