Reviewer’s report

Title: Intensified household contact tracing, prevention and treatment support versus enhanced standard of care for contacts of tuberculosis cases in South Africa: Study protocol for a household cluster-randomised trial

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Reviewer: Ray Chen

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The previously conducted ZAMSTAR trial found that neither enhanced TB case-finding nor household level TB-HIV care reduced TB prevalence, although the household intervention appeared to be associated with a non-statistically significant reduction in TB. The current protocol builds on the ZAMSTAR study with the goal to provide policy makers with evidence to make decisions on how best to eliminate TB in line with the End-TB strategy. The hypothesis of this study is that intensified household contact tracing and treatment support will improve TB-free survival among household contacts, in particular among children. The major question that arises, then, is how this study's household intervention compares with ZAMSTAR's household intervention and whether these differences will be enough to result in a significant difference in TB rates between arms.

ZAMSTAR BMC ID protocol
Visits baseline, 2mo, EOT baseline, 1 week, 3 mo
TB/HIV education Y Y
TB symptom screen, referral for sputum exam Y Y
sputum exam for all with GeneXpert N Y
TST to all without TB N Y
HIV counseling and testing Y Y
linkage to HIV care and adherence support Y Y
Isoniazid preventive therapy Y Y

A very cursory comparison shows that the major difference seems to be provision of a sputum GeneXpert MTB/RIF for all household contacts regardless of symptoms whereas the ZAMSTAR trial only examined sputum for contacts with symptoms. This might be expected to capture those less symptomatic, which may include early active infection and those HIV-infected. Provision of TST to contacts is also a difference but a TST by itself will not affect TB rates. The difference here may actually be in who was provided isoniazid preventive therapy. Who precisely received IPT in the ZAMSTAR trial is not clearly described in the appendix document published online with the Lancet article (just states “isoniazid preventive therapy to all consenting household members”) so there may be some differences here too.

This new study is being conducted in 2 areas of South Africa: Mangaung Municipality with high rates of TB and HIV and Capricorn Health District with medium rates of TB and HIV. The study is a household cluster-randomized controlled trial to reduce TB among household contacts of index TB cases, particularly among children. Households will be randomized to receive either an intensified home screening with linkage to TB and HIV care or an enhanced standard of care, which consists of educational information, a referral letter for TB and HIV screening, and a follow-up phone call 1 week later. The primary outcome of TB-free survival
in the household will be measured at 15 months after randomization and will be done for all TB cases diagnosed as well as only for microbiologically confirmed cases.

The protocol is well written and appropriately designed to test the hypothesis. I do not have any major issues with the protocol but do have a few clarifying comments/questions:

It would be helpful to list your secondary outcomes using numbers rather than bullets since you refer to specific secondary outcomes in the protocol by number.

For your first secondary outcome about prevalence of TB infection at month 15, will you exclude those already positive at baseline?

Will you track TB treatment outcomes and IPT uptake among those diagnosed with TB (active and latent)? This could affect future TB cases among contacts (particularly IPT uptake) and could be an analysis stratification point.

Will you track HIV ART uptake among those diagnosed with HIV? Both the START and TEMPRANO studies showed that early ART prevented TB. This could be an important analysis stratification point.

Blinding of research assistants to the intervention arm at the outcome visit is a good thought, however I'm not sure how practically feasible this will be to implement. As they discuss with household members any TB or HIV events of the previous 14 months, how will they prevent household members from discussing which arm they were assigned to and whether they received IPT? In fact, collecting data about IPT and ART uptake and adherence seems like an important outcome for analysis.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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