Reviewer's report

Title: Early detection of tuberculosis through community-based active case finding in Cambodia

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Reviewer: Ellen Mitchell

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This study represents an important advance in TB control. It is one of many innovative and experimental strategies that are currently tested to resolve a pressing problem in our field – the declining rates of return from the conventional TB control strategy. It is one of the first to provide concrete information and as such it will be of great interest to TB policy makers, practitioners, researchers, and donors.

This manuscript has particular value because it mines existing routine program data to derive lessons for global TB policy making instead of relying on the artificial conditions of a controlled trial which cannot be replicated in real life. This is also its chief limitation.

The following are some observations and a series of suggestions regarding the framing and semantic/terminology situating of this scientific work.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. Is the “overall cost per case” another way of saying “the mean cost” of diagnosing all the TB cases via ACF using smear microscopy? If so, would it be possible to give separate estimates for smear + and smear neg? This seems important because ACF seems to detect more smear neg.

2. Authors may want to consider the strength of causality claim in the final ¶ of the abstract. What was the timing of this exercise in relation to the timing of the prevalence survey? Are you confident that this exercise caused the increase in awareness and health seeking behavior or was it the prevalence survey? Were any of these operational districts also survey clusters? If so, can you attribute the heightened awareness only to the contact investigation?

3. In the conclusion, the authors assert that “early case finding” (UNDEFINED) finds vulnerable groups (plural). Is ECF equivalent to contact investigation and ACF (active case finding)? How does this relate to Enhanced Case Finding, (the other ECF)? Authors may want to be very precise with the terminology since it causes confusion to use them interchangeably and dilutes the meaning of each.

4. These data indicate that (slightly) older TB patients are found through ACF, can you really conclude that therefore “patients from vulnerable populations and
“age groups” are found? This seems to be a slight stretch from a single finding to multiple groups.

5. To me it is noteworthy that there were not more differences found—gender, children, etc. (did you look only a children to see if they were picked up more with ACF?). I am curious as to why patients under 15 were excluded from the study? Please elaborate on why more differences were not found.

6. The authors do not say why there have been “general recommendations against community-ACF” in the past, and the reader is left wondering why WHO would have opposed such a logical step.

7. Is this correct that that there was a single CXR reader for all cases? Is it correct to assume that PCF patients did not get a CXR? If so, it may be clarifying to readers to state this explicitly. It is not clear to this reader how PCF patients were diagnosed.

8. Figure 2 would be easier to appreciate if it were collapsed into one graph (like Fig 3) because the reader can compare within age stratum, which is the intended message of the image.

9. The conclusion is that further research is required to determine if benefits outweigh the costs. If that is so, then how can you simultaneously suggest that cost effectiveness is established? I would suggest not to call for more cost effectiveness research, but rather to propose more research on the impact of ECF/ACF on reducing on-going transmission by detecting and treating early silent transmitters.

a. How do the authors know that the initial defaulter rate is already low in Cambodia? The complexity of initial defaulters is that they are rarely recorded in the TB treatment register and so it is practically impossible to gauge how large or small the magnitude of the problem is by looking in the TB tx register unless one compares a TB suspect register (does Cambodia maintain a TB suspect register?) against a lab register. The citation given as evidence that Cambodia’s initial defaulter problem is small is the regular WHO annual report, which does not report such special studies.

10. Why is HIV status not included in Table 1 – too low numbers??

11. Why are women not given as a category in Table 1? Why are the PCF-post ECF patients not listed in Table 1 to allow for comparison?

12. Would the authors consider producing a comparative table of socio-demographic characteristics of TB suspects identified by the 2 methods, similar to Table 1? This could be instructive to readers to help to perceive some of the types of persons who are not seeking care.

13. The authors say that ethical clearance was not required and therefore it was not done. Wouldn’t it be slightly more appropriate to also clarify that because no identifying information was collected there was also no risk of deductive disclosure or social or physical harm to individuals that is why no ethical
clearance was sought?

14. A little additional detail on the statistical methods would be illuminating for the reader. Much of the data are ordinal and not normally distributed. Would chi-square be the best test in this instance?

- Minor Essential Revisions to be done:

1. The definition of ACF given in the intro “systematically looks for cases of TB, rather than waiting for people to develop…” is vague and appears to be an adapted version of the Royal College of Physicians standard definition. More problematically it overlaps with the definition of “enhanced case-finding”. To me authentic ACF implies two related pre-conditions:
   • No health seeking whatsoever on the part of the patient.
   • Sample collection on the spot – i.e. at the home.

A prevalence survey is ACF. The intervention described in this paper does meet part of the 2nd criterion because of the mobile CXR, but not the first. In my opinion, the intervention described in the manuscript is rather an elegant form of contact investigation, i.e. systematic mobilization of TB contact s to promote health seeking, via traditional facility-based diagnosis. or perhaps ECF: “enhanced case finding” but not ACF per se. When the authors use the term “campaign” in the last Para of the discussion, I think they are correctly describing the intervention and its social mobilization dimension.

2. Passive and active case finding are not dichotomous as implicitly suggested in the manuscript but rather points on a continuum of patient effort. The diagnostic mobilization contact investigation intervention described in the manuscript falls somewhere in the middle of the effort spectrum, because symptomatic persons were screened locally but still needed to be motivated enough to travel to the facility and go through the traditional systems for diagnosis. I recommend to re-title the paper and to use the term “Enhanced Case Finding” or “contact investigation” throughout to describe the intervention that was conducted.

3. I think this ECF study describes an approach that is very novel and important and should not be subsumed in the ACF category, because it is very likely that in systematic lit review of ACF studies, we will find that ACF is NOT cost effective for most NTPs. However, a very strategic, middle-ground approach, such as the one described in this manuscript, is clearly feasible, has high yield, and is probably cost effective. Lumping this innovative approach in with other miscellaneous forms of ACF will make it harder to convince policy makers of its value because it will tar with the same brush of cost ineffectiveness.

4. Please tell readers what were the proportions of refusal and lost to follow up at each step on the diagnostic pathway if possible.

5. Please clarify what is meant by “were involved” the first sentence of the result section. You call these 33,631 TB suspects, but how many were symptomatic?
6. Please recalculate the NNS according to first screening step i.e. symptom screen. As I understand it,

a. The first screening step was a symptoms screen (n=?).
b. Then CXR (n=33631)
c. Then sputum microscopy was done (n=5844)
d. Then 885 cases were found
e. So the real NNS would be = [885/# of symptomatics]. Not 38 (=885/33631) as stated.

1. Please also report the NNS for the particular study population also. If this unknown, perhaps give the number of villages, number or days, or number of households as some sort of proxy.

7. Since CXR seems to be the main screening tool, it would be essential to indicate what were the “predefined criteria” used to classify the CXR.

8. The term “ACF session” is new to some of us and should be defined. Is a’ session’ a particular program effort? Or is it time bound? How does it differ from the term “13 ACF activities were conducted”? Is this equivalent to “the massive ACF campaign” referred to in the last Para of the discussion?

9. “Initial defaulters” should be defined. Do the authors refer to persons diagnosed who never start treatment (i.e. standard definition) or those who began treatment and then desisted?

10. In addition to the p values given in the abstract, it would be instructive for readers to have the 95% Confidence Intervals for the estimates for the main comparisons. This additional information helps readers to determine for themselves if the differences are clinically and/or programmatically meaningful or not.

11. Rather than say “high treatment success rates”, which takes up a lot of text characters in the abstract and is not optimally informative, just give the figures-94.6% and 95.2%.

12. The only study limitations mentioned are issues that I do not find to be limitations at all. For example, the issue of quality of smear. Since it applies to both PCF and ECF equally, I fail to see why it would be a limitation in a comparative study. I suggest striking this text and instead focusing the discussion on the other limitations. To my mind, the potential limitations of this study are as follows:

a. I suspect that no accurate records were kept on the number of TB suspects identified by symptom screen at the household level, so the universe and the refusal rates are unknown. This is the major limitation and should be acknowledged because it means that yield cannot really be calculated.
b. The differences in the sensitivity and specificity of the 2 different diagnostic
algorithms applied to ECF and PCF suspects are a potential confounder, but this is only opaquely referred to in the limitations section.

c. Day-time home-based mobilization will naturally find fewer persons in the economically active age group, and this study is no exception. This selection bias slightly undermines the argument about ECF detecting older age groups. Night-time home based mobilization might find just as many younger TB patients to void the difference detected.

d. This ECF effort still may have missed TB cases among symptomatic suspects who could not travel or would not travel to the facility. Therefore the true benefit of ECF may be underestimated by the logistical requirements.

e. The exclusion of children probably diluted the beneficial effect of ECF as there is good evidence from the Cambodia DHS that families do not routinely bring children with cough and ARI symptoms to care in a timely manner.

13. One of the conventional arguments against ACF has been that the treatment completion will be low due to low motivation, lesser severity, etc. etc. This study seems to provide powerful evidence against that criticism. This could be better highlighted more explicitly in the discussion and the abstract.

a. Tell readers explicitly what were the treatment outcomes of the sub-group of initial defaulters in particular. If they were high, then it is recommended to state this, and to strike the whole ¶ that begins with “on a negative note” if study results were not negative.

14. Please also consider to include an estimate of the cost of detecting a case through the routine passive system if possible, calculated by the same method. Include this in the abstract. This would then justify the use of the term “cost effective” in the conclusion. Include a foot note to indicate that a rigorous measure of cost effectiveness of ECF vs. PCF would be calculated in DALYs. Such a task is currently impossible because it would have to take into account the likely impact on reduced transmission, which cannot be measured cross-sectionally.

15. Since this excellent work may wish to be replicated elsewhere, it would be good to have supplemental document describing the programmatic details of the intervention.

a. Were community leaders involved?

b. Would transport reimbursement have worked better than rounding up suspects?

c. Was it one CXR per patient? Which view(s) were taken?

d. Were CXR read on the spot and then again later?

16. The authors have done a solid job reporting, but can do even better to “market” the positive results to program implementers by adding a paragraph discussing the feasibility of this exercise.

a. How many staff did it take?
b. How was the performance of the mobile CXR units?
c. Did it cause any problems for the lab or could the lab handle the extra work?
d. How did the community respond? What about stigma?
e. When I first read mobile CXR, I assumed it was at the household, but reading it again, I see maybe it was at the facility? where was the mobile CXR parked?

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

"Minor issues not for publication"

The authors do not use ‘the Oxford comma”, which sometimes makes the sentences more complex to interpret than necessary. Suggest adding throughout when listing 3 or more items.

Intro ¶ 2- substitute the word “symbols” for the word “symptoms”.

The Intro is very standard, and has no journalistic “hook” to engage the reader and pull them into the text. This is a burning question in our field but the tone is clinical and could be a bit more enticing.

Intro ¶ 4- substitute “could contribute to” for ‘would present’- less presumptuous of a positive outcome.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.