Reviewer's report

Title: Influence of environmental exposure on response to antimicrobial treatment in pulmonary Mycobacterial avium complex disease

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Reviewer: Melissa Nyendak

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Major Revisions:
Drs. Yutaka et al. seek to better understand if environmental exposure directly affects the antimicrobial response in MAI pulmonary disease in non immune compromised patients.

They recruited 72 HIV negative patients with MAC and these individuals underwent a standard survey about risk factors for MAC. They were provided standard 3 drug therapy with clarithromycin, rif and EMB. We are not told, but assume medical adherence to this regimen.

Although the patients were recruited prospectively, this study is essentially a retrospective case control study, looking at patients that improved on therapy and the characteristics that were noted in each group.

1. The question is defined – they hypothesize that environmental exposures lead to more MAC (they have shown this before) and will influence antimicrobial treatments and response.

2. The methods are ok, but there is no information on whether or not all of the cultures were macrolide susceptible. This could be a major confounder for relapse. I found the terminology confusing: sputum conversion to me sounds like going from afb smear positive to smear negative – here the authors use sputum conversion to mean negative culture.

Sputum relapse is also confusing; they state two consecutive positive cultures are sputum relapse, but I don’t know the time interval here – is this within the 12 months of planned treatment?

Treatment success also needs a time interval – how long were patients followed to indicate treatment success. Another concern is that not all patients were tested for HIV – using ‘no obvious risk factors for HIV infection’ in my opinion not ideal as this has been shown to miss patients with HIV.

The statistics section needs to be clearer. My understanding is that the outcome variable was relapse or not/ or treatment success or not? This would be a binary outcome and there for logistic regression would be used. Need to clarify this in the methods although I do appreciate that this is mentioned in the results.
Also need to clarify what is the reference in logistic regression – in table 2. That is, negative smear (no) is the reference? The text does clarify, but the table is not stand alone without referring to the text.

3. Is the data sound?
I am unsure. We don’t have any data that tells us if patients who relapsed had macrolide resistant disease. This needs to be clarified. Table 1 tells us that 20 patients did not have sputum conversion. In their regression analysis, a lower burden seemed to fall out (negative smear) more likely to lead to negative cultures which makes sense.

Table 3 is confusing: there are 37 patients without relapse and 15 with. I thought there were 72 people in the study so the authors need to clarify where the other 20 patients are or why they are not in this table.

Again, knowing if culture/susceptibility was done will be important as a major confounder will be macrolide resistant disease.

I also would be interested to know more about why we are looking both at relapse as an outcome and then later at treatment success as an outcome? This seems duplicative since the authors state that treatment success is no relapse.

Table 4: Treatment success and patients without treatment success. How long were patients followed to define ‘patients without treatment success’? Instead of this wording, should you call ‘patients without treatment success ‘treatment failure’? Is it microbiologic failure, is it chemotherapeutic failure? There is nothing in the discussion that goes into other types of failure (were they absorbing the drug?)

For the radiographic findings – why is it characterized as (none) or (none or < 2) . Seems like this latter category is confusing (and in the discussion they talk about large cavitory lesions but these are not in the tables). I worry that there may be some confounding if the persons without treatment success had a higher burden of disease to begin with and could explain the findings.

Is there an interaction between negative smear and low soil exposure?

Minor essential revisions

This paper could be strengthened by ensuring that the two groups (relapse/no relapse) are as similar as possible prior to the analysis. The confusing way the radiographic findings are presented are also of note. Is the relapse/no relapse table and results univariate? Please clarify why this is presented with the treatment success data.

The authors might comment on the width of the confidence intervals as well, which gets at the small sample size in the groups.

It does seem entirely plausible that ongoing soil exposure in patients with
abnormal lung architecture are at risk for relapse.

With respect to the writing, while grammatically ok, with the re-write, would make sure the introduction is more streamlined.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare no competing interests