Author's response to reviews

Title: Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy

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Author’s response to reviews:

Dear editor
Thank you for valuable comments from reviewers. We hereby submit a revised version of our report of acute undifferentiated fever in India. Revisions are shown as track changes in the manuscript. Our respond to the reviewers is as follows:

Harriet Mayanja (Reviewer 1):

I find this manuscript well written, relevant and with well presented methodology, data, results and discussion. The issue of diagnosis of the multiplicity of infections in developing countries has been an enigma over the years.

This paper used a multicentre study, employing routine and gold standard blood diagnostic tests to answer the questions on prevalence and causes of AUF in India.

Overall, this is an excellent well written paper.

Minor Issues to consider

1. The HIV status of the patients is not included. This would have been useful if the data was available.

We agree that HIV status is relevant for interpretation of clinical manifestations. HIV status was recorded, and 5% were known positive, however, in this observational study HIV tests were not performed as part of the study. Clinical information including HIV status will be analysed and published later.

2. In the same vein, no mycobacteriosis was looked for in this study. In one study done in Uganda, mycobacteriosis accounted for about a quarter of the sepsis of undefined cause in an HIV population of in patients.

TB is highly relevant and a common cause of fever in India. We have looked at this previously in a pilot study of fever aetiology in India (Abrahamsen et al. BMC infect Dis 2013. Fever in the tropics: aetiology and case-fatality) were tuberculosis was the most common cause (19%) and mean fever duration was 5 weeks. However, in the present study we wanted to investigate acute undifferentiated fever and restricted the inclusion period to two weeks, in order to focus also on acute life threatening infections other than tuberculosis.

3. It would have been useful to group the diseases by clinically relevant age groups, e.g. the very young, below 5 years and the older population above 60 years, as the prevalence and issues of diagnosis have different challenges at these extremes of age.

Thank you for this suggestion. Grouping by age groups is informative, and we have included this in table 2. Children < 5 were not included in this study.
4. The authors did allude to the complexity of differentiation between active disease, past disease, or asymptomatic carrier issues, and described this well in the discussion.

In a clinical setting these are areas that can be addressed by the attending clinician. The same applies to co-infection, as not all infections indicate disease; this can be emphasized more.

A key message in this article is to inform the clinicians about the need to interpret diagnostic tests in a clinical context and be aware of their limitations. We thank you for this comment, and have included a sentence underlining this in the discussion.

5. This paper made me excited about a possibility of multiplex POC serology tests for common infections in high endemic countries. The authors could probably point to this in the discussion - as this may be the future of infection diagnosis in our settings.

The paper underlines the need for accurate and affordable diagnostic tests in resource poor settings. Tests that already exist such as sensitive and specific PCR methods should be made available, and tests should be designed to meet the needs in these settings. Future tests should be discussed in the context of the enormous problem with inequality and resource limitations and have not been included in this paper.

Archana Sud, MD, FRACP (Reviewer 2) The study is not terribly well designed nor is the working hypothesis very clearly stated.

1. It is not clear why these particular pathogens were picked for testing as cause for an acute febrile illness. Whereas Malaria, Dengue and Chikungunya serologies are relevant are there any data to suggest leptospira and scrub typhus as common diagnoses in this setting?

Leptospirosis and scrub typhus were selected as potential causes of acute undifferentiated fever based on the awareness by clinicians in our study group that they are common causes of acute severe disease among hospitalised patients in India. The impression that they are underreported based on the gap between clinical experience and reported cases, was a motivation to investigate the prevalence of these infections.

2. There is no mention of a full blood count, liver functions, chest X ray, a urine culture; all of these would be part of routine investigations for an undiagnosed acute fever and aid and guide etiological testing.

Clinical and biochemical findings will be analysed and presented in future publications, but we chose to show the results and limitations of gold standard diagnostic tests in a separate paper in order to emphasise these findings.
3. Relying on PCR for diagnosing malaria without any mention of thick and thin films is unusual.

Malaria PCR is more sensitive than microscopy, and will pick up both asymptomatic and clinical cases. This has been discussed, and results from microscopy has also been included in this paper (table 4), used as a more strict definition of clinical malaria. Malaria diagnostics has been shown more in detail in a previous publication, which is referred to in the paper (Haanshuus et al. A high malaria prevalence identified by PCR among patients with acute undifferentiated fever in India. PloS one 2016).

4. Absence of convalescent serology perhaps underestimates some of the etiological diagnoses tested for. Under study conditions ideally convalescent serology should be done.

We fully agree that convalescent serology would have been extremely valuable. Unfortunately this was not possible to include in this study due to practical and financial issues. This reflects a real life situation in resource poor settings, which we also have pointed out in the discussion.

5. Cross reactions should be considered when multiple etiologies are being suggested on basis of serology.

We agree that cross reactions should be considered when multiple aetiologies are detected by serology, and we feel that this has been thoroughly discussed and pointed out in the paper.

6. The discussion is really long winded and as such an elaboration of the already stated results—a focus of interest would be good.

We wanted to discuss the importance of interpreting diagnostic tests in the light of potential background positivity, cross reactivity and subclinical infections, and at the same time present the results as prevalence of etiologies with these limitations taken into consideration. The discussion of this had to be a little long. We therefore hope that we can keep the discussion as it is.

Pandey Kishor, PhD (Reviewer 3):

This paper describes the Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. This paper is interesting, and could be useful for differential diagnosis in developing countries. The manuscript is well written. I have the following minor comments.

1. There are many tables in this manuscript. I suggest author to remove the table 1 for demographic characteristic of each study sites. Some of the information of this table in also included in table 2. The table is not informative and description given by author in result section is enough.
We would like to keep table 1, since it shows the distribution of rural versus urban population at the sites relevant for prevalence of infectious diseases, and that this differs. It also shows the gender inequality among hospitalised patients which is a known problem in India, and that this differs between sites.

1. In table 4, author compare different serological with malaria and bacteraemia. If malaria PCR is gold standard method, why next column author keep malaria PCR+Microscopy? It makes the table more complicated.

We agree that tables should be informative and kept simple. However, in table 4 we show the important point that serology is equally common among malaria positive and negative cases, also when we use the strict definition of PCR+microscopy positive that potentially rule out some subclinical cases detected by PCR only. We would therefore like to keep this information in the table.

Regards

Kristine Mørch, MD, PhD