Author’s response to reviews

Title: Title: Risk Factors for Acquisition of Scrub Typhus in children admitted to a tertiary care centre and its surrounding districts in South India: A Case Control Study and Vector Survey

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Author’s response to reviews:

Reviewer reports:

Ranjan Premaratna, MD FRCP (Reviewer 2): Risk Factors for Acquisition of Scrub Typhus in children: A Case Control Study and Vector Survey

Thank you for sending the revised paper for review. Authors seem to have addressed some of the points raised in the previous review. May I suggest following essential revisions for it to be suitable for publication in BMC Infectious Diseases.

Change Title to read as: Risk Factors for Acquisition of Scrub Typhus in children admitted to a tertiary care centre and its surrounding districts in South India: A Case Control Study and Vector Survey.

We have changed the title as suggested.

I am concerned over the methodology in selecting controls;
As authors have agreed, there seems to be a methodological error in selecting the study populations. The cases seems most probably representing a higher socio-economic background due to many reasons. [if authors have included a table to highlight the true numbers of cases and controls with their social status this error would have been clearer]; "belonging to a middle or high socio-economic stratum, father having a skilled occupation, living in a house with plastered walls, living in a house with more than 2 rooms, having furniture to sit and cots for sleeping, having piped drain for sullage, having a toilet, owning a pet, using sitting on furniture, usually sleeping on a cot, and going to school by a vehicle." Therefore inclusion of above data in the discussion may not be appropriate; authors may consider removing the univariate analysis based discussion.

The background information on cases and controls including SES, the father having a skilled occupation, the highest education in the family being high school are included in Table 1. All these three parameters were of a higher proportion among the cases.

As suggested by the reviewer, we have removed the discussion based on univariate analysis and confined ourselves to only discussion based on multivariate analysis.

An inclusion of a map to show the geographical region highlighting the water bodies etc and indexed patients would be helpful. "The presence of a water body within 100 meters of the house"; authors should highlight what these water bodies are; there can be garden ponds in affluent houses; or are they water streams? Reservoirs? Paddy field related irrigation canals?

Since the cases were distributed over a large area within a radius of 80km, we did not attempt to include a map with a resolution to show water bodies within 100 metres of the houses of the cases. The water bodies were irrigation canals and small lakes. We have included this information in the results.

The argument of exposure to a mite island is likely to be valid if several patients present at the same time and when they have had an activity in a single given location or if one patient comes with multiple eschars.

The mite islands described have been areas which provide optimal environment for infected mites to thrive. We believe that the increased number of cases near water bodies represents such islands where infected mites thrive thereby transmitting disease to children.

The acquisition of scrub typhus through pets goes with the same argument; as given in authors reply: "The transmission of scrub typhus is from the bite of a chigger infected with Orientia
tsutsugamushi. The chigger seeks a mammalian host and humans are accidental hosts. Transmission does not occur from a rodent to human. Instead, humans get infected instead of a rodent. Hence, exposure to a rodent on the way to school does not matter to transmission.”

We agree that scrub typhus cannot be transmitted from a pet to a child. However, the presence of a pet in the house may increase the presence of mites in the vicinity of the house. This could offer an explanation to the increased risk of scrub typhus among those who owned pets. We have added an explanation in the discussion.

Vaddambal Gopalakrishna Manjunath, MBBS, DCH,DNB (Reviewer 3): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.Vaddambal Gopalakrishna Manjunath, MBBS, DCH,DNB (Reviewer 3):

1 In statistical methods - Please specify- Is multivariable or multivariate analysis was used as there is difference between these two, though it is used by some researchers interchangeably Multivariate analysis was done.

--accepted.

2 Whether vector survey was done in house hold of controls? It appears that vector survey was done only in and around the household of the cases.

Vector survey was done only in and around the household of cases.

Reviewer's comments

--Vector survey in household of the controls would have been useful as it would have given more valid data to calculate risk of infection. Rodent density may differ on various factors (e.g., socioeconomic status, storage of food grains, and type of construction of house) which may influence the vector load.

The vector survey was not part of the case control study. In adult studies, occupation was an important determinant in the acquisition of scrub typhus. Since this study was on children we hypothesized that children could acquire scrub typhus in the vicinity of their homes and did the
vector survey to determine whether mites that transmit scrub typhus were present in the vicinity of their homes.

3 there is an error in table 1 in calculation of percentage

Thank you for pointing out the error. The percentage has been corrected from 61.7 to 64.1 for the category highest family education at least high school.

--accepted.

4 Please specify whether multinomial or multivariate logistic regression was used. If multinomial better to define as adjusted odds rate instead of odds ratio.

Multivariate logistic regression was used.

--accepted.

5. Though it appears there are few risk factors with increased odds rate, these has to be biologically plausibility. eg, skilled profession of father, going to school by vehicle. It would have been ideal to have the data about distance and time of travel to reach school, type of school dress/uniform (limbs exposed or not)

We agree that skilled profession of father and going to school by vehicle are surprising to be among the risk factors for increased risk of scrub typhus. We believe it is because of intrinsic bias in patients with a higher SES accessing health care in a tertiary care hospital, whereas the controls were neighborhood controls. We intentionally used neighborhood controls to study the effects of the micro-environment around the houses and the differences in the behavior of children

Reviewer's comments

--Is there any data about the SES of cases and controls? As pointed out by authors cases appear to seek health care at tertiary care centre. Is there any date showing the difference between the healthcare access behavior of cases and controls? Any data regarding the time spent playing outside the house in open ground, sleeping on the mat outside the house etc as these may expose the child to chiggers. These can be listed as few limitations

The background information on cases and controls including SES, the father having a skilled occupation, the highest education in the family being high school are included in Table 1. All these three parameters were of a higher proportion among the cases.
We do not have data on the healthcare access behaviour of cases and controls. We have included a question on whether the child played outside in the open ground. The duration was not asked. The OR was $0.42(0.14, 1.23; p 0.115)$ on multivariate analysis and was not statistically significant. Sleeping outside the house was asked as a question. We have now included the result in Table 2 in the child’s behavioural factors. The OR was $0.99(0.23, 4.24; p 0.991)$ and was not statistically significant. We have included the absence of information on the health seeking behaviour of cases and controls as a limitation.