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

Authors:

Winsley Rose (winsleyrose@cmcvellore.ac.in)
Gagandeep Kang (gkang@cmcvellore.ac.in)
Valsan Philip Verghese (valsan@cmcvellore.ac.in)
Sadanandane Candassamy (cs_anandane@yahoo.com)
Prasanna Samuel (prasanna.samuel@cmcvellore.ac.in)
John Jude Antony Prakash (prakjaj@yahoo.com)
Jayaprakash Muliyil (jpmuliyil@gmail.com)

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Reviewer reports:

Katia Abarca, MD (Reviewer 1): I do not have any comments to author.

The manuscript meets the scientific requirements, has methodological quality (including ethical aspects, rodents sampling, controls selection and statistical analyses) and conclusions are pertinent.

Authors recognize the limitations of the study. Conclusiones could be useful to prevent scrub typhus in children in India.

Note: There is one mistake in the number of the Table 3 in the text in Methods (says Table 2). Figures legends: there are legends for 3 figures instead of 4 (Map legend is missing), the numbers in the text does not match with the figures.

Thank you for pointing out the error in Table 3. The error has been rectified. There are only 3 figures. The map has been removed as it does not add too much to the manuscript.
Ranjan Premaratna, MD FRCP (Reviewer 2): Review of article entitled: Risk Factors for Acquisition of Scrub Typhus in children: A Case Control Study and Vector Survey

Thank you for sending the above article for review. Authors have carried out the study over two years to identify risk factors for scrub typhus in children using index cases who are children less than 15 years with confirmed scrub typhus admitted to a tertiary care hospital (CMC) and compared relevant risk factors with age matched controls selected from the community in the vicinity of the index patients.

I have following concerns over the outcome of the study.

Authors seems to have collected parameters that probably represent of socio-economic status of the household rather than their detailed behavioral patterns; with the argument that age match would include a study sample with similar behaviors. However illnesses such as scrub typhus is linked with exposure risk; such as bushes, scrub land etc. Therefore, a study that look into childrens' behavior in greater datail; ie how much time they spend in the garden / in agriculture activities / fields/ where they play, the school environment, types of sports they are involved in and garments they wear during such activities would have been more useful.

We have collected data on the children’s behaviour based on the usual behaviour patterns of the children in this region. Most households don’t have an organized garden, school environment is similar for all children and children wear uniform clothes to school. Hence we did not collect such data. We collected data on the immediate surroundings of the house especially with regards to scrub vegetation around the house and presence of a water body. The parameters that we assessed were based on a preliminary pilot survey done by the investigators.

Although the sex match has not been carried out, probably presuming multivariate analysis would not influence the final outcome, I am under the impression that authors should have selected a sex matched controls. This is because, the garments they wear (female / males) may have an influence on acquisition of vector borne illnesses such as scrub typhus.

58.4% of the cases and 62.3% of controls were males. In a much larger series on 431 cases of scrub typhus published by us (Ref. J Trop Pediatr. 2016 Oct;62(5):415-20.), 55% were males. Since we did not find a significant preponderance of scrub typhus in males or females, we did not control for gender.
They also discuss that, the index patients would represent a more affluent and a biased sample as this sample has been obtained from a tertiary care hospital (CMC), probably this fact must have contributed to the outcome. What is the likelihood that the vehicles they use to travel to school would get exposed to small domestic / wild rodents?

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.

The discussion should be mainly on the outcome of multivariate analysis rather than the univariate analysis and conclusions should be arrived at based on such analysis.

We have indicated in our discussion that though some of the factors were significant on univariate analysis, they were not significant on multivariate analysis. Majority of the discussion is based on multivariate analysis.

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.

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.

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 atleast high school.
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.

5. Though it appears there are few risk factors with increased odds rate, these has to be biologically plausibility. e.g., 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 neighbourhood controls. We intentionally used neighbourhood controls to study the effects of the micro-environment around the houses and the differences in the behaviour of children.