Original Article

"Is it time to initiate scrub typhus surveillance in Karnataka?"—Lessons from a seroprevalence survey in a rural district

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Abstract

Background: Scrub typhus, caused by *Orientia tsutsugamushi*, is a commonly occurring, but underdiagnosed rickettsial infection in India. Considering the high incidence of scrub typhus among patients with acute febrile illness in the hospital setting and the paucity of community seroprevalence studies, we aimed to estimate the prevalence of scrub typhus in the community in the Bengaluru Rural District. **Methods:** A pilot cross-sectional survey was conducted between October and December 2022 among eligible asymptomatic adults from five randomly selected villages of the Bangalore Rural District after obtaining written informed consent. Serum immunoglobin M (IgM) and immunoglobin G (IgG) antibodies were tested using the respective enzyme-linked immunosorbent assay (ELISA) kits from InBios International Inc, Seattle, USA. Seroprevalence was defined as positivity to either IgG or IgM antibodies or both. **Results:** The study reported a seroprevalence of 8.9% (95% CI 4.8%–14.7%) among 146 asymptomatic adults. The IgG and IgM antibodies were positive in 7.5% and 2.1% of participants, respectively. **Conclusions:** A community seroprevalence of 8.9% warrants further epidemiological surveys and surveillance in the context of climate change, variable clinical presentations of scrub typhus, and the possible need to include this disease in the clinical practice algorithm in the primary care setting. We recommend study designs with "One Health" lens to monitor the trend of this re-emerging public health problem.

Keywords: Adult, India, Orientia tsutsugamushi, Rickettsial disease, rural seroprevalence, scrub typhus

Introduction

Scrub typhus is the most common occurring rickettsial infection in India.[1] It is a febrile illness caused by *Orientia tsutsugamushi*. The immune response to scrub typhus involves cellular and humoral immunity (immunoglobin G (IgG) and immunoglobin M (IgM)) and is complicated by the great antigenic diversity of *O tsutsugamushi*. The infection is transmitted by the larvae (chiggers) of trombiculid mites which infect mammals as incidental hosts and is influenced by a complex ecology.[2]

Scrub typhus is known to be endemic in a region known as the "tsutsugamushi triangle", which includes the Indian subcontinent.[3,4] Epidemiology studies indicate that scrub typhus occurs all over India. Cases were reported from Maharashtra, Tamil Nadu, Karnataka, Kerala, Himachal Pradesh, Jammu and Kashmir, Uttaranchal, Rajasthan, West Bengal, Bihar, Meghalaya, and Nagaland.[5-8]

We did a literature review to understand the community seroprevalence scrub typhus in India. To identify relevant

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articles, two databases PubMed and Google Scholar were utilized. PubMed yielded 585 studies and Google Scholar contributed 14 studies. After removal of duplicates (16), and screening of title and abstract (564), twelve studies were accessible with full texts. Data extraction was conducted on six pertinent studies from this subset. Among the relevant studies, five seroprevalence studies were conducted among healthy adults in a community setting and one study was conducted among blood donors. There were no community seroprevalence studies from Karnataka.

Literature review showed varied prevalence with seasons (peak of the disease is reported between July and February), occupation, literacy, and socioeconomic status.[8,9]

Scrub typhus is known to have early nonspecific symptoms which may be confused for a viral illness, malaria, or bacterial illness. The presentation usually begins with fever, chills, headache, cough, nausea, vomiting, myalgia, and skin rash. However, at times, the disease may have life-threatening complications with a high mortality, such as myocarditis, pneumonia, acute kidney injury, meningoencephalitis, gastrointestinal bleeding, and multi-organ dysfunction syndrome.[10] It is likely that many patients with scrub typhus present with early symptoms to the outpatient setting before the need for acute care arises.[11] Changes in disease epidemiology and emergence in a geographical area are of importance for general practice as family physicians are likely to be the first contact for any infection.

Scrub typhus is still an underdiagnosed disease in India.[1] Most published literature has described positive cases reported from hospitals in different parts of the country. The vast variability of clinical features of Rickettsial diseases makes it a difficult diagnosis. They also have a high fatality rate when they are not diagnosed and appropriately treated.[1]

There is paucity of studies to understand the true prevalence of this disease and its changing trends.

Even though there were limited studies in Karnataka, we have noticed a high incidence of scrub typhus in our hospital setting (400 bed multispecialty urban hospital). Among the clinical samples received in the main hospital laboratory for IgM antibody testing from October to December 2022 from adult patients, the incidence was 19.7%. Among them, 92% were admitted and 39% were critically ill at the time of testing. Hospital incidence may indicate change in disease epidemiology but may not be truly reflective of endemicity of scrub typhus in the locality. Community prevalence studies are necessary to understand the burden and changing trends of the disease. The Community Health Division of the hospital has been providing curative and preventive health services through a rural health center and network of mobile clinics to residents of Bangalore Rural District for over a decade. Hence, we aimed to estimate the seroprevalence of scrub typhus in the community in the Bengaluru Rural District.

Materials and Methods

We conducted the seroprevalence study in Bangalore Rural District which is located in the southeastern part of Karnataka and lies between the latitudinal parallels of 12 15' N and 13 35' N and the longitudinal meridians of 77 05' E and 78 E. It is reported to have a maximum temperature of 33.6°C and minimum temperature of 15°C, with has two rainfall seasons, one of which is from October to December, and vegetation which is of the deciduous jungle type.[12,13]

A cross-sectional serosurvey was conducted among healthy adults (18–60 years) between October and December 2022 in five randomly selected villages of Bangalore Rural District, namely Alur, Bettanahalli, Duddanahalli, Thindlu, and Jalige. We used a simple random sampling technique to recruit patients using the voter's list in the villages as the sampling frame. Those with a history of fever within the last 2 weeks were excluded.

All samples were collected after taking an informed consent from the participants. Blood was collected in gel vacutainer tubes and transported to the hospital laboratory by storing on ice within 4 to 5 hours after collection. The serum was separated and stored at minus 70-degree centigrade till the assays could be run.

Enzyme-linked immunosorbent assay (ELISA) was performed to detect IgM and IgG antibodies using the respective Scrub Typhus Detect ELISA kits (InBios International Inc, Seattle, USA). The kits estimate the antibodies in human serum to O. *tsutsugamushi*-derived recombinant antigen. The IgM ELISA has been described to use a mixture of recombinant p56-kDa Karp, Kato, Gilliam, and TA716 strain antigens.[14] The standard procedure as described in the kit insert was followed. Within-run repeatability was performed on 10% of the samples tested.

We used an optical density (OD) cut-off value greater than 1 for the IgM ELISA which is reported to be 95% sensitive and 100% specific for diagnosis of scrub typhus in a recent study in India.[15] We used an OD cut-off value greater than 0.5 for the IgG ELISA as used in a previous study.[16] The testing was performed in the hospital laboratory, which is accredited according to the ISO 15189:2012 standards by the National Accreditation Board for Laboratories, India (NABL).

A risk factor questionnaire was also administered to the participants by the Community Health Team in the local language. The questionnaire included questions related to their occupation (agriculture, animal husbandry, and owning of livestock) living conditions (number of people in the house), and practices (use of footwear, open defecation, and bathing).

This study was approved by the Institutional Review Board of the hospital (Approval No. BBH/IRB/2022/029).

Results

Among the 148 eligible participants, two were excluded during analysis because of incomplete data and inadequate blood sample. The age ranged from 18 to 47 years, and 55.5% were females. Among the population studied (n = 146), 51% lived in a household with less than five members, 41% were engaged in agriculture, 51% owned livestock, and 33% had a practice of going into the fields to graze the cows. No one practiced open defecation.

Seroprevalence in the community was calculated as 8.9% (95% CI 4.8%–14.7%) (n = 13) using positivity in either IgG or IgM or both. The IgG antibody was positive for 7.5% (n = 11) of participants (n = 146), and the IgM antibody was positive in 2.1% of participants (n = 3). One individual was positive for both IgM and IgG antibodies.

Age, gender, number of people in the house, occupation, possession of livestock, and practice of going to graze cows were not associated with seroprevalence ($P > 0.05$).

Discussion

We report a seroprevalence of 8.9% for scrub typhus among asymptomatic adults in Bengaluru Rural District. This falls within the wide range of seroprevalence reported in India. In Tamil Nadu, the seroprevalence varied between 2% and 26.4% in different geographic areas.[17] A more recent serosurvey in northeast India found an overall prevalence of 0.8% for scrub typhus.[16] Two earlier studies showed a higher seroprevalence (31.8% in Vellore, Tamil Nadu, and 55% in Arunachal Pradesh in northeast India).[18,19] "Mite islands" which are known to expand and contract over time based on many factors, such as climatic conditions, and topography is reported to be a factor in explaining such variations.[2,20] Occupation, hygiene, and lifestyle also would contribute to the variation.

Significant variation in the burden of scrub typhus is seen in India (4%–96.8%) and globally (1–96.9%) in published literature.[8,21] Almost all the studies were incidence studies that were conducted in hospital settings among symptomatic patients in whom scrub typhus was suspected. Tamil Nadu had the highest density of cases in India at 37.6%, and Karnataka had a lower density at 8.8%.[8]

The variation of incidence may be attributed to differences in endemicity in different geographical areas, diagnostic modalities, and patient selection methods used for conducting studies.[4] The cut-off OD values used in different studies vary widely between studies and locations and would have contributed to the differences in the stated seroprevalence in different studies.[22]

The incidence of scrub typhus (19.7%) in our urban hospital setting during the same period is higher than the community seroprevalence. This can be attributed to the fact that testing in the hospital was conducted in clinically suspected scrub typhus patients as compared to healthy adults in the community seroprevalence study. The difference could also be related to a floating population visiting the hospital from many districts and towns. The incidence in our hospital is like other hospital studies (mean estimate of 25.3% among those with acute undifferentiated febrile illness).[8]

This study has many strengths. Firstly, to the best of our knowledge, this is the first community-based seroprevalence study of scrub typhus from Karnataka. This study is of immense importance when we look through the lens of climate change and one health approach. This study can form a base for future studies and to monitor the changing trend of this infection in the community.

The study has few limitations. Firstly, we used cut-off values based on the published literature rather than deriving OD cut-off values for the ELISA tests which is specific to this geographic region. Another limitation is that we did not elucidate the previous history of a diagnosis of "scrub typhus" or an "eschar" during the interview. However, this is unlikely to have any implication on the estimated seroprevalence.

Based on the findings of our study, we propose few recommendations. A community seroprevalence of 8.9% warrants further epidemiological surveys and surveillance in the context of climate change, antigenic heterogeneity of O. tsutsugamushi, diagnostic variability, overlapping clinical presentation of scrub typhus, and its high-case fatality rate. Regular surveillance may also help to understand the changing trend of the prevalence and to necessitate appropriate public health action. Studies, including both symptomatic and asymptomatic individuals in the population, can yield overall burden of the disease. Incorporating a possible diagnosis of scrub typhus in the clinical practice algorithm would be prudent when there is increased regional endemicity as the clinical spectrum of scrub typhus can vary from a mild fever to life-threatening complications. We recommend study designs with "One Health" lens which is collaborative, multisectoral, and transdisciplinary to monitor the trend of this re-emerging public health problem.[23]

Conclusions

We report a community seroprevalence of 8.9% of scrub typhus among healthy adults in Bengaluru Rural District during the months of October to December 2022. In the context of changing climatic conditions and re-emergence of scrub typhus globally, regular surveillance is a required from this and wider geographies especially from the countries in the "Tsutsugamushi triangle" to monitor the changing trend in the community.[4] A clinical practice pathway to cater to such changing trends at the primary care level would be an important mechanism to provide early treatment. A "One Health" approach to further evaluation of the seroprevalence would play an important role in understanding the disease and devising control strategies for this re-emerging public health problem.

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Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the hospital (Approval No. BBH/IRB/2022/029). Informed consent was taken from all the participants before data collection.

Authors' contributions

SC contributed to the conception and design of work, supervision and validation of the blood analysis, participated in analysis and interpretation, and contributed to the writing of the article. CEG contributed to the conception and design of work, supervised data collection, participated in analysis and interpretation, and contributed to the writing of the article. TM participated in developing the study tool and statistical analysis. RFJ contributed to the data acquisition and contributed to the writing of the manuscript. All authors revised the work for important intellectual content and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

References

1. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR Guidelines for diagnosis and management of Rickettsial diseases in India. Indian J Med Res 2015;141:417-22.
2. Elliott I, Pearson I, Dahal P, Thomas NV, Roberts T, Newton PN. Scrub typhus ecology: A systematic review of Orientia in vectors and hosts. Parasit Vectors 2019;12:1-36.
3. Walker DH. Scrub typhus—scientific neglect, ever-widening impact. N Engl J Med 2016;375:913-5.
4. Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of scrub typhus. PLoS Negl Trop Dis 2017;11:e0006062.
5. Sinha P, Gupta S, Dawra R, Rijhawan P. Recent outbreak of scrub typhus in North Western part of India. Indian J Med Microbiol 2014;32:247-50.
6. Varghese GM, Abraham OC, Mathai D, Thomas K, Aaron R, Kavitha ML, *et al.* Scrub typhus among hospitalised patients with febrile illness in South India: Magnitude and clinical predictors. J Infect 2006;52:56-60.
7. Khan SA, Dutta P, Khan AM, Topno R, Borah J, Chowdhury P, *et al.* Re-emergence of scrub typhus in northeast India. Int J Infect Dis 2012;16:e889-90.
8. Devasagayam E, Dayanand D, Kundu D, Kamath MS, Kirubakaran R, Varghese GM. The burden of scrub typhus in India: A systematic review. PLoS Negl Trop Dis 2021;15:e0009619.
9. Kelly DJ, Fuerst PA, Ching WM, Richards AL. Scrub typhus: The geographic distribution of phenotypic and genotypic variants of Orientia tsutsugamushi. Clin Infect Dis 2009;48(Suppl 3):S203-30.
10. Varghese GM, Trowbridge P, Janardhanan J, Thomas K, Peter JV, Mathews P, *et al.* Clinical profile and improving mortality trend of scrub typhus in South India. Int J Infect Dis 2014;23:39-43.
11. Isaac R, Varghese GM, Mathai E, Manjula J, Joseph I. Scrub typhus: Prevalence and diagnostic issues in rural Southern India. Clin Infect Dis 2004;39:1395-6.
12. About District | Bangalore Rural District, Government of Karnataka, India (no date). Available from: https://bangalorerural.nic.in/en/about-district. [Last accessed on 12 Jan 2024].
13. Bengaluru Rural, Karnataka State Envis Newsletter, Issue Number 53, 2019. Available from: karenvis.nic.in/WriteReadData/Publication/BR_V03.pdf. [Last accessed on 13 Jan 2024].
14. Blacksell SD, Tanganuchitcharnchai A, Nawtaisong P, Kantipong P, Laongnualpanich A, Day NP, *et al.* Diagnostic accuracy of the InBios scrub typhus detect enzyme-linked immunoassay for the detection of IgM antibodies in Northern Thailand. Clin Vaccine Immunol 2016;23:148-54.
15. Jain A, Jain P, Rebello SC, Todaria M, Kaur H, Gupta N, *et al.*; VRDL Team. Determination of a cut-off value for the serological diagnosis of scrub typhus by detecting anti-Orientia tsutsugamushi immunoglobulin M. Indian J Med Res 2023;157:519-23.
16. Sengupta M, Anandan S, Daniel D, Prakash JA. Scrub typhus seroprevalence in healthy Indian population. J Clin Diagn Res 2015;9:DM01.
17. Khan SA, Murhekar MV, Bora T, Kumar S, Saikia J, Kamaraj P, *et al.* Seroprevalence of Rickettsial infections in Northeast India: A population-based cross-sectional survey. Asia Pac J Public Health 2021;33:516-22.
18. D'Cruz S, Perumalla SK, Yuvaraj J, Prakash JA. Geography and prevalence of rickettsial infections in Northern Tamil Nadu, India: A cross-sectional study. Sci Rep 2022;12:20798.
19. Trowbridge P, *P* D, Premkumar PS, Varghese GM. Prevalence and risk factors for scrub typhus in South India. Trop Med Int Health 2017;22:576-82.
20. Jakharia A, Borkakoty B, Biswas D, Yadav K, Mahanta J. Seroprevalence of scrub typhus infection in Arunachal Pradesh, India. Vector Borne Zoonotic Dis 2016;16:659-63.
21. Bonell A, Lubell Y, Newton PN, Crump JA, Paris DH. Estimating the burden of scrub typhus: A systematic review. PLoS Negl Trop Dis 2017;11:e0005838.
22. Saraswati K, Tanganuchitcharnchai A, Ongchaikupt S, Mukaka M, Day NP, Baird JK, *et al.* Serosurvey of scrub typhus in Indonesia: A cross-sectional analysis of archived fever studies samples. Trans R Soc Trop Med Hyg 2024;118:321-7.
23. Centers for Disease Control and Prevention, "One Health" (CDC, December 1, 2023). Available from: https://www.cdc.gov/onehealth/index.html. [Last accessed on 2024 Jan 12].