



PREVALENCE AND GEOGRAPHICAL BURDEN OF SCRUB TYPHUS DISEASE IN CENTRAL INDIA: A CROSS-SECTIONAL STUDY

Santosh kumar^{1*}, Sohan lal², Suraj Yadav³, Ankur Pandey⁴, Sapna Kushwah⁵

^{1*,4,5}PhD Scholar, Department of Microbiology, Mansarovar Global University Sehore, MP, India

^{1*,4,5}Professor & Head, Department of Microbiology, Mansarovar Global University Sehore, MP

²Skill Department of Sports & Yoga, Shri Vishwakarma Skill University, Palwal, Haryana, India

³Department of Statistics, Institute of Science, Banaras Hindu University, Varanasi, UP, India

***Corresponding Author:** Santosh Kumar

Email: santoshmicrobiology28@gmail.com

Abstract:

Background and objectives: Scrub typhus, a vector – borne zoonotic disease is produced through bacteria *Orientia tsutsugamushi*, a potentially lethal re-emerging infectious disease in India. Scrub typhus, produce severe multiorgan failure and has a circumstance fatality rate of up to 70% if not treated properly. The geographical burden of the disease remains unclear in this region. Our goal is to present the geographical burden and prevalence of scrub typhus in Madhya Pradesh Central India with the management of scrub typhus in both long standing endemic regions and newly identified infection foci and to identify the integration with the effectiveness of various available serological diagnostic methods, ELISA, rapid immunochromatography test, weil Felix test, clinical and medical laboratory results to support the diagnosis of scrub typhus patients.

Methodology: A total 524 patients undiagnosed acute undifferentiated febrile illness (AUI) >5 days with the age of 3 yrs to 75 yrs included in the study with suspected scrub typhus. Various serological diagnostic methods rapid immunochromatography test, ELISA, Weil Felix test applied for the detection of scrub typhus cases with the clinical features, medical laboratory parameter and final result analyzed.

Principal findings: Scrub typhus epidemiology varies due to Climate conditions, etiological agents and arthropod vectors involved in transmission. Scrub typhus is a disease with a unique epidemiology in MP and its regional distribution were found to be varied in this study, with the highest percentage of cases recorded (66.6%) in Mandsaur (22.2%) in Ratlam and (11.1%) in Betul districts of Madhya Pradesh, Central India. These seroprevalence was increases during the month of August (48.1%), September (40.7%) and October (11.1%). The study shows that 5.1% (n=524) positive cases of scrub typhus through the various serological diagnostic methods.

Conclusion: Our study revealed an increasing trend of scrub typhus in MP, Central India, Morbidity and Mortality will be reduced if diagnosed early through ICT, ELISA and treated appropriately. The general population's awareness of the patterns of disease transmission and the implementation of preventive measures like insect repellents and protective clothing are crucial in decreasing the prevalence of disease.

Keywords: Scrub typhus disease, MP, *Orientia tsutsugamushi*

Introduction

Scrub typhus is caused by *Orientia tsutsugamushi*, a stringent intracellular Gram-negative obligate intracellular bacillus bacterium which primarily infects rodents and accidentally human. The term "tsutsuga" refers to something small and potentially dangerous, while "mushi" denotes insect, mite, or creature(1). Clinical signs and symptoms include fever, headache, eschar, lymphadenopathy, muscular pain, and gastrointestinal issues. If not treated, severe cases of these conditions result in multiple organ failure and may be fatal. The observation of the eschar is often missed and other symptoms of the disease possess the problem of delayed diagnosis by the clinician.

Scrub Typhus was first documented in the Indian States of Assam and West Bengal in the midst World War II (2). Numerous areas in various Indian States, including Maharashtra, Tamilnadu, Karnataka, Kerala, Jammu and Kashmir, Uttarakhand, Himachal Pradesh, Rajasthan, West Bengal, Assam, Arunachal Pradesh, Sikkim, Nagaland and Meghalaya have recorded cases of the Scrub Typhus disease. Its nonspecific presentation, low index of suspicion, and lack of confirmatory diagnostic resources, scrub typhus is grossly underdiagnosed in India. [4]. Due to the generic nature of the symptoms, particularly in the absence of the typical eschar, and the lack of accurate diagnostic testing, misdiagnosis and underdiagnosis of this significant cause of acute undifferentiated fever are frequent. Awareness among the clinicians on clinical presentations, laboratory parameters, and confirmatory diagnostic testing display a crucial role for the identification and treatment of scrub typhus (5).

The purpose of the current study was to determine the geographic burden of scrub typhus disease from clinical suspect patients during the months of August 2022 to December 2022 in three districts of Madhya Pradesh, India.

Materials and Methods

A cross-sectional study was conducted from August 2022 to December 2022. Every patient conducted a complete clinical examination, which included a thorough search for eschar. The standard laboratory tests (complete blood count, peripheral smear, urine analysis, kidney function test, glucose, liver function tests) were performed in these cases. Study included patients examined by tests such as blood cultures, Urine culture, chest X-rays, Widal tests for malarial antigen test and dengue serology were also performed. Serum samples of patients with clinical suspected undifferentiated fever from three districts Mandasaur, Ratlam and Betul of Madhya Pradesh collected for screening and Diagnosis of Scrub Typhus.

A total of 524 serum samples were screened by Weil Felix test (Tulip Diagnostics Pvt.Ltd.) and diagnosed by SD Bioline Tsutsugamushi, a solid phase immunochromatographic (ICT) assay which identifies the IgG and IgM antibodies to Scrub Typhus. Scrub typhus Detected by IgM ELISA (InBios International Inc., Seattle, WA, USA) against 56-Kda antigen was used to perform IgM ELISA. In the IgM ELISA, a cut off optical density (OD) >0.5 was considered as positive. Clinical characteristics, laboratory parameters, and results were assessed in patient records of samples that tested positive for IgM ELISA and ICT. The statistical software Graph Pad Prism was utilized for statistical analysis, and the Fisher's Test was employed to compare categorical variables. A p-value of less than 0.05 was considered significant.

Results

The geographical burden of Scrub Typhus disease found 5.1% (27/524) in three districts of Madhya Pradesh in the present study. The patients with acute undifferentiated febrile illness (AUI) ranging in age from 3 to 75 years old, as well as 20 healthy controls, for scrub typhus in order to discover anti-Orientia IgM. The majority of the patients had a rural background and belonged to the Betul (11%), Ratlam (22%) and District Mandasaur (67%) (Figure-1). Scrub typhus peaked in August, September, and October, with a subsequent reduction in the months that followed (Figure -2).

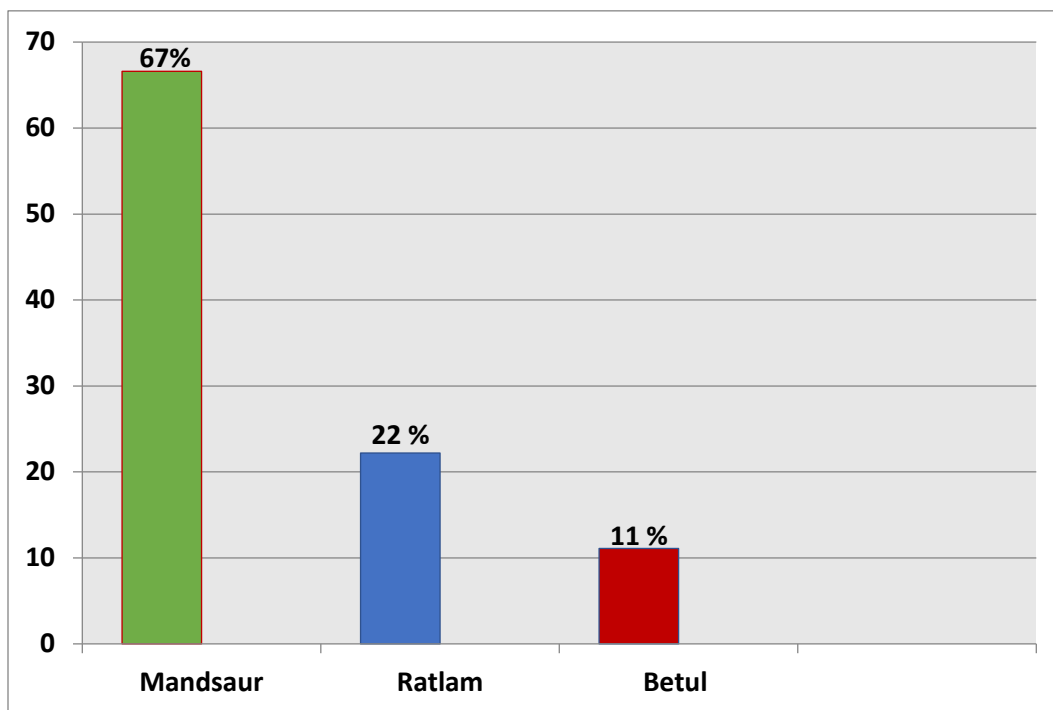


Figure – 1: District wise distribution of scrub Typhus Patients.

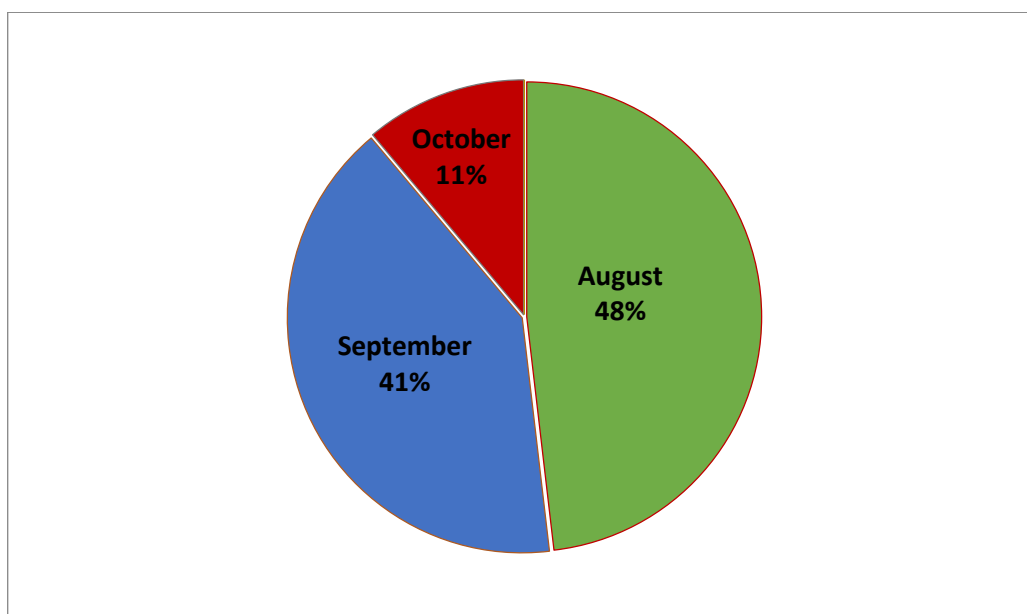


Figure-2-Month Wise distribution of Scrub Typhus Cases.

Age wise comparison of the prevalence indicated that 41-75 yrs age group were most affected (prevalence 59.2%) followed by 19 – 40yrs age group (22.2%) and 13-18 yrs (11. 1%).The age group 7-12 yrs showed least seropositivity (7.4%) and the age group 3-6 yr, no cases found. (Figure-3). The gender wise comparison showed that males 73.6% were higher prevalence rate than females 26.3%. No mortality found as compare to 4.5% to 45% mortality found in other study in India.

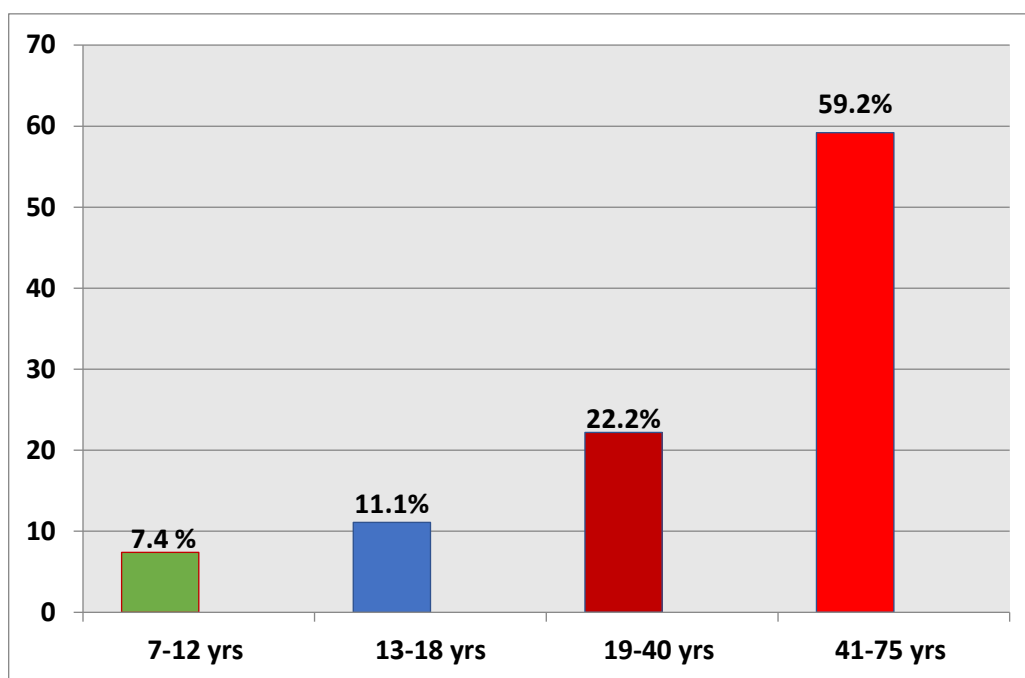
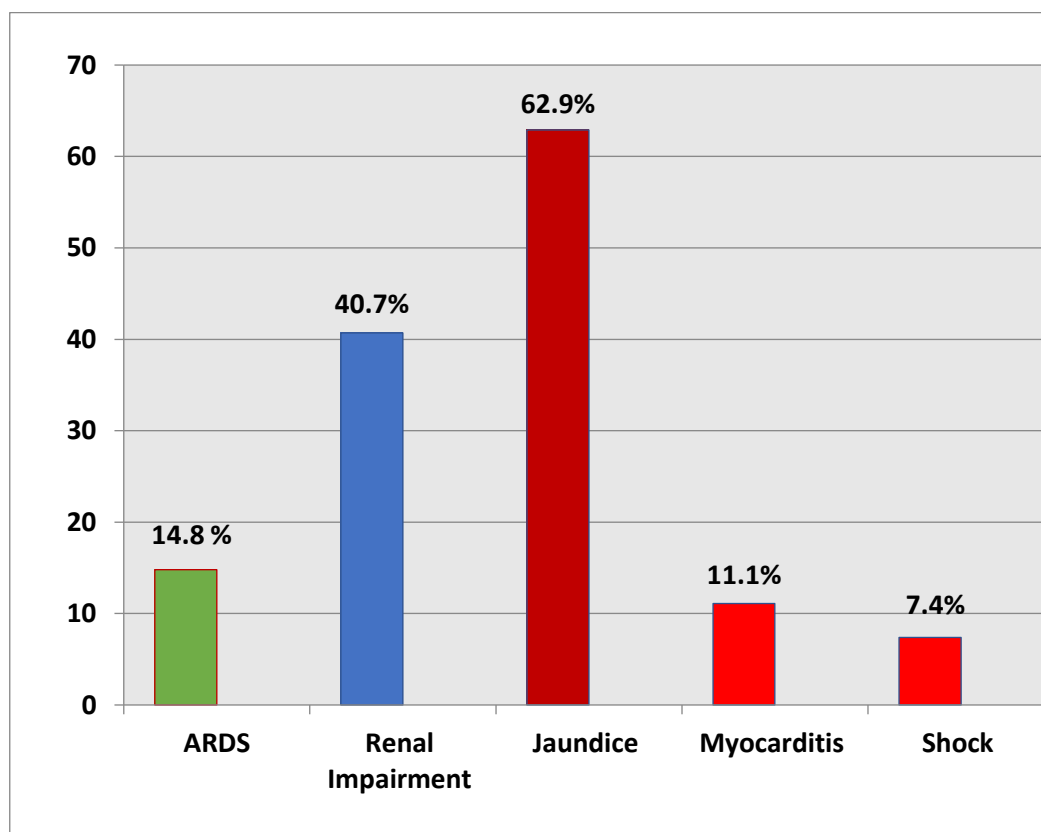


Figure-3: Age wise distribution of Scrub Typhus Patients

Some of the patients show complications of scrub typhus with the salient features with multisystem involvement. Three patients were young females below 30 years and leucocytosis was present. Acute respiratory syndrome (ARDS) was present in 4(14.8%). 17 (62.9%) patients had clinical jaundice. 11 (40.7%) patients had renal function impairment. 3 (11.1% patients had myocarditis. 2(7.4%) patients had shock (figure-4).



ARDS: Acute Respiratory Distress Syndrome.

Figure 4: Clinical Complications of Scrub Typhus patients

Discussions

Scrub Typhus is emerging life threatening infectious disease in India, which is caused by *O. Tsutsugamushi*. Many outbreaks have been reported from several parts of the country (7). The disease has resurfaced as a leading source of Acute Febrile illness ((AFI) in India, particularly cooler seasons between August to December. This infection is also known to occur in diverse geographical places like deserts, rice fields and seashores. India is an integral component of the "Tsutsugamushi Triangle". In India the disease had occurred among soldiers during World War II in Assam and West Bengal. After that the scrub typhus has been spread in pan India particularly from south India and Himalayan regions of north India (12). Now the outbreaks were seen in sub Himalayan north India and Central India.

Scrub typhus is one of the most under-diagnosed and under-reported febrile illness sometimes requires hospitalization. Eschar painless, punched out ulcer up to 1cm in width with a black necrotic centre) (17). It is an important finding for the diagnosis of scrub typhus. Positive eschar finding is very low in India (22.2%). The diagnosis of scrub typhus is totally depended on various laboratory tests.

Scrub typhus is a severe community well being issue across India and worldwide. It poses a hazard to one billion people worldwide and sickens individuals every year. Scrub typhus, produced through *Orientia tsutsugamushi*, can cause severe multiorgan failure and has a circumstance fatality rate of up to 0-60% if not treated properly. The bite site of scrub typhus is marked by necrotic eschar, which is a pathognomonic characteristic. Hepatitis, severe kidney injury, and myocarditis leading to heart failure are all symptoms of Acute Respiratory Distress Syndrome (ARDS).

O. tsutsugamushi's antigenic heterogeneity prevents general immunity and allows for re-infection. As neglected illness, we still don't know much about it, as indicated by the occasional epidemiologic data and other public health information available about scrub typhus in its prevalent locations.

Scrub typhus has resurfaced as a leading source of AFI in many parts of India, particularly throughout the monsoon and postmonsoon seasons. Scrub typhus has been confirmed in 23 out of India's 29 states (15). Scrub typhus can manifest itself in a variety of ways, from asymptomatic illness to multiorgan failure and death. The Disease found across India, The Shivalik Mountains, The Vindhya and Satpura mountains, as well as the Eastern and Western Ghats in the centre region of the nation go from Kashmir to Assam. In Himanchal Pradesh, Sikkim, and Darjeeling, outbreaks of scrub typhus have been observed (32). Our study revealed an increasing trend of scrub typhus in Madhya Pradesh, indicating a worsening condition since 2019.

Conclusion:

It is essential to timely diagnose scrub typhus, to reduce associated morbidity and mortality. No mortality found as compared to 4.5% to 45% mortality found in other study in India. This improvement attributed to the accelerated attention of the various clinical presentation of scrub typhus by the treating clinicians with early diagnosis and treatment.

Conflict of Interest: The authors declare no conflicts of interest.

Ethical Consent: The Institutional Review Board and Ethics Committee approved the study, and each patient obtained informed consent.

References

1. Ram Mohan Mylavaram Venkata Naga Lakshmi^{1*}, Teja Vijay Dharma¹, Sukanya Sudhaharan¹, Subbalaxmi Malladi Venkata Surya², Rajkiran Emmadi², Satyanarayana Raju Yadati², Nageswara Rao, Modugu², Aparna Jyotsna¹ Prevalence of scrub typhus in a tertiary care centre in Telangana, south India Volume 12 Number 3 (June 2020) 204-208 Iranian journal of microbiology.

2. Aung AK, Spelman DW, Murray RJ, Graves S. Rickettsial infections in Southeast Asia: implications for local populace and febrile returned travelers. *Am J Trop Med Hyg* 2014; 91:451-460.
3. Pote K, Narang R, Deshmukh P. Diagnostic performance of serological tests to detect antibodies against acute scrub typhus infection in central India. *Indian J Med Microbiol* 2018; 36:108-112.
4. Mahajan, S.K. Rickettsial diseases. *J Assoc Physicians India* 2012, 60, 37–44.
5. Rathi, N.B.; Rathi, A.N.; Goodman, M.H.; Aghai, Z.H. Rickettsial diseases in central India: proposed clinical scoring system for early detection of spotted fever. *Indian Pediatric* 2011, 48, 867–872.
6. La Scola, B.; Raoult, D. Laboratory diagnosis of rickettsioses: current approaches to diagnosis of old and new rickettsial diseases. *J Clin Microbiol* 1997, 35, 2715–2727.
7. Bakshi, D.; Singhal, P.; Mahajan, S.K.; Subramaniam, P.; Tuteja, U.; Batra, H.V. Development of a real-time PCR assay for the diagnosis of scrub typhus cases in India and evidence of the prevalence of new genotype of *O. tsutsugamushi*. *Acta Tropica* 2007, 104, 63–71, doi: 10.1016/j.actatropica.2007.07.013.
8. Usha, K.; Kumar, E.; Kalawat, U.; Kumar, B.S.; Chaudhury, A.; Gopal, D.V.R.S. Molecular characterization of *Orientia tsutsugamushi* serotypes causing scrub typhus outbreak in southern region of Andhra Pradesh, India. *Indian J Med Res* 2016, 144, 597–603, doi:10.4103/0971-5916.200886
9. Kocher, C.; Jiang, J.; Morrison, A.C.; Castillo, R.; Leguia, M.; Loyola, S.; Ampuero, J.S.; Cespedes, M.; Halsey, E.S.; Bausch, D.G.; et al. Serologic Evidence of Scrub Typhus in the Peruvian Amazon. *Emerg. Infect. Dis.* 2017, 23, 1389–1391, doi:10.3201/eid2308.170050.
10. Vivekanandan, M.; Mani, A.; Priya, Y.S.; Singh, A.P.; Jayakumar, S.; Purty, S. Outbreak of scrub typhus in Pondicherry. *J Assoc Physicians India* 2010, 58, 24–28.
11. Siraj Ahmed Khan Re-emergence of scrub typhus in northeast India. *International Journal of Infectious Diseases* 2012, 16, 889–890.
12. Tilak, R.; Wankhade, U.; Kunwar, R.; Tilak, V. Emergence of *Schoengastiella ligula* as the vector of scrub typhus outbreak in Darjeeling: Has *Leptotrombidium deliense* been replaced? *Indian Journal of Public Health* 2011, 55, 92, doi:10.4103/0019-557X.85239.
13. Chauhan; S. Mahajan; Manish S Scrub typhus: An emerging scourge. *Indian Journal of Basic and Applied Medical Research* 2015, 4, 394–401.
14. Sankhyan, N.; Saptharishi, L.G.; Sasidaran, K.; Kanga, A.; Singhi, S.C. Clinical profile of scrub typhus in children and its association with hemophagocytic lymphohistiocytosis. *Indian Pediatr* 2014, 51, 651–653.
15. Rajneesh Joshi; SP Kalantri Acute Undifferentiated Fever: Management Algorithm. In *Update on Tropical Fever; Association of Physicians of India*, 2015.
16. Chrispal, A.; Boorugu, H.; Gopinath, K.G.; Chandy, S.; Prakash, J.A.J.; Thomas, E.M.; Abraham, A.M.; Abraham, O.C.; Thomas, K. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors – an experience from a tertiary care hospital in South India. *Trop Doct* 2010, 40, 230–234, doi:10.1258/td.2010.100132.
17. Laskar, A.R.; Suri, S.; Acharya, A.S. Scrub Typhus: Re-emerging Public Health Problem in India. *Journal of Communicable Diseases* 2015, 47, 19–25.
18. Annual Report 2014 -15 2016.
19. Singh, S.I.; Devi, K.P.; Tilotama, R.; Ningombam, S.; Gopalkrishna, Y.; Singh, T.B.; Murhekar, M.V. An outbreak of scrub typhus in Bishnupur district of Manipur, India, 2007. *Trop Doct* 2010, 40, 169–170, doi:10.1258/td.2010.090468.
20. Dass, R.; Deka, N.M.; Duwarah, S.G.; Barman, H.; Hoque, R.; Mili, D.; Barthakur, D. Characteristics of Pediatric Scrub Typhus during an Outbreak in the North Eastern Region of India: Peculiarities in Clinical Presentation, Laboratory Findings and Complications. *Indian J Pediatr* 2011, 78, 1365–1370, doi:10.1007/s12098-011-0470-5.

21. Prakash, J. a. J.; Kavitha, M.L.; Mathai, E. Nested polymerase chain reaction on blood clots for gene encoding 56 kDa antigen and serology for the diagnosis of scrub typhus. *Indian Journal of Medical Microbiology* 2011, 29, 47, doi:10.4103/0255-0857.76524. Peter JV, Sudarsan TI, Prakash JA, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. *World J Crit Care Med* 2015;4:244-50.
22. 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.
23. Roopa KS, Karthika K, Sugumar M, Bammigatti C, Shamanna SB, Harish BN. Serodiagnosis of scrub typhus at a tertiary care hospital from Southern India. *J Clin Diagn Res* 2015;9:C05-7.
24. Sugita Y, Nagatani T, Okuda K, Yoshida Y, Nakajima H. Diagnosis of typhus infection with *Rickettsia tsutsugamushi* by polymerase chain reaction. *J Med Microbiol* 1992;37:357-60.
25. 26.Kim DM, Yun NR, Yang TY, Lee JH, Yang JT, Shim SK, *et al.* Usefulness of nested PCR for the diagnosis of scrub typhus in clinical practice: A prospective study. *Am J Trop Med Hyg* 2006;75:542-5.
26. 27.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.
27. 28.Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR guidelines for diagnosis and management of rickettsial diseases in India. In *Rickettsiales*. Cham Switzerland; Springer International Publishing; 2016. p. 125-33.
28. 29.Shivalli S. Diagnostic evaluation of rapid tests for scrub typhus in the Indian population is needed. *Infect Dis Poverty* 2016;5:40.
29. 30.CD alert monthly newsletter of national centre for disease control, directorate general of health services, government of India. *Scrub Typhus and Other Rickettsioses* 2009;13:1-8.
30. 31.Venkategowda PM, Rao SM, Mutkule DP, Rao MV, Taggu AN. Scrub typhus: Clinical spectrum and outcome. *Indian J Crit Care Med* 2015;19:208-13.
31. 32.Issac R. Scrub Typhus: Prevalence and diagnostic issues in rural southern India. *Clin Infect Dis* 2004;39:1395-6.
32. 33.Pradutkanchana J, Silpapojakul K, Paxton H, Pradutkanchana S, Kelly DJ, Strickman D. Comparative evaluation of four serodiagnostic tests for scrub typhus in Thailand. *Trans R Soc Trop Med Hyg* 1997;91:425-8.
33. 34.Koraluru M, Bairy I, Varma M, Vidyasagar S. Diagnostic validation of selected serological tests for detecting scrub typhus. *Microbiol Immunol* 2015;59:371-4.
34. Mahajan SK, Kashyap R, Kanga A, Sharma V, Prasher BS, Pal LS. Relevance of Weil-Felix test in diagnosis of scrub typhus in India. *JAPI* 2006;54:619-21.
35. Pote K, Narang R, Deshmukh P. Diagnostic performance of serological tests to detect antibodies against acute scrub typhus infection in central India. *Indian J Med Microbiol* 2018;36:108-12.
36. 37.Anitharaj V, Stephen S, Pradeep J, Park S, Kim SH, Kim YJ, *et al.* Serological diagnosis of acute scrub typhus in Southern India: Evaluation of InBios scrub typhus detect IgM rapid test and comparison with other serological tests. *J Clin Diagn Res* 2016;10:C07-10.
37. 38.Watthanaworawit W, Turner P, Turner C, Tanganuchitcharnchai A, Jintaworn S, Hanboonkunupakarn B, *et al.* Diagnostic accuracy assessment of immunochromatographic tests for the rapid detection of antibodies against *Orientia tsutsugamushi* using paired acute and convalescent specimens. *Am J Trop Med Hyg* 2015;93:1168-71.
38. 39.Rawat V, Singh RK, Kumar A, Singh Y, Chaturvedi P, Saxena SR, *et al.* Diagnostic validation of IgM and IgG ELISA and real-time PCR in detecting scrub typhus infection in endemic regions. *J Vector Borne Dis* 2018;55:165-7.
39. 40.Lim C, Paris DH, Blacksell SD, Laongnualpanich A, Kantipong P, Chierakul W, *et al.* How to determine the accuracy of an alternative diagnostic test when it is actually better than the reference tests: A re-evaluation of diagnostic tests for scrub typhus using bayesian LCMs. *PLoS One* 2015;10:e0114930.

40. Kingston HW, Blacksell SD, Tanganuchitcharnchai A, Laongnualpanich A, Basnyat B, Day NP, *et al.* Comparative accuracy of the inbios scrub typhus detect IgM rapid test for the detection of IgM antibodies by using conventional serology. *Clin Vaccine Immunol* 2015;22:1130-2.
41. Gupta N, Chaudhry R, Thakur CK. Determination of cutoff of ELISA and immunofluorescence assay for scrub typhus. *J Glob Infect Dis* 2016;8:97-9.
42. 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.
43. Kelly DJ, Forest 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:S203-230.
44. Varghese G, Abraham O, 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.
45. Sinha P, Gupta S, Dawra R, Rijhawan P. Recent outbreak of scrub typhus in North Western part of India. *Indian J Med Microbiol* 2014;32:247-250.
46. Dass R, Deka NM, Duwarah SG, Barman H, Hoque R, Mili D, *et al.* Characteristics of paediatric scrub typhus during an outbreak in the North Eastern region of India: peculiarities in clinical presentation, laboratory findings and complications. *Indian J Pediatr* 2011;78:1365-1370.
47. Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, *et al.* Scrub typhus: an unrecognized threat in South India—clinical profile and predictors of mortality. *Trop Doct* 2010;40:129-133.
48. 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(12):e889-890.
49. Jung HC, Chon SB, Oh WS, Lee DH, Lee HJ. Etiologies of acute undifferentiated fever and clinical prediction of scrub typhus in a non-tropical endemic area. *Am J Trop Med Hyg* 2015;92:256-261.
50. Taylar AC, Hill J, Kelly DJ, Davis DR, Lewis GE Jr. A serological survey of scrub, tick, and endemic typhus in Sabah, East Malaysia. *Southeast Asian J Trop Med Public Health* 1986;17:613-619.
51. Anitharaj V, Stephen S, Pradeep J, Park S, Kim SH, Kim YJ, *et al.* Serological diagnosis of acute scrub typhus in Southern India: evaluation of InBios Scrub typhus detect IgM rapid test and comparison with other serological tests. *J Clin Diagn Res* 2016;10:DC07- DC10.