



## IMPACT AND TRENDS OF SCRUB TYPHUS IN INDIA A SYSTEMATIC REVIEW

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### KEYWORDS :

#### BACKGROUND

Scrub typhus was called bush typhus, caused by *Orientia tsutsugamushi*. It is a mite-borne bacterium belonging to the family Rickettsiaceae, one of the widespread and severe rickettsial infections<sup>1</sup>. It has four stages: egg, larva, chigger, nymph, and Adult. Both nymphs and adults are free-living in soil. Only larva feeds on small mammals or birds feeding on the ground, and humans are accidental hosts. It was first reported in Japan by Hakuju Hashimoto in 1810<sup>2</sup> and first described by Naosuke Hayashi in 1920<sup>3</sup>, giving it the name *Theileria tsutsugamushi*. It was renamed *Orientia tsutsugamushi* in 1995.<sup>4</sup>

Scrub typhus is historically endemic to the Tsutsugamushi Triangle. In INDIA, it is prevalent in the foothills of the Himalayas viz Jammu & Kashmir, Himachal Pradesh, Sikkim, Manipur, Nagaland, and Meghalaya. However, scrub typhus outbreaks were reported from Delhi, Haryana, Rajasthan, Maharashtra, Uttarakhand, Chhattisgarh, and Tamil Nadu to Kerala<sup>5</sup>. Although many studies stated the reemergence of scrub typhus in India, there were no proper epidemiological studies and surveillance systems for reporting scrub typhus. In the current study, we aimed to show the impact of scrub typhus.

#### METHODS AND MATERIALS

This review was performed according to the PRISMA method (Appendix A in S1 File: PRISMA Checklist)<sup>6</sup>. Different keywords related to scrub typhus were used in the literature search strategy. After extensive searching of the database, PUBMED was included to cover the maximum number of articles published in international and Indian journals. PUBMED, restricted to the English language, human subjects, and India, and published over the last two years, was performed on 1st April 2022. The search terms included 'scrub typhus' and '*Orientia tsutsugamushi*', used with 'AND India'. A second search had 'scrub typhus' used with 'AND' and either 'epidemiology', 'mortality', or 'death' 'prevalence', 'incidence'. Studies on diagnostic evaluation and epidemiological factors associated with scrub typhus were also included. Articles (studies) on all observational studies cross-sectional, case-control studies, as well as Prospective studies conducted in India among patients of all age groups that reported or laboratory-confirmed scrub typhus, were included. The outcomes evaluated were the number of patients diagnosed and deaths due to scrub typhus. The diagnostic confirmation used in the study is as follows: IgM or IgG detection using ELISA, immunofluorescence test, and polymerase chain reaction (PCR) were searched and documented.

#### DEFINITIONS

Scrub typhus case: "Patients with a febrile illness with or without an eschar confirmed by a molecular/serological diagnostic test"<sup>7</sup>.

Case fatality proportion: Deaths due to scrub typhus.

Acute respiratory distress syndrome (ARDS) is defined as patients with a P/F ratio < 200 mmHg<sup>8</sup>

Respiratory dysfunction is a clinical condition that happens when the

respiratory system fails to maintain its main function, which is gas exchange, in which PaO<sub>2</sub> is lower than 60 mmHg and/or PaCO<sub>2</sub> is higher than 50 mmHg. (Respiratory dysfunction can be hypoxemic that has a PaO<sub>2</sub> < 60 mmHg with normal or subnormal PaCO<sub>2</sub> in which the gas exchange is impaired at the level of the alveolar-capillary membrane or hypercapnic that has a PaCO<sub>2</sub> > 50 mmHg commonly due to respiratory pump failure. While ARDS is a sudden life-threatening condition characterised by poor oxygenation and non-compliant or "stiff" lungs associated with capillary endothelial injury and diffuse alveolar damage)<sup>9</sup>

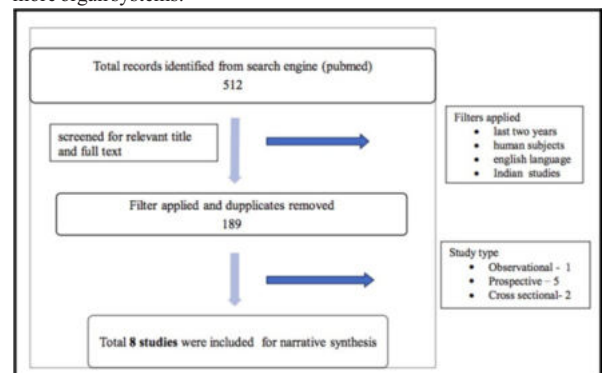
Hepatitis was defined as total bilirubin >2mg/dl with an elevation of SGPT (alanine aminotransferase)/SGOT (aspartate aminotransferase)<sup>10</sup>

Acute kidney injury AKI was defined as an S.creatinine level of more than 1.5 mg/dL.<sup>11</sup>

The shock was defined as an arterial SBP < 90 mmHg (systolic blood pressure) requiring vasopressors.<sup>12</sup>

Meningitis was defined as neurological symptoms including fever with neck rigidity seizure, vomiting, headache, and altered sensorium, with or without CSF analysis, indicating Increased protein level with no other changes<sup>13</sup>

Multi-organ dysfunction syndrome (MODS) is a dysfunction of two or more organ systems.<sup>14</sup>



**Fig 1:** Prisma flow chart schematic representation for data extraction

#### SELECTION AND DATA EXTRACTION

Based on data search results, abstracts were selected through each phase of screening eligibility and inclusion. While screening articles for review, duplicates were removed using Zotero software. Data were extracted to Microsoft Excel database -Study ID, author, name, study, sample size, hospital or community based, diagnostic tests used for confirmation, demographic data, complications, symptoms, and fatality.

#### RISK

The studies were independently assessed for quality using a data

extraction sheet. To minimise the risk of bias, we followed the Quality assessment checklist for prevalence studies (adapted from Hoy et al.) and segregated them into high low and moderate risk groups.

**OUTCOME MEASURES**

- The scrub typhus +ve cases in the last two years in India
- Overall case fatality or mortality
- Scrub typhus causes acute undifferentiated febrile illness

**RESULTS**

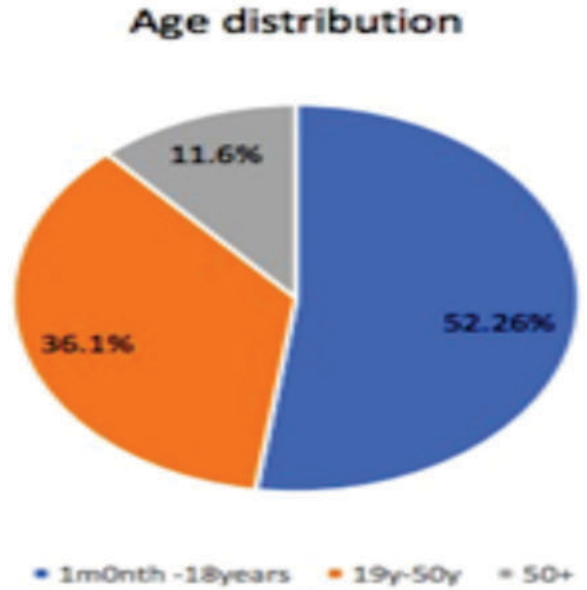
With the help of keywords and search strategies, 512 articles were identified from two databases. After screening, duplicates were removed using Zotero software. Out of which eight papers were selected.<sup>15-22</sup>

**Table No: 1 Demographic, Clinical Characteristics And Organ Involvement Of Patients**

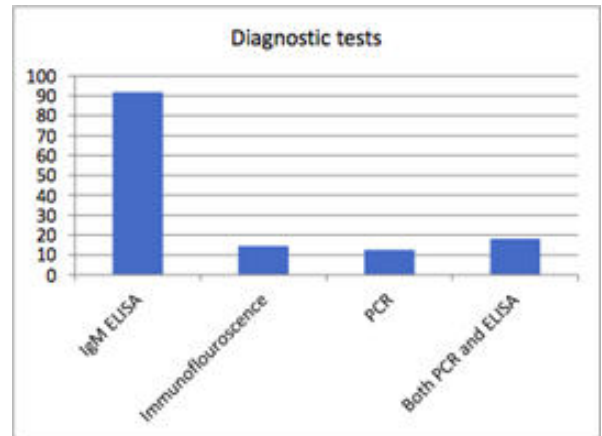
VARIABLES	No.of patients/ total no of cases	%
<b>AGE IN YEARS</b>		
1month -18years	1964/3758	52.26
19y-50y	1357/3758	36.10
50+	437/3758	11.6
<b>GENDER</b>		
Male	1554/3365	46.18
Female	1811/3365	53.81
<b>PLACE OF RESIDENCE</b>		
Urban	1239/2618	47.32
Rural	1442/2618	55.08
<b>CLINICAL CHARACTERISTICS</b>		
Fever	1251/1398	89.48
Rash	40/441	9.07
Eschar	353/1129	31.26
Myalgia	187/2820	6.6
Jaundice	49/967	5.6
Nausea/Vomiting	105/422	24.88
Altered sensorium	43/124	34.67
Seizures	22/270	8.14
Splenomegaly	23/124	18.54
Hepatomegaly	76/124	61.29
Abdomen pain	102/441	23.14
Dyspnea	157/2680	5.8
Diarrhoea	17/198	8.52
<b>COMPLICATIONS</b>		
Cardiovascular	42/834	5.03
CNS dysfunction	94/1129	8.32
AKI	62/708	8.75
ARDS	27/124	21.7
Encephalopathy	10/72	13.88
MODS	78/760	10.26
Shock	120/760	15.78
Respiratory	214/906	23.62
Mechanical ventilation	99/708	13.98
Invasive ventilation	52/636	8.17
Mortality	22/708	3.10
<b>DIAGNOSTIC TESTS</b>		
IgM ELISA	3450/3758	91.80
Immunofluorescence	28/198	14.14
PCR	4/32	12.5
Both PCR and ELISA	13/72	18.05

Note: as values are presented proportionally as per the number of cases reported for each variable in the review articles, denomination values will change based on the total number of cases reported for respective variable. A total of eight studies<sup>15-22</sup> had data on the clinical characteristics of scrub typhus. The most common presenting symptoms are as follows Fever (89.48%) followed by nausea/vomiting (24.88%), Altered sensorium (34.67%), eschar (31.26%), hepatomegaly (61.29%), and seizure (8.14%). The presence of Fever was reported in six studies. Scrub-positive typhus cases were seen more in the <18years patient population when compared to adults and the geriatric population. Prevalence of scrub typhus was noted more in rural areas than urban. The overall proportion of scrub typhus affecting females (53.81%) is more compared to males (46.18%). The IgM ELISA was considered to be a more accurate and easy accessible laboratory test for scrub typhus in our

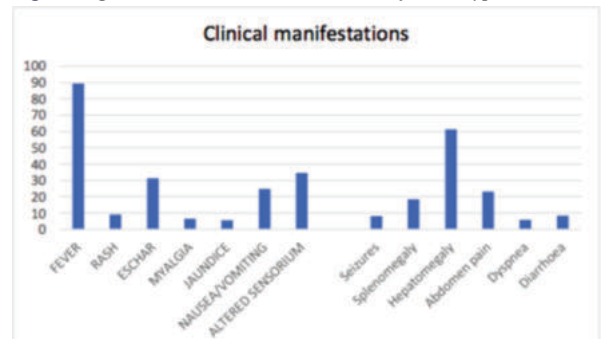
study, 91.8% of cases were confirmed using IgM ELISA, and 14.14% were confirmed by immunofluorescence assay, 12.5% confirmed by PCR. All the observations have been diagrammatically represented as shown in Fig 2-5.



**Fig 2: Prevalence Among Different Age Groups**



**Fig 3: Diagnostic Tests Used For Evaluation Of Scrub Typhus**



**Fig 4: Graphical Representation Of Various Clinical Manifestations**

Scrub typhus cases with various organ involvement were reported in 8 studies with 3758 scrub typhus cases. The most common complications included Respiratory dysfunction (23.62% of cases of scrub typhus), acute respiratory distress syndrome or ARDS (21.7%), acute kidney injury (8.75%), shock (15.78%), Encephalopathy (13.88%). MODS (Multiple organ dysfunction syndromes) were reported in 3 studies and were seen in 10.26% of the cases. As reported by two studies, fever duration and organ involvement may increase the patient's ICU admission and 13.1% required mechanical ventilation and invasive ventilation 8.17%. The overall case fatality rate from 4 studies was 3.1%. Different organ involvement in scrub typhus and mortality rate was shown with the help of a bar diagram in Fig 5 and Fig 6.

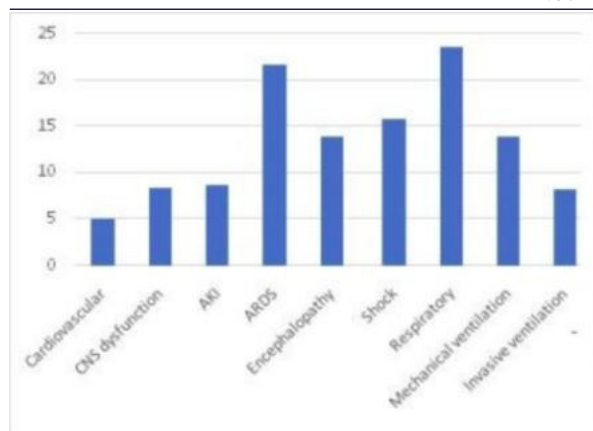


Fig 5: Various Organ Involvement

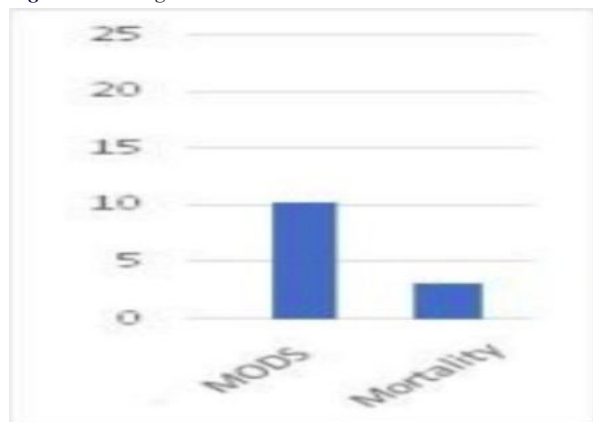


Fig 6: MODS and Mortality rate

## CONCLUSION

The overall proportion of Scrub typhus affected females (53.81%) and was more prevalent in rural areas (55.08%) compared to males and people living in urban areas, respectively. The most commonly noted multiple organ involvement was Respiratory dysfunction (23.62%). MODS were reported in 10.26%; 13.98% of patients required mechanical ventilation, and 8.17% required invasive ventilation during the hospital stay. The overall case-fatality rate was 3.1%. CFR was high in patients with cardiovascular (5.08%), shock (15.78%), MODS (10.26%), encephalopathy (13.88%), acute kidney injury (8.75%), ARDS (21.7%). Out of all diagnostic tests, IgM ELISA was most commonly used (91%). In this study, we conclude that there is an increase in scrub typhus cases among acute undifferentiated febrile illnesses and by proper diagnosis and management case fatality rate can be reduced.

## REFERENCES

- Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM (2017) A review of the global epidemiology of scrub typhus. *PLoS Negl Trop Dis* 11(11): e0006062.
- Richards AL, Jiang J. Scrub Typhus: Historic Perspective and Current Status of the Worldwide Presence of *Orientia* Species. *Trop Med Infect Dis*. 2020 Apr 1;5(2):49. doi: 10.3390/tropicalmed5020049. PMID: 32244598; PMCID: PMC7344502.
- Lalchhandama, Kholhring. (2018). The saga of scrub typhus with a note on the outbreaks in Mizoram. *Science Vision*. 18. 50-57. 10.33493/scivis.18.02.01.
- Richards AL, Jiang J. Scrub Typhus: Historic Perspective and Current Status of the Worldwide Presence of *Orientia* Species. *Trop Med Infect Dis*. 2020 Apr 1;5(2):49. doi: 10.3390/tropicalmed5020049. PMID: 32244598; PMCID: PMC7344502.
- Shivalli, S. Diagnostic evaluation of rapid tests for scrub typhus in the Indian population is needed. *Infect Dis Poverty* 5, 40 (2016). <https://doi.org/10.1186/s40249-016-0137-6>
- BMJ (OPEN ACCESS) Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* 2021;372:n160. doi: 10.1136/bmj.n160
- 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 Jul 27;15(7):e0009619. doi: 10.1371/journal.pntd.0009619. PMID: 34314437; PMCID: PMC8345853.
- Rawal G, Yadav S, Kumar R. Acute Respiratory Distress Syndrome: An Update and Review. *J Transl Int Med*. 2018 Jun 26;6(2):74-77. doi: 10.1515/jitim-2016-0012. PMID: 29984201; PMCID: PMC6032183.
- Shebl E, Mirabile VS, Sankari A, et al. Respiratory Failure. [Updated 2022 Jul 7]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526127/>
- Lala V, Goyal A, Minter DA. Liver Function Tests. [Updated 2022 Mar 19]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482489/>
- Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical

Phenotypes. *Clin Biochem Rev*. 2016 May;37(2):85-98. PMID: 28303073; PMCID: PMC5198510.

- Lee SM, An WS. New clinical criteria for septic shock: serum lactate level as new emerging vital sign. *J Thorac Dis*. 2016 Jul;8(7):1388-90. doi: 10.21037/jtd.2016.05.55. PMID: 27501243; PMCID: PMC4958885.
- Hersi K, Gonzalez FJ, Kondamudi NP. Meningitis. [Updated 2022 Jul 5]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK459360/>
- Marshall JC. The multiple organ dysfunction syndrome. In: Holzheimer RG, Mannich JA, editors. *Surgical Treatment: Evidence-Based and Problem-Oriented*. Munich: Zuckschwerdt; 2001. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK6868/>
- Ahmed, A. et al. (2022) 'Analysis of Causes of Hepatic Dysfunction in Obstetric Patients in India: A Systematic Review', *Indian Journal of Critical Care Medicine: Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine*, 26(1), pp. 114–122. Available at: <https://doi.org/10.5005/jip-journals-10071-24083>.
- Devasagayam, E. et al. (2021) 'The burden of scrub typhus in India: A systematic review', *PLoS neglected tropical diseases*, 15(7), p. e0009619. Available at: <https://doi.org/10.1371/journal.pntd.0009619>.
- Garg, D. and Manesh, A. (2021) 'Neurological Facets of Scrub Typhus: A Comprehensive Narrative Review', *Annals of Indian Academy of Neurology*, 24(6), pp. 849–864. Available at: [https://doi.org/10.4103/aian.aian\\_739\\_21](https://doi.org/10.4103/aian.aian_739_21).
- Gupta, S. et al. (2022) 'Scrub typhus manifesting as electrocardiographic disturbance: A case report and review of literature', *Turkish Journal of Emergency Medicine*, 22(1), pp. 47–50. Available at: <https://doi.org/10.4103/2452-2473.336103>.
- Mukhopadhyay, K. et al. (2021) 'Mortality and complications of scrub typhus in the paediatric population: a systematic review and meta-analysis', *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 115(11), pp. 1234–1246. Available at: <https://doi.org/10.1093/trstmh/traab143>.
- Wilairatana, P. et al. (2021) 'Prevalence of malaria and scrub typhus co-infection in febrile patients: a systematic review and meta-analysis', *Parasites & Vectors*, 14(1), p. 471. Available at: <https://doi.org/10.1186/s13071-021-04969-y>.
- Xu, G. et al. (2017) 'A review of the global epidemiology of scrub typhus', *PLoS Neglected Tropical Diseases*, 11(11), p.e0006062. Available at: <https://doi.org/10.1371/journal.pntd.0006062>.
- Rathi P, Siddiqui KA, Shah P. Scrub typhus-related hepatotoxicity: The Indian scenario. *Tropical Doctor*. 2021;51(2):228-231. doi:10.1177/0049475521991353