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## Review

# Scrub Typhus: Epidemiology, Clinical Presentations, and Diagnostic Approaches

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**Abstract:** Scrub typhus (ST) is one of the most neglected tropical diseases, a leading cause of acute undifferentiated febrile illness in areas of the 'tsutsugamushi triangle', diagnosed frequently in South Asian countries. The bacteria *Orientia tsutsugamushi* is the causative agent of the disease, which enters to human body through the bite of trombiculid mite (Chigger) of the genus *Leptotrombidium deliense*. The diagnosis of the disease becomes challenging as its early symptoms mimic other febrile illnesses like dengue, influenza, and corona viruses. Lack of rapid, reliable, and cost-effective diagnostic methods further complicates the identification process. Northeast India, a mountainous region with a predominantly rural tribal population, has witnessed a resurgence of scrub typhus cases in recent years. Various ecological factors, including rodent population, habitat characteristics, and climatic conditions, influence its prevalence. Entomological investigations have confirmed the abundance of vector mites, highlighting the importance of understanding their distribution and the probability of transmission of scrub typhus in the region. Proper diagnosis, awareness campaigns, and behavioral interventions are essential for controlling scrub typhus outbreaks and reducing its impact on public health in Northeast India. Further research and community-based studies are necessary to accurately assess the disease burden and implement effective prevention strategies.

**Keywords:** Northeast India; scrub typhus; *Orientia tsutsugamushi*; clinical presentations; co-infections; diagnosis; genetic diversity; entomology

## 1. Background

Scrub typhus is a vector-borne zoonotic disease caused by *Orientia tsutsugamushi*, an intracellular gram negative bacteria [1]. It belongs to the order Rickettsiales within the family Rickettsiaceae [2]. The disease is transmitted to humans through the bites of infected chiggers, which are small mites of the species *Leptotrombidium deliense* [3]. Scrub typhus is primarily known to be endemic in the Asia-Pacific region, often referred to as the "tsutsugamushi triangle,". However, with the passage of time, this disease has spread beyond tsutsugamushi triangle including Chile, Peru, parts of Africa, and the Arabian Peninsula [4,5]. Scrub typhus is considered a neglected tropical disease, and a significant cause of undifferentiated febrile illness [3,6]. It can be life-threatening if left untreated. It is estimated that scrub typhus intimidates more than one million infected people per year by causing substantial mortality all over the world [6].

The World Health Organization (WHO) recognizes scrub typhus as an important rickettsial infection and considers it as one of the most underreported diseases that often requires

hospitalization [7]. Scrub typhus is prevalent in tropical areas throughout the year favoring the growth and reproduction of mites, while in temperate regions, the disease can occur seasonally [8].

In the early phase, the symptoms of scrub typhus resemble those of other infections like dengue, encephalitis, influenza, and corona viruses, leading to acute febrile illness [9]. After 5-14 days of bites by an infected mite, the patient starts to exhibit an appearance of non-specific flu-like symptoms such as fever, headache, cough, myalgia, nausea, vomiting, abdominal pain, and lymphadenopathy. If not treated on time this can lead to severe complications that event in multi-organ failure including jaundice, acute renal failure, pneumonitis, acute respiratory distress syndrome (ARDS), meningoencephalitis, and disseminated intravascular coagulation. The bacteria primarily target the lungs, leading to varying degrees of pulmonary complications [10].

Eschar is a key clinical presentation of scrub typhus, a necrotic lesion on skin [11], although its absence does not rule out the infection. Laboratory-based diagnosis of scrub typhus relies on various serological assays, including the Weil-Felix test (WFT), indirect immunofluorescence assays (IFA), immunochromatographic tests (ICT), and enzyme-linked immunosorbent assay (ELISA). Although indirect IFA are considered the gold standard for diagnosing scrub typhus, they require high technical expertise. As an alternative, the IgM ELISA-based method is considered the most reliable for the diagnosis of scrub typhus [12]. ICT are particularly valuable as rapid and early diagnostic tools, especially in resource-limited areas where immediate diagnosis is essential for timely treatment [9].

A higher prevalence of this disease has been observed in rural areas of Southeast Asian countries, particularly among individuals who engage in occupational or recreational activities that expose them to mite-infested environments, such as brush and grasslands [13–15]. However, there has been a recent spread of scrub typhus in urban areas [16,17]. The mortality rate can vary as high as 30% or more among untreated individuals [3,9]. Imported cases of scrub typhus have also been identified in some travelers returning from the Tsutsugamushi triangle [18,19].

This disease scrub typhus was a major epidemic during the Second World War in Assam and West Bengal and in 1965 Indo-Pak war in the Jammu - Sialkot sectors among the militants [20]. After decades of rare occurrence, the re-emergence of the disease has been reported in different states of India including Tamil Nadu, Kerala, Maharashtra, Rajasthan, Himachal Pradesh, West Bengal, and in the entire North Eastern states [8]. This article highlights the prevalence of scrub typhus in Northeast region and addresses the existing gaps in diagnosis and management. We also described the clinical features, laboratory investigations, risk factors, entomological investigations and treatment outcome during the studies.

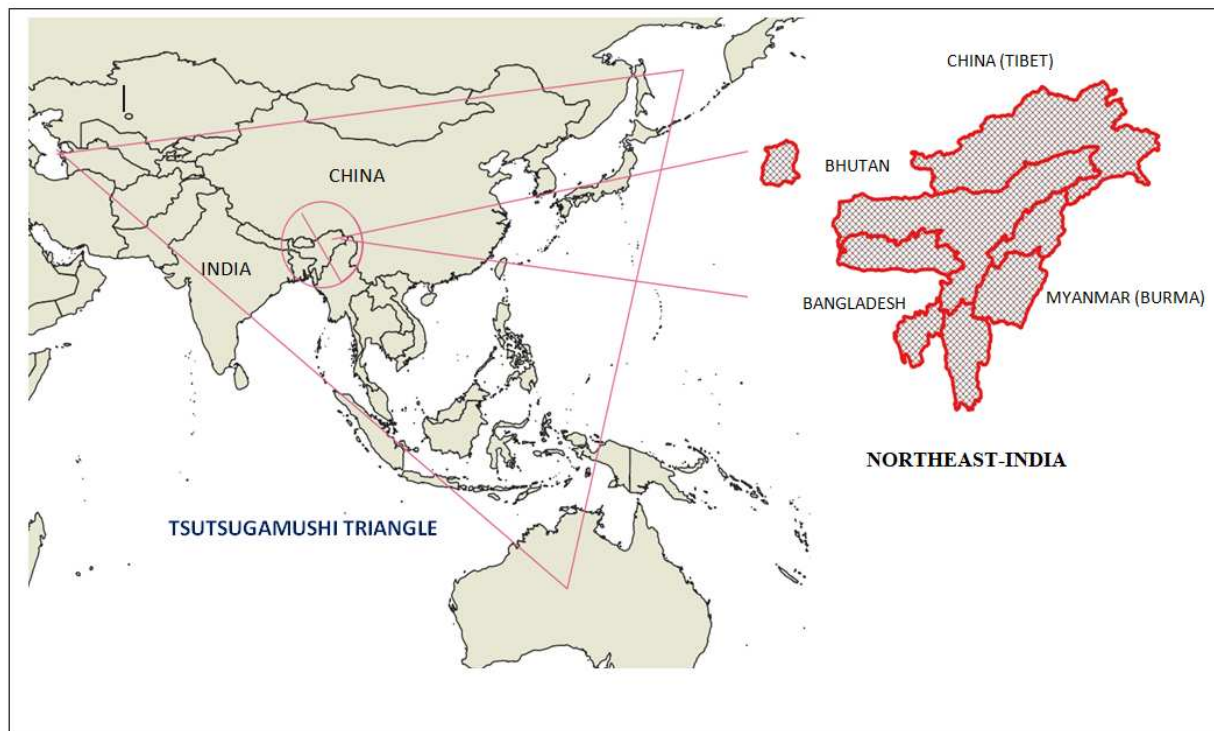
## 2. Search Methodology

A literature search was conducted on studies documenting scrub typhus in Northeast India. All papers published between the years 2010 to 2022 from PubMed, Scopus, and Google Scholar (including non-indexed papers) were retrieved using the following search terms: 'Scrub', or '*Orientia tsutsugamushi*', and 'AND Northeast India'. A second search included 'Scrub typhus' used with 'AND' and either 'Mizoram', 'Arunachal Pradesh', 'Meghalaya', 'Nagaland', 'Sikkim', 'Assam', 'Tripura', or 'Manipur'. All the available information on the occurrence of scrub typhus in Northeast India, including exposure histories, case reports, antibiotics administered, age, sex, address, diagnosis, and laboratory test, were included. We also included the entomological investigations conducted as well as risk factors associated with the disease. Additionally, review articles were excluded to avoid duplication.

## 3. Geography of North-East India

Northeast India located at the easternmost part of the country, is characterized by its predominantly rural tribal population, comprising 82% of the total population whose livelihoods rely on agriculture and forest-based activities [21,22]. About two-thirds of this region is occupied by hilly and mountainous terrain ranging from 50 meters (Brahmaputra valley) to 7000 meters (Himalayan borderland) above sea level [23]. It comprises eight states and spans an area of approximately 0.26

million square kilometers. It is situated between 22°N and 29°5'N latitude and 88°E and 97°30'E longitude, sharing international borders with Bhutan (north), Tibet (north), Myanmar (east), and Bangladesh (south) (Figure 1) [24]. The forest covers around 14.2 million hectares with an approximate of 54.16% to 60% of the total geographical area [22]. Northeast India experiences a humid subtropical climate. During winter the average temperature is 16 °C and rises to approximate 30 °C during summer [25]. The temperatures in the region, as anywhere else, may vary with height. No part in the Northeast receives a rainfall of less than 1,200 mm [25]. This region serves as a vital gateway to Southeast Asian countries, facilitating trade and cultural exchange.



**Figure 1.** Map locating Tsutsugamushi triangle and North-East (NE) India. Red line shows the boundaries of the eight states of NE India.

#### 4. Scrub Typhus in Northeast India

The Northeast India region falls within the Southeast Asia rice domain and is known for its unique practice of 'slash and burn' shifting cultivation, locally referred to as '*jhuming*' [26]. This traditional method involves clearing the jungles, creating an environment conducive to the growth of scrub vegetation. Consequently, the region becomes an ideal habitat for the mites that are responsible for transmitting scrub typhus [10]. Northeast India is also renowned for its abundant biodiversity [26], with lush vegetation providing a suitable environment for the presence of these mites [27]. The Northeast Indian states bordering Myanmar are strategically important as they can serve as a conduit for vector-prone diseases.

In Southeast Asian countries, febrile illnesses contribute significantly to morbidity and mortality [28]. Among these, Rickettsial infections stand out as the most identifiable cause of febrile illness in the region. Prevalence rates of *O. tsutsugamushi*, *Rickettsia typhi*, and some members of Spotted fever group rickettsiae (SFGR) range from 7% to 90% of overall rickettsial infections [29]. The sub-tropical climate of Northeast India accounts for most of acute febrile illnesses such as malaria, scrub typhus, leptospirosis, chikungunya, and dengue. There has been a report of mixed infections, overlapping cases, or co-infections among febrile illnesses in India including the Northeast region [30,31]. There is widespread prevalence of rickettsial infections in the Northeast region [32]. In addition, Japanese encephalitis virus (JEV) infection, West Nile virus (WNV) infection, scrub typhus infection and



leptospirosis have been identified as key contributors to acute encephalitis syndrome (AES) in the Northeastern region of India [33].

Scrub typhus, an acute febrile illness has been recognized and referred to by different names in various regions of Asia throughout history [34]. In Northeast India, the local population has long been aware of this disease and has specific names for it in different areas. In the Meghalaya region, it is referred to as "Niangsohot," which signifies an organism associated with chestnut [35]. In Manipur, it is called "Khullai-laipha" [36]. In Mizoram, there is a possible association between the disease and the flowering of bamboo, which leads to an increase in the rodent population that feeds on the nutritious bamboo fruits and flowers [37]. In the Noklak district area of Nagaland, the disease is locally known as "Hokia" meaning disease of legs. According to local people of Noklak region, the disease appears to be associated with the neighbouring region of Myanmar due to the porous border (unpublished record). It is speculated that the pathogen responsible for scrub typhus, *O. tsutsugamushi*, may be transported within the state through migrating rodents from various potential sources outside the state [38]. These local associations and names reflect the regional prevalence of scrub typhus in Northeast India.

The first cases of scrub typhus in Northeast India were documented along the Indo (Assam now Manipur)-Burma border during Second World War (1943-1945) [39], following which 91 cases of scrub typhus were reported among troops during the period 1965-69 [40]. Since 2001, there have been outbreaks of febrile illnesses accompanied by eschar formation reported in various parts of Northeast India [36,37,41,42], marking a resurgence after decades. Despite this, specific data regarding the occurrence of scrub typhus in many of Northeast states is still lacking. In 2004, a clinically positive scrub typhus from Sikkim was reported, which might likely be the first clinical report from Northeast India after its initial documentation [41]. Subsequently, the first outbreak in Manipur was reported in 2007 by Singh *et al.* [36]. Resurgence of scrub typhus was also reported in Assam, Arunachal Pradesh, and Nagaland states during 2010-2011 [43]. Since then, scrub typhus cases have been reported, indicating the continued presence of the disease in the region.

In 2020, during the COVID-19 pandemic, over 600 cases of scrub typhus were confirmed in the Noklak district of Nagaland, which borders Myanmar. Unfortunately, five people succumbed to the disease out of a total population of 24,189 (according to the 2021 Aadhar estimates). In 2022, local reports revealed that three individuals, including a three-year-old girl and an eight-year-old boy, died from scrub typhus infection, while approximately 20 people were under medical care in Manipur's Kangpokpi district [44,45]. Numerous similar outbreaks have been reported by K. Lalthandama in different district of Mizoram [46].

Various ecological factors have the potential to influence the risk of scrub typhus such as the abundance and diversity of vector species, infection rates of *Orientia* chigger, the presence of small mammals, habitat characteristics including the presence of invasive plants, geographic latitude, seasonality, climate conditions, alterations in land use, as well as specific occupations and human behaviors [47,48].

4.1. Descriptive Epidemiology:

The epidemiology of scrub typhus varies geographically based on different climatic conditions, the presence of diverse etiological agents, vectors involved in transmission, various human behaviors and the susceptibility of population [49,50]. We identified 45 published papers including case reports of scrub typhus conducted between 2010- 2022 [Tables 1 and 2]. A total of 3697 clinically diagnosed and laboratory confirmed cases of scrub typhus were reported in Northeast region (2010–2022), among whom 88 patients died. The overall case fatality was 2.4%.

**Table 1.** Prevalence of scrub typhus in North-East India.

Region	Outbreak/ study Duration	Age in months/ Years	Diagnostic confirm cases	Method of diagnosis	Antibody/ marker gene	Fatalities	Affected groups/Outcome/Remarks	References
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Lawngtlai District, Mizoram	December , 2019	Mean age was 40 years	80	WFT	OxK	NA	Affected group: adults (31-40 age group), farmers, female, rural areas.	(Pautu et al. 2022) [51]
Assam	April 2017 to March 2018	3 to 85 yrs (mean age 39.6 yrs)	56	ICT	IgG, IgM, IgA	NA	Liver function evaluation and proteinuria attained statistical significance.	(Palani et al. 2022)* [71]
Mizoram	October 1, 2018 to September 31, 2019	7 months to 94 years	36	ICT, ELISA	IgG, IgM, IgA, IgM	NA	The sensitivity of IgM ELISA and Rapid test were 44.19% and 46.40% respectively. 36 positive for both ICT and ELISA.	(Vanlalruati et al. 2022) * [72]
Nagaland	December 2018	NA	2 (pcr) 87 (WFT)= 89	PCR WFT	56 kDa OxK	NA	Closest homology with the prototype strain TA763 (endemic in Thailand and Taiwan).	(Khan et al. 2022) [73]
Manipur	August 2017 to December 2018 Peak season : July to November	≥12 years Mean age: 41 years (±16)	176	ICT	IgG, IgM, IgA	8	Affected group: rural areas, farmers, and adults.	(Ngulani et al. 2021) <sup>s</sup> [65]
Assam, Meghalaya, and Tripura	September 2017 to February 2018	3 to 45 years	18	ELISA	IgG	NA	Community based studies Documented low prevalence (0.76%) of scrub typhus.	(Khan et al. 2021)* [74]
Meghalaya	June 2019 to May 2020	NA	37	WFT ELISA PCR	OxK IgM 56 kDa	NA	14% OxK positive 34 % ELISA positive 50% PCR positive (27/54)	(Durairaj et al. 2021) # [75]
Tripura	January 2018 to December 2018 Peak season: September	Mean age 28 to 50 years.	40	NA	NA	1	Deranged liver function and thrombocytopenia significant.	(Debnath et al. 2021)* [64]
Assam	January 2017 to September 2017	≥11 years Mean age: 20-29 years	14	ELISA	IgM	NA	Prevalence rate of Scrub typhus: 20%.	(Dhar et al. 2020)* [63]
Manipur	August 2017 to November 2018	≥20 years	8	WFT ELISA	OxK IgM	1	Scrub typhus Presenting as Acute Abdomen case.	(Singh et al. 2019) # [76]
Meghalaya	January 2013 to December 2015	≥ 18 years	129	ICT WFT ELISA	IgM OxK IgM	NA	Eschar was found in 24.8% of the scrub typhus patients.	(Jamil et al. 2019) <sup>s</sup> [67]
Assam and Arunachal	December 2014 to December 2016. Peak season: May to August	3 to 80 years	278	ELISA PCR	IgM, IgG, 47 KDa, 56 KDa, 16S rRNA	NA	Pre-dominance of Karp-like strains.	(Bora et al. 2018) [66]
Assam	NA	1- >60years Mean age: 25-36 yrs	33	ELISA	IgM	NA	Prevalence rate of scrub typhus: 22.2%	(Mohan et al. 2018) [78]
Mizoram	January 2012 to July 2017	22 months -85 years	907	ICT	IgM, IgG and IgA	34	Age group 20-30 years were affected more. The youngest patient recorded was a 2 months old male.	(Lalmalsawma, et al. 2017) [37]

	Peak season: July and November	Mean age: 34 years					Male affected more.	
Manipur	January 2016 to May 2017	6 to 67 years	24	ICT	IgM, IgG and IgA	NA	Affected group: Rural background. One patient was Dengue positive	(Huidrom et al. 2017) ^ [58]
Tezpur, Assam	April 2011– November 2012	≥5 years	75	IFA ELISA	IgM	NA	Affected group: Rural areas Scrub typhus co-infection observed.	(Mørch et al. 2017)* [31]
Dibrugarh, Assam	2013–2015 Peak season: July– September	3 to 80 years	104	ELISA PCR	IgM 56-kDa	26	13 (12.5%) co-infected with JEV IgM. Resemblances of Karp strain. Occupation= NA High case-fatality rate of 49% (26/53 follow-up)	(S A Khan et al. 2017) * [33]
Aizawl, Mizoram	October 2014 to December 2016. Peak season: November to February and September to October (autumn)	1 to ≥60 years	283	ICT	IgM	NA	21–30 age groups were most affected. Prevalence of ST 6.9%.	(Lalrinkima et al. 2017) * [77]
Nagaland	2014	-	31	ELISA	IgM	NA	Community based studies. 7.2% samples positive by IgM ELISA.	(Khamo et al. 2016) [42]
Meghalaya	January 2014 to December 2014	Below 18 years	75	ICT	IgM, IgG and IgA	1	Inclusion: children below 18 years. Antibiotics data not available.	(Lurshay et al. 2016) [54]
Arunachal Pradesh	2009 to 2013	2– 80 years	121	ELISA	IgG	NA	Community based studies. Farmers, adults, females were affected more. Seroprevalence was 40.3%.	(Jakharia et al. 2016) * [56]
Meghalaya	September 2011 to August 2012 Peak season: September to December	≥ 18 years Mean age: 21–30 years	90	ICT	IgM, IgG and IgA	5	Farmer, 21–30 years were more affected. 13.6 % ST positive. Malaria co-infection observed in two patients.	(Sivarajan et al. 2016) ** [68]
Arunachal Pradesh	NA	0 - ≥ 15 years	30	ELISA	IgM	NA	25% cases were co-infected with leptospira.	(Borkakoty et al. 2016)* [52]
Assam, Arunachal, Nagaland	2013 to 2015	-	390	ELISA PCR	IgM 56-kDa	NA	Community based studies 30.8% positive for scrub typhus. Sequence analysis revealed Karp-like strains from Thailand, Taiwan and Vietnam.	(Khan et al. 2016)* [32]
Meghalaya	October 2009 to November 2011	19 to 68 years	23 (meningitis)	WFT ELISA	OX K IgM	NA	Scrub meningitis cases. Majority of patients were either farmers or housewives.	(Sharma et al. 2015) * [70]
Meghalaya	January 1, 2013 to December 31, 2014. Peak season: October to November	Above 12 years Mean age: 34.84 ± 16.21 years	113	WFT ICT	OXK IgM	2	13.2% featured with meningitis/meningoencephalitis. 0.07% had multiple eschar.	(Jamil et al. 2015)* [69]
Meghalaya	September 2010 to August 2012	Mean age 40 ± 12 years	96	ELISA PCR	IgM 56-kDa	NA	Kato (Hualien-13) closest to Cambodia and Neimang-65 strains were observed.	(Varghese et al. 2015) [79]

							Karp and Gilliam like strains were also observed.	
Meghalaya	7th January 2013 to 6th January 2014 Peak season: September to November	≥ 18 years	61	WFT ICT	OXX IgM, IgG and IgA	5	18 to 30 year's age group was affected. 4.9% scrub typhus patients' pregnant women were treated with azithromycin.	(Jamil et al. 2014) <sup>#</sup> <sup>++</sup> [35]
Manipur	July to October	15-65 years	6	ICT	IgM, IgG and IgA	NA	Affected group: rural areas. 2 scrub typhus patients had eschar	(Singh et al. 2014) [80]
Sikkim	January 2011 to December 2011 Peak season: July and October	Above 2 years	63	WFT ICT ELISA	OXX IgA, IgM, and IgG IgM	1	Eschar was seen in 10 pediatric patients. 55.56% had pedal edema. 30.8% scrub typhus positive for IgM ELISA.	(Gurung et al. 2013) <sup>+</sup> [41]
Assam, Arunachal Pradesh, and Nagaland	2010 to 2011	NA	108	ELISA PCR	IgM 56-kDa	NA	34.39% scrub typhus positive for IgM ELISA. 15.38% were PCR-positive for ST.	(Khan et al. 2012) [43]
Meghalaya	October 2009 to January 2010	Average age: 9.4 years	24	WFT	OXX	NA	Pediatric scrub typhus cases.	(Dass et al. 2011) [53]
Manipur	2007	0 to ≥ 45 years	38	WFT	OXX	2	71% received treatment from traditional healers. 55% had eschar on the perineal area.	(Singh et al. 2010) [36]

\$ Retrospective study ; # Cross sectional study / prospective study ; ^ Antibiotics administered before confirmation of diagnosis ; + Antibiotics used in younger children or pregnant women ; \* Co-infection with leptosptosis, JEV IgM, Dengue and other febrile illness. IFA: Immunofluorescence Assay, WFT: Weil Felix Test, ELISA: Enzyme-linked Immunosorbent Assay, PCR: Polymerase chain Reaction.

**Table 2.** Case report of Scrub typhus from Northeast-India.

Region	Cases	Diagnosis	Treatment	Fatalities	References
Mizoram	1	IgM ELISA	Ceftriaxone-sulbactam Doxycycline Azithromycin	-	(Lallawmkima et al. 2022) [99]
Sikkim	3	WFT IgM ELISA	Ceftriaxone <sup>^</sup> , Amiodarone <sup>^</sup> Doxycycline +	-	(Mohanty et al. 2019) [100]
Sikkim	1	WFT, ELISA	Ceftriaxone <sup>^+</sup> , Doxycycline <sup>+</sup>	-	(Mohanty et al. 2017) [101]
Assam	3	WFT	Cefotaxime, Doxycycline Derriphylline	-	(Mangaraj et al, 2017) [102]
Nagaland	2	ICT	Doxycycline	-	(Biradar et al. 2015) [103]
Assam	3	ELISA	NA	-	( Baruah et al.2015) <sup>*</sup> [81]
Meghalaya	1	ICT	Ceftriaxone, Doxycycline, Azithromycin	-	(Ete et al. 2015) [104]
Meghalaya	1	WFT	Inj. Artesunate, Inj. Acyclovir and Inj. Ceftriaxone <sup>^</sup> Tab. Doxycycline Pantoprazole Inj. Dobutamine Inj. Azithromycin	1	(Karim et al. 2014) [105,112]



Manipur	1( Guillain-Barre syndrome)	ICT	Doxycycline	-	(Sawale et al. 2014) [107]
Sikkim	1	WFT, ICT, ELISA	Cefotaxime, Doxycycline	-	(Dhakal et al. 2014) [106]
Meghalaya	1	WFT	Doxycycline, Ceftriaxone Chloramphenicol.	-	(Goswami et al. 2013) [108,109]
Sikkim	5	WFT ELISA	Doxycycline <sup>+</sup> Ceftriaxzone <sup>+</sup>	1	(Gupta et al. 2012) [85,113,114]

\$ Retrospective study ; # Cross sectional study / prospective study ; ^ Antibiotics administered before confirmation of diagnosis ; + Antibiotics used in younger children or pregnant women ; \* Co-infection with leptosptosis, JEV IgM, Dengue and other febrile illness. IFA: Immunofluorescence Assay; WFT: Weil Felix Test; ELISA: Enzyme-linked Immunosorbent Assay .

The majority of patients presented with clinically suspected cases of scrub typhus, exhibiting symptoms such as prolonged fever and acute undifferentiated febrile illness. An outbreak of scrub typhus-like illness with eschar has been reported in the Northeast India since 2001 following the initial report of the disease in 1945 [36,39]. This review includes various types of studies conducted on patients attending healthcare facilities, comprising a retrospective study, a cross-sectional study, and a study carried out in a community setting. Meghalaya accounted for majority of the reported cases. The highest numbers of cases were reported during the months of July to November (monsoon or post monsoon)/autumn [Table 1]. The majority of cases and suspected cases were identified among farmers and rural inhabitants.

#### 4.2. Age and Gender Cases

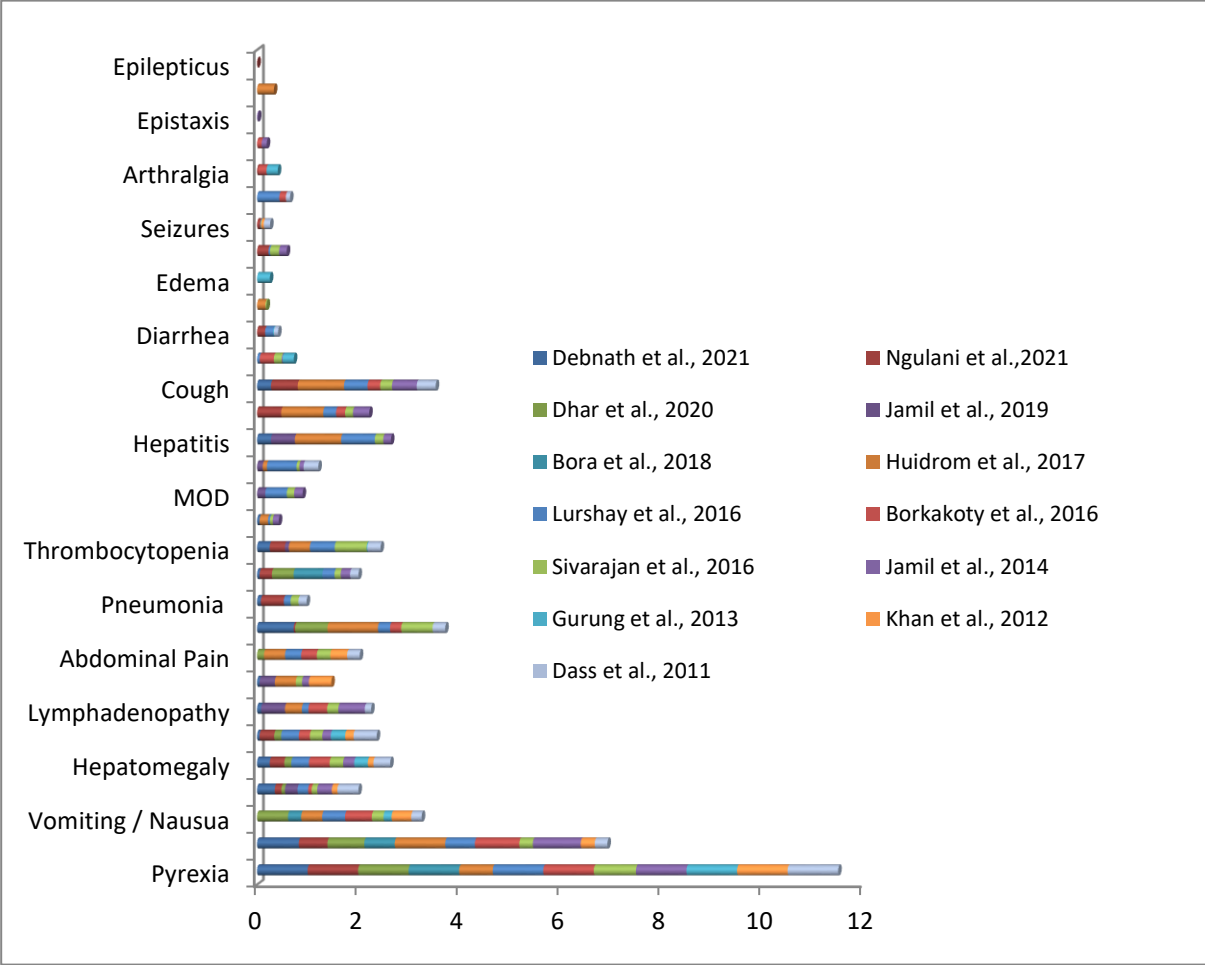
The majority of confirmed scrub typhus cases in the laboratory were among adults, with significantly higher seropositivity observed in males compared to females. This gender difference may be attributed to males engaging in more outdoor activities than females. However in some studies, positivity for scrub typhus was significantly higher among female [51,52]. In the outbreak that took place in Meghalaya, the affected individuals were primarily children, with an average age of nine years [53]. It reported a higher percentage of children being infected with scrub typhus compared to the adult population [53]. Lurshay *et al.* reported a higher incidence of meningoencephalitis among pediatrics patients [54]. Eschar was also observed among pediatric patients. In Mizoram, five positive cases were recorded in patients under the age of one year, unfortunately resulting in the death of a two-month-old male [55]. In addition several studies have also reported cases of scrub typhus among pediatric patients [35,41,52,55,56]. The occurrence of scrub typhus among pediatric patients could be attributed to activities like playing outdoors or being taken to fields by parents during fieldwork. It also indicates the presence of a high population of mites in an area contributing to the transmission of scrub typhus not only to adults but also to pediatric.

#### 4.3. Diagnostic Conformation

The study's findings suggest that young adults exposed to scrub vegetation account for the majority of laboratory-confirmed cases of scrub typhus in Northeast-India. The analysis included studies that employed serological or molecular methods to confirm scrub typhus cases (excluding case report). A significant number of studies relied on ELISA (56%), an accurate and easily accessible diagnostic test, as the confirmatory measure. In a recent study comparing molecular and serologic tests for scrub typhus diagnosis, ELISA demonstrated a sensitivity of 94.2% and a specificity of 93.6%, which makes it more reliable test [57]. Additionally, ELISA is a more cost-effective alternative to polymerase chain reaction (PCR). PCR was used in combination with the WFT or ELISA to confirm 22% (7/32) of the studies (n=2 and n=6, respectively). Approximately 40% (13/32) of the studies relied on the ICT, known for its low sensitivity.

#### 4.4. Clinical Presentations

In all the studies, fever/pyrexia was the most prevalent clinical manifestation observed among the case patients, followed by headache ranging from 25% to 100% [54,58]. The various clinical manifestations are listed in Figure 2. While the presence of an eschar is a valuable clinical clue for diagnosing scrub typhus, its absence does not rule out the possibility of the disease. According to Yoo *et al.*, the overall prevalence rate of eschars was 58.0%, with the highest prevalence in East Asia (78.7%), followed by Oceania (52.2%), Southeast Asia (41.4%), and the lowest in South Asia (32.8%) [59]. In this review, the occurrence of eschars among the studied population ranged from 7% to 41.7% [52,53], which is similar to other states in India, where the range is between 9.5% and 55% [60,61]. Some studies did not identify any eschars in their cases. This may be attributed to unawareness of the disease in rural areas. In endemic areas, it is common for Indigenous patients to have less severe illness, often with or without rash and eschar [62].



**Figure 2.** Proportion (%) of clinical manifestation among scrub typhus patients.

Other clinical features observed included: nausea or vomiting (15.8% to 61.29%) [41,63], splenomegaly (5% to 45.8%) [53,64], hepatomegaly (11.1% to 41%) [34,43], lymphadenopathy (8% to 52.54%) [35,64], acute kidney injury/acute renal failure (AKI/ARF) (5% to 44.4%) [43,64], abdominal pain (13.7% to 41.6%) [58,63], myalgia (2.8% to 100%) [58,65], pneumonia (7.5% to 45.5%) [64,65], altered sensorium (5% to 56.9%) [64,66], thrombocytopenia (1.5% to 63.6%) [41,68], acute respiratory distress syndrome (ARDS) (4% to 16.6%) [54,58], multiple organ dysfunction (MOD) (14.4% to 42.6%) [54,68], meningoencephalitis (5.5% to 58.6%) [54,68], hepatitis (15.25% to 91.6%) [35,58], breathing/tachypnea (15.5% to 83.3%) [58,68], cough (23.3% to 91.6%) [58,68], rash (1.69% to 28%) [52,54], diarrhea (1.5% to 16%) [41,54], shock (2.2% to 16.6%) [58,68], icterus/jaundice (3% to 22.7%) [54,65], seizures (1.5% to 12.5%) [41,53], conjunctival redness (8.3% to 44%) [53,54], arthralgia (2.8%

to 22%) [41,65], anuria/oliguria (9% to 10.17%) [35,52]. Less common manifestations included: haemoptysis (33.3%) [58], edema (25.3%) [41], epistaxis (1.69%) [35], and status epilepticus (0.5%) [65].

A publication from South India reported scrub typhus meningitis as a common central nervous system (CNS) complication. In this review, two papers presented the clinical profiles of patients with scrub typhus meningoencephalitis [69,70], where patients exhibited neurological manifestations as the main presenting feature. Various neurological manifestations include headache, meningitis, neck rigidity, seizures, and neurological deficits.

A retrospective study conducted by Khan *et al.* in 2017 reported *O. tsutsugamushi* infection as a leading cause of AES with a mortality rate of 49% [33].

#### 4.5. Co-Infection

In tropical countries, co-infections commonly occur alongside scrub typhus infection due to the similarity in clinical features. Failing to receive treatment on time for co-infections can result in life-threatening situations [81]. A study conducted in various Indian states including Assam, Meghalaya, and Arunachal Pradesh revealed the occurrence of scrub typhus co-infections along with other febrile illnesses such as leptospirosis, dengue, chikungunya, bacteraemia, pulmonary tuberculosis, and malaria [31,35,52,68,82]. High prevalence of co-infections of about 35% between scrub typhus and malaria was observed in Thailand and low prevalence in India exclusively, according to the recent review report [83].

Scrub typhus and leptospirosis might share similar transmission routes when rodent animals are significant [84]. Borkakoty *et al.* observed that 25% of scrub typhus cases in Arunachal, Northeast India, had co-infection with leptospira [52]. A report however suggests that the elevated rate of co-infection could be due to cross-reactivity and the presence of background positivity in patients residing in endemic areas, rather than true co-infection [31]. Therefore, it is advisable to interpret the outcomes of a single serological test for diagnosing scrub typhus with caution.

#### 4.6. Genetic Diversity

An extensive genetic variation has been observed across different geographical area with over 20 antigenically distinct strains including three prototypic strains—Karp, Gilliam, and Kato. In this review, we identified the circulating genotypes of *O. tsutsugamushi* in five different studies from Northeast India [32,33,66,73,79]. Sequences analyzed from different Northeastern states showed the presence of Karp, Kato, and Gilliam-like strains similar to those found in Southeast Asian countries [32,73,79]. Neimeng-65 strains were also reported in Shillong, Meghalaya [79]. Two studies revealed the presence of the TA763 genotype, also known as the Fan strain, which is endemic in Thailand and Taiwan [66,73].

#### 4.7. Treatment and Outcomes

The majority of studies have documented the use of doxycycline (including pediatric cases) [85] and azithromycin as treatment option for patients with scrub typhus with better outcome. However, it is worth noting that in earlier times, traditional healers were often sought for treating illnesses that exhibited similarities to scrub typhus in some Northeast states [36,37].

Dass *et al.* reported the use of intravenous chloramphenicol in pediatric patients with complications such as meningoencephalitis, septic shock, or myocarditis, and azithromycin in 3 cases (12.5%) of patients below 8 years of age [53]. Furthermore, three studies have specifically reported the administration of azithromycin for the treatment of pregnant women with scrub typhus [35,41,68].

These findings highlight the commonly used antibiotics, such as doxycycline and azithromycin, for the treatment of scrub typhus, including in pediatric and pregnant populations.

#### 4.8. Entomological Investigations

Entomological investigations were conducted in four studies (Table 3), involving the trapping of rodents in domestic and predomestic areas. Standard procedures were followed to collect and identify ectoparasites found on these rodents. *Leptotrombidium deliense*, known as the main vector of scrub typhus (*tsutsugamushi* disease) in various parts of the world [86], was abundant in three of the studies [32,87,88]. Among the trapped rodents, the infestation of vector mites was found to be the highest [87,88].

In Meghalaya and Mizoram, the chigger index exceeded the critical index of 0.69 per rodent, with values of 1.80 and 12.33 respectively. Similarly, the chigger infestation rate in Meghalaya and Mizoram were recorded as 4.8 and 18.5 respectively [87,88].

In one of the recent study conducted by Pautu *et al.* chigger index was 12.33 which was 27 times higher than the critical value [52].Among the two studies conducted for serological test in rodent sample; one study yielded positive results for scrub typhus pathogens [32], while the other study exhibited reactivity to one or all of PROGEN OXK, OX19, or OX2, indicating the presence of scrub typhus along with other rickettsial diseases [52].

Table 3. Entomological studies on vectors.

Region	Host	Ectoparasites	Outcome	References
Mizoram	Rodent Species	Mites (chigger)	Reactive with any one or all of PROGEN OXK, OX19 or OX2. Chigger (mite) index =19.2	[52]
Mizoram	Rodent Species	Mites, Lice, Fleas	Chigger (mite) index =12.33 Chigger infestation rate=18.5	[88]
Assam, Arunachal Pradesh and Nagaland	Rodents, dogs, cats, cattle, and human	Ticks, mites, fleas and lice	NA for ST(scrub typhus) Positive for spotted fever group <i>Rickettsia</i> species.	[32]
Meghalaya	Rodent Species	Ticks, mites, fleas and lice	Chigger (mite) index =1.8 Chigger infestation rate=4.8	[87]

5. Discussion

This review article highlights the continued presence of scrub typhus in the Northeast India over the past few decades. However, due to limited literatures available, the actual scenario of cases might be hidden since years. In this region scrub typhus cases are commonly reported in rural areas, as such this review attempts to highlight the scarcity of studies, underscoring the neglect of scrub typhus as a disease in terms of research and policy framing. In the course of time, different seroprevalence studies were carried out, revealing the vast variance in the prevalence rate, ranging from 0.76% to 40.3% [56,74]. This finding might be suggestive of geographical restrictions of the disease, based on varied factors.

Latest epidemiological review of scrub typhus in India reported the highest proportion of cases from South India (55.5%), while the Northeast region had the second lowest proportion (7.4%) [89].This discrepancy may be partly attributed to differences in disease awareness and the availability of diagnostic facilities. Despite scrub typhus primarily affecting rural regions, most of the studies were conducted in semi-urban or urban settings, indicating an uneven distribution of healthcare facilities and research sites, highlighting limited healthcare access for rural patients.

Scrub typhus presents diagnostic challenges, as it closely resembles other febrile illnesses such as dengue, typhoid fever, leptospirosis, murine typhus and corona virus [8,90].The presence of an eschar in patients can aid in the clinical diagnosis of scrub typhus with higher specificity, but it often

goes unnoticed as it is non-itching, painless, and typically present in areas like the perineum, groin, and axilla [91]. Available studies reported the prevalence of eschar and rash ranging from 7% to 28.8% and 1.69% to 28%, respectively. The most commonly reported clinical presentations during the review included fever, followed by headache, vomiting/nausea, myalgia, cough, and breathing difficulty. Respiratory tract involvement is a frequent manifestation of scrub typhus, and clinicians need to differentiate it from community-acquired pneumonia caused by usual organisms like *Streptococcus* species [92]. Common complications associated with scrub typhus include acute kidney injury, hepatitis, acute respiratory distress syndrome (ARDS), meningoencephalitis, myocarditis, and septic shock.

Confirming suspected cases through appropriate laboratory tests is crucial for documenting scrub typhus infection. While the IgM-based IFA is considered the gold standard for diagnosis [93], a recent review article reported higher sensitivity and specificity for IgG and IgM ELISA compared to the IFA method [57]. In most of the studies, confirmation was primarily done using IgM ELISA, followed by ICT and WFT. Weil–Felix test has very less specificity and sensitivity due to the use of non-rickettsial antigen for agglutination. Despite its drawbacks, it is widely used in rural areas for screening scrub typhus. Further confirmation is required so as to avoid negative result during diagnosis. The use of diagnostic kits such as ICT reflects the limited resources in hospitals, as ELISA readers are not readily available in most remote care centers. Lalrinkima *et al.* reported a low prevalence of 6.9% using ICT [72,110,111], contrasting with Ki-Deok Lee *et al.* who reported higher sensitivity rates of 66.7% and 72.6% for SD Bioline ICT in Thailand and the Korean population, respectively [94]. The low sensitivity of ICT kits could be attributed to the *O. tsutsugamushi* antigens used in their preparation. Therefore, ICT test should be followed by confirmatory tests to ensure accuracy. Relying solely on the ICT test may lead to potential false-positive or false-negative results. The time of blood sample collection also plays a significant role in determining seropositivity in scrub typhus patients. Other studies using ICT also demonstrated low sensitivity at the time of admission but showed a gradual increase in positivity over time [95,96]. Additionally, the presence of IgG antibodies in kits may lead to false positives for scrub typhus, as the patient may have had a secondary infection. Therefore, caution should be exercised when interpreting ICT results. Understanding the circulating genotype in a specific geographical area is also crucial for the development of region-specific diagnostic kits.

Although the Indian Council of Medical Research (ICMR) recommends ELISA techniques, particularly immunoglobulin M (IgM) for scrub typhus diagnosis, ICT has been found to be useful in most remote hospital settings [97,98]. Nevertheless, the findings of this review shed light on certain issues regarding the epidemiology and control of scrub typhus in India. Conducting larger studies to compare ICT results with confirmatory tests would be of tremendous value in resource-poor settings for presumptive diagnosis and management of scrub typhus.

## 6. Conclusions and Future Prospect

In conclusion, our review highlights the distribution of scrub typhus diseases in several parts of Northeast India, mainly hospital-based studies and only 4 community-based studies. In the majority of the papers, we observed a lack of uniform case definition, analytical studies, confirmatory laboratory tests, and entomological surveys. Most studies lacked information on the total number of participants, population patterns, and distribution, making it difficult to obtain precise epidemiological information. Thus, the actual cases of scrub typhus are likely to be substantially higher than what has been reported and summarized in this study, suggesting that our findings represent only the tip of the iceberg.

Further exploration is needed to understand the role of different vector mites and their distribution in an area. It is also crucial to examine seasonal variations of mite's activity and their correlation with case incidence and distribution in affected areas. More research is required to assess the seroprevalence of this disease in domestic and pre-domestic areas in Northeast India, as it can provide valuable epidemiological insights.



Hospital-based studies may not accurately reflect the prevalence of scrub typhus in the community, it is important to conduct additional studies that focus on wider seroprevalence in the community and well-planned prospective evaluations of patients presenting with acute undifferentiated febrile illness (AUF) across different states. This will enable us to understand the exact burden of the disease and implement appropriate control and prevention measures. Many studies did not provide information on the clinical presentation of the disease. As a result, the comprehensive details regarding the clinical presentation of scrub typhus may be limited in the context of this review.

It is also essential to raise awareness among doctors practicing in high-risk areas, to evaluate patients with acute febrile illness carefully. Scrub typhus is prevalence primarily among the villagers where there is the lack of adequate healthcare facilities. Health promotion programs on behavioral interventions should be prioritize, such as avoiding urination or defecation in jungle or bushy areas, protective clothing outdoors, regular bathing after field work, and using mats when lying on the floor. Implementing good sanitation practices in and around the house can effectively reduce the rodent population in the vicinity. Educating the community about the common symptoms of the disease by displaying the poster in a local dialogue, awareness campaigns and encouraging the villagers to seek early treatment from nearby health settings are vital strategies for controlling outbreaks thus reducing mortality rates.

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