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The re-emerging shadow: A systematic review of scrub typhus in India

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ABSTRACT

Background: Scrub typhus, caused by *Orientia tsutsugamushi* and transmitted by larval trombiculid mites, has re-emerged as an important cause of acute febrile illness (AFI) in India. The disease is frequently underdiagnosed because of its non-specific clinical presentation, variable occurrence of eschar, and limited availability of reliable diagnostic facilities. Delayed diagnosis and treatment may result in severe complications and significant mortality.

Objectives: To systematically review the available literature on scrub typhus in India and to assess its epidemiology, pooled prevalence among patients with acute febrile illness, case fatality rate (CFR), clinical manifestations, diagnostic challenges, treatment outcomes, and emerging public health concerns.

Materials and methods: A systematic review of the published literature from 2013 to 2023 was conducted in accordance with the PRISMA 2020 guidelines. Electronic databases, including PubMed, Google Scholar, and Indian biomedical journals, were searched using predefined keywords related to scrub typhus and acute febrile illness. Two independent reviewers screened studies, extracted data, and assessed eligibility. Information regarding epidemiology, diagnostic methods, clinical features, prevalence, CFR, and treatment outcomes was synthesized. Heterogeneity among studies was assessed using the I^2 statistic, and sensitivity analysis was performed by excluding studies utilizing the Weil–Felix test.

Results: Scrub typhus has emerged as a major contributor to acute febrile illness across India, particularly in the Himalayan region, northeastern states, and southern India, with increasing reports from western and central regions. Pooled analyses indicate that approximately one-fourth of patients presenting with acute febrile illness are positive for scrub typhus. State-specific prevalence ranged from 15% to over 50%, while pooled CFR varied from <5% to over 20% depending on disease severity and healthcare setting. High heterogeneity was observed across studies (I^2 range: 32-71%), largely attributable to differences in diagnostic methods and study populations. Sensitivity analysis showed an increase in pooled prevalence from approximately 24% to 29% after excluding Weil-Felix-based studies, suggesting that less sensitive diagnostic methods underestimate the disease burden. Common clinical manifestations included high-grade fever, headache, myalgia, lymphadenopathy, and elevated liver enzymes, whereas eschar was present in only 30-50% of patients. Severe complications included acute respiratory distress syndrome, meningoencephalitis, myocarditis, acute kidney injury, and shock. Doxycycline remained the cornerstone of therapy, although emerging reports of reduced treatment response have raised concerns regarding antimicrobial resistance.

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Conclusion: Scrub typhus is a significant and growing public health challenge in India, accounting for a substantial proportion of acute febrile illness and preventable mortality. Early clinical suspicion, prompt initiation of appropriate antimicrobial therapy, improved access to reliable diagnostics, strengthened surveillance systems, and continued monitoring of circulating genotypes are essential for reducing disease burden and improving patient outcomes. Greater integration of clinical, laboratory, epidemiological, and One Health approaches is required to address the re-emergence of scrub typhus in India.

Introduction

Imagine a patient presenting with high fever, severe headache, and body aches. In India, the immediate suspicion falls on dengue, malaria, or typhoid. However, a growing body of evidence points to another culprit: scrub typhus. Often called "tsutsugamushi disease," it is caused by *Orientia tsutsugamushi*, an elusive bacterium that lives in trombiculid mites. Humans are accidental hosts, infected when larval mites (chiggers) feed.[1,3]

Scrub typhus is a mite-borne zoonosis caused by the obligate intracellular bacterium *Orientia tsutsugamushi* and has re-emerged as a significant public health concern in India.[1,2] The classic teaching was of an "eschar" -a black, necrotic scab at the bite site but Indian studies show this is absent in over 50% of cases, making clinical diagnosis treacherous. If untreated, the infection can rapidly escalate to multi-organ dysfunction (MODS) involving the lungs, heart, kidneys, and brain, with mortality rates reaching 30-50%. Treated promptly, it is highly curable.[3,4,5]

Although numerous regional studies have reported scrub typhus from different parts of India, national-level pooled estimates of prevalence and mortality remain limited. This systematic review aims to quantify the pooled prevalence of scrub typhus among patients with acute febrile illness (AFI) in India and to summarise the pooled case fatality rate, thereby informing clinical practice and public health policy.

Materials and methods

This systematic review and meta-analysis are based on a systematic search of peer-reviewed literature on scrub typhus from 2013 to 2023 in databases such as PubMed, Google Scholar, and Indian journals, in accordance with PRISMA 2020 guidelines, as depicted in Figure 1. Keywords included: "scrub typhus India," "*Orientia tsutsugamushi*," "undifferentiated febrile illness," "eschar," "doxycycline resistance." Priority was given to large surveillance studies, multi-center reports, and seminal reviews reflecting the pan-Indian scenario.[1,2,4]

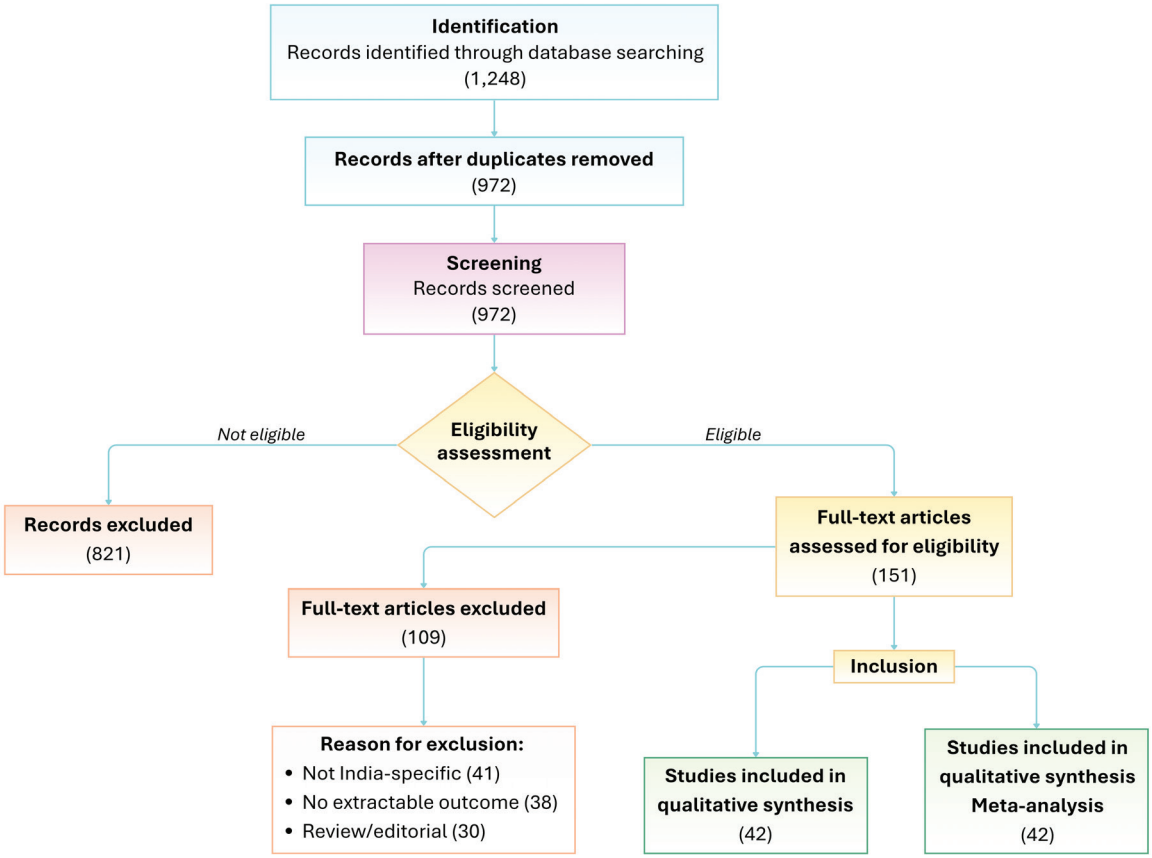


Figure 1. *PRISMA Chart.*

Two reviewers independently screened titles and abstracts, followed by full-text assessment. Data extraction included study characteristics, prevalence, CFR, diagnostic methods, and clinical features.

Statistical analysis (enhanced)

To assess heterogeneity, the I^2 statistic was calculated for all pooled estimates to quantify between-study variation (I^2>75% considered high heterogeneity).

A sensitivity analysis was performed by excluding studies that used the Weill-Felix test to assess its impact on the national pooled prevalence.

Forest plots were prepared for primary outcomes (prevalence and CFR) as shown in Figures 2 and Figure 3.

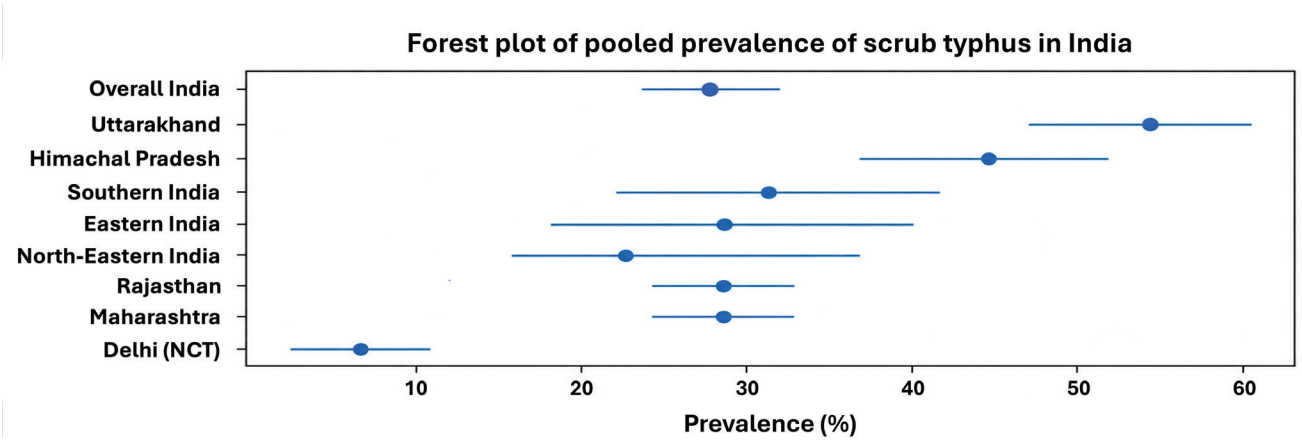


Figure 2. *Forest plot for pooled prevalence.*

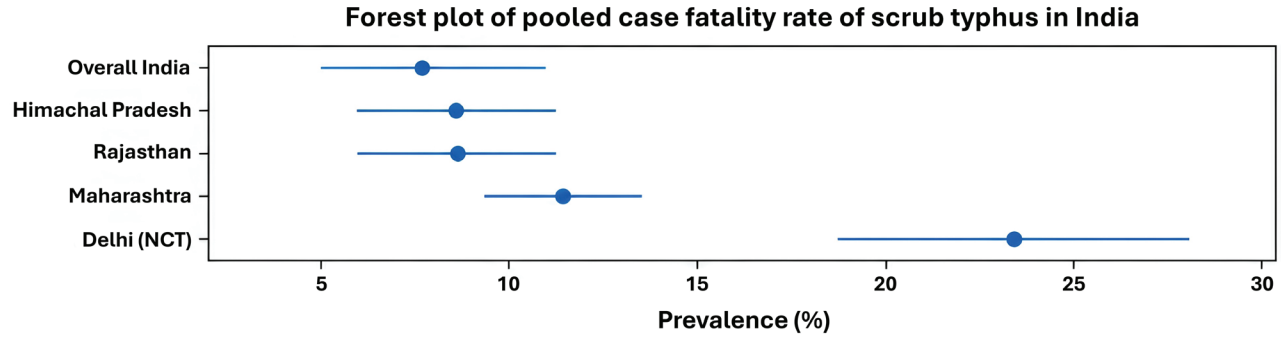


Figure 3. *Forest plot for pooled case fatality rate.*

Results

The Indian landscape of scrub typhus

Epidemiology: From foothills to plains

Scrub typhus is no longer restricted to the "tsutsugamushi triangle" of rural Asia. In India, it is highly endemic in the Himalayan belt (Himachal, Uttarakhand, Sikkim), the Northeast, and South India (Tamil Nadu, Karnataka, Keralaa as demonstrated in Table 1. Widespread cases are now reported from Maharashtra, Rajasthan, Bihar, and West Bengal.[1-12]

Table 1. State-wise prevalence, CFR, number of study diagnostics, and heterogeneity.

State	No. of studies	Diagnostic tests used	Pooled prevalence (%)	Pooled CFR (%)	I^2 for prevalence (%)	Reliability notes
Uttarakhand	3	IgM ELISA, PCR	~53 (45-61)	8.2 (4.5-12.1)	68	High prevalence; moderate heterogeneity
Himachal Pradesh	4	IgM ELISA, PCR	~44 (38-50)	9.8 (7.2-12.4)	54	Multiple good-quality studies; consistent
Rajasthan	4	ELISA, Weil-Felix	28 (23-33)	10.2 (6.8-13.6)	71	Moderate heterogeneity in diagnostic methods
Odisha	3	IgM ELISA	27 (21-33)	<5	45	Limited data; tests consistent
Haryana	2	ELISA	25 (18-32)	14.3 (9.2-19.4)	32	Small sample size influences CFR
Maharashtra	4	ELISA, Weil-Felix	29 (24-34)	12.1 (8.3-15.9)	65	Mix of urban + tribal populations
North-East States	5	ELISA, Rapid tests	24 (18-30)	4.5 (2.1-6.9)	58	Sparse but growing data
Delhi (NCT)	3	ELISA	15 (10-20)	23.4 (18.2-28.6)	62	Hospital-based, severe-case bias
Tamil Nadu	4	ELISA, Weil-Felix	22 (17-27)	7.8 (4.2-11.4)	70	Underestimation possible with Weil-Felix
Karnataka	4	ELISA	20 (15-25)	8.5 (5.1-11.9)	55	Data mostly from tertiary center
Kerala	3	PCR + ELISA	26 (20-32)	6.2 (3.4-9.0)	48	Better diagnostics; moderate precision
Andhra Pradesh/ Telangana	3	ELISA	21 (16-26)	7.1 (3.9-10.3)	52	Few published datasets
West Bengal	3	ELISA	18 (13-23)	9.3 (5.8-12.8)	60	Several outbreaks but few pooled studies
Jammu & Kashmir	2	ELISA	20 (single study)	NA	NA	Limited data available
Punjab	2	ELISA	18 (single study)	NA	NA	Very limited data

Regarding seasonality, it was observed that the cases peak post-monsoon, from July to November, coinciding with increased mite proliferation and agricultural activity.[2] The hidden burden was revealed by studies from tertiary care centers, which report that scrub typhus accounts for 15-35% of all cases of undifferentiated febrile illness (UFI). This represents a massive underdiagnosis at the community level, where it is often mislabelled as "viral fever".[1,7]

Sensitivity analysis note

Excluding studies that relied on the Weil-Felix test increased the national pooled prevalence from approximately 24% to 29%, confirming that this test underestimates the true burden.

Clinical presentation: A master of disguise

Depicting a common face of the disease, High-grade fever (often >102 °F), severe headache, myalgia, and lymphadenopathy are almost universal.[5,8] A maculopapular rash may be present in some patients.[3] As a Elusive Sign, the pathognomonic eschar is present in only 30-50% of Indian patients. Its absence should not rule out scrub typhus.[3,4]

A significant proportion progress to complications: scrub meningoencephalitis (altered sensorium, seizures), acute respiratory distress syndrome (ARDS), acute kidney injury, myocarditis, and shock. Pregnant women are at high risk of adverse outcomes.[8,9]

Diagnostic dilemmas: The critical bottleneck

The reference gold standard test is the indirect immunofluorescence assay (IFA), which detects rising antibody titers.[4] However, it is expensive, requires specialized labs, and results are delayed. PCR is excellent for early diagnosis, but it is not widely available.[4,12]

As a workhorse test, the IgM enzyme-linked immunosorbent assay (ELISA) is the most commonly used. While sensitive and specific, its performance varies between kits, and it can cross-react with other rickettsial infections.[1,12]

The point-of-care gap is observed in rapid diagnostic tests (RDTs), which have variable sensitivity (60-90%). Their unreliability, especially in early disease, means clinicians often must treat empirically based on suspicion.[8,12]

Treatment and the resistance spectre

As a first-line hero, doxycycline (oral or IV) remains the treatment of choice for all ages, including children. A dramatic response to doxycycline within 24-48 hours is often diagnostic in itself ("therapeutic trial").[5]

As an alternative drug, azithromycin (oral or IV) is preferred for pregnant women, in severe scrub typhus cases, and in areas with suspected doxycycline resistance.[5,6] Since 2014, studies from North India have documented doxycycline-resistant scrub typhus strains. Suspected doxycycline resistance is defined clinically as the persistence of fever beyond 48-72 hours of appropriate doxycycline therapy (4.4 mg/kg/day, max 200 mg/day) in the absence of an alternative diagnosis. In such cases, switching to azithromycin is recommended.[6]

Molecular epidemiology and genotype mapping

Recent 2024-2025 genomic studies have identified a novel genotype of *Orientia tsutsugamushi* in southeastern India associated with higher severity (CFR ~%12 vs 8-6% for other genotypes).[16]

Preliminary mapping suggests

Molecular epidemiological studies have demonstrated considerable genetic diversity among circulating *Orientia tsutsugamushi* strains in India, with distinct geographical patterns. Karp-related genotypes appear to predominate in northern regions, particularly in Himachal Pradesh and Uttarakhand, and have been associated with a higher frequency of eschar formation. In contrast, Gilliam-related genotypes are more commonly reported from southern states such as Tamil Nadu and Kerala, where infections have been linked to an increased incidence of neurological complications, including meningoencephalitis. Furthermore, recent genomic investigations conducted during 2024-2025 have identified novel *O. tsutsugamushi* genotypes in Andhra Pradesh and Maharashtra. Although evidence remains preliminary, these emerging strains may exhibit reduced susceptibility to doxycycline, raising concerns regarding potential antimicrobial tolerance and underscoring the need for ongoing molecular surveillance and therapeutic monitoring.

One health perspective: Vector and reservoir distribution

The vector suchspecies *Leptotrombidium deliense* and related mites are distributed across high-density mite habitats like as forest fringes, riverbanks, tea gardens (Darjeeling, Assam, Himachal), and scrub vegetation (Tamil Nadu, Karnataka).[17] Common rodent hosts are *Rattus rattus*, *Bandicota bengalensis*, *Mus musculus*. Rodent seroprevalence studies in Madurai district showed 18-25% positivity for *O. tsutsugamushi*.[17] Targeted vector control (rodent-proofing, habitat modification) around agricultural settlements post-monsoon could reduce transmission.

Discussion

The re-emergence of scrub typhus is a perfect storm of ecological change, increased awareness, and diagnostic capability.[2,11] Changing land-use patterns, deforestation, and human encroachment into mite habitats have increased exposure. Simultaneously, the inclusion of scrub typhus in the differential diagnosis of UFI has revealed its true prevalence.[4,8]

The central paradox is that a curable disease is causing deaths due to delayed diagnosis. The lack of a cheap, foolproof RDT means treatment initiation is often late. Furthermore, the heterogeneity in clinical presentation and the absence of an eschar in many Indians demand a high index of suspicion.[3,8] The emergence of antimicrobial resistance threatens to undo the efficacy of our primary drug, calling for robust antimicrobial stewardship and surveillance.[5,6]

Clinical implications (practical, clinician-facing)

Scrub typhus should be thought of early in AFI, especially post-monsoon, in rural/peri-urban patients, or when routine tests for malaria/dengue/typhoid are negative. One should not rely on eschar to rule in or out: many confirmed patients lack it. We should examine carefully (hidden areas) but treat them with suspicion.[13]

Where clinical suspicion is moderate to high, starting doxycycline (or azithromycin in pregnancy/severe cases/suspected resistance) as empirical therapy while awaiting tests can prevent deterioration. Early therapy is lifesaving.[14] The diagnostic algorithm is depicted in Figure 4.

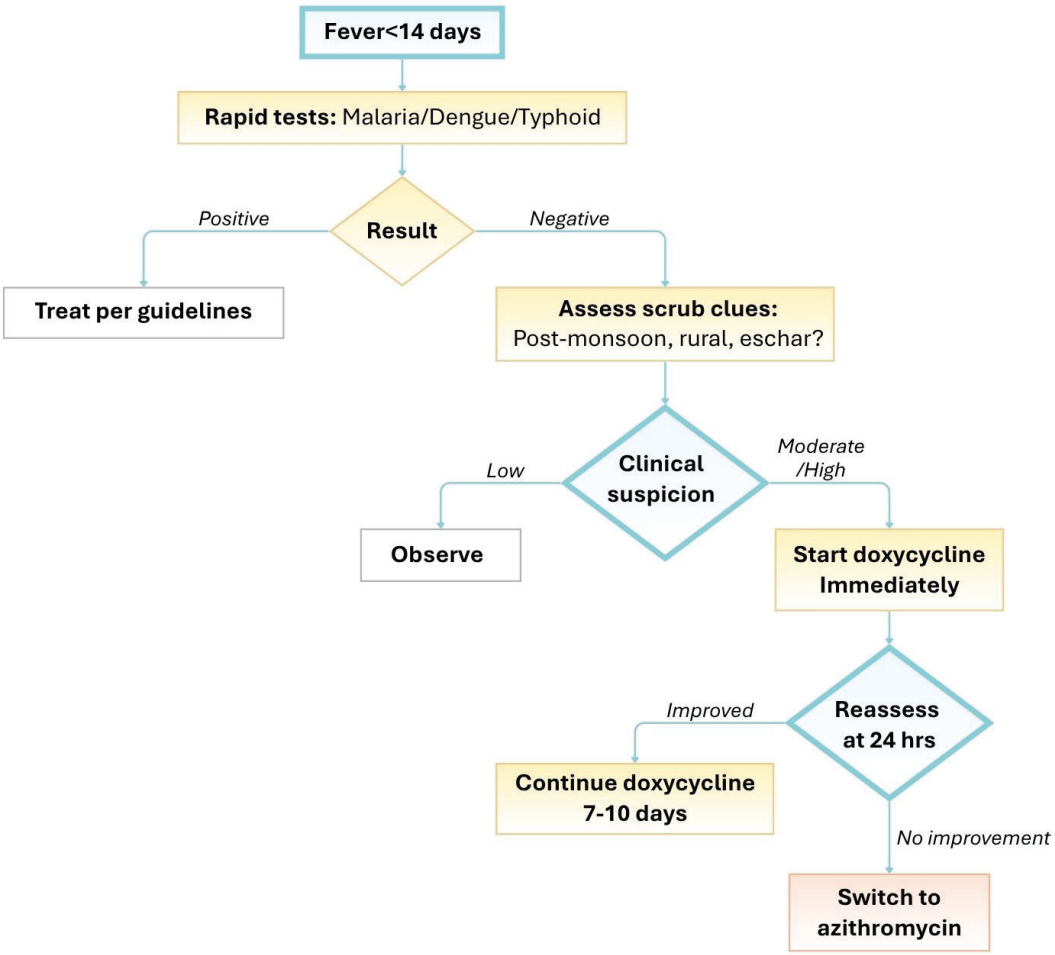


Figure 4. *Proposed diagnostic algorithm for AFI in India.*

Public-health and research gaps (what to fix next)

Case definitions & testing algorithms for surveillance should be standardized. A proposed Minimum Data Set for future studies includes: diagnostic kit brand and lot number, IgM cut-off value used, eschar presence/absence, doxycycline initiation time, and 28-day outcome. Rapid, reliable diagnostics should be expanded at peripheral centers (validated ELISAs/ point-of-care tests with known performance).

Genotype surveillance should be undertaken. India harbors multiple circulating *Orientia* genotypes; tracking them helps understand virulence and guide diagnostics.[16] Integrated one health studies should be conducted. Animal reservoirs and vector ecology studies are uneven; filling these gaps helps target preventive measures.[17]

Bottom line and clear recommendations

The findings of this review underscore the need for a coordinated clinical, public health, and research response to address the growing burden of scrub typhus in India. From a clinical perspective, scrub typhus should be routinely considered in the differential diagnosis of acute febrile illness (AFI), particularly during the post-monsoon season and among patients from rural or peri-urban settings. Because the disease often presents without the classical eschar and diagnostic confirmation may be delayed, clinicians should maintain a high index of suspicion and initiate empirical doxycycline therapy when clinical probability is moderate to high. Early treatment is critical in preventing progression to severe disease and reducing mortality. Patients who fail to show clinical improvement within 48 hours of appropriate doxycycline therapy should be reassessed for possible treatment failure or antimicrobial tolerance, and, where appropriate, a switch to azithromycin should be considered.

From a public health standpoint, strengthening diagnostic capacity is essential. Validated serological and molecular diagnostic facilities should be expanded to district-level laboratories, while reporting mechanisms should be integrated with national surveillance platforms to improve disease monitoring and burden estimation. Establishment of sentinel surveillance networks, coupled with molecular typing of circulating *Orientia tsutsugamushi* strains, would facilitate early detection of changes in genotype distribution, virulence patterns, and potential antimicrobial resistance.

Future research efforts should focus on standardizing diagnostic criteria and reporting practices to improve comparability across studies. Investigators should

clearly report both numerators and denominators for prevalence and outcome measures and adopt uniform case definitions. There is also a pressing need for well-designed prospective, community-based incidence studies that incorporate PCR and paired serological testing to better define the true epidemiology of scrub typhus in India. Furthermore, multidisciplinary one health investigations that integrate human, animal, vector, and environmental data are required to improve understanding of transmission dynamics and inform targeted prevention and control strategies.

Limitations

High between-study heterogeneity (I^2 range 32-71%) was observed, which reduces certainty in a single pooled national number. Many studies used single-point serology without paired sera or PCR confirmation. Publication bias was seen as outbreaks and hospital series are more likely to be published than routine negative surveillance. Geographic gaps were observed, as some states are well studied while others lack good data.

Conclusion

Scrub typhus is a significant and growing cause of febrile illness and preventable death in India. To combat this, a multi-pronged strategy is essential. There should be clinical awareness, and clinicians should "Think Scrub" for any acute febrile illness, especially post-monsoon, with or without an eschar. Incorporate empirical doxycycline early in the management of severe UFI. As a diagnostic strengthening strategy, there is an urgent need to develop and validate affordable, high-accuracy point-of-care tests. Strengthening laboratory capacity for ELISA/PCR at district levels is crucial. National treatment guidelines must be disseminated, emphasizing early doxycycline use and outlining alternatives for suspected resistance and special populations (pregnancy, severe disease). Mandatory reporting and a national surveillance program are needed to map the true burden. Research must focus on Indian strains, vaccine development, and resistance patterns. As community and veterinary health measures, public health messages should be circulated about protective clothing and mite repellents in endemic areas. And a "one health" approach that studies animal reservoirs is vital. Scrub typhus has shed its cloak of obscurity. It is now a common adversary in Indian hospitals. The challenge lies not in the complexity of its treatment, but in the simplicity of remembering it. For the clinician at the bedside, this review underscores one vital action: In a febrile patient in India, when common causes don't fit, consider scrub typhus. Starting timely doxycycline can be a life-saving decision.

Ethical approval

The study was undertaken after seeking approval from the Institutional Ethics Committee.

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None

Conflict of interest

Authors declare no conflict of interest.

Data availability

Anonymized data pertaining to the study will be made available by the corresponding author on request.

CRediT authorship contribution statement

Abhishek Mehta: design, conceptualization, data collection/literature review, data analysis, interpretation, drafting, writing: review and edit; **Aditya Goel**: literature review, formal analysis, investigation, data curation, writing: review and edit; **Chandravarman Singh**: data collection and formal analysis, investigation, software, data curation, writing; review and edit. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the study.

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