OPEN ACCESS
Global Journal of Research in Medical Sciences
ISSN: 2583-3960 (Online)
Volume 05 | Issue 03 | May-June | 2025
Journal homepage: https://gjrpublication.com/gjrms/
Review Article

A Comprehensive review of Scrub Typhus: An emerging masquerade of fever

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DOI: 10.5281/zenodo.15679961 **Submission Date: 10 May 2025 | Published Date: 17 June 2025**

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Abstract
This article delves into scrub typhus, a zoonotic infectious disease caused by Orientia tsutsugamushi, an obligate intracellular bacterium transmitted through the bite of infected chigger mites (larval Trombiculidae). The disease is endemic to the Asia-Pacific region, including Southeast Asia, India, China, Japan, and northern Australia. It has been increasingly recognized as a global health concern owing to its expanding geographical range and deadly complications if it is undetectable in nature. The clinical presentation of scrub typhus varies from mild febrile illness to severe life-threatening complications. Common symptoms include high fever, headache, rash, lymphadenopathy, and myalgia, and a characteristic eschar at the site of the mite bite is the hallmark clinical clue to arrive at the diagnosis. If untreated or undiagnosed, the disease may progress to severe complications such as pneumonitis, acute respiratory distress syndrome (ARDS), myocarditis, meningoencephalitis, renal failure, and multi-organ dysfunction, leading to high mortality rates. The diagnosis of scrub typhus remains clinically challenging because of its nonspecific symptoms and overlaps with other secondary febrile illnesses such as dengue, malaria, and leptospirosis. Laboratory confirmation is commonly performed using serological tests such as the Weil-Felix test, indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA), or molecular techniques such as polymerase chain reaction (PCR). Early diagnosis is crucial because delayed treatment can result in poor outcomes in rural areas. Doxycycline remains the first-line treatment for scrub typhus, with azithromycin as an alternative, particularly for pregnant women and children. In regions where scrub typhus is endemic, increased awareness, improved diagnostic capabilities, and vector control strategies are essential to reduce the disease burden. Further research on vaccine development and novel therapeutics is necessary to effectively combat this re-emerging infectious disease.

Keywords: *Scrub typhus, eschar, doxycycline, zoonosis, chigger, pyrexia of unknown origin, public health, mimicker of fever, acute febrile illness.*

INTRODUCTION

Tsutsugamushi disease, commonly known as scrub typhus, is caused by the rickettsial bacteria *Orientia tsutsugamushi*, which is a tiny obligate intracellular gram-negative coccobacillus bacterium. This zoonotic rickettsial disease is transmitted to humans through the bite of infected trombiculid (chigger) larval mites. The disease is also known as bush typhus (1), river fever, or flood fever, because infected chiggers are typically found in places with a large amount of vegetation (6). The term 'scrub' refers to vegetation and bushes, while 'typhus,' derived from Greek, refers to fever with stupor or delirium (2).

One of the main causes of curable non-malarial fever in tropical countries, scrub typhus, has been identified by the World Health Organization (WHO) as a neglected tropical illness that is underrecognized and poses a severe public health risk in the Asia-Pacific area (3). After the 2015 earthquake in Nepal, scrub typhus cases were reported nationwide for three years, highlighting the possibility of epidemic outbreaks (4). Every year, an estimated one million new cases of scrub typhus are reported, putting over a billion people at risk worldwide (3). Scrub typhus is a major public health concern in the Asia-Pacific region because of its nonspecific presentation and the potential for severe complications. It was previously believed that scrub typhus was endemic solely to the Tsutsugamushi triangle (southeastern countries), which is an area of approximately 13,000,000 km (5). However, reports of scrub typhus from outside this area have since been made on due course (1). It is found in most Southeast Asian countries and is endemic in some areas of India, Indonesia, the Maldives, Myanmar, Nepal, Sri Lanka, and Thailand. This disease is known to occur in various ecological settings in India. Many cases have been reported from Tamil Nadu, Andhra Pradesh, Karnataka, and Kerala in the South; Himachal Pradesh, Uttarakhand, Jammu, and Kashmir in the North; Meghalaya, Assam, and Nagaland in the North-East; West Bengal and Bihar in the East; and Maharashtra and Rajasthan in the West (6). North India accounted for 31.5% of scrub typhus cases, while South India accounted for 55%, East India accounted for 4.5%, North-East India accounted for 7.4%, and West India accounted for 1.1%. If treatment is not received, the likelihood of fatality can reach 30% or more, with regional variations (7). Different regions have varying case fatality rates; China has a 13.8% fatality rate, whereas Japan has a far lower rate of 1%. The rates reported in South Korea, Thailand, and India are 6.3%, 13.6%, and 33.3%, respectively (8). According to many studies, there is a higher mortality rate in North India than in South India, which could be due to the delay in seeking medical attention (7).

The prevalence of scrub typhus varies seasonally among China, Taiwan, South Korea, and Japan. In general, Japan has its cases peaking in November and December, Taiwan peaking in June-October, and South Korea peaking in October-December. China has experienced cases from spring to early winter. In India, scrub typhus outbreaks generally occur during the monsoon season from June to September (9).

The disease is thought to be acquired primarily by several circumstances, including the presence of woodpiles, scrub vegetation, water bodies, livestock near homes, rodents, and when livelihood is done outside the houses (10). The main environmental factors that contribute to infection growth are low temperature and heavy rainfall. Some behavioral characteristics, such as sleeping on grassy or muddy fields, wearing unhygienic clothing, working with bare hands or short sleeves, and open defecation, contribute to the spread and development of infections other than scrub typhus. Farmers (paddy-field workers), hunters, athletes, shepherds, and others face greater occupational risks, especially in rural tropical areas (1). Nonetheless, a study reported that scrub typhus appears to be caused mostly by environmental factors rather than behavioral or demographic variables, but behavioral factors are a key component of primordial prevention (11).

This obligate intracellular bacterium, *Orientia tsusugamushi,* is the causative agent of bush typhus. However, it is vectored by the bite of larvae of infected *Leptotrombidium* mites (6). Scrub typhus is difficult to diagnose because its febrile symptoms, including fever, headache, muscle soreness, and stomach problems, are like those of other disorders. One of the most important signs of the disease is the development of an "eschar," or sore, at the bite site. An “eschar” is a black crusted lesion, typically 5-20 mm in size, that develops at the site of chigger bite. This lesion begins as a red, indurated papule, which then vesiculates, ruptures, and becomes covered with a black scab. The eschar is often painless and non-pruritic and is a crucial diagnostic clue for scrub typhus, although it is not always present. Scrub typhus can cause serious side effects such as sepsis, shock, myocarditis, meningitis, acute respiratory distress syndrome, severe kidney injury, hepatitis, and multi-organ failure if left untreated. Although there are no vaccines, antibiotics such as rifampicin, macrolides, quinolones, tetracycline, doxycycline, and chloramphenicol are used to treat the disease (2). Future research directions for scrub typhus involve the creation of vaccines that confer long-term immunity and prevent outbreaks, as no specific vaccine is available. Drug resistance is also a priority, with continued research aimed at identifying new treatments and enhancing current therapies to fight resistant forms of the disease (12).

ECOLOGY AND ENTOMOLOGY

O. tsutsugamushi requires a host cell to survive and the major vectors and reservoirs of this bacterium are the larvae of *Leptotrombidium* mites. These larval mites are usually found in tropical and subtropical regions. They live on grass, trees, leaves, and twigs above porous, moist soil, and exhibit host-seeking behavior. Even though some important vector species, *such as L. deliense*, appear to be able to colonize a wider range of habitats, chiggers seem to be largely habitat-specific. *Leptotrombidium deliense* is commonly found in forests and scrubs, *Leptotrombidium fletcheri* can be observed in specific grassy places, and *Leptotrombidium arenicola* can be found in the vegetation around beaches (13). Ecotones may offer an ideal environment for the growth of chiggers and rodents, which are usually vectors. In one study, chiggers adhering to rodents were most abundant in ecotones containing forests and open scrublands (14).

Orientia tsutsugamushi, an obligatory intracellular bacterium that lives in *Leptotrombidium* mites, causes scrub typhus. With an oval shape and dimensions of 0.5 to 0.8 micrometers in width and 1.2 to 3.0 micrometers in length, *O. tsutsugamushi* is a unicellular organism. The typical peptidoglycan cell wall is absent in *O. tsutsugamushi*, in contrast to many other bacteria. On its surface, it forms a structure resembling a peptidoglycan. Strains of the species differ from one another because of this special characteristic, as well as variations in the protein makeup of their cell membranes. The bacterial cytoplasm is transparent, and ribosomes and unique DNA are discernible. The distinctive extracellular components, known as surface cell antigens (Sca), define *O. tsutsugamushi*. The bacterium uses these antigens as adhesions to attach to and infiltrate host cells. Some strains of the bacterium have both linear and circular plasmids that encode different genes linked to interactions with host cells, demonstrating the great diversity of the system in which O. tsutsugamushi accumulates on the host cell surface during its budding process, which takes approximately 9–18 h to complete (2). The six-legged larval form of trombiculid mites, also known as chiggers, is parasitic on terrestrial vertebrates worldwide. They have an intricate life cycle, which includes eggs, larvae, nymphs, and adults. Chigger mites have a complicated life cycle that includes an egg, an inactive larval stage called deutovum, a parasitic, six-legged chigger larva, an inactive nymphal stage called nymphochrysalis, an eight-legged, free-living nymph, an inactive deutonymph or imagochrysalis, and an adult that is eight-legged and free-living (15).

Chigger classification depends almost entirely on the morphological traits of the larvae. The two halves of a chigger's body are called idiosomas and gnathosomas, respectively. The four components of the chigger's mouthparts—the cheliceral blades, palps, cheliceral base, and gnathobase make up gnathosoma. For chigger identification, factors include the scutum's shape (usually the only sclerotized plate on the idiosoma, next to the gnathosoma), the number and arrangement of dorsal setae, leg chaetotaxy, leg segmentation, and various lengths or forms of gnathosoma (cheliceral blades, galeal setae, palpal setae, and palpal claw), among others (16). In terms of taxonomic traits, *L. imphalum* has 28–32 dorsal setae, 30-32 ventral setae (number). and an average body length of 250-600 µm (17).

Climate change, characterized by rising temperatures and altered precipitation patterns, is likely to expand the geographical range of chigger mites, which are the primary vectors of scrub typhus caused by Orientia tsutsugamushi. Increased temperatures can enhance chigger survival and reproduction, enabling their spread to higher latitudes and elevations, which were previously unsuitable due to cooler climates. For instance, studies in Korea have noted the northward expansion of Leptotrombidium scutellare, a key vector correlated with warmer temperatures above 10°C, which facilitates higher chigger indices in autumn. Similarly, increased rainfall and humidity, which create favourable moist habitats, have been linked to greater chigger abundance and species richness in regions, such as Thailand, where dry seasonal conditions also correlate with higher mite populations. These environmental shifts driven by climate change may increase the risk of scrub typhus in new areas, particularly in boreal and temperate regions, necessitating enhanced surveillance and vector control strategies to mitigate emerging public health threats.

LIFE CYCLE

Scrub typhus is transmitted by the trombiculid mite larvae (chiggers). These mites undergo four primary stages in their life cycle: eggs, larvae, nymphs, and adults, with three other dormant stages in between. Environmental elements, such as temperature, humidity, and availability of food and nutrients, have a direct impact on their life cycle. The female mite lays eggs in humid environments, which hatch into larvae depending on the environmental conditions. The larval stage is parasitic in nature and feeds on a wide variety of vertebrate hosts including rodents and humans (2,18). These larvae, which are found in the vegetation, exhibit host-seeking behavior where they detect carbon dioxide and other chemical cues from a potential host (vertebrates) (13). The larvae attach to humans or rodents and inject histolytic salivary fluid through their sharp chelicerae to pierce the upper dermis. They feed on digested vertebral fluids and ingest *O. tsutsugamushi* in the bloodstream of the host. The engorged chigger larvae separate from the host body after feeding and fall into the ground. A few days later, they changed to a pupa-like stage, which was followed by an eight-legged nymphal stage. Two weeks later, the nymphs go through a second pupa-like stage before emerging as adults (18).

Infected female chigger mites can directly transfer *O. tsutsugamushi* to their eggs via transovarial transmission. This implies that the infection cycle will continue as mites can transfer bacteria from one life stage to the next. Once the eggs hatch into larvae, they remain infected and transmit bacteria when attached to a host (2,18).

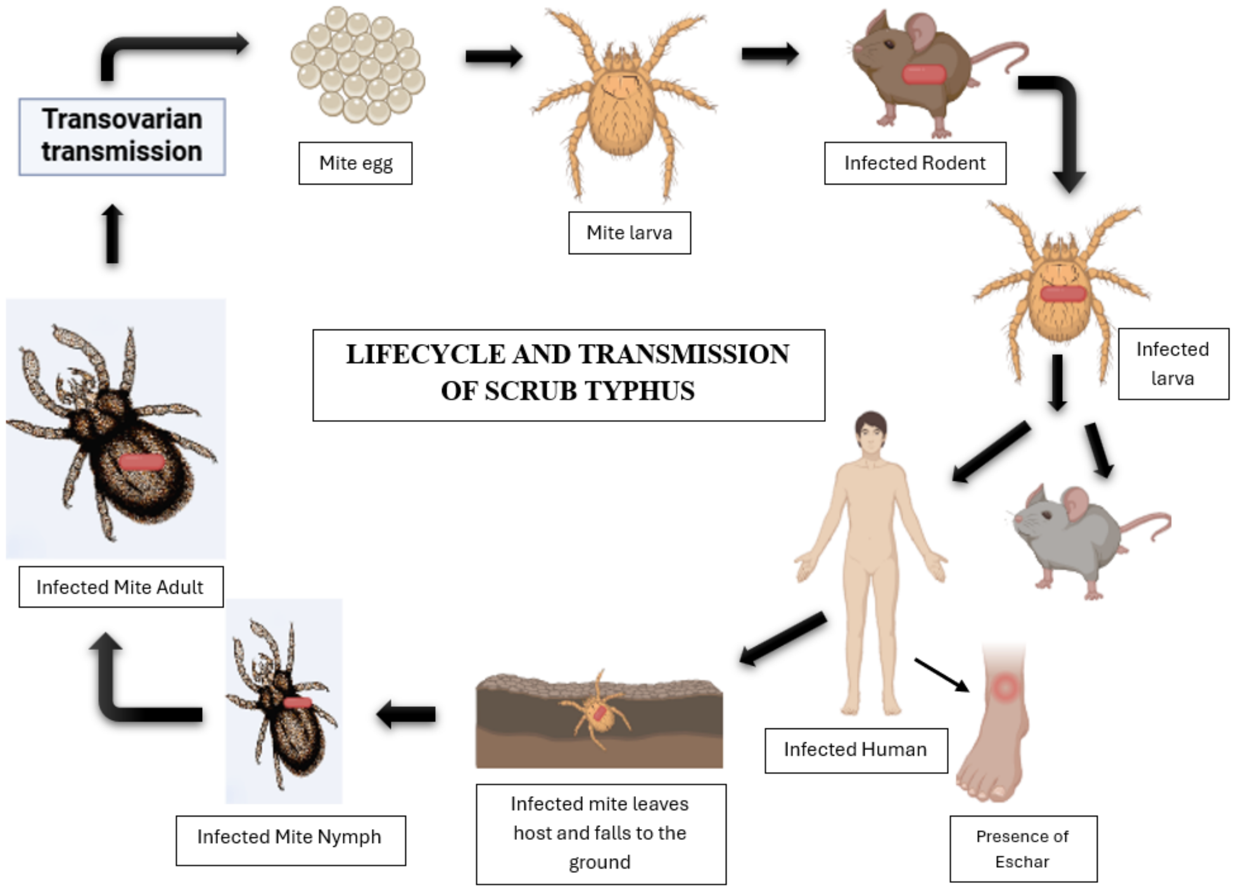

***Fig 1:** Lifecycle and transmission of Scrub Typhus*

CLINICAL MANIFESTATIONS

In its early stages, scrub typhus can cause an acute febrile illness that is comparable to symptoms of other illnesses such as dengue, encephalitis, influenza, and coronaviruses (1). Scrub typhus symptoms include fever, rash, myalgia, lymphadenopathy, nausea, vomiting, eschar (black mark that forms at the mite biting site), abdominal pain, and general flu-like symptoms that emerge 5–14 days after a *Leptotrombidium* bite (10). In regions where scrub typhus is endemic, it serves as a helpful diagnostic tool for patients with acute febrile illnesses. Its presence in patients varies greatly, regardless of the patient (19). Common symptoms of scrub typhus include fever, dyspnea, coughing, headache, nausea, vomiting, and altered sensory perception (7) A painless black crust at the site of the chigger bite, known as an eschar, is a pathognomonic marker of scrub typhus and indicates the mite bite entry point. After entry, bacteria invade endothelial cells and trigger macrophages, leading to widespread vasculitis and perivascular inflammation. This immune response leads to the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α, which mediate the febrile response. Systemic infections disrupt vascular integrity, causing leakage, edema, and organ dysfunction, particularly in the lungs, liver, and central nervous system.

THE GREAT MASQUERADER

A small percentage of individuals may develop eschar, a macular rash, on the trunk five–eight days after the onset of fever. This rash may spread to the arms and legs (20). A wide range of clinical disorders affecting the respiratory, circulatory, renal, hepatic, gastrointestinal, and ophthalmic systems are associated with scrub typhus (21). The intracellular bacterium, *Orientia tsutsugamushi*, elicits a complex immunopathogenic response that targets endothelial cells, dendritic cells, and macrophages, leading to widespread vasculitis and perivasculitis. The immune system reacts vigorously to initiate both innate and adaptive immune responses. Pro-inflammatory cytokines, such as TNF-α, IL-6, and IFN-γ, are upregulated, contributing to systemic inflammation and endothelial activation.

Endothelial injury disrupts vascular integrity and causes plasma leakage, tissue hypoperfusion, and microvascular thrombosis. These events are central to the pathogenesis of complications such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and meningoencephalitis. Additionally, excessive immune activation, often referred to as a "cytokine storm," can exacerbate tissue damage, especially in the lungs and central nervous system. Macrophage activation syndrome and disseminated intravascular coagulation (DIC) may also occur in severe cases.

Persistent infection and delayed clearance of the pathogen further aggravates tissue injury and organ dysfunction. Dysregulated immune response, rather than the direct cytotoxicity of the pathogen, plays a key role in determining disease severity. Therefore, early recognition and antimicrobial therapy are critical for modulating immune responses and preventing complications.

- **RESPIRATORY SYSTEM:**

Respiratory problems are common in patients with scrub typhus. Patients may experience severe hypoxia due to bronchitis, interstitial pneumonia, or acute respiratory distress syndrome (ARDS), which is characterized by a rapid onset of extensive lung inflammation (20). A case of scrub typhus was reported in which a patient was admitted to a hospital with cough and breathlessness. In addition, she developed orthopnea. Her respiratory rate rapidly increased over time. A respiratory examination showed scattered crepitations in both lung areas and bilaterally reduced breath sounds with bronchial breath suggestive of consolidation, which later progressed to Type 1 Respiratory Failure, leading to the need for ventilatory support (22). These issues have a substantial impact on disease morbidity and fatality rates (20).

- **CARDIOVASCULAR SYSTEM:**

Cardiac involvement includes rhythm abnormalities, myocarditis, and pericarditis. There have been reported cases of acute heart failure, with individuals displaying abnormal echocardiograms with HFrEF and HFpEF with increased cardiac biomarkers like NT-BNP and Troponin I. Myocardial damage may result from the infection-induced inflammatory response, raising the likelihood of arrhythmia such atrial fibrillation is a life threatening (23). If left untreated, patients can develop pericardial effusion and florid heart failure. Individuals with predisposed cardiac diseases are more likely to develop heart failure, and when the interventricular septum, coronary artery, or heart valves are affected during an acute illness, arrhythmia results to ventricular fibrillation. Only a small number of cases of scrub typhus have been reported to have myocarditis, which can range in severity from mild to fulminant and necessitates anti-failure measures and mechanical support in certain cases (24).

One such case was reported in a patient with acute febrile illness, which revealed an eschar on his lower limb and an unusual murmur, further confirmed with 2DEcho and NT-pro BNP. The patient also had significantly elevated cardiac enzyme levels. The patient received anticoagulation, antibiotic, and cardiopulmonary support with anti-failure measures, which recovered later (25).

- **RENAL SYSTEM:**

Acute kidney damage linked to scrub typhus, which was once thought to be uncommon, has now been documented in several endemic nations, making it a noteworthy consequence (26). The mechanisms include immune-mediated damage, cardiogenic shock-induced hypoperfusion, and direct pathogen invasion of multiple organs. In patients with scrub typhus, biomarkers such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) have been tested for early AKI identification in resource rich settings (23). There is a clear correlation between acute kidney injury secondary to scrub typhus and both short- and long-term morbidity and mortality. For early intervention to enhance patient outcomes, quicker diagnosis is necessary (26). Scrub typhus was shown to be responsible for between 21% and 43% of acute kidney injury (AKI) cases in both the southern and northern regions of India, with an increase in AKI cases in recent years, most of which are linked to multiple organ dysfunction (MOD). Fluid therapy and early recognition prevent AKI, which may later progress to RPGN and CKD.

Scrub typhus was present in 32.14% of 140 patients with AKI who had been admitted to a hospital with acute febrile illness or a history of acute febrile illness; eschar was observed in 17.8% of these individuals. Of.4 of all the scrub typhus-positive cases, 24.4% had multiple organ dysfunction. RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria classified most AKI patients (60%) as "renal failure." 20.0% was the death rate. Among the 45 patients, 51.1% had oliguria and 15.5% had anuria (26) treated with SLED and Dialysis have improved on due course.

- **HEPATIC SYSTEM:**

Patients with scrub typhus often have acute liver injury or liver shock, which manifests as deranged liver enzymes. Although it is less frequent, it may lead to hepatic encephalopathy (20). Although most of these biochemical anomalies are nonspecific, transaminitis in infected individuals may indicate moderate localized inflammation caused by cytopathic liver damage and vasculitis of the intrahepatic sinusoidal endothelium. A deranged coagulation profile with Vit K supplementation and supportive measures is needed to counteract failure measures (27).

A case of severe hepatic involvement was reported in a pregnant woman who worked as an agricultural field worker in a village with symptoms of fever, encephalopathy, jaundice, and seizures. She suffered shock liver with hepatic encephalopathy, which later succumbed to a still birth (28).

- **NEUROLOGICAL AND PSYCHATRIC MANIFESTATIONS**

Twenty percent of scrub typhus infections are accompanied by neurological symptoms that might affect either the central or peripheral nervous systems, or occasionally both. Neurological involvement is caused by a variety of processes such as immune-mediated mechanisms (opsoclonus, myoclonus, optic neuritis, Guillain-Barre syndrome), vasculitis (myositis), or direct invasion (meningitis and encephalitis). Although some neurological indications have an immunological foundation, the response to doxycycline is outstanding and remarkable. However, significant involvement may require immunological therapy (29).In a reported case of scrub typhus, prominent neurological manifestations were observed when a patient was brought to the hospital after experiencing chills, headaches, myalgia, and decreased appetite for the past three weeks due to high-grade fever. An eschar resembling a "cigarette burn" was discovered over the right shoulder during physical examination. His symptoms included new-onset symmetrical resting tremors, axial and rigidity, significant slowness of all bodily movements, hypophonic speech, and classical extrapyramidal signs and symptoms. The IgM-ELISA and Weil-Felix serology results for scrub typhus were both positive and required escalated antibiotic coverage. His symptoms progressively improved without antiparkinsonian drugs (30). Neuropsychiatric symptoms arise due to the pathogen's affinity for the vascular endothelium and central nervous system, leading to vasculitis, meningoencephalitis, and secondary cerebral dysfunction. Psychiatric presentations include delirium, hallucinations, agitation, anxiety, depression, and psychosis. These symptoms often overlap with those of encephalopathy, making the diagnosis challenging in resource-limited settings. A documented altered sensorium in 33% of patients with scrub typhus, with some exhibiting symptoms, such as disorganized behavior and paranoid ideation. Case reports have described acute psychosis in the absence of overt meningoencephalitis, which suggests a possible direct or immune-mediated neuropsychiatric mechanism. The onset of psychiatric symptoms typically occurs during the acute febrile phase but may persist in convalescence.

- **HEMATOLOGICAL MANIFESTATIONS**

Thrombocytopenia, leukopenia, or leukocytosis can be observed in patients with co-infections, such as dengue and chikungunya. In severe situations, bleeding problems due to disseminated intravascular coagulation (DIC) have been documented. Hemophagocytic lympho histiocytosis (HLH) is another life-threatening hyperinflammatory disease associated with higher mortality (20). In addition to perivasculitis, it also results in disseminated vasculitis. *O. tsutsugamushi* grows at the site of inoculation, causing skin necrosis where eschar is present, and expansion of local lymphadenopathy. Vascular damage affecting several organs, including DIC, platelet consumption, and vascular leak due to endothelial dysfunction caused by fluid shift, leads to shock (31).

In a reported case of scrub typhus with significant hematological manifestations, a patient who had no chronic illnesses due to diarrhea spent a week in the hospital. However, she had fever for approximately three days, reaching a high temperature of 39°C, with leukopenia and thrombocytopenia. A stool OB test was performed, which was positive due to low hemoglobin. Physical examination revealed purpuric rashes on her right waist and belly, small pustules on her proximal right leg with ulceration and mild discharge, facial edema, mild shortness of breath, and coarse breath sounds in both lungs. She responded to treatment after early recognition of the illness (32).

- **GASTROINTESTINAL MANIFESTATIONS:**

More than one-third of scrub typhus patients have gastrointestinal symptoms, which usually include diarrhea, indigestion, nausea, vomiting, hematemesis, melena, and accompanying abdominal pain or tumor soreness. Scrub typhus is characterized by several erosions and peptic ulcers without apparent preferential areas, and hematemesis due to superficial mucosal hemorrhage. It may manifest as or mimic acute appendicitis, pancreatitis, cholecystitis, or peritonitis (33).In one case, a patient from a rural hilly forest area had a history of an acute febrile illness. The patient experienced a high temperature for seven days before developing a rash, abdominal pain, and signs and symptoms suggestive of peritonitis. The patient needed ventilator assistance due to flash pulmonary edema. However, the first Weil-Felix test was negative, and the body had no eschar, as epidemics and endemic typhus were common. Scrub IgM confirmed the diagnosis of scrub typhus. She was treated appropriately with antibiotics, taking home to the importance of history and prudent judgment in handling practical medicine (34). Patients may present with an acute abdomen, simulating acute appendicitis**,** acute cholecystitis, pancreatitis, or intestinal perforation. Cases of necrotizing fasciitis and eschar-associated cellulitis have been reported. Ascites, hepatosplenomegaly, and peritonitis-like features can mislead clinicians toward exploratory laparotomy. In a retrospective study, 9% of the patients underwent abdominal surgery due to presumed surgical pathology before a diagnosis of scrub typhus was confirmed.

- **OPHTHALMIC MANIFESTATIONS**

Conjunctival infections are also frequently encountered. It has been noted that more severe ocular involvement, like optic neuritis, can result in visual loss if left untreated.

In addition to meningitis, *O. tsutsugamushi* illness may present with uveitis and red eyes, which are common manifestations. Rapid, involuntary, and multi-vectorial eye movements are the hallmarks of opsoclonus, an uncommon but increasingly recognized ophthalmic symptom of scrub typhus identified during clinical examination. It usually appears 1-2 weeks after the onset of fever, although it might occur earlier in the disease. When treated with appropriate antibiotics, the disease usually has a good prognosis, which emphasizes the importance of prompt clinical diagnosis and treatment (35). A case of scrub typhus with ocular and neurological involvement was reported in a patient. He had primary open-angle glaucoma (POAG) after trabeculectomy, and intraocular pressure (IOP) in both eyes (OU) was controlled. He had been experiencing a red eye (OU) and a headache for ten days. Physical examination revealed a fever of up to 38.2°C, stiff neck, and two eschars: one at the left ankle and one at the left forearm. Elevated intraocular pressure, mild conjunctival congestion, subconjunctival hemorrhage, anterior uveitis, cotton-wool patches on the retina, and numerous white dots on the temporal retina (OU) were observed during ophthalmic examination. Additionally, visual degradation was observed, but responded well to treatment after the scrub IgM test was positive (36).

- **ORAL MANIFESTATIONS:**

Oral signs of scrub typhus may include enanthem**s**, mucosal lesions that appear inside the mouth. These lesions are often present as petechiae, erythematous macules, or ulcers**,** typically on the buccal mucosa, soft palate, or tongue. Additionally, gingival bleeding and swelling have been reported, which sometimes correlates with thrombocytopenia caused by infection. In some cases, painful stomatitis or sore throat may occur, which may mimic other infectious or systemic diseases. Clinicians should consider scrub typhus in patients presenting with febrile illness and unexplained oral lesions, especially if other hallmark signs, such as eschars, are absent or overlooked.

STRATEGIC CONTROL AND FUTURE DIRECTIONS

An extremely specific sign for identifying scrub typhus is the presence of an eschar at the location of mite bite. It is not a suitable approach for diagnosing scrub typhus because eschars are uncommon in certain populations owing to ethnicity. Consequently, laboratory testing is the primary diagnostic method. Indirect immunofluorescence assays, indirect immune peroxidase assays, enzyme-linked immunosorbent assays (ELISA), immune chromatographic tests (ICTs), and serological tests, such as the Weil–Felix test, are the most common tests used to identify rickettsial diseases. For the diagnosis of scrub typhus, the IgM ELISA-based approach is the most accurate of all serological assays if Weil-Felix results are negative (37). For quick and early diagnosis, especially in rural areas or emergency situations, a point-of-care assay that identifies *O. tsutsugamushi*-specific antigens in the patient's blood, plasma, or serum, such as an immunochromatographic test (ICT) or dipstick test, is ideal and practical.

The main antibiotics that are known to work against O. tsutsugamushi are rifampicin, azithromycin, doxycycline, and tetracycline. Patients with scrub typhus may not always benefit from antimicrobial therapy with doxycycline or azithromycin; however, they have been used to address serious side effects such as resistance (5). Tetracycline is the most cost-effective medication for the treatment of scrub typhus. Therefore, tetracycline is recommended as the initial treatment option for scrub typhus (38). However, numerous failures and mortalities have been associated with the administration of these antibiotics, followed by reports of resistance. Furthermore, antibiotics have become a significant health concern worldwide, particularly the emergence of antibiotic resistance and their irrational use in all acute febrile illnesses. Multidrug-resistant (MDR) bacterial strains can develop concurrently with the ongoing use of several antibiotics to treat scrub typhus. Therefore, vaccines are required to treat scrub typhus when an epidemic or endemic outbreak occurs (5).

The vast genetic diversity of the circuiting genotypes in endemic locations, which strongly favors the PAN-*Orientia* vaccination method, is the main reason why a viable vaccine for humans remains unavailable. Moreover, there has long been a need for efficient vaccination to supplement conventional vector and rodent control methods. Traditional vaccine development techniques are still used, but more creative and successful approaches with great promise are urgently needed (39). The weakening of protective immunity and comparatively short persistence of antibodies against *O. tsutsugamushi* present another significant obstacle to the development of an effective vaccine against scrub typhus. Scrub typhus should be prevented by vaccination with *O. tsutsugamushi* antigens that promote humoral and T cell-mediated defenses (40). According to our hypothesis, a multiplex vaccine comprising conserved antigens of p56, Sca-A, and potentially p47, as well as confirmational, neutralizing antibody-stimulating p56 hypervariable antigens of the clinically and epidemiologically most significant strains of *O. tsutsugamush*i, would be a reasonable way to address the unmet need for vaccine development for scrub typhus. Researchers must ensure that the vaccines they produce are safe, free from adverse reactions, nontoxic, environmentally friendly, cost-effective, and ethically approved, in addition to technological improvements (39).

Challenges in Vaccine Development

The development of an effective vaccine for scrub typhus remains a significant challenge because of the complex biology of *Orientia tsutsugamushi* and its interaction with the host immune system. One of the primary obstacles is the extensive antigenic diversity among *O. tsutsugamushi* strains, driven by variations in the 56-kDa type-specific antigen and surface cell antigens (Sca proteins). This diversity complicates the design of vaccines that provide broad, cross-protective immunity across different genotypes prevalent in endemic regions [39]. Additionally, the short-lived nature of protective immunity against scrub typhus poses a challenge, as antibodies to *O. tsutsugamushi* wane rapidly, necessitating vaccines that stimulate both robust humoral and T-cell-mediated responses [40]

Another hurdle is the lack of suitable animal models that can accurately mimic human disease progression, which hinders preclinical vaccine testing. Traditional vaccine approaches, such as live-attenuated or inactivated vaccines, have been largely unsuccessful owing to safety concerns and limited efficacy against diverse strains. Emerging strategies, such as mRNA vaccines and subunit vaccines targeting conserved antigens, such as p56 and Sca-A, show promise but require further validation in clinical trials. The high genetic variability of *O. tsutsugamushi* also raises concerns regarding vaccine escape mutants, necessitating a pan-Orientia approach that includes multiple antigens to ensure comprehensive protection [39].

Socioeconomic and logistical barriers further complicate the development of vaccines. Endemic regions, often resource-limited, face challenges in terms of vaccine distribution, storage, and administration. Developing cost-effective thermostable vaccines is critical to ensure accessibility in rural areas where scrub typhus is prevalent. Moreover, ethical considerations such as ensuring safety and minimizing adverse reactions are paramount in vaccine design. Collaborative international research efforts are needed to address these challenges by leveraging advances in genomics and immunology to develop a safe, effective, and affordable vaccine for scrub typhus.

MANAGEMENT OF SCRUB TYPHUS

A) Investigations for the Diagnosis of Scrub Typhus

The diagnosis of scrub typhus is challenging because of its nonspecific clinical presentation, which overlaps with other febrile illnesses such as dengue, malaria, and leptospirosis. A combination of clinical suspicion and laboratory investigations is necessary for accurate diagnosis. Serological tests are commonly used, with the Weil-Felix test being an older and less specific method that detects cross-reacting antibodies but has low sensitivity and specificity. More reliable serological methods include the indirect immunofluorescence assay (IFA), which is considered the gold standard owing to its high sensitivity and specificity, and enzyme-linked immunosorbent assay (ELISA), which detects IgM antibodies and is widely used in endemic areas. Polymerase chain reaction (PCR) is a highly sensitive molecular technique that detects Orientia tsutsugamushi DNA in blood, eschar, or tissue samples, providing early and definitive diagnosis. Other laboratory findings included elevated liver enzymes, thrombocytopenia, leukopenia, and increased inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In cases with complications, imaging studies, such as chest radiography or CT scans, may be necessary to assess pulmonary or central nervous system involvement.

Emerging point-of-care (POC) diagnostics such as loop-mediated isothermal amplification (LAMP) assays offer promising solutions for rapid and accessible diagnosis, particularly in resource-limited rural settings. LAMP assays are highly sensitive and specific and are capable of detecting O. tsutsugamushi DNA without the need for sophisticated laboratory equipment or extensive technical expertise. Unlike PCR, which requires thermal cyclers and controlled laboratory conditions, LAMP operates at a constant temperature (approximately 60 °C–65°C), making it suitable for use in portable heating devices. This simplicity enhances its feasibility in rural health centers, where electricity and advanced infrastructure may be limited. LAMP assays can provide results within 60–90 min, enabling faster initiation of treatment compared to traditional serological methods, which often require days for results (10). Additionally, LAMP assays can be adapted for use with blood, eschar, or other clinical samples, thereby increasing their versatility. Studies have demonstrated their efficacy in detecting scrub typhus in endemic regions, with a sensitivity comparable to that of PCR and improved accessibility over IFA (10). However, challenges remain, including the need for standardized protocols, cost reduction for widespread adoption, and the training of healthcare workers to perform and interpret LAMP assays accurately. Integrating LAMP into existing diagnostic algorithms can significantly reduce diagnostic delays in rural areas, improve patient outcomes, and reduce the burden of scrub typhus.

Since no single test is 100% reliable, a combination of serological and molecular tests, along with good clinical acumen, is essential for the accurate and early diagnosis of scrub typhus.

B) Treatment of Scrub Typhus

Management of scrub typhus primarily involves early diagnosis and prompt antibiotic treatment to prevent severe complications and mortality. Doxycycline is the first-line treatment and is highly effective in reducing disease severity and duration. The recommended dosage is 100 mg twice daily for adults and 2.2 mg/kg twice daily for children above eight years, typically administered for 7 to 10 days (41). Alternatively, azithromycin is an effective option, especially for pregnant women and children under eight years, because doxycycline is contraindicated in these populations. Azithromycin is administered as a single 500 mg dose daily for three days or a single dose of 1 g in adults (42). Studies have shown that both doxycycline and azithromycin have similar efficacies, but azithromycin may be preferable in cases of doxycycline resistance or treatment failure (43).

In severe or complicated cases of scrub typhus, such as those presenting with multiple organ dysfunction, acute respiratory distress syndrome (ARDS), or meningoencephalitis, intravenous (IV) therapy with doxycycline or azithromycin may be required (44). Rifampicin has been identified as a potential alternative treatment, particularly for doxycycline-resistant strains of *Orientia tsutsugamushi*, and is sometimes used in combination therapy for refractory cases (45). Chloramphenicol, though effective, is less commonly used because of the risk of severe adverse effects, such as bone marrow suppression (46).

Supportive care is essential for managing scrub typhus, particularly in patients with severe disease manifestations. Fever control with antipyretics, adequate hydration, and electrolyte balance should be maintained (47). Patients with ARDS or respiratory failure may require oxygen therapy or mechanical ventilation, and those with hypotension should receive fluid resuscitation with careful monitoring to avoid fluid overload (48). Vasopressors may be necessary in cases of myocarditis or septic shock. Renal replacement therapy may be required in patients who develop acute kidney injury (49).

Timely diagnosis is critical in preventing complications, but this is often challenging in endemic regions where scrub typhus symptoms overlap with other febrile illnesses, such as malaria, leptospirosis, and dengue. Therefore, empirical treatment with doxycycline is often initiated in patients with suspected scrub typhus, particularly in endemic areas, even before laboratory confirmation (50). Given the lack of a licensed vaccine, preventive measures, such as avoiding mite-infested areas, using protective clothing, and applying insect repellents containing DEET, are crucial in reducing the risk of infection. Continued research into vaccine development and novel therapeutic options is necessary to enhance the management and prevention of scrub typhus.

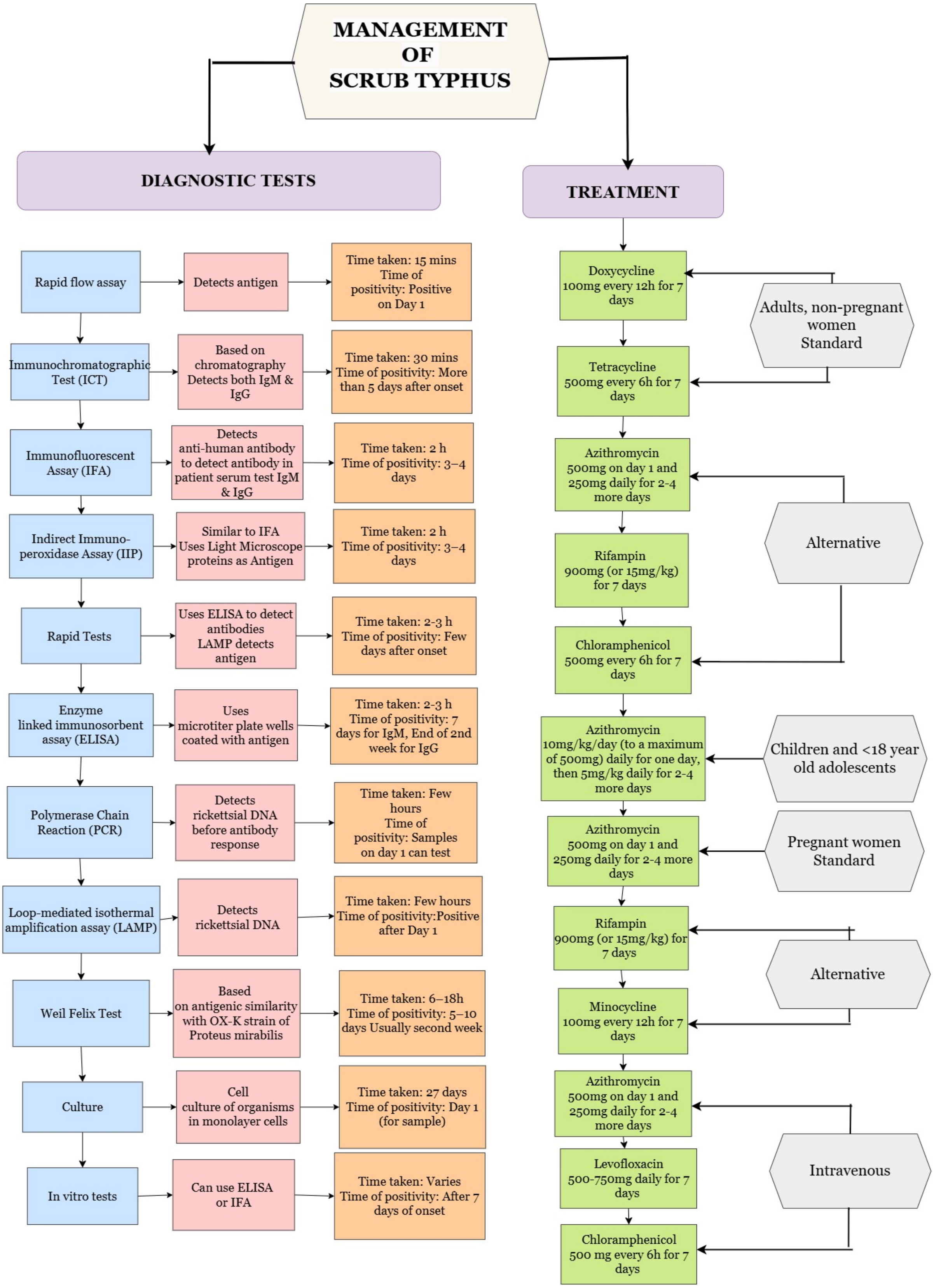

Fig 2: *Flow chart of management of Scrub Typhus with diagnostics*

RECOMMENDATIONS FOR SCRUB TYPHUS PREVENTION

The prevention of scrub typhus requires a combination of personal protective measures, environmental management, and public health strategies. *Orientia tsutsugamushi* is transmitted through infected chigger mites, and avoiding mite-infested areas, particularly dense vegetation, forests, and agricultural fields, is essential. Individuals living in or traveling to endemic regions should wear long-sleeved clothing, tuck pants into socks, and use insect repellents containing DEET or permethrin on the skin and clothing to reduce the risk of chigger bites. Environmental control measures such as clearing vegetation, controlling rodent populations, and maintaining proper sanitation can help reduce the habitats of chigger mites. Farmers and outdoor workers should be educated on the risk factors and encouraged to use protective gear. Travelers to endemic areas should be aware of the symptoms of scrub typhus and seek early medical attention if they develop febrile illness. Public health initiatives should focus on increasing awareness, improving surveillance, and ensuring early diagnosis and treatment. As no vaccine is currently available, research into vaccine development remains a priority. Additionally, healthcare workers in endemic regions should receive training to effectively recognize and manage scrub typhus, reduce disease burden, and prevent complications.

CONCLUSION

Scrub typhus remains a significant global health challenge, particularly in the Asia-Pacific region, with emerging cases in non-endemic areas, signalling its potential for global spread. Its non-specific presentation and diagnostic challenges contribute to delayed treatment and increased morbidity. Strengthening surveillance, improving access to rapid diagnostics, and investing in vaccine research are critical for reducing the disease burden.

Prevention strategies, including personal protective measures, environmental control, and public health awareness, are essential to reduce disease transmission. Given the absence of a licensed vaccine, continued research is necessary to develop effective immunization strategies and novel therapeutics. Strengthening surveillance systems, improving healthcare infrastructure, and educating healthcare professionals and at-risk populations will play a vital role in reducing disease burden. With increasing reports of scrub typhus cases beyond traditional endemic regions, global health initiatives should prioritize enhanced detection, treatment, and prevention strategies to mitigate its impact.

Authors' contribution statement

All authors made substantial, direct, and intellectual contributions to the work and approved it for publication. Sneha Ann Shibu contributed to the main writings, diagrammatic conceptualization and overall supervision including appropriate cross references. Dr. John Abraham, Dr. Alvin J Joseph, Dr. Clement Prakash, Dr. Anieta Merin Jacob played a key role in peer reviewing and editing the final manuscript.

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

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CITATION

Sneha A. S., John A., Alvin J. J., Clement P., & Anieta M. J. (2025). A Comprehensive review of Scrub Typhus: An emerging masquerade of fever. In Global Journal of Research in Medical Sciences (Vol. 5, Number 3, pp. 164–176). https://doi.org/10.5281/zenodo.15679961