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## Scrub typhus: A review of current understanding and future directions

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### Abstract

Due to occupations and environment like people's working in fields, tunnels or rural areas with dense vegetation are at the higher risk Scrub typhus is an infectious disease caused by a bacterium called *Orientia tsutsugamushi*. People get it when they are bitten by tiny infected mite larvae, known as chiggers. The disease is common in many parts of Asia and the western Pacific, and it is now being reported from newer areas too.

Scrub typhus is often missed or diagnosed late because its symptoms—such as fever, headache, body aches, and sometimes a black scab at the bite site are similar to those of many other illnesses. The bacteria mainly survive in mites by being passed from one stage of the mite's life to another and from mother mites to their eggs. It does not spread from one person to another. Most cases can be treated easily with antibiotics like doxycycline if diagnosed early. However, if treatment is delayed, the infection can become severe and lead to serious complications.

Doxycycline is the most used medicine and is given for about 7–10 days. It works very well in most patients. If doxycycline cannot be used (such as in pregnant women or young children), azithromycin is a safe and effective alternative. In severe cases or when tablets cannot be taken, antibiotics may be given through a vein in the hospital. Early treatment leads to complete recovery, but delay in treatment can cause serious complications. There is no vaccine, so early diagnosis and prompt antibiotics are the key to saving lives

**Keywords:** Scrub typhus, *Orientia tsutsugamushi*, Doxycycline, azithromycin

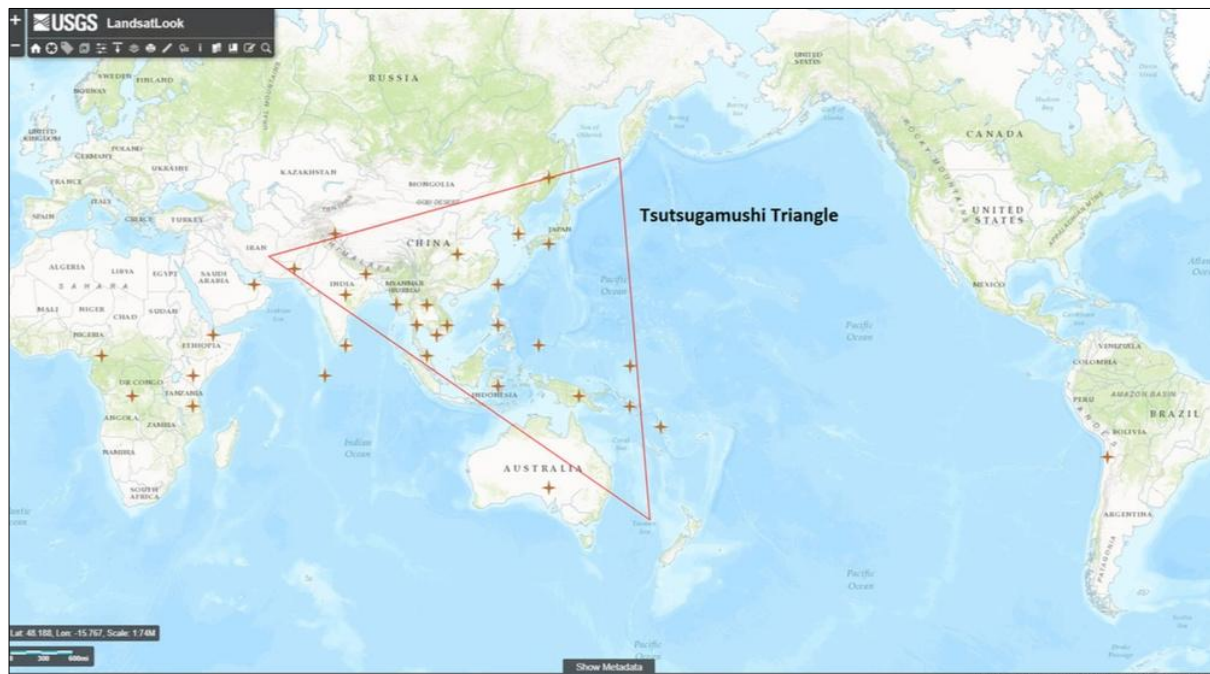
### Introduction

Scrub typhus is a gram negative, alpha-proteobacterium belonging to the family Rickettsiaceae. The organism was first discovered and described in Japan in 1930. This disease is caused by the bacterium *Orientia tsutsugamushi*, a member of the rickettsial group, and represents a major public health challenge throughout the Asia-Pacific region, particularly within the well-known "tsutsugamushi triangle." More than one billion people across this vast zone—from Pakistan in the west to Australia in the south and Japan in the east—are at risk, making it an area of considerable epidemiological concern with potentially high fatality rates. Transmission occurs when infected larval trombiculid mites bite humans, leading to widespread vasculitis, inflammation around blood vessels, increased vascular permeability, and possible injury to multiple organs. Individuals of any age, including travellers to endemic regions, can contract the infection. Clinical features commonly include fever, headache, muscle pain, and gastrointestinal disturbances. A characteristic eschar—a dark, necrotic ulcer—may appear at the bite site, though its occurrence varies across different geographic areas. Diagnosis primarily depends on clinical evaluation, with confirmation achieved through serological testing, highlighting the necessity for rapid and precise detection. Early identification allows for appropriate interprofessional management, ensuring coordinated care and effective prevention measures. This overview provides an extensive discussion of the assessment, diagnosis, treatment, and complications associated with scrub typhus, while emphasizing the essential role of collaborative healthcare teams in delivering timely and efficient patient care [1].

A systematic review examining the burden of scrub typhus in India—situated within the "tsutsugamushi triangle"—found that the disease is responsible for at least 25.3% of cases of acute undifferentiated febrile illness. Although it is one of the major pathogens contributing

to these unexplained fevers, scrub typhus continues to be overlooked in both research efforts and healthcare policy development (1). Although rickettsial infections were once believed to have largely vanished from the country, cases continue to be reported across various regions of India, and the infection has emerged as a frequent cause of fever accompanied by rash. Despite these ongoing reports, scrub typhus often remains undiagnosed because of its diverse clinical manifestations, limited awareness among clinicians,

low index of suspicion, and inadequate diagnostic facilities. The illness commonly presents with a rash, which may appear as a single lesion or multiple lesions in the same patient. In our cases, the presence of an eschar was a key finding that guided clinical suspicion and supported the final diagnosis. Only a small number of documented scrub typhus cases involve children, and when it occurs in the paediatric population, the disease typically manifests with systemic complications [2].



**Fig 1:** World map showing the areas infected from scrub typhus [3]

Transmission of *Orientia tsutsugamushi* occurs through vertical transmission within mites, which includes both:

- Transstadial transmission – passage of the organism from larva to nymph and from nymph to adult.
- Transovarial transmission – transfer of *O. tsutsugamushi* from an infected female mite to her offspring through the eggs.

Although vertical transmission is the primary mode of maintenance of *O. tsutsugamushi* in mite populations, horizontal transmission has also been reported rarely. In this process, a chigger acquires the pathogen from an infected vertebrate host, and its progeny are then capable of infecting new hosts. However, current evidence is insufficient to confirm that horizontal transmission plays a major role in the natural cycle of the organism.

Importantly, there are no known cases of person-to-person transmission of scrub typhus. Understanding mite biology, especially feeding behaviour and engorgement patterns, may help improve prevention and control strategies.

Despite its public health significance, many aspects of scrub typhus pathogenesis and host–pathogen interactions remain unclear. This is largely due to the challenges associated with studying an obligate intracellular bacterium. Factors such as marked antigenic variability, reemergence of the disease, and short-lived immunity contribute to frequent primary infections and reinfections. Research on *O. tsutsugamushi* has been limited over the past decades, resulting in significant gaps in knowledge. Only preliminary studies indicate that the disease has long been present in endemic

regions, and available epidemiological data remain sporadic both within endemic areas and globally. In this review, we present a comprehensive overview of the current epidemiology, prevention, and control of scrub typhus in endemic regions as well as among international travellers.

**Background:** Scrub typhus is transmitted by the larval stage (chiggers) of trombiculid mites. These mites maintain the infection in nature through trans-ovarian transmission, meaning infected female mites pass the bacteria to their eggs. The mite life cycle has four stages egg, larva, nymph, and adult—but only the larval stage is parasitic, making it the only stage capable of infecting animals or humans. The larvae feed mainly on small wild rodents (especially species of *Rattus*), and humans are infected accidentally, most commonly during the rainy season. Infection occurs when people enter areas where infected mites live. These habitats often include secondary scrub vegetation, which appears after forests are cleared—hence the name “scrub typhus.” However, mite habitats can be diverse, including seashores, rice fields, and even semi-desert regions. Outbreaks often occur in these environments.

Chiggers attach to hosts by crawling onto the skin and choosing areas that are thin, soft, wrinkled, or compressed by clothing. Instead of piercing the skin deeply, they insert their mouthparts into hair follicles or skin pores. They inject digestive enzymes that liquefy surrounding tissue, which they then ingest. Because the salivary glands of infected chiggers contain large numbers of *Orientia tsutsugamushi*, the bacteria enter the host during feeding.

After feeding, the chigger drops off, burrows into the soil, and matures into a nymph, completing the next stage of its life cycle. *Orientia tsutsugamushi* is an intracellular bacterium, living and multiplying inside host cells, especially phagocytes. The organism can avoid destruction inside white blood cells, multiply within them, and later escape back into the bloodstream. Inside the body, the bacteria multiply on the endothelial lining of small blood vessels, releasing cytokines that damage the vessel wall [4].

This leads to:

- fluid leakage,
- platelet clumping,
- proliferation of monocytes and polymorphs,
- focal occlusive end-angiitis, and
- micro-infarctions.



Fig 2: The red mark on the hand indicates the chigger bite [5]

**Epidemiology:** It is estimated that approximately 1 billion people are at risk of scrub typhus and only 1 million cases

are reported annually. Increase prevalence of scrub typhus has been reported from Asian countries and pacific islands, Japan, south Korea, Nepal, Northern Pakistan and South China. *Rickettsia* is generally believed to have disappeared from many parts of India. The serological testing of 37 residents of southern India who were diagnosed from fever of unknown aetiology in 1996 to 1998 confirmed that spotted fever in symptom of scrub typhus. Scrub typhus is known to occur all over India including the hills of northern India.

Scrub typhus is infected in all age groups but mostly occurs in working age and adults from the age group of 20's to 40s. Children's from age 1 to 15 years and the elderly can get infected with peak incidence.

- Adults: in adults from age of 21 to 60 years scrub typhus shows the higher rate of infection and this age group is most infected as per studies.
- Children: in children's from age of 1 to 15 years significant cases are reported in younger populations.
- Elderly: in elderly it is not much infected. But seen at least a one in hundreds.

Of 'mite bites' outdoors activities during monsoon or post monsoon increases the exposure to infected chiggers. As they are seen mostly during the monsoon season (July to December in India). People at higher risk of getting infected by scrub typhus are those in rural, grassy or forested areas. Specially farmers, outdoor workers and people living in endemic zones during monsoon seasons. Scrub typhus is most likely to occur primarily in the 'tsutsugamushi triangle' vast region in the Asia pacific spanning from Russia's for east. Rural and forested areas is where infection is most likely to occur. The Asia pacific is the main global hotspot for scrub typhus.

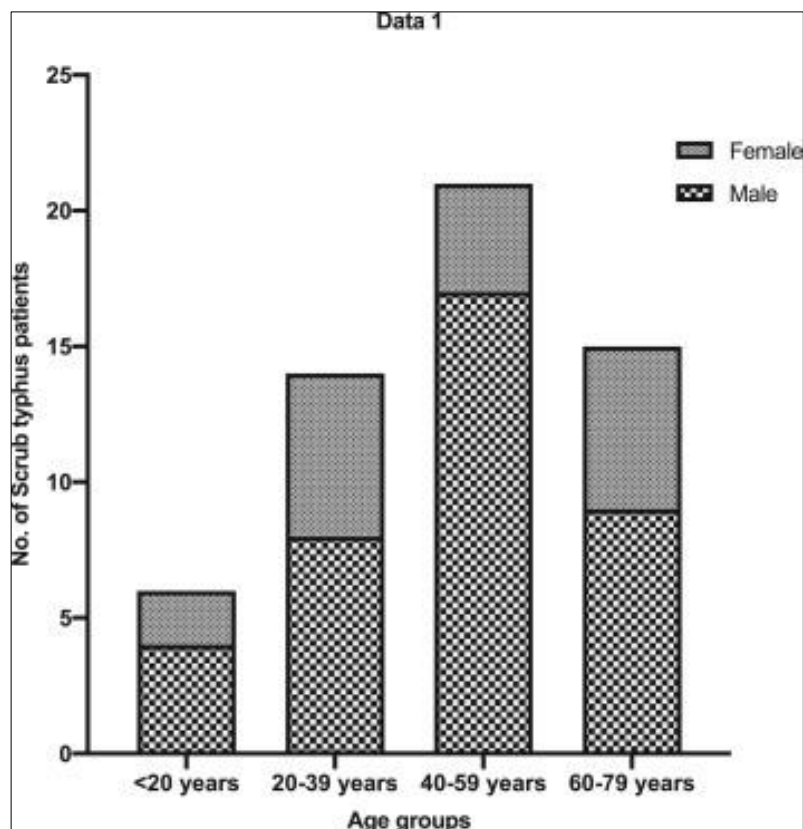


Fig 3: Graph showing the age groups where the scrub typhus mostly occur. As per the graph age group of 40 to 59 is showing the high cases [7]

## Aetiology

**Causative agent:** caused by *orientia tsutsugamushi* a gram negative obligate intracellular bacterium.

They are obligate intracellular pathogens which needs to infed eukaryotic cell in order to multiply. They are 0.5 to 0.8  $\mu\text{m}$  wide and 1.2 to 3.0  $\mu\text{m}$  long. They are rod shaped bacterium. They can be cultured with cell monolayers. Thin organism in highly virulent and should only be handled in a laboratory with biosafety level 3 facilities. They exhibit extensive genomic and antigenic heterogeneity they may lead to the definition of multiple species in the genes. The genome is approximately 2000kb. They are found throughout the mites body but is present in the greatest number in the salivary gland. This pathogen does not have vascular membrane. Thus, it grows freely in the cytoplasm of the infected cell [11]. It is transmitted in humans through the bite of infected larval mites (chiggers). If mites lives in vegetation and the infection occur when the chiggers injects the bacteria into the skin during feeding leading to an acute febrile illness.

## Transmission cycle

**Infection of mites:** chiggers acquire the bacteria by feeding on infected small mammals.

**Humans exposure:** humans come into contact with infected chiggers in rural or semi rural areas with dense vegetation.

**Bite and infection:** the chiggers bites attach to the skin and transmits *orientia tustsugamushi* through it's saliva.

scrub typhus is the systemic illness that primarily infects the endothelial cells lining the blood vessels throughout the body leading to wide spread infection. Thus subsequently vascular injury can effect virtually any organ but most commonly the lungs, liver and kidneys. This conditions often progress to multi organ dysfunction syndrome (MODS) leading to severe unwanted cases.

**Respiratory system:** Scrub typhus affects the lungs mainly by causing intense inflammation of the blood vessels. This inflammation makes the vessels leaky, allowing fluid to collect in the lungs and damage lung tissue. The illness may start with mild breathing problems or bronchitis, but in severe cases it can progress to acute respiratory distress syndrome (ARDS). As the condition worsens, inflammation, immune cell buildup, and bleeding in the lungs occur, leading to breathlessness, pneumonia-like symptoms, and difficulty in getting enough oxygen into the blood [16].

## Pathophysiology of lung involvement

- Bacterial Entry and Blood Vessel Damage:** *Orientia tsutsugamushi* enters the body and mainly infects the cells lining blood vessels, leading to inflammation of these vessels (vasculitis).
- Exaggerated Immune Reaction:** The infection stimulates the immune system to release large amounts of inflammatory substances (cytokines), which cause further injury to lung tissues.
- Leaky Vessels and Fluid Accumulation:** As the blood vessels in the lungs are damaged, they become leaky, allowing fluid and proteins to seep into the air spaces and surrounding lung tissue, resulting in pulmonary edema.

- Influx of Inflammatory Cells:** Immune cells such as neutrophils and macrophages accumulate in the lungs, worsening inflammation and causing tissue damage.
- Progression to ARDS:** Together, these processes lead to severe lung injury and may progress to acute respiratory distress syndrome (ARDS), marked by very low oxygen levels and characteristic changes on chest imaging [16].

**Liver:** Liver damage in scrub typhus happens because the bacteria *Orientia tsutsugamushi* cause inflammation in the liver and its blood vessels. This inflammation, along with an overactive immune response, injures liver cells and leads to raised liver enzyme levels in blood tests. Liver cells may swell, accumulate fat, or even die, and immune cells like lymphocytes can collect in the liver tissue. In severe cases, this damage can progress to acute liver failure. Much of the injury occurs because the body's immune system—especially T-cells and macrophages—attacks infected blood vessel cells, which unintentionally harms the surrounding liver tissue.

## Mechanisms of liver damage

- Blood Vessel Inflammation:** The bacteria infect the lining of small blood vessels in the liver, causing inflammation. Immune cells gather around these vessels and release inflammatory chemicals, which damage the tiny liver blood channels.
- Liver Cell Damage:** Because of this inflammation and the infection itself, liver cells become swollen, show signs of injury, and some may die in small patches.
- Overactive Immune Reaction:** While the immune system tries to fight the infection, its strong response can also harm the liver, leading to inflammation of the liver (hepatitis).
- Disturbed Blood Flow:** Small clots can form in the liver's tiny blood vessels, further interfering with normal liver function.

**Kidney:** Kidney damage in scrub typhus, usually seen as acute kidney injury (AKI), happens due to several factors. The bacteria can directly injure kidney tubules, leading to tissue damage. At the same time, widespread inflammation and inflammation of blood vessels reduce blood flow to the kidneys, causing functional failure. Severe infection (sepsis) and muscle breakdown (rhabdomyolysis) can further strain the kidneys. In most cases, this kidney damage is temporary and improves with early treatment using antibiotics such as doxycycline [17].

## Mechanisms of kidney injury

- Direct Bacterial Damage:** The scrub typhus bacteria can directly infect kidney cells, causing inflammation and damage to the kidney tubules, which may lead to acute tubular necrosis.
- Widespread Inflammation and Blood Vessel Injury:** The infection causes inflammation of small blood vessels throughout the body. This reduces blood flow to the kidneys, leading to functional kidney failure, and can also cause loss of proteins from the blood.
- Severe Infection and Organ Failure:** In serious cases, the infection can progress to sepsis, resulting in shock and failure of multiple organs, including the kidneys.

4. **Muscle Breakdown:** Breakdown of muscle tissue releases harmful substances into the blood, which place extra stress on the kidneys and worsen kidney injury.
5. **Inflammation Within the Kidneys:** Inflammation may affect the kidney filters (glomeruli) or the surrounding kidney tissue, further impairing normal kidney function [17].

**Central nervous system:** Damage to the central nervous system (CNS) in scrub typhus mainly occurs due to widespread inflammation of blood vessels in and around the brain. The bacteria *Orientia tsutsugamushi* infect the cells lining blood vessels, triggering inflammation and immune reactions that lead to tissue injury.

This process happens through several mechanisms:

1. **Direct spread to the brain:** The bacteria enter the bloodstream and infect endothelial cells. They can reach the brain by crossing the blood–brain barrier, either directly or by being carried inside infected immune cells.
2. **Blood vessel injury:** Infection and immune activation cause inflammation of small blood vessels in the brain. This makes vessels leaky, allows immune cells to collect around them, and can lead to tiny clots. These changes may result in brain damage, including strokes or bleeding.
3. **Immune-related nerve damage:** In some cases, the immune system mistakenly attacks nerve tissue after the infection. This can lead to delayed neurological problems such as Guillain–Barré syndrome (GBS), acute disseminated encephalomyelitis (ADEM), or opsoclonus-myoclonus syndrome, which may appear days or weeks after the fever has resolved [18].

**Cardio vascular system:** Scrub typhus affects the cardiovascular system mainly by causing widespread inflammation of blood vessels and an excessive immune response. This inflammation involves small blood vessels in the heart and other organs, leading to serious and sometimes life-threatening complications.

How the damage occurs:

1. **Infection of Blood Vessel Lining:** The bacteria *Orientia tsutsugamushi* infect the endothelial cells that line blood vessels.
2. **Blood Vessel Inflammation:** This infection causes inflammation of the vessel walls and the surrounding tissues, a process known as vasculitis and perivasculitis.
3. **Excessive Immune Reaction:** Immune cells release large amounts of inflammatory chemicals (cytokines) to fight the infection. However, this strong response can also damage the body's own tissues.
4. **Impaired Vessel Function and Clot Formation:** Injury to the blood vessel lining makes vessels leaky, disrupts normal blood flow, and can lead to the formation of small clots.
5. **Heart and Organ Injury:** Reduced blood and oxygen supply can damage the heart muscle and other important organs, leading to cardiovascular complications.

#### Clinical manifestations

After a person is bitten by the infected mite, the symptoms usually start after 10–12 days (sometimes 6–21 days). The

illness can be mild, like normal fever, or can become very serious, affecting many organs (called MODS – multi-organ dysfunction syndrome).

#### Common Symptoms

People with scrub typhus usually develop:

1. Fever
2. Stomach problems (like nausea, vomiting, or loose stools)
3. Tiredness and weakness
4. Cough
5. Body pain and muscle pain
6. Headache
7. A red rash may appear on the body, starting from the chest area and spreading to the arms and legs by the end of the first week.
8. Swollen lymph nodes (lymphadenopathy) are also common.
9. Eschar (Black crust at bite site).

A very important sign of scrub typhus is an eschar. It is a small bump at the bite site that later becomes black after the skin in the center dies. This sign is almost diagnostic of scrub typhus. But in people with dark skin, it may be hard to see.

#### Eschars usually appear on:

1. Groin
2. Armpit
3. Waist
4. Chest or abdomen
5. Other exposed skin areas

#### Second Week – Severe Symptoms

If the disease is not treated, after the second week, the infection may spread to different organs:

**Treatment of scrub typhus:** The management of scrub typhus depends on early initiation of appropriate antibiotic therapy. Doxycycline is the first-line treatment for most patients, while Azithromycin is an effective and safer alternative, particularly for pregnant women and individuals who cannot tolerate doxycycline or in areas where resistance is suspected. In addition to antibiotics, supportive care—such as adequate hydration and fever control—is essential. Antibiotics should be continued for several days after the fever subsides to prevent relapse. Severe cases may require intravenous therapy and close inpatient monitoring.

#### Antibiotic Therapy

- **Doxycycline (drug of choice):**
  1. Adults: 100 mg twice daily
  2. Children weighing <45 kg: 2.2 mg/kg twice daily
- **Azithromycin:**
  1. A highly effective alternative, especially for pregnant women and doxycycline-intolerant patients
  2. Adults: 500 mg once daily for 5 days (or other recommended short-course regimens)
- **Chloramphenicol:** Effective but generally reserved for severe cases due to the risk of serious adverse effects and limited availability in some regions
- **Rifampicin:** Considered a second-line agent and used cautiously, particularly in tuberculosis-endemic areas.

### Key Principles of Management

- **Early treatment:** Antibiotics should be started promptly based on clinical suspicion, without waiting for laboratory confirmation
- **Treatment duration:** Therapy should continue for at least 3 days after fever resolution to prevent relapse
- **Supportive care:** Includes fever management, fluid replacement, and monitoring for complications such as organ dysfunction
- **Severe disease:** May require IV antibiotics, hospitalization, and intensive supportive management

### Special Considerations

- **Pregnancy:** Doxycycline is contraindicated; Azithromycin is the preferred drug
- **Children under 8 years:** Doxycycline is used with caution due to potential effects on teeth and bone; Azithromycin is safer
- **Antibiotic resistance:** Reports of doxycycline resistance in some regions make Azithromycin an important alternative(20)

Prevention from scrub typhus:

Preventing scrub typhus mainly involves reducing exposure to infected mites, as no vaccine is currently available. This can be achieved through personal protective measures, environmental control, and awareness of high-risk areas.

### Personal Protective Measures

- **Insect repellents:** Apply repellents containing DEET (diethyltoluamide) to exposed skin and permethrin to clothing, footwear, and outdoor gear, following product instructions.
- **Protective clothing:** Wear long-sleeved shirts, long trousers tucked into socks, and closed shoes to minimize skin exposure.
- **After outdoor exposure:** Bathe with soap and warm water after returning indoors and wash worn clothes thoroughly to remove any attached mites.

### Environmental Control

- **Avoid high-risk areas:** Stay away from grasslands, dense vegetation, scrubby areas, and brush piles where mites are commonly found.
- **Vegetation management:** Keep surroundings clean by clearing bushes and tall grass to reduce mite habitats.
- **Rodent control:** Store food in sealed containers and block entry points to homes to limit rodents, which serve as hosts for mites.

### Additional Measures

- **Chemoprophylaxis:** In high-risk or outbreak settings, doxycycline may be considered for short-term preventive use under medical guidance.
- **Vaccine status:** There is currently no vaccine for scrub typhus, making preventive measures essential.

### Summary table: key takeaways

Topic	Simple Explanation
<i>Causative organism</i>	Scrub typhus is caused by <i>Orientia tsutsugamushi</i> .
<i>Main mode of transmission</i>	Infection is mainly maintained in mites.
<i>Vertical transmission</i>	Infection passes within mite generations.
<i>Transstadial transmission</i>	Infection passes from larva → nymph → adult mite.
<i>Transovarial transmission</i>	Infection passes from infected female mite to eggs.
<i>Importance of vertical transmission</i>	This is the main method of survival of bacteria in mites.
<i>Horizontal transmission</i>	Very rare; mite gets infection from infected animal.
<i>Role of horizontal transmission</i>	Not proven to be important in natural cycle.
<i>Person-to-person spread</i>	No human to human transmission.
<i>Vector feeding behavior</i>	Mite feeding and engorgement helps in spread.
<i>Difficulty in research</i>	Bacteria lives inside cells, hard to study.
<i>Antigenic variation</i>	Bacteria changes its structure frequently.
<i>Immunity</i>	Immunity is short-term, reinfection can occur.
<i>Re-emergence</i>	Disease is coming back in many areas.
<i>Research status</i>	Very limited studies done.
<i>Epidemiological data</i>	Data is incomplete and scattered.
<i>Public health importance</i>	Scrub typhus is an important health problem.
<i>Prevention &amp; control</i>	Better knowledge of mites helps prevention.
<i>Affected population</i>	Seen in endemic areas and travelers.

### Conclusion

Scrub typhus is a serious but treatable infection that spreads to people through the bite of tiny infected mites. It is

common in many parts of Asia, including India, but is often missed or mistaken for other fevers because the symptoms are not very specific. People usually have high fever,

headache, body pain, and sometimes a black scab-like wound (eschar) at the bite site. If scrub typhus is not treated on time, it can damage important organs like the lungs, heart, kidneys, and brain, and may even become life-threatening. The good news is that early diagnosis and simple antibiotics can cure the disease completely. Raising awareness, seeking medical care early for fever, and taking preventive measures to avoid mite bites can greatly reduce the illness and save lives.

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