Frequently Asked Questions

Scrub Typhus

World Health Organization
Regional Office for South-East Asia

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Scrub Typhus

What is it?

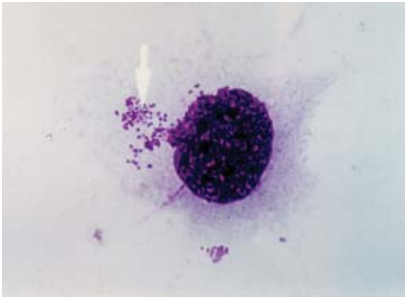
Scrub typhus is an acute, febrile, infectious illness that is caused by *Orientia* (formerly *Rickettsia*) *tsutsugamushi*. It is also known as *tsutsugamushi disease*. Scrub typhus was first described from Japan in 1899. Humans are accidental hosts in this zoonotic disease.

Why is it known as scrub typhus?

The term scrub is used because of the type of vegetation (terrain between woods and clearings) that harbours the vector; however, the name is not entirely correct because certain endemic areas can also be sandy, semi-arid and mountain deserts.

What are the characteristics of the causative organism?

It is an obligate intracellular gram-negative bacterium that has a large number of serotypes.



Orientia tsutsugamushi under microscope [Courtesy: Department of Entomology, Armed Forces Research Institute of Medical Sciences (AFRIMS)]

This pathogen does not have a vacuolar membrane; thus, it grows freely in the cytoplasm of infected cells. Because they are intracellular parasites, they can live only within the cells of other animals. Even though it is recognized as one of the tropical rickettsioses diseases, *O. tsutsugamushi* has a different cellwall structure and genetic composition than that of the rickettsiae. *O. tsutsugamushi* includes heterogeneous strains classified in

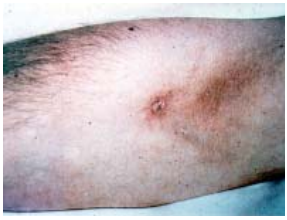
five major serotypes: Boryon, Gilliam, Karp, Kato and Kawazaki [1]. Differentiation of serotypes is important for laboratory diagnosis. *Orientia tsutsugamushi* can be cultivated on L929 cells and stained using the Giemsa method [2].

How is the disease transmitted?

Chigger mite (Courtesy: AFRIMS Bangkok)

Scrub typhus is transmitted to humans and rodents by some species of trombiculid mites ("chiggers", *Leptotrombidium deliense and others*). The mite is very small (0.2 – 0.4mm) and can only be seen through a microscope or magnifying glass.

Humans acquire the disease from the bite of an infected chigger [3,4]. The bite of the mite leaves a characteristic black eschar that is useful to the doctor for making the diagnosis.

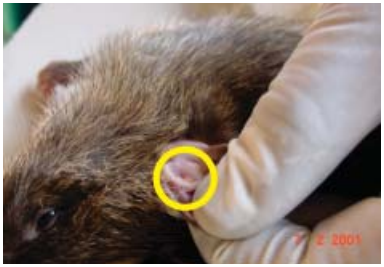


Characteristic eschar in a patient

The adult mites have a four-stage lifecycle: egg, larva, nymph and adult. The larva is the only stage (chigger) that can transmit the disease to humans and other vertebrates, since the other life stages (nymph and adult) do not feed on vertebrate animals. Both the nymph and the adult are free-living in the soil.

How is the disease transmission cycle maintained in nature?

Chigger mites act as the primary reservoirs for *O.tsutsugamushi*. Once they are infected in nature by feeding on the body fluid of small mammals, including the rodents, they maintain the infection throughout their life stages and, as adults, pass the infection on to their eggs in a process called transovarial transmission. Similarly, the infection passes from the egg to the larva or adult in a process called transtadial transmission. In this way, chigger mite populations can autonomously maintain their infectivity over long periods of time.



Chigger mites fed on the inner's ear lobe of wild-caught rat

Early workers thought that rodents were the natural reservoir of infection, but it is now believed that mites are both the vector and the reservoir [4]. Naturally-infected mites, reared in the laboratory, have transmitted the infection for more than twenty generations, while uninfected chiggers, if fed experimentally on infected mice, take up *R. tsutsugamushi*, but fail to transmit the infection transovarially to the next generation [5].

This mite is fastidious in matters of temperature, humidity and food, and finds everything suitable in restricted areas. Scrub typhus is generally seen in people whose occupational or recreational activities bring them into contact with ecotypes favourable with vector chiggers [6].

Why is scrub typhus historically linked to war and military operation?

Scrub typhus, a dreaded disease in pre-antibiotic era, is a militarily important disease that caused thousands of cases in the Far East during the Second World War. Soldiers were exposed to chigger bites in forest areas during the military operation. It is estimated that 36,000 soldiers were either incapacitated or died during World War II [7]. The overall mortality varied from 7% to 9%, second only to malaria among infectious diseases. Furthermore, severe epidemics of the disease occurred among troops in Myanmar (Burma) and Sri Lanka (Ceylon) during World War II [8]. There was a military base in Addu Atoll of Maldives during that time and more than 2000 East African and British soldiers were victims of scrub typhus [9]. The first known batch of scrub typhus vaccine actually used to inoculate human subjects was dispatched to India for use by the Allied Land Forces, South-East Asia Command, in June 1945 [10]. The disease continued to be of military significance during the Malayan Emergency [11]. It was suspected to be the leading cause of pyrexia of unknown origin (PUOs) in forces of the United States (US) of America during the Viet Nam conflict, and caused two confirmed cases among the US troops during the Korean War.

What are the epidemiological features of scrub typhus in Asia?

Scrub typhus is endemic to a part of the world known as the "tsutsugamushi triangle", which extends from northern Japan and far-eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west [12].

Scrub typhus is essentially an occupational disease among rural residents in the Asia-Pacific region. In oil-palm workers in Malaysia, the incidence of antibodies to scrub typhus declines with declining grass density between the rows of maturing oil-palm. This correlates with the decline of chigger populations in this habitat [4]. An increased in the prevalence of scrub typhus has been reported from some Asian countries, which coincides with the widespread use of β-lactam antimicrobial drugs and urbanization in rural areas [13].

Scrub typhus-affected countries of Asia

Scrub typhus is difficult to recognize and diagnose because the symptoms and signs of the illness are often non-specific. The non-specific presentation and lack of the characteristic eschar in 40% patients makes the misdiagnosis and underreporting of scrub typhus common. On the other hand, diagnostic facilities are not available in much of its native range. Therefore, the precise incidence of the disease is unknown. An estimated one billion people are at risk for scrub typhus and an estimated one million cases occur annually [14]. Mortality rates in untreated patients range from 0-30%.

The characteristic feature of an outbreak of scrub typhus are: (i) the obvious association with certain types of terrain; (ii) the marked localization of many cases within certain small foci; (iii) the large percentage of susceptible people, who may be infected simultaneously following exposure over relatively short periods; (iv) the absence of a history of bites or attack by arthropods [15].

What is the status of scrub typhus in the South-East Asia Region?

The vector of scrub typhus is present in most countries of the South-East Asia Region and it is endemic in certain geographical regions of India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka and Thailand.

India

Scrub typhus is prevalent in many parts of India but specific data are not available [16]. There have been outbreaks in areas located in the sub-Himalayan belt, from Jammu to Nagaland. There were reports of scrub typhus outbreaks in Himanchal Pradesh, Sikkim and Darjeeling (West Bengal) during 2003-2004 and 2007. Outbreaks of scrub typhus are reported in southern India during the cooler months of the year. Scrub typhus is a reemerging infectious disease in India [17].

Indonesia

Though endemic foci of scrub typhus are present in Indonesia, no information is available on the burden of this disease. However, several serological and entomological

studies carried out in the Eighties clearly illustrated the presence of vectors in rural settings. *L. deliense* was identified in central Sulawesi as a vector of scrub typhus and the prevalence of antibodies against the *O. tsutsugamushi* antigen was 23% in the sampled rat sera [18]. Similarly, a preliminary serological survey carried out in Sumatra in 1982 revealed that human and rodent samples were seropositive against scrub typhus 12% and 43% respectively. Two species of chigger vectors, *L. deliense* and *L. fletcheri* were found in the area studied [19]. *O. tsutsugamushi* was isolated from *L. arenicola* chiggers and three species of rats in an area of scrub and sedge along the Bay of Jakarta. This is the only finding in Indonesia of a cycle of the agent of scrub typhus associated with *L. arenicola* [20]. A survey of small mammals and their ectoparasites conducted on the islands of Biak and Owi in August 1976 found *L. deliense* and *L. flectcheri* as vectors and *O. tsutsugamushi* was isolated from local rodents [21]. The favoured ecotype of the chigger and rat hosts of *O. tsutsugamushi* appeared to be coarse, low-lying native vegetation on a porous coralline soil [22].

Maldives

Scrub typhus cases have been reported from Seenu atoll and Gaafu DhaaL. No cases had been recorded in humans on the island since the 1940s. But in 2002, 70 people contracted the disease out of whom three died [23].

Leptotrombidium deliense chiggers were found in a variety of habitats and *L. acuscutellaris* were found only in swamps [24]. Outbreaks occur on islands when predators of rats appear generally to be absent and rat populations are saturated.

There are innumerable small, sharply-delimited typhus islands in southern Maldives where infectious agents, vectors and suitable rodents exist simultaneously. Adult villagers come into contact with chiggers when they visit the islands for wood collection and agricultural activities.

An uninhabited island, Maldives

Nepal

A study on the etiology of febrile illness among adults in Patan hospital showed that 3.2% patients (N=876) were serologically positive to scrub typhus [25]. The southern terai region of Nepal is a suitable environment for scrub typhus [26].

Sri Lanka

In Sri Lanka, sporadic cases occur throughout the year in urban and semi-urban areas. The western province, which represents the low country wet zone of Sri Lanka, is the endemic area. A recent rise in the numbers of cases has been noted there though there are no formal studies documenting the disease's epidemiology or disease burden in Sri Lanka.

Thailand

Scrub typhus is most commonly found in northern Thailand and has been associated with paddy farming. *L. deliense* is the most dominant chigger during the rainy season in [27]. In rural Thailand, murine and scrub typhus accounts for around a quarter of all adults presenting to hospital with fever and negative blood cultures [28]. In 2000 there were 3914 cases (6.34 cases per 100 000 population) of scrub typhus reported to the Thai Ministry of Public Health.

Is the occurrence of scrub typhus outbreaks seasonal?

Yes. The seasonal occurrence of scrub typhus varies with the climate in different countries. The period of epidemic is influenced by the activities of the infected mite. It occurs more frequently during the rainy season. However, outbreaks have been reported during the cooler season in southern India. Certain areas such as forest clearings, riverbanks, and grassy regions provide optimal conditions for the infected mites to thrive.

What is the incubation period of scrub typhus?

The incubation period of scrub typhus is about 5 to 20 days (mean, 10-12 days) after the initial bite.

What are the clinical symptoms of scrub typhus?

The chigger bite is painless and may become noticed as a transient localized itch. Bites are often found on the groin, axillae, genetalia or neck [4]. An eschar is often seen in humans at the site of the chigger bite. The illness begins rather suddenly with shaking chills, fever, severe headache, infection of the mucous membrane lining the eyes (the conjunctiva), and swelling of the lymph nodes. A spotted rash on the trunk may be present. Eschars are rare in patients in countries of South-East Asia and indigenous persons of typhus-endemic areas commonly have less severe illness, often without rash or eschar [13]. Whether this is due to past exposure to the organism, or to other factors, is unknown. Symptoms may include muscle and gastrointestinal pains. More virulent strains of *O. tsutsugamushi* can cause haemorrhaging and intravascular coagulation. Complications may include atypical pneumonia, overwhelming pneumonia with adult respiratory distress syndrome (ARDS)–like presentation, myocarditis, and disseminated intravascular coagulation (DIC). Patients with scrub typhus often exhibit leucopenia.

Acute scrub typhus appears to improve viral loads in patients with HIV. This interaction is currently unexplained [29]. Clinical scrub typhus is not known to occur naturally in animals.

How to differentiate scrub typhus from other diseases?

Differentiating scrub typhus from other forms of typhus as well as from fever, typhoid and meningococcal infections is often difficult during the first several days before the

initial rash appears. The most common signs are similar to a variety of other infectious diseases (typhoid fever, murine typhus, leptospirosis and dengue fever, etc.) which should be taken into consideration [30].

The geographical location of scrub typhus, the initial sore caused by the chigger bite, and the occurrence of specific proteins capable of destroying the organism (antibodies) in the blood, provide helpful clues and are useful in establishing the diagnosis.

What diagnostic tests are available for confirmatory diagnosis of scrub typhus?

The diagnosis may be confirmed by a laboratory test such as serology. The cheapest and most easily available serological test is the Weil-Felix test, but this is notoriously unreliable. Fifty per cent of patients have a positive test result during the second week. This test is now being replaced by a complement-fixation test. It is a serological test to detect specific antibody or specific antigen in a patient's serum. Each patient's serum is systematically tested against five *O. tsutsugamushi* serotypes. An IgM titer > 1:32 and/or a four-fold increase of titers between two sera confirm a recent infection. However, due to cross-reactions among serotypes, it is difficult to identify accurately a specific serotype [12].

The gold standard is indirect immunofluorescence antibody (IFA). Indirect immunoperoxidase (IIP) is a modification of the standard IFA method that can be used with a light microscope, and the results of these tests are comparable to those from IFA [31,32,33]. Serological methods are most reliable when a four-fold rise in antibody titre is looked for. Although many techniques have been used successfully for sero diagnosis, relatively few are used regularly by most laboratories.

Commercial rapid diagnostic kits provide reliable and well-accepted preliminary results within one hour, but the availability of these tests is severely limited by their cost [34]. However, other serological tests must be used in order to obtain confirmation of *O. tsutsugamushi* infection. ELISA provides more sensitivity and equal specificity when compared to commercial test kits.

The organism can be grown in tissue culture or mice from the blood of patients with scrub typhus but results are not available in time to guide clinical management. Molecular detection using polymerase chain reaction (PCR) is possible from skin rash biopsies, lymph node biopsies or ethylenediaminetetraacetic acid (EDTA) blood. *O. tsutsugamushi* can be demonstrated by standard and by nested PCR [35]. Real-time PCR assays are as sensitive as standard PCR but are more rapid and can give quantitative results [36].

What types of specimen should be collected for laboratory diagnosis and how should they be dispatched?

Different types of samples can be collected for laboratory investigation but it depends on diagnostic method to be used. The laboratory should be contacted in advance to decide on the types of specimen to be collected. The following specimens can be collected for laboratory investigation provided they are preserved and shipped as follows [2]:

Skin or lymph node biopsy

- If frozen at -80°C after sampling, ship in dry ice for culture.
- If not frozen at -80°C after sampling, ship at room temperature for PCR.
- If formalin-treated or paraffin-embedded, ship at room temperature for immunohistochemistry.

Heparinized blood

- Conserve at -80°C and then ship in dry ice for culture.

EDTA blood

- Conserve at +4°C and then ship at room temperature for PCR.

Serum

- Conserve at +4°C, then ship at room temperature. Collect two serum specimens 10 days apart.

What is the effective treatment against scrub typhus?

Scrub typhus is treated with antibiotics. The drug most commonly used is doxycycline; but chloramphenicol is an alternative. A combination therapy with doxycycline and rifampicin should be used in areas where there is poor response to doxycycline alone [37]. Azithromycin or chloramphenicol is useful for treating infection in children or pregnant women (doxycycline is relatively contraindicated in children). Antibiotic therapy brings about prompt disappearance of the fever and dramatic clinical improvement. Rapid defervescence after antibiotic treatment is so characteristic that it is used as a diagnostic test for *O. tsutsugamushi* infection [38]. These antibiotics are bacteriostatic and merely slow the multiplication of the organism while the patient develops a protective immune response. Both animals and humans develop non-sterile immunity and viable rickettsiae have been recovered from lymph tissue long after infection [39].

If the antibiotic treatment is discontinued too quickly, especially in patients treated within the first few days of the fever, relapses may occur. Secondary infections, such as bacterial pneumonia, should be treated appropriately. No significant morbidity or mortality occurs in patients who receive appropriate treatment.

Is there any prophylactic treatment against scrub typhus?

Yes. It has been shown that a single oral dose of chloramphenicol or tetracycline given every five days for a total of 35 days, with 5-day non-treatment intervals, actually produces active immunity to scrub typhus. This procedure is recommended under special circumstances in certain areas where the disease is endemic.

Is there any vaccine against scrub typhus?

There are no effective vaccines for scrub typhus. It is now known that there is enormous antigenic variation in *Orientia tsutsugamushi* strains, and immunity to one strain does not confer immunity to another [40]. Any scrub typhus vaccine should give protection to all the strains present locally, in order to give an acceptable level of protection. A vaccine developed for one locality may not be protective in another locality, because of antigenic variation. This complexity continues to hamper efforts to produce a viable vaccine [41].

What precautions should be taken to protect you from scrub typhus?

In endemic areas, precautions include wearing protective clothing. Insect repellents containing dibutyl phthalate, benzyl benzoate, diethyl toluamide, and other substances can be applied to the skin and clothing to prevent chigger bites. Do not sit or lie on bare ground or grass; use a suitable ground sheet or other ground cover.

Clearing of vegetation and chemical treatment of the soil may help to break up the cycle of transmission from chiggers to humans to other chiggers.

What control strategy should be taken to contain scrub typhus?

Case identification; public education; and rodent control and habitat modification are the three pillars of programme aimed at controlling the impact of scrub typhus on the human population.

Rapid case identification by health-care workers

The early diagnosis of acute scrub typhus can greatly reduce the chance of life-threatening complications and guide optimal therapy. It will be necessary to increase awareness of empirical therapy options for scrub typhus and to develop diagnostic assays that are affordable, require limited expertise and equipment, and are sensitive and specific such that can be used in endemic, resource poor countries.

Public education on case recognition and personal protection

Advocacy, awareness and education activities should be targeted at schoolchildren, teachers and women groups in endemic areas. Involvement of community-based organizations in prevention and control of scrub typhus is important.

Rodent control and habitat modification

Rodent control is a multidimensional activity that requires multisectoral cooperation. Different control strategies such as trapping, poisoning and use of natural predators are in practice. Rodent control is primarily the responsibility of the agriculture sector - poisoning is a common practice.

Several wildlife rehabilitation organizations encourage the natural form of rodent control through exclusion and predator support and preventing secondary poisoning altogether [42].

Habitat modification will make areas less attractive to commensal rodents and thereby prevent new populations from recolonizing the habitat. Allowing weeds to grow around buildings also encourages rats and mice. Good sanitation in and around buildings creates an environment that is less suited for rodent populations. Proper sanitation may not eliminate rat populations but often can prevent them from flourishing in high numbers. Repeated increase in rodent population even after the use of poisons is a good indication that habitat modification is needed.

Which is the appropriate institution for research and training on scrub typhus in the South-East Asia Region?

The Armed Forces Research Institute of Medical Sciences (AFRIMS) Bangkok, Thailand is the WHO Collaborating Centre (CC) for Emerging Diseases that is providing technical support for outbreak investigation and capacity building for diagnosis and control of scrub typhus. The Department of Entomology, AFRIMS is the only laboratory in the world that has the ability to rear and colonize scrub typhus-infected *Leptotrombidium* mites, the vector of *O. tsutsugamushi*.

Acknowledgements

We gratefully acknowledge the contribution made by the AFRIMS Bangkok, Thailand WHO CC for EID, in providing technical comments and graphic illustrations.

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