CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

August, 2024

Scrub Typhus

INTRODUCTION

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

Rickettsial diseases are considered some of the most covert emerging and re-emerging diseases and are being increasingly recognized in India. Rickettsial diseases are classically divided into the typhus group and spotted fever group (SFG), although the genus has been subdivided further based on phylogenetic analysis. Orientia spp. makes up the scrub typhus group.

Scrub typhus is the commonest occurring rickettsial infection in India.

GLOBAL SCENARIO

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.

There is an estimated one million new scrub typhus infections each year, and over one billion people around the world are at risk. Scrub typhus is a serious public health problem in the Asia-Pacific area. 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.

Without appropriate treatment, the case fatality rate of scrub typhus can reach 30% or even higher.

The seasonal occurrence of scrub typhus varies with the climate in different countries. However, outbreaks have been reported during the cooler season in southern India.

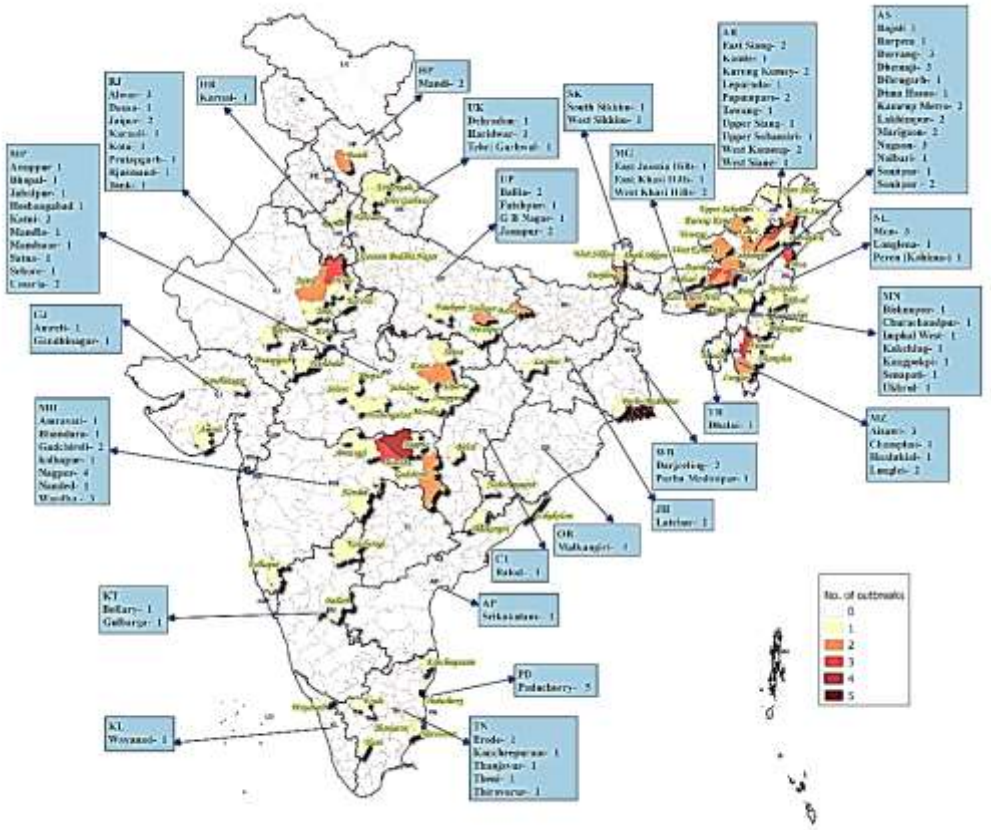
Recent research studies suggest possible link of changing climate with prevalence and seasonality of Scrub typhus within endemic countries.

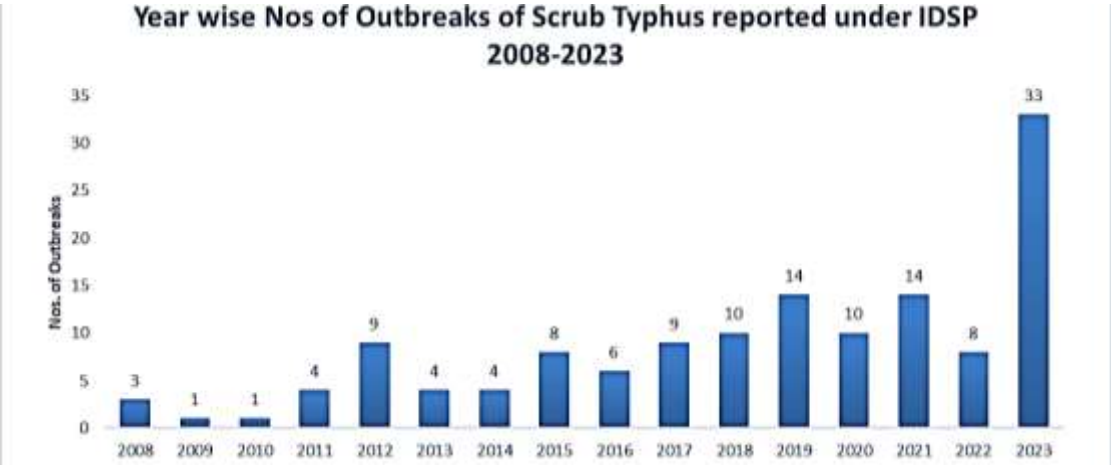
INDIAN SCENARIO

Rickettsial diseases have been documented in India since the 1930s with reports of scrub typhus from Kumaon region, in soldiers during the Second World War in Assam, scrub and murine typhus from Jabalpur area in Madhya Pradesh and of murine typhus from Kashmir. Surveillance in animals and humans in different parts of India has documented significant levels of exposure to infections.

With the increasing awareness, availability of diagnostics and improved surveillance, scrub typhus and other Rickettsiosis is being widely detected from various parts of the country including north eastern states (Assam, Arunachal Pradesh, Manipur, Mizoram, Meghalaya, Nagaland, Sikkim, Tripura), Jammu and Kashmir, Uttar Pradesh, Delhi, Himachal Pradesh, Uttarakhand, Bihar, West Bengal, Rajasthan, Gujarat, Maharashtra, Karnataka, Tamil Nadu, Puducherry and Kerala.

In some regions, scrub typhus accounts for up to 50 per cent of undifferentiated fever presenting to hospital.





FEATURES OF OUTBREAKS

The characteristic features of an outbreak of scrub typhus in Indian context are:

I. It is no longer associated with certain types of terrain;
II. It is no longer localized to certain small foci;
III. a large percentage of susceptible people may be infected simultaneously following exposure over relatively short periods;
IV. The history of bites or attack by arthropods may not be easily elicited from the patient;
V. Rapid response to treatment to tetracyclines/ macrolide group of drugs.

EPIDEMIOLOGY

Agent: Scrub typhus (Chigger borne typhus, Tsutsugamushi fever) is caused by Orientia tsutsugamushi. Orientia is a small (0.3 to 0.5 by 0.8 to 1.5 μm), gram negative bacterium of the family Rickettsiaceae. It differs from the other members in its genetic makeup and in the

composition of its cell wall structure since it lacks lipopolysaccharide and peptidoglycan and does not have an outer slime layer. It is endowed with a major surface protein (56kDa) and some minor surface protein (110, 80, 46, 43, 39, 35, 25 and 25kDa). There are considerable differences in virulence and antigen composition among individual strains of O. tsutsugamushi which has many serotypes (Karp, Gillian, Kato, Kawazaki and Boryong).

DISEASE TRANSMISSION

Scrub typhus is transmitted by the mite Leptotrombidium deliense. The vector mites inhabit sharply demarcated areas in the soil where the microecosystem is favorable (mite islands). Human beings are infected when they trespass into these mite islands and are bitten by the mite larvae (chiggers). Only the larval stages take blood meal. The mite feeds on the serum of warm-blooded animals only once during its cycle of development, and adult mites do not feed on man. The microbes are transmitted transovarially in mites. Scrub typhus normally occurs in a range of mammals, particularly field mice and rodents.

The L.deliense group of vector mites are widely distributed all over the country coexisting primarily with rodents and other small mammals. On the body of small mammalian hosts, the chiggers attach in clusters on the tragus of the ear, the belly and on the thighs. The Leptotrombidium mites, on the rat host, may appear orange or pink. The typical vector L.deliense is generally found associated with either established forest vegetation or secondary vegetation after clearance of forest areas. This species is generally abundant on grasses and herbs where bushes are scarce.

Incidence of scrub typhus is higher among rural population though also being increasingly reported from urban areas. Cases are more likely to have exposure to rodents at home or at work. Cases are exposed to the risk of encountering chiggers sitting in grass blades, bushes and shrubs during occupational (farming) or outdoor activities such as open defecation and recreation. The disease is seasonal in many parts of India, which correlates with the appearance and activity of mites.

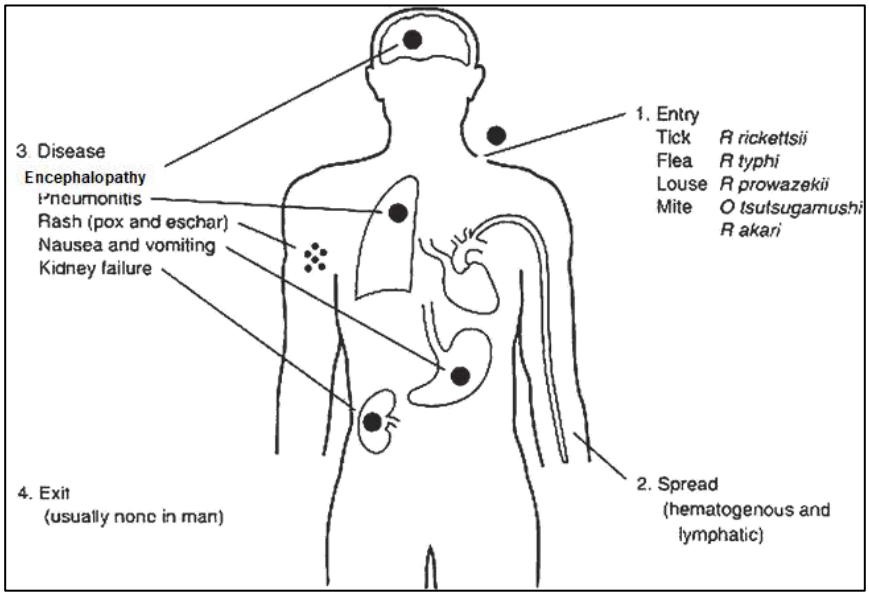
Sentinel animals can also be used for collection of trombiculid mites from the field. These animals are generally white laboratory mice or rats kept in small cages containing food and water and placed in the field overnight to attract chiggers. Chiggers can also be collected from field directly on human beings, by walking in the field after wearing stockings. The following morning, chiggers can be collected from the body of the sentinel animals. The mites can be preserved in 70% alcohol till they reach laboratory for identification. Chigger index (average number of chiggers infesting a single host) of > 0.69 (critical value) is an indicator for implementation of vector control measures.

Incubation Period

Incubation Period: 5-20 days (average 10-12 days) after the initial bite.

CLINICAL PICTURE

- The chigger bite is painless and may become noticed as a transient localized itch.
- Bites are often found on the groin, axillae, genitalia, perianal area or neck.
- 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.
- Symptoms may include muscle and gastrointestinal pains.



Common clinical manifestations of the Rickettsial Infections

- More virulent strains of *O. tsutsugamushi* can cause haemorrhage and intravascular coagulation.
- Complications may include atypical pneumonia, overwhelming pneumonia with adult respiratory distress syndrome (ARDS)–like presentation, encephalopathy, myocarditis, disseminated intravascular coagulation (DIC) and multiple organ dysfunction syndrome (MODS).
- Patients with scrub typhus often exhibit leucopenia.
- **Case fatality rate** of scrub typhus can be as high as 30-70% if no appropriate treatment is received.

Scrub Typhus axillary eschar

Maculopapular rash on the back of a case of scrub typhus

Chigger mite

CASE DEFINITION

Suspected/clinical case: Acute undifferentiated febrile illness of five days or more with or without eschar should be suspected as a case of rickettsial infection (if eschar is present, fever of less than five days duration should also be considered as scrub typhus). Other presenting features may be headache and rash (rash more often seen in fair persons), after encephalopathy lymphadenopathy, multi-organ involvement like liver, lung and kidney and acute respiratory distress. Patients presenting with features of AES could be scrub typhus.

The differential diagnosis of dengue, malaria, pneumonia, leptospirosis and typhoid should be kept in mind.

Probable case: A suspected clinical case showing significant titres (1:80 or above) in OX2, OX19 and OXK antigens by Weil-Felix test and an optical density (> 0.5 or evaluated with locally determined cutoff) for IgM antibodies by specific group ELISA is considered positive.

Confirmed case: A case compatible with the clinical description of scrub typhus with at least one of the following:

1. High titre of IgM antibodies in ELISA (evaluated with locally determined cutoff) for single clinical sample*.
2. A four-fold rise in the Weil-Felix test (total antibodies) between acute and convalescent-phase serum specimens run in parallel.
3. Seroconversion on ELISA/ IFAT (demonstrating the conversion of IgM to IgG antibodies).

*A single serum sample showing high titres of IgM antibodies may indicate acute infection.

These 1-3 tests are the preferred tests as ELISA are widely acceptable.

Other: Isolation and Validated PCR can be done in patients who have not received antibiotic and in early stage of diseases (preferably less than 7 days)

SUPPORTIVE INVESTIGATIONS

- TLC during early course of the disease may be normal but later in the course of the disease, leucocytosis is seen i.e. WBC count > 11,000/µl.
- Thrombocytopenia
- Deranged liver function tests: Elevation of transaminases and alkaline phosphatase
- Deranged renal function tests (Proteinuria, Albuminuria)
- Chest X-ray shows infiltrates, mostly bilateral

LABORATORY DIAGNOSIS

Laboratory diagnosis

Rickettsial diseases may be diagnosed in the laboratory by:

(i) Serology
(ii) molecular diagnosis (PCR).
(iii) isolation of the organism

Collection, storage & transportation of specimen

The collection, transportation and storage of specimens are extremely vital steps in laboratory diagnosis and hence, must be undertaken with utmost care.

Specimen

- Serum
- Blood collected in tubes containing EDTA or Sodium citrate
- Blood clot
- Eschar, whole blood, buffy coat fraction and tissue specimen

I. Serological diagnosis

Serological assays are the simplest & mainstay diagnostic tests for rickettsial diseases and some of the available tests can easily be done in modest laboratory facilities available at PHC/District hospitals.

Several serological tests are currently available for the diagnosis of rickettsial diseases like Weil Felix test, Enzyme linked Immunosorbent assay (ELISA), Indirect Immunofluorescence (IIF), etc. Further, baseline titres and Cutoffs for ELISA needs to be standardized for each region.

(A) Weil-Felix Test (commonly used test)

The Weil Felix test uses antigens from three proteus strains: *P.vulgaris Ox 2, P. vulgaris Ox 19 and P. mirabilis Ox k.* Weil-Felix test has reasonable sensitivity and specificity as per NCDC experience of last 10 years and can be performed even in resource poor settings. High titre in single specimen has higher positive predictive value. However, fourfold rise in titre is confirmatory in paired serology. Whenever possible IgM/IgG based serologic test may be done for scrub typhus.

The interpretation of Weil-Felix test is given in table below:

	OX 19	*OX 2*	*OXK*
Epidemic typhus	++++	+	*0*
Brill Zinsser disease	++++	+	*0*
Murine typhus	++++	+	*0*
Scrub typhus	*0*	*0*	+++
RMSF	++++	+	*0*
Other tick borne infection	+	++++	*0*
Indian tick typhus	+	++++	*0*

(B) Enzyme linked Immunosorbent Assay (ELISA)

ELISA techniques, particularly IgM and Ig G capture assays to specific antigen, are probably the most sensitive tests available for rickettsial diagnosis. The presence of IgM antibodies, indicate recent infection with rickettsial diseases. In cases of infection with *O.tsutsugamushi*, a significant IgM antibody titer is observed at the end of the first week, whereas IgG antibodies appear at the end of the second week. . Paired serology/ IgM and IgG ELISA certainly help in diagnosis of Rickettsial diseases in resource constrained settings.

(C) Indirect Immunofluorescent antibody (IFA) test

Traditionally, Micro immunofluorescence is used as a reference technique to test several antigens simultaneously to help identify the causative organism *Orientia* and strain identification. The availability and cost of reagents/ equipments are major constraints and is not available in most of the laboratories. Further technique requires standardization, a pool of reference antisera and expertise. Therefore, it is recommended only for research and as reference test in areas where seroprevalence of rickettsial diseases has been established.

I. Molecular diagnosis – PCR

Molecular techniques may be used for detection of *O.tsutsugamushi, R.prowazeki, R.conorii, R.typhi*. DNA extracted from clinical specimens (eschar, whole blood, buffy coat fraction and tissue specimen) can be used to diagnose rickettsial infections by PCR/Real time PCR.

The specific target sequence for 56 kDa / 47kDa surface antigens have been attempted for identification of *O.tsutsugamushi*. The other targets for identification of rickettsial diseases attempted are 16 s r RNA, outer membrane protein, lipoprotein gene etc. The results are best within the first week for blood samples because of presence of rickettsemia (O.tsutsugamushi, R.rickettsii, R. typhi and R. prowazekii) in first 7-10 days especially if patients have not received antibiotics.

II. Isolation of the organism (Not for Routine Diagnosis)

As rickettsiae are highly infectious and have caused several serious and fatal infections among lab workers, it comes under the Risk Group 3 organisms. Isolation should be done in laboratories equipped with appropriate safety provisions preferably BSL-3 laboratory following strict biosafety precautions. Rickettsiae have been isolated by several different methods such as animal inocaulation, embryonated eggs and various cell lines.

Rickettsia may be isolated in male guinea pigs or mice; yolk sac of chick embryos; vero cell line or MRC 5 cell lines from patients in early phase of the disease. Egg and animal inoculation methods have been replaced by faster and more sensitive cell cultures. Rickettsiae grow well in 3-5 days on Vero cell and MRC 5 cell coverslip cultures and can be identified by immunofluorescence using group and strain specific monoclonal antibodies or gene-based identification.

Rapid Diagnostic Tests do not give consistent results and may not be used as a single test for diagnostic purposes.

TREATMENT

Prompt institution of effective antibiotic therapy against rickettsiae is the single most effective measure for preventing morbidity and mortality due to rickettsial diseases. Anti rickettsial therapy improves the outcome of all rickettsioses, with the occasional exception of fulminate or complicated cases of RMSF, epidemic typhus and scrub typhus. Cardiac, pulmonary, renal, and central nervous systems should be assessed and additional measures instituted to prevent complications.

Tetracyclines and chloramphenicol remain the only proven therapy for the rickettsial diseases. Macrolides are an effective alternative class for therapy. Without waiting for lab confirmation of the rickettsial infection, antibiotic therapy

should be instituted when rickettsial disease is suspected.

At primary level: The health care provider needs to do the following:

I. Recognition of disease severity. If the patient comes with complications to primary health facility and treating physician considers it as rickettsial infection, treatment with doxycycline should be initiated before referring the patient.

II. Referral to secondary or tertiary center in case of complications like ARDS, acute renal failure, meningoencephalitis, multi-organ dysfunction. In addition to recommended management of pneumonia, treatment of scrub typhus (doxycycline) is to be provided to the patient.

III. In fever cases if scrub typhus is established the following drugs should be administered:

In adults:

A. Doxycycline 200 mg/day in two divided doses for individuals above 45 kg for a duration of seven days. **OR**

B. Azithromycin 500 mg in a single dose for five days.

If the clinical sign and symptoms persist, alternative diagnosis should be considered.

In children:

A. Doxycycline in the dose of 4.5 mg/kg body weight/day in two divided doses for children below 45 kg. OR

B. Azithromycin in the dose of 10 mg/kg body weight/day for five days.

In pregnant women: Azithromycin 500 mg in a single dose for five days. Azithromycin is the drug of choice in pregnant women, as doxycycline is contraindicated.

At secondary and tertiary care level

I. The treatment as specified above in uncomplicated cases.

II. In complicated cases the following treatment is to be initiated:

- Intravenous doxycycline (wherever available) 100 mg twice daily in 100 ml normal saline to be administered as infusion over half an hour initially followed by oral therapy to complete 7-15 days of therapy. OR
- Intravenous azithromycin in the dose of 500 mg intravenous (iv) in 250 ml normal saline over one hour once daily for 1-2 days followed by oral therapy to complete five days of therapy. OR
- Intravenous chloramphenicol 50-100 mg/kg/day 6-hourly doses to be administered as infusion over one hour initially followed by oral therapy to complete 7-15 days of therapy.

III. Management of the individual complications should be done as per the existing practices.

Doxycycline and/or chloramphenicol resistant strains have been seen in South-East Asia. These strains are sensitive to azithromycin.

Tetracyclines may cause discoloration of teeth, hypoplasia of the enamel, and depression of skeletal growth in children; the extent of discoloration is directly related to the number of courses of tetracycline therapy received. Therefore, tetracycline should not be used for children under 8 years of age and for pregnant women.

CHEMOPROPHYLAXIS

Pre-exposure chemoprophylaxis is recommended for short period, high- risk exposure. A single oral dose of chloramphenicol or tetracycline is to be given every 5 days for a total of 35 days, with 5-day non-treatment intervals. In children, weekly doxycycline started before and for 6 weeks after exposure is recommended.

PREVENTION AND CONTROL

An effective vaccine for humans has not been developed till now, mainly due to serotypic heterogeneity of the organism.

Preventive measures for general public

- People who cannot avoid infested terrain should wear protective clothing (Full pant, full sleeves and shoes), impregnate their clothing and bedding with a miticide.
- People should wash themselves and their clothes after every potential exposure.
- Insect repellents containing dimethyl

phthalate (DMP), benzyl benzoate and diethyl toluamide (DEET) can be applied to the skin and clothing to prevent chigger bites.

- It is advisable to 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 vegetation/ soil may help to break up the cycle of transmission from chiggers to humans.

CONTROL STRATEGIES

I. **Rapid case identification by health-care workers can help provide prompt treatment:** The early diagnosis of acute scrub typhus can greatly reduce the chance of life-threatening complications and guide optimal therapy. States should consider planning for prepositioning diagnostic kits for scrub typhus, ahead of peak seasons, to actively detect and manage cases

II. **Public education on case recognition and personal protection will help in the identification and prompt treatment of cases:** Advocacy, awareness and education activities should be targeted at schoolchildren, teachers and women groups in endemic areas.

III. **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 agriculture sector - poisoning is a common practice.
- Vector control: Chiggers can be controlled by insecticide treatment of the vegetation/ forest pathways.
- Several wildlife rehabilitation organizations encourage the natural form of rodent control through exclusion and predator support and preventing secondary poisoning altogether.
- Habitat modification such as good sanitation in and around buildings creates an environment that is less suited for rodent populations. This 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.
- Repeated increase in rodent population even after use of poisons is a good indication that habitat modification is needed.

….about CD Alert

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