



## STATUS OF SCRUB TYPHUS: A REVIEW

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### AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration between both authors. Author GV designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AB managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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### ABSTRACT

The disease caused by Rickettsiae in human, the most widespread is Scrub typhus. It exists as zoonoses in nature between certain species of trombiculid mites and their small mammals i.e. rats, field mice, shrews. In this humans are the accidental host of the mite-rodent-mite cycle. Scrub typhus has re-emerged in India with ancient outbreaks. It is presently seen in increasing numbers in various south Indian states, north east and of late from north Indian states, and Himalayan foothills –Himachal Pradesh and uttrakhand. The mode of transmission is the bite of infected larval mites and the incubation period is usually 10 to 12 days; varies from 6 to 12 days. Scrub typhus resembles epidemic typhus clinically. The onset is acute with chills and fever is about 104° to 105°F, headache, malaise, prostration and a macular rash appearing around the 5<sup>th</sup> day of illness, generalized lymphadenopathy and lymphocytosis are common. The main abide in tsutsugamushi disease diagnosis remains in serology. The oldest test is that the Weil-Felix OX K agglutination reaction that is cheap, easy to perform and results are come in one-night. ELISA for the detection of IgM antibodies against Orientia tsutsugamushi offers advantages of being able to test large number of samples at a time and can be automated. Indirect fluorescent antibody assay is the gold standard assay for the serological detection of antibodies in scrub typhus. In children and pregnant women Azithromycin is preferred. Rifampicin is an alternative drug but is not to be given alone to avoid the development of drug resistant.

**Keywords:** Scrub typhus; *Orientia tsutsugamushi typhus*; mite born fever; chigger; prevention.

### 1. INTRODUCTION

Scrub typhus is a zoonotic disease caused by bacteria orientia tsutsugamushi [1] and it is known as miteborne typhus or Japanese-river fever [2] an obligate intracellular gram negative bacteria. It is transmitted by the bite of larval form of trombiculid mite [3].

Humans are the accidental host of the mite-rodent mite cycle [4]. The standard geographical location for

scrub typhus is described as tsutsugamushi triangle extending from Russian for east in the north to Pakistan in the west Australia in the south and the Japan in the East [5]. Scrub typhus has re-emerged in India with ancient outbreaks [6]. It is presently seen in increasing numbers in various south Indian states, north east and of late from north Indian states, and Himalayan foothills –Himachal Pradesh one of the first state to identify scrub Pediatric Scrub typhus in Himalayas (SK Mahajan et al.) and uttrakhand [7]. The clinical manifestations are diverse ranging from

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subclinical stage to fatal organ failure and its is grossly under diagnosed [8,9]. The incubation period scrub typhus is 1-3 weeks and patients usually present with fever, Eschar, headache, vomiting, myalgia, lymphadenopathy and maculopapular rash.

Scrub typhus is a disease which frequently goes undiagnosed due to its vague clinical symptoms and lack of a definitive protocol for its Diagnosis. The clinical syndrome classically consists of fever, rash and Eschar and requires laboratory confirmation of diagnosis [10]. It should be considered as a differential diagnosis in patients with acute febrile illness including those with thrombocytopenia, renal impairment, Liver function test (LFT) abnormality, altered sensorium, pneumonitis or Acute respiratory distress syndrome (ARDS) thorough search for Eschar, particularly hidden areas is useful for diagnosis [11].

The main abode in tsutsugamushi disease diagnosis remains serology. ELISA for the detection of IgM antibodies against Orientia tsutsugamushi offers advantages of being able to test large number of samples at a time and can be automated [12]. Indirect fluorescent antibody assay is the gold standard assay for the serological detection of antibodies in scrub typhus [13].

All the currently available serological tests for scrub typhus have some limitations of which the clinician needs to be aware. Serological diagnosis based on a single acute serum sample requires a cut off antibody titer varying from 1:10 to 1:400 depending on the endemic titer [10].

### 1.1 Brief Review of History of Scrub Typhus

Scrub typhus is a historically significant disease. Evidence of this disease has been found in writings from way back in 313A.D. in China [14]. The term ‘akamushi’ that originates the Japanese term for this rickettsial disease that means red chig. The rural residents of these countries knew that the best way to avoid being infected was to avoid those areas that are infected by the arthropods [15]. Coyttarus in 1578 was the first to suggest that typhoid and typhus were different diseases. The illness was then later described by Hashimoto in 1810.

Scrub typhus, tsutsugamushi disease or chigger borne rickettsiosis is an acute febrile illness among humans that is caused by infection with the bacterium Orientia tsutsugamushi, an obligate intracellular gram negative bacterium following the bite of infected mite vectors [16].

The ‘typhus’ word that has been derived from the Greek word ‘Typos’ for fever which suggest ‘fever with stupor’ or smoke. This organism was formerly known as *Rickettsia tsutsugamushi*, but then it was found to be different genetically and in cell wall structure and was reclassified as Orientia.

### 1.2 Epidemiology of Scrub Typhus

They are endemic across extensive in different parts of Asia, south Asia, Australia and therefore the Pacific. They were clinically described within the Far East quite 1500 years ago.

- I. International Impact of tsutsugamushi disease: The typhus is endemic in different parts of the world known as the “triangle of tsutsugamushi” which extends from Northern Japan and far-eastern Russia within the north, to Northern Australia within the south, and to Pakistan within the west.
- II. National Impact of scrub typhus: Scrub typhus is a re-emerging infectious disease in India. It is the most common rickettsial disease in India; it is prevalent in many parts of the country.

### 1.3 Clinical Features

- Headache
- Fever
- The Papule followed by an Eschar (dark black circular sign) at the site of chigger feeding (only in 50%).
- Myalgia, Cough and Lung infection.
- Diarrhea, abdominal pain, nausea and vomiting.
- Regional lymphadenopathy, Maculopapular rash and Blood-shot eyes.
- Fatal cases can develop interstitial pneumonia and encephalitis.

**Table 1. Given below are the types of Rickettsial diseases in typhus group**

Disease	Rickettsial agent	Insects vectors	Mammalian reservoirs
Epidemic typhus	<i>R. prowazekki</i>	Louse	Humans
Murine typhus	<i>R. typhi</i>	Flea	Rodents
Scrub typhus	<i>O. tsutsugamushi</i>	Mite	Rodents

**Table 2. Scientific classification**

Domain	Bacteria
Phylum	Proteobacteria
Class	Alphaproteobacteria
Order	Rickettsiales
Family	Rickettsiaceae
Genus	Orientia
Species	<i>O. tsutsugamushi</i>

### 1.3.1 Specific investigations for scrub typhus

1. **Weil Felix:** The sharing of the antigens between Rickettsia and proteus is that the basis of this heterophil antibody test. Though this test lacks high sensitivity and specificity but still is a helpful, useful and cheap diagnostic tool for laboratory diagnosis of scrub typhus diseases.
2. **IgM and IgG ELISA:** Enzyme linked immunosorbent assay techniques, particularly immunoglobulin M capture assays for serum, are probably the most of sensitive tests available for rickettsial diagnosis and the presence of IgM antibodies indicate comparatively recent infection with rickettsial unwellness. Just in case of infection with *O. tsutsugamushi*, a major Immunoglobulin M antibody titre is determined at the last of 1st week, whereas IgG antibodies appear at the end of second week.
3. **Polymerase chain reaction (PCR):** It's a rapid and specific test for diagnosis. It are often wont to detect rickettsial DNA in blood and eschar samples. The PCR is targeted at the gene encoding the main 56 Kda and 47Kda surface antigen gene. The result are good within first week for blood samples as a result of presence of rickettsemia in initial 7-10 days.
4. **Immuno-floresence Assay (IAF):** This is often a reference serological methodology for diagnosis of Rickettsial disease and is considered serological 'Gold standard'; however, cost and requirement of technical expertise limit its wide use.
5. **Indirect Immunofloresence Assay (IFA):** It offers comparable result as IFA but requires special instrument and experience personnel for interpretation of the test.
6. **Immunochromatographic test (ICT):** The ICT has been considered some extent of care diagnosis system for the detection of

tsutsugamushi disease with reported sensitivity and specificity almost like the opposite standard methods used for the detection of tsutsugamushi disease .ICT uses a recombinant mixture of 56-kDa outer-membrane proteins of Karp, Kato and Gilliam strain as captured antigen for detection of IgM and IgG antibodies to Orientia tsutsugamushi.

### 1.3.2 Future of scrub typhus diagnosis

Biosensor based disease diagnosis with higher sensitivity and specificity become the longer term of disease diagnosis. It's becoming a robust point of care diagnosis system for hasty and precise diagnosis of several diseases that aren't facile to diagnose by other laboratory diagnosis methods.

## 2. TREATMENT

Without treatment, the Scrub typhus disease is often fatal. The drug most commonly used is Doxycycline or Tetracycline but chloramphenicol is an alternative drug. Strains that are resistant to Doxycycline and chloramphenicol have been reported in northern Thailand [17, 15].

## 3. VACCINE

No licensed vaccines are available.

### 3.1 Preventive Measures

- Avoid getting to places where infected mites are found, i.e. mainly near animals as mites breed on animals skin and avoid visiting areas with many of vegetation as mites can easily breed on them.
- Use bug repellent sprays while visiting such places.
- Wear gloves and boots when cleaning garden or handling with soil.
- Not sitting directly on the grass.

## 4. CONCLUSION

Health education of the people regarding the modes of transmission and individual prophylaxis is of paramount importance and may go an extended way in prevention of the disease. Educate peoples creating the general awareness, improving personal hygiene, methods of individual and private protection, and general cleanliness in living environments.

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Authors have declared that no competing interests exist.

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