Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Review Article

Scrub typhus strikes back: Are we ready?

Rina Tilak [a,*], *Air Cmde Renuka Kunte* [b]

[a] *Scientist 'G', Department of Community Medicine, Armed Forces Medical College, Pune 411040, India*
[b] *Professor & Head, Department of Community Medicine, Armed Forces Medical College, Pune 411040, India*

ARTICLE INFO

Article history:
Received 12 December 2018
Accepted 31 December 2018
Available online 10 January 2019

Keywords:
Scrub typhus
Leptotrombidium
Orientia tsutsugamushi
Acute undifferentiated febrile illness
Acute encephalitis syndrome

ABSTRACT

Scrub typhus has struck back, albeit with renewed vigour, impacting areas with previously known endemicity as also impressing newer expanses. It is not surprising, therefore, that Scrub typhus has emerged as a leading cause of public health concern globally as well as in India, but are we ready to take on the challenge?

Over the last decade, there has been a global increase in the number of outbreaks of Scrub typhus, be it the military occupied areas or the civil population at large. The innumerable outbreaks of Scrub typhus, although disconcerting, have nonetheless contributed phenomenally towards better understanding of the dynamics of scrub typhus. There have been significant contributions to awareness of the disease amongst medical professionals, scrub typhus as a cause of Acute Undifferentiated Febrile Illness (AUFI) and newer clinical manifestation – Acute Encephalitis Syndrome (AES), availability and advances in diagnostics and management, man-vector-pathogen interactions, new records of *Leptotrombidium* species, newer vectors and *Orientia* species.

Antigenic diversity and the varied clinical presentation of scrub typhus, absence of scrub typhus surveillance system and a lack of political will to recognize the disease as one of the important reemerging public health problem are areas seeking concerted deliberations and actions so that the challenges posed by scrub typhus can be addressed.

Introduction

> **'After decades of feigned obscurity, scrub typhus strikes back'**

The global reemergence of scrub typhus has dealt a deadly blow to the public health professionals and medical fraternity alike surpassing even malaria and dengue by its sheer magnitude in terms of geographical expanse, morbidity and mortality in areas endemic for both.[1] Scrub typhus, a chigger (larvae of trvombiculid mite) borne disease caused by intracellular obligate bacterium *Orientia tsutsugamushi* has finally expanded its area of influence from the famous 'tsutsugamushi triangle' to impress newer areas in Africa and South America caused by the newly identified *Orientia* species – *Candidatus Orientia chuto* & others[2,3] (Fig. 1). Today, regrettably, the world stands a mute witness to its increasing sphere of activity and the day is not far when scrub typhus will likely

* *Corresponding author.*
E-mail address: rinatilak@hotmail.com (R. Tilak).
https://doi.org/10.1016/j.mjafi.2018.12.018

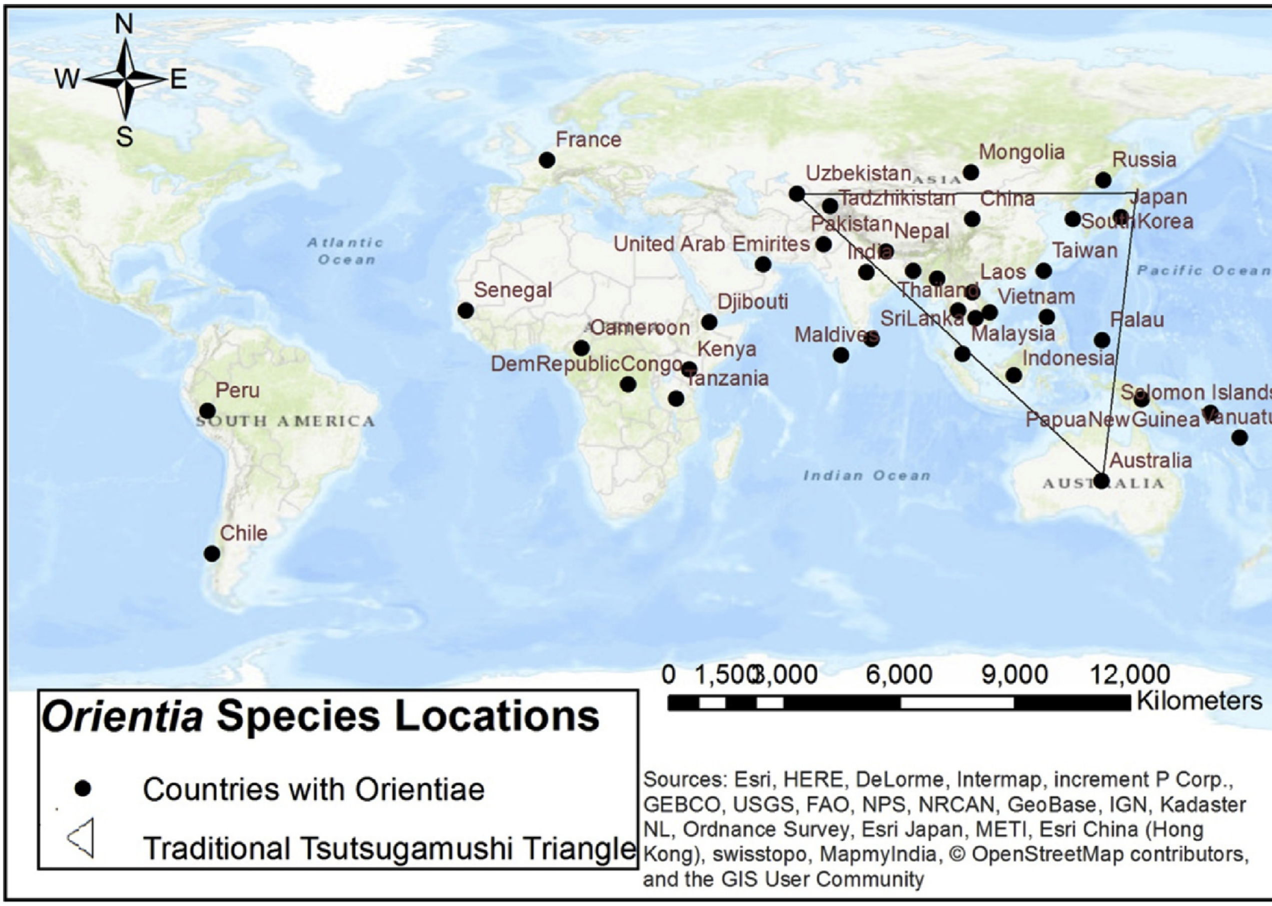

Fig. 1 – Global distribution of *Orientia* species in & outside tsutsugamushi triangle.

emerge as a major global vector borne disease to reckon with. It is imperative to appreciate that unless scrub typhus is accorded its due importance and efforts are launched to contain its onward march given the impact of climate change, travel and industrialization on its likely global spread, the situation may become rather demanding and spiral out of control.

The earliest published record of scrub typhus can be traced to the 3rd century A.D from the Ming Dynasty in China. It was in China in 313 AD, that symptoms associated with scrub typhus were first described in Chinese "Material Medica".[4] It was during the same time that the vector of scrub typhus also finds a mention in Chinese literature as red insects found along river banks referring probably to the chiggers of trombiculid mites. However, the first description of scrub typhus in recent times is from Japan in the year 1899. The history of scrub typhus is indebted to the Japanese and British researchers who did pioneering work prior to World War II on characterizing scrub typhus and the epoch making discovery of etiological agent of scrub typhus by Nagayo.

Scrub typhus, nevertheless, shot into prominence during World War II (WW II) afflicting millions in the China- Burma-India corridor of military action. The impact of Scrub typhus on military was so enormous that commanders were forced to withdraw troops from the affected areas, changing the course of the war itself. Scrub typhus, thereafter, came to be established as a disease of military significance but by the end of WW II, it had lost its prominence and was nearly forgotten barring its mention in the medical textbooks as a disease of historical importance. Nonetheless, the changing paradigms of human behaviour coupled with the environmental influences and their interaction led to the resurgence of scrub typhus and other rickettsial diseases globally; scrub typhus struck back, albeit with renewed vigour, impacting areas with previously known endemicity as also impressing newer expanses. It is not surprising; therefore, that scrub typhus has emerged as a leading cause of public health concern in known areas of endemicity. The disease is currently estimated to impact 1 billion populations globally with 1 million casualties.[5]

> **"Typhus is not dead. It will live on for centuries and it will continue to break into the open whenever human stupidity and brutality give it a chance, as most likely they occasionally will"- Hans Zinsser, Rats Lice and History 1934.**

Man has indeed made brutal assaults on nature and transgressed into ecological niches of mites called the 'mite islands' to influence and amplify opportunities of enhanced man-vector contact. Zinsser has not been let down; the last decade is witness to increasing number of outbreaks of Scrub typhus being reported from Asia pacific to Africa and South America. One of the reasons postulated for the repeated outbreaks of scrub typhus is the antigenic heterogeneity of

Orientia species[3,6] coupled with the fact that exposure to one strain does not confer long lasting heterologous immunity in exposed individuals leading to repeated episodes. Increasing awareness and high index of suspicion in endemic areas has also contributed to greater reporting of outbreaks.[7] It is astonishing that despite stupendous advances in epidemiology of scrub typhus, we are still struggling to contain scrub typhus and its associated morbidity & mortality. **Scrub typhus has struck back, but are we ready** to tackle the challenges posed by the reemergence of scrub typhus?" In an attempt to answer the question, the authors have endeavoured to examine the challenges as on date.

Expanded endemicity

Scrub typhus, currently known to be endemic in about 13,000,000 sq km area in countries of Asia–Pacific region located in the oft quoted 'tsutsugamushi triangle', has eventually expanded its territorial endemicity with reports of scrub typhus like illness from Chile, Peru, and West Africa caused by *O. chuto* and others.[2,3] The occurrence of the disease in these newer distant countries from the currently known endemic region is inexplicable as also the absence of a known vector of scrub typhus in these areas till date. The hypothesis that leeches could have transmitted scrub typhus could not be evidenced and has been shelved as of now.[2] It is indeed a challenging task to screen all arthropods as also other probable vectors to unravel this mystery. The fact that scrub typhus can be caused by other *Orientia* species warrants exploration of other such species capable of transmitting scrub typhus illness globally. It is also important to undertake worldwide search for presence of scrub typhus or like illnesses in countries not reporting such illnesses as on date, the task is daunting but warranted.

Seasonal deviation and habitat diversity

Scrub typhus was historically known to occur in post monsoon season, however reports of occurrence of outbreaks in cooler months[7] has widened the seasonal window of scrub typhus activity necessitating public health machinery to remain on toes nearly throughout the year barring a very limited period of hot weather. The disease, which was earlier known to be restricted to rural habitats is currently reported from a wide variety of habitat ranging from hills to plains, forests to deserts and beaches, agricultural to dry lands, rural to urban and also from inhabited to abandoned areas. This brings out an important aspect that scrub typhus outbreaks or like illnesses can be expected anywhere and everywhere in the world and we need to be alert to its heightened activity and increasing presence in hitherto naive areas.

Surveillance inadequacy

World Health Organization (WHO) states that scrub typhus is probably one of the most under diagnosed and underreported febrile illnesses requiring hospitalization in the endemic regions.[8] Despite the global reemergence of scrub typhus and a case fatality rate ranging from 0 to 70% (based majorly on host factors and antigenic strain),[9] it is really surprising that WHO has not felt the need to list scrub typhus as a neglected disease or disease necessitating surveillance. The fact that all the currently endemic countries have nearly non existential or poor surveillance system challenges the containment of scrub typhus and its slow yet steady global spread. There is an urgent need to put in place a surveillance system and declare scrub typhus a notifiable disease in all areas of known endemicity. WHO document on the subject, recommends immediate case-based reporting of all suspected cases from the peripheral level to the intermediate and central level and all suspected cases and outbreaks to be mandatorily confirmed. It further recommends establishment of a parallel laboratory surveillance system which would report all confirmed cases to the central level. The authors feel that instituting public private partnership involving governmental and other nongovernmental stakeholders to work collectively in establishing an effective surveillance system will help prevent outbreaks and ensure prompt and effective management of cases with a spinoff benefit of reducing the morbidity and mortality due to scrub typhus.

Elusive epidemiology of scrub typhus

Exploring the vector, host and pathogen interaction

Scrub typhus is transmitted by the bite of an infected trombiculid mite larva called chiggers generally belonging to the sub family Trombiculinae, genus *Leptotrombidium* of the tribe Trombiculini. *O. tsutsugamushi* is maintained through transovarian transmission in the trombiculid mites making them the reservoirs as well as vectors of scrub typhus. Apart from the *Leptotrombidium* species, *Schoengastiella ligula* of the tribe Gahrliepiini has also been incriminated as a vector in India[10–21] (Table 1). The report of *S. ligula* as a vector of scrub typhus in India has opened up the possibility of the role of other trombiculid mite genus/species as vectors of scrub typhus. This fact further assumes significance in the context of scrub typhus like illness in Chile where the vector is still elusive.

The impact of environmental factors and climate change on enhancing the activity range of rodents, the natural hosts of chiggers, the ecological adaptability of vectors to diverse habitats coupled with human exploratory forays in mite islands for leisure or livelihood have all contributed to the expansion of mite islands and establishment of 'zoonotic tetrad' thus augmenting transmission of scrub typhus. But the exact dynamics of the interplay of these factors need to be ascertained to understand the likely extent of global distribution of the disease.

The importance of index animal – insectivore, *Suncus murinus* (shrew), in scrub typhus vector surveillance cannot be under emphasized. The authors feel that the infestation of the index animal with vector species and the presence of pathological changes in liver & spleen in the animal post *O. tsutsugamushi* natural challenge is likely to not only provide an early indication of an impending outbreak but also as a likely

Table 1 – Important trombiculid vectors of scrub typhus & their geographic foci.

S. No	Vector	Geographic focus	References
1	*Leptotrombidium deliense*	Australia, China, India, Malaysia, New Guinea, Pakistan, Philippines, Thailand Sumatra (Indonesia), Myanmar and Pescadores islands (Taiwan)	Oaks SC Jr et al, 1983
2	*Leptotrombidium scutellare*	Japan, China, Korea, Malaysia and Thailand	Rapmund G. 1984, Kitaoka M et al, 1967
3	*Leptotrombidium akamushi*	Japan and Solomon Islands	Traub R, Wisseman CL Jr. 1974
4	*Leptotrombidium chiangraiensis*	Thailand	Tanskul P, Linthicum KJ. 1997
5	*Leptotrombidium arenicola*	Indonesia and Malaysia	Shirai A et al, 1982
6	*Leptotrombidium imphalum*	Thailand	Tanskul P, Linthicum KJ. 1999
7	*Leptotrombidium pallidum*	Japan, Korea Primorski Krai (Russia)	Traub R, Wisseman CL Jr. 1974, Takada N. 1995
8	*Leptotrombidium fletcheri*	Indonesia, Malaysia, New Guinea, Philippines	Dohany AL et al, 1978
9	*Leptotrombidium pavlovskyi*	Primorski Krai (Russia)	Kulagin SM et al, 1968
10	*Leptotrombidium gaohuensis*	Zhejiang Province, China	Fan MY et al, 1987
11	*Schoengastiella ligula*	India	Tilak R et al, 2011

indicator of the virulence of the circulating antigenic strain. However, this aspect calls for further studies and validation.

The spatio-temporal differences in distribution of vector species and the antigenic diversity of circulating *O. tsutsugamushi* in local endemic areas is likely to encourage genetic recombination amongst varied prevalent genotypes. It is thus imperative that a careful monitoring of not only the dominant vector species but also the prevalent *O. tsutsugamushi* genotypes may be important for forecasting epidemiological trend of scrub typhus in endemic areas.

Another important area which warrants investigations is the role of mites like *Ascoschoengastia indica* in the transmission of rickettsiae between rats and its implication in scrub typhus epidemiology.

Pathogen variability

The 56-kDa type specific surface antigen (tsa56) of *O. tsutsugamushi* presence is credited to be responsible for the immense antigenic diversity (sub-types) of the scrub typhus pathogen. Differentiation of the various genotypes has been facilitated by genetic analysis of the tsa56 gene which has helped identify about 40 serotypes or antigenic strains of *O. tsutsugamushi* globally worldwide as on date[22] with probably more to be discovered. Although the strains of *O. tsutsugamushi* are many, six basic antigenic strains are well recognized viz. Karp, Gilliam, Kato, Kawasaki, Kuroki and Shimokoshi. Another strain reported is Boryang which is reported as the most dominant strain in Korea. Globally, the antigenic strain Karp is reported to account for about 50% of all infections, Gilliam about 25%, Kato less than 10% followed by Shimokoshi, Kuroki and Kawasaki and each strain exhibiting further strain variability.[5] The widely prevalent *Orientia* antigenic strains are presented in Table 2. In India, a study conducted in northern states reported Boryong as the predominant strain (63.4%) followed by Karp like (23.6%), Gilliam (11.8%) and Kawasaki like (1.2%) strains[23] whereas another multicentric study conducted in three regions of India reports the occurrence of Kato like followed by Karp like and Gilliam strain in order of prominence.[24] What emerges importantly is that studies on the distribution of various *O. tsutsugamushi* antigenic strains in all endemic areas needs to be undertaken as each strain is known to have unique virulence, clinical presentation and the linked morbidity and mortality profile. The fact that mixed infections of multiple *O. tsutsugamushi* genotypes often has been recorded in the vector mites[25] as well as human patients,[26] enables possibility of genetic recombination of different genotypes[27] and might lead to newer genotypes. This aspect is crucial in understanding the differences in clinical spectrum, severity and response to antibiotic treatment, antibiotic resistance rate and pattern,

Table 2 – Global prevalence of Common *Orientia tsutsugamushi* antigenic strains.

Strain	Source	Location	Year
Gilliam	Human	Myanmar	1943
Karp	Human	New Guinea	1943
TA678	*Rattus rattus*	Thailand	1963
TA686	*Tupaia glis*	Thailand	1963
TA716	*Menetes berdmorei*	Thailand	1963
TA763	*Rattus rajah*	Thailand	1963
Ikeda	Human	Japan	1979
Shimokoshi	Human	Japan	1980
Kawasaki	Human	Japan	1981
Kuroki	Human	Japan	1981
Matsuzawa	Human	Japan	1984
Taguchi	Human	Japan	1984
LP-1	*Leptotrombidium pallidum*	Japan	1986
LX-1	*Leptotrombidium* species	Japan	1986
Kanda	Human	Japan	1987
Nishino	Human	Japan	1988
Oishi	Human	Japan	1988
Akita 7	*Apodemus speciosus*	Japan	1989
Yonchon	Human	South Korea	1989
Omagari	*Apodemus speciosus*	Japan	1990
LA-1	*Leptotrombidium arenicola*	Malaysia	1993
LF-1	*Leptotrombidium fletcheri*	Malaysia	1993
Iwataki-1	*Microtus montebelli*	Japan	1996
Litchfield	Human	Australia	1996
Boryong	Human	South Korea	1998
Kamimoto	Human	Japan	1998
Mori	Human	Japan	1998
Okazaki	Human	Japan	1998
Sxh 951	Human	China	1998
IHS II	Human	India	2010
Neimeng-65	Human	India	2010

immunogenicity and host-pathogen interactions and the development of diagnostics and vaccines for scrub typhus.

Rodents and role of birds in scrub typhus transmission

The natural hosts of trombiculid mites are vertebrates which cohabit the mite islands, amongst which rodents are the most preferred host. Though the host range may be varied but the role of birds as phoretic supplemental hosts to rodents needs serious consideration.[28] As mites are the reservoirs of scrub typhus, their carriage to areas far from their original habitat may additionally influence introduction and transmission in newer naive areas with optimal environmental conditions.[29]

Clinical course and complications

Scrub typhus has a presentation that is wide-ranging from mild to moderate severity and is nonspecific. The detailed description of clinical profile of scrub typhus although published as early as 1938, yet it still holds well till date.[30]

The clinical course of scrub typhus is essentially determined by the unique pathology of *O. tsutsugamushi* that initially infects myeloid cells in the inoculation eschar and thereafter the endothelial cells lining the vasculature. Once the infection turns systemic, monocytes and macrophages in all organs become secondary targets too.[31]

Scrub Typhus basically manifests as an acute febrile illness (Acute Undifferentiated Febrile Illness -AUFI) after an incubation period of 6–21 days (mean 12 days). The first sign of the disease before the person develops symptoms, is a vesicle at the site of feeding of the mite which later ulcerates and gets a scab to become an *eschar* (Fig. 2), which is pathognomonic of scrub typhus. It is a painless punched out dark lesion 3–6mm in size, with mildly erythematous margins and without oedema, usually present in the covered areas of the body i.e. axilla, groin or on the neck or the trunk.[32–34] Various studies have reported the presence of eschar varying from 7 to 97% in patients of scrub typhus.[32–34] Rarely multiple eschar have been reported. It has been postulated that these variations in the presence of eschar possibly reflect differences in host immunity, heterogeneity in the virulence of strains, geographical differences in disease epidemiology, or the clinical diagnostic skills of the investigator.[35]

The symptoms of scrub typhus commence with abrupt onset of fever with headache and myalgia. Apathy is a dominant feature of the fever with the patient appearing dull and indifferent to his surroundings.[30] The classic features of Typhus are present i.e. high grade fever with drowsiness and stupor, congested or 'suffused conjunctiva', and body pain. Severe headache is present almost invariably. Painful lymphadenopathy usually axillary or inguinal is seen. (It has been described as tender, discrete enlarged lymph glands which appear on the third day and disappear on the fifteenth day).[36] A maculopapular rash appears on the fifth day of fever which is localized to the trunk. An unproductive cough is also present. Studies report that up to 40% of patients present as community acquired pneumonia with non-productive cough and bilateral infiltrates resembling atypical pneumonia.[37] Splenomegaly and deafness has been often reported.[33,37] Studies in India have also reported abdominal pain and diarrhoea.[35]

The clinical outcome of scrub typhus is diverse – patients may either recover completely or may suffer from complications which may lead to high mortality rate if not promptly diagnosed and adequately treated. Severe complications include acute respiratory distress syndrome (ARDS), shock, hepatitis, renal failure, meningoencephalitis, and myocarditis which may occur in varying proportions. Acute kidney injury, pneumonitis and Multi Organ Dysfunction Syndrome (MODS) have also been reported from studies across India and abroad. Some studies have found age more than 50 years, longer

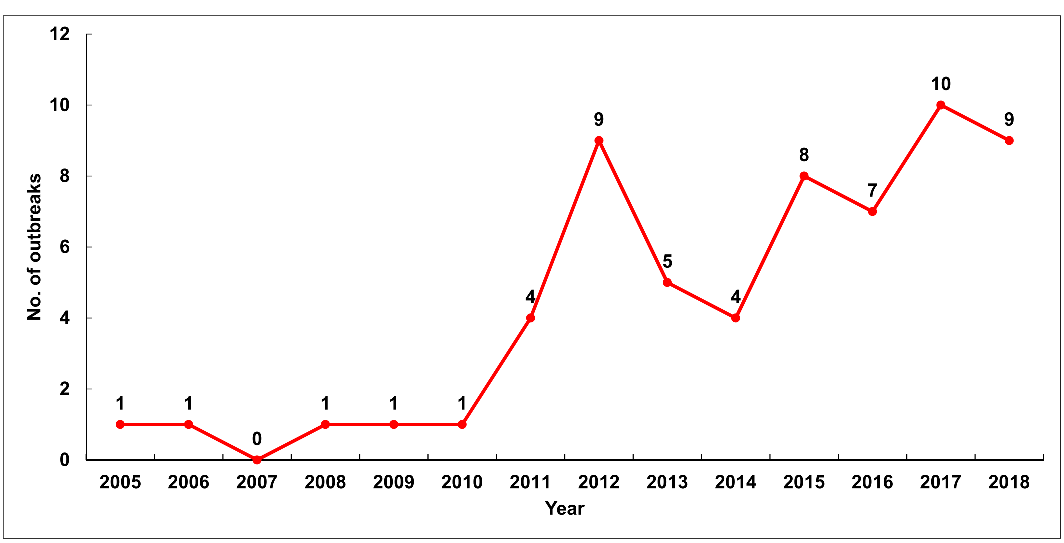

Fig. 2 – Reported outbreaks of scrub typhus in India (till 42nd week of 2018). Source: Integrated Disease Surveillance Programme (IDSP).

duration of fever and absence of an eschar associated with higher mortality.[35,37] The same is supported by systematic reviews.

The outcome & lethality is determined by multiple factors viz. the infecting strain of *O. tsutsugamushi*, bacterial proliferation and the time of initiation of antibiotic. Cross-protection among divergent strains is weak and transient, and homologous immune protection is also lost after a few years. It has been postulated that cellular immunity provides cross-protection against divergent strains while humoural immunity facilitates phagocytic removal of *Orientia* when appropriate antibodies are present.[38]

Acute Encephalitis Syndrome (AES) – the new Avatar of scrub typhus

Scrub typhus has recently been implicated as a cause of Acute Encephalitis Syndrome in children in India. JE was earlier implicated as the cause of AES in most outbreaks leading to the initiation of JE vaccination programme in affected areas.[39] Recent surveillance in Deoria and Gorakhpur districts in Uttar Pradesh report *O. tsutsugamushi* positivity amongst children of 2–15 years age[40]; it has also been recognized as a notable etiologic agent contributing to the occurrence of AES and resulting illness and death in Assam,[41] Although the Government of India has a multi-pronged strategy for surveillance and management of AES including preventive aspects,[42] nevertheless the authors feel that in the light of recent evidence, the protocol should also include scrub typhus as a manifestation of AES. This clinical complexity is a definite cause for concern necessitating focused approach.

Diagnostic challenges

Clinically diagnosis of scrub typhus is challenging given the non-specific symptoms. A systematic review of studies published over 20 years has found that 66% scrub typhus cases may be under diagnosed based on comparison of both 'clinical judgment' approach (Lab tests based on high index of suspicion) versus 'complete approach' (Lab tests irrespective of clinical picture).[43] In endemic areas, ideally all cases of AUFI with eschar and history of occupational or recreational exposure to vegetation should be suspected as a probable case of scrub typhus.

Routine laboratory investigations of scrub typhus patients though show thrombocytopaenia, elevated transaminases (in up to 95% cases) hypoalbuminemia in up to 50% of cases and raised creatinine,[33,36,43] nonetheless, these are not specific indicators of scrub typhus. However, confirmatory diagnosis of scrub typhus is constrained due to non-availability of specific tests in most clinical settings. The available diagnostic tests are summarized in Table 3.

Clinicians' dilemma

It is important to consider scrub typhus in the differential diagnosis of febrile illnesses in endemic areas even in the absence of eschar or in patients reporting with no apparent history of exposure to vegetation or chiggers. Diagnosis, therefore, should depend on clinical suspicion, prompting the clinician to request for an appropriate laboratory investigation.[35,36,44] The failure to suspect scrub typhus is likely to result in treatment with ineffective β-lactam–based regimens thereby increasing the risk of complications.[45] The indicators to suspect scrub typhus based on current knowledge is presented in Table 4.

Treatment protocols & management issues

Timely and appropriate antibiotic regime ensures complete recovery as well as prevents mortality. Patients respond well to Doxycycline, including those with respiratory symptoms within 2–3 days except those with severe MODS/ARDS. Alternative drugs to use in such cases include Rifampicin (600–900 mg/d) or Azithromycin (500 mg the first day and 250 mg/d later) for 7 days. The latter regimen is also safe to use during pregnancy and in children.[46] These drugs should be administered in cases of fever of more than five days or more where malaria, dengue and typhoid have been ruled out. Oral treatment is the most prescribed & also effective in mild cases, but the parenteral route may be necessary for severely ill patients. It is notable that treatment with appropriate antibiotics leads to rapid defervescence of fever-usually in 48 h serving as a diagnostic indicator.[47] There is need to explore newer antibiotics as well as regimes for effective treatment of scrub typhus, given the development of antibiotic resistance and it's potential to impact other endemic areas.

Prevention: keeping scrub typhus at bay

Prophylaxis

Prophylaxis with Doxycycline is generally used by the Armed Forces personnel while moving temporarily in endemic areas, however, its use as prophylaxis for rickettsial diseases including scrub typhus is not recommended because this preventive treatment may simply delay onset of disease and make diagnosis more difficult.[47]

Personal protection

Adoption of barrier clothing, use of topical repellents, repellent patches, and repellent/insecticide treated clothing, bivouacs, camping essentials etc. are methods of prevention of man-vector contact. Scrubbing of body and bathing post visit to likely mite infested areas with strict compliance of the various do's and don'ts viz. not sleeping on ground, not standing for long in one place in infested areas, not drying clothes on jungle floor or vegetation while camping, sleeping on cots or treated sleeping bags etc.) are effective in any endemic settings. The need to develop effective and safe mite repellents and its wider availability is the call of the day.

Vaccine woes

As there are no effective vaccines for scrub typhus at present, the development of a prophylactic vaccine to prevent scrub typhus is necessary. The complexities which hamper the

Table 3 – Characteristics of various Diagnostic tests for scrub typhus.

Test	Principle	Time taken	Time of Positivity	Sensitivity & specificity	Remarks
1. Serological					
a Weil Felix	Based on antigenic similarity with OX-K strain of *Proteus mirabilis* Detects IgM	6–18 h	5–10 days Usually second week	Poor sensitivity Good Specificity	Cheap Readily available Ideally requires paired samples
b Immunofluorescent assay (IFA)	Fluorescent anti-human antibody to detect antibody in patient serum Tests IgM & IgG	2 h	3–4 days	Highly sensitive and specific **GOLD STANDARD**	Expensive Requires bio containment facilities for antigen preparation, Technical expertise required Retrospective
c Indirect immuno-peroxidase Assay (IIP)	Similar to IFA Uses Light Microscope	2 h	3–4 days	Highly sensitive and specific	Relatively easy to perform Requires multiple samples
d Enzyme linked immunosorbent assay (ELISA)	Uses outer membrane proteins as Antigen Detects both IgM & IgG	30 min	7 days for IgM, End of 2nd week for IgG	IgM capture assays most sensitive	Relatively cheap Baseline titres need to be established for regional variation, cut offs depend on endemicity Requires multiple samples at a time
e Immunochromato graphic Test (ICT)	Based on chromatography Detects both IgM & IgG	30 min	More than 5 days after onset	Good sensitivity and specificity	Cheap, simple to perform, Retrospective, positivity increases with fever duration Can be used as Point of care testing (POCT)
2. Molecular					
a Polymerase chain reaction (PCR)	Detects rickettsial DNA before antibody response Eschar/Lymph node biopsy/ Skin Biopsy as sample	Few hours	Samples on day 1 can test positive	Highly sensitive and specific	Confirmatory Requires technical expertise High resource costs Better results during rickettsaemic period
b Rapid flow assay	Recombinant 56 kDa protein used as antigen	15 min	Positive on Day 1	Highly sensitive and specific	Confirmatory Requires technical expertise, High resource costs
c Loop-mediated isothermal amplification assays (LAMP)	Uses amplification and detection of DNA	2–3 h	Positive after day 2 of fever up to 10 days	Sensitive and specific	Does not require sophisticated equipment Cheap Accuracy increases with time Can be used as (POCT) for early diagnosis
3. Culture					
In vitro	Cell culture of organisms in monolayer cells	27 days	Day 1 (for sample)	Most sensitive and specific	Requires BSL 3 facility, Useful for research Retrospective
4. Rapid tests					
	Can use ELISA or Immunochromatography to detect antibodies LAMP detects antigen	Few min 2–3 h	After 7 days Day2 of onset	Sensitive and specific Sensitive and specific	Can be used for individual or limited samples Cheap, easy to store and handle Can be used as a POCT **Currently NOT recommended as per ICMR guidelines** As mentioned in (c) above **Currently NOT recommended as per ICMR guidelines**

Table 4 – Indicators for scrub typhus infection (INSTI).

Scrub Typhus to be suspected in all cases of fever of >5 days duration presenting as	
• AUFI with severe headache	
• Eschar	Black scab 3–7 mm, punched out, no erythema or swelling in margins Painless, No itching Localised in covered areas axilla, trunk May not be present*
• Maculopapular rash on 5th day and/or	Centripetal
• Lymphadenopathy	Appears on day 3 of fever Discrete, painful axillary/inguinal nodes Disappears on 15th day
• Dry unproductive cough	Especially in cases of fever > 1 week duration
OR Fever > 1 week directly presenting as any of	
• MODS	
• ARDS	
• AES	Especially in children below 15 years in endemic areas
Lab investigations	
• Thrombocytopaenia	Platelet < 100,000
• Raised aspartate transaminase (AST)/alanine transaminase/ALT) and mild Jaundice	
AND negative for dengue/malaria/enteric fever	
Not responding to β lactam antibiotics	
With/or without history suggestive of occupational/recreational exposure to vegetation & vector bite (Irrespective of Socio economic status/occupation/rural or urban setting)	

development of a viable vaccine are – intracellular nature of *Orientia*, the genetic heterogenicity and antigenic variability, the role of antibodies and T cells in immune response, the role of endothelial cells which are the primary target of infection as the regulator of immune response and identification of immunomodulators in the saliva of the vector.[31] In the past 70 years, all approaches to stimulate protective immunity against the challenge with *O. tsutsugamushi* have failed to prevent scrub typhus. The use of formalin-killed *Orientia*, inoculation with viable organisms followed by antimicrobial treatment, irradiated *O. tsutsugamushi*, and subunit vaccines have been included in these efforts.[31] The results have been variable – from failure to protect to short-term protection. It is pertinent to understand the variability of the natural immune response against *Orientia* and its failure to induce long lasting cross protective immunity and explore the potential of genomic approach for development of vaccines against scrub typhus.[38]

Outbreak investigation & response – strengthening prevention

The basic tenets of prevention and management of scrub typhus though are well established, yet the importance of undertaking a thorough epidemiological investigation of all outbreaks cannot be under emphasized. The investigations will help identify the local risk factors and enable generation of specific recommendations for prevention. Mapping of circulating antigenic strains is also a necessity. This will provide base for development of region specific diagnostics and vaccine. There is a further need to organize local outbreak response teams which can work in tandem with the community to launch prompt action during outbreaks and also mobilize the general population for behaviour changes as appropriate.

Knowledge dissemination, women empowerment and concept of 'Health Messiah'

One of the reasons propounded for higher mortality rate in scrub typhus (0–70% in untreated cases)[9] is low index of suspicion and non-inclusion of scrub typhus in differential diagnosis schema for pyrexia of unknown origin in endemic areas. This leads to delayed treatment and higher case fatality rate especially when a virulent antigenic strain is in circulation in the affected area. It is essential that knowledge on clinical presentation and management be imparted to physicians operating in endemic areas either through Continued Medical Education programs organized under the aegis of local or National Medical Associations or through inclusion in Government implemented Health programs at local or National level. A bottoms up approach involving the community with special focus on empowerment of women as '**health messiah**' will go a long way in not only preventing outbreaks but ensuring prompt treatment of cases which will in turn effect reduction of disease burden. The concept of women as 'health messiah' proved very successful in outreach rural settings undertaken by the authors for prevention of mosquito borne diseases. The community needs to be sensitized that adoption of preventive measures will itself reduce the incidence of disease and case fatality rate.

Indian scenario

Though the history of Scrub typhus chronicles its presence in India since WWII to this date (courtesy the Indian Armed Forces), the civil population as well as the public health professionals have blissfully remained oblivious of its presence till the last decade. One of the most neglected, underreported and severe disease (although easily amenable to treatment) has reemerged with all its might and poses serious challenge to our clinical, public health, diagnostics and entomological expertise and unabashedly we have been found wanting. Currently all 29 states and 4 out of the 7 Union territories are reporting outbreaks of scrub typhus spanning areas not only under military presence but also the civil populations.[48–53] Although, the data on true prevalence of scrub typhus in India is currently not available as majority of cases go unreported in the country, yet it is evidenced that the number of outbreaks as well as cases of scrub typhus are on a rise (Fig. 3). The innumerable outbreaks of Scrub typhus in India have, nonetheless, contributed towards better understanding of the dynamics of scrub typhus. The published literature from the various outbreaks/endemic areas as well as few community based and

Fig. 3 – Eschar – pathognomonic of scrub typhus.

majorly hospital based data have all facilitated (although meagre) mapping of vector distribution and diversity,[21,54] role of newer vectors,[21] rickettsial activity and hot spots,[55] antigenic variations,[23,24] variable clinical spectrum, management dogmas and guidelines, diagnostics as well as development of sound preventive measures. Despite the public health importance of chiggers, studies in India have been neglected.

The trombiculid mite studies in India was first documented by Mehta in 1937,[56] showcased the rich and diverse Indian fauna, nonetheless it was World War II which saw a significant rise in interest in scrub typhus. A monumental work on trombiculid mites 'Studies on the Trombiculid Mite Fauna of India' records 204 species of trombiculid mites from India.[57] It is nonetheless surprising that very limited efforts are being undertaken to study the trombiculid mite fauna in the recent times. The information is pertinent in the context that the information on dominant vector species could facilitate accurate forecasting of an impending outbreak. This work would also throw light on the role of newer species in the transmission of scrub typhus.

The paucity of information on antigenic diversity of *O. tsutsugamushi* pan India, which is essential for understanding the virulence pattern, varied clinical presentation and response to antibiotics needs urgent attention.

Armed Forces take the lead

The Indian Armed Forces have played a pivotal role not only in chronicling the history of scrub typhus in India but has taken the lead in investigation of outbreaks. Development of indigenous management protocols, prophylactic measures, establishment of entomological repository, newer modalities of prevention and training of personnel in outbreak response have been the highlights of focused research and action on scrub typhus in Armed Forces.

Conclusion

The reemergence of scrub typhus, as a major vector borne disease cannot be ignored. Readiness to deal with this easily treatable, yet, potentially fatal disease warrants a high level of awareness amongst community as well public health professionals and clinicians alike. It is needless to emphasize that slow, yet steady appreciation of the impact of scrub typhus is finally gaining momentum.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Chattopadhyay S, Richards AL. Scrub typhus vaccines: past history and recent developments. *Hum Vaccin*. 2007;3:73–80.
2. Izzard L, Fuller A, Blacksell SD, et al. Isolation of a novel *Orientia* species (*O. chuto* sp. nov.) from a patient infected in Dubai. *J Clin Microbiol*. 2010;48(12):4404–4409.
3. Luce-Fedrow A, Lehman ML, Kelly DJ, et al. A review of scrub typhus (*Orientia tsutsugamushi* and related organisms): then, now, and tomorrow. *Trop Med Infect Dis*. 2018;3(1):8.
4. Shih-Chen Li, Ts'ao Kang Mu Pen. *A Chinese Material Medica of the Ming Dynasty, 1591–1592*. 1885:28 Chapter 432.
5. Kelly DJ, Fuerst PA, Ching WM, Richards AL. Scrub typhus: the geographic distribution of phenotypic and genotypic variants of *Orientia tsutsugamushi*. *Clin Infect Dis*. 2009;48:203–230.
6. Maina AN, Farris CM, Odhiambo A, et al. Q fever, scrub typhus, and rickettsial diseases in children, Kenya, 2011–2012. *Emerg Infect Dis*. 2016;22(5):883–886.
7. Mathai E, Rolain JM, Verghese GM, et al. Outbreak of scrub typhus in Southern India during the cooler months. *Ann N Y Acad Sci*. 2003;990:359–364.
8. World Health Organization, Recommended surveillance standards WHO/CDS/CDR/ISR/99.2, second edition.
9. Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (*Orientia tsutsugamushi*). *PLoS Neglected Trop Dis*. 2015;9(8):e0003971.
10. Oaks Jr SC, Ridgway RL, Shirai A, Twartz JC. Scrub typhus. *Inst Med Res Malays Bull*. 1983;21:1–98.
11. Rapmund G. Rickettsial diseases of the Far East: new perspectives. *J Infect Dis*. 1984;149:330–338.
12. Kitaoka M, Okubu K, Asanuma K. Epidemiological survey by means of complement fixation test on scrub typhus in Japan. *Acta Med Biol Niigata*. 1967;15(suppl l):69–85.
13. Traub R, Wisseman Jr CL. The ecology of chigger-borne rickettsiosis (scrub typhus). *J Med Entomol*. 1974;11:237–303.
14. Tanskul P, Linthicum KJ. A new species of *Leptotrombidium* (Acari: Trombiculidae) collected in active rice fields in northern Thailand. *J Med Entomol*. 1997;34:368–371.
15. Shirai A, Huxsoll DL, Dohany AL, Montrey RD, Werner RM, Gan E. Characterization of Rickettsia tsutsugamushi strains in two species of naturally infected, laboratory-reared chiggers. *Am J Trop Med Hyg*. 1982;31:395–402.
16. Tanskul P, Linthicum KJ. Redescription of *Leptotrombidium* (Leptotrombidium) *imphalum* (Acari: Trombiculidae), with observations on bionomics and medical importance in northern Thailand. *J Med Entomol*. 1999;36:88–91.
17. Takada N. Recent findings on vector Acari for rickettsia and spirochete in Japan. *Jpn J Sanit Zool*. 1995;46:91–108.
18. Dohany AL, Shirai A, Robinson DM, Ram S, Huxsoll DL. Identification and antigenic typing of Rickettsia tsutsugamushi in naturally infected chiggers (Acarina: Trombiculidae) by direct immunofluorescence. *Am J Trop Med Hyg*. 1978;27:1261–1264.
19. Kulagin SM, Tarasevich IV, Kudryashova NI, Plotnikova LF. The investigation of scrub typhus in the USSR. *J Hyg Epidemiol Microbiol Immunol*. 1968;12:257–264.

20. Fan MY, Walker DH, Yu SR, Liu QH. Epidemiology and ecology of rickettsial diseases in the People's Republic of China. *Rev Infect Dis*. 1987;9:823–840.
21. Tilak R, Kunwar R, Wankhade UB, Tilak VW. Emergence of *Schoengastiella ligula* as the vector of scrub typhus outbreak in Darjeeling: has *Leptotrombidium deliense* been replaced? *Indian J Public Health*. 2011;55:92–99.
22. Ohashi N, Koyama Y, Urakami H, et al. Demonstration of antigenic and genotypic variation in *Orientia tsutsugamushi* which were isolated in Japan, and their classification into type and subtype. *Microbiol Immunol*. 1996;40(9):627–638.
23. Biswal M, Kumar A, Sharma N, Bhalla A, Singhi S, Sethi S. Genetic diversity of *Orientia tsutsugamushi* strains from patients in North India. *Int J Infect Dis*. 2016;45:166–167.
24. Varghese George M, Jeshina Janardhanan, Mahajan Sanjay K, et al. Molecular epidemiology and genetic diversity of *Orientia tsutsugamushi* from patients with Scrub typhus in 3 Regions of India. *Emerg Infect Dis*. 2015;21(1):64–69.
25. Takhampunya R, Tippayachai B, Promsathaporn S, Leepitakrat S, Monkanna T, et al. Characterization based on the 56-Kda type-specific antigen gene of *Orientia tsutsugamushi* genotypes isolated from *Leptotrombidium* mites and the rodent host post-infection. *Am J Trop Med Hyg*. 2014;90:139–146. https://doi.org/10.4269/ajtmh.13-0393.
26. Sonthayanon P, Peacock SJ, Chierakul W, et al. High rates of homologous recombination in the mite endosymbiont and opportunistic human pathogen *Orientia tsutsugamushi*. *PLoS Negl Trop Dis*. 2010;4(7):e752. https://doi.org/10.1371/journal.pntd.0000752. Published 2010 Jul 20.
27. Zhang M, Zhao ZT, Wang XJ, Li Z, Ding L, et al. Mixed scrub typhus genotype, Shandong, China. *Emerg Infect Dis*. 2014;20:484–485. https://doi.org/10.3201/eid2003.121349, 2011.
28. Tsiodras S, Kelesidis T, Kelesidis I, Bauchinger U, Falagas ME. Human infections associated with wild birds. *J Infect*. 2008;56:83–98.
29. Traub R, Wisseman Jr CL. Ecological considerations in scrub typhus. 2. Vector species. *Bull World Health Organ*. 1968;39:219–230.
30. Blewitt B. Fevers of the typhus group in the Bhim Tal area, Kumaun hills, U.P., India. *J R Army Med Corps*. 1938;70:241–245.
31. Valbuena G, Walker DH. Approaches to vaccines against *Orientia tsutsugamushi*. *Front Cell Infect Microbiol*. 2013;2:170.
32. Philomena J, Rangaswami M, Prathiba P. A study on demographic, clinical profile and outcome of scrub typhus. *Int J Adv Med*. 2016;3:586–590.
33. Tattersall RN. Tsutsugamushi fever on the India-Burma border. *Lancet*. 1945;2:392–394.
34. Premraj SS, Mayilananthi K, Krishnan D, Padmanabhan K, Rajasekaran D. Clinical profile and risk factors associated with severe scrub typhus infection among non-ICU patients in semi-urban south India. *J Vector Borne Dis*. 2018;55:47–51.
35. Nachega JB, Bottieau E, Zech F, Gompel A. Travel acquired scrub typhus: emphasis on the differential diagnosis, treatment, and prevention strategies. *J Trav Med*. 1 September 2007;14(5):352–355.
36. Kurup A, Issac A, Loh JP, et al. Scrub typhus with sepsis and acute respiratory distress syndrome. *J Clin Microbiol*. 2013;51(8):2787–2790.
37. Bhargava A, Kaushik R, Kaushik RM, et al. Scrub typhus in Uttarakhand & adjoining Uttar Pradesh: seasonality, clinical presentations & predictors of mortality. *Indian J Med Res*. 2016;144:901–909.
38. Paris DH, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. *Am J Trop Med Hyg*. 2013;89(2):301–307.
39. Narain JP, Dhariwal AC, MacIntyre CR. Acute encephalitis in India: an unfolding tragedy. *Indian J Med Res*. 2017;145:584–587.
40. Thangaraj J, Vasanthapuram R, Machado L, et al. Risk factors for acquiring scrub typhus among children in Deoria and Gorakhpur districts, Uttar Pradesh, India, 2017. *Emerg Infect Dis*. 2018;24(12):2364–2367.
41. Khan SA, Bora T, Laskar B, Khan AM, Dutta P. Scrub typhus leading to acute encephalitis syndrome, Assam, India. *Emerg Infect Dis*. 2017;23:148–150.
42. Govt of India. *Guidelines Clinical Management of Acute Encephalitis Syndrome Including Japanese Encephalitis. DNVDCP. DGHS*. New Delhi: Ministry of Health and Family Welfare; 2006.
43. Eekeren L, de Vries G, Wagenaar J, et al. Under-diagnosis of rickettsial disease in clinical practice: a systematic review. *Trav Med Infect Dis*. 2015;26:7–15.
44. Laskar A, Suri S, Acharya AS. Scrub typhus. Re emerging public health problem in India. *J Commun Dis*. 2015;47(3):19–25.
45. Koh GC, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of scrub typhus. *Am J Trop Med Hyg*. 2010;82:368–370.
46. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR Guidelines for diagnosis & management of Rickettsial diseases in India. *Indian J Med Res*. 2015;141(4):417–422.
47. Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of scrub typhus. *PLoS Negl Trop Dis*. 2017;11(11):e0006062. https://doi.org/10.1371/journal. pntd.0006062.
48. Sharma N, Biswal M, Kumar A, Zaman K, Jain S, Bhalla A. Scrub typhus in a tertiary care hospital in north India. *Am J Trop Med Hyg*. 2016;95(2):447–451.
49. Vivekanandan M, Anna Mani, Yamini Sundara Priya, Pratap Singh Ajai, Samuel Jayakumar, Shashikala Purty. Outbreak of scrub typhus in Pondicherry. *J Assoc Phys India*. 2010;58:24–28.
50. Sharma Anuradha, Mahajan Sanjay, Gupta ML, Anil Kanga, Sharma Vijay. Investigation of an outbreak of scrub typhus in the Himalayan region of India. *Jpn J Infect Dis*. 2005;58:208–210.
51. Kumar K, Saxena VK, Thomas TG, Lal S. Outbreak investigation of scrub Typhus in Himachal Pradesh (India). *J Commun Dis*. 2004 Dec;36(4):277–283.
52. Dass Rashna, Mani Deka Nayan, Gohain Duwarah Sourabh, et al. Characteristics of pediatric scrub typhus during an outbreak in the north eastern region of India: peculiarities in clinical presentation, laboratory findings and complications. *Indian J Pediatr*. 2011;78(11):1365–1370.
53. Sinha P, Gupta S, Dawra R, Rijhawan P. Recent outbreak of scrub typhus in North Western part of India. *Indian J Med Microbiol*. 2014;32:247–250.
54. Gurung S, Pradhan J, Bhutia PY. Outbreak of scrub typhus in the North East Himalayan region-Sikkim: an emerging threat. *Indian J Med Microbiol*. 2013;31:72–74.
55. Tilak R, Kunwar R, Tyagi PK, Khera A, Joshi RK, Wankhade UB. Zoonotic surveillance for rickettsiae in rodents and mapping of vectors of rickettsial diseases in India: a multi-centric study. *Indian J Public Health*. 2017;61:174–181.
56. Mehta DR. Studies on typhus in the Simla Hills. Part VIII. Ectoparasites of rats and shrews with special reference to their possible role in transmission of typhus. *Indian J Med Res*. 1937;25:353–365.
57. Fernandes SJ, Kulkarni SM. Studies on the trombiculid mite fauna of India. *Record Zool Surv India Occas Pap*. 2003;212:1–539.