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REVIEW ARTICLE OPEN ACCESS

Rising Menace of Scrub Typhus – Current Status and Challenges

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Abstract

Scrub typhus, an age old disease, is caused by the intracellular bacterium *Orientia tsutsugamushi*. It has reemerged in recent years due to factors like climatic changes and human encroachment because of rampant urbanization. The disease is endemic in the area known as the 'tsutsugamushi triangle' and has recently spread its fangs into various other continents like South America and Africa. Although the disease is endemic in India, there is a lack of appropriate sero-epidemiology in community settings. It is one of the essential causes of acute undifferentiated fever in tropical locations and, if untreated, can cause mortality ranging from 2-30% of cases. Early diagnosis is an important parameter in administering the non beta-lactam regimen to prevent complications and mortality. Yet, there is a lack of accurate and rapid methods for diagnosis in the early stage of the disease, more so in rural areas where the disease is supposed to be predominant. The gold standard diagnostic test has its problems. Recently, there have been reports of drug resistance to the standard scrub typhus regimen. There is a gap of a decade in the research into this entity. Thus, a new look into the disease, its epidemiology and the challenges in its diagnostic scenario is an apt topic for discussion.

Keywords: Scrub Typhus, *Orientia tsutsugamushi,* IgM Capture ELISA, Indirect Immunofluorescence Assay

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INTRODUCTION

Scrub typhus was a disease of the pre-antibiotic era, especially during military operations, but even today causes one million cases annually worldwide.[1] In the recent years it has reemerged as a significant public health issue due to multiple factors like climatic changes, human activities disturbing the ecological balance, beta-lactam antibiotics overuse and urbanization of rural areas.[2] This disease is an underdiagnosed entity due to a lack of typical pathognomonic clinical features coupled with inadequate availability of appropriate laboratory methods. Thus there is limited epidemiological data regarding the disease globally.

Epidemiology of Scrub typhus

Scrub typhus is caused an intracellular Gram negative small pleomorphic coccobacilli named *Orientia tsutsugamushi*,[3] which was previously under Rickettsia family. It is named as 'tsutsugamushi' (dangerous bug), after a jungle mite or chigger, which acts as a reservoir and transmits the disease to man by biting through pores or hair follicles on exposed skin. Human encroachment during deforestation, logging, road building, military operations, rice cultivation, etc., bring us close to infected chiggers, the parasitic stage in the vector Leptotrombidium mite. Climatic change due to global warming also has a role in the reemergence of this disease (Figure 1).[4]

Tropical regions have appropriate temperatures and humidity for chigger activity and maintaining the pathogen in transovarian and transstadial transmission in the mites. Researchers have also noted horizontal transmission of *Orientia* among mites.[5] Thus, the disease occurs around the year. However, in temperate zones like in the northern part of Japan, the mite activity is seasonal corresponding to the disease.[6]

Scrub typhus is endemic to a region denoted as the ''tsutsugamushi triangle''.South East Asian region is endemic for scrub typhus.[7] But in recent times, the disease has surfaced in other non endemic areas like Europe, Chile, Peru, Middle East, African peninsula and sometimes with a different species of the bacteria, like *O.chuto* seen in the Middle East (Figure 2).[8] In India, several states have varying ecological profile, like Haryana, Jammu, and Kashmir, Himachal Pradesh, Uttaranchal in north; Kerala, Tamil Nadu in South; Bihar, West Bengal, Assam in East; Maharashtra in West report this disease.[9,10] Sero-prevalence of

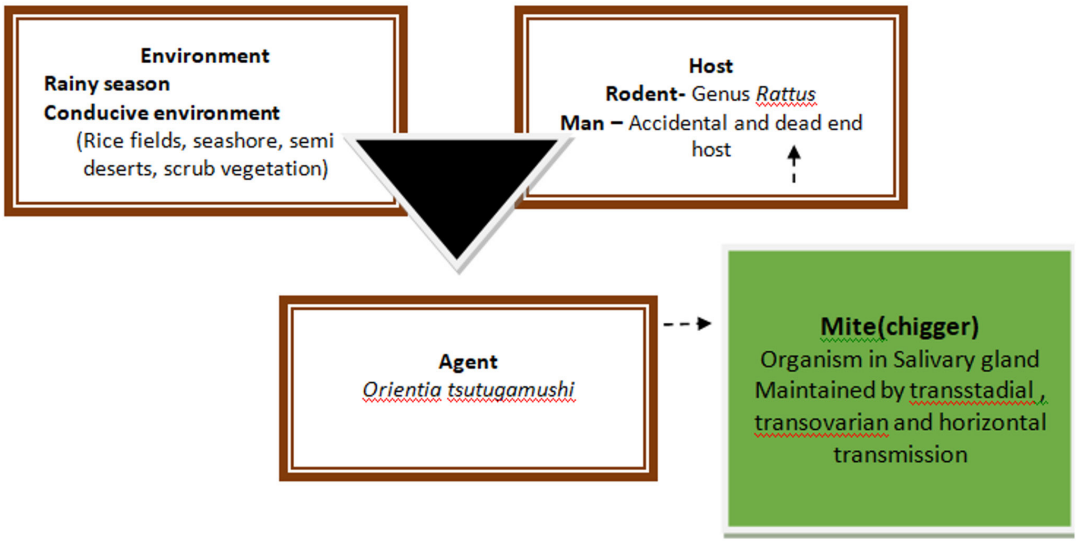

Figure 1. The epidemiological triad of scrub typhus
The agent *O. tsutsugamushi* is maintained in its reservoir mites by transstadial and transovarian transmission and transmitted to man by bite of the larvae (chigger) in cases of human encroachment into mite habitat. Man to man transmission is not seen.

Table 1. Tabulation of recent studies in India on scrub typhus
Majority of the studies included acute undifferentiated fever cases in their inclusion criteria and were hospital based studies including adult patients.

Author and year	Place	Time period	Target population	No. of patients	No. of cases detected	No. of deaths	Test used	Predominant month	Age & sex of patients
Subbalaxmi et al. [64]	Andhra Pradesh	Aug 2011 to Dec 2012	AUFI Cases > 12 years	NA NA	176	8	Weil felix test (>1:80) ICT	NA	41 years; M>F
Sinha et al. [65]	Jaipur, Rajasthan	Oct-2012 to Dec-2012	AUFI cases	170	42	7	IgM ELISA	NA	M>F
Stephen et al. [66]	Puducherry Tamilnadu	Sep2012 to March 2013	AUFI cases	45	25	0	ICT test IgM, IgG ELISA (paired) Weil felix (Initial titre1:40 or OXK>320)	NA	31 years; M=F
Krishna, Vasuki et al. [67]	Chennai Tamilnadu	Sep 2010 to June 2011	Paediatric AUFI	NA	52	0	IgM ELISA	NA	
Jakharia et al. [68]	Arunachal Pradesh	NA	Seroprevalence study in community	300	120	0	IgG ELISA	NA	>40 years; M=F
Rajendra Prasad Thakar [69]	Rajasthan	July to Oct 2014	AUFI	290	66	14	IgM ELISA	NA	20 -50 year; F>M
H. Lalrinkima [70]	Mizoram	Oct 2014 to Dec 2016	AUFI	4081	283		ICT test	Nov -Feb	21 - 30 year; M>F
Deepak Jain [71]	Haryana	July to Nov 2017	>14 yrs AUFI	230	39	7	IgM ELISA	NA	39 year; F>M
Thakur et al. [72]	Various parts of India	2013- 2018	AUFI in hospitalized patients	1742	210	14	IgM ELISA and IFA (Gilliam and Karp strains)	NA	
Laxmi R et al. [73]	Telangana	July to Oct 2018	Suspected Scrub typhus	645	89	0	ICT+ IgM ELISA	August	20 TO 50 year; F>M
Verma et al. [74]	Lucknow	Sep 2019 to Jan 2020	AUFI >18 yrs		52	NA	IgM ELISA	NA	20 TO 50 year; F>M

this infection in India is between 9.3% and 27.9%, and the mortality rate is around 30% among untreated individuals, as noted in passive national surveillance systems.[7,11] Among acute onset febrile illness, scrub typhus constitutes about 25.3% of cases in India (Table 1).[12]

Orientia shows many genetic and antigenic variations resulting from variations in tsa gene, which codes for 56-kDa type specific antigen.[1,13] There are around 30 serological types like kato, karp, kuroki, gilliam and kawasaki that as detected by immunoperoxidase reaction[14] Litchfield strain is a novel strain detected in Australia.[15] The correlation between this antigenic diversity and virulence is still unclear.

Clinical presentation

Fever is the commonest presentation, seen in 95-100% of cases.[16,17] Scrub typhus accounts for a significant chunk of "fever of unknown origin" in endemic regions. Even the term "typhus" is derived from Greek terminology 'Typos' meaning 'fever with stupor' The age group of 50-60 is commonly afflicted while, sex preponderance varies across different countries.[3] A papular lesion is formed at the chigger bite site, which becomes larger with time, followed by necrosis and crusting in the centre and finally developing a black eschar, which is a pathognomonic feature of scrub typhus. The presence of eschar is specific (98.9%) for diagnosis of this disease but is limited by sensitivity, which varies between 7%-97%.[7] Further, eschar is often absent in the South East Asian population and in endemic areas with less severe illness.[18-20] Scrub typhus can present in varied forms ranging in severity from asymptomatic to multi organ failure.[21] Common symptoms are myalgia, headache, nausea, vomiting, abdominal pain, cough, generalized lymphadenopathy and skin rash in varying combinations.[3,22,23] Owing to its mimicking signs and symptoms, it took almost 30 years to prove the original finding of Coyttarus (1578) that typhoid and typhus were different diseases. Untreated cases may develop several complications generally occurring after the first week of illness. Various complications like acute renal failure, jaundice with rising liver enzymes, pneumonitis and acute respiratory

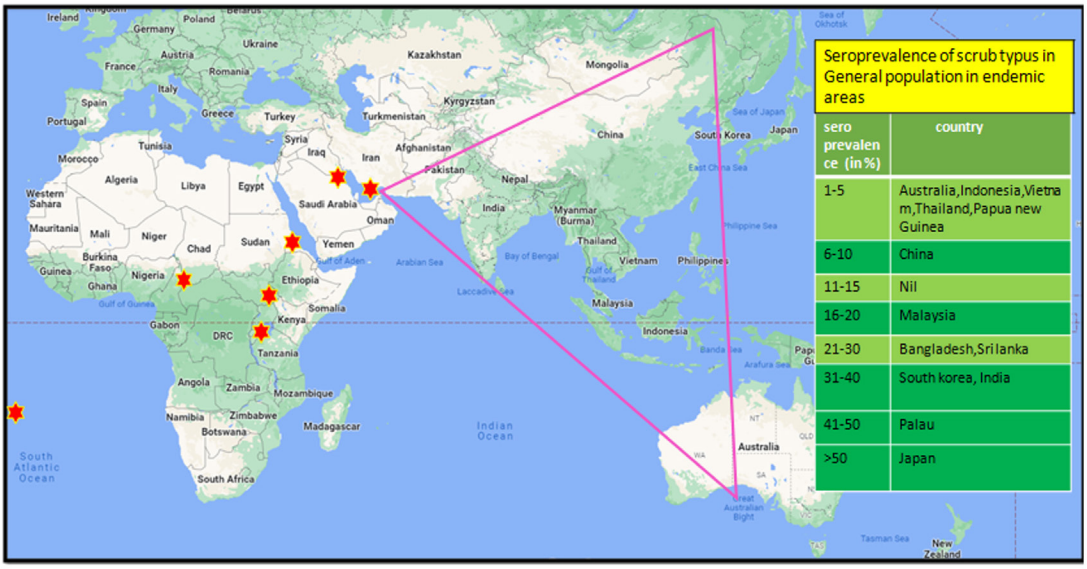

Figure 2. The Tsutsugamushi triangle and other area in the world where the disease has been reported. Tsutugamushi triangle, an area approximating about 8 million km^2 is endemic for scrub typhus. This extends in North from the Russian Far East, to Pakistan in the west, Australia in the south, and the Japan in the east. Seroprevalence of scrub typhus detected in recent studies,[63] have been tabulated which ranges from mere 1.1% in Vietnam to 68.4 % in Japan. But apart from this, other area in globe like - Chile, United Arab Emirates, African countries (Camroon, Kenya, congo, Tanjania) also have reported cases of scrub typhus.

distress syndrome, septic shock, myocarditis, meningoencephalitis and reversible deafness have been noted in prior studies.[18,20] Renal involvement can be expected in about 9% of patients. Patients of meningoencephalitis often have CSF changes indistinguishable from viral or tuberculous meningitis. Unusual presentations include conjunctival hyperemia or erosion, gastrointestinal mucosal erosion without any predilecting site and acute abdomen.[24,25] Septic shock ensues with further organ damage to liver, lungs, kidneys along with DIC.[26,16,27,28] Elevated transaminases, thrombocytopenia and leukocytosis are the biochemical investigations pertinent to diagnosing the disease when used in combination (specificity and positive predictive value for diagnosis - 80%).[29]

Mortality from this disease varies from 7-30%,[30] but much less in children.[31] The possible patient factors associated with complicated cases are - age (≥60 years), patients without eschar, WBC counts >10000/mm and serum albumin level ≤3.0 g/dL.[31,2] Being a great mimicker, diagnosis in the early stages is challenging yet important for successfully treating scrub typhus. The median case fatality rate is reduced to 1.4% in treated patients from 6% seen in late or untreated ones.[11,29,32] Diagnosis is based on clinical suspicion with appropriate lab investigation.

Lab diagnosis of scrub typhus

Serological assays

Serological tests that detect antibodies to against scrub typhus, like Weil Felix test, ELISA, Immunofluorescence and immunoperoxidase tests are the commonly performed tests for lab diagnosis. IgM is preferred over IgG detection as it can help diagnose recent infections. But, all there tests have many issues that needs addressing. A ≥ 4-fold increase in antibody titer between two consecutive samples is diagnostic,[33] but often not practical. Secondly, a baseline titer (cut-off) is to be established in the geographical setting based on the endemicity of the disease for appropriate reporting, which is often lacking. There is wide variation across India in cut-off values of the various serological tests (Table 2). Then again, most serological tests use an antigen cocktail of Karp, Kato, and Gilliam serotypes. But there are many other antigenic variations apart from these three, differing in different geographical regions of the world.[1] For example, in mites collected from a single field in Malaysia, eight different serotypes

Table 2. Cut off value calculated in different studies from various hospital based studies across India

Study	Setting	Cut off value	Sensitivity	Specificity
ELISA				
Manjunathachar et al. [87]	Madhya Pradesh	0.73 (IgM)	95	100
Koraluru et al. [79]	Karnataka	1.0 (IgM)	85	95
Gupta et al. [88]	New Delhi	0.87 (IgM)	100	94.12
Gupta A et al. [89]	Himachal Pradesh	0.46 (IgM)	91.7	99.5
Gautam et al. [81]	Nepal	0.5 (IgM)	-	-
Karthikeyan et al. [85]	Puducherry	0.4	-	-
Rawat et al. [90]	Uttarakhand	0.6 (IgM)	96.4	82.7
		1.6 (IgG)	91	75
Verghese et al. [91]	Vellore,	0.8 (IgM)	-	-
	South India	1.8 (IgG)	-	-
Immunofluorescence assay				
Fomda et al. [82]	Kashmir	1:128 (IgM)	-	-
		1:256 (IgG)	-	-
Gupta et al. [88]	New Delhi	1: 64	100	93.5
Gupta et al. [88]	New Delhi	1:512		98
Gautam et al. [81]	Nepal	1:128	-	-
Rawat et al. [90]	Uttarakhand	1:512 (IgM)		
		1:2048 (IgG)		
Verghese et al. [91]	Vellore, South	0.251 (IgM)	-	-
	India	0.205(IgG)	-	-

Table 3. Various methods for laboratory diagnosis of scrub typhus
Indirect diagnostic methods comprise of method which detect antibodies developed against Orientia tsutsugamushi while direct methods detect the organism from the samples either by culture, animal inoculation or the DNA of the bacteria by amplification methods

INDIRECT DIAGNOSTIC METHODS Test	Principle	Advantages	Issues
Weil Felix	≥ 4 times rise in titre to proteus OX-K and no reaction to proteus OX-2 or OX-19 Single titre ≥1:160 is also diagnostic (normal is ≤1:40[75]	Antibodies are detectable after 5 -10 days following the onset of fever [9] Inexpensive Easy to perform Results are available overnight	Not a sensitive test When positive, it is specific test.[76] False negative - in UTI by Proteus, Leptospira infections etc.
ELISA KpKtGm-wc ELISA or KpKtGm	56-kDa protein (located on the outer membrane of O.tsutsugamushi highly reactive inducing antibodies[77]	Higher sensitivity and specificity than Weil felix	Specified Cut off is needed
r56 ELISA	Antigen used - whole cell antigen / r56 from the Karp, Kato, and Gilliam strains of O. tsutsugamushi [78]	85% sensitive and specificity in comparison to IFA (InBios kit)	Need paired sera
IgM capture ELISA		IgM capture ELISA can capture the acute infection	Many serotypes may need constant monitoring
Indirect immunofluorescence antibody detection test (IFA)	Uses fluorescein linked anti-human reporter antibody to detect the presence of scrub typhus-specifc antibodies (mostly against Karp, Kato, Gilliam) in the serum sample.[33] An 20-fold rise in titre in paired (e 14 days) sampling is considered positive	Current Gold standard test for	Need Paired sera diagnosis Specified cutoffs needed Specialized equipments required Costly Other methods offer fair sensitivity and specificity Reexamination not possible
Indirect immunoperoxidase antibody detection test (IPA)	Fluorescent antibody tagging is substituted by peroxidase tagging	Preparations can be preserved for reexamination All cells infected and uninfected can be visualised Any serotype can be used as an antigen Can measure either IgG or IgM Sophisticated instruments are not necessary	Subjective readings
Immunochromatographic test (ICT) kit tests	Recombinant antigen mixture of 56-kDa outer-membrane proteins of Karp, Kato and, Gilliam strain is captured for detection of IgG and IgM antibodies to *Orientia tsutsugamushi*. The serotypes can be changed as per endemicity in different geographical location	Fairly good sensitivity and specificity which is increased when used with other techniques like LAMP assays or IFA Total antibody(IgG+IgM+ IgA) test has lesser specificity than IgM alone IgM ICT kit is an important ruling in test	Sensitivity and specificity lesser than other serological techniques All issues as in serological tests

Table 3. Cont...

Test	Priniciple	Advantages	Issues
DIRECT DIAGNOSTIC METHODS			
PCR	On blood sample targeting 56 kDa tsa, GroEL, 16s RNA and 47 kDa HtrA genes Can be performed as conventional PCR, nested PCR, qualitative or quantitative real time PCR and LAMP assays	Diagnosis during first week of illness (Rickettsiamia) No paired sera necessary Eschar PCR has better sensitivity than blood/serum	Genetic diversity may cause false negativity False negative with previous treatment Extensive clinical evaluation is pending.
LAMP	PCR based point of care test (POC) Targets the groEL gene, the 60 kDa heat shock protein of *Orientia tsutsugamush* . [37] The reaction can be quantitatively interpreted in real-time by measuring the turbidity or by fluorescence using intercalating dyes such as SYTO 9.	Thermo cyclers and other PCR set up for extraction and interpretation are not needed Diagnostic accuracy more than other PCR methods Advantage over serological testing in first week of illness	Further clinical evaluation needed
Cell culture	Culture in cell lines like HeLa, BHK 21, Vero cells	Improves sensitivity and specificity	BSL-3 facility required 27 days for positivity
Animal inoculation	Detection of organism by Giemsa stain in tissues following intraperitoneal inoculation Scrotal reaction following intra peritoneal injection of blood into male guinea pig	Sensitivity and specificity good	BSL-3 facility Time taking affair

were found.[34] Boryong is the commonest serotype in South Korea in three-fourths of total isolates.[35] Similarly, Kawasaki or Kuroki serotypes accounted for >90% of Kyushu island isolates of Japan.[36] In India, data on serotype prevalence in different areas is still lacking. Thus, common serotypes must be explored and included as the antigen for serological testing purposes.

IFA

IFA, the gold standard test for detection suffers from many pitfalls. For example, in a Korean study, IFA had false negative results in six patients with a typical eschar which was positive for *O. tsutsugamushi* DNA.[37] Further, it is labor intensive, needs resource settings and can have interoperator variations.[7]

Rapid test

The dot blot immunoassay dipstick is rapid, semi-quantitative, accurate and easy to use inexpensive point of care test that can also be used in rural settings.[19,38] Rapid immunochromatographic test is another POC test with higher sensitivity and specificity of 96.8% and 93.3%, respectively when used for detection of IgM.[39] Studies considering Bayesian class models show that ICT kits can even have higher specificity than IFA.[40-42] ICT kits can be used with another method like LAMP/ PCR assays for improving accuracy (Table 3).

Molecular assays

PCR, either conventional, nested or real-time PCR can be used for diagnosis of scrub typhus.[43,44] Q-PCR is faster, has higher sensitivity and specificity and produces quantitative results than other methods.[45] Q PCR has been already reported with targets like- 16S rRNA gene (using hydrolysis probes), 60-kDa heat shock GroEL gene and 47-kDa HtrA outer membrane protein gene. [46-48] Q PCR with 16S r RNA as the desired target has the highest sensitivity and accuracy compared to other targets and also when compared with Immunofluorescence assay for

Table 4. The sensitivity, specificity, Positive predictive value and Negative predictive value of the common tests available for scrub typhus from various studies conducted from low and middle income country settings

Test for Scrub Typhus	Type of assay evaluated	Reference/Gold standard assay	Reported Sensitivity (95%CI) and specificity (95% CI)	Reported PPV (95%CI) and NPV (95% CI)	Study setting	Reference
Scrub Typhus Detect IgM ELISA kits InBios International	IgM ELISA	IgM Microimmuno-fluorescen ce	85.3% (78.4–90.7) 95.5% (93.0–97.3)	87.1%(80.4–92.2) 94.8% (92.2–96.7)	Tertiary care hospital, Karnataka, India	Koraluru M, et al. [79]
Scrub Typhus Detect IgM ELISA kits from InBios International	IgM ELISA	Conventional PCR positive for *O.tsutsugamushi*56kDa type specific antigen (TSA) or 47kDa htrA (high temperature requirement A) qPCR positive	92.41% (86.8–96) 93.67% (88.7–96.9)	93.59% (88.5–96.9) 92.50% (87.3–96.1)	Tertiary care hospital, Tamil Nadu India	Kannan K et al. [80]
Scrub Typhus Detect IgM ELISA kits from InBios International	IgM ELISA	IgM Immunofluorescence test	84% (79.73–87.68) 94.82% (93.43-95.99)	82.12%(78.28–85.42) 95.44% (94.27–96.38)	Hospital setup, Central Nepal	Gautam R et al. [81]
IgG ELISA InBioS International, Inc. USA	IgG ELISA	IgG IFA	86.67% (73.21–94.95) 97.86% (95.08–99.30)	88.64% (76.49–94.93) 97.45% (94.77–98.77)	Tertiary care hospital, Kashmir	Fomda et al. [82]
Conventional PCR	56 KDa gene	IgM Microimmuno-fluorescence	75.32% (67.8–81.8) 100% (95.4–100)	100% (96.5–100) 80.20% (73.9–85.5)	Tertiary care hospital, Tamil Nadu India	Kannan K et al. [80]
Real time PCR (47 KDa)	47 KDa gene	IgM Microimmuno-fluorescence	97.47% (93.8–99.3) 100% (96.5–100) 97.53% (93.6–99.3)	100% (96.5–100)	Tertiary care hospital, Tamil Nadu India	Kannan K et al. [80]
Real time PCR	16S rRNA qPCR	Fourfold increases in IgM or IgG titer on IFA	91.9% (86.3- 95.7) - -	- Korea	Tertiary care hospital ,	Yun et al. [83]
Nested PCR	nPCR	IgM IFA	29.73% (15.87- 46.98) 99.58% (97.67- 99.99)	70.46% (9.37- 52.98) 0.71% (0.57 to 0.87)	Tertiary care hospital, Wardha, Maharastra	Roy S et al. [84]

Table 4. cont...

Test for Scrub Typhus	Type of assay evaluated	Reference/Gold standard assay	Reported Sensitivity (95%CI) and specificity (95% CI)	Reported PPV (95%CI) and NPV (95% CI)	Study setting	Reference
LAMP	47 kDa gene of O. tsutsugamushi	IgM IFA	16.22% (6.19- 32.01) 99.16% (96.99–99.9)	19.22%(4.03-91.66) 0.84% (0.73 to 0.97)	Tertiary care hospital, Wardha, Maharastra	Roy S et al. [84]
LAMP	groEl gene	IgM ELISA	100% 73%	- -	Tertiary care hospital, Puducherry, India	Karthikeyan PA et al. [85]
Immune med ICT test kit	IgM IgG	IgM IFA IgG IFA	98.6% (96-100) 98.2% (96-99) 97.1% (94-99) 97.7 %(95-99)	97.2%(97-99) 99.1% (98-100) 96.4% (93-99) 98.2% (93-99)	Korea	Kim YJ et al. [86]
SD Bioline Tsutsugamushi ICT kit	IgM IgG	IgM ELISA IgG ELISA	91.67%(72.96-98.73) 90.48%(69.58-98.55) 85.71% (67.32-95.88) 100% (80.33-100)	91.67% (72.96-98.73) 90.48% (69.58-98.55) 100% (65.62-100) 80.95% (58.08-94.44)	Tertiary care set up, Tamil Nadu, India	Stephen S et al. [66]

diagnosis. Specimens from which PCR can be done are eschar, whole blood, clots or buffy coat. Immunohistochemical staining and PCR from eschar material are more sensitive and remains positive even after treatment.[37,49] All the PCR assays remain positive only during the period of rickettsemia. Common genetic targets for OT detection are- tsa gene encoding the 56-kDa type-specific antigen; htrA gene coding for 47-kDa periplasmic serine protease[48]; groEL gene - Hsp60; 16S rRNA.[50,51] Although the56-kDa antigen is highly specific,[52,53] but variability in sequence can affect the annealing of the primer and reduce test sensitivity.[44] Assay targeting the 16S rRNA gene showed a higher sensitivity than 56-kDa gene.[51]As *O. tsutsugamushi* genome has a high degree of genetic variations, improving specificity of the detection by using multiple genes approach either by conventional or real-time PCR is the need of the hour.

LAMP assay

LAMP assay with the groEL gene of *Orientia tsutsugamushi* has been tried.[37] LAMP assay has many advantages such as not needing a thermal cycler and visual result reading. But, clinical use warrants further validation. A study has also shown that limit of detection with LAMP assay is 14 copies/µL compared with three copies/µL for real-time PCR.[50]

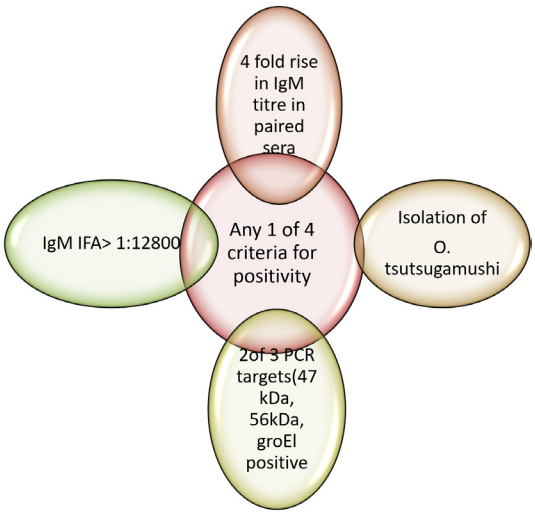

Figure 3. STIC criteria for diagnosis of scrub typhus

STIC criteria for diagnosis of scrub typhus

Gold standard or reference test for scrub diagnosis includes IFA or IIP assays, which have many limitations for accurate diagnosis. Bayesian model showed that the IFA IgM assay has sensitivity and specificity of 70.0% and 83.8%, respectively.[41] Keeping this in mind, STIC criteria (Figure 3) using a battery of tests with high specificity has been proposed as an alternative reference comparator for accurate diagnosis.[54] Table 4 summarizes the commonly available serological and molecular tests for scrub typhus diagnosis.

Treatment of scrub typhus

The treatment options for scrub typhus are- doxycycline and tetracycline. Azithromycin, ciprofloxacin and rifampicin are effective alternatives where there is poor response to doxycycline. In pregnant women and children less than 8 years old, azithromycin is the preferred regimen. Severe disease needs to be treated with intravenous chloramphenicol with intravenous tetracycline. A recent multicentric study has concluded that combination therapy of intravenous doxycycline and azithromycin is a better treatment option for severe scrub typhus than any agent alone.[55] There is no significant difference in outcome when azithromycin therapy is compared with other antibiotics singly or in combination in paediatric patients as noted in a recent meta-analysis.[56] But recently, there have been reports of drug resistance, which needs further pondering.[57-59]

Prophylaxis of scrub typhus

Different localities have different antigenic variants of *O. tsutsugamushi* strains showing no to weak cross-protection. Thus, an effective vaccine for scrub typhus must account for multiple strains thriving in the population.[60-62] WHO recommends single oral dose of tetracycline, doxycycline or chloramphenicol every 5 days for a total of 35 days for prophylaxis against *Orientia* infection[63] as opposed to CDC which opines that such a prophylactic treatment may only delay the disease and also hinder diagnosis. Other safety measures include avoiding exposure to vegetation by using full-sleeved clothing, mats to sit on the grass, using shoes, cleaning the garments with insect repellant after a possible exposure to get rid of mites, and rodent control.[63]

CONCLUSION

Scrub typhus, a disease of wars, has raised its fangs with growing climate change and human activities encroaching on the habitat of the mite reservoir. Despite its long presence, there needs to be more data citing its actual prevalence, serotypes involved and determinants of clinical course, especially in India. One of the important reasons for this is the lack of a diagnostic test with desirable accuracy. Molecular methods are helpful early in the disease and are yet to be widely used for diagnosis. Adopting a rapid, accurate test protocol for clinical diagnosis of scrub typhus is necessary. Further clinical trials and research is needed for evaluating various regimens used for scrub typhus, keeping in mind the evolving drug resistance and its intracellular persistence causing relapses.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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