

An update on the Epidemiology, Diagnosis and Management of the Reemergent Life Threatening Scrub Typhus

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Abstract

Scrub typhus represents a robust Public Health ailment that is Prevalent in the Asia-Pacific region that is inclusive of although not restricted to Korea, China, India, Taiwan Indonesia, Thailand, Sri Lanka, as well as the Phillipines, This area has been referred to as the tsutsugumashi triangle. One billion people have a threat globally to get afflicted, that results in a disease generation in one million individuals. Scrub typhus alias tsutsugumashi disease occurs every year. Here we have stressed on the epidemiology world wise besides the significance of Scrub typhus in Indian scenario that presents as an acute febrile illness having life threatening consequences. We conducted a Here we conducted a systematic review utilizing search engine pubmed, google scholar; web of science; embase; Cochrane review library utilizing the MeSH terms like Scrub typhus; other rickettsios is; differential diagnosis with other acute febrile illnesses; epidemiology of Orientia tsutsugumashi (etiologic agent); malaria; Indian scenario; Leptrombidium bites larvae; mites; serology; WeilFelix reaction; immunofluorescence assay; met genomic next generation sequencing (mNGS), Scrub typhus cell surface display technology; treatment; doxycycline; azithromycin; rifampicin; chloramphenicol; innovative early diagnostics. We found a total of 3500 articles out of which we selected 51 articles for this update. Nometa-analysis was done. Since this disease has reemerged it is usually not kept in mind as a differential diagnosis in acute febrile illnesses that is why we chose to review and update this life threatening disease having central nervous system (CNS), Gastrointestinal Tract (GIT), complications, myocarditis, besides usually diagnostic eschar. Avoidance is equally important specifically for farmers other vegetation areas etc.

Keywords: Scrub typhus; epidemiology; complications; avoidance; Public Health problem

Introduction

Epidemiology & Presentation

Scrub typhus represents a robust Public Health ailment that is Prevalent in the Asia-Pacific region that is inclusive of although not restricted to Korea, China, India, Taiwan, Indonesia, Thailand, Sri Lanka, as well as the Phillipines (fig1). One billion people have a threat globally to get afflicted, that results in a disease generation in one million individuals. Scrub typhus alias tsutsugumashi disease occurs every year [1, rev I ref2] secondary, to the arthropod transmitted gram negative obligate intracellular bacillus *Orientia tsutsugumashi*

as an etiological agent [3,4]. About 5-14 days subsequent, to getting bitten by an infected vector, a Leptrombidium mite, the presentation of the patients with non particular, flu like symptomatology, like fever, rash, eschar or dry scab at the area of bite, headache, myalgia generalized lymph node enhancement ,nausea ,vomiting as well as abdominal pain [5,6]. Of these the commonest symptom are fever as well as headache. Amongst, 95-100% of the corroborated patients noticeably had high fever in various studies [7].

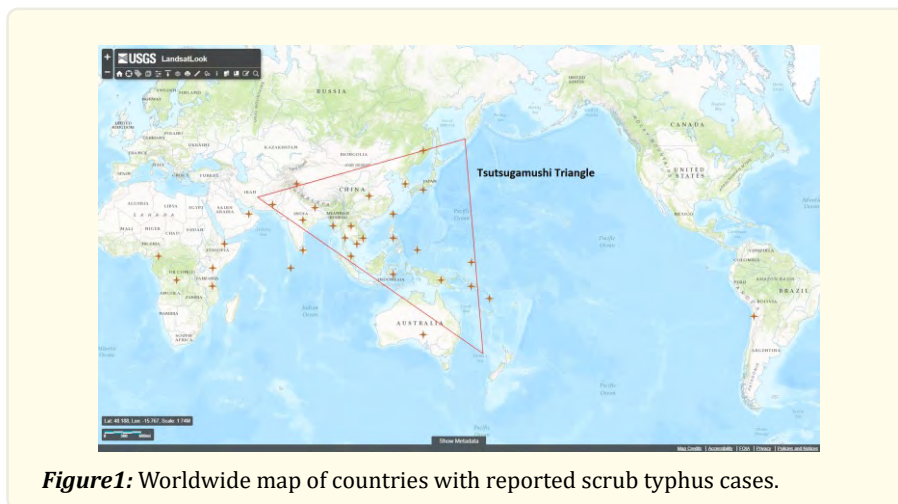


Figure1: Worldwide map of countries with reported scrub typhus cases.

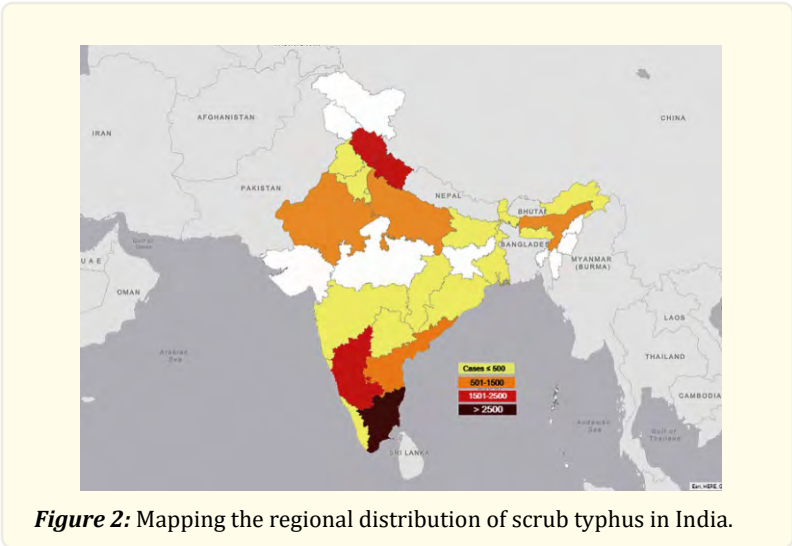
Courtesy ref no-2-The majority of scrub typhus cases occur in the “tutsugamushi triangle” in the Asia-Pacific area. Countries with human cases are labeled with a star. [<https://landsatlook.usgs.gov/viewer.html>].

The existence of an eschar at the region of chigger (alias larval mites) feeding is a typical characteristic of Scrub typhus. Its initiation occurs in the form of a papule at the region of chigger feeding, that is followed by ulceration as well as generation of a black crust akin to a skin burn from a cigarette. On existence, it takes place ahead of the fever initiation as well as other symptomatology [5, 8]. The manifestation of eschar ranges from 1-97% of the patients of Scrub typhus based on the geographical region as well as studies [7,9]. In case of Caucasians it is more readily visible as well as in East Asian subjects in contrast to South Asian subjects who possess dark skin [10]. Maximum eschar generation occurs in the front aspect of the body with regards to male subjects (equivalent, to 80%). Moreover, they occur basically with in 30cm below the umbilicus in male subjects, with other usual areas affected are the lower limbs as well as anterior aspect of chest. As compared to that in female subjects, anterior aspect of chest, head as well as neck are the most usual areas implicated [10]. In case of children the commonest location are the axillae besides other aforementioned regions [11].

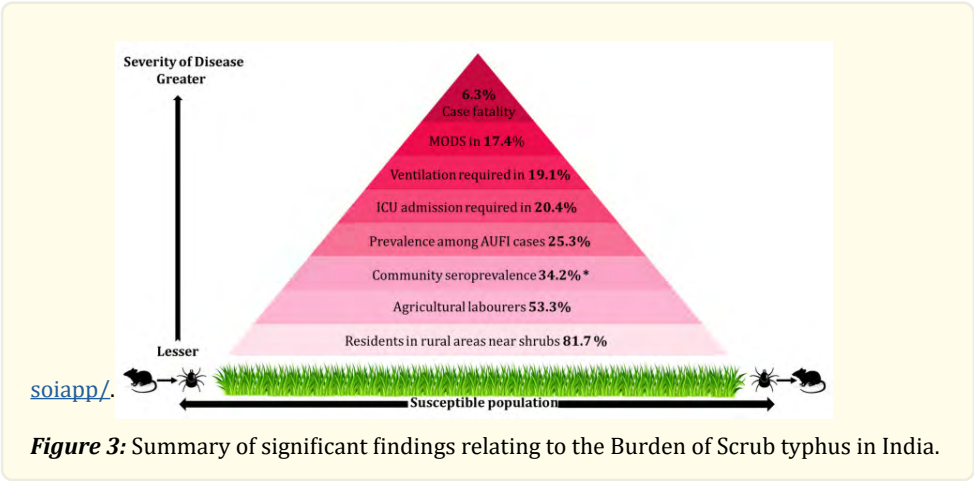
The greater robust complications are multi organ failure. These robust multi organ presentation are inclusive of jaundice, acute renal failure, Pneumonias, acute respiratory distress syndrome (ARDS), myocarditis, septic shock, meningoencephalitis, pericarditis, disseminated intravascular coagulation (DIC), [5,6,12,13]. The lung is one of the commonest targets for this infections with *Orientia* that result in pulmonary complications having variable robustness. There might be interstitial Pneumonitis in robust cases [6]. Meningitis as well as/or encephalitis generation might occur in these patients with robust disease that results in agitation, patients might get delirious or convulsions might get generated. Despite, focal neurological signs occurrence is occasional they have known to take place. Laboratory investigations might illustrate alterations in the CSF that are akin to the ones observed in meningitis caused by *Mycobacterium Tuberculosis* or viruses [12]. Hearing loss/ impairment might get generated further [14]. The rate of mortality different as per country, areas in addition to various studies [15]. This mortality ranges from 30-70%, in case no proper treatment is given then the median mortality of untreated patients is 1.4% [15, 16]. Hence the generation of efficacious approaches for therapy, for regulation as well as avoidance of the disease is a key Public Health issue.

More recently, a systematic review conducted in India with regards to epidemiology, morbidity, along with mortality of Scrub typhus

by Devasagayametal. [17] Demonstrated that during the last decade, there were 18,781 validated ed scrub typhus cases documented in 138 hospital-dependent studies along with two community-dependent studies. Utilization of IgM ELISA was done in 122 studies for the corroboration of cases in maximum subjects (89%). The percentage of scrub typhus among acute undifferentiated febrile illness (AUFI) studies was 25.3%, besides community seroprevalence was 34.2%. Ninety studies had data published on multiple organ implication out of which 17.4% of cases revealed multiple organ impairment syndromes, 20.4% patients required ICU admission, and 19.1% required ventilation. The overall case-fatality rate was 6.3%, in addition to the mortality among those with multi-organ dysfunction syndrome was high considerably high upto 38.9% [17]. Their conclusions were that Scrub typhus is a prevalent acute febrile illness in India resulting in robust morbidity that was responsible for numerous deaths. The burden of the disease has been underappreciated. Early diagnosis and immediate treatment can result in significant reduction in complications along with mortality. Establishing good surveillance and instituting proper regulatory ion measures are urgently required [17]. see figure2 &3.



Courtesy ref no-17-Number of scrub typhus cases less than or equal to 500 is represented as yellow, 501–1500 cases is represented as orange, 1501–2500 cases is represented as red and more than 2500 cases is represented as maroon. This map was created in the free version of ARC GIS by the first author. Please see the ARC GIS link <https://arcg.is/1iDvKu>. The base layer map was used from the Survey of India, Department of Science & Technology which gives open access to the general public <https://indiamaps.gov.in/>



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Courtesy ref no-17-Scrub typhus is vector borne febrile illness in susceptible population caused by chigger bites harbouring *Orientia tsutsugamushi*. It was noted in this study that 81.7% of residents from rural areas exposed to shrubs are affected. Agricultural labourers (53.3%) were at the highest risks of contracting the illness. Community sero prevalence was reported to be 34.2% in India (*this was based on 2 community based study). 25.3% of all the hospitalised AUI are reported to be scrub typhus. Among the severe scrub typhus cases 20.4% needed ICU admission and 19.1% were eventually put on ventilation. Multi organ dysfunction syndrome was reported in 17.4% of the patients. Scrub typhus has a case fatality rate of 6.3%. Further epidemiological studies need to be carried out to suffice the dearth of evidence of scrub typhus seroprevalence and severity in the community. The figure was created in Microsoft Paint and PowerPoint. The glass blades and mice silhouette are taken from <https://openclipart.org/detail/164635/grass> and <https://www.publicdomainpictures.net/en/view-image.php?image=145546&picture=mouse-silhouette-sitting> respectively and modified in Paint to get desirable effect.

Akin to that Wei et al. [18], conducted an retrospective study with regards to Clinical along with epidemiological data in 4501 patients admitted in Guangzhou City, China as well as gave the anticipating model factors for robust disease besides how to recognize in addition to avoid these fatal complications by promotion of good public health measures [18].

The other signs might be seen in subjects with Scrub typhus. Significant hyperemia with haemorrhages as well can be seen in these subjects in the conjunctiva with Scrub typhus at the time of acute phase of the disease. It has been illustrated that haemorrhages, mainly in Gastrointestinal Tract (GIT) occur as complications. In critically ill patients there has been documented haemorrhages in addition to coagulation disorders. Might be gastrointestinal mucosal haemorrhage, lot of erosions as well as ulcers [5, 19].

The transmission of *Orientia tsutsugamushi* occurs in case of mammalian hosts that is inclusive of humans occurs via the larval stage of *Leptrombidium* bites, alias chiggers [20]. Mites represent the primary reservoirs for *O. Tsutsugamushi*. They continuously remain infected throughout their lifecycle (larval, nymph, adult as well as egg) [6]. It is believed that mites just feed once in a mammalian hosts. These chiggers mostly feed on the thin, tender or the wrinkled skin. This, feeding occurs for 2-4 days [21]. It has been demonstrated that chiggers don't pierce the skin of the hosts however take benefit of the hair follicles or pores [6]. The saliva that get liberated by the mites possess the capacity of dissolution of host tissues surrounding the feeding region, in addition to the mites consume the liquefied tissue. Observation of *Orientia tsutsugamushi* has been visualized in the salivary glands of the mites [6]. Transovarial as well as transtadial transmission are the major modes of sustenance of *Orientia* in the mite, with restricted documentation that bacterial transmission mode to the mites can further be seen at the time of co feeding as well as/or via wild rodents [22]. Transtadial transmission implies the sustenance of the pathogen within the vector from a particular life stage towards the subsequent, like the passage of *Orientia tsutsugamushi* from the mite larva to nymph as well as from nymph to the adult, whereas transovarial transmission signifies the event of the *Orientia tsutsugamushi* getting transmitted from female to the offspring via the eggs [9, 22]. There is implication of both the approaches in case of vertical transmission. Occasional reports with regards to horizontal transmission of *O. tsutsugamushi* in the mites [23]. At the time of horizontal transmission acquisition by the chigger of *O. tsutsugamushi* from an infected host, with its offspring resulting in new host infection. Although there is not adequate proof existent to corroborate that horizontal transmission is a significant mode for sustenance of *Orientia* in nature [23, 24]. There are no reports of a person to a person transmission of Scrub typhus [6]. Greater studies are required with regards to mites, besides their engagement on the host, would promote regulation in addition to avoidance of Scrub typhus.

Even existently lot of modes with regards to pathogenesis as well as cell biology of the crosstalk, of this bacteria with the host cell, in view of the hurdles in greater research for evaluation of the obligatory intracellular bacteria [25]. With the existence of antigen heterogeneity, reemergence, besides, existence of immunity of minimal time period of *O. tsutsugamushi* cause significant amount of primary infections in addition to repeated infections. Nevertheless, basic as well as epidemiological work on *O. tsutsugamushi* has not received adequate attention in the recent past decades [26]. With the preliminary work it has been illustrated that this particular disease has been existent in the endemic regions for considerable time period [27]. Just sporadic epidemiological results are existent with regards to Scrub typhus in the endemic regions, in addition to other areas of the world, that causes significant gap; pertinent to information.

Avoidance as well as regulation of Scrub typhus

Diagnosis

In view of *Orientiatsutsugumashi* resulting in a flu like illness with fever that is akin to numerous diseases, the Clinical diagnosis become markedly tough. Existence of an eschars on the body of the patients along with history of travel to or residing in endemic regions facilitates diagnosis. However eschars is not evident in each patient of Scrub typhus as well as cutaneous lesions that are resultant from other diseases like spider bites, leishmaniasis, spotted fever rickettsiosis along with anthrax might make the existence of an eschar < as a definitive sign with regards to diagnosis. Moreover, Scrub typhus can be misdiagnosed in the form of numerous acute illnesses whose presentation is in form of acute high grade fever like malaria, dengue, leptospirosis, other rickettsiosis, meningococcal disease, typhoid fever, infectious mononucleosis as well as HIV [5, 28].

Laboratory investigations meant for diagnosis of rickettsial diseases that are inclusive of Scrub typhus are basically the serological investigations as well as molecular assays. The occurrence of cross reaction of *O. tsutsugumashi* with other rickettsiosis is occasional [29]. With regards to the gold standard for diagnosis of Scrub typhus is the indirect Immuno fluorescence assay (IFA) [29, 30]. Nevertheless, IFA is very costly as well as complex, with need of intensive training, besides a facility with regards to biocontainment for the generation of reagents. Despite, the availability of this assay for numerous years, its application in the endemic regions is still restricted. This test does not yield diagnosis at the early stage of infection in view of those antibodies are representative of adaptive immunity, thus their development does not occur in early stage of infection. Its diagnostic value lies just when this serological investigations demonstrates a 4 times escalation [31]. The other restrictions of IFA being the debatable cutoff antibody titre, besides the result determined being subjective, along with specificity of this test [30, 32].

The other serological investigations are inclusive of the indirect Immunoperoxidase assay (IIP), Weil Felix test (WF), enzymes linked Immuno assays (ELISA) as well as separate commercially existent Immuno chromatographic tests (ICT)[30].

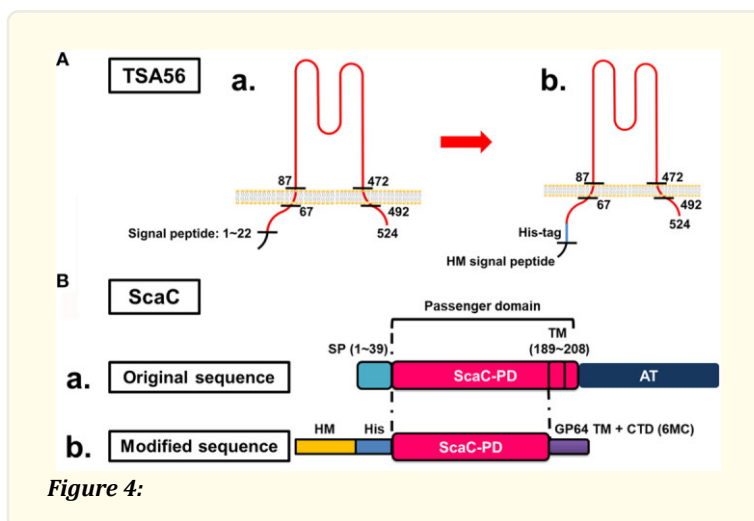
- i. The commercial presence of WF agglutination tests has been existent for numerous years. There is utilization of *Proteus mirabilis* OXK strains with absence of sensitivity as well as specificity in particular the specificity, with regards to routine diagnosis [33]. At the time of 2d wk of this illness sensitivity is just 50% [5, 28].
- ii. IIP represent a modification of IFA that yields a sensitivity as well as specificity that is comparable without the need of an ultraviolet microscope for diagnosing Scrub typhus [34]. Either of IIP as well as IFA utilization is done in the form of reference standards. No significant difference was the observation as far as correctness of the 2 strategies were concerned, other than a single study where claims were made of higher sensitivity with IIP in contrast to IFA with acute sera (79.6% vs 68.5% at titer \geq 1:400)[35].
- iii. ELISA with their different forms, like the commercially existent dipstick test, utilization of pooled cell lysates of various strains of *O. tsutsugumashi* in the form of antigen, or the recombinant p56 or the other outer membrane proteins in the form of antigen. Both sensitive as well as specific outcomes are obtained with ELISA. In the end the other tests replacement might occur like IIP as well as IFA assays. However the sensitivity as well as specificity of dipstick test are lesser in contrast to ELISA, however their ease of use, as well as readily performed in areas with <facilities [6,28, 9]. Their experiences were shared by Black sell et al. [36] with In Bios Scrub typhus Detect IgM ELISA, that they reported was simple to use, cheap besides possessed the capacity of accurate screening along with diagnosis [36]. Hence ELISA dependent tests need to be taken into reckoning with regards to a good option for the IFA that is the gold standard.
- iv. ICT represents another commercially existent kit with regards to rapid as well as early diagnosis. In this test further utilization of recombinant outer membrane protein of *O. tsutsugumashi* for the finding of IgG, IgM as well as IgA, antibodies towards *O. tsutsugumashi*. The analysis of this test pointed to moderate to high sensitivity (equivalent to 70%) of Scrub typhus patients. Furthermore, escalation of sensitivity resulted with the time period of fever. Numerous studies have corroborated that akin to passive haemagglutination assay (PHA), ICT possesses numerous false negative outcomes [32]. Replacement of PHA with ICT occurred in view of the lesser sensitivity of PHA. Nevertheless, Lim et al, illustrated that the specificity of IFA IgM was lesser thus results in comparison that was not correct amongst IFA in contrast to other diagnostic assays. In contrast to that the ICT IgM possessed

equivalent sensitivity, whereas significantly greater specificity as compared to IFA when evaluation done with the utilization of Bayesian latent class models [30, 32]. Kingston et al. [37], illustrated In Bioscrub typhus Detect IgM Rapid test possessed greater specificity as well as correctness that was advantageous [37].

The molecular strategy with regards to of diagnosis of Scrub typhus comprises of detection of the bacteria with the utilization of PCR assays. PCRs generally target the genes of the outer membrane protein of 56 kDa, 47kDa as well as groELgenes [30]. It got documented that nested PCR might possess greater sensitivity in contrast to other serological investigations that was inclusive of the gold standard IFA [39]. This molecular biology approach posses, the capacity of detecting the DNA of *Orientia* in the blood at the time of the continued phase of the infection, i.e. at the time with no overt clinical symptoms visualized. Nevertheless, there is reduction of sensitivity of PCR with treatment initiation [5, 28, 40].

From the time of May 2018 to March 2021, Liu et al. [40], harnessed 13 samples from 10 patients with suspected scrub typhus. Met genomic next-generation sequencing (mNGS) and other diagnostic methods (-that were inclusive of serology with the utilization of Weil-Felix reaction in addition to IFA for scrub typhus along with respiratory tract profile IgM, besides as culture for routine bacteria utilization were done for Identification of the pathogens in this study. The outcomes of mNGS were all positive, with mapped reads of *O.tsutsugamushi* varying from 1 to 460. Eight patients (80%) were diagnosed as scrub typhus. In the other two that were diagnosed as suspected scrub typhus in view of restricted amounts the reads of the pathogen (one and two, respectively). As per the clinical proof, nine of the 10 patients were ultimately diagnosed as scrub typhus, other than for patient 9 (with suspicion of scrub typhus by mNGS with one particular reads of the pathogen) diagnosed as acute amplification of chronic obstructive pulmonary disease. For the five scrub typhus patients without classical eschar, mNGS gave all positive results (4–460 particular reads). For other methods, only Weil-Felix reaction of one patient detected the pathogen. Additionally, the respiratory tract profile (IgM) detected different pathogens, however but all were corroborated to be false positive. Thus their conclusions were that the performance of mNGS was of greater advantage in contrast to the other traditional approaches for early along with appropriate diagnosis. The utilization of this strategy might be done for early along with appropriate diagnosis in case of clinical infection, in particular for the ones where diagnosis is tough with the utilization of other classical diagnostic approaches [40].

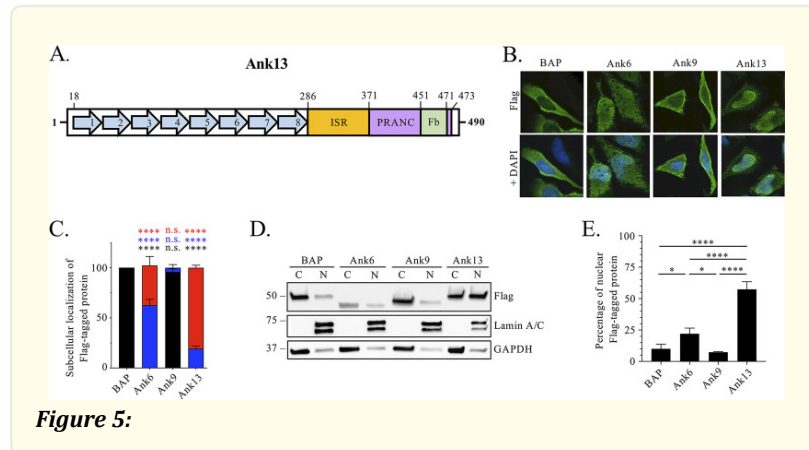
Scrub typhus (ST), is an underestimated fatal epidemic in the Asia-Pacific region, resulting in a million human infections each year. ST is easily misdiagnosed as clinical diagnosis is based on non-specific skin eschar and flu-like symptoms. Thus, the absence of precise, simple, in addition to economical detection methods for ST poses a global health threat. To address this problem, Liao et al. [41] adopted baculovirus surface-display technology for expression of three variants of TSA56, the major membrane antigen of *O. tsutsugamushi*, in addition to the passenger domain of ScaC (ScaC-PD), on insect Sf21 cell surfaces instead of biosafety level 3 bacteria in an enzyme-linked immunosorbent assay (ELISA). Recombinant TSA56 and ScaC-PD were all properly expressed and displayed on Sf21 cells. Their cell-dependent ELISA having the four constituent antigen-displaying cell types cross talked with monoclonal antibodies along with serum samples from ST-positive field-caught rats. This cell-based ELISA presented high accuracy (96.3%), sensitivity (98.6%), and specificity (84.6%) when tested against the ST-positive rat sera. Results of a pilot study with the utilization of human sera were further significant in that they circumvented complex purification and refolding events needed for generation of recombinant *O. tsutsugamushi* antigens along with caused reduction the requirement for expensive equipment in addition to extensively trained operators. Hence, their system had the capability to become a widely used serological platform for the diagnosis of ST [see figure4][41].



Courtesy ref no-41-Cloning strategies for surface display of recombinant TSA56 and ScaC-PD using a baculovirus-insect cell system. (A) Structure and strategy for displaying TSA56 protein on Sf21 cells. (A-a) TSA56 protein has a signal peptide from residues 1 to 22 and two TM domains (residues 67 to 87 and 472 to 492, respectively). (A-b) The signal peptide was replaced by an HM signal peptide and a His-tag, but the rest of the protein was preserved. (B) Structure and strategy for displaying ScaC-PD on Sf21 cells. (B-a) ScaC contains a signal peptide (SP), a passenger domain (PD), and an autotransporter (AT) domain. (B-b) The signal peptide (SP) was replaced by an HM signal peptide (HM) and a His-tag (His), and the TM-truncated passenger domain was fused with the TM and cytoplasmic-tailed domain (CTD) of GP64 protein (6MC) from baculovirus

Mode of Action

Orientia tsutsugamushi is the etiologic agent of scrub typhus, the deadliest of all diseases caused by obligate intracellular bacteria. Nucleomodulins, that represent bacterial effectors which result in impairment of eukaryotic transcription, are escalatingly being recognized as key virulence factors. The mode of their translocation into the nucleus in addition to their functionally necessary domains are illdefined. Adcox et al. [42] illustrated that Ank13, an *O. tsutsugamushi* effector conserved among clinical isolates and its expression occurred during infection, that got to reside to the nucleus in an importin β 1-independent way. Instead, Ank13 nucleotropism needed an isoleucine at the thirteenth position of its fourth ankyrin repeat, that was in agreement with utilization of eukaryotic RaDAR (RanGDP-ankyrin repeats) nuclear import. RNA-seq analyses of cells expressing green fluorescent protein (GFP)-tagged Ank13, nucleotropism-deficient Ank13_{1127R'} or Ank13 Δ F-box, which lacks the F-box domain that is necessary for crosstalk with SCF ubiquitin ligase, which showed Ank13 to be a nucleomodulin that predominantly results in down regulation of transcription of greater than 2,000 genes. Its capacity of doing so implicated its nucleotropism and F-box in synergistic and mutually exclusive ways manners. Ank13 further possessed the capacity of action in the cytoplasm to result in impairment of smaller cohorts of genes. The effector's toxicity in yeast robustly is based on its F-box in addition to lesser on its nucleotropism. Genes negatively controlled by Ank13 include those implicated in the inflammatory response, transcriptional regulation, along with epigenetics. Significantly, maximum of the genes that GFP-Ank13 most robustly down regulated were quiet or repressed in *O. tsutsugamushi*-infected cells when Ank13 expression was most robust. Ank13 is the first nucleomodulin identified to coopt RaDAR along with a multifaceted effector that functions in the nucleus and cytoplasm through F-box-based as well as independent modes to globally reprogram the host cell transcription [see figure 5 [42]].



Courtesy ref no-42-Ank13 is nucleotropic. (A) Schematic of Ank13 depicting its eight tandemly arranged ankyrin repeats (blue arrows), ISR (orange), and F-box (Fb; green). The Fb occurs as part of a larger encompassing PRANC domain (purple). Amino acids that constitute each domain are indicated. (B to E) Flag-Ank13 predominantly localizes to the nucleus. Transfected HeLa cells expressing Flag-tagged BAP, Ank6, Ank9, or Ank13 were examined by immunofluorescence microscopy (B and C) and Western blot analysis of nuclear [N] and cytoplasmic [C] fractions (D and E). (B) Representative images of fixed cells immunolabeled with Flag antibody and stained with DAPI. (C) One hundred cells were examined per condition in triplicate to quantify the means \pm the standard deviations (SD) for the percentages of cells exhibiting Flag immunosignal localization, which was scored as being exclusively cytoplasmic (black), throughout the cell (blue), or exclusively in the nucleus (red). Two-way ANOVA with Dunnett's correction determined significance between subcellular locations of Flag-tagged proteins compared to Flag-BAP. The data are representative of three experiments with similar results. (D) Fractions were probed with lamin A/C and GAPDH antibodies to verify fraction purity and Flag antibody to determine localization of Flag-tagged protein. (E) The nuclear densitometric value was divided by the sum of nuclear and cytoplasmic densitometric values for Flag-tagged proteins in panel D. The quotient was multiplied by 100 to yield the percentage of Flag-tagged protein in the nucleus. Data presented are percentages (means \pm the SD) of Flag-tagged proteins exhibiting nuclear localization from three separate experiments. One-way ANOVA with Tukey's *post hoc* test was used to test for significant difference in percentage of nuclear Flag-tagged protein among the conditions. Statistically significant values are indicated. *, $P < 0.05$; ****, $P < 0.0001$. n.s., not significant.

Treatment

Being a gram negative bacillus *Orientiatsutsugumashi* infection can be treated with effectiveness with the utilization of precise antibiotics. With early treatment more advantageous results with reduction in the time period of the course of therapy besides reduction in mortality. Oral therapy is efficacious with regards to mild disease, however for the robust ill patients, mostly intravenous, subcutaneous or other parenteral injections are required for the critically ill patients. Akin to therapy for other ricketssial diseases doxycycline is one of the antibiotics that possesses maximum effectiveness in the context of treatment of Scrub typhus. Generally with antibiotics the reduction of fever occurs rapidly, with this result getting commonly employed in the form of a diagnostic pointer. Certain randomized clinical trials observed no significant variation in the results with regards to the treatment with tetracyclines, doxycycline, telithromycin as well as azithromycin with the last one advocated therapy that is believed to be as efficacious as doxycycline [43]. Rifampicin was illustrated to possess greater efficacy in contrast to doxycycline [5, 44]. WHO (World Health Organization) advocates that pregnant women or childrenutilization of azithromycin or chloramphenicol can be done. Numerous studies corroborated that azithromycin in addition to other macro ides possessed effectiveness that was equivalent to that of azithromycin or chloramphenicol [45]. Occasional publication sdocumented the existence of antibiotic resistance. Generation of innovative diagnostic tools as well as treatments to establish the modes of poor reaction in some patients in addition to find mechanistically the cause of antibiotic resistance of this pathogen [5, 46].

Avoidance strategies that are existent

Existently no vaccine availability is there with regards to any rickettsial that is inclusive of Scrub typhus. The significant antigenic differences in various strains of *O. tsutsugumashi*, as well as cross protection of markedly short duration in various strains inhibits the generation of an effective various vaccine. The action with regards to generation of vaccine get hampered by various antigenic strains of *O. tsutsugumashi* that possess variable antigenicity in separate endemic countries/areas or in same geographical region as well amongst separate strains [47].

WHO advocates prophylactic therapy just in particular situations in the endemic regions [48]. A Single oral dosage of doxycycline, chloramphenicol/tetracycline repeated 5 days for a full 35 days confers protection against infection with *Orientia* [rev ref2]. A prospective randomized double blind study was conducted amongst the Taiwanese military personnel corroborated that prophylactic therapy with doxycycline resulted in reduction in the incidence of Scrub typhus to 1/5th of that in the placebo group [49]. Akin to that in the US army a weekly doxycycline dosage utilization was done for avoidance of Scrub typhus infection [rev ref2]. Never the less, CDC in US does not advocate utilization of antibiotics in the form of prophylaxis with regards to Rickettsial diseases [rev ref2] inclusive of Scrub typhus in view that this prophylactic therapy might just postpone the initiation of the disease, thus making diagnosis establishment a tough job [50]. For the treatment of Rickettsial diseases with greater effectiveness, CDC advocated treatment initiation just on mere suspecting [50]. For the patients residing in the endemic regions certain precautions are required.

- i. Avoidance of outbreaks-like visitors that plan travel to endemic regions need to check this website <http://www.cdc.gov/travel>
- ii. Avoidance of exposure situations –as chiggers are located in grass, woodlands as well as other vegetations individuals are need to avoid the outdoors as well as not lie on ground which is bare, or grass, utilization of sheets rather on ground.
- iii. Wear proper clothes like shirts that possess long sleeves, pants, boots, hats for reduction of exposure.
- iv. Utilization of insect as well as spatial repellents-like with Dibutyl phthalate, benzyl benzoate or other chemicals on skin like permethrin on clothes for avoidance of chiggers bites
- v. Utilization of insecticides as well as habitat modifications-framers to enhance sanitation, clear vegetation, regulation of rodents.
- vi. Clean thoroughly subsequent to visit to high risk regions–in view of small size 0.2-4mm, mite larva detection on skin /clothes is tough. Immediate change as well as good cleaning with detergent can aid in reduction of infection risk as well as.

B. Approaches for avoidance as well as regulation

The occurrence of resurfacing as well as geographic expanding of Scrub typhus in the Asia-Pacific region in addition to escalation of antibiotics resistance has woken us up with regards to how urgent is the generation as well as utilization of regulation along with avoidance measures [49].

Despite, non availability of vaccines utilization of numerous other avoidance measures can be done. For guaranteeing that these measures implementation occurs with effectiveness, public education on recognizing as well as personal avoidance measures assume priority. As far as WHO advocacy is concerned their recommendations are become aware along with educational actions are required for targeting the school children.

Diagnostic Dilemma on Coexistence of Diseases Causing acute febrile manifestation

Of the 542 studies that were obtained from three databases, Wilairatana made utilization of 14 studies that met the inclusion criteria in the systematic review and meta-analysis. The pooled prevalence of malaria and scrub typhus co-infection (56 cases) among febrile patients (7920 cases) was 1% (95% CI: 0–1%, I^2 : 78.28%), whereas the pooled prevalence of scrub typhus infection (321 cases) in patients with malaria (1418 cases) was 21% (95% CI: 12–30%, I^2 : 98.15%). Subgroup evaluation demonstrated that the pooled prevalence of scrub typhus infection among patients with malaria in India was 8% (95% CI: 4–13%, I^2 : 85.87%, nine studies with 59/794 cases), whereas the pooled prevalence of scrub typhus infection among patients with malaria in Thailand was 35% (95% CI: 7–64%, I^2 : 98.9%, four studies with 262/624 cases). The co-infections did not occur by chance ($P = 0.013$, odds: 0.43, 95% CI: 0.22–0.84%, I^2 :

60.9%). In the sensitivity evaluation the pooled prevalence of malaria along with scrub typhus co-infection amongst febrile patients was 0% (95% CI: 0–1%, I²: 59.91%). Hence their conclusions were that this existent study demonstrated that the pooled prevalence in addition to significant correlation amongst malaria along with scrub typhus. Their outcomes demonstrated the exact status of co infection. Actually greater research in the endemic regions is required specifically for evaluation whether coof co-infection possesses the capacity of amplification of the propagation of disease [51].

Conclusions

Scrub typhus is a deadly Public Health that has assumed lot of significance since its reemergence in the Asia-Pacific region. Besides having become a threat for a billion people, it results in acute illness in a million individuals annually. Occuring secondary to infection with *Orientia tsutsugumashi*, Scrub typhus might result in multiorgan failure with a mortality as high as 70% if correct Antibiotics are not initiated for its treatment. In view of antigenic heterogeneity generic immunity gets avoided. With its neglected a lot of requirement is there for getting full epidemiological data in endemic areas. Here we have highlighted the epidemiology with regards to the world in addition to focused on Indian scenario. Furthermore how its early diagnosis along with treatment can be attempted to avoid robust life threatening complications.

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