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# Editorial: Scrub typhus & its changing dynamics

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## Editorial on the Research Topic

### Scrub typhus & its changing dynamics

## Changing epidemiology of scrub typhus

The epidemiology of scrub typhus, caused by *Orientia tsutsugamushi*, has experienced concerning changes in recent years. It traditionally was endemic to the “tsutsugamushi triangle” (including Southeast Asia, parts of Japan, and northern Australia); interestingly, the disease is now being reported in previously non-endemic regions including South America and Africa. There are several factors implicated in these changes. One major factor contributing to this spread is global warming, impacting the changing epidemiology of infectious agents worldwide. As temperatures rise, the geographic range of the vectors for scrub typhus, *Leptotrombidium* mites, changes. Warmer climates provide ideal environments for these mites to expand their natural habitat, thereby increasing the risk of disease transmission in previously unaffected areas (1, 2).

Another critical factor in the changing epidemiology of scrub typhus is the growing impact of environmental encroachment, such as deforestation and urbanization. As human populations expand their footprint into forested areas for agriculture or housing, they will come into closer contact with mite-infested reservoirs, thereby increasing the probability of human exposure and infection. This is of particular concern in tropical and subtropical regions where rapid urbanization is being seen (3).

These environmental changes cause shifts in animal reservoirs for scrub typhus. Small mammals, such as field mice and other rodents, are key hosts for *Leptotrombidium* mites. Environmental disturbances lead to loss of habitat and alter the ecologic niche and population dynamics of these mammals, further influencing the spread of scrub typhus (4). This pattern of human activities disrupting natural ecosystems, allowing animal reservoirs to encroach in new areas, is being seen with a wide variety of zoonotic infections and is contributing to the expanding global burden of scrub typhus.

Finally, other factors, including the lack of a robust public health infrastructure and international travel also play an important role in the changing dynamics of scrub typhus epidemiology.

## Diagnostic tools and treatment

Diagnosis of scrub typhus is challenging. Usually, it is done with the help of clinical findings along with epidemiological data supported mostly by a serological test. Although widely available, serological tests may fail to detect infection in the acute stage. For example, the test result may be false negative since the IgM may take up to 5-7 days to turn positive, or it may be false positive because of cross-reactivity with other endemic infections (5, 6). Hence, the newer diagnostic tools based on Polymerase Chain reaction (PCR), Loop Mediated Isothermal Amplification (LAMP), Recombinase Polymerase Amplification Reaction (RPA), etc., are getting popular. In one of the papers published in this Research Topic, the authors have highlighted the use of metagenomic next-generation sequencing (mNGS) in the retrospective diagnosis of scrub typhus in an undiagnosed case of sepsis (Jian et al.). While doxycycline has been the mainstay of treatment of scrub typhus and azithromycin is mostly used to treat during pregnancy, a recent randomized control trial has highlighted a better clinical outcome with a combination therapy of intravenous doxycycline and azithromycin as compared to the monotherapy with either drug in severe scrub typhus (7).

## Papers in this Research Topic

In response to the call for papers for this Research Topic “*Scrub typhus & its changing dynamics*” published in the *Frontiers of Tropical Diseases and Frontiers in Public Health*, there were 7 submissions. Finally, 5 manuscripts that met the scope of the Research Topic, were published after going through several rounds of the peer review process.

In the first paper, “*The impact of meteorological parameters on the scrub typhus incidence in Baoshan City, western Yunnan, China*”, the authors examine the effect of meteorological factors on the incidence of scrub typhus in Baoshan City, China, from 2010 to 2019 using a lag non-linear model (8). During this time, Baoshan City recorded 9,034 scrub typhus cases, with an annual incidence rising from 8.49 to 62.96 per 100,000, peaking in August. Monthly scrub typhus incidences correlated positively with mean temperature, maximum temperature, relative humidity, and precipitation; however, they did not correlate with the monthly temperature range, which showed a negative correlation. The study showed that mean and maximum temperatures had the highest relative risk (RR) at lag 0. The RR was highest at 3.74 for a mean temperature of 20°C. High relative humidity of more than 70% was associated with higher RR, with the highest RR of 2.30 for 83% humidity with a 1-month lag. The precipitation fluctuation showed the highest RR of 2.39 at 33cm at lag 2. The study concluded that warmer monthly temperatures increased the occurrence of scrub typhus in the current month. In contrast, lower mean and maximum temperatures were associated with a delayed rise in cases several months later.

The second paper, “*mNGS helped diagnose Scrub Typhus-associated HLH in children: a report of two cases*” is a case report

of two patients in the South of Sichuan, China, highlighting the role of metagenomic next-generation sequencing (mNGS) in the diagnosis of scrub typhus (Jian et al.). The first case was a 6-year-old girl with an unexplained fever, initially diagnosed with sepsis, Hemophagocytic Lymphohistiocytosis (HLH), and a pulmonary infection. The second patient had a more severe condition with multiple organ dysfunction and was initially diagnosed with septic shock, HLH, acute kidney injury, and a pulmonary infection. Neither patient initially underwent specific testing for scrub typhus due to the absence of a typical eschar, and conventional blood cultures were negative, with no response to routine antibiotics. However, metagenomic next-generation sequencing (mNGS) detected the causative pathogen, *O. tsutsugamushi*, in plasma samples from both patients, which was later confirmed by polymerase chain reaction. Both patients responded rapidly to doxycycline treatment. The study concluded that unbiased mNGS enabled the diagnosis of a rare pathogen-associated infectious disease that had eluded conventional diagnostic methods, providing a clinically actionable outcome.

The third paper, titled “*Linking the Increasing Epidemiology of Scrub Typhus Transmission in India and South Asia: Are the Varying Environment and the Reservoir Animals the Factors Behind?*” aims to highlight epidemiology, transmission dynamics, clinical features, and the current challenges faced in diagnosis and treatment of scrub typhus, emphasizing on both ecological factors and reservoir animals' roles in the transmission. Environmental conditions—temperature, humidity, sunlight, and atmospheric pressure—affect the development and activity, specifically of the chigger mites, the vector (Mohapatra et al.). For example, cooler temperatures in northern regions can hinder the ability of chiggers to attach to humans, thereby limiting transmission in those areas. Ideal environments for these vectors are often found in humid green spaces, riverbanks, and forest clearings, which are termed “scrub typhus islands.” Chiggers typically become infected after feeding on small mammals, such as wild rodents, which are the primary reservoir animals for the disease. Strategies like controlling the population of these small mammals and managing humidity levels can help reduce the risk of scrub typhus in endemic areas. The paper highlights the need for surveillance, better diagnostic tools, and enhanced public health strategies to alleviate the burden in endemic regions.

The fourth paper, “*Molecular diagnosis and genotyping of Orientia tsutsugamushi in Maesot and Chiangrai, Thailand*” highlights the genetic diversity of *Orientia tsutsugamushi* strains, particularly in regions like Chiangrai and Tak provinces in Thailand, where significant cross-border population movements occur (Rungrojn et al.). Between June 2018 and December 2019, 31 patients with acute undifferentiated febrile illness (AUFIs) were recruited for clinical trials and tested positive by a scrub typhus IgM RDT. The analyses reported that 94% of buffy coat samples and 100% of eschar samples were positive for *O. tsutsugamushi* by PCR, predominantly identifying Karp-like strains. This study demonstrates that the eschar remains the most reliable biological sample for PCR diagnosis of scrub typhus. Northwestern Thailand

has a significant diversity of *O. tsutsugamushi* strains, and this underlines the requirement for ongoing surveillance to increase understanding of its diversity and to ensure accurate diagnostics and treatment.

The fifth and final paper in this Research Topic, “*Comprehensive review on the cardiac manifestation of Scrub Typhus*” provides an extensive review of this important topic (Sivasubramanian et al.). In endemic areas, pericarditis resulting from scrub typhus should be suspected in patients who present with fever, thrombocytopenia, and pericardial effusion. If not identified, it can lead to conditions such as cardiomegaly, pericardial effusion, and congestive heart failure. Heart failure often results from myocardial inflammation, particularly in individuals with pre-existing cardiac conditions. Myocarditis due to scrub typhus is relatively uncommon but presents a significant risk, with a mortality rate of up to 24%. Arrhythmias can occur from the involvement of the interventricular septum, coronary arteries, or cardiac valves, leading to various ECG abnormalities, including sinus arrhythmia, T wave alterations, and prolonged QTc intervals. Atrial fibrillation related to scrub typhus is linked to a 1.3-fold increase in mortality over three months. These cardiac issues are primarily evaluated using electrocardiography (ECG) and echocardiography, with serology being the primary diagnostic method for *O. tsutsugamushi*. The authors discuss diagnostic methods including Immunofluorescence Assay (IFA) test (100% sensitive), Weil Felix test, nested PCR, and ELISA. Treatment for cardiac complications typically involves a combination of doxycycline and azithromycin alongside guideline-directed management. The review emphasizes the importance of increased clinical awareness and timely treatment of scrub typhus and further directs the need for further research to understand better the mechanisms of cardiac involvement and more effective diagnostic tools and therapies.

This Research Topic is a collection of literature highlighting an emerging but neglected tropical disease, and its multifaceted

challenges, including the complex epidemiology, diverse clinical manifestations, and the need for improved diagnostics, therapeutics, and vaccines.

## Author contributions

PA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. SD: Conceptualization, Formal analysis, Investigation, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. JK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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