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Review Article

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The saga of scrub typhus with a note on the outbreaks in Mizoram

K. Lalchhandama

Department of Zoology, Pachhunga University College, Aizawl 796001, India

Scrub typhus is one the most important re-emerging infectious disease, and perhaps, the most important bacterial disease. Caused by Orientia tsutsugamushi, it is transmitted through the bite of mites belonging to the genus Leptotrombidium, in which the bacteria are obligate parasites. Though the mites are natural ectoparasites of rodents and other animals, in which there is no disease, opportunistic infection to humans gives rise to a serious disease. Known to Japanese physicians as tsutsugamushi (insect disease), human infection is caused by the larvae of trombiculid mites, the fact established by Mataro Nagayo and co-workers established in 1917. The pathogen was discovered by Naosuke Hayashi in 1920. In Mizoram, the disease has been rampant since 2011. This paper summarises available data on the prevalence of the infection in different districts base on collective information from various sources. Records between 2012 and 2018 show that over a thousand people had been infected and 35 people had died of the disease.

Key words: Scrub typhus; *Orientia tsutsugamushi*; *Leptotrombidium*; rodent; Mizoram.

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*For correspondence ✉:
chhandama@pucollege.edu.in

Contact us ✉:
sciencevision@outlook.com

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Introduction

Scrub typhus has become arguably the most important bacterial disease in the world. It is caused by Gram-negative rickettsial bacteria called *Orientia tsutsugamushi*. Just like Augustus De Morgan rhyme, "Big fleas have little fleas upon their backs to bite 'em, And little fleas have lesser fleas, and so, *ad infinitum*," the bacteria are obligate parasites of trombiculid mites, which are in turn ectoparasites of animals such as birds, rodents and other mammals. In this ladder of life history, they are happy-going parasite with no ill intentions; but when infected mites bite accidental hosts such as humans, severe infections occur. They attack endothelial cells in the periphery as well as in the brain, but it also can be found in professional phagocytes such as macrophages of the liver and spleen.[1] As a consequence, clinical manifestations are presented by febrile fever, headache, myalgia, lymphadenopathy, and skin rash. In cases of misdiagnosis and failure of treatment, systemic complications rapidly develop including septic shock, acute respiratory distress syndrome, acute renal failure, meningitis, myocarditis, gastrointestinal bleeding, and multi-organ dysfunctions.[2,3]

The bacteria are oval shaped and measure 1.2 -3.0 μm in length and 0.5-0.8 μm in width. Adaptation to obligate parasitism resulted in reduced genome to about 2.4–2.7 Mb, which as it stands

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is the most highly repeated bacterial genome sequenced. There are more than 30 antigenically different strains apart from the six important prototype serotypes – Gilliam, Karp, Kato, Shimokoshi, Kawasaki, and Kuroki.[4] They naturally infect trombiculid mites, of which *Leptotrombidium deliense* and *L. akamushi* are the two most important hosts. A continuum of transmission is maintained in the mite population, from adult to their eggs (transovarial transmission), and thence to larvae and adults (transstadial transmission).[1] The larvae, commonly referred to as chiggers, are the reservoirs and vectors as they are the only vertebrate-feeding stage. They normally feed on the extracellular body fluid of small mammals such as rodents; and wild rats of the species *Rattus* are the principal natural hosts. But the chiggers are opportunistic feeders and often attack birds and mammals, including humans.[5]

Clinical symptoms of scrub typhus are not specific, and are known to cause acute undifferentiated febrile illnesses, which are similar to those of malaria, leptospirosis, typhoid and dengue, making the infections difficult to diagnosed from the symptoms. For this confusion and difficulty in diagnosis, mortality at some point soared to 24%.[2] A dark, scab-like circle at the site of the chigger bite known as eschar is considered a valuable diagnostic clue,[6] but is not present or identifiable in most cases, and moreover, is by no means unique to scrub typhus – spotted fever and rickettsialpox also are indicated by eschar. Blood tests are also limited by non-specificity of the blood-bacteria (antibody-antigen) reaction, and sensitive immunological and molecular tests are expensive for mass diagnosis, particularly in endemic areas. For such problematic identification, the World Health Organization (WHO Recommended Surveillance Standards, 1999) had acknowledged that:

> "Scrub typhus is probably one of the most under-diagnosed and underreported febrile illnesses requiring hospitalization in the region. The absence of definitive signs and symptoms combined with a general dependence upon serological tests make the differentiation of scrub typhus from other common febrile diseases such as murine typhus, typhoid fever and leptospirosis quite difficult."[7]

Origin and Etymologies

Scrub typhus as a disease was known in 3rd century A.D. in China as indicated by legends and folktales. Japanese were more specific and familiar with the link between the infection and mites. They had given various names such as Nippon/Japanese river fever, akamushi (red mite) or kedani (hairy mite) disease of northern Japan, and most popularly as tsutsugamushi disease (Japanese *tsutsuga* means fever or harm or noxious, and *mushi* means bug or insect). Japanese physician Hakuju Hashimoto was the first to give a medical account of the disease from Niigita prefecture in 1810. He recorded the disease that he referred to as "*tsutsuga*" among the inhabitants of the banks of the upper tributaries of Shinano river.[8] The first report to the Western world was made by Theobald Adrian Palm, a physician of the Edinburgh Medical Missionary Society at Niigita, in 1878. He used the local name of the disease "*shima-mushi*", which he rendered in English as "island-insect disease".[9]

The name scrub typhus was given for the scrub vegetation of secondary growth in tropical regions as a result of clearing the primary forest where they (are believed to) originate. Coining the English name in 1929, William Fletcher, J. E. Lesslar and Raymond Lewthwaite at the Institute for Medical Research, Kuala Lumpur, F.M.S. Malaysia, wrote:

> The distribution of the K. form is very different from that of the W. form, which was later identified to be endemic typhus, it is essentially a disease of the open country and affects outdoor workers. It has a patchy distribution and outbreaks occur particularly in areas which, after being cleared of jungle, are allowed to grow up in weeds and scrub. For this reason, we propose the name scrub-typhus for the K. form of tropical typhus. Some of the cases of typhus-like diseases described in India are probably the same as

scrub-typhus.[10]

The agent of scrub typhus, *Orientia tsutsugamushi*, stands out among rickettisial or any other Gram-negative bacteria in having a cell wall that lacks lipophosphoglycan and peptidoglycan, which are otherwise hallmarks of bacteria. Its behavioural peculiarity caused much confusion as to its biological nature. It was first identified by Naosuke Hayashi at the Aichi Medical College, Nagoya, Japan, in 1920. Noticing peculiar "granular bodies" inside the red blood cells, lymphoid cells and in the blood plasma of infected patients, he concluded that these bodies were protozoans, the etiological agents of scrub typhus, remarking:

> I have reached the conclusion that the virus of the disease is the species of *Piroplasma* a protozoan in question. Among various species of *Piroplasma*, the cause of African cattle fever, *Thieleria parva*, (see Gonder, 1911), seems closely allied to the forms found in Tsutsugamushi disease, on account of morphological similarity, and of affinities for lymphocytes or endothelial cells... I consider the organism in Tsutsugamushi disease as a hitherto undescribed species, and at the suggestion of Dr. Henry B. Ward designate it as *Theileria tsutsugamushi*.[11]

Noting the major difference from protozoans, the name *Rickettsia orientalis* was introduced in 1930 by Mataro Nagayo and colleagues, who demonstrated the infection in the anterior chamber of the eye of the rabbit, and recognised the "virus" as member of the bacterial genus *Rickettsia*.[12,13] (*R. prowazekii* was the first rickettsial bacteria discovered, described by H. T. Ricketts and Russell M. Wilder in 1910. In 1916, Henrique da Rocha-Lima gave the name in honour of the pioneer Ricketts and his colleague Stanislaus Josef Mathias von Prowazek.[14,15]) Rinya Kawamüra and Yoso Imagawa inoculated the pathogen in the testicle of rabbits from which they confirmed the *Rickettsia*-like nature, and introduced the name *Rickettsia akamushi* in 1931. At the same time, Norio Ogata also gave the name *Rickettsia tsutsugamushi*, which he had identified in 1928 from experimental infection of rabbit testicle.[16] This name was accepted as a valid name for several decades. Akira Tamura and colleagues discovered novel properties of the scrub typhus bacterium such as thicker leaflet of the cell wall, peptidoglycan and lipopolysaccharide, such as muramic acid, glucosamine, hydroxy fatty acids, and 2-keto-3-deoxyoctonic acid. These features warrantee significant deviation from *Rickettsia* and designation of a novel genus. In 1995, they created *Orientia tsutsugamushi*,[17] crediting the geographical region and language of its original discovery.

The Mite Story

A systematic mite theory of the transmission of tsutsugamushi disease was formulated by Taichi Kitashima and Mikinosuke Miyajima in 1908.[18] In 1915, Hirst reported that the larval forms of trombiculid mites occurring in Japan are capable of transmitting Kedani or river fever. He reported the larvae of *Microtrombidium akamushi* present on the ears of field mice, thereby suggesting that mites carry and transmit the infection.[19] (French zoologist Émile Brumpt had described mite species in 1910 as *Trombidium akamushi* having seen only the larval specimens.) Back then the nature of the infectious agent was not yet resolved, and hence often referred to as either virus or protozoan of some sort. Miyajima and T. Okumura demonstrated the complete life cycle in 1917. They found that the larva is naturally attracted to field mice. They also experimentally infected Japanese monkey by letting the larval mites bite; and the monkeys developed severe symptoms of the infection. They named the mite as *Leptus Akamushi*.[18] In 1917, Mataro Nagayo and colleagues gave the first complete description of the developmental stages such as egg, nymph, larva, and adult; and noted that the larva is the carrier of tsutsugamushi disease in man. They observed that the nymph and adult do not bite humans or mammals.[20]

Hayashi successfully induced infection from human patients to guinea pigs in 1917. He observed granular bodies in the infected lymphoid

tissue.[21] That the larvae only feed they presume it was on blood once in each stage, and that adult also carried the "virus" indicating transtadial transmission in mites was reported by Nagay and co-workers in 1918.[22] Jūrō Hatori established in 1919 that the transmitter of the virus is a mite, apparently identical with the Japanese species, which he referref to as *Trombidiam* (*Trombicula*) *akamushi*. The natural hosts of this parasite include *Mus rattus rufescens* (common house rat of the island), *M. decamanus*, *M. musculus*,. agrarius, etc., and such insectivores as *Crocidura muschata*. He further established that mites acquire the virus in the adult stage and transfer it to their offspring and that the spread of the mites is chiefly due to the migration of their hosts, such as rodents, etc. But he failed to identify the pathogen.[23] By 1921, it was established that *T. akamushi* can parasitise a range of animals including, rats, mice, buffalos, dogs, cats, monkeys, and birds.[24] E. Walch described a new species of mite *Trombicula deliensis* in 1922 from Indonesia, as a vector for Japanese river fever.[25] In 1923, he demonstrated that out of several species of *Trombicula*, on three species, namely *T. pseudoakamushi*, *T. schüffneri* and *T. deliensis* do attack humans; and that *T. deliensis* was the principal carrier of the infection and that was found on rats.[26]

Rinya Kawamüra and Yoso Imagawa were the first to show that the *Rickettsia* "virus" are stored in the salivary glands of mites, and that mites feed on body (lymph) fluid as indicated by predilection of the pathogens in the lymph glands draining the area of the site of the primary sore or mite bite.[27] They were also the first to discover the *Rickettsia* bodies in the salivary glands of larval mites collected from infected field mice, thus establishing the facts beyond doubt that *Rickettsia* is the causative agent of tsutsugamushi and that mite larvae are the vectors.[28] Important discoveries made by Charles Nicolle (who won the Nobel Prize in Physiology or Medicine 1928 for his discovery of lice as the vectors of typhus) and his student Hélène Sparrow led to better understanding of the transmission of scrub typhus. In 1934, they reported that continuous infection could maintained from one rat to another, and symptoms never developed in rats; in contrast, inoculation in monkeys produced severe symptoms. The serum of some of the infected monkeys reacted to form agglutinins with *Proteus* OXK, but not OX19. Lice and fleas (*Xenopsylla cheopis*) fed on infected monkeys harboured viable "virus"; but only fleas could transmit during biting.[29]

Infestation in Mizoram

Now, I will try to make a collective report of scrub typhus cases in Mizoram through publicly available sources (**Table 1 and 2**). Fatal infections due to unspecified insect bite were known towards the end of the first millennium and beginning of the second millennium. The saga started with rumours and undescribed medical conditions. In 2011, senior physician Thangchungnunga wrote about deaths due to some unknown insect bite.[30,31] The same year, there was a clinical case at Champhai Hospital. A woman had severe attack of fever, and went to Champhai Hospital for diagnosis. The doctor there noted a dark scab on her body, but the doctor simply remarked that the birthmark – which most likely would have been an eschar – appeared to be growing, and dismissed the case as generic fever. Then, the fever struck with utmost severity and the patient fell unconscious. When she was taken to the MED-AIM Adventist Hospital, the vital signs were already gone. But with resuscitation, she was saved and survived the ordeal. As the case was discussed, it was retrospectively realised that at least 3 patients has similar conditions in the past, and at least 3 had died of similar conditions. It was then seriously suspected that scrub typhus was in Mizoram.[32]

The first medical records started in 2012 when the Health and Family Welfare Department, Government of Mizoram, launched the Integrated Disease Surveillance Programme. There is a vague reference of "Scrub typhus (The first clinical case report from Mizoram, India)" in 2011 at the 49th annual meeting of the Infectious Diseases Society of America (IDSA) in Boston, by George M. Varghese and Dilip Mathai

Table 1 | District-wise incidence of scrub typhus in Mizoram. Data compiled from various sources. Discrepancies (reports of IDSP are contradictory) are reconciled as far as possible.

District/Place	Incidence per year						
	2012	2013	2014	2015	2016	2017	2018
Aizawl East	98	28	85	35	0	81	0
West	112	54	49	23	0	0	0
Lunglei	0	47	38	3	0	0	162
Saiha	9	10	2	0	0	0	0
Champhai	20	26	4	0	41	0	0
Kolasib	6	0	0	0	0	0	0
Serchhip	4	3	0	0	0	0	0
Mamit	3	7	0	0	0	0	0
Lawngtlai	0	0	1	0	0	0	0
Referral Hospital	0	0	0	52	0	0	0
Total	252	175	179	113	41	81	162

Table 1 | Fatality cases due to scrub typhus in Mizoram compiled from various sources.

District/Place	Fatality cases per year						
	2012	2013	2014	2015	2016	2017	2018
Aizawl East	5	2	2	3	0	3	0
West	9	0	1	2	0	0	0
Lunglei	0	2	1	1	0	0	0
Saiha	0	0	0	0	0	0	0
Champhai	2	0	0	0	0	0	0
Kolasib	0	0	0	0	0	0	0
Serchhip	0	0	0	0	0	0	0
Mamit	0	0	0	0	0	1	0
Lawngtlai	0	0	0	0	0	0	0
Referral Hospital	0	0	0	1	0	0	0
Total	16	4	4	7	0	4	0

from the Christian Medical College, Vellore, Tamil Nadu. No such record is available with IDSA; although Varghese, Mathai and others did presented a paper "Scrub Typhus: Clinical and Laboratory Manifestations, Genetic Variability and Outcome" at CMC, but no mention of Mizoram.[33]) According to the 2017 official publication of the IDSP, there were 907 confirmed cases of scrub typhus in Mizoram between January 2012 and July 2017; with the total fatality amounting to 34.[34] Presenting slightly different epidemiology, IDSP entomologist Lalfakzuala Pautu stated that as of 2017, 985 people had scrub typhus, and 37 had died.[35] There were 252 cases in Mizoram in 2012. 16 of them died, out of which 14 were in Aizawl district and 2 were in Champhai district.[36]

In 2013, Vanlalrengpuia, Medical Officer at Khawbung, a village in Champhai district, encountered several febrile illnesses at the Primary Health Centre. He confirmed that 6 of them had scrub typhus.[37] It was then obvious that there was annual recurrence of the infection in Mizoram, and infection spread from one place to another. By 2015, record raised to 715 cases, with 31 fatality.[38] In 2016, there was an outbreak at Khawbung village in Champhai district, where 41 people were tested positive. Fortunately, all received medical treatment and survived.[39]

There was a huge commotion of infection in 2015 in Aizawl, the capital city of the state. Following the outbreak, 76 cases were examined at

Hunthar Veng in November. An investigative report of the IDSP Nodal Officer Lalmalsawma Pachuau declared that the it was not the case of scrub typhus, but a febrile inflammation due the bite of rove beetles, and that it was not lethal.[40] Although the false alarm was clinically proven, the media reports mentioned the causative as insect bite, which is factually not true. Rove beetles do not bite to induce inflammation. But they contain toxin called paederin. When they are accidentally brushed or crushed by humans, they excrete the toxin in their heamolymph. Paederin is an amide and is more potent than cobra venom.[41]

The first and only seroprevalence report was in 2017. The study conducted between October 2014 and November 2016 at Synod Hospital, Aizawl, revealed that out of 4081 human blood samples examined, 6.9% (n = 283) were positive in rapid-ICT test.[42]

Winter of 2017-2018 saw unprecedented outbreaks. Initial report indicated that outbreak started in December 2017 at Phullen village in Aizawl district, 47 people were infected claiming one person's life.[43] According to the official report on 5 January 2018, another 8 cases were diagnosed.[44] According to official IDSP news announcement, a total of 81 cases were rconfirmed at Phullen and surrounding villages such as Luangpawn, Thanglailung and Zawngin.[45,46]

Another wave of infection buffeted Lunglei district around the same time. Initial report claimed 33 cases with 3 mortalities at Haulawng village. Mass diagnosis by IDSP team confirmed additional 45 cases in January 2018.[47] According to Pachuau, infection was experienced in the village in early January. By the end of January, at least 161 people were infected at Haulawng and the neighbouring villages.[48] But according to Pautu, 162 cases were diagnosed in January 2018.[35]

Summing up the records, Lal Thanzara, Minister of Health and Family Welfare, reported at the Mizoram Legislative Assembly in March 2018 that 540 cases were confirmed during 2017-2018; 4 people died, 3 of them were from Aizawl district, and one from Mizoram-Tripura-Bangladesh border at Mamit district. He said that were found to be infected with the scrub typhus.[49] The infection was indiscriminate; R. Lalzirliana, Minister of Home Affairs, was diagnosed with scrub typhus at Aizawl Civil Hospital in January 2018.[50]

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