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Rickettsiosis as a critical emerging infectious disease in India

K. Lalchhandama

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

Gram-negative bacteria belonging to the order Rickettsiales such as *Anaplasma*, *Ehrlichia*, *Neorickettsia*, *Rickettsia*, and *Orientia* are the causative agents of infectious diseases collectively known as rickettsioses. Of the different rickettsial diseases, spotted fever and scrub typhus have ravaged India for the past couple of centuries. Specifically called the Indian tick typhus, spotted fever was discovered in India in the latter half of the 19th century. After several decades of dormancy, the disease re-emerged in several parts of India. Scrub typhus, originally discovered in Japan, has been recognised to be endemic to a so-called Tsutsugamushi Triangle, extending from Russian Far East and Korea in the north to northern Australia in the south and Afghanistan in the west, but the geographical description has now been breached. Not only in India, scrub typhus has emerged as the leading infectious disease in all endemic areas. Almost all Indian states have records of recurrent outbreaks. Infection can be of dire consequences, as multi-organ dysfunction and neurological disorder (meningocephalitis) are the common complications. This article discusses the historical background and scientific reports of rickettsioses in India.

Key words: Rickettsiosis; typhus; spotted fever; scrub typhus; India.

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

Contact us ✉:
sciencevision@outlook.com

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Introduction

Rickettsiosis is a group of infectious diseases caused by Gram-negative bacteria belonging to the order *Rickettsiales*. Species of *Anaplasma*, *Ehrlichia*, *Neorickettsia*, *Rickettsia*, and *Orientia* are responsible for the disease.[1] They 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. Because of lack of diagnosis or misdiagnosis, mortality at some point soared to 24%.[2] Human ehrlichiosisis is also tickborne caused by at least three different species including *Ehrlichia chaffeensis*, *E. ewingii*, and *E. muris*-like. *Neorickettsia sennetsu* is a trematode-borne bacterium that cause sennetsu ehrlichiosis in humans. Members of the family Rickettsiaceae, *Rickettsia* and *Orientia* are broadly classified into spotted fever and typhus groups. Typhus fever is further divided into murine (or endemic) typhus, epidemic typhus, and scrub typhus. Scrub typhus is transmitted by larval mites, murine typhus by fleas, and epidemic typhus by lice. They are named typhus because of the hallmark symptom, which is a cloudy sensorium with severe illness; the Greek word "*typhos*" meaning fever with stupor or delirium. General symptoms of the spotted fever and typhus groups are acute febrile fever, headache, arthralgia (joint pain), myalgia (muscle pain), rash, and regional lymphadenitis (lymph node

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inflammation).[3] Clinical diagnosis is notoriously difficult as they produce non-specific fever, and-the hallmark diagnostic clue in spotted fever and scrub typhus, the presence of a dark scab (*tache noire*) called eschar on the skin, is absent in most of the cases.[4]

Spotting an Indian Fever

Spotted fever is caused by about sixteen species of *Rickettsia* in ticks and mites. The most well-known are Rocky Mountain spotted fever caused by *Rickettsia rickettsii*, boutonneuse fever or Indian tick typhus or Mediterranean spotted fever caused by *R. conorii*, North Asian tick typhus caused by *R. sibirica*, Queensland tick typhus caused by *R. australis*, rickettsialpox caused by *R. akari*, and Oriental spotted fever caused by *R. japonica*. Murine typhus is caused by *R. typhi*, also a flea (*Xenopsylla cheopis*) bacteria. *R. felis* is considered as member of the transitional group between the spotted fever and typhus groups.[5] Epidemic typhus and scrub typhus are historically and infamously recognised as wartime diseases. Epidemic typhus is caused by *R. prowazekii*, which is transmitted by body louse (*Pediculus humanus*). It is the only non-zoonotic and strictly human or demic rickettsial disease, being infected from lice to humans. At the aftermath of World War I, up to 1922, there were staggering 30 million cases in Russia, with death toll of 3 million. According to official record, there were half a million (0.427) cases during World War II in the West, which clearly is underreported.[6] In the East, comparable scourge was inflicted by scrub typhus. Mortality at one time was as high as 33.5% among American soldiers stationed at the Dutch New Guinea—and no Japanese was there to fight.[7] Described as an "unavoidable disaster", the Assam-Burma campaign at the height of the war in 1943 had a casualty ratio of disease (apparently mostly of scrub typhus) to battle as 121 to 1;[8] and mortality rate was noted as 40-45%.[9]

The most common rickettsioses in India, spotted fever and scrub typhus are re-emerging. There are two isolated cases of unusual rickettsioses in India. Two cases of rickettsial pox were identified in Tamil Nadu during 2003-2004.[10] An isolated case of Rocky Mountain spotted fever was also reported from New Delhi in 2017.[11]

The tick and the typhus

Spotted fever in India, specifically called Indian tick typhus is caused by *R. conorii*. British physicians had much trouble in India under the British Empire in the 19th century trying to solve the enigma of fevers and plagues, such as typhoid (enteric) fever, malaria, plague (bubonic and pneumonic). Most leading physicians then concurred that typhus did not exist in India. But, unusual symptoms of infection were defined differing from the known febrile diseases in details. William Walker recorded peculiar typhus-like disease at the Central Prison at Agra in 1961.[12] But his report failed to convince anyone. Soorjo Coomar Goodeve Chuckerbutty was confident that 12 patients he treated in Calcutta (now Kolkata) in 1864 were cases of typhus.[13] In 1871, John Ince made a series of reports on the epidemic diseases in Rawalpindi Jail in Punjab, and the last one mentioned the occurrence of typhus.[14] A bit of discrete biology was required for complete validation, which had to wait the next half a century.

Sir John W. D. Megaw reported in 1917 of his own infection in Kumaon district (now in Uttarakhand) in 1916. "On 1 July," reporting in second person, he said, "he found a tick firmly fastened on the skin of the neck." He started developing fever on the 20th day. He suggested that:[15]

- The disease was due "an invisible virus" transmitted by a tick bite.
- The tick species could be *Rhipicephalus sanguineus* or *Byalloma cegypticum*.
- Clinical symptoms and tests ruled out malaria, typhoid, and dengue, which would show similar fever.
- Comparing with an unpublished medical record from the same region in 1913, the symptoms indicate those of typhus (specifically epidemic typhus, or Brill's disease, as it was known).

- Since the environment was not conducive to lice that cause epidemic typhus, it could be a typhus closely related to but not Rocky Mountain spotted fever.

He made more elaborate analysis in 1921, and suggested a name "tick typhus" for the disease but with a question mark.[16] Convinced that the evidences were compelling enough in 1925, he advocated the name "tick typhus" to distinguish it from other typhus diseases; thus was born the name "Indian tick typhus".[17] The tick vector was identified in 1950 by Cornelius B. Philip and co-workers when they isolated the typhus bacterium from the brown dog tick *R. sanguineus*.[18] (*R. sanguineus* as a conveyor of Mediterranean spotted fever was established in 1933 in Kenya.[19]) Megaw's naming of the Indian tick typhus was fully justified.

The disease subsided but was suspected to have re-emerged in the 1970s in southern India.[20] Sudden increase in clinical cases among residents and travellers were documented in the new millennium.[21] In 2006, a new strain named *Candidatus Rickettsia kellyi* was discovered.[22] Further studies during 2006-2008 confirmed 58 cases using molecular detection.[23] In 2009, 52 (69.3%) cases of spotted fever and 23 (30.7%) scrub typhus were recorded.[24] 14 cases were diagnosed at the Christian Medical College in Tamil Nadu during 2003-2004.[10]

The Japanese Fever with a Terror

Of all the typhus and related febrile fevers, scrub typhus has become the most important re-emerging disease in India, and the world. The World Health Organization had conceded that "Scrub typhus is probably one of the most underdiagnosed and underreported febrile illnesses requiring hospitalization in the region."[25] First described in Japan in 1878 by Theobald A. Palm,[26] and popularly known as tsutsugamushi disease (Japanese word *tsutsuga* means fever or harm or noxious, and *mushi* means bug or insect), is due to infection with the bacterium *Orientia tsutsugamushi*. The name scrub typhus was given for the scrub vegetation of secondary growth in tropical regions as a result of clearing the primary forest.[27] It is endemic to a part of the world known as the "Tsutsugamushi Triangle" which extends from Northern Japan and Far-Eastern Russia in the North, to Northern Australia in the South, and to Pakistan and Afghanistan in the West.[2]

The bacterium with a distinction

O. tsutsugamushi stands out among rickettsial or any other Gram-negative bacteria in having a cell wall that lacks lipophosphoglycan and peptidoglycan, which are otherwise characteristics of bacteria. Its peculiarity caused much confusion as to its biological nature. It was first identified by Naosuke Hayashi in 1920, who named it *Theileria tsutsugamushi*.[28] A new name *Rickettsia orientalis* was introduced in 1930 by Mataro Nagayo and colleagues.[2930] In 1931, Norio Ogata gave the name *Rickettsia tsutsugamushi*,[31] while Rinya Kawamüra and Yoso Imagawa independently introduced the name *Rickettsia akamushi*.[32] Based on the unique morphological and biochemical properties, Akira Tamura and colleagues reclassified and renamed it to its final resting name *Orientia tsutsugamushi* in 1995.[33] Adaptation to obligate intracellular parasitism in insects resulted in reduced genome of about 2.4-2.7 Mb, which is the most highly repeated bacterial genome sequenced so far. There are more than 30 antigenically different strains apart from the six important prototype serotypes – Gilliam, Karp, Kato, Shimokoshi, Kawasaki, and Kuroki.[34]

Of the different species of trombiculid mite, *Leptotrombidium deliense* and *L. akamushi* are the two most important vectors of *O. tsutsugamushi*. The third-stage larvae, commonly referred to as chiggers, are the reservoirs and vectors, and when they bite humans, humans become accidental hosts—but upon whom the gravest maladies are bequeathed. Wild rats of the genus *Rattus* are the principal natural hosts; however, there is no host specificity as chiggers are opportunistic feeders on a wide range of mammals.[9] Bacterial transmission is maintained exclusively within the mite population: infected mites pass the bacteria on to their eggs in a process called transovarial transmission; and the infection is

passed on from the egg to the larva or adult in a process called transstadial transmission.[35] Hence, any infection in humans, the bacteria meet a dead-end in their life history.

Scrub typhus is a perilously complex and dangerous infection. It is responsible for nearly a quarter of all the febrile episodes in endemic areas. Even though the infection can be effectively cured with antibiotics, mortality in severe case or with improper treatment or misdiagnosis may be as high as 30-70%. The associated pathological complication involving multiple organ failure and neurological impairment are difficult to treat, and can be lifelong debilitation or directly fatal.[36] Manifestation of the central nervous system is complicated by cerebellitis, cranial nerve palsies, plexopathy, transverse myelitis, neuroleptic malignant syndrome and Guillan-Barré syndrome.[37] One of the alarming revelations in recent time is that scrub typhus is the major cause of acute encephalitis syndrome in India, where viral infection Japanese encephalitis has been attributed to as the main factor.[38]

Epidemiology

Although scrub typhus is historically endemic to the Asia-Pacific region the Russian Far East and Korea in the north to northern Australia in the south and Afghanistan in the west, including islands of the western Pacific Oceans such as Japan, Taiwan, Philippines, Papua New Guinea, Indonesia, Sri Lanka, and the Indian Subcontinent (the Tsutsugamushi Triangle),[2] it has spread to Africa, Europe and South America.[39] One billion people are estimated to be at risk of infection at any moment and an average of one million cases occur every year in the endemic Asia-Pacific region. In the absence of proper medical care, the case fatality rate can go beyond 30% to as high as 70% in some areas.[40] The burden of scrub typhus in rural areas of Asia is huge, accounting for up to 20% of febrile sickness in hospital, and sero-prevalence over 50% of the population.[41]

India has a rather bleak history with scrub typhus epidemics during the last century. The first case report of scrub typhus in India was in 1934 in Himachal Pradesh.[34] There were massive outbreaks in Assam and West Bengal during World War II, and Indo-Pak war in the 1965 and 1971. An outbreak in Jamshedpur, Bihar (now in Jharkhand) resulted in 912 cases between 1947 and 1950. [42] It was an endemic disease in many parts of India in the 1960s and 1970s. However, due to widespread use of insecticidal in the later years, with the empiric use of novel antibiotics such as tetracyclines and chloramphenicol for the treatment of febrile illnesses and common bacterial infections, the disease was suppressed to a long pause. For a moment, it was thought to have been eradicated; but resurgence of rapid epidemics emerged at the turn of the new millennium.

After two decades of hiatus, eleven soldiers in a unit of an army deployed at the Pakistan border of India were diagnosed with the disease in 1990.[43] In 1993, there were six cases from the eastern and two cases from the northern sectors.[44] From thence, it has become the most common re-emerging rickettsial infection in India. It spread all over the country, and outbreaks have been reported in several states - Delhi, Haryana, Jammu and Kashmir, Himachal Pradesh, Uttarakhand, West Bengal, Assam, Maharashtra, Kerala and Tamil Nadu.[45]

Integrated Disease Surveillance Project, which reports disease outbreaks throughout India, shows that during 2005-2013, yearly an outbreak was reported from Nagaland (2005), Manipur (2006), Uttarakhand (2008), Meghalaya (2009), and Assam (2010). Thereafter, the number of outbreaks reported increased to 4; 1 each in Himachal Pradesh, Karnataka, Nagaland and Uttarakhand (2011), which increased to 9, 1 each in Arunachal Pradesh, Himachal Pradesh, and Uttarakhand, and 2 each in Tamil Nadu, Rajasthan and West Bengal (2012), which dropped to 5-1 in Andhra Pradesh, 2 each in Odisha, and West Bengal. 2013 saw a significant decline, there were 1 outbreak each in Arunachal Pradesh, Karnataka, Manipur and Rajasthan. There were also 4 outbreaks in 2014, 1 each in Manipur, Meghalaya, Nagaland, and Arunachal Pradesh. There was doubling incidence in 2015, 1 each in Arunachal Pradesh, Meghalaya, Rajasthan and Tamil

Nadu, and 2 each in Assam and Maharashtra. In 2016 1 Tamil Nadu, 2 Rajasthan.[46] 2017 1 in Tamil Nadu, 1 in Nagaland, 1 in Mizoram.[47] It is important to note that in the absence of outbreaks, sporadic clinical cases prevail.[4849]

Heavy outbreaks have clouded South India. Between 2006 and 2008, 50 cases of scrub typhus were diagnosed at Pondicherry Institute of Medical Sciences.[50] In 2009, 29 cases were confirmed at Kasturba Medical College at Manipal in Karnataka.[51] From January 2009 to December 2010, 259 patients were recorded as having the disease, and the associated acute kidney injury was fatal in 2 patients.[52] There were 53 confirmed cases in children during 2010-2011, and one of them died.[53] 28 cases were reported in 2012-2013 winter months.[54] 65 cases were recorded during 2011 -2012 in Pondicherry, with 17 of them having meningitis/meningoencephalitis.[34] Clinical record at Sri Manakula Vinayagar Medical College & Hospital from November 2014 through March 2015 indicated 117 children having the infection.[55] 44 cases were diagnosed from January 2013 to December 2014 around Chinaoutpalli. Mortality rate was 4.5%.[56] Among the least likely places, Uttarakhand had 9 positive cases in 2010.[57] At the Himalayan Institute of Medical Sciences, SRH University in Dehradun, 284 patients were diagnosed between 2012 and 2013, out of which 24 died.[58] 96 children were reported in 2017.[59]

37 patients were retrospectively confirmed in Tamil Nadu between 1996 and 1998.[60] An outbreak between October 2001 and February 2002 resulted in 10.7% mortality at the Christian Medical College in Vellore.[61] 5 pregnant women were diagnosed between October 2001 and February 2002, three had stillbirths, one an abortion and one a low birthweight baby.[62] Between 2002 and 2003, about 50% (18) of patients with undiagnosed febrile fevers were found to be due to scrub typhus.[63] From November 2003 to November 2004, serological test among children showed that 27 (62.8%) had scrub typhus, 14 (32.6%) had spotted fever and 2 (4.7%) had murine typhus.[10] From January 2004 to December, 204 case were diagnosed with scrub typhus, while 44 people had spotted fever or other rickettsial diseases.[64] 154 patients admitted to the hospital between August 2009 and October 2010 were confirmed with fatality rate of 7.8%.[65] In 2010-2011, 67 children were diagnosed with scrub typhus, with mortality rate of 11.94%.[66] In 2010, the Christian Medical College reported a high mortality rate of 12.2% due to scrub typhus.[67] From 2005 to 2010, there were 623 cases of scrub typhus, with an annual fatality case of 9%.[68] 189 patients between 2005 and 2011 had meningitis/meningoencephalitis due to scrub typhus, and 11 of them died.[69] A report in 2017 indicated that 427 children were diagnosed at Christian Medical College.[70]

Between October 2010 and March 2011, 67 children were diagnosed with scrub typhus in Chennai, with an overall mortality rate of 11.94%.[71] In 2014, 6 (30%) patients with acute encephalitis syndrome in Apollo Main Hospitals, Chennai, were due to scrub infection.[72] 80 patients were diagnosed at General Hospital Thiruvananthapuram between June 2014 and May 2015.[73] 60 people had scrub typhus during 2014 to 2015 at Tirumala Hospital in Vizianagaram, Andhra Pradesh, out of which 2 patients died.[74] Out of 57 patients with meningitis, 28 had scrub typhus at the Malabar Institute of Medical Sciences in Calicut.[75]

There was a dramatic outbreak in northern India as well. Only in three months from October to December 2002, 42 people in Jaipur were diagnosed positive and before that 7 patients already died.[76] 12 cases were diagnosed in 2002 at Military Hospital in Namkum, Jammu.[77] 3 cases of scrub typhus and one case of Indian tick typhus were reported from Haryana in 2009.[78] 49 patients were tested positive for scrub typhus.[79] Scrub typhus (48.2%), spotted fever (27.5%), and typhus (6.8%) were detected during 2005-2009.[80] Between 2013 and 2015 33 cases were confirmed.[81] During the dengue outbreak in 2015, 6 positive cases of scrub typhus were identified at PGIMER and Dr Ram Manohar Lohia Hospital.[82] A report from Christian Medical College & Hospital in Ludhiana, Punjab, showed 62 cases, with 3 deaths due to multiple organ failure.[83] A report in 2015 from Sanjay Gandhi Postgraduate Institute of Medical Science in Lucknow, Uttar

Pradesh, indicated 37 cases of the disease, with two-third of the total cases associated with meningoencephalitis/encephalopathy.[84]

During 2009-2010, 15 cases were found in Goa, and 5 died during medical treatment.[85] The district of Darjeeling is historically considered as one of the scrub typhus-endemic areas in the 1960s. In 2000, several suspected cases died. In 2005, 62 cases were confirmed.[86] Regular outbreaks of scrub typhus have been reported in in Kurseong, Mirik (Darjeeling district), in 2010, 2011, and 2012. In 2017, five cases were reported from South 24 Parganas and Kolkata.[3] There was a heavy outbreak in Himachal Pradesh in 2003 with 113 confirmed cases and 19 deaths.[87] From 2012 to 2015, 97 cases were recorded among children at Institute of Child Health in Kolkata.[88] Serological survey in Bihar during 2015-2016, 33.3% (180) positivity.[38]

In 2003, 46% (45 out of 96) were diagnosed at the Indira Gandhi Medical College in Shimla, and 15 died before proper diagnosis.[89] During 2004 to 2006, 27 cases were detected.[90] Among 204 blood samples collected in 2004, 2008, and 2009, 63 were confirmed with scrub typhus.[91] 81 confirmed cases, 6 of them with meningoencephalitis and multiple organ dysfunction syndrome were also reported.[92]

Northeast India has been afflicted recently. From 2009 to 2010, 42 confirmed patients were treated at the North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS) in Shillong, Meghalaya.[93] There were 23 cases with meningitis between October 2009 and November 2011.[94] 90 cases were diagnosed in 2011-2012.[95] 61 patients were diagnosed in 2014, with mortality rate of 8.47%.[96] During 2010–2011, 108 patients were diagnosed at the Tezpur Christian Hospital, Assam and Mon District Hospital, Nagaland.[97] Record from March 2014 to February 2016 indicated 802 suspected cases out of which 124 (15.46 %) were tested positive at Assam Medical College & Hospital in Dibrugarh between 2014 and 2016.[98] During an outbreak in Manipur in 2007, 38 patients were tested positive.[99] During 2013-2014, 53 (36.6%) from Nagaland, and 80 (53.33%) from Meghalaya were tested positive.[100] Sero-prevalence in seven districts of Arunachal Pradesh was 40% (120/300).[101]

In Mizoram, there has been recurrent outbreaks every year since 2012. More than 900 cases have been confirmed since then. Serological tests were conducted from October 2014 to December 2016 from patients with undifferentiated fever from different parts of Mizoram admitted to the Synod Hospital, Aizawl. A total of 4081 sera were examined of which 6.9% (n=283) using rapid immunochromatographic test. Seasonal fluctuation was noted; 13.5% (154/1141) in winter (November–February), 10.9% (141/1287) in autumn (September–October), 4.8% in summer, and 5.5% in spring.[102]

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