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THE EPIDEMIOLOGY OF SCRUB TYPHUS ALL OVER THE WORLD: A SYSTEMATIC LITERATURE REVIEW

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author PYP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors YPC and LX managed the analyses of the study. Authors YJZ and BSY managed the literature searches. All authors read and approved the final manuscript.

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Systematic Review

ABSTRACT

Scrub typhus, a bacterial infection caused by *Orientia tsutsugamushi*, is cumulatively recognized as an important cause of pyrexia in Asia, with an estimated one million infections occurring per year. Scrub typhus is a natural focus disease transmitted to humans after being bitten by chigger mites and its host were mainly rodents especially rats. It has a great influence on the combat effectiveness of the armed forces and had caused a large number of non-combat attrition in the past. It is considered an emerging or re-emerging disease in several countries. There are no authorized vaccines, or vector control efforts in place. As a neglected disease, there is still a large gap in our knowledge of this disease, as evidenced by the sporadic epidemiologic data and other related public health information regarding scrub typhus in its endemic areas. Our objective is to provide a comprehensive review of current epidemiology of the disease all over the world to attract great attention of the governments.

Keywords: Scrub typhus; *Orientia tsutsugamushi*; epidemiology; all over the world.

1. INTRODUCTION

Tsutsugamushi disease, also called scrub typhus, or, more accurately, chigger-borne rickettsiosis is an acute, febrile, infectious disease among humans that is caused by infection with the bacterium *Orientia tsutsugamushi* by the bite of infected mite vectors [1, 2]. Tsutsugamushi disease was later called scrub typhus because humans often acquired the disease following exposure to areas with scrub vegetation [3, 4]. *O. tsutsugamushi* is transmitted to mammalian hosts including humans by the larval stage of chigger mites and the major vector mites is the *Leptotrombidium* species [5]. Mites act as the main reservoirs for *O. tsutsugamushi*. They remain infected through their life cycle (egg, larva, nymph and adult) [6].

During the World War II, scrub typhus was associated with a higher case fatality ratio than any other infectious disease in the China-Burma-India theatre of operations [7, 8]. The clinical manifestations of tsutsugamushi disease can range from unapparent or atypical febrile disease to life-threatening symptoms

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including lymphadenectasis, acute hearing loss, eschar and multiple organ failure [9, 10]. Fever and headache are the most common features among scrub typhus patients and the presence of eschars is considered pathognomonic [11]. To date, there is still no effective and reliable human licensed vaccine for scrub typhus and no point-of-care diagnostics available [8]. In the lack of effective human vaccines and convenient and quick diagnostic methods, scrub typhus poses a significant threat to public health [8, 12].

The traditional endemic region of scrub typhus is known as the "tsutsugamushi triangle" [13]. It is a region covering more than 8 million km^2, from the Russian Far East in the north, to Pakistan in the west, Australia in the south, and the Japan in the east [14, 15]. The vector of scrub typhus is present in most countries of the South-East Asia region and it is endemic in certain geographical regions of India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka and Thailand.

It is estimated that there are currently more than 1 billion people living in scrub typhus endemic areas, and the incidence has begun to increase over the last decade [16]. The incidence of scrub typhus has showed an upward trend, and the geographical distribution has also expanded since 1980s, which has attracted global attention [17]. And in recent years scrub typhus has struck back impacting regions with previously known endemicity as also expanding epidemic areas [18]. Despite increasing awareness in endemic regions, global distribution and epidemiology of scrub typhus remains poorly known. There are only sporadic epidemiological data reported regarding scrub typhus in the endemic areas, as well as other parts of the world, resulting in a current gap in knowledge. Therefore, we searched systematically for available information in medical database on scrub typhus, mainly in the Google Scholar and PubMed databases to provide the most comprehensive review of current epidemiology of the disease all over the world to attract great attention of the governments, and then to reduce the disease burden globally.

2. MATERIALS AND METHODS

Literature was searched in the Google Scholar and PubMed databases. All published papers regardless of year of publication were included in the search. The following search terms were adopted: (scrub typhus or tsutsugamushi disease or *Orientia tsutsugamushi* or *Rickettsia tsutsugamushi* or *Orientia tsu* or Akamushi disease or mite typhus or Japanese river fever or tropical typhus) AND (case report or epidemiology or distribution). There was a total of 1123 records identified, and 682 records were screened after removal of duplicates. Titles and abstracts were used to assess the eligibility of each study. Journals in English language was included but those in other languages (Chinese, Japanese, Korean, Russian etc.) were excluded. Full details of reasons for article inclusion and exclusion are displayed in Fig. 1.

3. RESULTS

Scrub typhus is caused by *Orientia tsutsugamushi* and is transmitted to humans by an arthropod vector of the Trombiculidae family. The myriad of typical and atypical features poses a clinical conundrum. It is endemic to a part of the world known as 'the tsutsugamushi triangle'. River banks, grassy areas generally harbour scrub typhus infection. The majority of scrub typhus cases were reported in the "tsutsugamushi triangle" (Table 1).

3.1 Epidemiology in the Traditional "Tsutsugamushi Triangle" Regions of East Asia and Northeast Asia

China: In China, scrub typhus is historically significant and evidence of the disease has been found in writings from as early as 313 AD [2, 19]. Scrub typhus is a notifiable disease that must be reported to the China Center for Disease Control and Prevention in China. From 1952 to 1979, 400 ~1534 cases of tsutsugamushi disease were reported annually in mainland China, and then the number of cases showed an upward trend, reaching 2590 in 1988 [19]. There is no monitoring data from 1990 to 2005. The number of reported cases of tsutsugamushi disease increased rapidly from 2006 to 2016, increasing by 15.4 times within 11 years. China reported 22,558 cases (including suspected cases), with a reported incidence rate was 1.64/100,000 people in 2016 [20]. The reported incidence rates vary widely by area with the southern provinces more affected. Guangdong province saw an increase in reported annual minimum incidence from 0.4/100,000 to 3.6/100,000 people from 2006 to 2013 (more than eight-fold), whereas in 2012 the provinces of Laiwu and Guangzhou city had annual incidences of 5.5/100,000 and 9.9/100,000 people, respectively [21, 22, 23]. While the incidence of scrub typhus is increasing rapidly, the incidence area is also expanding. Before 1986, tsutsugamushi disease epidemic areas were only distributed in the south of Yangtze River, including provinces of Guangdong, Yunnan, Fujian and Zhejiang. Recent studies showed that the geographic distribution of the disease has expanded to northern China. It has existed in southern China for thousands of years [24]. To date, according to the latest monitoring data, tsutsugamushi disease has spread to all over China except Ningxia and Shanghai [20]. There are six vector mite species have been proven to be the main vectors of scrub typhus in China, and these are *Leptotrombidium deliense*, *L. scutellare*, *L. rubellum*, *L. kaohuense*, *L. insulare* and *L. jishoum* [25, 26, 27, 28]. May is usually the beginning of the scrub typhus season, and June and July are the peak months. The pattern correlates with the weather and life cycle of chigger mites [29].

Japan: Scrub typhus is a notifiable disease and must be reported to the National Epidemiological Surveillance of Infectious Diseases within 7 days of diagnosis by a physician in Japan. Studies of scrub typhus begin in Japan. In 1860, it was recorded that the disease was epidemic in the northeastern part of Honshu Island, Japan. The epidemic season was from April to May and vector mite was *Leptotrombidium akamushi* [30]. After World War II, cases of tsutsugamushi disease were discovered in various parts of Japan. A remarkable resurgence and a prominent outbreak occurred in 1976-1984 due to the growth of mite populations carrying *O. tsutsugamushi*. There was no explanation available for the increased number of chiggers within that years [31]. Data collected in 1998 show that 462 cases occurred throughout the year, 88% of which were serologically diagnosed, and the cases were distributed throughout Japan except Hokkaido and Ryukyu Islands. Seasonal differences in the occurrence of cases show that there were two peaks: a big large one in November and a small one in May. The large peak represents the cases in Kanto and Kyushu and a few cases in Tohoku-Hokuriku. The small peak represents mainly the cases in Tohoku-Hokuriku. Seventy-six percent of the patients were more than 51 years old, and 36% and 16% of the patients were engaged in farm work and forestry, respectively [32]. In contrast to China, in Japan, most cases were diagnosed in late spring through early summer in the northern part of the country, and in late summer through early winter in the southern part of the country [33].

Korea: Since six cases of scrub typhus occurred among United Nations Army soldiers in Korea between 1951 and 1953 [34, 35, 36], no cases had been reported for more than thirty years until sixty-four Korean cases of this disease were reported in 1985 [37]. The results of a nationwide seroepidemiological and microbiological survey between 1986 and 1993 demonstrated that the seropositive rate of *O. tsutsugamushi* among patients with acute febrile disease varied from 27.7 to 51% during these years [35]. Because of this result, scrub typhus became a reportable disease in Korea in 1994. Physicians must report all confirmed or suspected tsutsugamushi disease cases to both the local health bureau and the Korean Centers for Disease Control and Prevention. Subsequently, approximately 300 cases were reported annually, with a peak incidence

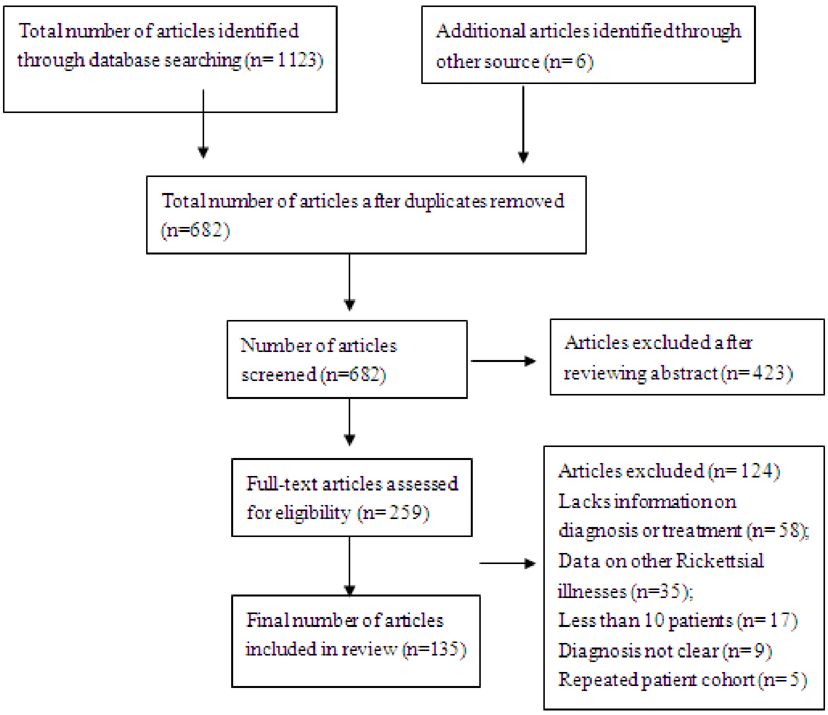

Fig. 1. Prisma flow chart showing the process of selecting articles for analysis

of 6,562 cases in 2005 and a plateau pattern thereafter [16, 38]. The incidence rapidly increased in 2012 -

2013, with 10,485 cases reported in 2013 [39]. In Korea, October and November are the peak months for scrub typhus cases [16, 39]. *Leptotrombidium pallidum* and *L. scutellare* are the main and virulent vectors of scrub typhus in Korea [40]. A study investigated the effects of deforestation on the incidence of scrub typhus in South Korea. The results suggested that districts with higher deforestation tended to have significantly higher incidence rates [41].

Russia: In the South Primorye region, Far East Russia, There were more than 40 human cases of tsutsugamushi disease were reported in the1960s. There were also reports from the Kamchatka Peninsula and kuril Islands in the 1970s [42]. Sera from rodents captured in the South Primorye region was detected by indirect immunofluorescence tests showed that the highest antibody titer was 1:160, suggesting that these rodents were infected much less often than rodents in Japan [43]. Since then, there have been no reports of tsutsugamushi disease.

3.2 Regions of Southeast Asia

Burma: The Burma campaign and the fighting on the Assam-Burma border caused an alarming increase in incidence reaching a climax with approximately 5,000 cases and 350 deaths occurred in the autumn of 1944. The serious outbreak of cases among troops in 1944 was the biggest outbreak ever recorded in history in Burma [44]. After that there was no report of scrub typhus in Burma.

Thailand: In Thailand, tsutsugamushi diseaes patients have been reported to the Bureau of Epidemiology, DDC, MoPH. A human case was first reported from the central region of Thailand in 1952 [45] and *O. tsutsugamushi* was first isolated from rodents captured from the same area in 1955 [46]. The primary vector of *O. tsutsugamushi* is *L. deliensis.* Moreover, several other mite species have been implicated as vectors such as *L. imphalum*, *L. Chiangraiensis*, and *Blankaartia acuscutellaris* [47]. There was a substantial rise in the number of confirmed cases from the 1980s to the 2000s in Thailand [48]. Data from the Bureau of Epidemiology presented a rise of annual minimum incidence from 6.0/100,000 in 2003 to 17.1/100,000 in 2013 (almost 3-fold) [49]. Sero-epidemiological studies nationally showed a high prevalence ranged from 13% to 31% of inhabitants in suburban Bangkok [50], to 59-77% of inhabitants of three villages in the northern and northeastern region, respectively [51]. The reason for the high incidence of scrub typhus is that the tropical climate of this country provides an ideal environment for the vectors of *O. tsutsugamushi*, *L. deliense* and *L. chiangraiensis* [8]. The burden of scrub typhus was estimated in Thailand. A total of 103,345 cases of scrub typhus were recorded from 2003 to 2018 in this study. The results indicated that the burden of scrub typhus in Thailand is high with disease incidence rising significantly over the last two decades [52].

Malaysia: The history of scrub typhus in Malaysia could be traced back to 1915 [53, 54, 55]. Scrub typhus has been reported as the most frequent infection among febrile hospitalized patients in rural areas of Malaysia since early 1970s [53, 56, 57]. Studies revealed that antibody prevalence to *O. tsutsugamushi* varied widely from as low as 0.8% in East Malaysia [58] to as high as 73% in West Malaysia [53]. Data collected from a serosurvey of febrile patients in rural areas of Malaysia gained a prevalence of 24.9% to *O. tsutsugamushi* [59]. Study indicated that in different aboriginal subgroups in west Malaysia the antibody prevalence to *O. tsutsugamushi* varied from 0 to 36.4% in seven subgroups, with high infection rates noted in subgroups engaged in agricultural production and the lowest infection rates noted in subgroups whose main careers were associated to fishing [59].

Vietnam: In Vietnam, the earliest reports of tsutsugamushi diseaes case records can be dated back to the 1960s during the Vietnam War [60, 61, 62, 63]. During this war by using a fourfold rise in indirect fluorescent antibody titer as criteria, the diagnosis of scrub typhus was confirmed in 109 patients among American soldiers and logistics personnel in southern part of Vietnam and the overall incidence rate was 50/100,000 [64]. Scrub typhus had been neglected in Vietnam since that time until the end of the last century and the beginning of 21st century, resulting in a gap in publications during that time [65]. However, after 2000, case reports of scrub typhus in Vietnam have been focused on the northern part and the central part, while there was no case reports on the southern part of this country. A serological test for *O. tsutsugamushi* of 579 hospitalized patients with acute undifferentiated fever in northern Vietnam from 2001 to 2013 found that 237 (40.9%) had scrub typhus among these patients [66]. Quang Nam province in the central part of Vietnam identified the main genotype showed that it was the Karp group [67]. Patients presented throughout the year, though incidence was highest in the summer months [68].

Laos: The Lao People’s Democratic Republic (Laos) is situated mostly east of the Mekong River and borders Thailand, Cambodia, Burma, China and Vietnam. Most of the population (88%) of 5.6 million people are rural rice farmers (2005 census from National Statistics Centre). As we all know, scrub typhus would be more common in rural areas. Therefore, scrub typhus is widespread in Laos. A study in 2010 in Vientiane of anti-scrub typhus IgG ELISA assays demonstrated the positive rate for IgG against *O. tsutsugamushi* was 20.3% [69]. Serologic analysis was conducted for fever patients (excluding malaria) in three hospitals in Vientiane, northern Luang Namtha and Savannakhet provinces to reveal that the positive rate for *O. tsutsugamushi* was 14.8%, 7% and 2.6%, respectively [70, 71, 72].

Cambodia: Twenty scrub typhus cases were reported in Cambodia in 1938. All the patients were male coolies engaged in clearing scrub in the forest regions and the cases occurred during the rainy season [73]. Indonesian peacekeepers in Cambodia provided a unique study population to estimate the threat of rickettsial exposure to *Orientia tsutsugamushi* (scrub typhus) for the region. Predeployment prevalence for antibodies to *O. tsutsugamushi* was 8% [74]. Molecular epidemiology of *O. tsutsugamushi* in Cambodia demonstrated that there was five genotypes [75].

Indonesia: Cases of scrub typhus in Indonesia can date back to 1902 in Deli and Sumatra. Indonesian military personnel stationed in Malang. Therefore, a seroepidemiologic survey involved civilian personnel was conducted in the Malang area. Examination of civilian blood samples disclosed that 1.3% of the study participants were seroreactive to *O. tsutsugamushi* [76]. Scrub typhus was a significant cause of illness and disability in the United States military in Papua during the World War II [77, 78]. Data collected from serologic test of fever inpatient in Papua Indonesia during 1997-2000 elucidated that positive serologic result for scrub typhus was 2.97% (7/236) [79].

Singapore: The risk of scrub typhus at Changi was first realized in March, 1953. sixteen scrub typhus cases were reported again at Changi in 1957 and the vector was *L. deliense* [80].

Philippines: The Philippines did not confirm the occurrence of tsutsugamushi disease until the Second World War. Cases of scrub typhus have occurred in troops during actions on the Islands of Leyte, Samar, Mindoro, Luzon, Negros and Mindanao. The case fatality rate was 4.5%. *L. deliensis* was taken from rats of all the above islands except Leyte and *Trombicula* (now *Leptotrombidium*) *akamushi* was identified from rats on Luzon and Negros, which made incontrovertible evidence of the presence of tsutsugamushi disease in the Philippine for the first time during military operations [81]. The first American tsutsugamushi disease vaccine was prepared from the spleens and lungs of white rats infected with Volner strain of *O. tsutsugamushi*, but it failed. The Volner strain was exactly isolated originally from the blood of a soldier in the Philippines [82].

3.3 South Asia, Western Asia and Central Asia

India: Tsutsugamushi disease was recognized as a typhus-like fever in India in 1917 [8, 83]. During the second World War and the 1965 Indo-Pak war, scrub typhus was a main cause of fever among military personnel along the Assam-India- Burma border [8, 84]. There was a resurgence of the disease in 1990 in a unit of an army deployed at the Pakistan border of India [85]. Serological and molecular detection has confirmed the reemergence of scrub typhus in the northeast region of India in 2010-2011[86]. A study determined the seroprevalence of scrub typhus in healthy Indian adults by measuring IgM and IgG antibodies to scrub typhus by ELISA in 100 healthy blood donors. The study demonstrated a 15% seroprevalence of scrub typhus in adults [87]. The peak season of the disease is from August to October. *L. deliense* is the primary vector mite species of *O. tsutsugamushi* [8, 88]. A total of 645 serum samples with suspected scrub typhus was tested by rapid immunochromatographic test and IgM ELISA. Scrub typhus was diagnosed in 13.7% of patients and majority of them were observed in August [89]. A 19-day-old newborn was diagnosed with scrub typhus infection with features suggestive of severe sepsis ruling out vertical transmission [90]. The epidemiology is showing an upward trend as is evidenced by increasing records and concomitant publications from India on scrub typhus in recent years. The various factors like global warming, urbanization and the population explosion will be responsible for resurgence and increase of this disease [91].

Maldives: Scrub typhus was first recorded by British troops in the Maldives during World War II. Following their arrival in 1941 on Gan Island, Addu Atoll, the Royal Marines suffered an outbreak of 42 cases. In 1942, the British had another 582 cases, 382 in 1943, 92 in 1944, and none in 1945 [92]. Since then there was no case reported between 1945 and 2001. In summer 2002, an outbreak of scrub typhus began in the Maldives. Through April 2003, officials recorded 168 cases with 10 deaths. The disease mainly focused on the Gaafu Dhaalu Atoll [93].

Bangladesh: A prospective seroepidemiologic survey across six major teaching hospitals in Bangladesh was conducted by using an IgM enzyme-linked immunosorbent assay. Results indicated that 23.7% (287 of 1,209) seropositive for *O. tsutsugamushi* [94]. Data collected from blood samples of febrile patients at six tertiary hospitals in Bangladesh from 2008 to 2009. In this study, out of 720 enrolled patients, 63 patients against scrub typhus fever [95].

Pakistan: About the middle of September 1961, a sudden outbreak of scrub typhus was reported among soldiers stationed in a village in the Sialkot district of West Pakistan [96]. The presence of scrub typhus infection in these unusual habitats and geographical areas in West Pakistan including the Kaghan Valley, the mountain deserts of Gilgit Agency, the semi-desert of Multan and the plains of Lahore District [97].

Nepal: A scrub typhus IgM ELISA was first developed in Nepal in 1979, when it was shown to have a similar sensitivity and specificity to the IFA (immunofluorescence antibody assay) [98]. A study was conducted to investigate the sero-epidemiology of scrub typhus in patients suffering from acute febrile illness in 2015. The results showed that 40.3% were positive for IgM antibodies to *O. tsutsugamushi* and the IgM antibodies to *O. tsutusugamushi* were positive in specimens of various geographical regions including 30 districts of Nepal [99]. There is increasing reports of outbreak of scrub typhus after the earthquake hit Nepal in 2015 [100]. In total, 84 children at Tribhuvan University Teaching Hospital in Nepal were found to have serologically confirmed scrub typhus [101].

Bhutan: In Bhutan, located within the tsutsugamushi triangle, scrub typhus was first identified as a cluster of pyrexia cases of unknown origin reporting to the Gedu hospital in the summer of 2008 [102]. Scrub typhus has been included in the national list of notifiable diseases since 2008 and reporting was initiated in 2010. Nevertheless, by lack of awareness among health-care workers, very few samples were received initially. The number of referred samples and the number of positive results increased thereafter. The test positivity ranged between 22% and 60% among the cases sampled [103, 104]. A survey about the outbreak of scrub typhus in a remote primary school in 2014. Delay in recognition and treatment has led to two deaths from meningoencephalitis [105].

Sri Lanka: Scrub typhus is a re-emerging infection in Sri Lanka [106, 107]. In 1976, the seropositive rate of patients in the hospital in Colombo, the capital of Sri Lanka, was <6% [108]. A survey in 2003 using a specific immunofluorescent technique in patients clinically diagnosed as ‘typhus fever’ in the Central Province of Sri Lanka found that there were 8 patients positive for *O. tsutsugamushi* antibodies [106]. The seropositivity rate of fever patients in hospitals from the western province of Sri Lanka was 66% in 2008 [107]. According to the above studies from 1976 to 2008, the epidemic area has covered the entire island of Sri Lanka. It often poses a diagnostic challenge and tends to present as a febrile illness of uncertain origin [109]. Because there was no specific information on the type vector of *O. tsutsugamushi*, transmission patterns or host factors are available for Sri Lanka. It would be related to ecological factors such as abundant rural scrub jungles, jungle grasses and wild rodent populations in Sri Lanka.

3.4 Western Asia and Central Asia

There were cases reported in Tajikistan in 1962. *O. tsutsugamushi* infection was confirmed in the serum of people in Iran in 1974. And cases have been reported in Afghanistan [19]. Since then, there have been no relevant scrub typhus case reported in these countries, and the prevalence of scrub typhus is still unclear.

Oceania: The presence of scrub typhus was reported on several occasions in Papua New Guinea, the Torres Strait Islands and across northern Australia, the Solomon Islands, northern Vanuatu and Palau.

Papua New Guinea: Within Oceania, the largest cluster of scrub typhus cases occurred in Papua New Guinea during World War II with 809 cases and 2840 cases confirmed from American troop and Australian troop respectively. A serological survey performed for evidence of rickettsial infection by measuring rickettsia-specific antibody levels in the blood of 191 non-randomly selected Papua New Guineans living in Port Moresby (n=93) and in the highland villages of Samberigi (n=98). All positive individuals (7/191) were residents of Port Moresby [110]. A medical investigation was carried out in April 2001 into an outbreak of a mysterious haemorrhagic disease and deaths in the remote picturesque Strickland River area of Papua New Guinea. Nine villages were visited and 140 persons were physically examined. Surprisingly, a number of the sera were positive for scrub typhus (*Orientia tsutsugamushi*) (28%) [111].

Australia: Scrub typhus has been recognized as being endemic to north Queensland since the 1920s [112]. In 1996, diagnosis of scrub typhus in a Queensland soldier led to recognition of an earlier outbreak with up to 17 cases. Another outbreak occurred a year later with 11 confirmed cases [113]. Foci of scrub typhus have recently been identified in Litchfield National Park, near Darwin, and in the Kimberley region of Western Australia [114]. In Australia, distribution of published scrub typhus cases and seropositivity appears to be restricted to areas receiving more than 1500 mm of precipitation annually. Because rainfall is an important limiting factor for this predominantly tropical disease [115, 116, 117]. However, in Litchfield National Park in northern Australia, cases of scrub typhus have occurred during the drier tourist season [116].

Solomon Islands: In the Solomon Islands, Anderson & Wing (1945) reported 49 scrub typhus cases in US troops. The survey of the eastern Solomon Islands in 1971-1972 found that the seropositive rate was 21%~82% [118]. An outbreak investigation was conducted to identify the etiology and risk factors of undifferentiated fever in a cluster of patients in western province, Solomon Islands, May 2014. The result showed that 9 cases met the outbreak case definition [119].

Vanuatu: Scrub typhus was widely reported in soldiers during World War II, and one case was reported in 1975 in Vanuatu. Human sera from Vanuatu were collected in 1973 and were localized only as coming from the Banks Island. Result revealed that thirteen of 72 sera were positive [118].

Palau: The first known outbreak of scrub typhus in Palau occurred in 2001 to 2003 among residents of the remote southwest islands [120]. To determine the extent of scrub typhus distribution in Palau, serum samples were tested from humans and rodents for antibodies to *O. tsutsugamushi*. In 2003, of 212 Palau residents surveyed, 101 (47.6%) had IgG antibody titers >1:64, and 56 (26.4%) had concurrent IgG and IgM antibody titers >1:512 and 1:64, respectively. In 1995, 34 (5.4%) had IgG antibody titers >1:64 among 635 banked serum samples collected from Palau residents [121].

Epidemiology outside the "tsutsugamushi triangle": Our literature review revealed that evidence of human or animal infection with scrub typhus has been found in the South America, Europe, Middle East and Africa outside the known the traditional "tsutsugamushi triangle" in the Asia-Pacific area. However, evidences of serological, molecular and genetic have been slowly accumulating for decades that we should no longer consider the tsutsugamushi triangle to be the only endemic region for scrub typhus [122, 123] (Table 2).

Table 1. Part of outbreaks of scrub typhus in the traditional "tsutsugamushi triangle" Regions

First Author	Country/Province /State	Outbreak Duration	Laboratory Confirmed or Suspected Cases
Li et al. [20]	China	2006-2016	97,775
Wei et al. [21]	Guangzhou, China	2006-2012	4001
Matsui et al. [33]	Japan	2000	756
Lee et al. [39]	South Korea	2001 -2013	70,914
Willcox [44]	Burma	1944-1946	5000
Wangrangsimakul et al. [52]	Thailand	2003-2018	103,345
Nadjm et al. [68]	Vietnam	2001-2003	251
Mayxay et al. [71]	Laos	2008-2010	122
Punjabi et al. [79]	Papua, Indonesia	1997-2000	15
Sinha et al. [84]	India	Oct.-Dec. 2012	42
Khan et al. [86]	India	2010–2011	314
Sengupta et al. [87]	India	Jan.2013	15
Lakshmi et al. [89]	south India	Jul.-Oct.2018	645
Lewis et al. [93]	Maldives	May 2002-Apr. 2003	168
Faruque et al. [95]	Bangladesh	Dec. 2008- Nov. 2009	63
Upadhyay et al. [99]	Nepal	Jul.- Nov. 2015	175
Thapa et al. [100]	Nepal	Jun.- Sep. 2016	410
Bajracharya [101]	Nepal	2015-2018	84
Tshokey et al. [103]	Bhutan	2009-2014	778
Marks et al. [119]	Solomon islands	May 2014	9
Durand et al. [120]	Palau	2001-2003	15
Demma et al. [121]	Palau	2003	101

South America: A case of scrub typhus-like illness was reported in Chile. A patient was bitten by several terrestrial leeches during a trip to Chiloé Island in southern Chile in 2006 [124]. PCR and IFA revealed diagnostic confirmation of *O. tsutsugamushi* infection. However, the molecular analysis further showed that the causative agent was closely related but not identical to other *O. tsutsugamushi* and *O. chuto* species. Experiment results reminded us that there might be other vectors, such as leeches, for *Orientia*

[124]. Three native cases were reported on the same island in 2016 [125]. The patients reported had not been bitten by leeches. however, all the patients reported the handling or collecting of firewood, which has previously been identified as a risk factor for chigger bites in Asia [126]. A study reported nine patients who had scrub typhus diagnosed after visiting different areas of continental Chile during 2016–2018 [127].

The presence of trombiculide mites in Peru has been reported in other areas, but this species has not been studied as a local vector for pathogens [128]. Using ELISA, IFA and PCR, A retrospective test of human blood specimens for scrub typhus group orientiae was conducted in Iquitos, Peru. Of 1,124 participants, 60 (5.3%) were seropositive, and 1 showed evidence of recent active infection. The serologic data indicated that scrub typhus was present in the Peruvian Amazon [129].

Europe: In order to generate a global picture of zoonotic *Orientia* bacteria that are likely to be harboured by rodents, a metagenomic approach was applied to use spleen samples of 1334 rodents from France, Senegal and Thailand. In France, *Orientia* sp. was detected in three rodent species: *Myodes glareolus* (44/302), *Arvicola scherman* (2/64) and *Microtus arvalis* (6/49). This finding had important implications for public health. Surveillance outside Asia, where the disease is not expected by sanitary services, needs to be improved [130].

Middle East: Formerly thought to be geographically restricted to Asia [8], *Orientia* was recently identified in sick patients from the Arabian Peninsula [15]. An Australian tourist returning from Dubai, in the United Arab Emirates, developed acute scrub typhus in 2006. An IFA, PCR and sequencing were used to determine the etiologic pathogen. The molecular variance of the 47-kDa gene, 56-kDa gene and other nucleotide sequences, and geographical difference led the researchers to believe that this organism should be considered a novel species named *Orientia chuto*. Before this case, there was only one known *Orientia* species, i.e., *O. tsutsugamushi* [14, 15].

Africa: Miscellaneous reports of scrub typhus-like illness have previously questioned the presence of the bacterium in the Kenya, Cameroon, Congo, Djibouti and Tanzania in Africa [131, 132, 133, 134]. Serum samples from patients in Kenya with febrile illnesses were screened for antibodies against bacteria that cause scrub typhus. Western blot was performed to confirm the specificity. Seroprevalence was 5% for scrub typhus group [131]. A male from the United States visited Cameroon before he subjected a febrile illness [132]. The patient's IFA titer to *O. tsutsugamushi* rised from 1:256 to more than 1:1,024 two weeks after admission. However, the Weil-Felix reaction and paraffin-embedded skin samples were negative. Several clinical features were not typical [132]. A patient who resided and was diagnosed in Japan visited Congo for 23 days, and noticed symptoms 8 days after he left Congo. The researcher contacted two local centers for disease control and found that no cases of tsutsugamushi disease. Taking into account the patient's area of residence and work, and his pattern of activities after returning to Japan, we therefore conclude that the patient contracted tsutsugamushi disease while he was staying in the Congo [134]. Of 49 workers at a Djiboutian abattoir, three were seropositive against orientiae. One worker seroconverted against orientiae during the study period. This is the first evidence of orientiae exposure in the horn of Africa [135]. The case was reported of a Dutch woman who contracted *Orientia tsutsugamushi* in Tanzania [133].

Table 2. Part of outbreaks of scrub typhus outside the "tsutsugamushi triangle"

First Author	Country/Province /State	Outbreak Duration	Laboratory Confirmed or Suspected Cases
Weitzel et al. [127]	Chile	2016-2018	37
Kocher et al. [129]	Peru	2013	60
Thiga et al. [131]	Kenya	2015	212
Horton et al. [135]	Djibouti	Sep. 2010	8

4. CONCLUSIONS

Results of this study show that scrub typhus outbreaks are being reported both within the known area of endemicity, as well as beyond the originally defined borders of the "Tsutsugamushi Triangle". More concerning is scrub typhus caused by *Orientia* species other than *O. tsutsugamushi* well beyond the limits of the tsutsugamushi triangle. It is not known whether the vectors of *O. tsutsugamushi* will be the same for the new *Orientia* species, and this should be a consideration during outbreak or surveillance investigations. In conclusion, we have comprehensively reviewed the epidemiology of scrub typhus all over the world to draw the government's attention to this neglected disease and take measure to control and prevent the wider outbreak.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this case report.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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