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Scrub typhus: Epidemiology, Diagnosis, Treatment, Prevention and Control in the Asia-Pacific Area and Worldwide

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Scrub typhus: Epidemiology, Diagnosis, Treatment, Prevention and Control in the Asia-Pacific Area and Worldwide

by

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Dedication

I would like to dedicate this capstone to my parents, my sister and my close friends for their continuous support and encouragement throughout the many years I have been in school.

Acknowledgements

The two years of MPH courses and training has taught me a lot. It did not only train me in basic public health concepts but also enables my critical thinking in basic biomedical sciences. I would like to extend my gratitude to my committee chair, Dr. Christine Arcari first for her support and guidance during the MPH study and Capstone work. I would also like to thank the other members of my committee, Dr. Peter Melby and Dr. Daniel Jupiter, throughout my study at UTMB. I would like to acknowledge Dr. Pennel for guiding me through the preparation of this Capstone and foundation of Public Health. Last but not least, I would like to give my special thanks to my PhD mentor, Dr. David Walker, co-mentor, Dr. Donald Bouyer, and colleague as well as good friend, Dr. Lucas Blanton for supporting my decision to join the MPH program. This would not be possible without your support.

Scrub typhus: Epidemiology, Diagnosis, Treatment, Prevention and Control in the Asia-Pacific Area and Worldwide

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The long term goal of this study is to develop effective measures to control and even eradicate scrub typhus and other related infectious diseases. Scrub typhus is a serious public health problem in the Asia-Pacific area. It threatens one billion people globally, and causes illness in one million people each year. It can cause severe multiorgan failure with a case fatality rate up to 30% without appropriate treatment. The antigenic heterogeneity of *Orientia tsutsugamushi* results in reinfection with scrub typhus. As a neglected disease, there is still a large gap in our knowledge of the disease, as evidenced by the sporadic epidemiology data and other related public health data regarding scrub typhus in its endemic areas. Our objective is to provide a systematic analysis of current epidemiology, diagnosis, treatment, prevention and control of scrub typhus in its endemic area and the rest of the world.

We first described the epidemiology of scrub typhus through a thorough review of the epidemiology and public health impacts of the disease. This specific

aim helps us understand the disease, and provides a foundation for disease prevention and control. We then described the diagnosis and treatment of scrub typhus, which will facilitate the development of the next generation of diagnostics and treatment. The last part of the capstone focused on the prevention and control of scrub typhus in the Asia-Pacific region, and worldwide. This analysis will aid in the control of the disease and promotion of public health.

This project helps better understand the epidemiology, diagnosis, treatment, and control of scrub typhus. It can aid in the identification of effective new approaches to prevent and control the endemic disease. The research also provides strategies that could be applicable to combat other infectious diseases and public health threats.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

AP	Asia-Pacific area
ARDS	acute respiratory distress syndrome
CDC	Centers for Disease Control and Prevention
DIC	disseminated intravascular coagulation
ELISA	enzyme-linked immunosorbent assay
ICT	immunochromatographic test
IFA	indirect immunofluorescence assay
IIP	indirect immunoperoxidase assay
PCR	polymerase chain reaction
PHA	passive hemagglutination assay
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
UAE	United Arab Emirates
W-F	Weil-Felix test
WHO	World Health Organization

Chapter 1 Introduction

Scrub typhus is a serious public health problem in the Asia-Pacific area including but not limited to Korea, Japan, China, Taiwan, India, Thailand, Sri Lanka, and the Philippines (Figure 1). It threatens one billion people globally, and causes illness in one million people each year (Kelly, Fuerst et al. 2009). Scrub typhus, also known as tsutsugamushi disease, is caused by the arthropod-borne gram-negative obligately intracellular bacillus *Orientia tsutsugamushi* (Cho, Jun et al. 2010; Valbuena and Walker 2013). After being bitten by an infected vector, a *Leptotrombidium* mite, patients begin to exhibit signs of infection such as fever, rash, and eschar, while complaining of non-specific flu-like symptoms approximately 5 to 14 days later. Severe complications such as multiorgan failure

Figure 1. Distribution of *Orientia* infection. Majority of scrub typhus cases happen in “tsutsugamushi triangle” in the Asia-Pacific area [Modified from http://worldmap.harvard.edu/]

occur in some cases. The severe multiorgan complications involve acute renal and hepatic failure, acute respiratory distress syndrome (ARDS), cardiomyopathy, encephalitis, disseminated intravascular coagulation (DIC), etc. (Chi, Huang et al. 1997; Deshpande, Mittal et al. 2015). The case fatality rate of scrub typhus can be up to 30% if no appropriate treatment is received (Varghese, Abraham et al. 2006). Therefore, development of effective measures to control, prevent and even eradicate the disease is a critical public health issue.

The antigenic heterogeneity of, reemergence of, and short-lived immunity to *Orientia* result in a substantial number of cases and reinfections. However, both the basic research and epidemiological study of *O. tsutsugamushi* have been largely neglected during recent decades (Lee, Cho et al. 2008; Cho, Cho et al. 2010; Ge and Rikihisa 2011). Preliminary studies demonstrated that the disease has existed in the endemic areas for some time (Berman and Kundin 1973; Ogawa, Hagiwara et al. 2002; Sinha, Gupta et al. 2014; Kwak, Kim et al. 2015; Yang, Liang et al. 2015). **There is only** sporadic epidemiological data available regarding scrub typhus in the endemic areas, as well as other parts of the world, resulting in **a current gap** in knowledge.

Specific Aims

The objective of this study is to provide a systematic analysis of current epidemiology, diagnosis, treatment, prevention and control of scrub typhus in the endemic area as well as the rest of the world. The **rationale** for this study is that a strong epidemiologic description of scrub typhus will inform the development of effective measures to control and even eradicate scrub typhus and other related infectious diseases. We will accomplish our objective by carrying out the following **specific aims**:

Specific Aim 1: Describe the epidemiology of scrub typhus.

Scrub typhus is a life-threatening disease endemic to the Asia-Pacific region (Kelly, Fuerst et al. 2009). There have been many case reports in the endemic area. However, there is still lack of comprehensive analyses of the epidemiology of scrub typhus. A thorough review of the epidemiology and public health impacts of scrub typhus will facilitate better understanding of the disease, and provide a foundation for prevention and control.

Specific Aim 2: Describe the diagnosis and treatment of scrub typhus.

The diagnosis of scrub typhus is difficult due to its undifferentiated flu like symptoms (Jung, Chon et al. 2014). The current treatments for scrub typhus also face new challenges, such as antibiotic resistance (Valbuena and Walker 2013; Yang, Liang et al. 2015). Antigenic variants and transient cross-protective immunity lead to reinfection, and make vaccine development extremely challenging. A comprehensive review of the current available diagnosis methods and treatments will help direct future research and public health efforts.

Specific Aim 3: Determine the prevention and control efforts of scrub typhus in the Asia-Pacific region and worldwide.

As an infectious disease with case fatality rate up to 30% and 1 billion people at risk, scrub typhus causes huge threats to the public health in its endemic area (Varghese, Abraham et al. 2006). Unfortunately, no effective vaccine has been developed. Doxycycline and a few other antibiotics are used to treat the disease, but antibiotic resistance has been noticed in recent decades (Valbuena and Walker 2013). An analysis and discussion of disease prevention and control efforts will benefit the promotion of public health not only in the endemic area but the rest of the world.

Chapter 2 Background of Scrub Typhus

History of Scrub Typhus

Scrub typhus, a severe arthropod-borne gram-negative bacterial infection, is also known as tsutsugamushi disease. The reason for naming the disease scrub typhus is that the vector resides on this type of vegetation, i.e., terrain between woods and clearings (Kuo, Huang et al. 2012). Tsutsuga is a Japanese word meaning disease, while mushi means mite in Japanese. As its name indicates, tsutsugamushi disease is endemic in the Asia-Pacific area extending from Japan, Korea and New Guinea to Afghanistan, from Russia to the north of Australia (Rapmund 1984; Valbuena and Walker 2013). Diseases with symptoms very similar to scrub typhus appeared as “恙” in ancient Chinese documents between 25 to 225 A.D., which means “stricken with grief” or “an insect sticking to the human beings” (Ito 1967). The disease was first reported as far back as at least the 16th century, and the Institute for Infectious Diseases in Tokyo, Japan began investigation of this disease in the early 1890s (Quintal 1996). The disease was first reported in the Western world in 1878 and 1879 (Palm 1878; Baelz 1879). Severe outbreaks of scrub typhus among American servicemen in the Asia-Pacific area during World War II made the Western World aware of this disease (Quintal 1996). Scrub typhus is a neglected disease but a robust public health response can result in prevention and control of the disease.

O. tsutsugamushi, the causative agent of scrub typhus, is a gram-negative obligately intracellular bacterium (Seong, Choi et al. 2001; Jeong, Kim et al. 2007). There are still many unknowns regarding the mechanisms of pathogenicity and the cell biology of this bacterium, due to the extra research obstacles of studying an obligately intracellular bacterium (Giengkam, Blakes et al. 2015). The pathogen was identified as a *Rickettsia* by a Japanese researcher, N. Ogata, in 1929 (Sasa 1967). The bacterium was named *Rickettsia tsutsugamushi* and *R. orientalis* by Nagayo et al. in 1930, and it was reclassified as a new genus of *Orientia* in 1995 (Nagayo, Tamiya et al. 1930; Allen and Spitz 1945; Ohashi, Tamura et al. 1990; Tamura, Ohashi et al. 1995). *O. tsutsugamushi* was the only species in the genus of *Orientia* until a new species, *O. chuto*, was reported in the United Arab Emirates in 2010 (Izzard, Fuller et al. 2010).

Vector of Scrub Typhus

O. tsutsugamushi is transmitted to mammal hosts including humans by the

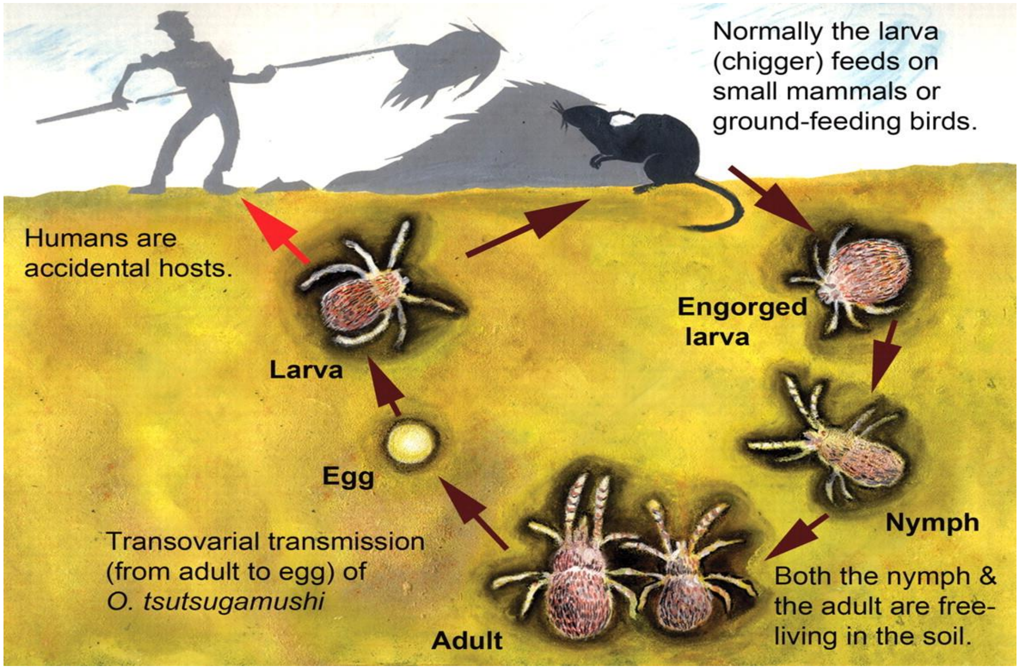

Figure 2. Life cycle of a leptotrombidium mite. Only the larva stage of a mite bite and transmit *Orientia* to mammal hosts (Source: Jeong YJ et al, Radio Graphics 2007)

larval stage of *Leptotrombidium* mites, also called chiggers (Illustration 2) (Phasomkusolsil, Tanskul et al. 2012). Keisuke Tanaka, a physician in Japan, was the first person who linked the bug to scrub typhus in 1899. *Trombidium akamushi* was the first scientific name given to the vector by Brumpt, referring to Tanaka's drawing in 1910 (Nagayo, Miyagawa et al. 1921; Sasa 1967). The finding that the field rodent is the natural host of the mite by Miyajima in 1908 greatly contributed to the investigation of the vector of scrub typhus (Sasa 1967). In 1916, Nagayo and others collected and reared the engorged larvae of the mites from field voles, and they further proposed a new generic name *Leptotrombidium* for *Trombidium akamushi* (Nagayo, Miyagawa et al. 1916; Sasa 1967). Nagayo further described four new species of *Trombicula* besides the principal vector between 1919 and 1921: *T. pallida*, *T. palpalis*, *T. intermedia*, and *T. scutellaris* (Nagayo, Miyagawa et al. 1921; Sasa 1967). Two more species of trombiculid mites were placed in the genus *Neotrombicula*: Tanaka *et al.* discovered and named *Trombicula autumnails japonica* in 1930, and Philip and Fuller discovered and named *Trombicula tamiyai* in 1950 (Sasa 1967). The research on scrub typhus significantly increased after the outbreak among American servicemen during World War II (Rapmund 1984; Quintal 1996). *L. delicense* was reported as the primary vector of *O. tsutsugamushi* in India. Both *L. delicense* and *L. chiangraiensis* were identified as the vector of the pathogen in Thailand (Kelly, Fuerst et al. 2009).

Mites act as the primary reservoirs for *O. tsutsugamushi*. They remain infected through their life cycle (larva, nymph, adult and egg) after the mites are

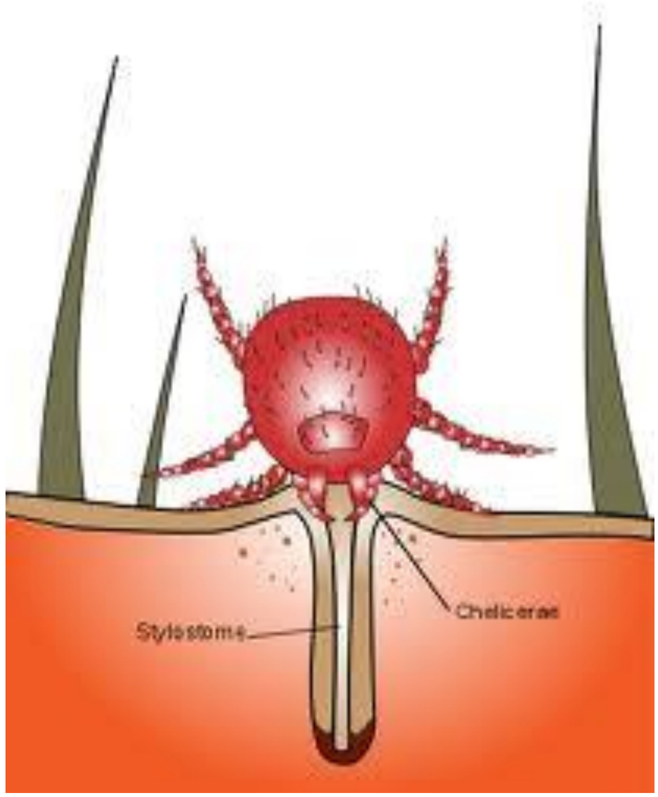

Figure 3. Engorgement of a mite on a mammal host. The engorgement usually lasts 2-4 days. [Modified from http://www.infectionlandscapes.org/2011/06/typhus.html]

infected through feeding on the infected small mammals (Jeong, Kim et al. 2007). It is known that larva of mites only feed once on a mammal host. Chiggers usually feed on thin, tender or wrinkled skin (Figure 3). The feeding lasts 2 to 4 days (Philip 1948). It has been shown that chiggers do not pierce the host skin but rather take advantage of hair follicles or pores. The liquid the mites secrete can dissolve host tissue around the feeding site and the mites eat the liquefied tissue. *O. tsutsugamushi* has been found in the salivary glands of mites (Mahajan 2005) Transovarial and transstadial transmission is thought to be the main mechanism for maintaining *Orientia* in the mite, but the bacteria can also be transmitted to mites during co-feeding and/or from wild rodents (Walker, Chan et al. 1975; Lerdthusnee, Khlaimanee et al. 2002; Lerdthusnee, Khuntirat et al. 2003; Phasomkusolsil, Tanskul et al. 2009). There has been rare documented occurrences of horizontal transmission of *Orientia* among mites (Traub, Wisseman et al. 1975). During horizontal transmission, a chigger acquires *Orientia* from an infected host, and then infects a new host through transststsdial and transovarial transmission (Frances, Watcharapichat et al. 2000; Lerdthusnee, Khlaimanee et al. 2002). There has been no person-to-person transmission of scrub typhus reported (Jeong, Kim et al. 2007). Further studies on mites and their engorgement on the host can facilitate the control and prevention of scrub typhus.

Chapter 3 Epidemiology of Scrub Typhus

As a life threatening disease that causes illness in one million people each year, scrub typhus is a serious but long neglected public health problem mainly in the Asia-Pacific area (Watt and Parola 2003). The traditional endemic area of scrub typhus is known as “tsutsugamushi triangle”. It is a region covering more than 8 million km^2, from Siberia in the north, Pakistan in the west, Australia in the south, and the Kamchatka Peninsula in the east (Seong, Choi et al. 2001; Izzard, Fuller et al. 2010). There are one billion people at risk of infection; the endemic area is highly populated (Kelly, Fuerst et al. 2009). The progress of globalization and associated travel contributes to the exportation of the disease to non-endemic areas (Kuo, Huang et al. 2012). The antigenic and genetic diversity of *Orientia tsutsugamushi* strains, and their unclear correlation with virulence for humans, confound the epidemiological study of scrub typhus (Walker and Fishbein 1991). Better understanding of the epidemiology of scrub typhus will help prevent and control the disease. This part of the thesis describes studies of the distribution and risk factors of scrub typhus in both the endemic area and the rest of the world.

Methods

A systematic literature review of epidemiological studies and case reports of scrub typhus was carried out using the methods of Hemingway et al. and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Figure 4) (Hemingway and Brereton 2009; Moher, Liberati et al. 2009).

Briefly, we first defined the research question as the epidemiology of scrub typhus. Literature was searched in the PubMed and Google Scholar databases. The following search terms were used: (scrub typhus) AND (epidemiology OR distribution OR case report). As the flow chart shows, there were a total of 827 records identified, and 792 records were screened after removal of duplicates. Eighty-two records were further filtered out in PubMed due to being nonhuman studies. Titles and abstract were used to assess the eligibility of each study. Only English peer-reviewed literatures were included in the study. Two hundred and forty-two records were excluded due to non-English language and non-human case reports. Among the 710 records remained, 647 records were either simple case reports that the abstracts provide complete case information, or only abstracts were available during analysis. Sixty-three full-text articles were obtained and assessed. Eight articles were excluded which reported on imported cases in Belgium, France, Germany, Italy, the Netherlands, New Zealand, Scandinavia, and the U.S. (Maher 1976; Henderson, Reynolds et al. 1986; McDonald, MacLean et al. 1988; Dupon, Rogues et al. 1992; Marschang, Nothdurft et al. 1995; Ciceroni, Pinto et al. 2006; Jensenius, Montelius et al. 2006; Nachega, Bottieau et al. 2007; Vliegenthart-Jongbloed, de Mendonca Melo et al. 2013). Fifty-five articles were included in this qualitative synthesis and analysis.

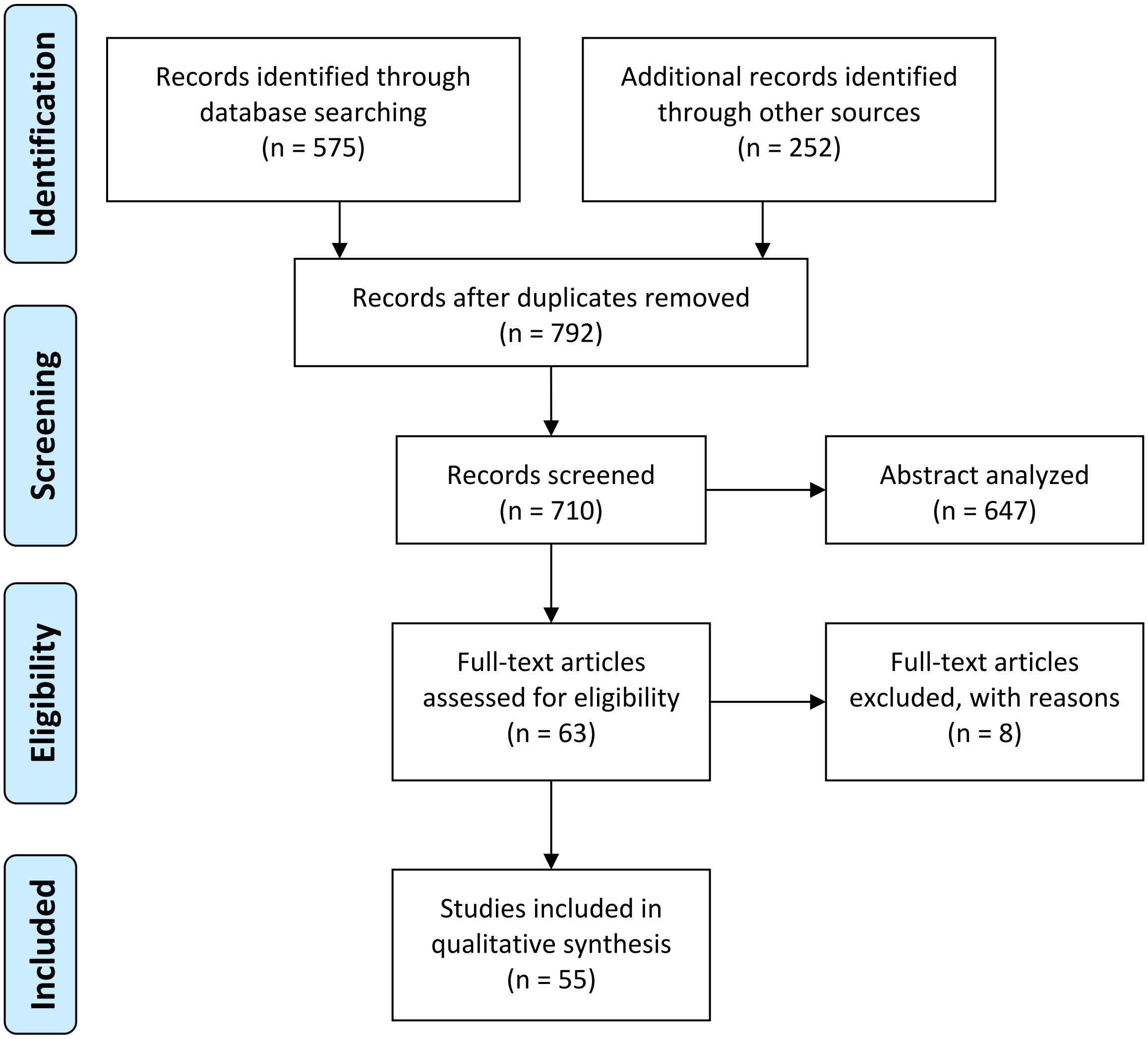

Figure 4. PRISMA flow diagram.

Transmission of Scrub Typhus

As a potentially fatal mite-borne febrile illness, scrub typhus causes one million cases annually, and one billion people are at risk (Watt and Parola 2003). Even with its recent re-emergence in the traditional endemic areas and worldwide, scrub typhus is still a neglected infectious disease (Watt and Parola 2003; Mahajan 2005; Kelly, Foley et al. 2015). The geographical distribution of scrub typhus is determined by the distribution of its vector - mites, primarily of the genus *Leptotrombidium*. Humans are accidental hosts (Walker and Fishbein 1991; Kelly, Fuerst et al. 2009).

Outdoor workers, especially field workers in rural areas, have higher risk of acquiring the disease (Kweon, Choi et al. 2009). It is reported that rice fields are an under-appreciated location where the biting of mites and transmission of *O. tsutsugamushi* happens in the endemic area (Watt and Parola 2003). Tropical weather provides stable and ideal conditions for transmission of the disease. High temperature and high humidity are optimal for mite activity. In more temperate climates, the transmission of scrub typhus is more seasonal due to the activity of chiggers (Matsui, Kramer et al. 2002; Ogawa, Hagiwara et al. 2002; Watt and Parola 2003). The list of countries with published cases of scrub typhus is found in Table 1 and Figure 5.

Figure 5. Worldwide map of countries with reported scrub typhus cases. The "tsutsugamushi triangle" in the Asia-pacific area is the cluster of scrub typhus cases. [Modified from traveltip.org]

Table 1. Global Distribution of Reported Scrub Typhus Cases, by Country

Country/Region	Region	Cases Reported Type
Australia	AP Triangle[1]	Human
Bangladesh	AP Triangle	Human
Cambodia	AP Triangle	Human
Cameroon[2]	Africa	Human
Chile	South America	Human
China	AP Triangle	Human
India	AP Triangle	Human
Indonesia	AP Triangle	Human
Japan	AP Triangle	Human
Kenya	Africa	Human
Laos	AP Triangle	Human
Malaysia	AP Triangle	Human
Maldives	AP Triangle	Human
Micronesia	AP Triangle	Human
Myanmar (Burma)	AP Triangle	Human
Nepal	AP Triangle	Human
Pakistan	AP Triangle	Rodent & mites[3]
Palau	AP Triangle	Human
Papua New Guinea	AP Triangle	Human
PR Congo	Africa	Human
Russia	AP Triangle	Rodent only
Solomon Islands	AP Triangle	Human
South Korea	AP Triangle	Human
Sri Lanka	AP Triangle	Human
Taiwan	AP Triangle	Human
Tajikistan	AP Triangle	Human
Tanzania	Africa	Human
Thailand	AP Triangle	Human
the Philippine	AP Triangle	Human
United Arab Emirates	Middle East	Human
Vanuatu	AP Triangle	Human
Vietnam	AP Triangle	Human

1. AP: the Asia-Pacific area (Figure 1).
2. This case could not be confirmed by the researcher (Ghorbani, Ghorbani et al. 1997)
3. The bacteria were only found in rodents and mites. No human case was reported (Traub, Wisseman et al. 1967; Wisseman, Traub et al. 1967)

Epidemiology in the Asia Pacific Region

The literature review confirmed that the majority of scrub typhus cases were reported in the “tsutsugamushi triangle” in the Asia-Pacific region (Table 2) (Seong, Choi et al. 2001). There were a few cases reported in Central Asia and the Middle East, which are outside the traditional definition of the Asia Pacific region, but neighboring it (Kulagin, Tarasevic et al. 1968; Kudriashova 1972; Izzard, Fuller et al. 2010). Those cases reported in other continents such as Africa and South America will be discussed in the next section.

Table 2. Characteristics of Scrub Typhus in Main Endemic Areas

Country/Region	Largest Age-specific Proportion	Gender Ratio (F:M)	High Risk Season
China	50-60 yr (23%)	1:1	June & July
Japan	51-75 yr (62%)	1:1	November
South Korea	60-69 yr (27%)	13:7	October & November
India	N/A	N/A	August - October
Thailand	50-59 yr (22%)	1:2	N/A

N/A means the data is not available from literature search.

China

Scrub typhus has an especially long history in China. It was called “sha shi du”, meaning “chigger fever” in ancient times there (Fan, Walker et al. 1987). The cases mainly distribute in Southwest China, and the Southeast Coastal and Eastern regions. May is usually the start of the case reporting, and June and July are the peak months. The pattern is correlated with the weather and life cycle of mites (Fan, Walker et al. 1987). 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 (Zhang, Song et al. 2010; Zhang, Wang et al. 2013). Scrub typhus cases can be divided into 6 clusters in China (Figure 6). Cluster 1, the significant primary cluster, is located in South and Southeast China, which included provinces of Guangdong, Fujian, Jiangxi, and Guangxi. The secondary cluster is mainly in Southwest China, which includes Yunnan and Sichuan Provinces. Jiangsu, Anhui and Shandong provinces in East China are the third cluster for scrub typhus. Shaanxi province in the Northwest and Beijing

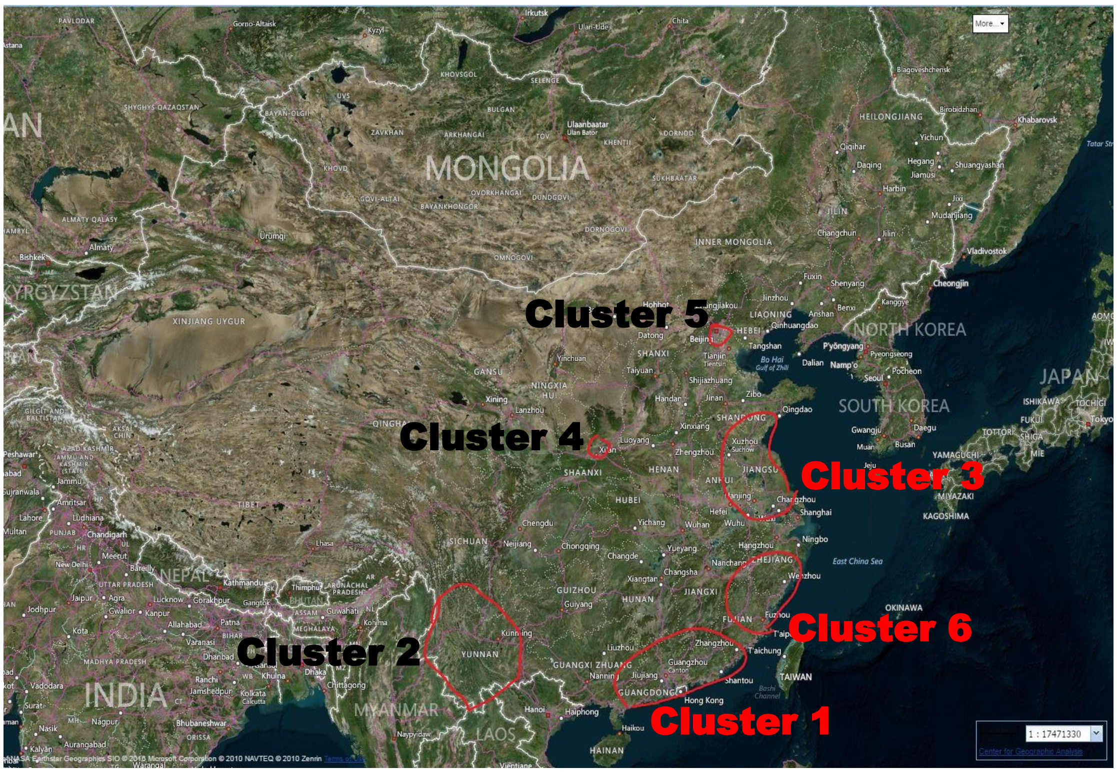

Figure 6. Six clusters of scrub typhus cases in China. Most clusters locate in South, Southwest and East China [Modified from http://worldmap.harvard.edu]

Municipality were recognized as the fourth and fifth clusters in the analysis done by Zhang *et al*. The provinces of Zhejiang and Fujian were cluster 6 (Zhang, Wang et al. 2013). In other studies, there were reported cases in Hunan province and Tibet (Fan, Walker et al. 1987).

Data collected between 2006 and 2012 shows that the highest cumulative incidence was in the 60-69 year-old age group (0.66 per 100,000), and the lowest one was in the 10-19 year-old age group (0.11 per 100,000). The 50-60 year-old group accounted for the largest portion of all scrub typhus patients in China (21.36%). There was no difference in incidence between genders (Zhang, Wang et al. 2013).

Japan

The epidemiology of scrub typhus in Japan shares some similar characteristics as well as some differences with China. Study of scrub typhus in Japan first started in the 1890s. It was a life-threatening disease in the Tohoku-Hokuriku area in the northern part of Honshu in Japan. The disease became known to the Western world during and after deployed American servicemen got infected during World War II (Ogawa, Hagiwara et al. 2002). A remarkable resurgence and a prominent outbreak happened between 1976 and 1984 due to an increase of mite colonies carrying *O. tsutsugamushi*. There was no explanation available for the increase number of mites during that period (Kawamura and Tanaka 1988). The disease has now been found in almost all areas of Japan except in Okinawa and Hokkaido prefectures. A retrospective study in 1998 demonstrated that Kyushu (51% of total cases), Tohoku-Hokuriku (27%) and Kanto (19%) had the largest number of cases (Ogawa, Hagiwara et al. 2002). In contrast to China, November accounted for the largest proportion of reported cases driven by the large number of cases in Kanto and Kyushu. May had the second highest monthly number cases due to the cases in Tohoku-Hokuriku (Ogawa, Hagiwara et al. 2002). The age distribution differs between Japan and China. In Japan, 62% of cases were 51-75 years old, while in China this age group accounted for less than half of the total patients (~48.2%) (Ogawa, Hagiwara et al. 2002; Zhang, Wang et al. 2013). No significant gender differences were observed in *Orientia* infection in Japan. Not surprisingly, working in farming and forestry is an important risk factor for the infection with scrub typhus (Kawamura and Tanaka 1988; Ogawa, Hagiwara et al. 2002).

South Korea

Scrub typhus was first reported in South Korea during the Korean War but it was still unfamiliar to Korean civilians until 1986 (Chang 1995). The disease has been recognized as the most common rickettsial disease in South Korea (Chang 1995; Kim, Kim et al. 2010; Lee, Cho et al. 2015). Nation-wide seroepidemiologic and microbiologic surveys demonstrated that 27.7% to 51% of acute febrile illness patients in South Korea were seropositive for *O. tsutsugamushi* between 1986 and 1993 (Chang 1995). The study confirmed that scrub typhus was widely spread in the country, and that it was frequently underdiagnosed (Chang 1995). Scrub typhus became a reportable disease in South Korea in 1994. Physicians must report all confirmed or suspected scrub typhus cases to both the local health bureau and the Korean Centers for Disease Control and Prevention (CDC). The gender inequality of scrub patients is unique in this country. Several studies confirmed that more female patients were reported than male patients (~65% vs 35%) (Kweon, Choi et al. 2009; Lee, Cho et al. 2015). One possible explanation is due to the conventional working behavior in farms in South Korea. Female workers typically work in a squatting position in dry fields, while male farmers tend to stand with tools in rice fields during work (Kweon, Choi et al. 2009). Another characteristic of the epidemiology of scrub typhus in South Korea is the increasing incidence in urban area (Kweon, Choi et al. 2009; Kim, Kim et al. 2010). The proportion of cases identified in urban areas increased from 20% (388 cases) in 2002 to 26.9% (1,345 cases) in 2009, while that in farmers decreased from 43.3% to 25%. However, further analysis revealed that outdoor activity in urban area is the most common risk factor (Kweon, Choi et al. 2009; Kim, Kim et al. 2010). Similar to Japan, October and November are the peak months for scrub typhus cases. Age group 60-69 years old is the largest group for scrub typhus cases in South Korea (27.48%), and 72.2% patients were 50-79 year-old (Kweon, Choi et al. 2009; Lee, Cho et al. 2015).

India

Scrub typhus was recognized as a typhus-like fever in India in 1917 (Tattersall 1945; Kelly, Fuerst et al. 2009). It was a major cause of fever among military personnel along the Assam-India-Myanmar (formerly Burma) border during World War II, and the 1965 Indo-Pak war (Kelly, Fuerst et al. 2009; Sinha, Gupta et al. 2014). The disease resurged at the Pakistan border of India in 1990 (Sinha, Gupta et al. 2014). The widespread use of insecticides and empiric treatment of febrile illness as well as changes in lifestyle all contributed to the subsequent drop in incidence (Isaac, Varghese et al. 2004; Sinha, Gupta et al. 2014). However, scrub typhus is still an under-diagnosed disease in India (Sinha, Gupta et al. 2014). Field epidemiology studies indicate that the disease occurs all over India, from South India to Northeast India and Northwest India. There were cases reported from Maharashtra, Tamil Nadu, Karnataka, Kerala, Himachal Pradesh, Jammu and Kashmir, Uttaranchal, Rajasthan, West Bengal, Bihar, Meghalaya, and Nagaland (Varghese, Abraham et al. 2006; Chrispal, Boorugu et al. 2010; Dass, Deka et al. 2011; Khan, Dutta et al. 2012; Sinha, Gupta et al. 2014). The peak of the disease is between August and October. *L. delicense* is reported as the primary vector of *O. tsutsugamushi* (Kelly, Fuerst et al. 2009). Socioeconomic status and occupation were important risk factors for scrub typhus. Most scrub typhus patients in India are uneducated and live in rural areas (Varghese, Abraham et al. 2006; Sinha, Gupta et al. 2014).

Thailand

The tropical climate of Thailand provides an ideal environment for the vectors of *O. tsutsugamushi*, *L. delicense* and *Leptotrombidium chiangraiensis* (Kelly, Fuerst et al. 2009). Nationwide sero-epidemiological studies revealed the high prevalence of scrub typhus in Thailand (Puranavej, Winter et al. 1968; Suputtamongkol, Suttinont et al. 2009). The seropositive rates of *O. tsutsugamushi* varied from 13% to 31% of residents in suburban Bangkok, to 59% to 77% of residents in northern and northeastern regions (Suputtamongkol, Suttinont et al. 2009). A human case was first reported from the central region of Thailand in 1952 (Trishnananda, Vasuvat et al. 1964; Suputtamongkol, Suttinont et al. 2009). The pathogen was first isolated from rodents in the same part of the country 2 years later (Traub, Johnson et al. 1954). There was a substantial increase in the number of confirmed cases in Thailand from the 1980s to the 2000s (Suputtamongkol, Suttinont et al. 2009). Growing awareness of the disease and development of new diagnostic tools may at least partially contribute to this trend (Manosroi, Chutipongvivate et al. 2006; Suputtamongkol, Suttinont et al. 2009; Wongprompitak, Anukool et al. 2013). Different from the other Asia-Pacific countries we analyzed above, the male to female gender ratio of scrub typhus patients in Thailand is 2:1 (Suputtamongkol, Suttinont et al. 2009). The age distribution of the disease in Thailand is that the 50-59 year old group is the largest group (22.3%) but both the 30-39 year old and 40-49 year old groups are similar, ~20%. Outdoor activity, especially occupational exposure, is a critical risk factor (Suputtamongkol, Suttinont et al. 2009).

Others

In addition to the countries described above, there are quite a few other countries with reported scrub cases in the tsutsugamushi triangle. Scrub typhus has been present on the islands of the Southwest Pacific including the Indonesian, Philippine and Australia for almost a century (Noad 1946; Philip, Woodward et al. 1946; Currie, O'Connor et al. 1993; Corwin, Soderquist et al. 1999; Graves, Unsworth et al. 2006). It was recognized as “coastal fever” in 1913 and scrub typhus after 1920s in Australia. The endemic areas for Australia are the tropical coastal periphery of northeastern Queensland, the tropical region of the Northern Territory, and the adjacent Kimberly region of Western Australia (Currie, O'Connor et al. 1993; Graves, Unsworth et al. 2006; Kelly, Fuerst et al. 2009). A new strain, Litchfield, different from those from other Asia-Pacific area countries was isolated in Australia in 1998 (Odorico, Graves et al. 1998). The Philippines did not confirm the occurrence of scrub typhus until World War II. The first but failed US scrub typhus vaccine was prepared from the lungs and spleens of rats infected with Volner strain of *O. tsutsugamushi*. The Volner strain was originally isolated from the blood of a soldier in the Philippines (Philip, Woodward et al. 1946; Berge, Gauld et al. 1949). The history of scrub typhus in Malaysia could be traced back to 1915 (Cadigan, Andre et al. 1972; Robinson, Gan et al. 1976; Tay, Nazma et al. 1996). World War II made the disease known to the Solomon Islands, Republic of Vanuatu, and Papua New Guinea (Irons and Armstrong 1947; Bekker, Dinger et al. 1964; Bekker, Dinger et al. 1968; Miles, Austin et al. 1981; Spicer, Taufa et al. 2007). Our literature search only found positive *Orientia* infection in rodents and mites in Russia and Pakistan, and no human patient has been reported in these countries (Traub, Wisseman et al. 1967; Wisseman, Traub et al. 1967; Urakami, Tamura et al. 1999; Nelyubov 2002). The distribution of scrub typhus covers a large and diverse area. In the Asia-Pacific region alone, different countries in the endemic area have different climates, environment, culture, and history, which all contribute to the different characteristics of epidemiology of the disease (Kelly, Fuerst et al. 2009; Kelly, Foley et al. 2015). Our study has the limitation that we only analyzed literature in English within the databases of PubMed and Google Scholar. There were quite a few publications in Chinese, Japanese, Korean, Russian, etc. not included in the analysis.

Epidemiology outside "tsutsugamushi triangle"

Our literature review determined that there are a few sporadic scrub typhus cases from the countries and regions outside the traditional "tsutsugamushi triangle" in the Asia-Pacific area (Figure 2).

United Arab Emirates (UAE)

UAE is outside the traditional endemic triangle. However, the case reported in 2010 demonstrated not just a confirmed scrub typhus case in UAE but also a new *Orientia* species, *O. chuto* (Izzard, Fuller et al. 2010). The Australian patient concerned had traveled to Dubai, UAE and the United Kingdom before the onset of her febrile illness. She noticed an eschar on her abdomen after the Dubai visit. An indirect immunofluorescence assay (IFA), polymerase chain reaction (PCR), and sequencing were employed to determine the etiologic pathogen. The molecular variance of 47-kDa gene, 56-kDa gene and the nucleotide sequence, and geographical difference led the researchers to propose the new *Orientia* species. There was only one known species, i.e. *O. tsutsugamushi*, before this (Seong, Choi et al. 2001; Izzard, Fuller et al. 2010).

Chile

Before this first and so far the only reported scrub typhus case in Chile, there was no reported scrub typhus case in the Western Hemisphere. The patient was bitten by terrestrial leeches on Chiloé Island in southern Chile in 2006 (Balcells, Rabagliati et al. 2011). Both PCR as a molecular biological test and IFA as a serological test showed positive results for *O. tsutsugamushi*. The molecular analysis further indicated that the pathogen is close but not identical to other *O. tsutsugamushi* and *O. chuto* species isolated from the Asia-Pacific region and the Middle East. It was significantly closer to *Orientia sp.* than other rickettsiae. The results suggested that the pathogen from the Chilean sample was not a simple import from an endemic area. In addition, the case also reminds us that there might be other vectors, such as leeches, for *Orientia* (Balcells, Rabagliati et al. 2011). More follow-up studies could help us fill these gaps.

Africa

There are case reports from Cameroon, Kenya, Congo and Tanzania in Africa (Osuga, Kimura et al. 1991; Ghorbani, Ghorbani et al. 1997; Groen, Nur et al. 1999; Thiga, Mutai et al. 2015). The only case report from Cameroon was an American who visited Cameroon before getting fever (Ghorbani, Ghorbani et al. 1997). The Weil-Felix test (W-F) tested positive for *O. tsutsugamushi* but PCR analysis of formalin-fixed, paraffin-embedded skin samples was negative. Several clinical features were not typical either. W-F has been notorious for its bad sensitivity and specialty (Shivalli 2016). It was possible that the febrile illness was caused by another pathogen, such as other Rickettsia species, with similar features that was cross-reactive to the scrub typhus antibody (Ghorbani, Ghorbani et al. 1997). The researchers in Kenya screened serum samples from patients with febrile illness in Kenya. Western blot was performed to confirm the specificity. About 5% of the serum samples were positive for scrub typhus (Thiga, Mutai et al. 2015). The clinical features and serological test (indirect immunoperoxidase assay, IIP) confirmed the diagnosis of *O. tsutsugamushi* Kato strain in the only case in Congo. However, the patient lived and was diagnosed in Japan. The patient visited Congo for 23 days, and noticed symptoms 8 days after he left Congo. The researchers contacted local centers for disease control in Japan where the patient lived and worked. They did not find similar reports in Japan so they concluded that the patient contracted the disease in Congo. No other case in Congo has been reported (Osuga, Kimura et al. 1991). Therefore, it is reasonable to suspect that the researchers failed to rule out the possibility of domestic infection in Japan instead of in Congo in that case report. More epidemiologic studies of scrub typhus are necessary to confirm the existence of scrub typhus in Congo. A Dutch traveler to Tanzania contracted *O. tsutsugamushi* there. Researchers in the Netherlands confirmed the case with clinical features (fever, eschar, etc.) and serological tests, i.e., IFA (Groen, Nur et al. 1999). No other case has been reported in the same country.

Chapter 4 Diagnosis of Scrub Typhus

Scrub typhus is a widespread acute febrile illness in the Asia and Pacific area. The disease has reemerged in the endemic area in recent years. (Watt and Parola 2003; Gupta and Gautam 2004; Mahajan 2005). The public health impact of this disease is critical because of its high prevalence in highly populated area and high case fatality rate without timely treatment. In addition, there is absence of effective and feasible diagnosis and laboratory tools (Mahajan 2005). Understanding the clinical features and diagnostic tools used for diagnosing scrub typhus will help us better treat and prevent the disease.

Clinical Manifestations

The symptoms of scrub typhus are usually mild and limited, and patients can recover spontaneously after a few days. However, there are more severe cases that can be even fatal (Jeong, Kim et al. 2007). The case fatality rate reached 50% before antibiotics became available for use (Mahajan 2005). The case fatality rate can still ranges up to 15% without timely appropriate treatment (Varghese, Abraham et al. 2006).

The incubation period for scrub typhus is typically 10 to 12 days after a bite from an infected chigger. There has been a report that the incubation period can range from 6 to 21 days (Jeong, Kim et al. 2007). The common symptoms at the onset of scrub typhus are fever, rash, headache, myalgia, cough, diffuse lymphadenopathy, and gastrointestinal symptoms (Warrell, Cox et al. 2003; Mahajan 2005; Jeong, Kim et al. 2007). Fever and headache are the most common features among scrub typhus patients. About 95% to 100% of confirmed cases noted fever in several studies (Tsay and Chang 1998; Jamil, Lyngrah et al. 2014).

Eschar at the site of chigger feeding is one of the most classic clinical features for rickettsial diseases. Eschar is a papule formed at the site of bite (Figure 6). The papule ulcerates and gets a black crust like a skin burn from a cigarette butt (Gupta and Gautam 2004; Mahajan 2005). An eschar is present in ~60% of scrub typhus patients (Kawamura 1995; Tsay and Chang 1998). It is more frequently found on Caucasian and East Asian patients. It's less common on dark skinned South Asian patients. Most eschars develop on the front of the body (~80%). In male patients, eschars are primarily within 30 cm under the umbilicus. The other common locations are lower extremities and front chest. There is a different pattern in female patients (Kim, Won et al. 2007). The front

◄▲**Figure 7.** Rash (left) & axillary eschar (right) caused by a mite bite infected with scrub typhus. (Source: Cowan G, Postgrad Med J 2000) chest is the most prevalent area.

Maculopapular rash and regional lymphadenopathy are other typical clinical features. In a study from Taiwan, rash occurred among about 20% of scrub typhus patients (Tsay and Chang 1998). The rash starts 5 to 8 days after the start of fever. Macular or maculopapular rash may first appear on the trunk, e.g., the chest or abdomen, before it spreads to the extremities. It's very rare to have rash on the face, palms or soles (Seong, Choi et al. 2001; Mahajan 2005; Jeong, Kim et al. 2007).

Regional lymphadenopathy, one of the classic clinical symptoms, emerges at the end of the first week after the onset of the disease. The draining lymph nodes appear swollen and tender around the primary eschar. In some cases, the lymphadenopathy becomes more generalized (Seong, Choi et al. 2001; Jeong, Kim et al. 2007; Bennett, Dolin et al. 2014).

It has been reported that splenomegaly and hepatomegaly are also common at physical examination (~20% of the cases) (Jeong, Kim et al. 2007; Jamil, Lyngrah et al. 2014). Scrub typhus can cause various other complications including jaundice, renal failure, pneumonitis, ARDS, septic shock, myocarditis, pericarditis and meningoencephalitis (Mahajan 2005; Jeong, Kim et al. 2007; Jamil, Lyngrah et al. 2014). The lung is one of the main target organs for *Orientia*, which can thus cause pulmonary complications of variable severity. The pulmonary complications can lead to the formation of interstitial pneumonia in severe cases (Song, Kim et al. 2004; Jeong, Kim et al. 2007). Clinicians are able to observe elevated levels of aspartate and alanine aminotransferases which are hepatic enzymes, or alkaline phosphatase which is a biliary canalicular marker (Jeong, Kim et al. 2007). About 9% of scrub patients have renal injury (Attur, Kuppasamy et al. 2013; Jamil, Lyngrah et al. 2014; Sun, Kim et al. 2014). Patients may suffer hypoalbuminemia and albuminuria in some cases (Mahajan 2005).

Neurological injury occurs in some scrub patients with various severities. Headache is the most common cerebral disorder of scrub typhus. Meningitis and/or encephalitis caused by *Orientia* develops in severe illnesses, and may cause patients to become agitated, delirious or even have seizures. Focal neurological signs are rare but have been known to occur. Laboratory tests may demonstrate changes in cerebrospinal fluid similar to those found in viral or tuberculous meningitis (Silpapojakul, Ukkachoke et al. 1991; Ben, Feng et al. 1999; Kim, Lee et al. 2000; Seong, Choi et al. 2001).

There are other non-classic symptoms that doctors can observe on scrub typhus patients. Marked hyperemia and even hemorrhage can be found on the conjunctiva during the acute phase of the disease. There were reports of hemorrhages and coagulation disorders, mostly gastrointestinal complications, among scrub typhus patients. Severely ill patients can suffer mucosal hemorrhage, multiple erosions and ulcers. (Kim, Chung et al. 2000; Seong, Choi et al. 2001; Mahajan 2005).

In severe scrub typhus cases, septic shock can cause multiple organ failures, respiratory failure, and DIC. Those severe complications may result in fatal cases, without appropriate immediate treatment. It has been demonstrated that absence of eschar, intensive care unit admission and severe complications are risk factors for fatal outcome in scrub typhus patients (Lee, Hwang et al. 2009). Early diagnosis can lead to effective treatment of the disease and save lives (Tsay and Chang 1998; Cracco, Delafosse et al. 2000; Thap, Supanaranond et al. 2002; Lee, Hwang et al. 2009).

Diagnosis

As described above, *Orientia* causes flu-like febrile illness, which makes the diagnosis of scrub typhus quite difficult. Generally, its diagnosis is based on the patient's clinical presentation and history. Presence of an eschar and history of travel to an endemic area can help the diagnosis. An eschar is not observed in every confirmed patient, and lesions from other diseases, e.g., spider bites, leishmaniasis and anthrax, may confuse the clinician. Scrub typhus can be misdiagnosed as malaria, dengue, leptospirosis, meningococcal disease, typhoid, infectious mononucleosis and HIV (Mahajan 2005; Li, Dou et al. 2013; Koraluru, Bairy et al. 2015).

Laboratory methods of diagnosing rickettsial diseases including scrub typhus are mainly based on serological tests and molecular assays. Cross-reactivity of *Orientia* with other rickettsiae is rare but exists, and cross-reactivity against hepatitis A, EBV and malaria were observed (Kelly, Wong et al. 1988; Tay, Kamalanathan et al. 2003; Wilkinson, Rowland et al. 2003). The gold standard test for diagnosis of scrub typhus is the indirect immunofluorescence assay (IFA) (Koraluru, Bairy et al. 2015; Lim, Paris et al. 2015). However, IFA is expensive and complicated, and requires extensive training and a biocontainment facility. Even though the assay has been available for quite some time, the application of IFA in the endemic area is still limited for the above mentioned reasons. The test fails to provide positive results at early stages of infection because those antibodies that are parts of adaptive immunity are not be generated at early acute infection stage. It is more reliable to apply the serological tests when the antibody titer has a 4 fold rise. There are other limitations of IFA, from the controversial cut-off antibody titer, subjective determination of results, to imperfect specificity of the test (Lee, Moon et al. 2014; Lim, Paris et al. 2015).

Other serological tests include the IIP, the W-F, enzyme-linked immunosorbent assays (ELISAs), and various commercially available immunochromatographic tests (ICT) (Koh, Maude et al. 2010; Lim, Paris et al. 2015). The W-F agglutination test has been commercially available for screening for many years. This test using the Proteus OXK strain lacks both specificity and sensitivity, especially the latter, for routine diagnosis (La Scola and Raoult 1997; Shivalli 2016). Studies have shown that the sensitivity is only 50% during the second week of illness (Mahajan 2005; Koraluru, Bairy et al. 2015).

IIP is a modification of IFA, which provides a comparable sensitivity and specificity in diagnosis of scrub typhus (Yamamoto and Minamishima 1982; Kelly, Wong et al. 1988). Both IFA and IIP have been used as the reference standard. No significant difference was found in the accuracy of the two tests, except for one study which claimed that IIP was more sensitive than the IFA with acute sera (79.6% vs. 68.5% at titer ≥1:400) (Pradutkanchana, Silpapojakul et al. 1997; Coleman, Sangkasuwan et al. 2002).

ELISAs and their variants, such as commercially available dipstick tests, use either pooled cell lysates of different strains of *O. tsutsugamushi* as antigen, or recombinant r56 or other outer membrane proteins as the antigen. Studies demonstrated that ELISAs provide sensitive and specific test results. They eventually may be able to replace the IFA and IIP assays. The sensitivity and specificity of dipstick assays are inferior to ELISAs but the commercially available assays are easy to use, and could be performed in underserved areas (Pradutkanchana, Silpapojakul et al. 1997; Coleman, Sangkasuwan et al. 2002; Mahajan 2005)

ICT is another commercially available kit for early rapid diagnosis. The test also uses the recombinant *Orientia* outer membrane proteins to detect IgG, IgM and IgA antibodies to *O. tsutsugamushi*. Review of the test indicated that ICT has moderate to high sensitivity (~70%) among scrub typhus patients. The sensitivity increases with the fever duration. Several studies claimed that, similar to the passive hemagglutination assay (PHA), ICT also provides a substantial number of false negative results (Lee, Moon et al. 2014). PHA was replaced by ICT due to the former's lower sensitivity. However, Lim *et al.* demonstrated that the specificity of IFA IgM is low, which caused inaccurate comparisons between IFA and other diagnostic assays. By contrast, the IgM ICT has comparable sensitivity and significantly better specificity than IFA as assessed using Bayesian latent class models (Lee, Moon et al. 2014; Lim, Paris et al. 2015).

The molecular method to diagnose scrub typhus is detecting the bacteria from isolation and culturing of the pathogen, and PCR assays. PCRs usually target the genes of the outer membrane proteins of 56kDa, 47kDa, and groEL genes (Lim, Paris et al. 2015). It was reported that the nested PCR may be more sensitive than the serological test (Saisongkorh, Chenchittikul et al. 2004; Paris, Blacksell et al. 2008). This molecular biology method can detect *Orientia* DNA in blood even during the persistent phase of the infection, when no obvious clinical symptoms can be observed. However, the sensitivity of PCRs reduces with treatment (Smadel, Ley et al. 1952; Mahajan 2005; Chung, Lee et al. 2012; Koraluru, Bairy et al. 2015)

Treatments

As a gram-negative bacterium, *Orientia* infection can be effectively treated with antibiotics. Early treatment shows better outcomes, e.g., shortening the disease course and reducing fatality (Watt and Parola 2003). Oral treatment is effective for mild cases but the injectable route is necessary for severely sick patients. Similar to the treatment for other rickettsial diseases, doxycycline is one of most effective antibiotics for treating scrub typhus. Antibiotics are usually able to abate patients' fever rapidly, and this sign is even used as a diagnostic method. Some randomized clinical trials reveal that there is no significant difference among tetracycline, doxycycline, telithromycin, and azithromycin (Liu and Panpanich 2002). Rifampicin was shown to be more effective than tetracycline in patients responding poorly to doxycycline (Mahajan 2005). World

Health Organization (WHO) recommends that children or pregnant women use azithromycin or chloramphenicol. Antibiotic resistance has been reported on a few papers (Watt, Chouriyagune et al. 1996; Kuo, Huang et al. 2012). There is much unknown regarding the antibiotic resistance. It will be useful for the development of new diagnostic tools and treatments to elucidate the mechanisms of poor response in certain patients, as well as the antibiotic resistance of the pathogen (Watt and Parola 2003; Mahajan 2005; Chogle 2010).

Chapter 5 Prevention and Control of Scrub Typhus

According to WHO, scrub typhus could be recognized as an occupational disease among rural residents and outfield workers in the endemic area (Kuo, Huang et al. 2012). CDC claims most travel-acquired scrub typhus cases take place when visiting rural parts of the endemic areas, especially during camping, hiking, or rafting (CDC 2015).

Outbreaks of scrub typhus are seasonal and associated with certain types of terrain such as semi-desert, sandy beach, dense but disturbed forest glacier slope (Traub and Wisseman 1968; Traub and Wisseman 1974). Taiwan CDC claimed that mites wait to attach and engorge on humans or other mammals at the tips of weeds. Outbreaks are usually clustered into small foci, and simultaneously infect susceptible people shortly after exposure (WHO 2016). Patients frequently do not recall the history of being bitten or attacked by the vector (Watt and Parola 2003; Kuo, Huang et al. 2012).

Current Prevention Methods

There is no working vaccine for any rickettsial infections including scrub typhus. The enormous antigenic variation in different *O. tsutsugamushi* strains, and weak and short cross protection among different strains hamper the development of any viable vaccine. Vaccine efforts are also hindered by the different dominant strains of *O. tsutsugamushi* in different endemic countries/regions and different virulence of each strain (Sharma 2010; Kuo, Huang et al. 2012; CDC 2015).

WHO recommends prophylactic treatment under special circumstances in the endemic areas (WHO 2016). A single oral dose of chloramphenicol or tetracycline every 5 days for a total of 35 days provides protection against to *Orientia* infection (Kuo, Huang et al. 2012). A prospective randomized double blind study among Taiwanese military personnel confirmed that prophylactic treatment with doxycycline could decrease the incidence of scrub typhus to 1/5 of that in placebo group (Olson, Bourgeois et al. 1980). However, CDC in the U.S. does not recommend using antibiotics as prophylaxis for rickettsial diseases including scrub typhus (CDC 2015). CDC claims there is no evidence of effectiveness of prophylaxis for any rickettsial diseases (CDC 2010). The preventive treatment may simply delay onset of disease and make diagnosis more difficult. To treat rickettsial diseases more effectively, CDC suggest start treatment based on clinical suspicion alone (Chapman, Bakken et al. 2006; CDC 2010).

General protective measures can be followed to avoid the infection. These precautions are critical for people living in or visiting endemic areas especially those with compromised immunity (Kuo, Huang et al. 2012; CDC 2015; CDC 2015):

1. Avoid outbreaks. Persons should avoid known foci of outbreak areas to the extent that this is possible. Travelers can check the regional disease transmission and outbreak information at http://www.cdc.gov/travel.

2. Avoid exposure regions. Chiggers reside in grass, woodlands, and other vegetated areas. Persons are encouraged to avoid the outdoors or take preventive actions. Do not sit or lie on bare ground or grass; use a sheet or a cover on the ground instead.
3. Wear appropriate clothing. Persons should wear long-sleeved shirts, long pants, boots and hats to reduce exposure. Persons should tuck in shirts and pants, and wear closed shoes.
4. Insect and spatial repellents. Persons should apply insect repellents containing dibutyl phthalate, benzyl benzoate, diethyl toluamide and other chemicals to their skin and/or clothing to prevent chigger bites.
5. Insecticides and habitat modification. Farmers and outfield workers can improve sanitation, clear vegetation, control rodents, use insecticides and chemically treat the soil. These steps can impede the propagation of chiggers and the transmission cycle.
6. Check for mites. Persons should inspect themselves and their outfits frequently for mites during work or travel and at the end of the day. Prompt removal of engorged mites and thorough cleaning can reduce the risk of infection.

Strategies of Prevention and Control

The reemergence of scrub typhus in the Asia-pacific area as well as the increase in antibiotic resistance remind us of the urgency of developing and adopting effective control and prevention measures (Olson, Bourgeois et al.

1980; Brezina 1985; Kazar and Brezina 1991; Sharma 2010; Kuo, Huang et al. 2012).

Primary prevention is to evaluate the risk factors and take appropriate actions to prevent the onset of scrub typhus. Though no vaccine is available, a number of other prevention measures can be taken. To make these measures work, public education on case recognition and personal protection is the priority. WHO recommends that advocacy, awareness and education activities should be targeted at schoolchildren, teachers and women in endemic areas (WHO 2016). However, field workers and outdoor travelers may have higher risks of getting infected, so the education program should not be only limited to the three groups mentioned above. Farms and other places with bushes, wood piles, rodents, and domestic animals increase the risk of infection. One strategy is to avoid high risk areas. For field workers and those people who cannot avoid the risk factors, taking the precautions as described in the last section will help prevent the diseases (Olson, Bourgeois et al. 1980; Sharma 2010; Kuo, Huang et al. 2012; CDC 2015; CDC 2015; WHO 2016).

Kwak et al. simulated incidence of scrub typhus with selected meteorological predictors, such as temperature, precipitation, relative humidity, wind speed, duration of sunshine, cloud amount (Kwak, Kim et al. 2015). The study indicated that the seasonality of meteorological factors affects model prediction. We should consider these factors when predicting the disease cycle, and employ appropriate strategies of prevention and control (Sharma 2010; CDC 2015; Kwak, Kim et al. 2015; WHO 2016)

Rodent control and habitat modification are helpful for disease control and prevention. Different rodent control strategies can be in use, from trapping, to poisoning, to use of natural predators (WHO 1974; WHO 2016). Rodent control is important but difficult, especially maintaining the positive outcomes for long-term. Public education is a priority for the control of rodent and mite (WHO 1974; Brown and Laco 2015). Poisoning is widely used in the agriculture sector in the endemic area but secondary poisoning poses hazards to other animals and humans. For this reason using the natural predators of rodents and other natural forms of control are preferred. Habitat modification, such as good sanitation in and around buildings, clearing vegetation around fields, and closing of grain stores, can make areas less suited for rodents, and prevent them from flourishing in high numbers (Brezina 1985; Kazar and Brezina 1991; Kuo, Huang et al. 2012; WHO 2016).

Secondary prevention for scrub typhus is better case identification, i.e., early diagnosis and treatment. The great clinical and public health challenge of scrub typhus is its difficulty in diagnosis, especially early diagnosis. Early diagnosis and early treatment can significantly reduce the complications and fatality rate caused by *Orientia*. WHO suggests improving the awareness of empirical therapy (WHO 2016). It also urges researchers to develop affordable and easy diagnosis assays with high sensitivity and specificity (Mahajan 2005; Sharma 2010; Kuo, Huang et al. 2012; Koraluru, Bairy et al. 2015; Lim, Paris et al. 2015).

Even though scrub typhus can be a life threatening disease, collaborative actions from not only the countries and regions in the endemic areas but also the rest of the world using the strategies mentioned above can effectively control and prevent the outbreak and further spread of this neglected disease.

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