Review Article: Rickettsial Infections in Southeast Asia: Implications for Local Populace and Febrile Returned Travelers

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Abstract. Rickettsial infections represent a major cause of non-malarial febrile illnesses among the residents of Southeast Asia and returned travelers from that region. There are several challenges in recognition, diagnosis, and management of rickettsioses endemic to Southeast Asia. This review focuses on the prevalent rickettsial infections, namely, murine typhus (*Rickettsia typhi*), scrub typhus (*Orientia tsutsugamushi*), and members of spotted fever group rickettsiae. Information on epidemiology and regional variance in the prevalence of rickettsial infections is analyzed. Clinical characteristics of main groups of rickettsioses, unusual presentations, and common pitfalls in diagnosis are further discussed. In particular, relevant epidemiologic and clinical aspects on emerging spotted fever group rickettsiae in the region, such as *Rickettsia honei*, *R. felis*, *R. japonica*, and *R. helvetica*, are presented. Furthermore, challenges in laboratory diagnosis and management aspects of rickettsial infections unique to Southeast Asia are discussed, and data on emerging resistance to antimicrobial drugs and treatment/prevention options are also reviewed.

INTRODUCTION

Although mortality rates for malaria have decreased globally, non-malarial infections remain a major cause of morbidity and mortality in many parts of Southeast Asia.[1] Overall, rickettsial infections rate as the second most frequently reported infections for non-malarial febrile illnesses among residents of Southeast Asia, just after dengue.[1] Rickettsioses also remain a substantial risk among refugee populations,[2] particularly those living along Thailand–Myanmar border, where they may contribute up to 33% of febrile illness presentations.[3] They are also associated with stillbirth in pregnancy or low birth weight in infants.[4]

Conversely, Southeast Asia is a region of growing tourism. Although rich in natural, cultural, and historical attractions, increasing business and investment opportunities and the relative ease of air travel mean that millions of tourists from all over the world travel to Southeast Asia yearly for a wide range of urban and ecotourism activities. For these tourists returning home, imported fevers are a common occurrence and rickettsial infections are a relatively frequent contributor (2–3.3% of all imported fevers).[5–7] Rickettsial infections ranked fourth among the identifiable causes of systemic febrile illness in returned travelers from Southeast Asia (16 [2.9%] of 547 identified etiologies).[8]

Detailed epidemiology and understanding on the burden of rickettsioses in Southeast Asia has been limited. Hundreds of fatal cases and thousands of non-fatal cases probably go undiagnosed in the region each year.[9] Under-recognition and under-testing of potential cases, lack of facilities for testing and non-standardized reporting systems likely contribute to the underestimation of true epidemiology.[5,10] Physicians caring for the local populace and febrile returned travelers face the extremely difficult task of recognizing and differentiating rickettsial infections from other equally prevalent and important diseases.[11] The greatest challenge lies in diagnosing rickettsioses in a timely manner early in the course, when antibiotic use is most effective.[12]

This report aims to provide a comprehensive review on the prevalence of rickettsial infections in Southeast Asia, with particular emphasis on the characteristics and clinical features of *Rickettsia typhi*, *Orientia tsutsugamushi*, and spotted fever group rickettsiae (SFGR). This report also reviews rickettsial diagnostics, associated challenges in resource-limited settings of Southeast Asia, and available treatment options. The aim overall is to provide awareness and understanding of rickettsial diseases to the physicians caring for the local populace and returned travelers from Southeast Asia. Other related vector-borne infections, such as leptospirosis, Q fever, erlichiosis and bartonellosis, are not within the scope of this review.

OVERVIEW

Rickettsiae are small (0.3 × 1–2 μm) obligate intracellular, gram-negative rods that can cause disease in humans as accidental hosts. The pathogenic species of *Rickettsia* and *Orientia* are maintained in animal and arthropod reservoirs and are transmitted by arthropod vectors, such as ticks, mites, lice, and fleas (Figure 1). Generally, species within the genus *Rickettsia* can be subdivided into two groups: the typhus group (containing two species: endemic murine typhus *R. typhi* and epidemic typhus *R. prowazekii*) and the spotted fever group (SFG). The list of SFG *Rickettsia* species recognized as causing human infections is increasing. The genus *Orientia* contains only two species: *O. tsutsugamushi* and *O. chuto*.[13]

Among residents of Southeast Asia, *R. typhi*, *O. tsutsugamushi*, and some members of SFG *Rickettsia*, including *R. honei*, are important rickettsial species that cause human diseases. Amongst returned travelers with rickettsial infections, *R. typhi* and *O. tsutsugamushi* infections are largely found in persons who visited Southeast Asia.[14,15]

EPIDEMIOLOGY

The nations of Southeast Asia are Brunei, Cambodia, East Timor (Timor Leste), Indonesia, Laos, Malaysia, Myanmar

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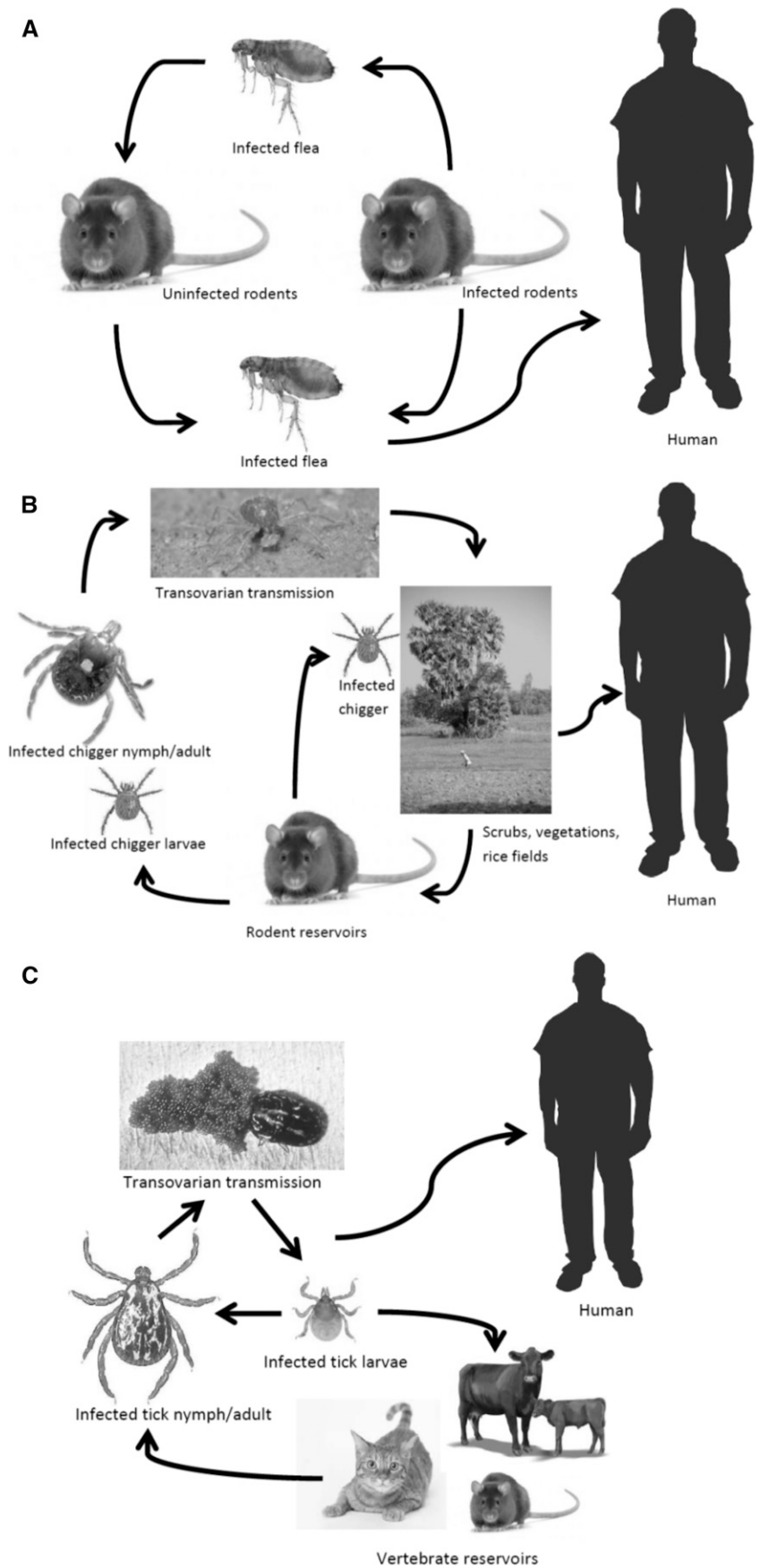
FIGURE 1.   Simplified diagrams on the life cycles of rickettsiae. **A**, *R. typhi*, **B**, *O. tsutsugamushi*, and **C**, spotted fever group rickettsiae. Image source: Google images (www.google.com).

TABLE 1
Summary of prevalent rickettsiae in Southeast Asia, their reservoirs, and vectors for disease transmission

Rickettsiae	Main reservoirs	Main vectors
Typhus group		
Murine typhus (*R. typhi*)	Rats (*Rattus rattus, Rattus norvegicus,* other *Rattus* sp.)[12,32,33,37]	*Xenopsylla cheopis*[37]
Scrub typhus (*O. tsutsugamushi*)	Rats (*Rattus* sp.and *Bandicota* sp.)[29,33]	Trombiculid mites (larval stage)[29]
Spotted fever group		
R. honei	Rats (*Rattus* sp. and *Bandicota indica*)[32,34,73]	*Ixodes granulatus, Ixodes* sp., *Rhipicephalus* sp.[73]
R. felis	Rats (*Rattus* sp.) and shrews (*Suncus murinus*),[37] domestic cats, dogs, cows and pigs[36,38]	*Ctenocephalides orientis, C. felis felis,*[36] *X. cheopis*[12,35,37]
R. conorii subsp. *indica*	Rats (*Rattus* sp.)[32]	*R. sanguineus*[2]
R. helvetica	Unknown	*Ixodes* sp.[3,62,76]
R. japonica	Rats (*Rattus* sp. and *B. indica*)[34]	Various species of animal ticks[2]

(Burma), the Philippines, Singapore, Thailand and Vietnam. A summary of clinical studies published within the last 15 years (1999–2014) with regards to prevalence of rickettsial infections in SEA is provided in Supplemental Table. Most studies originated in Thailand; published epidemiologic data are not available for Brunei, East Timor, Myanmar, and Vietnam. Singapore reported 41 serologically confirmed cases of rickettsial diseases in the country during 1999–2000; most were murine typhus.[16–18] Further information on the reported prevalence of rickettsial infections specific to the Mekong delta region from all published literature is outlined by Acestor and others.[1] Incident rates of rickettsial infections in Southeast Asia are largely unknown and may be increasing in some countries, partially attributable to improved diagnostic methods.[18,19]

An important aspect to note regarding these epidemiology studies is that although variations in seroprevalence rates may exist between countries and also within each country, such figures need to be interpreted with caution because of several limitations, such as different study populations (e.g., all acute undifferentiated fevers versus exclusion of patients with malaria, which affect the overall reported proportions), variations in serologic methods used, and the diagnostic criteria for seropositivity (single positive titer values versus ≥ 4-fold increase in titers for paired serum samples).[20] In addition, in those studies that used a single positive titer as diagnostic criteria, the values ranged from 1:50 to 1:400. Therefore, a direct comparison between the studies is not valid. In addition, there have only been few prevalence studies using the polymerase chain reaction (PCR) method (Supplemental Table) because of its limited availability.

Nevertheless, some useful conclusions can be drawn. First, overall rickettsial infections in Southeast Asia are probably more common than previously perceived, and a significant proportion of patients were found to be seropositive for any rickettsial infections at low titers, many of whom likely had previous infections/exposures.[21–24] Second, when relative contributions from the 3 rickettsial groups were compared, it was found that murine typhus was more commonly reported among the urban dwelling patients and scrub typhus and SFGR infections were more prevalent among rural patients.[22,25] Geographically, as noted previously, scrub typhus was prevalent in northern and northeastern regions of Thailand, and incidence rates may be as high as 16 cases/100,000 population per year in some areas such as Chiang Mai.[26–29] Socioeconomically, agricultural, plantation, or forest workers in Thailand, Malaysia, and Indonesia were frequently affected by scrub typhus and SFGR infections.[21,23,27,30,31] Third, despite their predilection

for certain geographic areas or human populations, none of the 3 rickettsial groups discriminated between urban and rural dwellers (or tourists). Thus, equal consideration should be given for testing of all rickettsial groups in patients with suspected diseases.

The main reservoirs and vectors for rickettsioses found in Southeast Asia are summarized in Table 1. A number of rodent and ectoparasite studies may also shed further light on human epidemiology.[32–38] Rodents were found to be important reservoirs for SFGR and murine typhus; high seropositive rates (up to 39.1% for SFGR) were observed in some parts of rural Indonesia.[32,33] Infection of rat flea *Xenopsylla cheopis* with *R. felis* has also been found in Indonesia, which increases the possibility of human infections with *R. felis* in the region, although no clinical case has been reported to date.[35,37] Ectoparasite field surveys of villages in Laos and Malaysian Borneo of domestic animals also showed significantly high overall *R. felis* DNA detection rates of 76.6% and 74.4%, respectively.[36] However, in contrast, another study in peninsula Malaysia showed a lower rate (2.9%) of *R. felis* DNA detection.[38] In addition, previously unrecognized vectors or rickettsial species have also been reported in these studies. Studies in rural mountainous areas of Thailand demonstrated that *Bandicota* species and *Rattus argentiventer* may be the main rodent vectors for transmission of SFGR (*R. japonica* and *R. honei*)[34] and *O. tsutsugamushi*.[29] Another study in Thailand found 3 novel phylogentically distinct SFGR DNAs (ATT, HOT1 and HOT2) in 30% of *Amblyomma testudinarium* and 16.8% of *Hemaphysalis ornithophila* tick species collected from animals and vegetation in Khao Yai National Park.[39] However, it is unclear if these newly discovered SFGR could cause human disease and whether the ticks species carrying these rickettsiae could feed on humans as a host.[39]

Despite extensive data, these epidemiologic studies may not have captured the true prevalence and regional variance of rickettsioses in Southeast Asia. In addition, prevalence studies in popular tourist destinations are lacking. Thus, risks to visitors are unknown. References to case reports of infections in returned travelers from different parts of Southeast Asia are provided below in relevant sections. Further co-ordinated effort is urgently needed among nations in Southeast Asia to ascertain regional prevalence.

IMMUNOPATHOGENESIS

Rickettsiae attach and enter the host cell receptors by means of surface proteins ompB and ompA in SFGR.[40] Rickettsial infections are vasculotrophic in nature and current

hypothesis regarding immunopathogenic mechanisms concerns that of oxidative stress, leading to endothelial cell injury, increased microvascular permeability, and possibly development of a procoagulant state.[40] *Rickettsia*-infected endothelium produces interleukin-6 (IL-6), IL-8, and monocyte chemoattractant protein-1.[40] Host immune responses determine the clinical severity and other clinical predictors include older age, glucose-6-phosphate dehydrogenase deficiency, diabetes, and male sex.[41] Notably, an *in vitro* study showed that scrub typhus infection was associated with more prominent levels of inflammatory cytokines production and more pronounced activation of coagulation pathways compared with murine typhus.[42] Further studies have suggested that scrub typhus infection induces type 1 immune response and results in increases in levels of interferon-γ, tumor necrosis factor-α, IL-12p40, IL-18, and IL-15.[43] These intrinsic differences in host responses may help explain why scrub typhus can produce more severe disease and deranged biochemical parameters compared with murine typhus or SFGR.

Cytotoxic CD8+ T cells clear acute rickettsial infections and CD4+ and CD8+ T cells are involved in the differentiation of B lymphocytes to plasma cells and the production of antibodies against ompA and ompB, which are protective against reinfection.[44] Antibodies against rickettsial lipopolysaccharides are also produced but they do not appear to confer any protection.[45]

CLINICAL FEATURES

Clinical manifestations of most rickettsioses represent a continuous spectrum.[40] Rickettsial infections generally begin as an acute, non-specific, febrile illness often accompanied by headache, myalgia, nausea, and vomiting.[41] After 3–5 days of illness, a macular, maculopapular, or even vesicular rash appears.[41] An eschar at the site of an ectoparasite bite, with local or generalized lymphadenopathy may also occur (Figure 2).[2] The eschar may be the only clinical sign that differentiates scrub typhus and tick-borne SFG *Rickettsia* from other infectious diseases, including murine typhus.[28,41] Travelers with imported rickett-
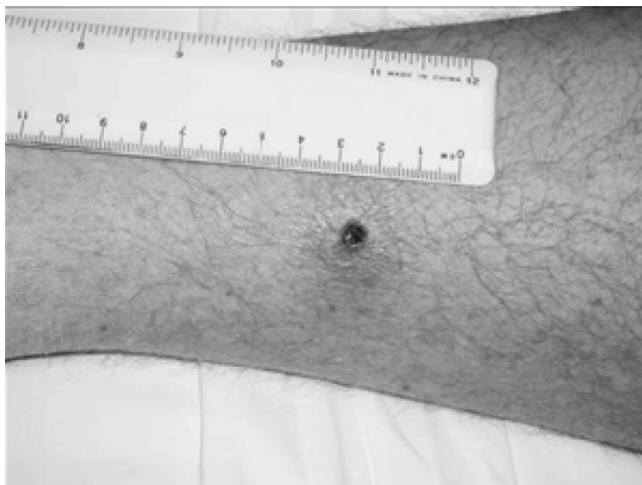

FIGURE 2. Rickettsial eschar. Reproduced with written permission from The Commonwealth of Australia, Department of Defense, Joint Health Command (http://www.defence.gov.au/health/infocentre/journals/adfhj_apr06/adfhealth_7_1_10-13.html).

sial diseases often become sick before or within a few days of returning from a disease-endemic region. Because the incubation period for most rickettsial infections is 6–20 days, an illness that begins more than 18 days after return from a disease-endemic area is unlikely to be rickettsial in origin.[11,41]

Because clinical features of rickettsial infections are non-specific, many common febrile illnesses can mimic rickettsioses.[46] Differential diagnoses are wide and include viral infections, such as dengue, chikungunya, Epstein-Barr virus, cytomegalovirus, other herpesviruses, enteroviruses, flaviviruses, viral hepatitis, and human immunodeficiency virus; bacterial infections, such as typhoid fever, leptospirosis, disseminated gonococcal infections, and syphilis; and parasitic infections, such as malaria and toxoplasmosis.[41,47] Because of the undifferentiated nature of presentation, delay in diagnosis is common.

A case-control study along the Thailand–Myanmar border identified jungle excursion (odds ratio [OR] = 5.3), history of arthropod bites and/or rash (OR = 22.9), thrombocytopenia (OR = 3.4), and an increased level of alanine aminotransferase (OR = 3.0) as clinical predictors for diagnosing rickettsial infections in patients with undifferentiated fever.[46] Presence of an eschar was further noted to be a strong predictor (OR = 21.1, 95% confidence interval = 5.4–82.4).[46] A small comparative case series study in febrile returned travelers also found that an increased level of C-reactive protein and absence of neutropenia may help differentiate rickettsial infections from dengue.[48] Although a thorough history and clinical examination may assign a pre-test probability of rickettsial infections, no single factor reliably separates rickettsioses from other infections in either the local populace or returned travelers.

Because the diagnosis of rickettsial infections relies on serologic or molecular tests, often with considerable delay, some clinicians advocate a trial of doxycycline therapy in patients with ongoing undifferentiated fever that exceeds the expected duration of common viral illnesses, or in patients in whom the illness is rapidly progressive. Defervescence within 48–72 hours after initiation of doxycycline is often taken as a marker of rickettsial infections.[41] Up front administration of doxycycline has also been tested in a resource-limited country (Laos) for treatment of patients with undifferentiated acute hepatitis where doxycycline responsive infections such as rickettsioses and leptospirosis made up 7.3% and 6.8% of acute hepatitis presentations.[49]

Endemic (murine) typhus. Endemic (murine) typhus caused by *R. typhi* occurs in tropical and temperate climates.[11] It is carried by rat flea *X. cheopis* and typically thrives in markets, grain stores, breweries, and garbage depots where rats (mainly *R. rattus* or *R. norvegicus*) serve as the main reservoir. However, other rodent species and cats have also been implicated as reservoirs and cats fleas can also transmit the infection.[12,32,33,50,51]

Overcrowding, poor public health and sanitation measures provide ideal conditions for transmission of murine typhus. In addition, clearing of land for urban development and construction enable rodent populations to increase and expose humans to the zoonotic life cycle, thus leading to increasing seroprevalence observed in some of the rapidly developing countries, such as Malaysia.[19] More aggressive infections have also been reported in refugee camps,[2] and this finding may be significant for refugee populations along the Thailand–Myanmar border. It is important to note that imported murine typhus can be acquired after travel to exclusively urban areas. Infections

have been reported among city dwellers in more affluent countries such as Singapore, and immigrant workers living in poor and unhygienic conditions seemed to be at a higher risk.[11,12,16,52,53] However, no associated seasonal or festive variation with murine typhus has been observed.[16,19,28,54]

Flea bites and contamination of excoriated skin or respiratory tract with flea feces cause infections, and *R. typhi* can remain infectious in dried flea feces for ≥ 100 days.[11,12,41] the incubation period is usually approximately 8–16 days.[41] Infection usually produces a mild or self-limiting illness that lasts 3–7 days; symptoms include headache, rash, and arthralgia.[12] Rash can be of variable frequency, ranging from 20–80%, and is described as non-pruritic, macular or maculopapular spreading from center to periphery and occurring a few days after the onset of fever.[12] Murine typhus is frequently misdiagnosed in cases where rash is absent or fleeting and atypical symptoms, such as gastrointestinal manifestations, are prominent.[11] Severe complications appear rare, but where present, can cause meningoencephalitis, pneumonia, shock, renal failure, myocarditis, endocarditis, and splenic rupture.[12,28,41,54,55] Reported mortality ranges from 1% to 4%, and higher mortality is associated with lack of antibiotics.[12]

Imported murine typhus has been reported in travelers returning from Bali and Lombok regions in Indonesia[55–57] and also from southern Vietnam (Cu Chi) where murine typhus has not been reported since the 1960s, but probably occurs sporadically among the local population.[58] A severe case of imported murine typhus from northern Thailand causing septic shock and acute respiratory failure has also been described.[59] Murine typhus complicated by dengue hemorrhagic fever has also been reported in a returned traveler from Brunei.[60]

Scrub typhus. *O. tsutsugamushi* is acquired from the bite of the larval stage of infected trombiculid mites (chiggers) living on the waist-high grass growing in previously cleared jungle around villages and plantations.[2,61] Chiggers have also been found on many rodent vectors.[29] Cases were acquired during land clearing, logging, road building, and military operations.[42] Active rice fields are also an important and underappreciated sources of infection.[62] Travelers with eco-tourism activities, such as trekking, camping, or rafting in rural areas, are at most risk.[47,52,61] Outbreaks have also been reported

mainly in rural agricultural areas,[29] but cases have been seen in urban centers of Southeast Asia.[22,30,63] Unlike murine typhus, seasonal variations can be found with scrub typhus; incidence increases towards the end of the rainy season and the beginning of winter months (July–November) in Southeast Asia.[27,28]

Most scrub typhus cases are mild and characterized by acute onset fever, myalgia, generalized lymphadenopathy, maculopapular rash, and splenomegaly. Eschar is variably seen in 20–90% of cases, typically on torso, axilla, or groin, and may be diagnostic (Figure 3).[2,28,52,64,65] Conjunctival suffusion can also occur.[41] Of all rickettsial diseases, scrub typhus is more likely to present with a severe clinical picture because of a more prominent inflammatory response,[42] which causes multiorgan dysfunction, meningoencephalitis, coma, and persistent neurologic deficits.[11,66] Pulmonary involvement occurs in up to 50% of patients[28,65] but clinical manifestation of acute respiratory distress syndrome is rare.[67–70] Mortality rates can be up to 25% and scrub typhus could be potentially mistaken for melioidosis or leptospirosis, which are more common in the region.[69,70] Atypical clinical features and absence of eschar may result in delayed diagnosis, complications, or death.[47,66–68] Laboratory abnormalities of scrub typhus may include leukopenia or mild leukocytosis and thrombocytopenia. Hepatic dysfunction is common and transaminitis was noted in 90% of patients in a cases series.[28] Overall mortality rates for scrub typhus range from 2.6% to 15%.[28,41] Most case reports for imported scrub typhus were from Thailand or the Thailand–Myanmar border.[66,67]

Spotted fever group rickettsiae. The SFGR contain a large number of species transmitted from rodents, dogs, and wild animals by ticks and sometimes by lice. Clinical presentation may vary between species and geographic regions. *R. honei*, *R. conorii* subsp. *indica* (Indian strain), *R. helvetica*, *R. japonica*, and *R. felis* have been reported to cause human infections in Southeast Asia on the basis of serodiagnostic studies (Supplemental Table). Some authors considered *R. felis* to be part of a transitional group of rickettsiae. However, the presence of the *ompA* gene confirms its membership in the SFGR.[12,71] It is also important to note that with SFGR, given the limitations of immunofluorescence serologic tests,
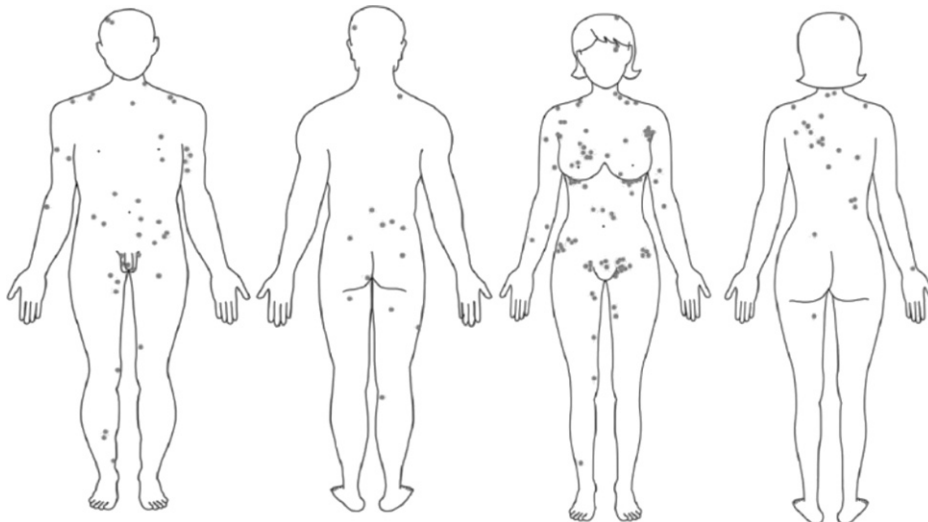

FIGURE 3.   Typical distribution (grey dots) of scrub typhus eschar on body sites.[64]

antigenically cross-reacting but phylogenetically distinct SFGR species, which are yet to be identified by culture or molecular methods, may be present in Southeast Asia.

R. honei, formerly known as Thai tick typhus TT-118, was first isolated from *Ixodes* (particularly *I. granulatus*) and *Rhipicephalus* species of ticks in Chiang Mai Province, Thailand in 1962.[72] *R. honei* is now considered to be one of the SFGR endemic to Thailand (and possibly the remainder of Southeast Asia) that causes human disease[73,74] and may be used as a reference species in serologic tests for SFGR in this region (Supplemental Table). Infections likely occur in rural areas throughout Southeast Asia, where human and animal interactions are more common, although one clinical case from urban Bangkok, Thailand, without any antecedent exposure to rural setting has been reported.[75] Infections usually cause mild disease with fever, headache, and myalgia. Lymphadenopathy, maculopapular rash, or rarely, petechial rash may be present and an eschar may be seen.

R. felis is transmitted mainly by the cat flea *C. felis* (the rat flea and other arthropods can also transmit it), and is an emerging infection globally.[71] In Southeast Asia, two serologically confirmed clinical cases have been reported from the Thailand–Myanmar border and Vientiane, Laos (Supplemental Table).[3,63] The presence of *R. felis* in this region was further supported by rodent and entomologic studies. *R. felis* infections produce a clinical syndrome similar to that of murine typhus.[35] Given the clinical similarities, some authors believe that previously reported outbreaks of murine typhus infections may have been caused by the more recently recognized *R. felis*.[12]

R. helvetica is transmitted by *Ixodes* spp., and clinical cases of infection have been reported in Thailand, along the Thailand–Myanmar border, and Laos.[3,63,76] Infection with *R. helvetica* presents as a mild disease, especially in warm seasons, with fever, headache, and myalgia but no rash.[76] Human infection with SFGR species closely related to *R. japonica* acquired from camping at Khao Yai National Park in Thailand has also been noted.[77,78]

DIAGNOSIS

Historically, the Weil-Felix agglutination test has been used to diagnose rickettsial infections on the basis of the observation that cross-reactivity occurs between antibodies to *Rickettsia* and phylogenetically unrelated bacteria of the genus *Proteus* (strains OX2, OX19, and OXK).[79,80] Although this test lacks sensitivity and specificity and thus is no longer recommended,[79–81] it may still provide cheap and rapid diagnostic option for rickettsial infections in many resource-limited areas of Southeast Asia.

Serologic diagnosis using indirect immunofluorescence assays (IFAs) is the gold standard serologic test for diagnosing rickettsial infections.[12,79] The IFA serologic test uses whole rickettsial cells and a positive antigen–antibody reaction is visualized as fluorescence by using an ultraviolet microscope.[79] The IFA can also differentiate between different antibody classes (IgM, IgG, and IgA), and antibody concentration is reported as a titer, the highest serum dilution that shows a positive result.[79]

The IFA often identifies the rickettsial species causing infection by measuring microimmunofluorescence assay titers of serum against different rickettsial species.[80] Antigens

against the Wilmington strain of *R. typhi* are commonly used for diagnosing murine typhus, and three serotypes (Karp, Kato, and Gilliam) of *O. tsutsugamushi* are usually used for diagnosing scrub typhus. Usually, homologous antibody titers are higher than heterologous antibody titers.[80] However, among members of the same biogroup, heterologous titers may be as high as homologous titers and cross-absorption studies may help differentiate between the two results, as for identification of the SFGR species.[80]

Conversely, the IFA is expensive, requires a fluorescence microscope, and also requires training.[82] There is also little consensus on the choice of IFA method (i.e., antigenic strains used and antibody isotypes measured) and titers selected as positive may vary for diagnostic and epidemiologic studies.[20] At low dilutions, patient serum may also cross-react with other related bacteria such as *Anaplasma phagocytophilum*, *Ehrlichia chaffeensis*, and even unrelated *Coxiella burnetti*.[3,80,83]

The indirect immunoperoxidase test has been accepted as an alternative standard assay by the World Health Organization to diagnose rickettsial diseases (particularly for scrub typhus) without the need for an ultraviolet microscope by replacing fluorescein with peroxidase, thus reducing laboratory staff training.[80,82,84] The performance of this test has been validated by comparing it against IFA on clinical samples in Thailand.[85]

There are several pitfalls for all serologic methods. First, paired serum samples obtained at least 10 days apart are usually required for diagnosis ($\geq$ 4-fold increase between acute- phase and convalescent-phase antibody titers). Thus, where access is limited and resources are scarce, it may not be a practical approach in many parts of Southeast Asia. Second, host antibody response may be abrogated by early antibiotic treatment or inability (genetic and acquired) to mount an antibody response.[79] This finding is especially important in situations in which empiric doxycycline is given or in parts of Southeast Asia where human immunodeficiency virus prevalence is high. Third, sensitivity and specificity of tests vary,[12,79] and positive and negative predictive values for any assay also vary with the population being examined.

Nucleic acid amplification tests (NAATs) are fairly recent developments in rickettsial diagnostics, and may enable early detection and diagnosis of infection before seroconversion, but they are not yet commercially available and remain restricted mainly to research settings and developed countries.[79] In the NAAT, the citrate synthase gene and 17-kDa antigen gene can be amplified to detect all *Rickettsia* spp. because these genes are present in all species.[79] However, detection of the *ompA* gene is specific to SFGR.[79] The 47-kDa outer membrane protein antigen gene has been shown to be highly specific for *O. tsutsugamushi*.[86] Such PCR methods can be used for eschar and blood (eschar is more sensitive than blood).[82] Conversely, cell cultures for *Rickettsia* are still a research tool.[79] Cell culture is necessary to obtain a rickettsial isolate, although NAAT can often identify the rickettsial species involved in an infection. Serologic analysis is the best tool for determining prevalence.

Unfortunately, at the present time, in many parts of Southeast Asia where rickettsial infections are rampant, and where the local populace would benefit from rapid PCR tests[83] or serologic methods, they remain unavailable and presumptive clinical diagnosis by trial of doxycycline remains the standard practice.

TREATMENT AND PREVENTION

Doxycycline (100 mg, twice a day) is the mainstay of treatment of murine typhus for adults and children (weighing ≥ 45 kg), and should be continued for a minimum of five days in total, or three days after the resolution of symptoms.[12] For children weighing < 45 kg, doxycycline at a dose of 0.9 mg/kg/day in two divided doses is recommended. Doxycycline is considered safe in children < 9 years of age, has limited risk of dental staining with short courses, and fever resolution is seen within 48 hours in most.[54] Chloramphenicol (250–500 mg every 6 hours) can be used to treat women in first or second trimester of pregnancy, and quinolones may be an alternative.[12] However, murine typhus may show variable responses to quinolones, and treatment failure has been reported with ciprofloxacin in a returned traveler from Thailand.[87]

Doxycycline (100 mg, twice a day) or chloramphenicol (250–500 mg every 6 hours) can be used to treat scrub typhus.[88] The *O. tsutsugamushi* Kato strain has been reported to be intrinsically resistant to quinolones.[89] Reduced susceptibility to doxycycline and chloramphenicol has also been reported from Chiangrai in northern Thailand.[90] A randomized controlled trial from the same area showed that treatment with rifampicin (300–450 mg, twice a day) for one week was superior to doxycycline in terms of time to defervescence and relapse rates.[91] However, combination therapy with rifampicin and doxycycline did not have any added efficacy.[91]

In areas where reduced susceptibility to tetracyclines is present, a prospective, open-label, randomized trial showed that a single dose of azithromycin (500 mg) may be equally effective as a seven-day course of doxycycline (100% versus 93.5% cure; $P = 0.12$) with similar median time to defervescence (21 hours versus 29 hours; $P = 0.97$).[92] A randomized control trial in northern Thailand involving 57 patients with scrub typhus, 14 patients with murine typhus, and 11 patients with leptospirosis comparing a three-day course of azithromycin to a seven-day course of doxycycline showed that fever clearance was similar (48 hours, range = 8–336 hours versus 48 hours, range = 8–118 hours; $P = 0.57$), although more adverse effects were found with doxycycline treatment.[93] Azithromycin is also considered safe in pregnant women. A five-day regimen of 800 mg/day of telithromycin may have efficacy similar to that of doxycycline in treatment of mild-to-moderate scrub typhus.[94] Optimal duration of treatment with doxycycline is uncertain, and courses as short as three days have been studied.[95]

Doxycycline (100 mg, twice a day for 5–7 days) is recommended for treatment of all SFGR infections. Once a week doses of doxycycline (200 mg) can prevent scrub typhus,[96,97] but there have been no studies on prophylaxis therapy for other rickettsioses. The use of insect repellents, such as N,N-diethyl-3-methylbenzamide (DEET) and permethrin-impregnated clothing and bedding, may also form part of preventive measures against scrub typhus in travelers to disease-endemic areas in Southeast Asia.

CONCLUSIONS

Rickettsial infections are a major cause of non-malarial febrile illnesses among the residents of Southeast Asia and remain an important differential diagnosis for febrile returned travelers from that region. However, many challenges remain in the diagnosis and management of rickettsial infections. The regional epidemiology needs to be established to determine the true burden of rickettsial diseases compared with other tropical illnesses in Southeast Asia. To achieve this epidemiology, improved diagnostic measures and facilities need to be made accessible to many areas within Southeast Asia, especially to rural and remote settings, where the disease burden may be higher. A collaborative effort between nations in Southeast Asia may be needed to address rickettsial epidemiology, diagnostics, and management. From an individual physician's perspective, rickettsial infections remain a diagnostic challenge in resource-poor settings. Therefore, it is important to recognize the clinical features promptly, include rickettsioses in the differential diagnoses, and consider early initiation of appropriate treatment.

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