Rickettsioses as causes of CNS infection in southeast Asia

Carole Eldin, Philippe Parola

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See Articles page e104

In *The Lancet Global Health*, Sabine Dittrich and colleagues[1] report that scrub typhus caused by *Orientia tsutsugamushi*, murine typhus caused by *Rickettsia typhi*, and leptospirosis caused by various *Leptospira* species account for more than a third of CNS infections diagnosed over 8 years in Vientiane Hospital in Laos. The study is one more great contribution from this team in their investigation of undocumented syndromes, as well as in the public health challenge of rickettsial diseases in southeast Asia. The same investigators have previously reported that scrub typhus was the second most common microbial cause of fever of unknown origin in rural Laos (122 [15%] of 799 diagnosed cases).[2] In 2006, rickettsial infection was detected in 115 (27%) of 427 adults admitted to Vientiane Hospital for fever with negative blood culture.[3] The most common rickettsial agent was *O tsutsugamushi* followed by *R typhi*. Fewer data are available about the prevalence of these diseases in other southeast Asian countries. In Thailand, scrub and murine typhus has been reported[4] in 16% and 2%, respectively, of fever of unknown origin, with mortality of 3–17% for scrub typhus. Even if epidemiological data for the whole region are unavailable, the substantial presence of rickettsial infections is shown by frequent reports in travellers returning from this area.[5] Because ecotourism and adventure travel are increasingly popular, the incidence of tick-borne rickettsioses among travellers is likely to continue to increase.

All patients with rickettsial infections reported by Dittrich and colleagues presented with fever at admission, and few patients presented with typical eschars of inoculation (only 3·6% of patients with murine typhus and 6·7% with scrub typhus).[1] This finding might be a result of poor awareness about pathognomonic signs of rickettsioses among clinicians rather than an absence of such disease.

Rickettsioses are treatable but remain underestimated. Besides murine typhus and scrub typhus, tick-borne spotted fever group rickettsioses cause much fever of unknown origin in tropical countries.[6] *R felis* is one such rickettsia; it has been detected worldwide in arthropod hosts (mainly fleas), with the cat flea *Ctenocephalides felis* the only confirmed biological vector. A growing number of reports implicate *R felis* in human disease, particularly in the tropics. It has been detected in 3–4% of cases of fever of unknown origin in rural Mali[7] and Kenya,[8] and 6% of cases in rural Senegal.[7] *R felis* has also been detected in mosquitoes[7] and it is common in countries in Africa with high prevalences of malaria.[7] Cases of *R felis* infection in Thailand have also been reported.[9]

Collaborations of investigators in the tropics combined with powerful diagnostic methods have increased the recognition of neglected pathogens in patients with acute undifferentiated fever. However, when studying the causes of fever of unknown origin, inclusion of local negative controls is essential because the incidence of many pathogens in these regions is totally different from their incidence in Europe, changing the predictive value of diagnostic tests. The lack of local negative controls causes false positives because of the commonness of asymptomatic forms of infectious diseases; therefore, European controls cannot be used to evaluate the specificity of diagnostic techniques in tropical countries.

Rickettsioses are severe diseases that can be fatal, yet in Dittrich and colleagues' study few patients with scrub and murine typhus received doxycycline (55% and 39%, respectively).[1] As a consequence, the use of an empirical doxycycline treatment for patients with fever of unknown origin should be discussed, especially when empirical treatment with β-lactams has failed or in cases with severe clinical presentation. Doxycycline is used for malaria prophylaxis in travellers. Only two prospective randomised studies[10] have shown the effectiveness of prophylactic doxycycline to prevent scrub typhus. Designing comparative studies to test the drug's effectiveness for preventing scrub typhus would be difficult. However, we propose that doxycycline be given as a priority for chemoprophylaxis against malaria in travellers to the tropics to thereby protect against rickettsioses and leptospirosis.

*Carole Eldin, *Philippe Parola*
Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), Faculté de Médecine, Aix Marseille Université, 13385 Marseille cedex 5, France
philippe.parola@univ-amu.fr

1 Dittrich S, Rattanavong S, Lee SJ, et al. Orientia, rickettsia, and leptospira pathogens as causes of CNS infections in Laos: a prospective study. *Lancet Glob Health* 2015; **3:** 104–12.

2 Mayxay M, Castonguay-Vanier J, Chansamouth V, et al. Causes of non-malarial fever in Laos: a prospective study. *Lancet Glob Health* 2013; **1:** e46–54.

3 Phongmany S, Rolain J-M, Phetsouvanh R, et al. Rickettsial infections and fever, Vientiane, Laos. *Emerg Infect Dis* 2006; **12:** 256–62.

4 Suputtamongkol Y, Suttinont C, Niwatayakul K, et al. Epidemiology and clinical aspects of rickettsioses in Thailand. *Ann N Y Acad Sci* 2009; **1166:** 172–79.

5 Jensenius M, Davis X, von Sonnenburg F, et al. Multicenter GeoSentinel analysis of rickettsial diseases in international travelers, 1996–2008. *Emerg Infect Dis* 2009; **15:** 1791–98.

6 Parola P, Paddock CD, Socolovschi C, et al. Update on tick-borne rickettsioses around the world: a geographic approach. *Clin Microbiol Rev* 2013; **26:** 657–702.

7 Mediannikov O, Socolovschi C, Edouard S, et al. Common epidemiology of *Rickettsia felis* infection and malaria, Africa. *Emerg Infect Dis* 2013; **19:** 1775–83.

8 Richards AL, Jiang J, Omulo S, et al. Human infection with *Rickettsia felis*, Kenya. *Emerg Infect Dis* 2010; **16:** 1081–86.

9 Edouard S, Bhengsri S, Dowell SF, Watt G, Parola P, Raoult D. Two human cases of *Rickettsia felis* infection, Thailand. *Emerg Infect Dis* 2014; **20:** 1780–81.

10 Twartz JC, Shirai A, Selvaraju G, Saunders JP, Huxsoll DL, Groves MG. Doxycycline propylaxis for human scrub typhus. *J Infect Dis* 1982; **146:** 811–18.