

Tick-transmitted human infections in Asia



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Vector-borne pathogens of human significance cause a predicted 17% of infectious diseases worldwide, of which, ~23% are tick transmitted¹. Although second to mosquitoes in terms of impact, ticks are thought to carry a greater diversity of pathogens than other arthropod vectors². Asia is a key region for tick-borne pathogens, with tick species typically restricted to latitudes below 60–55°N³ where the climate is warmer and wetter – from the steppe regions of Russia to the tropical rainforests of South East Asia.

There are approximately 896 species of tick (Ixodidae, Argasidae and Nuttalliellidae) worldwide⁴. In Asia the knowledge of key species is still limited, especially in the Southeast. Tick species that may transmit specific pathogens are highly dependent on distribution, with studies described below primarily identifying *Ixodes* spp., *Haemaphysalis* spp., *Hyalomma* spp. and *Dermacentor* spp. as important vectors for various pathogens.

Despite the prevalence of ticks and the clinical importance of the pathogens transmitted, very little information is available on the disease burden and distribution of tick-transmitted infections in Asia, particularly outside of Russia, China, Japan and Korea. This is most likely due to lack of research in ticks and tick-borne diseases (TBD) outside of the more developed northern Asian

countries, and a lack of knowledge in the healthcare systems of LMICs (lower to middle income countries) as many TBD infections have similar clinical presentations and available diagnostics may be limited. Knowledge of TBDs is highly dependent on whether the diseases are notifiable within the country; in Russia for instance, seven TBDs are reportable providing incidence data, but little is known about other non-reportable infections⁵. In Russia approximately 0.5 million tick bites are reported each year, with an estimated $\leq 2\%$ resulting in clinical infections, although this is likely to be much higher, particularly in rural regions⁵. In Japan, 12 TBDs are reportable, while in Korea, six diseases of potential tick origin are reportable^{6,7}. TBD in Asia can be categorised into four distinct groups: rickettsias, other bacterial pathogens, protozoa and viruses.

Rickettsias

The rickettsias form the largest group of TBD in Asia. Although globally distributed, at least thirteen clinically important rickettsial species have been identified throughout Asia (east of the Caspian Sea) in either patients or ticks^{8–11}. Currently a further 10 (including candidatus species) have been identified in ticks although their implications for public health is uncertain^{8,12–14} (Table 1). Often, identification in patients is made by serological

Table 1. Tick-borne rickettsias identified in Asia. Identification either by serology (S), PCR (G) or isolation (I) from patients and/or ticks within Asia.

| Known pathogenic rickettsias | | | Rickettsias of unknown pathogenicity | | |
|-----------------------------------|-----------|----------|--------------------------------------|-----------|----------|
| Species | Human ID? | Tick ID? | Species | Human ID? | Tick ID? |
| <i>R. aeschlimannii</i> | – | G | <i>R. asiatica</i> | – | I |
| <i>R. conorii indica</i> | G/S | I | <i>R. bellii</i> | – | G |
| <i>R. heilongjiangensis</i> | G | G/I | <i>R. hoogstraalii</i> | – | G |
| <i>R. helvetica</i> | S | – | <i>R. tarasevichiae</i> | – | G |
| <i>R. honei</i> | G/S | G | Candidatus <i>R. gannanii</i> | – | G |
| <i>R. japonica</i> | G/I | G/I | Candidatus <i>R. khammouanensis</i> | – | G |
| <i>R. massiliae</i> | G | G | Candidatus <i>R. laoensis</i> | – | G |
| <i>R. monacensis</i> | – | G | Candidatus <i>R. mahosotii</i> | – | G |
| <i>R. raoultii</i> | G | G/I | Candidatus <i>R. principis</i> | – | G |
| <i>R. rickettsii</i> | S | – | Candidatus <i>R. tibetani</i> | – | G |
| <i>R. sibirica sibirica</i> | G | G/I | | | |
| <i>R. sibirica mongolitimonae</i> | G | G | | | |
| <i>R. slovacae</i> | – | G | | | |
| <i>R. tamurae</i> | G/S | G/I | | | |
| Candidatus <i>R. kellyi</i> | G | – | | | |

techniques, limiting identification to non-specific genus-level rather than species-level, which may obscure the clinically important species circulating in the region. Symptoms for infections are variable, with most causing fever, chills, headache, malaise and myalgia with a variable proportion developing a maculopapular rash. *R. sibirica* results in a lymphangitis-associated rickettsiosis¹⁵.

Other bacterial pathogens

Closely related to the rickettsias are *Anaplasma* and *Ehrlichia*. *A. phagocytophilum* is the agent of Human Granulocytic Anaplasmosis (HGA)¹⁶, while *E. chaffeensis* is the cause of Human Monocytic Ehrlichiosis (HME)^{16,17}. Both share similar symptoms including fever, headache, leukocytopenia, with neurological symptoms more common in HME¹⁸. Borreliosis is becoming more important throughout the region, with *Borrelia afzelii* and *Bo. garinii* being the main species in Asia, although a *Bo. valaisiana*-related sp. has also been identified in patients^{12,19,20}. Despite its dominance in the western hemisphere, *Bo. burgdorferi sensu stricto* has only been isolated from rodents in Asia^{19,20}. Borreliosis may present with erythema migrans, fever, headaches and fatigue, and in a minority, cardiac and central and peripheral central nervous system abnormalities¹⁹. Although the following human

pathogens (*Francisella* spp., *Bartonella* spp., *Brucella* spp. and *Coxiella* spp.) have been identified in ticks in Asia, the tick-human route of transmission for these four organisms is highly disputed or considered infrequent. Infection is more likely through other routes such as other vectors, direct contact with animals, food items or aerosols; nevertheless, ticks may still play a vital, yet indirect role in disease incidence. *Francisella tularensis* has been detected in ticks from Japan, China and Thailand^{21,22}, while *F. novicida*, has been isolated from a patient in Thailand²³. At least 15 species of *Bartonella* are known in Asia, some of which have been identified in ticks²⁴. There are reports of clinical *Bartonella* spp. infections in China, Thailand, Japan and Korea^{24,25}, although these may be due to transmission via fleas or mammalian contact. The greatest human incidences of brucellosis infections are reported from central Asia²⁶. *Brucella melitensis* and *Br. abortus* (the most pathogenic species) have been identified in ticks and shown to be transmitted²⁷. A number of tick species have been shown to harbour *Coxiella burnetii* (the etiologic agent of Q fever) in Malaysia, Laos and Thailand^{12,22,28}. Transmission from ticks to mammalian hosts has been shown to occur experimentally but it remains to be seen if this is a viable route for human infections.

Protozoa

Although predominantly recognised as a TBD of veterinary importance, cases of human babesiosis have been identified throughout China (including the China-Myanmar border), Russia, Japan and Korea²⁹. Infections are predominantly *Babesia microti*, although *Ba. divergens* and *Ba. venatorum* have also been identified. Clinical symptoms are similar to malaria infections and therefore often result in misdiagnosis and under-reporting of this pathogen. *Ixodes persulcatus* is considered the key tick species for transmission²⁹.

Viruses

Tick-borne encephalitis viruses (TBEV) have been identified in both ticks and patients across Asia³⁰, including serological evidence in rodents and humans in Vietnam³¹. Infection may result in central nervous system abnormalities. Of the Bunyvirales, outbreaks of Crimean-Congo haemorrhagic fever (CCHF) have been reported in China, the first of which was in Xinjiang Province in 1965³² and in Pakistan and India³³. Clinical symptoms include severe fever, haemorrhage, fatigue, myalgia, oliguria and disturbance of consciousness. Severe Fever with Thrombocytopenia Virus (SFTV) has been reported in China, Japan and South Korea and is transmitted by *Haemaphysalis longicornis* ticks. SFTV is characterised by fever, thrombocytopenia, leukocytopenia, increased serum liver enzyme levels, and organ failure³⁴. Powassan virus is a rare, yet potentially fatal neurotropic virus seemingly restricted in Asia to Far Eastern Russia region. Symptoms vary between patients, making diagnosis difficult, but may rapidly develop into more severe symptoms including neurological defects³⁵. Kyasanur Forest Virus (KFV, a flavivirus) is found in southern India, presenting with haemorrhagic and neurological symptoms and is thought to be transmitted predominantly by *Haemaphysalis spinigera*³⁶.

The zoonotic nature of TBDs, combined with a higher proportion of rural populations in Asia, heightens the risk of exposure to TBDs and places a significant weight on scarce public health resources. Surveillance of ticks for potential human pathogens across Asia is needed to alert for clinical problems¹². Improved diagnostics, evidence for appropriate management and public and policy engagement are very much in need, supported by validated survey and surveillance research to better understand the distribution and epidemiology of these potentially life-threatening diseases.

Disclaimers

JCH is a military service member or federal/contracted employee of the United States government. The views expressed in this article reflect the results of research conducted by the author

and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defence, nor the United States Government.

Conflicts of interest

The authors declare no conflicts of interest.

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Biographies

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Dr Khamsing Vongphayloth is a medical entomologist based at Institut Pasteur of Laos in Vientiane, Lao PDR. His research

covers the systematics of arthropod vectors (mosquitoes, ticks, chigger mites and sandflies) and pathogens related to arthropods, in particular bacteria and arboviruses. He is currently working on the biology, ecology and taxonomy of arthropod vectors (mosquitoes, ticks and sandflies) in Laos, and the molecular techniques for identification of these arthropods.

Lieutenant Commander Jeffrey Hertz is the Head of the Laboratory and Field Research Department at U.S. Naval Medical Research Unit TWO, headquartered in Singapore. In this role, he oversees numerous bio-surveillance projects at the NAMRU-2 main laboratory in Phnom Penh, Cambodia and at dozens of governmental and non-governmental collaborative laboratories spanning seven countries. Dr Hertz received his Master's and Doctoral medical entomology training at the University of Florida in the United States

Dr Paul Brey was appointed Director General of Institut Pasteur of Laos in Vientiane, Laos, a Lao national institute, a project that he led from its inception in 2004 to its completion in 2012. The Minister of Health of the Lao People's Democratic Republic has since given Dr Brey the task to direct and develop Institut Pasteur of Laos into a regional center of excellence for infectious disease research and training. In addition to his role as director, Dr Brey also is head of the Medical Entomology Unit at IP Laos. Paul Brey's research has focused on insect innate immunity, insect genomics, host-parasite interactions and more recently on the natural history of pathogen-arthropod transmission cycles and viral/bacterial pathogen discovery in arthropods. He is the author of 90 peer-reviewed scientific articles. He also serves or has served on several scientific advisory boards at Institut Pasteur, at the World Health Organization, and the French Ministry of Science and Technology and is presently the Co-President of the 'Fondation Pasteur Suisse' Scientific Advisory Board.

Professor Paul Newton is an infectious disease physician, based from the Centre of Tropical Medicine and Global Health at the University of Oxford, and directs the Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU) in Vientiane, Lao PDR. He works on the epidemiology, diagnosis and management of fevers, especially rickettsial infections, in Asia and on the global issue of medicine quality. He is also Head of the Medicine Quality Group of the Worldwide Antimalarial Resistance Network (WWARN) in Oxford. He is Professor of Tropical Medicine at Oxford, an Honorary Professor at the London School of Hygiene and Tropical Medicine and at the National University of Laos and Visiting Scholar at Boston University, USA.