

Supplementary Table S3. Case definition of co-infection in humans.

	Human granulocytic anaplasmosis	Tick-borne encephalitis	Rickettsiosis	Human babesiosis
	Adapted from Dahlgren et al. (2015)	Adapted from EU (2012)	Adapted from Portillo et al. (2017)	Adapted from Krause et al. (2021)
Confirmed case	<p>Clinical criteria:</p> <p>Fever and at least one of the following symptoms: headache, myalgia, malaise, anemia, leukopenia, thrombocytopenia, or elevated hepatic transaminases.</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - A fourfold or greater increase in IgG titer by IFA observed in paired serum samples (with acute serum collected within the first week of illness and convalescent serum collected 2-4 weeks later). - Identification of DNA in blood by PCR. - Detection of antigen in a biopsy or autopsy by immunohistochemical (IHC) techniques. - Isolation by culture from a clinical specimen. 	<p>Clinical criteria:</p> <p>Inflammation of the CNS (e.g. meningitis, meningoencephalitis, encephalomyelitis, encephaloradiculitis).</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Detection of both TBE-specific IgM and IgG antibodies in the bloodstream. - Presence of TBE-specific IgM antibodies in cerebrospinal fluid. - Serological conversion or a 4-fold rise in TBE-specific antibodies in matched serum samples. - Identification of TBE viral nucleic acid in a clinical sample. - Isolation of the TBE virus from a clinical specimen. 	<p>Clinical criteria:</p> <p>Fever, rash, and eschar with different combinations.</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Positive PCR and/or culture in blood or skin biopsy samples. - Positive results in immunohistochemical assays conducted on tissues. - Seroconversion or a fourfold increase in specific antibodies observed in paired serum samples. 	<p>Clinical criteria:</p> <p>Fever, fatigue, chills, sweats, headache, and anorexia, and characteristic routine laboratory test abnormalities (anemia, thrombocytopenia, elevated liver enzymes, and/or evidence of intravascular hemolysis).</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Positive PCR result detected in blood. - Presence of intraerythrocytic Babesia parasites observed on blood smear. - Seroconversion or a fourfold increase in specific antibodies detected in paired serum samples.
Probable case	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - Elevated IgG or IgM titers. - Presence of morulae in the cytoplasm of neutrophils or eosinophils. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - Identification of TBE-specific IgM antibodies in a singular serum sample. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - Elevated IgG and IgM titers. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - Elevated titer of specific serum IgG >1/1024. - Elevated titer of specific serum IgM.

	Erythema migrans	Lyme neuroborreliosis (LNB)	Lyme arthritis	Acrodermatitis chronica atrophicans (ACA)	Lyme carditis
	Adapted from Stanek et al. (2011)				
Confirmed case	<p>Clinical criteria:</p> <p>A clinician diagnoses a "typical erythema migrans" rash, i.e., expanding red or bluish-red patch at least 5 cm in diameter may appear, sometimes accompanied by a central clearing. The advancing edge is usually well defined, often intensely coloured and not significantly raised from the surrounding skin</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Detection of <i>B. burgdorferi</i> (<i>s.l.</i>) by culture from skin biopsy. - Positive PCR from skin biopsy. 	<p>Clinical criteria:</p> <p>In adults, meningo-radiculitis and meningitis are the most common, encephalitis and myelitis are less common, and cerebral vasculitis is extremely rare. In children, meningitis and facial palsy are the most common manifestations</p> <p>and two laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Cerebrospinal fluid pleocytosis and demonstration of intrathecal specific antibody synthesis or positive PCR from CSF (early LNB). 	<p>Clinical criteria:</p> <p>A clinician diagnoses recurrent attacks or persistent objective joint swelling in one or a few large joints after ruling out alternative explanations</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Detection of <i>B. burgdorferi</i> (<i>s.l.</i>) by culture from synovial fluid and/or tissue. - Positive PCR from synovial fluid and/or tissue. - Specific serum IgG antibodies, usually in high concentrations. 	<p>Clinical criteria:</p> <p>ACA typically manifests as long-standing red or bluish-red lesions on limb extensor surfaces, initially with swelling, which may later become atrophic. Skin induration and fibroid nodules over bony prominences are possible</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Detection of <i>B. burgdorferi</i> (<i>s.l.</i>) by culture from skin biopsy. - Positive PCR from skin biopsy. - High level of specific serum IgG antibodies. 	<p>Clinical criteria:</p> <p>Any sudden AV conduction abnormalities (grades I-III), rhythm disturbances and possible myocarditis or pancarditis should be investigated to rule out other causes</p> <p>and one or more laboratory criteria for diagnosis:</p> <ul style="list-style-type: none"> - Detection of <i>B. burgdorferi</i> (<i>s.l.</i>) by culture from endomyocardial biopsy. - Positive PCR from endomyocardial biopsy.
Probable case	<p>Clinical criteria and one or more supportive serology result:</p> <ul style="list-style-type: none"> - Non-typical erythema migrans diagnosed by a clinician or compatible lesion reported by a patient after a tick bite. - Seroconversion or a fourfold rise in specific antibodies between paired serum samples. - Elevated levels of IgG or IgM antibodies. 	<p>Clinical criteria and one or more supportive serology result:</p> <ul style="list-style-type: none"> - Cerebrospinal fluid pleocytosis. - Demonstration of intrathecal specific antibody synthesis or positive PCR from CSF (early LNB). - After a duration of evolution ≥ 6 weeks, there have to be found specific IgG antibodies in the serum. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - High levels of specific serum IgG antibodies. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - High levels of specific serum IgG antibodies. 	<p>Clinical criteria and one supportive serology result:</p> <ul style="list-style-type: none"> - Recent or concomitant erythema migrans and/or neurologic disorders. - Specific serum IgG antibodies.