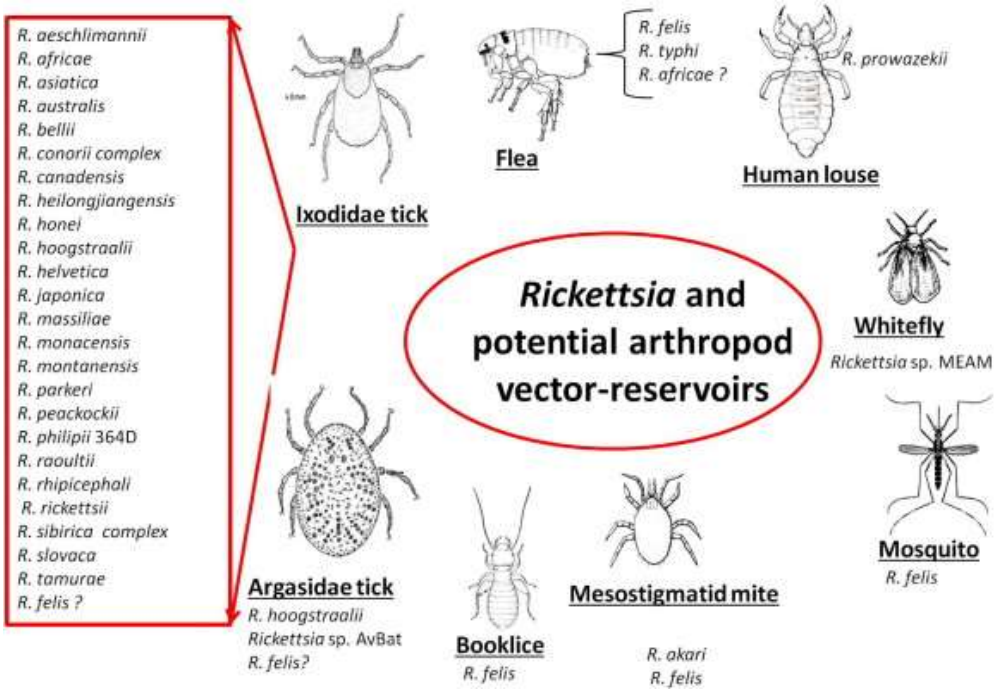
Rickettsial diseases

Definition

- Rickettsial disease in humans is caused by a number of related species of intracellular bacteria of the genus Rickettsia that have blood-feeding arthropod vectors.
- Each species is associated with a different spectrum of clinical features, geographical distribution, insect vector (tick, louse, flea or mite), seasonal incidence and other epidemiological factors.



History

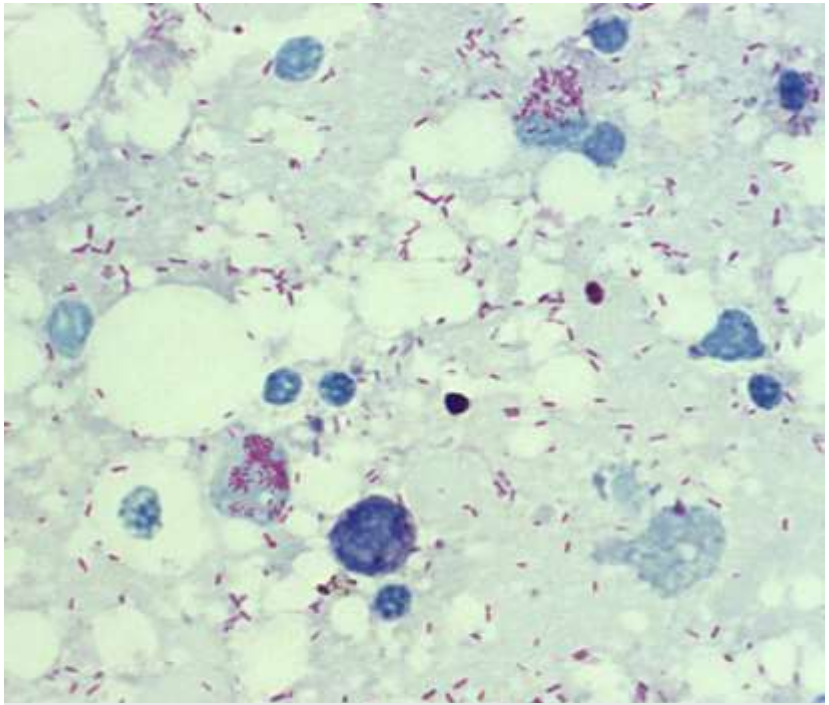
The name ***Rickettsiaceae*** honors Haword Taylor Ricketts for his brilliant experiments. Ricketts, as well as another famous rickettsiologist, Von Prowazek, died of rickettsia during their study period

Classification

Typhus group	Epidemic typhus or Brill Zinsser disease	R. prowazekii	Louse
	Murine/Endemic typhus	R.typhi (R.mooseri)	Flea
Spotted fever group	Rocky mountain spotted fever	R.rickettsii	Tick (Dermacentor)
	R. pox	R.akari	Mite
	Fever boutonneuse or Mediterranean spotted fever or Indian tick typhus	R.conorii	Tick
Other	Q. fever	Coxiella burnettii	**Nil (Air borne)**
	Trench fever / Five day fever / Quintan fever	Rochalimaea Quintana (Bartonella Quintana)	Louse
	Scrub typhus (Chigger borne typhus)	Rickettsia or Orientia tsutsugambushi	Mite
	Ehrlichiosis	Ehrlichiae – human granulocytic ehrlichiosis	Tick

Rickettsia – Characteristics

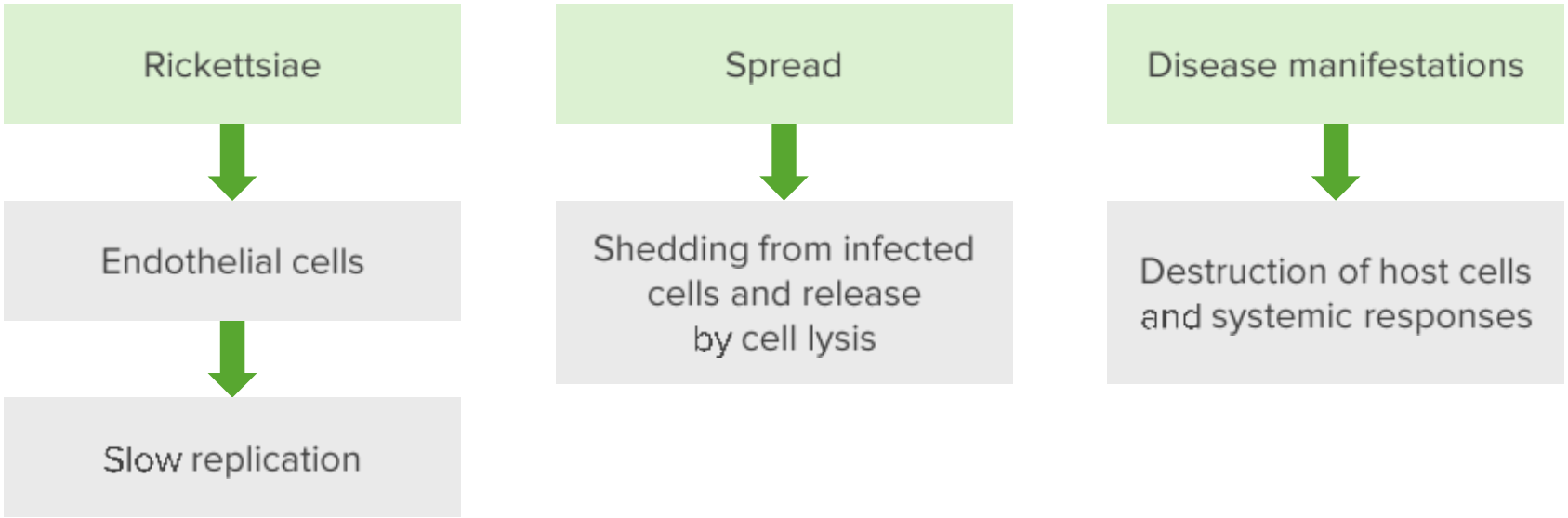
- Small, gram-negative
- Nonmotile pleomorphic
- Obligate intracellular parasites
- Zoonotic diseases
- Transmission: insect vectors from various animal reservoirs



Photomicrograph of a Gimenez-stained yolk sac smear revealed the presence of *Rickettsia rickettsii bacteria*

CDC/Billie Ruth Bird, PD

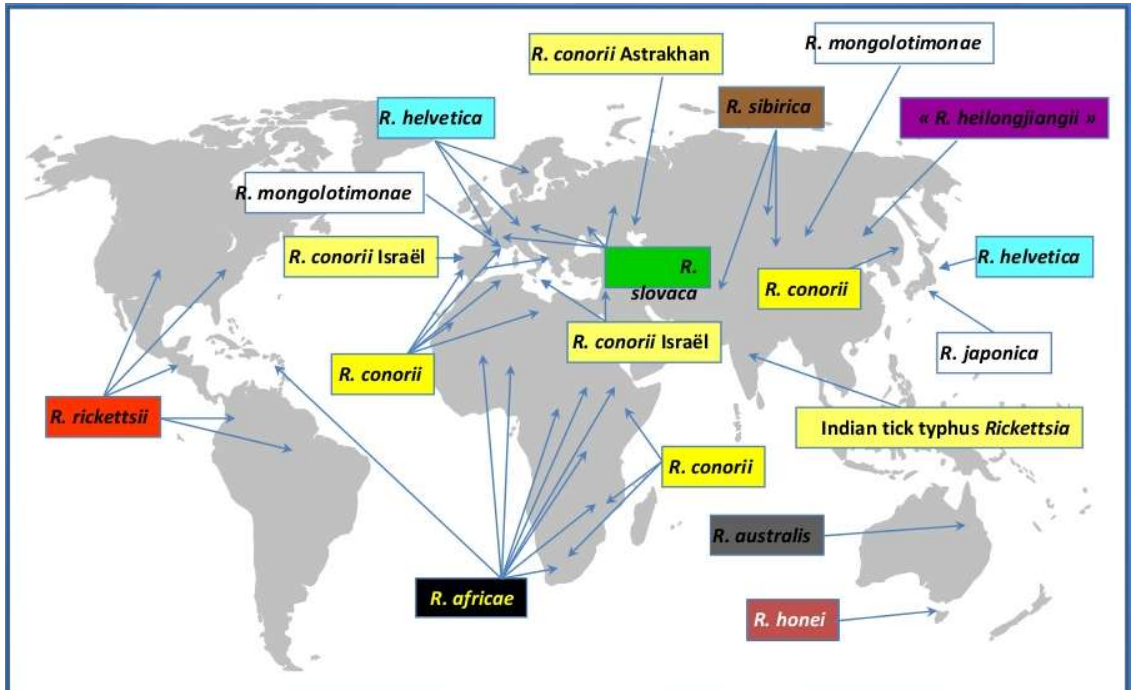
Mechanisms of Pathogenesis – Rickettsia



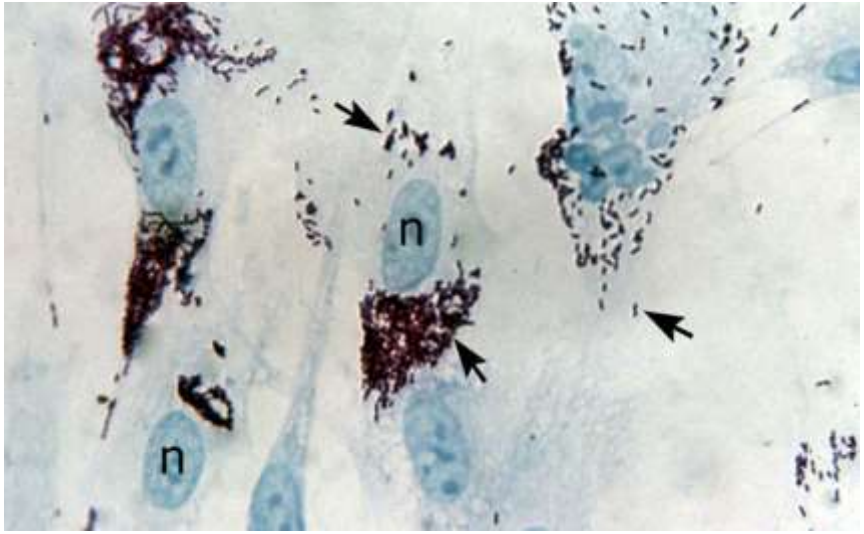
Rickettsial and Related Diseases

Incubation period	7–20 days Exception: chronic Q fever, prolonged incubation of months–years
Clinical features	• Abrupt onset exception: endemic typhus and chronic Q fever • Initial symptoms: fever, chills, headache, and myalgia (followed by rash)
Geographic distribution in US	• Rocky Mountain spotted fever: southeastern Atlantic/southcentral states • Endemic typhus: southeastern states/near the Gulf of Mexico
Reservoirs	Rodents
Vectors	Rat and cat fleas
Treatment	Doxycycline or chloramphenicol

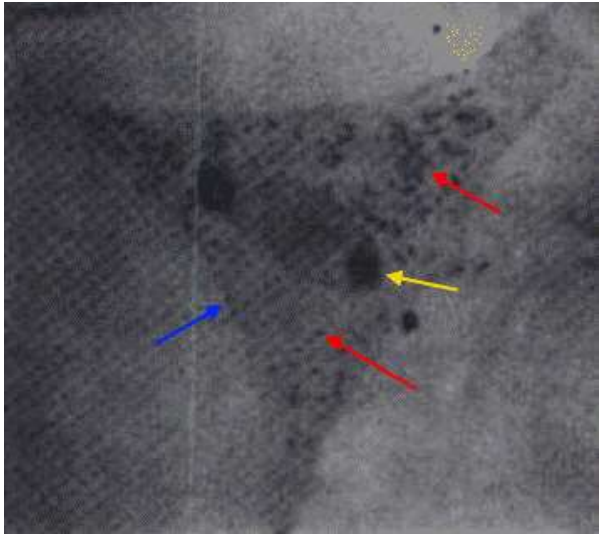
Epidemiology



•**Epidemic typhus** is a potentially lethal, febrile illness caused by the obligate intracellular gram-negative bacterium, Rickettsia prowazekii.
•Genomic analysis demonstrates two strains of *Rickettsia prowazekii*; one isolated only from humans and another identified in flying squirrels (*Glaucomys volans*) which is responsible only for sporadic typhus cases.



Rickettsia prowazekii bacteria growing inside Human fibroblasts. The black arrows point to the bacteria and the 'n' indicates host cell nuclei.



... a chicken embryo fibroblast infected with a large mass of R. prowazekii. The red arrows point to the bacteria, the blue arrow points to the fibroblast cell membrane, and the yellow arrow points to the nucleus of the fibroblast. Yu & Walker, 2005.

Transmission

- *Rickettsia prowazekii* is transmitted from human to human by the body louse *Pediculus humanus humanus*. The head louse (*Pediculus humanus capitis*) and crab louse (*Phthirus pubis*) can transmit *R. prowazekii* experimentally but known epidemics are linked to the body louse.

- Rickettsiae may remain viable and infectious in the dead louse for weeks and in louse faeces for up to 100 days.

- When feeding on an infected human, the body louse ingests *R. prowazekii* which multiplies in the epithelial cells of the midgut. When these burst, the pathogens are excreted with the faeces of the body louse. *R. prowazekii* has an impact on the longevity of the body louse and might kill it.

- On average a mature body louse will live for 20–30 days. Body lice multiply rapidly and their population can increase by 11% per day.

Photo of a body louse and larvae;
SOURCE: World Health Organization

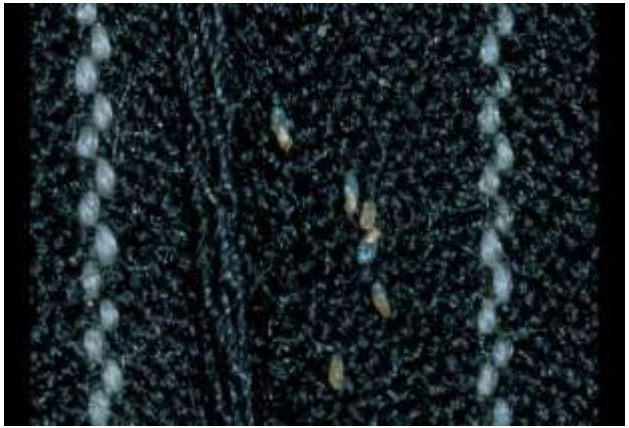


Image Source: SCIENCE SOURCE

Risk factors:

- Overcrowded conditions:
- Reported in army camps, refugee camps, prisons, and homeless shelters
- Sometimes called “jail fever”
- Poor hygiene:
- Civil strife
- War zones
- Malnutrition:
- Famine
- Extreme poverty

Historically, in facts

- The first description of epidemic typhus was thought to be made in 1546 by an Italian physician, Girolamo Fracastoro, who separated epidemic typhus from other typhus-like infections. It remains controversial as to whether typhus was imported into Europe from the New World or vice versa.
- Throughout the Middle Ages and into the early part of the 20th century, periodic epidemics of *R. prowazekii* infection killed millions of people. As an example, during the eight-year period from 1917 to 1925, over 25 million cases of epidemic typhus occurred in Russia, causing an estimated three million deaths. It has been estimated that epidemic typhus has caused more deaths than all the wars in history.
- Epidemic typhus was widespread globally prior to the introduction of modern antibiotics.
- Between the 1950s and 1980s, large epidemics of louse-borne typhus became less frequent and its geographical distribution has declined due to improvements in living standards. During this period, sporadic cases of plausible zoonotic origin (in the USA) and Brill–Zinsser disease were reported in the literature.
- During the 1990s, louse-borne typhus re-emerged in foci associated with poor sanitary conditions (such as in prisons and refugee camps) and a colder climate found in mountainous regions. Outbreaks were reported in the rural highlands of Central and South America (especially in Peru) and Africa (Burundi, Uganda, Ethiopia, Nigeria and Rwanda) . Sporadic cases or small suspected outbreaks were identified in Northern Africa, Russia and Kazakhstan, and among homeless populations in developed countries.
- Sporadic cases of epidemic typhus from a probable zoonotic origin have been reported in several states of the eastern United States in recent decades.

Pathophysiology

- After entering the body, Rickettsia infect and multiply in the endothelial cells of the small venous, arterial, and capillary vessels.
- Infected endothelial cells enlarge due to microbial proliferation.
- Multiorgan vasculitis develops.
- Vasculitis can lead to:
- Thrombosis of the supplying blood vessels: gangrene of the distal parts of the extremities, nose, ear lobes, and genitalia
- Deposition of leukocytes, macrophages, and platelets results in the formation of small nodules.
- Increased vascular permeability:
- Loss of intravascular colloid with subsequent hypovolemia
- Loss of electrolytes
- Decreased tissue perfusion → organ failure

Clinical Presentation

- Incubation period: usually < 14 days
- Clinical manifestations:
- General: Fever, Severe headache, Rash (a pink macular rash that spares the palms and soles), Chills, Myalgias, Arthralgias, Anorexia, Nonproductive cough
- GI: Nausea, Abdominal pain, Vomiting, Diarrhea
- Severe epidemic typhus can lead to: Hypotension, Gangrene with Loss of digits, limbs, or other appendages, CNS dysfunction (ranging from decreased mentation to coma), Multiorgan system failure
- **DEATH**

Image: "Epidemic typhus Burundi" by D. Raoult, V. Roux, J.B. Ndihokubwayo, G. Bise, D. Baudon, G. Martet, and R. Birtles. License: Public Domain

Confirmatory laboratory tests:

- Biopsy of rash using fluorescent antibody staining to determine the causative microbe
- Acute and convalescent serologic testing
- PCR

Antibiotics:

- Primary treatment: doxycycline (4 mg/kg/day)

- Alternative treatments:
- Tetracycline (25–50 mg/kg/day)
- Chloramphenicol 500 mg orally or IV 4 times daily for 7 days

Prevention:

- Louse control:
- Lice may be eliminated by dusting infested individuals with malathion or lindane.
- Washing of clothing in hot water
- Sweeping off dust particles, as they contain excreta of infected lice

- Immunization is highly effective for prevention; however, typhus vaccines are no longer available in Europe and the US.

- Antibiotic prophylaxis with doxycycline (once weekly) for individuals traveling to high-risk areas

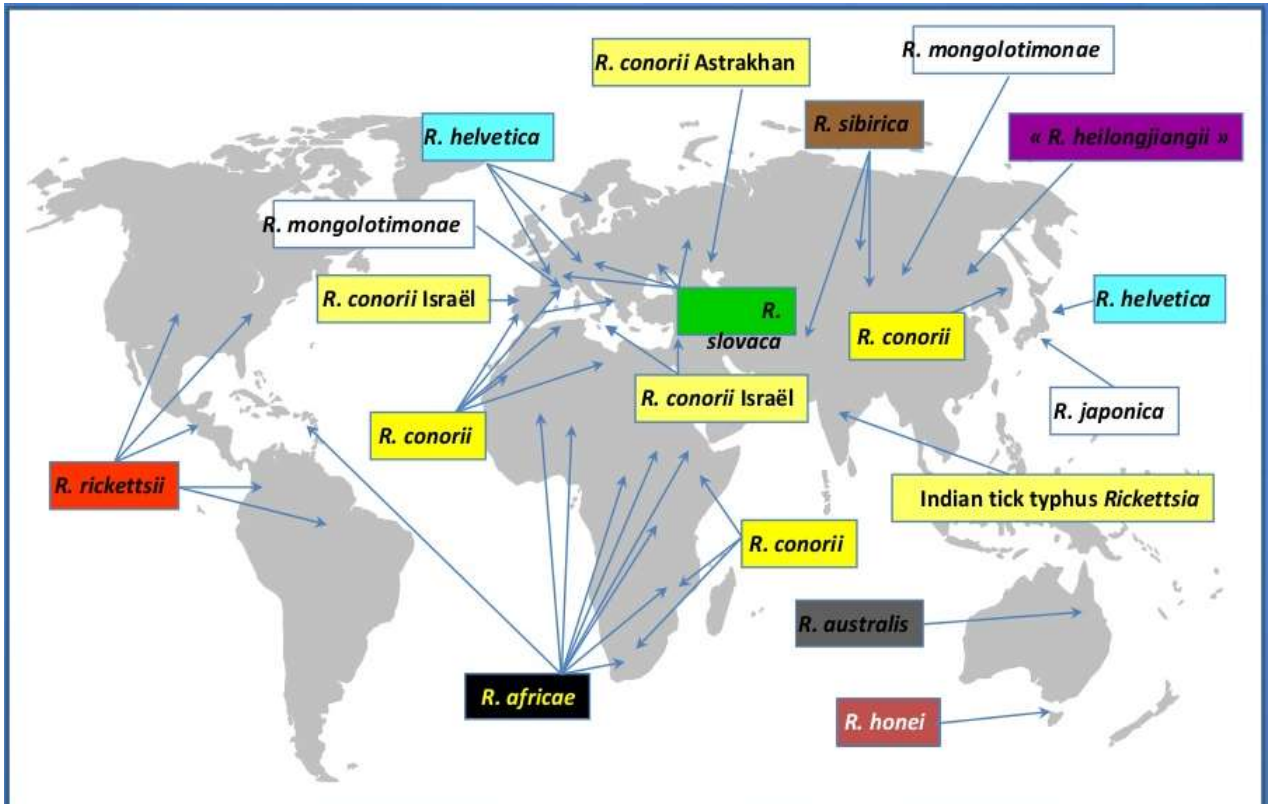
Prognosis:

- Mortality rate of untreated epidemic typhus:
- 20% in otherwise healthy individuals
- 60% in the elderly or in debilitated individuals
- When treated with appropriate antibiotics, the mortality rate can decrease to approximately 3%–4%.

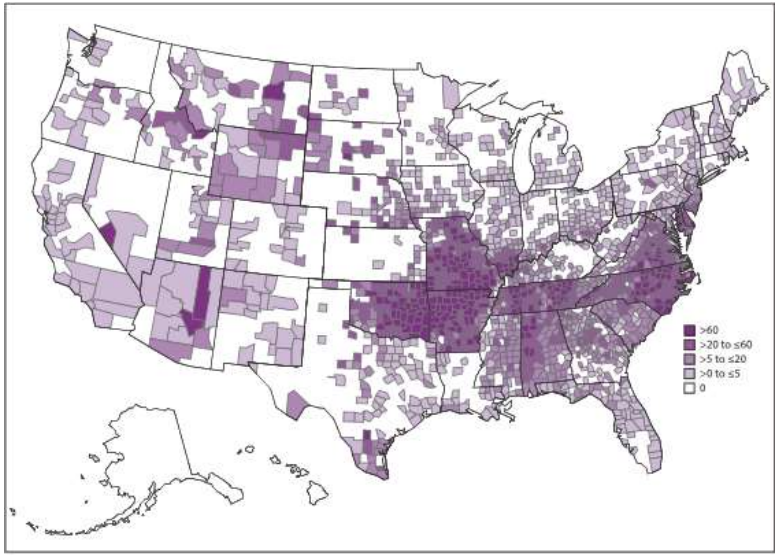
Brill-Zinsser disease:

- Recrudescence of epidemic typhus following an initial attack
- Patients can have a prolonged, asymptomatic R. prowazekii infection for years.
- A relapse that occurs months or years following the 1st illness, when the immune system is weakened due to certain medications, advanced age, or illness
- Symptoms are similar to the original infection, but usually milder.

Rocky Mountain Spotted Fever



Rocky Mountain Spotted Fever



In the United States, the tick species that is most frequently associated with transmission of ***R. rickettsii*** is the American dog tick, Dermacentor variabilis. This tick is found primarily in the eastern, central, and Pacific coastal United States. The Rocky Mountain wood tick, Dermacentor andersoni, is associated with transmission in the western United States.

FIGURE 2. Adult female *Dermacentor variabilis* (American dog tick)

Photo/CDC

FIGURE 3. Approximate U.S. distribution of *Dermacentor variabilis* (American dog tick)

FIGURE 4. Adult female *Dermacentor andersoni* (Rocky Mountain wood tick)

Photo/CDC

FIGURE 5. Approximate U.S. distribution of *Dermacentor andersoni* (Rocky Mountain wood tick)

Similar epidemiologic characteristics and transmission dynamics have been reported in parts of Mexico (*27–30*). A high incidence of RMSF occurs in several northern Mexican

R. rickettsii is an obligate intracellular pathogen that primarily infects vascular endothelial cells, and, less commonly, underlying smooth muscle cells of small and medium vessels. Infection with R. rickettsii leads to systemic vasculitis that manifests externally as characteristic petechial skin lesions. If disease progresses untreated, it can result in end-organ damage associated with severe morbidity and death.

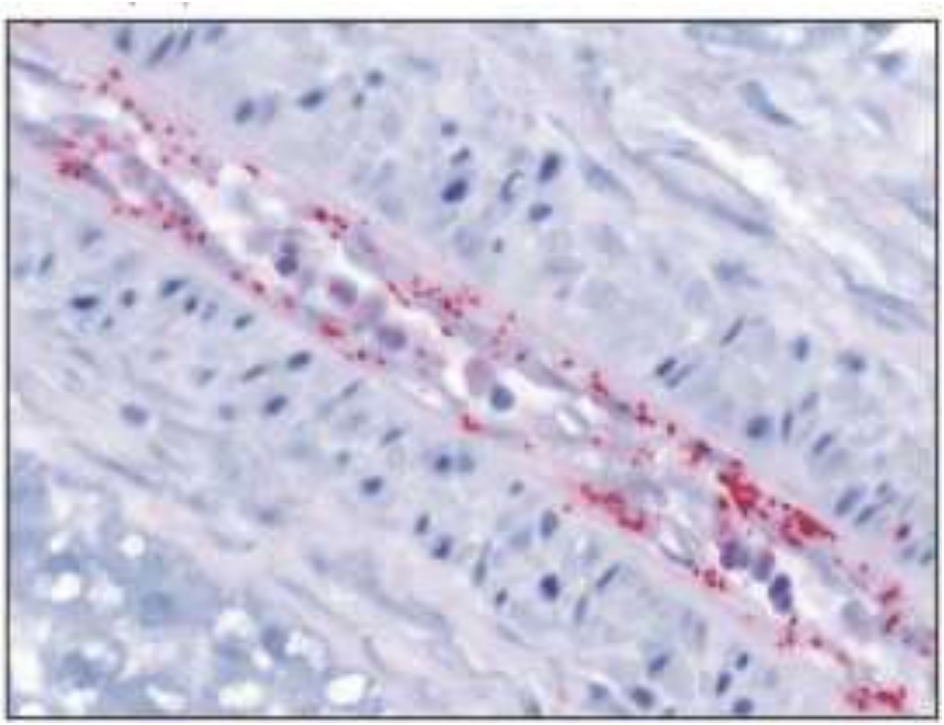


Photo CDC. Immunohistochemical stain demonstrating Rickettsia rickettsii (red) in blood vessel endothelial cells


A.D.A.M.

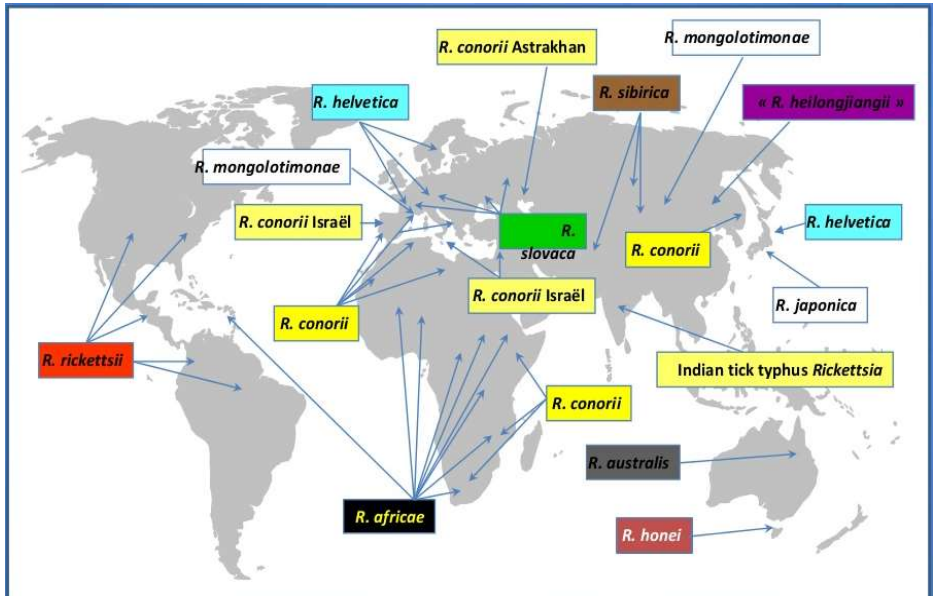
Definitive diagnosis — *R. rickettsii* cannot be cultured in most clinical laboratories. Thus, the clinical diagnosis must be confirmed through serologic testing or through the use of polymerase chain reaction (PCR) testing or special stains on a skin biopsy.

●Acute and convalescent serology should be sent on patients clinically suspected of having RMSF.

●Clinically available polymerase chain reaction testing of blood samples for RMSF may also be helpful to confirm the diagnosis, but a negative test does not rule out rickettsial infection.

●Testing of skin biopsies offers another potential method of disease confirmation, although these results are often delayed.

Rickettsia conorii



Marseilles fever (Rickettsia conorii subspecies conorii)

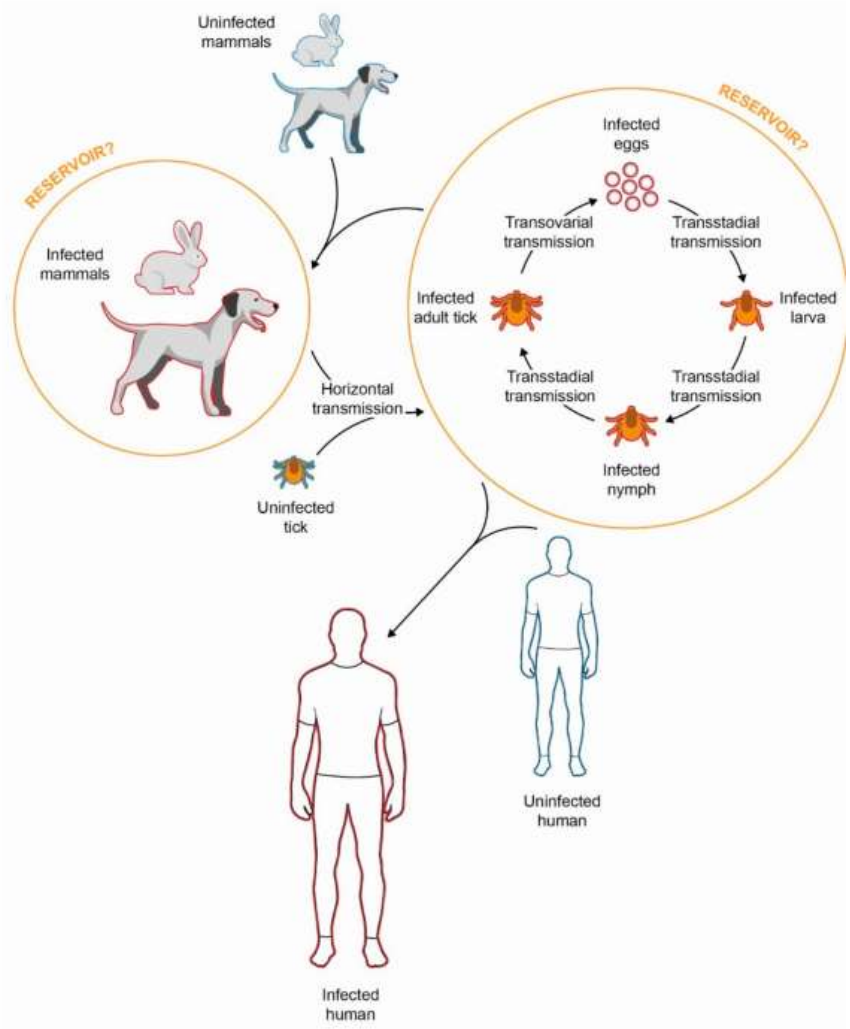
Kenya tick typhus (Rickettsia conorii subspecies conorii)

South African tick bite fever (Rickettsia conorii subspecies conorii)

Astrakhan fever (Rickettsia conorii subspecies caspia)

Israeli tick typhus (Rickettsia conorii subspecies israelensis)

Indian tick typhus (Rickettsia conorii subspecies indica)

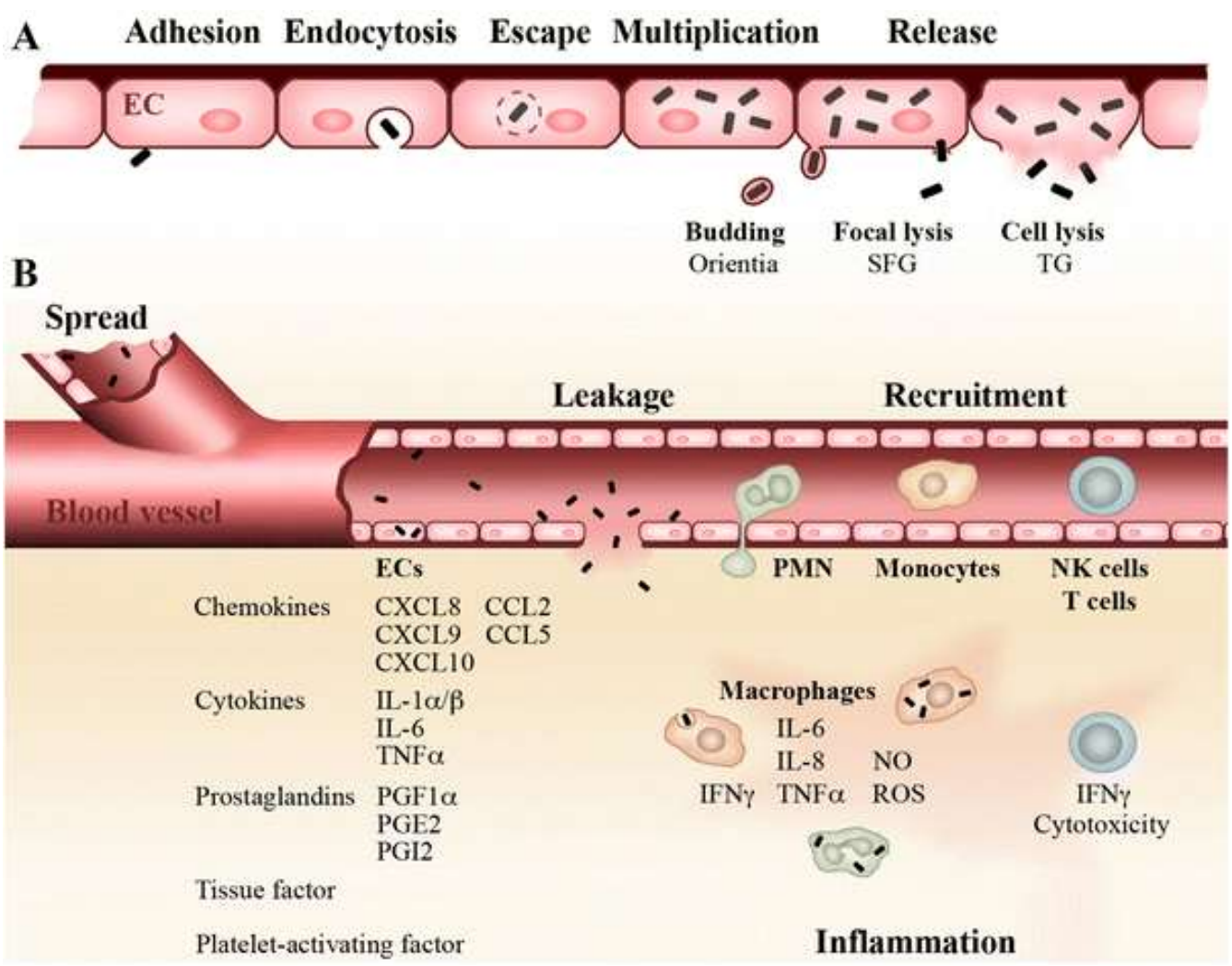


Rhipicephalus sanguineus can be infected with Rickettsia conorii through three mainroutes:

- when ticks feed on infected mammals (horizontal transmission),

- transovarially (vertical transmission),

- and transstadially (vertical transmission).


A
Adhesion
Endocytosis
Escape
Multiplication
Release
EC
Budding
Orientia
Focal lysis
SFG
Cell lysis
TG
B
Spread
Leakage
Recruitment
Blood vessel
ECs
PMN
Monocytes
NK cells
T cells
Chemokines
CXCL8 CCL2
CXCL9 CCL5
CXCL10
Cytokines
IL-1α/β
IL-6
TNFα
Prostaglandins
PGF1α
PGE2
PGI2
Tissue factor
Platelet-activating factor
Macrophages
IL-6
IL-8
NO
IFNγ TNFα ROS
IFNγ
Cytotoxicity
Inflammation

The major clinical features of MSF are as follows:

- Fever
- Exanthem (maculopapular rash)
- Eschar (tache noire) at site of tick bite

Eschar (tache noire) at site of tick bite on chest. Courtesy of José A Oteo, MD, Centro de Rickettsiosis y Enfermedades Transmitidas por Artrópodos Vectores, Hospital Universitario San Pedro - Centro de Investigación Biomédica de La Rioja (CIBIR).

Black spot or “tache noire” in Mediterranean spotted fever. Courtesy of Elsevier [Garcia-Fernandez-Bravo I, Demelo-Rodriguez P, Alejandre de Ona A, Del Toro Cervera J. Black spot or “tache noire” in Mediterranean spotted fever. Medicina Clinica (Barc). 2018 Aug 10;151(3):130.

Courtesy of José A Oteo, MD, Centro de Rickettsiosis y Enfermedades Transmitidas por Artrópodos Vectores, Hospital Universitario San Pedro - Centro de Investigación Biomédica de La Rioja (CIBIR).