• Rickettsioses surveillance is implemented in 14 countries of the EU/EEA
Overview of Medically Important Bacteria

Extracellular & Facultative

Gram-positive
- Cocci
  - Staphylococci
  - Streptococci
  - Enterococci
- Bacilli
  - Aerobes
  - Strict Anaerobes
    - Listeria
    - Bacillus
    - Corynebacteria

Gram-negative
- Cocci and coccobacilli
  - Haemophilus
  - Bordetella
  - Francisella
  - Brucella
  - Pasteurella
  - Neisseria

- Bacilli
  - Enterobacteriaceae
  - Pseudomonads
  - Legionella
  - Vibrio
  - Campylobacter
  - Helicobacter

Obligate Intracellular

- Rickettsia
- Chlamydia
- Mycoplasma*
Oder Rickettsiales

- Family Rickettsiaceae,
  - genus *Rickettsia*
    - 25 validated species

- Family Anaplasmataceae:
  - *Ehrlichia* (ticks)
  - *Anaplasma* (ticks)

*Coxiella* (Q fever), used to be classified into the *Rickettsiales* order; now belongs to *Legionellales* order (*Weisburg et al., 1989*).
Rickettsia

- bacteria, obligate **intracellular**, aerobic coccobacilli
- cell wall = Gram-neg structure (cell wall: outer membrane, peptidoglycan, LPS)
- Unlike Chlamydia, Mycoplasma, and Ureaplasma, Rickettsial organisms possess true cell walls similar to other Gram-negative bacteria.
- not detected by Gr staining
- Giemsa → red color
- cultivated in living tissues
- vector-borne disease
- natural cycles involve wild mammals & arthropod
- genus *Rickettsia*
  - endothelial cells and
  - more rarely underlying smooth muscle cells
- genus *Ehrlichia* - human granulocytic ehrlichiosis
- genus *Anaplasma* - human monocytic ehrlichiosis
## Difference between rickettsia and Virus

<table>
<thead>
<tr>
<th>Property</th>
<th>Rickettsia / typical bacteria</th>
<th>chlamydia</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA/RNA</td>
<td>both</td>
<td>both</td>
<td>any one</td>
</tr>
<tr>
<td>Multiplication by binary fission</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cell wall with muramic acid</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>ribosome</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Metabolically active enzymes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Inhibition by antibacterial enzymes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>ATP synthesis</td>
<td>yes</td>
<td>No</td>
<td>no</td>
</tr>
</tbody>
</table>
**Rickettsia** classified into typhus & spotted fever group based on on the basis of lipopolysaccharide Ag & genetic data

**Typhus group**
(mainly associated with human body **lice** (R.prowasekii) or **fleas** (R.typhi):
- found in **cytoplasm**
- **grows enormous** numbers
- **burst** the host cells

**Spotted fever group**
(mainly associated with **ticks** & **mites** (R.akari):
- found in **nucleus + cytoplasm**
- **seldom** accumulate in large numbers
- «**budded**» from host cells

In practical terms, these divisions are not so useful
Inoculated into the dermis & *lymphohematogenously* spread

↓

**intraendothelial multiplication & cell-to-cell spread**

↓

**destruction of endothelial cells, rickettsemia, toxemia**

↓

1. Microinfarctions
2. **Perivascular infiltration** (mononuclear+lymphocytes) & formation of **perivascular granulomas**
3. **Activation of platelets, platelet aggregation** & consumption
4. Generation of thrombin & **activation of the fibrinolytic system**

↓

**focal occlusive endangiitis** small venous, arterial, capillary vessels

Activation of platelets, generation of thrombin, activation of the fibrinolytic system all appear to be homeostatic physiologic responses to endothelial injury.
Endothelial cell damage:
- Vasodilation & increased vascular permeability
- Extracellular fluid shifts
- Loss of intravascular colloid:
  - hypotension, hypovolemia
  - decreased tissue perfusion
- Loss of electrolytes (hyponatremia ↔ extracellular fluid shifts, renal loss, cellular exchange of Na for K)
- Hypoalbuminemia (renal loss, ↓ intake, hepatic involv.)
- Decreased osmotic pressure

\[ \downarrow \]

multiple-organ dysfunction syndrome
brain, cardiac, skeletal muscle, skin, lungs, kidneys
or
the activation of immune systems, recovery

Immunity in epidemic typhus is non-sterile - the preservation of the pathogen in macrophages
<table>
<thead>
<tr>
<th>Antigenic group</th>
<th>Species</th>
<th>Disease</th>
<th>Vector</th>
<th>Reservoir(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotted fever group</td>
<td>R. aeschlimannii</td>
<td>Rickettsiosis</td>
<td>Tick</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>R. africae</td>
<td>African tick-bite fever</td>
<td>Tick</td>
<td>Ruminants</td>
</tr>
<tr>
<td></td>
<td>R. akari</td>
<td>Rickettsialpox</td>
<td>Mite</td>
<td>Mice, rodents</td>
</tr>
<tr>
<td></td>
<td>R. australis</td>
<td>Queensland tick typhus</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. conorii</td>
<td>Mediterranean spotted fever or Boutonneuse fever</td>
<td>Tick</td>
<td>Dogs, rodents</td>
</tr>
<tr>
<td></td>
<td>R. felis</td>
<td>Cat flea rickettsiosis</td>
<td>Flea</td>
<td>Cats, rodents, opossum</td>
</tr>
<tr>
<td></td>
<td>R. helongiængensis</td>
<td>Far Eastern spotted fever</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. helvetica</td>
<td>Arbovirus fever</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. honei</td>
<td>Flinders Island spotted fever, Variant Flinders Island spotted fever, Thai tick typhus</td>
<td>Tick</td>
<td>Rodents, reptiles</td>
</tr>
<tr>
<td></td>
<td>R. japonica</td>
<td>Japanese spotted fever or Oriental spotted fever</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. massiliae</td>
<td>Mediterranean spotted fever-like disease</td>
<td>Tick</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>R. parkeri</td>
<td>Maculatum infection</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. rickettsii</td>
<td>Rocky Mountain spotted fever, Fevre maculose, São Paulo exanthematic typhus, Minas Gerais exanthematic typhus, Brazilian spotted fever</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. sibirica</td>
<td>North Asian tick typhus, Siberian tick typhus</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. sibirica mongolotimonae</td>
<td>Lymphangitis-associated rickettsiosis</td>
<td>Tick</td>
<td>Rodents</td>
</tr>
<tr>
<td></td>
<td>R. slovaca</td>
<td>Tick-borne lymphadenopathy (T/BOLA), Dermacentor-borne necrosis and lymphadenopathy (DEBONEL)</td>
<td>Tick</td>
<td>Lagomorphs, rodents</td>
</tr>
<tr>
<td>Typhus group</td>
<td>R. prowazkii</td>
<td>Epidemic typhus, Brill-Zinsser disease</td>
<td>Louse</td>
<td>Humans, flying squirrels</td>
</tr>
<tr>
<td></td>
<td>R. typhi</td>
<td>Murine typhus</td>
<td>Flea</td>
<td>Rodents</td>
</tr>
</tbody>
</table>
TYPHUS GROUP

Insecta
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ORGANISM</th>
<th>VECTOR</th>
<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemic typhus</td>
<td><em>R. prowazekii</em></td>
<td>Louse</td>
<td>Humans, flying squirrels - fleas</td>
<td>Worldwide (&gt;South America and Africa)</td>
</tr>
</tbody>
</table>

- Excrete *R.* in feaces at time of feeding
- autoinoculates *R.* into bite abrasions
- Infected louse leaves a febrile person and deposits infected feces on its subsequent host
- Lice die in 2 weeks

extreme poverty, war, and natural disaster.
- Lice are flat-bodied, wingless insects
- Their legs are adapted for crawling through hair or on clothing, not jumping
- Body lice are known to transmit epidemic typhus
- Lice feed ~ every 5 hours
- Lice → persistent itching, dermatitis and considerable irritation
- Body lice lay >300 eggs, life cycle can be completed in 25 days.
- Eggs are deposited on clothing, nymphs & adults remain on clothing.
- R. multiply in epithelial cells of louse intestine → are voided with feces.
- After feeding, body lice defecate next to the bite
- Lice = host specific; do not leave the host unless the host’s t⁰ changes significantly
- Infected lice die within 14 days
Brill-Zinsser Disease

- Recrudescent epidemic typhus
- Establish latency in lymph nodes
- Occurs in elderly or immunocompromised persons -> malnourishment, poverty, and war!
- Milder disease (including absence of fever) and lower mortality
- RESERVOIR FOR NEW TYPHUS EPIDEMICS!
World Distribution of Louse-borne Typhus Fever at the End of World War II
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ORGANISM</th>
<th>VECTOR</th>
<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murine typhus / flea borne typhus / endemic typhus</td>
<td><em>R. typhi</em></td>
<td>Rat flea <em>Xenopsylla cheopsis</em>)</td>
<td>Rats, mouse, wild rodents</td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

**Geographic Distribution of Murine Typhus**

Saliva / feces rubbed on bitten area
DISEASE | ORGANISM | VECTOR | RESERVOIR | Distribution
---|---|---|---|---
Cat-flea typhus | *R. felis* | Flea | Cat, opossum | Worldwide

Also via inhalation of aerosolized rickettsiae from flea feces
Scrub typhus
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ORGANISM</th>
<th>VECTOR</th>
<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrub typhus</td>
<td><em>O. tsutsugamushi</em></td>
<td>Larval trombiculide mite (chiggers)</td>
<td>Wild rodents</td>
<td>Asia, northern</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Australia, Pacific</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Islands</td>
</tr>
</tbody>
</table>

has tropism by mononuclear leukocytes
SPOTTED FEVER GROUP

Female

Eggs

Larva

Feeds on small mammals

Nymph

Feeds on small and medium sized mammals

Male

Feeds on large and medium sized mammals and humans

Uninfected ticks

Infected rodents

Infected nymphaal tick

Uninfected rodents

Tick molts; trans-stadial maintenance

Infected female, adult tick

Transovarial transmission

Infected eggs

Infected human

Nature Reviews | Microbiology
Ticks & mites → transovarial transmission → vector + reservoir
Ixodes ticks & mites infect through their saliva
Figure 2. Current known situation of rickettsioses occurrence in Europe based on surveillance and literature data

Rickettsioses situation
- not detected or no data
- human cases
- Rickettsia detected in vectors or reservoir hosts
- human surveillance
- Not included

Non visible countries
- Lichtenstein
- Malta

0 250 500 1,000 Kilometers
Ticks & mites - transovarial → both vector + reservoir

R. multiply in the epithelium of the intestinal tract
<table>
<thead>
<tr>
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<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>R. rickettsii</em></td>
<td>Tick</td>
<td>Ticks, wild rodents</td>
<td>Western hemisphere</td>
</tr>
</tbody>
</table>

- 40% of pts do not report a history of a tick bite,
- but a history of travel or outdoor activity
Dermacentor variabilis:
- RMSF
- Tularemia

Dermacentor andersoni:
- RMSF
- Tularemia

Rhipicephalus sanguineus:
- RMSF

American Dog Tick (Dermacentor variabilis)

Rocky Mountain Wood Tick (Dermacentor andersoni)

Brown Dog Tick (Rhipicephalus sanguineus)
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ORGANISM</th>
<th>VECTOR</th>
<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boutonneuse fever</td>
<td><em>R. Conorii</em> subspecies:</td>
<td>Tick</td>
<td>wild rodents</td>
<td>India, Pakistan, Israel, Russia, Georgia,</td>
</tr>
<tr>
<td></td>
<td>*conori, israelensis,</td>
<td></td>
<td></td>
<td>Ukraine, Ethiopia, Kenya, South Africa,</td>
</tr>
<tr>
<td></td>
<td><em>caspia, ….</em></td>
<td></td>
<td></td>
<td>Morocco, and southern Europe</td>
</tr>
</tbody>
</table>

Infection has been designated by many geographic names—Marseilles fever, Mediterranean spotted fever, Kenya tick typhus, Israeli tick typhus, Astrakhan spotted fever, Indian tick typhus.
<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ORGANISM</th>
<th>VECTOR</th>
<th>RESERVOIR</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickettsialpox</td>
<td><em>R. akari</em></td>
<td><strong>House-mouse-mite</strong></td>
<td>House mouse, Wild rodents</td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

Mites (*Liponyssoides sanguineus*):
- subclass Akari, class Arahnida
- live primarily in the nests of birds and animals
- consume blood, skin, keratin

![Mite image](image)
• Rickettsiae are potential agents of bioterrorism.
• Infections with *R. prowazekii* and *R. rickettsii* have high case–fatality ratios & are highly infectious when inhaled as aerosols in the laboratory.
• Organisms resistant to tetracycline or chloramphenicol have been developed in the laboratory.
Incubation period

- Epidemic typhus: 6-15 days
- Murine (flea-borne) typhus: 6-18 days
- Scrub typhus: 6-21 days
- Rocky Mountain SF: 2-14 days
- Boutonneuse fever: 6-10 days
- Rickettsialpox: 9-14 days

Recrudescence in >30-40 years:
epidemic typhus - known as Brill-Zinser disease
  ➔ mild disease
**Eschar** at the inoculum site ("tache noire")

papula → vesicula → ulcer →
black scar 2-5mm – 1.5cm

+ Regional **lymphadenopathy**

All by the bite of ticks / mites
50-80% of cases
exception RMSF
Tick-borne rickettsiosis eschar
Tick-borne rickettsiosis eschar
Rickettsia conori eschar
Rickettsia sibirica mongolitimonae
Clinical manifestations

Early in the illness = difficult to d.d. from many self-limiting viral

Initial (prodromal) period is 3-4 days:
- Sudden onset, fever 38-40°C
- ↑ headache, malaise, chills, myalgia, arthralgia
- Conjunctiva injection (especially in children) rabbit eyes
- Hemorrhages at the base of the palatine tongue (2-3 days)
- Hemorrhages on the transitional fold of the conjunctiva (3-4 d)
- +/- Catarrh simpt.: rhinorrhea, cough, sore throat
- GI symptoms (nausea, vomiting, anorexia, ~diarrhea, ~ abdom. pain)

- Generalized lymphadenopathy: scrub typhus, rickettsialpox
Pts becomes **progressively more ill** as vascular injury advance.

- **Splenomegaly** (4-5 days)
- **Hepatomegaly** (from 2 week)
Rash in spotted fever

Centripetal fashion
*(starts on wrists & ankles and then spread over the legs and trunk.)*

- **RMSF**
- 90%, on the 3-5 days after onset of fever, **maculopapular** nonconfluent
- → 60% petechial-purpuric rash, if untreated → necrosis or gangrene (difficult to distinguish from meningococcemia).
- 50% +palms, +soles, + face;
- 10% - no rash
- **Buttonneuse**
- on the 3-5 days, **maculopapula** nonconfluent, +palms, +soles, +/- face,
Rash in typhus grup

Centrifugal fashion

- **Epidemic typhus** – **on the 4-5 days.** Small, pink macules, rapidly cover the body (usually in the axillae and on the upper trunk and **not on the palms, soles, and face**), nonconfluent.
- Later, the rash becomes maculopapular, in severe cases → petechial and hemorrhagic.
- 60% of African patients have spotless epidemic typhus.
- Brill-Zinsser disease (Recrudescent disease years after primary episode) - macular eruption
- **Murine thypus** – **on the 4-5 days**, less extensive than in epidemic, +palms, +soles, -/+ face, **maculopapular** nonconfluent
- **Scrub typhus (Tsutsugamushi)** on the 5-8 days, diffuse macular, short duration **maculopapular** nonconfluent

- **Rush fade after 2-3 days**
- Duration: 7-9 days.
Rash in rickettsiosis

Varicelliform Rickettsial disease (Rickettsialpox)

generalized maculopapular rash & intraepidermal vesicles followed by pustules
+palm, +sole, +face, do not leave scars.

Dd from varicella:
- eschar at the site of the mouse-mite bite
- papule/plaque base of each vesicle
- +sole
Syndrome: Exanthematic rickettsioses with low probability of inoculation eschar

Type of rash:
- Centripetal rash
- Centrifugal rash

Epidemiological background:
- The Americas: Ticks - *Amblyomma*, *Dermacentor* or *Rhipicephalus* genus
- Tropical or subtropical areas and Mediterranean Area: Fleas - *R. typhi*
- Populations at risk of parasitism by body lice: Flying squirrels (USA) - *R. prowazekii*

*Rickettsia* spp.:
- *R. rickettsii*
RMSF
Spotted fever group rickettsial infection
Eschar (tache noire) and maculo-papular rash in a patient with Mediterranean spotted fever.
Vasculitic rash affecting soles in a patient with Mediterranean spotted fever.
Epidemic typhus
*R. akari*, the causative agent of Rickettsialpox, which principally targets macrophages ([Walker et al., 2007](#))
Factors in Severity of Rickettsial Illness

- Older age
- Male gender
- Glucose-6-phosphate dehydrogenase deficiency (and possibly other causes of hemolysis)
- Diabetes mellitus
- Alcoholism
- Sulfonamide treatment
- Probably other co-morbid conditions (e.g., cardiovascular disease)
- IFN-γ SNP genetic polymorphism
Clinical manifestations in severe cases

- **Neurological involvement** (From 4-6 days of illness)-meningoencephalitis 35%
  - dizziness, drowsiness, disorientation, tinnitus, photophobia, delirium, meningismus, and visual disturbances are seen more commonly with typhus group rickettsioses.
  - confusion or lethargy,
  - stupor or delirium,

rare: focal neurologic deficits:
  - cortical blindness, seizures, central deafness, ataxia, paralysis, cranial palsies, coma

**Typhus syndrome refers to a febrile syndrome** with mental status impairment and rash.
Clinical manifestations in severe cases

- Pulmonary abnormalities 25%:
  - interstitial pneumonia 2 wk (vasculitis of small vessels is basic underlying pathology in R.)
  - pulmonary edema, acute respiratory distress syndrom
Clinical manifestations in severe cases

- **GI manifestation:**
  - Abdominal tenderness
  - Guaiac positive stools or vomitus
  - GI hemorrhage

- **Interstitial myocarditis:**
  - Arrhythmias,
  - Congestive cardiac failure

- **Circulatory problems:**
  - Tachycardia/bradycardia,
  - Low blood pressure,
  - High levels of blood nitrogen,
  - Thrombosis and cutaneous gangrene.

- **Renal failure** (acute tubular necrosis)

- **Ocular involvement** conjunctivitis, retinal vein engorgement, flame hemorrhages, arterial occlusion, papilledema
Severe manifestations of R

Death rate without treatment:

• Epidemic typhus 40-60%
• RMSP 20-30%
• Tsutsugamushis 7-35%
• In severe cases of Mediterranean spotted fever 50%

• In untreated severe cases → dL 8–15 days after onset.

• Fulminant RMSF (within 5 days after onset) glucose-6-phosphate dehydrogenase (G6PD) deficiency
• Use of sulfonamides.
DURATION OF FEVER

- Fever 38-40°C:
  - Epidemic typhus: 2-3 weeks
  - Boutonneuse fever, Murine typhus, Tsutsugamushi: 2 weeks
  - RMSF: 15-20 days, persistent
  - Vesicular rickettsiosis: <1 week
Brill-Zinssser Disease

- Occurs years after primary attack
  - Person previously affected or lived in endemic area
  - Viable retained organisms reactivated
  - Milder symptoms
    - Febrile phase 7-10 days
  - Rash often absent
  - Low mortality rate

Dr. T.V. Rao MD
**Laboratory findings:**

- Leukopenia, thrombocytopenia,
- Mild hyponatremia,
- Mildly elevated hepatic transaminase levels
- Elevated C-reactive protein, fibrinogen, ferritin
- CSF:
  - Pleocytosis (<100 cells/microliter)
  - Moderately elevated protein (100--200 mg/dL)
  - Normal glucose levels
  - Neutrophilic or lymphocytic pleocytosis
- Occasionally elevated serum creatine kinase (myositis, multifocal rhabdomyonecrosis)
**Serological reaction** (Quantitative serologic assays, paired serum obtained at the onset of illness and 10–14 days later = 4-fold increase in total antibody titer)

- Immunofluorescence assay (IFA) increased IgM or IgG titers by the end of 2 week
- Complement fixation test { + 14 days after infection
- Indirect hemagglutination, ELISA, Microagglutination

**Nucleic acid tests** (PCR…)

**WEIL-FELIX A HETEROPHILE AGGLUTINATION TEST**

Weil-Felix test is based on the cross-reactive antigens of OX-19 and OX-2 strains of Proteus vulgaris (poor sensitivity 33% and specificity 46%)
4. Enzyme-linked Immuno-Sorbant Assay (ELISA)

ELISA test is a technique for detecting & measuring antigen or antibody:
- One of the most reliable techniques to detect antibody against scrub typhus infection
- Its procedure is the principal for development of recent rapid diagnostic kits.
Widely used in laboratories & hospitals.
DD. Rickettsiosis

- Infective endocarditis
- Secondary syphilis
- Enteroviruses (coxsackie virus, echovirus)
- EBV infection
- Thrombotic thrombocytopenic purpura
- Drug hypersensitivity reactions
- Neisseria meningitidis infection
- Leptospirosis
- Disseminated gonococcal infection
Chemotherapy. Rickettsiosis

- **Tetracycline** - inhibit protein synthesis and are bacteriostatic. - drug of choice: (25–50 mg/kg per day) in four divided doses

- Sulfonamides stimulate rickettsial growth → contraindicated.

- **Doxycycline 100 mg x 2/day (orally or iv)**
- **Chloramphenicol 500mg x 4/day** - less effective, in pregnant
- **Fever subsides within 24–36 hours**
- **Optimal duration of therapy:**
  - 2-3 days after the fever subsides & evidence clinical improvement
  - typically course = 5-7 days
  - severe/complicated disease require longer treatment
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Indications</th>
<th>Dosage</th>
<th>Duration of treatment</th>
</tr>
</thead>
</table>
| Doxycycline (standard treatment for rickettsioses) | • Severe rickettsioses (including pregnant women and children), ideally intravenous  
• Adults or children >45 kg | • Adults or children >45 kg: 100 mg twice a day  
• Pregnant women (late trimester): 100 mg twice a day  
• Children <45 kg: 2.2 mg/kg twice a day | Continued for 3 days after symptoms have resolved |
| Macrolides (josamycin, clarithromycin, and azithromycin) | • Option for not severe rickettsioses in children and pregnant women | • Josamycin: children 50 mg/kg twice a day, pregnant women 1 g/8 h  
• Clarithromycin for children: 15 mg/kg/day divided doses  
• Azithromycin for children: 10 mg/kg/day in 1 dose | Josamycin 5 days, clarithromycin 7 days, and azithromycin 3 days |
| Chloramphenicol                  | • Alternative option in severe rickettsioses                                | • Adults and pregnant women (first and second trimesters): 60–75 mg/kg/day in 4 divided doses  
• Children: 12.5–25 mg/kg every 6 h | 5–10 days |

Treatment of rickettsioses; based on Botelho–Nevers et al., 2012