Human Rickettsiosis
RICKETTSIAL DISEASES

• Diverse group of zoonotic infections
• Obligate intracellular bacteria, pleomorphic Gram negative coccobacilli
• Primary parasites found in the alimentary canal of arthropods-transmitted to humans by Lice/flies/ticks and mites
• Humans are dead end hosts
Rickettsiosis

• One of the undiagnosed febrile illness due to lack of awareness and difficulties in diagnostics

• Typhus remains a substantially under-recognized disease entity, particularly in Asia, where up to 28% malaria negative fevers can be attributed to Rickettsial infections
MILESTONES

• Hippocrates in 460 BC used the term *typhus*, meaning ‘smoke’ to describe the **confused state of intellect i.e stupor**.

• In 1492, there was outbreak of febrile eruption in civil wars of Granada.

• Typhus was particularly associated with siege warfare which had high population density and poor hygiene.
During Napoleon's retreat from Moscow in 1812, more French soldiers died of typhus than were killed by the Russians.
Rickettsia named after HOWARD TAYLOR RICKETTS died of Typhus fever contracted during his studies. Discovered spotted fever Rickettsia (1906)
• 1909: Charles Nicolle discovers transmission of epidemic typhus by human body louse- **Nobel Prize in 1928**
• 1916: Weil and Felix first describe the diagnostic serum agglutination for typhus based on *Proteus vulgaris* strain – Proteus OX19

• 1924: Kingsbury introduces new strain *Proteus mirabilis* OXK for Weil Felix test
GENERAL PATHOGENESIS

- Rickettsia are transmitted to humans by the bite of infected arthropod vector.
- Multiply at the site of entry and enter the blood stream.
- Localize in the vascular endothelial cells and multiply to cause vasculitis and thrombosis.
Vectors

TICK

Louse

FLEA

Mite
FIG 2  Three tick vectors of spotted fever group rickettsioses. From top to bottom are *Rhipicephalus sanguineus*, the primary vector of *R. conorii* subsp. *conorii*, the agent of Mediterranean spotted fever; *Dermacentor marginatus*, vector of *R. slovaca* and *R. moletti*; and *Amblyomma variegatum*, vector of *R. africæ*, the agent of ATBF. Males are on the left side, and females are on the right. Bar scale, 1 mm.
<table>
<thead>
<tr>
<th></th>
<th>TICK-BORNE</th>
<th>FLEA-BORNE</th>
<th>LOUSE-BORNE</th>
<th>MITE-BORNE</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rickettsiae</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spotted fever group</td>
<td>R. rickettsii</td>
<td>R. felis</td>
<td></td>
<td>R. akari</td>
<td></td>
</tr>
<tr>
<td>R. conorii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. japonica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. sibirica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. australis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. slovaca</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. africae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. honei</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. aeschlimanii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. helvetica</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. parkeri</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. helongjiangensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. raoultii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. massilae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. amblyommii</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. monacensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. philipii strain 364D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Typhus group</strong></td>
<td></td>
<td>R. typhi</td>
<td>R. prowazekii</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrub typhus group (Orientia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>O. tsutsugamushi</td>
</tr>
<tr>
<td>Anaplasma</td>
<td>A. phagocytophilum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehrlichia</td>
<td>E. chaffeensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. ewingii</td>
<td>E. canis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoehrlichia</td>
<td>N. mikurensis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neorickettsia sennetsu</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Raw fish</td>
</tr>
<tr>
<td>Wolbachia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Helminths</td>
</tr>
</tbody>
</table>
GEOGRAPHICAL DISTRIBUTION (EUROPE)

FIG 7 Tick-borne rickettsiae in Europe. Colored symbols indicate pathogenic rickettsiae. White symbols indicate rickettsiae of possible pathogenicity and rickettsiae of unknown pathogenicity. (Adapted from reference 2.)
Geographic distribution of tick-borne rickettsioses.
SYMPTOMS

- Fever
- Headache
- Prostration
- Skin rash (except Q fever)
- Hepatosplenomegaly
- ESCHAR (not in all forms)
Epidemic Typhus

- Etiology: *Rickettsia prowazekii*
- Vector: Human body louse
- Body louse – Human – body louse cycle
- Most common in people living under unhygienic conditions
  - Refugee camps
  - Famine
  - Poverty
Transmission

- Human body louse
  - *Pediculus humanus corporis*
  - Infection acquired by feeding on infected person
  - Excrete *R. prowazeki* in feces at time of feeding
  - Lice die within 2 weeks
  - Louse feces rubbed into superficial abrasions
  - Inhalation of feces aerosols
Transmission

• Humans required for life cycle
  – Organism dies with louse
  – No trans-ovarian transmission
  – Host responsible for maintaining infection

• No person-to-person transmission
Clinical Symptoms

- Incubation: 7-14 days
- Sudden onset of high fever, chills, headache, cough, severe myalgia
- Macular eruption in 20-80% of patients
  - 5-6 days after onset
  - Initially in the axilla, spreads to entire body
    - Except face, palms and soles of feet
- Treatment with Doxycycline or Chloramphenicol
- Mortality: 6-30%
Brill-Zinsser Disease (Recrudescent Typhus)

- Occurs years after primary attack
  - Person previously affected or lived in endemic area
  - Reactivation of latent organisms in Reticulo Endothelial Cells
  - Milder symptoms
    - Febrile phase 7-10 days
  - Rash often absent
  - Same treatment as that of epidemic typhus
  - Low mortality rate
ENDEMIC TYPHUS

- Rickettsial agent: *Rickettsia typhi*
- Insect vector: Rat flea
- Mammalian reservoir: Rodents
- Incubation period: 1-2 weeks
- Symptoms
  - Similar to Epidemic typhus
  - Milder illness: gradual onset-fever, headache, myalgia, cough
  - Rash: 40-50%, maculopapular rash on trunk
  - Diagnosis by IFA (*R. typhi* cross-reacts with *R. prowazekii*)
  - Treated with Doxycycline with low mortality (1%)
SCRUB TYPHUS

• Rickettsial agent: *Orientia tsutsugamushi*
• Insect vector: Mite infective larvae (CHIGGERS)
• Mammalian Reservoir: Rodents
Scrub typhus - distribution
Scrub typhus

- Incubation period - 2-3 weeks
- Headache, chills, fever, myalgia
- Characteristic eschar at the site of mite bite
- Splenomegaly, Lymphadenopathy
- Maculopapular rash appears after a week
- Abortion commonly occurs in pregnant women
- IFA or ELISA tests
- Doxycycline, 100 mg orally twice a day for 7 days
- Case fatality: 0-30%
Scrub typhus - Eschar
Endemic Scrub Typhus in South America


Summary

Scrub typhus is a life-threatening zoonosis caused by Orientia tsutsugamushi organisms that are transmitted by the larvae of trombiculid mites. Endemic scrub typhus was originally thought to be confined to the so called “tsutsugamushi triangle” within the Asia-Pacific region. In 2006, however, two individual cases were detected in the Middle East and South America, which suggested that the pathogen was present farther afield. Here, we report three autochthonous cases of scrub typhus caused by O. tsutsugamushi acquired on Chiloé Island in southern Chile, which suggests the existence of an endemic focus in South America. (Funded by the Chilean Comisión Nacional de Investigación Científica y Tecnológica and the Wellcome Trust.)

Figure 1. Geographic Location and Clinical Presentation of Scrub Typhus Cases in Chile.
Panel A shows a map of Chiloé Island in southern Chile, where all the patients in this case report acquired scrub typhus in rural areas close to the city of Ancud (41°52′14″S, 73°48′58″W). Panels B through G show images of the maculopapular exanthema and eschar of Patient 1 (Panels B and C), Patient 2 (Panels D and E), and Patient 3 (Panels F and G).
ROCKY MOUNTAIN SPOTTED FEVER

- Rickettsial agent: *R. rickettsii*
- Insect vector: Ticks *Dermacentor* in USA and *Amblyomma* in Central and South America
- Mammalian Reservoir: Rodent, dogs
- Incubation period: 2-14 days
RMSF

- High grade fever, severe headache, myalgia, vomiting, abdominal pain, cough
- Rash (Maculopapular) appears on 3-4\textsuperscript{th} day
  - Initially on wrists, ankles, palms and soles, then generalizes
  - Rash becomes petechial / hemorrhagic
- Eschar at the site of bite is rare
- Complications: Hypovolemia, shock, jaundice, myocarditis, uremia, ARDS
- IFA (IgG e IgM) is highly sensitive and specific for diagnosis
- Doxycycline 200 mg/d orally or chloramphenicol
- Mortality in USA: 2.4 - 9\% in treated patients
RMSF - rash
Typical skin rash in Rocky Mountain spotted fever
Rickettsialpox

- Rickettsial agent: *R. akari*
- Insect vector: Mouse mite
- Mild disease resembling varicella
- Firm red macules at the bite site - deep seated vesicle - ESCHAR
Rickettsialpox

- Phase I (1 week incubation period)
  - papule at bite site
  - Eschar formation
- Phase II (1 -3 week later)
  - Sudden onset of fever, chills, headache and myalgia
  - Generalized rash – macular, then papular and vesicular, crusts
- Mild disease; fatalities are rare
- IFA for diagnosis
- Doxycycline
Table 1. Comparison of the epidemiological and clinical characteristics associated with *Rickettsia sibirica mongolotimonae* and *Rickettsia sibirica* sensu strito.

<table>
<thead>
<tr>
<th>Characteristic, by class</th>
<th><em>R. sibirica mongolotimonae</em> (PR) [3, 6]</th>
<th><em>R. sibirica</em> sensu stricto [7–9]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiological characteristic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognized tick vectors</td>
<td><em>Hyalomma asiaticum</em> [2], <em>Hyalomma truncatum</em> [38]</td>
<td><em>Dermacentor marginatus</em>, <em>Dermacentor nuttali</em>, <em>Dermacentor silvarum</em> [39], <em>Dermacentor pictus</em> [7], <em>Dermacentor sinicus</em>, <em>Dermacentor auratus</em>, <em>Haemaphysalis concinna</em>, <em>Hyalomma wolffingtoni</em>, <em>Hyalomma yoni</em> [40]</td>
</tr>
<tr>
<td><strong>Geographic area(s) of endemicity</strong></td>
<td>Algeria (PR), China [31], France (PR), Niger [38], and South Africa [41]</td>
<td>Siberia [8] and Western China [42, 43]</td>
</tr>
<tr>
<td><strong>Outbreak season(s) for human infection</strong></td>
<td>Spring&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Spring and summer</td>
</tr>
<tr>
<td><strong>Clinical characteristic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>Fever</td>
<td>100</td>
<td>Yes</td>
</tr>
<tr>
<td>Rash</td>
<td>78</td>
<td>100</td>
</tr>
<tr>
<td><strong>Enlarged lymph nodes</strong></td>
<td>55</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymphangitis</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Eschar</td>
<td>89</td>
<td>77</td>
</tr>
<tr>
<td>Multiple eschars</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Fatal outcome</td>
<td>0</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of reported patients with the specified characteristic, unless otherwise indicated. PR, present report.

<sup>a</sup> In France.
**Figure 11.** Lymphangitis and eschar on a patient with lymphangitis-associated rickettsiosis (LAR) (*Rickettsia sibirica mongolitimonae* infection). Courtesy of Dr Rita de Sousa.
Dermacentor-borne-necrosis-erythema lymphadenopathy/ Tick-borne-lymphadenopathy.

**Agent:**
- Vector: tick *Dermacentor marginatus*
- Agent: *Rickettsia slovaca*
- Reservoir: mammals.

**Epidemiology:**
- Emerging disease in Europe
- Second cause of Rickettsiosis (Mediterranean spotted fever is first).
- Incubation time: 1-15 days.
- Incidence: winter time
- More common in children and women.
- 90% tick bites are in the scalp
- 100% tick bites are in the upper part of the body.
CLINICAL SYMPTOMS:

- Exudative lesion
- Eschar
- Alopecia (Years)
- Painful regional lymphadenopathy
Diagnostic Criteria:

- Clinical and epidemiological criteria.
- PCR in the lymph node aspirate or eschar.

Serology Sensitivity:

- Serology is non-sensitive:
  - Positive: support diagnosis
  - Negative: doesn’t exclude

Cross reaction with *Rickettsia conorii*
DEBONEL/TIBOLA

Treatment:

- Adults (first option)
  - **Doxycycline** 10 mg/kg/day 12h during 7-14 days.

- Children alternative (macrolides)
  - **Azithromycin** 10 mg/kg/day 5 days.
  - **Clarithromycin** 15mg/kg/day 12h 7-10 days.
# WEIL FELIX REACTION (HETEROPHILE AGGLUTINATION)

<table>
<thead>
<tr>
<th></th>
<th>OX 19</th>
<th>OX 2</th>
<th>OX K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemic typhus</td>
<td>++++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Endemic typhus</td>
<td>++++</td>
<td>±</td>
<td>-</td>
</tr>
<tr>
<td>Tick born spotted</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Scrub typhus</td>
<td>−</td>
<td>−</td>
<td>++</td>
</tr>
</tbody>
</table>

False positives: UTI, Typhoid fever, liver disease
<table>
<thead>
<tr>
<th>Disease</th>
<th>Serological assay</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrub typhus</td>
<td>IFA IgG</td>
<td>91</td>
<td>96</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>70–87</td>
<td>84–100</td>
<td>[16,17**,60]</td>
</tr>
<tr>
<td></td>
<td>ELISA IgG</td>
<td>80–97</td>
<td>89–98</td>
<td>[60–63]</td>
</tr>
<tr>
<td></td>
<td>ELISA IgM</td>
<td>84–100</td>
<td>73–99</td>
<td>[60,64]</td>
</tr>
<tr>
<td></td>
<td>ImmChrom IgG RDT</td>
<td>86–95</td>
<td>96–100</td>
<td>[38,60,65]</td>
</tr>
<tr>
<td></td>
<td>ImmChrom IgM RDT</td>
<td>82–94</td>
<td>86–100</td>
<td>[35,38,40,60,65]</td>
</tr>
<tr>
<td></td>
<td>Dot EIA</td>
<td>60–100</td>
<td>94–99</td>
<td>[36,60,66]</td>
</tr>
<tr>
<td>Spotted fever rickettsiosis</td>
<td>IFA IgG</td>
<td>85–100</td>
<td>99–100</td>
<td>[67–69]</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>83–85</td>
<td>100</td>
<td>[68,69]</td>
</tr>
<tr>
<td></td>
<td>ELISA IgG</td>
<td>83</td>
<td>87</td>
<td>[68,70]</td>
</tr>
<tr>
<td></td>
<td>ELISA IgM</td>
<td>98</td>
<td>94*</td>
<td>[68]</td>
</tr>
<tr>
<td>Murine typhus</td>
<td>IFA IgG</td>
<td>≥83</td>
<td>≥93</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>IFA IgM</td>
<td>53–85</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

*Increasing data suggest lower specificity [56,59,68].

IFA, immunofluorescence assay; ImmChrom, immunochromatographic; RDT, rapid diagnostic test.
IMMUNOFUORESCENT ANTIBODY TECHNIQUE – UTILISES FLUORESCENT ANTIBODY TO DETECT RICKETTSIAL ANTIGEN IN INFECTED TISSUES
Tick removal technique.

Rickettsial Infections
Raoult, Didier, Goldman-Cecil Medicine, 327, 2046-2056.e2