Tick-Borne Rickettsial Diseases

Philippe PAROLA, MD, PhD
WHO coll. Center for Rickettsioses and Other Arthropod Borne Bacterial Diseases Marseille, France
What is a rickettsial agent? (1)

Bacteria belonging to the order *Rickettsiales*

Long time defined as:

- Gram négative
- Intracellular rods
- Stained by Gimenez staining

What is a rickettsial agent? (2)

Molecular tools / taxonomic changes:

- **Rickettsia**: spotted fever group and typhus group
- **Orientia tsutsugamushi** (scrub typhus)
- **Anaplasma, Ehrlichia, Cowdria, Neorickettsia and Wolbachia**

Excluded from **Rickettsiales**
- **Coxiella burnetii** (Q fever)
- **Bartonella** sp.

Rickettsia

Spotted fever group

Typhus group

Spotted fevers

mites

Fleas

lice

Murine typhus

Epidemic typhus

Ticks
Some clinical aspects related to...
the life and behaviors of ticks
Haematophagous Acarins
2 - 30 mm

3 Families

Ixodidae = Hard Ticks
694 species

Argasidae = Soft Ticks
77 species

Nuttalliellidae: 1 species

Ixodes ricinus

HARD TICKS

Hard ticks

= 1 blood meal / stage

HARD TICKS LIFE CYCLE

HARD TICKS LIFE CYCLE

Usually completed in 2–3 years
May take from 6 months to 6 years / environmental conditions:
- temperature – relative humidity - photoperiod

Each species:
- its own particular optimal environmental conditions and biotopes =
  - Geographic distribution of the ticks
  - Include seasonnal variation

Clinical and epidemiological consequences on tick-borne diseases
HOST SEEKING

AMBUSH STRATEGY

Ex: *I. ricinus (A), D. marginatus*

ATTACK STRATEGY

Ex: *Amblyomma variegatum, A. hebraeum*

**Endophytic Ticks**

*Rhipicephalus sanguineus*
Brown dog tick
Humlan houses Kennels
+ ambush
THEY KNOW WHERE YOU ARE!

[Image of a glass jar with various objects inside]
Récepteurs – Phéromones (1)

Agrégation - attachement

rassemblement

attaque

sexuelles
HOST SPECIFICITY

High: *R. sanguineus*

Low: *A. hebraeum*
BLOOD MEAL: 3-10 days!

During the first 24–36h of attachment:
no or little ingestion of blood
penetration and attachment = predominant activity

Initial slow feeding period
(3–4 d)
then rapid engorgement
(1–3 d)

Body weight increase up to 120-fold.

Alternating periods of sucking blood
Salivation
Regurgitation
BLOOD MEAL: 3-10 days!
Sites de Piqueure & Spécificité d’Hôtes

> 50 cm

15 cm

5 cm
TICK BITE SITE / SPECIES

Dermacentor

Amblyomma

Ixodes
Tick Borne Rickettsioses

What was thought... and was wrong!

1 SFG Rickettsiosis / continent
All Tick vectors = Reservoirs
All benign but RMSF

> 20 pathogens throughout the world including 15 described in the last 20 years


R. conorii

R. massiliae

R. slovaca

R. helvetica

EUROPE 1990
AFRICA
2009

- R. africæ
- R. conorii conorii
- R. conorii caspia
- R. conorii israelensis
- R. sibirica mongolitimonae
- R. aeschlimannii
- R. massiliae
- R. rhipicephali
- "R. raoultii"
- R. monacensis

African tick bite fever (*R. africæ*) +++
Mediterranean spotted fever (*R. conorii conorii*) +

A handful of travel-associated cases of:

- Rocky Mountain spotted fever (*R. rickettsii*)
- Queensland tick typhus caused by (*R. australis*)
- North Asian tick typhus (*R. sibirica*)
- Lymphangitis Associated Rickettsioses (*R. sibirica mongolotimonae*)
- Infection caused by *R. aeschlimannii*
Mediterranean Spotted fever

One of the oldest recognized vector-borne infectious diseases.

1909:
First cases in Tunisia (Conor and Brush)

1925:
The eschar in Marseille (Boinet and Pieri)

1930’s:
• The vector: *Rhipicephalus sanguineus* (Olmer – Durand & Conseil)
• The agent: *R. conorii* (Brumpt)
Experimental model: human inoculation patients with dementia paralitica (neurosyphilis) “asked by their doctors for pyretherapy”
Inoculation of crushed Eggs larvae, nymphs, engorged female, and over winter unfed males and females
100 years later
MANY GAPS IN THE ECOLOGY OF MSF

1910-1930: description
2009: réservoirs ?
Why not in America ?
The role of animal reservoirs?

Non-immune dogs as reservoirs???

Puppies in endemic areas?

Dogs living outside endemic areas of MSF or at least of *Rh. sanguineus*?
Other animal reservoirs?

- European rabbit?
- Spermophile?
- Guinea pigs?
- Mice?
- Hedgehogs?
“CLASSIC” CLINICAL ASPECTS

Incubation 6 – 7 d

Fever 100%

Eschar (single ?) 72 %

Conjonctivitis

Maculo Papular Rash 97%
“CLASSIC” CLINICAL ASPECTS

Marseille September 2009
“CLASSIC” CLINICAL ASPECTS
“CLASSIC” CLINICAL ASPECTS
SEVERE FORMS

167 Cases
Oran Algeria, 2006 -2007
49% hospitalized with severe forms
7% MODS
Case fatality rate 3%
55% of MODS cases

SEVERE CASES up to 40%
FATAL CASES 2 – 6%

A 50 year old Homeless in 2003

*Rhipicephalus sanguineus*
2003: French heat wave
New aspects: Multiple eschars

Oran Algeria: the hottest summer of the past decades!
A focus of tick borne spotted fever in Southern France, 2007

3 cases including 2 severe cases with chorioretinitis
Tick attack ++++

Dense populations of *Rh. sanguineus*

New genotypes of clonal populations of either *R. conorii* (24/133; 18%) or *R. massiliae* (13/133; 10%).
April 2007: the warmest since 1950

April, 15th - 30th 2007
Maximal between 25-30°C (up 33°C)

1971 – 2000
Maximal average

1971 – 2000
Minimal average
**Rh. sanguineus:**
a change in the affinity to bite human related to climatic changes?

Warmer Weather Linked to Tick Attack and Emergence of Severe Rickettsioses

Philippe Parola¹, Cristina Socolovschi¹, Luc Jeanjean², Idir Bitam¹, Pierre-Edouard Fournier¹, Albert Sotto³, Pierre Labauge², Didier Raoult¹x

1 patient infected with *R. conorii*
1 patient infected with *R. massiliae*
Table 2. Evidence of the influence of warmer weather and climate on *Rh. sanguineus* transmitted rickettsioses in humans.

<table>
<thead>
<tr>
<th>Epidemiological evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• France, this report. Unusual cluster of cases in an atypical period of the year: April 2007 was the warmest April since 1950, with summer-like temperature</td>
</tr>
<tr>
<td>• Southern USA, and Central America: role of <em>Rh. sanguineus</em> as a vector of <em>R. rickettsii</em> in warm states (Arizona) [14] or countries (Mexico) [5].</td>
</tr>
<tr>
<td>• Europe and North Africa: <em>Rh. sanguineus</em> starts to be active in May and June [24], but most cases of MSF are diagnosed during the warmest months, July and August.</td>
</tr>
<tr>
<td>• Southern Europe, the 1970s: the increase in the number of MSF cases [37] was correlated with higher temperatures and lower rainfall in Spain, and with a decrease in the number of days of frost during the preceding year in France [39].</td>
</tr>
<tr>
<td>• Oran, Algeria: the cases of MSF peaked in 2005 together with the hottest summer of the past decades [18].</td>
</tr>
<tr>
<td>• Sardinia, Italy: maximum temperature levels associated with increases in MSF incidence in Sardinia [40].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• France, French heat wave in 2003: hottest summer of the preceding 50 years. 22 <em>Rh. sanguineus</em>, including specimens infected by <em>R. conorii</em> and <em>R. massiliae</em>, were found attached to an homeless person, who died of MSF [41].</td>
</tr>
<tr>
<td>• This report: multiple eschars unusual finding in MSF, because the probability of being bitten simultaneously by several infected <em>Rh. sanguineus</em> ticks is considered to be rare.</td>
</tr>
<tr>
<td>• Multiple eschars in MSF reported in the warmest countries of southern Europe (Spain) [48].</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Experimental models</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased aggressiveness and propensity of <em>Rh. sanguineus</em> to bite unusual hosts (rabbit) in warmer conditions [42]</td>
</tr>
<tr>
<td>• This study: Increased aggressiveness and propensity of <em>Rh. sanguineus</em> to bite hosts in warmer conditions</td>
</tr>
</tbody>
</table>
P162 Global warning may increase Rhipicephalus sanguineus vectorized diseases

Idir Bitam, Philippe Parola, and Didier Raoult

<table>
<thead>
<tr>
<th>Ticks stages / température</th>
<th>Number of tick tested by experiment</th>
<th>Number of tick found attached after 40 minutes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larvae / 25°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 1</td>
<td>30</td>
<td>2 (6.7%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exp. 2</td>
<td>60</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exp. 3</td>
<td>30</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Larvae / 40°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 1</td>
<td>30</td>
<td>8 (27%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exp. 2</td>
<td>60</td>
<td>37 (66%)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exp. 3</td>
<td>30</td>
<td>17 (57%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nymphs / 25°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 1</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Exp. 2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Exp. 3</td>
<td>30</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nymphs / 40°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 1</td>
<td>30</td>
<td>6 (20%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Exp. 2</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Exp. 3</td>
<td>30</td>
<td>4 (13.3%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Warmer Weather Linked to Tick Attack and Emergence of Severe Rickettsioses

Philippe Parola¹, Cristina Socolovschi¹, Luc Jeanjean², Idir Bitam¹, Pierre-Edouard Fournier¹, Albert Sotto³, Pierre Labauge², Didier Raoult¹*
*R. slovaca* & TIBOLA - DEBONEL

**Dermacentor reticulatus**

**Dermacentor marginatus**
TIBOLA - DEBONEL
RICKETTSIA SLOVACA

Spring +++
Autumn +++

Imported cases in travelers
Recently reported
African Tick Bite Fever (*R. africae*)
The Typical Tick Borne SFG rickettsioses in Travelers

*NEJM* 2001; 344: 1504-10

**Rickettsia africae**, a Tick-Borne Pathogen in Travelers to Sub-Saharan Africa

Didier Raoult, M.D., Ph.D., Pierre E. Fournier, M.D., Ph.D., Florence Fenollar, M.D., Mogens Jensenius, M.D., Tine Price, M.D., Jean J. de Pina, M.D., Giuseppe Caruso, M.D., Nicola Jones, M.D., Herman Laferl, M.D., D.T.M.H., John E. Rosenblatt, M.D., and Thomas J. Marrie, M.D.

<table>
<thead>
<tr>
<th>Country of Origin</th>
<th>No. of Patients</th>
<th>Country in Which Infection Occurred</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>62</td>
<td>South Africa</td>
<td>71</td>
</tr>
<tr>
<td>Denmark</td>
<td>14</td>
<td>Swaziland</td>
<td>10</td>
</tr>
<tr>
<td>Norway</td>
<td>13</td>
<td>Lesotho</td>
<td>14</td>
</tr>
<tr>
<td>Italy</td>
<td>5</td>
<td>Zimbabwe</td>
<td>14</td>
</tr>
<tr>
<td>Great Britain</td>
<td>6</td>
<td>Botswana</td>
<td>1</td>
</tr>
<tr>
<td>Austria</td>
<td>12</td>
<td>Gambia</td>
<td>1</td>
</tr>
<tr>
<td>United States</td>
<td>3</td>
<td>Tanzania</td>
<td>1</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
<td>Kenya</td>
<td>1</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>Gabon</td>
<td>1</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>1</td>
<td>Central African Republic</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Côte d’Ivoire</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Great Britain*</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guadeloupe</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. Country of Origin and Country in Which the Disease Was Acquired in the Case of 119 Patients with Rickettsia africae Infection.**
African Tick Bite Fever in Travelers to Rural Sub-Equatorial Africa

Mogens Jensenius,1 Pierre-Edouard Fournier,6 Sirkka Vene,7 Terje Hoel,2 Gunnar Hasle,4 Arne Z. Henriksen,5 Kjell Block Hellum,6 Didier Raoult,8 and Bjørn Myrvang,3 for the Norwegian African tick bite fever study group.9

N= 940

Overall incidence-rate of ATBF: 4%  
25% in hunters  
2% leisure travellers  
3% business travellers

Clin Infect Dis 2003; 36: 1411-17
African Tick Bite Fever in Travelers to Rural Sub-Equatorial Africa

Factors associated with ATBF Multivariant regression model

**Hunting**

OR 10.2 (95% CI 3.9 – 27) (p<0.001)

**Travel to southern Africa**

OR 3.0 (95% CI 1.2 – 7.4) (p=0.013)

**Travel during summer season (Nov – April)**

OR 2.8 (95% CI 1.2 – 6.4) (p=0.015)

Clin Infect Dis 2003; 36: 1411-17
Rickettsia africaceae (1)

Now more than 15 years since the agent of ATBF was:
- rediscovered in sub-Saharan Africa (1992)
- definitely distinguished MSF

R. africaceae

50% & 50% vesicular

R. conorii conorii

Frequent & Maculo papular

Jensenius et al., Lancet Infect Dis 2003, 3: 557-564
**Rickettsia africae (2)**

Now more than 15 years since the agent of ATBF was:
- rediscovered in sub-Saharan Africa (1992)
- definitely distinguished MSF

<table>
<thead>
<tr>
<th></th>
<th><strong>R. africae</strong></th>
<th><strong>R. conorii conorii</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Eschar</td>
<td>75% multiple</td>
<td>Usually unique</td>
</tr>
<tr>
<td>Nodes</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>CFR</td>
<td>0%</td>
<td>up to 5%</td>
</tr>
</tbody>
</table>

Jensenius et al., Lancet Infect Dis 2003, 3: 557-564
Rickettsia africae (3)

**Amblyomma vectors = Reservoirs**

- Attack & readily bite people entering the biotope
- High rate of infection

Clusters Multiples eschars
Outbreak of *Rickettsia africae* Infections in Participants of an Adventure Race in South Africa

Pierre-Edouard Fournier, Veronique Roux, Eric Caumes, Marc Donzel, and Didier Raoult

*Clinical Infectious Diseases* 1998; 27:316–23

*Maladies Infectieuses et Tropicales, Groupe Hospitalier Pitié-Salpêtrière, Paris; and Le Centenaire, Bourg-Saint-Maurice, France*
African Tick-bite Fever in French Travelers

Paul H. Consigny,* Jean-Marc Rolain,† Daniel Mizzi,‡ and Didier Raoult§

*Institut Pasteur de Paris, Paris, France; †Université de la Méditerranée, Marseille, France; ‡Médecin de Santé au Travail, Plaisir, France; and Faculté de Médecine, Marseille, France

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/age (y)</th>
<th>Tick bite</th>
<th>Delay before onset (d)</th>
<th>Fever</th>
<th>Headache</th>
<th>Myalgia</th>
<th>Eschar (site)</th>
<th>Skin rash</th>
<th>1st serum† IgG/IgM</th>
<th>2nd serum† IgG/IgM</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/62</td>
<td>No</td>
<td>7</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Multiple (legs)</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Probable</td>
</tr>
<tr>
<td>2</td>
<td>F/58</td>
<td>No</td>
<td>6</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Multiple (legs, arms)</td>
<td>No</td>
<td>64/32</td>
<td>64/128</td>
<td>Confirmed</td>
</tr>
<tr>
<td>3</td>
<td>M/56</td>
<td>No</td>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Single (trunk)</td>
<td>No</td>
<td>64/32</td>
<td>128/16</td>
<td>Confirmed</td>
</tr>
<tr>
<td>4</td>
<td>F/51</td>
<td>No</td>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Multiple (legs, trunk)</td>
<td>No</td>
<td>0/64</td>
<td>128/16</td>
<td>Confirmed</td>
</tr>
<tr>
<td>5</td>
<td>M/58</td>
<td>No</td>
<td>5</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Multiple (legs)</td>
<td>No</td>
<td>512/0</td>
<td>512/0</td>
<td>Confirmed</td>
</tr>
<tr>
<td>6</td>
<td>F/57</td>
<td>No</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes (unknown)</td>
<td>Yes</td>
<td>NA</td>
<td>32/16</td>
<td>Confirmed</td>
</tr>
<tr>
<td>7</td>
<td>M/65</td>
<td>No</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Multiple (hands)</td>
<td>No</td>
<td>128/64</td>
<td>512/128</td>
<td>Confirmed</td>
</tr>
<tr>
<td>8</td>
<td>F/59</td>
<td>No</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Multiple (legs, arms, trunk)</td>
<td>No</td>
<td>64/8</td>
<td>128/32</td>
<td>Confirmed</td>
</tr>
<tr>
<td>9</td>
<td>M/53</td>
<td>No</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Multiple (legs, arms, trunk)</td>
<td>Yes</td>
<td>0/0</td>
<td>1,024/512</td>
<td>Confirmed</td>
</tr>
<tr>
<td>10</td>
<td>M/51</td>
<td>No</td>
<td>8</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Multiple (legs)</td>
<td>No</td>
<td>32/32</td>
<td>64/64</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60/40/70/30</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

*NA, not available; Ig, immunoglobulin; male-to-female ratio, 60%; mean age = 57.2 ± 4.5 years.
†Identical results obtained with both Rickettsia africae and R. conorii antigens.
Rural: Bush Safari

High seroprevalence to *R. africae* among native Africans

BUT

Nearly all acute cases of ATBF described in the literature (> 250) have occurred in European or American travellers

2004: ATBF cases documented by serology and molecular techniques among indigenous patients in Cameroon (7/118 FUO)

Rickettsia africae (5)

Marseille September 2009

42 yo woman
Back from a safari in Rep. South Africa
Rickettsia africae (5)

Sa fille
Rickettsia africae
Carribean Islands & West Indies

R. sibirica mongolitimonae (1)

1993: Detection in H. asiaticum

2001: Detection in H. truncatum
In Niger

1996: 1st cases in Marseille
Vector(s)???

2004: First case in Sub-Saharan Africa

Based on evaluation of a total of 9 cases, specific characteristics include the occasional findings, alone or in combination, of:

- multiple eschars
- draining lymph nodes
- a lymphangitis from the inoculation eschar to the draining node

*Lymphangitis-associated rickettsiosis*” (LAR)

Fournier et al., Clin Infect Dis 2005, 40: 1435-44
Tick-Borne Rickettsioses around the World: Emerging Diseases Challenging Old Concepts

Philippe Parola,¹ Christopher D. Paddock,² and Didier Raoult¹*  

<table>
<thead>
<tr>
<th>TICK-BORNE RICKETTSIAE IDENTIFIED AS HUMAN PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogens Described Prior to 1984</td>
</tr>
<tr>
<td>Rickettsia rickettsii (Rocky Mountain spotted fever)</td>
</tr>
<tr>
<td>“Rickettsia conorii subsp. conorii” (Mediterranean spotted fever)</td>
</tr>
<tr>
<td>“Rickettsia conorii subsp. israelensis” (Israeli spotted fever)</td>
</tr>
<tr>
<td>“Rickettsia sibirica subsp. sibirica” (Siberian tick typhus or North Asian tick typhus)</td>
</tr>
<tr>
<td>Rickettsia australis (Queensland tick typhus)</td>
</tr>
<tr>
<td>Emerging Pathogens (1984 to 2004)</td>
</tr>
<tr>
<td>Rickettsia japonica (Japanese or Oriental spotted fever)</td>
</tr>
<tr>
<td>“Rickettsia conorii subsp. caspia” (Astrakhan fever)</td>
</tr>
<tr>
<td>Rickettsia africae (African tick bite fever)</td>
</tr>
<tr>
<td>Rickettsia honei (Flinders Island spotted fever)</td>
</tr>
<tr>
<td>“Rickettsia sibirica subsp. mongoliënae”</td>
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<tr>
<td>Rickettsia slovaca</td>
</tr>
<tr>
<td>Rickettsia heilingjiangensis</td>
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<tr>
<td>Rickettsia aeschlimannii</td>
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<tr>
<td>Rickettsia parkeri</td>
</tr>
<tr>
<td>Rickettsia massiliae</td>
</tr>
<tr>
<td>“Rickettsia marmionii”</td>
</tr>
</tbody>
</table>

1984-2004
11 more pathogens

White symbols: Futur pathogens?

R. *rickettsii* the agent of RMSF

Considered as the single TB rickettsia pathogen for human in America all the XXth century

Courtesy: Christopher D. Paddock
**Rickettsia parkeri**
emerging as a human pathogen

- 1939: first isolation from *Amblyomma maculatum* (Gulf Coast ticks)

- considered as a “non pathogenic rickettsia”

- One isolate of a patient who died of “RMSF” in Ohio was similar to *R. parkeri* but considered *R. rickettsii*!

Ralph et al. Ann NY Acad Sc 1990
65 years after isolation from ticks: first cases definitely documented in southeast Virginia


Also prevalent in Uruguay
And probably misdiagnosed with *R. conorii*

Rickettsia parkeri

Rickettsia parkeri
Infection after Tick Bite, Virginia

Timothy J. Whitman,* Allen L. Richards,†
Christopher D. Paddock,‡ Cindy L. Tamminga,†
Patrick J. Sniezek,* Ju Jiang,† David K. Byers,*
and John W. Sanders*
Main vectors of RMSF in the USA:

**D. variabilis** and **D. andersoni**

The role of other tick species as important vector: long time poorly considered in the USA

1940s: convincing role of **Rh. sanguineus** in the transmission cycle of a severe spotted fever rickettsiosis (presumably RMSF)
2002-2004: 15 cases of RMSF identified in 2 rural communities in eastern Arizona.

Only *Rh. sanguineus* found in the areas frequented by the patients

- typically in peridomestic settings associated with abundant pet and stray dogs.
- also found occasionally attached to individuals most often children

*R. rickettsii* in *Rh. sanguineus* collected at case households


More evidence:

Rickettsia massiliae

• 1995: a new SFG Richettsia isolated from Rh. sanguineus and later from other Rhipicepalus spp. in Europe and Africa

• 2006: identification of a SFG rickettsia isolated from the blood of a patient in Sicily in 1984: R. massiliae!
  • 2006: R. massiliae in the USA
  • 2008: 2nd patient in France


SHORT COMMUNICATION

A tick-borne rickettsia of the spotted-fever group, similar to *Rickettsia amblyommii*, in French Guyana

+Coxiella burnettii* (Fièvre Q)
Cases are poorly documented

**R. sibirica sibirica**

- **Siberian tick typhus**
- First SFG rickettsiosis described in Asia: 1932-1936, Russia
- Geographical distribution: steppes and meadows in Asiatic Russia (Siberia, Russian Far East), Mongolia, China (Heilongjiang, Xinjiang, Beijing, Fujian provinces and Inner Mongolia), Kirgyzstan, Kazakhstan, northern Pakistan
- 2500 – 3500 cases per year in Russia, other data indisponible.

Typical landscape of Asiatic Russia in endemic region, 1936
• Tick vectors: *Dermacentor nuttalli*, *D. pictus*, *D. reticulatus* in Siberia and *Haemaphysalis concinna* in Far East. Probably other *Haemaphysalis* and *Ixodes* spp.

• First studies on transstadial and transovarial transmission of rickettsiae in tick vectors

• Infection with natural nidality (natural, or endemic foci) – E.N. Pavlovsky
R. sibirica sibirica

- Clinically benign
- History of tick bite, contact, or presence in endemic region 4-7 days (incubation period) prior to the onset of the disease.

- Seasonal peaks: through April to June
- Maculopapular rash, fever, eschar
- Mortality is lower 1%, usually due to severe underlying diseases
- Good response to tetracyclins
R. sibirica sibirica

Pre-antibiotic clinical case reports
Key issues:
- to diagnose in time
- not to forget about co-infection probability (tick-borne encephalitis, Lyme disease, human anaplasmosis, babesiosis)

Infection is highly probable in endemic regions because of high rates of natural infection in *Dermacentor* spp. (10 up to 65%) and likeliness of *Dermacentor* spp. to bite humans

Groups of risk:
- rural inhabitants
- travelers in endemic regions
**R. heilongjiangensis**

Far Eastern spotted fever: a history of neglected disease

**R. heilongjiangensis**

Isolation of first strain – 1982, Heilongjiang province, China (Fan MY, 1999)
- first proved human cases in Russian Far East – 2001

Tick vectors: predominantly *Haemaphysalis* spp. and *Dermacentor* spp.

Conjunctival rash and regional lymphangitis and lymphadenitis are common 
seasonal peak (in Russia) in July 
elder population is more likely affected

Recent points: 
Revision of old collections: 1966 rickettsial strain from *H.concinna* tick, Altai region, Southern Siberia = R.heilongjiangensis 
Overlapping area with *R. sibirica* is not consistent and not identified
Japanese spotted fever a history of a astute clinician

• 1984, Dr. F.Mahara observed clinically typical spotted fever patients in Shikoku island. Not a scrub typhus

• 1985, isolation of an agent from human

• Distribution: central and south-western Japan, around 40 cases per year

• Target population: bamboo shoot collectors, crop field workers

• Tick vector: *Haemaphysalis* spp., *I. ovatus*, *D. taiwanense*

• Closest relative by phylogenetic analysis: *R. heilongjiangensis*
• A number of severe cases with mortality were described in the literature

• Not ONLY Japanese fever. Strains from Korea (MH Chung, 2006)
R. japonica
**R. honei**

**Flinders Island spotted fever** and **Thailand spotted fever**

- 1991, Dr. R. Stewart, Flinders Island (Australia) (isolated 1992)
- 1962, RG Robertson, Thailand (*Ixodes* sp. + *Rhipicephalus* sp.), 2001

- J. Jiang, 2005 – amplified from patient in Thailand
- R. «marmioni» (Australia) = subsp. of R. honei

- Serological and molecular data from: Thailand, Sri Lanka, Cambodia, Laos, Papua New Guinea

- Ecology – reptiles
- Geographical distribution is not yet clear and areas does overlay with area of distribution or *Rickettsia conori indica*
DISPATCHES
Emerging Infectious Diseases • Vol. 9, No. 5, May 2003

Emerging Rickettsioses of the Thai-Myanmar Border¹

RESEARCH
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 12, No. 2, February 2006

Rickettsial Infections and Fever, Vientiane, Laos

Simaly Phongmany,¹ Jean-Marc Rolain,‡ Rattanaphone Phetsouvanh,³ Stuart D. Blacksell,⁴§

First Documentation of Rickettsia conorii Infection (Strain Indian Tick Typhus) in a Traveler

To the Editor:

Emerging Infectious Diseases
Vol. 7, No. 5, September-October 2001
The last emerged pathogens

Emerging Infectious Diseases
Vol. 12, No. 3, March 2006

“Candidatus Rickettsia kellyi,” India

Jean-Marc Rolain,* Elizabeth Mathai,† Hubert Lepidi,* Hosaagrahara R. Somashekar,† Leni G. Mathew,† John A.J. Prakash,† and Didier Raoult*

We report the first laboratory-confirmed human infection due to a new rickettsial genotype in India, “Candidatus Rickettsia kellyi,” in a 1-year-old boy with fever and maculopapular rash. The diagnosis was made by serologic testing, polymerase chain reaction detection, and immunohistochemical testing of the organism from a skin biopsy specimen.
Tick-Borne Rickettsioses around the World: Emerging Diseases Challenging Old Concepts

Philippe Parola,¹ Christopher D. Paddock,² and Didier Raoult¹*

TICK-BORNE SFG RICKETTSIAE PRESUMPTIVELY ASSOCIATED WITH HUMAN ILLNESSES .....738

“Rickettsia conorii subsp. indica” (Indian Tick Typhus) ..................................................................................................................738

Rickettsia canadensis .............................................................................................................................................................................738

“Rickettsia amblyommii” ...........................................................................................................................................................................738

“Rickettsia texiana” ................................................................................................................................................................................738

Rickettsia helvetica ..................................................................................................................................................................................739

RICKETTSIAE ISOLATED FROM OR DETECTED IN TICKS ONLY .................................................................................................739

Futur pathogens ?
RICKETTSIOSES
&
TRAVEL MEDICINE
2006: The second most frequent identified etiology after malaria for systemic febrile illness in ill returned travelers (Freedman et al, N. Engl J Med)
Rickettsial diseases in international travelers, 1996-2008: a multi-center GeoSentinel analysis


All GeoSentinel cases, 1996-2008:
$n=99,355$

Cases excluded: $n=51,440$
- Travel for immigration only: $n=15,715$
- Seen during travel: $n=30,956$
- Other reasons: $n=4,769$

Cases included in analysis:
$n=47,915$

With rickettsial diseases:
$n=280$

With other diseases:
$n=47,635$

Submitted
Rickettsial diseases in international travelers, 1996-2008: a multi-center GeoSentinel analysis


- **231 (82.5%) spotted fever group rickettsiosis**
  - 197 (88%) acquired in sub-Saharan Africa

- 10 (3.6%) cases of typhus group rickettsiosis
- 16 (5.7%) cases of scrub typhus
- 4 (1.4%) cases of indeterminable rickettsiosis
- 1 (0.4%) case of human granulocytic anaplasmosis
- 11 (3.9%) cases of acute Q fever
- 7 (2.5%) cases of bartonellosis

Submitted
DIAGNOSTIC OF RICKETTSIOSES
Serology

IMMUNOFLUORESCENCE
= REFERENCE METHOD

• commercial kits: usually 3 antigens tested
• acute serum / convalescent serum
• cross reactions

In specialized laboratories
several antigens tested in IFA
western blot
cross-absorption

Serology to report « emerging » diseases?

- Essential for diagnostic BUT Many cross reactions
- Interpretation according to a diagnostic score (clinical, epidemiological)
- **CAN NOT BE USED** to describe a new disease, a new clinical entity or a new epidemiological findings, which must be based on direct evidence

Histochemical and Immunohistochemical procedures

Escar in ATBF

In reference laboratories (L3)
Cells: HEL or L929
Staining (Giemsa / Gimenez) and immunodetection

Molecular tools:
- PCR using specific primers
- Identification by sequencing and comparison to genbank

Advantages:
sensitivity – specificity – reproductibility in non specialized lab

**Arthropods** also tools for the diagnosis

“Suicide PCR”: 
- a nested PCR using single-use primers targeting a gene never amplified previously in the laboratory.
- avoids “vertical” contamination by amplicons from previous assays, one of the limitations of extensive use of PCR.
- no positive control (does not impair the interpretation of positive results).
- appropriate negative controls

Real-time quantitative PCR assays (i.e., epidemic typhus).

EMERGING PCR CONTAMINATIONS ???

Spotted Fever Group and Typhus Group Rickettsioses in Humans, South Korea

Yeon-Joo Choi,*1 Won-Jong Jang,†* Jong-Hyun Kim,* Ji-Sun Ryu,* Seung-Hyun Lee,* Kyung-Hee Park,* Hyung-Suk Paik,† Young-Sang Koh,‡ Myung-Sik Choi,§ and Ik-Sang Kim§

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 2, February 2005

▷ Rickettsioses in South Korea, Materials and Methods, P.-E. Fournier et al.
▷ Rickettsioses in South Korea, Data Analysis, J.-S. Ma
# TREATMENT: DO NO WAIT LABORATORY CONFIRMATION!

<table>
<thead>
<tr>
<th>Rickettsiosis</th>
<th>Patient cohort</th>
<th>Selected antibiotic regimens</th>
<th>Strength of recommendation and quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean spotted fever</td>
<td>Adults</td>
<td>Doxycycline, two oral 200-mg doses separated by a 12-h interval</td>
<td>A I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline, 200 mg single dose or 100 mg twice a day for 2 to 5 days</td>
<td>A III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin, 150 mg/kg/day in two divided doses for 7 days</td>
<td>A II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin, 10 mg/kg/day in one dose for 3 days</td>
<td>A III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jaspamycin, 50 mg/kg every 12 h for 5 days</td>
<td>A I</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td>Doxycycline, 2.2 mg/kg every 12 h for children weighing &lt;99 lb (45 kg) or adult dosage if ≥100 lb, for 5 to 10 days</td>
<td>A I</td>
</tr>
<tr>
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<td>Clarithromycin, 150 mg/kg/day in two divided doses for 7 days</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Jaspamycin, 50 mg/kg every 12 h for 5 days</td>
<td>A II</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
<td>Jaspamycin, 50 mg/kg every 12 h for 5 days</td>
<td>A III</td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td>Adults</td>
<td>Doxycycline, 100 mg every 12 h for 5 to 10 days</td>
<td>A III</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Doxycycline, 2.2 mg/kg every 12 h for children weighing &lt;99 lb (45 kg) or adult dosage if ≥100 lb, for 5 to 10 days</td>
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</tr>
</tbody>
</table>

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PREVENTION OF SFG RICKETTSIOSSES

NO VACCINE

Prevention = Prevention against tick bites

Wearing of long trousers that are tucked into boots

Application of a topical deet ($N,N$-diethyl-$m$-toluamide) repellent to exposed skin

+ Treatment of clothing with permethrin.

WHAT IS THE EFFECT OF DOXYCYCLINE MALARIA CHEMOPROPHYLAXIS?
HOW TO REMOVE A TICK?