Rickettsiae: old enemies newly defined

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Russia, 1918. World War I is over but a tiny enemy is still on the move. It had killed millions –on both sides - during the war but isn't finished. By 1922 it strikes at least three million more, primarily civilians ravaged by war and famine. The deadly adversary is *Rickettsia prowazekii*, the tiny bacterium that causes epidemic typhus.

World War I wasn't the first conflict – or the last – in which typhus had an important (and even deciding) role, but it may have been the first time that humans realized the enormous potential of disease as a weapon: In the late 1920s the Soviet Union established their biological weapons program, and *R. prowazekii* was part of it.

The American pathologist Howard Taylor Ricketts was a dedicated researcher known to inject himself with pathogens in order to test their effects.

Rickettsia species cause some of the oldest known arthropod-borne diseases. Although *R. prowazekii* is historically the most important, it's not the most pathogenic; that honor belongs to *R. rickettsii*, the tick-borne causative agent of Rocky Mountain Spotted Fever (RMSF), which – if not treated promptly with the right antibiotics – can still cause lethality rates nearing 30%. Although both species were studied as potential biological weapons in the 20th century, the perceived threat to public health remained low. As did the number of scientists studying *Rickettsia*. However, the scientific and medical view of the importance of *Rickettsia* species has changed since the 1980s as new pathogenic species have been identified, old species have re-emerged and bioterrorism has become a realistic threat.

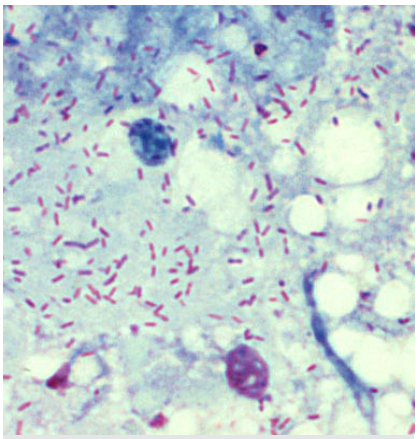
Rickettsia

- genus named after Howard Taylor Ricketts (1871–1910), who studied Rocky Mountain Spotted Fever (*R. rickettsii*) and typhus (*R. prowazekii)*, succumbing to the latter
- obligate intracellular rods, occupy cytoplasm (SFG also in nucleus
- 0.3 to 0.5 ?m in diameter and 0.8 to 2.0 μm in length
- Gram-negative-type membrane, difficult to identify using routine histological techniques (Gimenez stain-positive)
- very small genome (1.1 to 1.6 Mb), rely on host cells for synthesis of many amino acids and nucleotides
- closely related to the ancestor of mitochondria (particularly *R. prowazekii*)
- life cycle involves arthropod vector (ticks, lice, fleas, mites) and vertebrate host
- humans are incidental hosts for all except R. prowazekii

What's in a name?

Pathogenic *Rickettsia* are divided into the Spotted Fever Group (SFG) and the Typhus Group. The Typhus Group consists of two *Rickettsia* species, *R. prowazekii* and *R. typhi* (murine endemic typhus, flea-transmitted). Until the mid-1980s, six SFG species were thought to cause spotted fever in distinct geographic regions of the world ("One pathogenic rickettsiosis/continent"). Using molecular techniques it has since been shown that at least 15 species belong to the SFG group.

Why the sudden discovery of so many new rickettsioses? Several factors are probably involved – greater awareness of rickettsial infections among the medical community, improved culture methods for *Rickettsia* species, identification of previously identified "non-pathogenic" species as disease-causing agents. However, the most important reason for the explosion in *Rickettsia* species is the application of molecular tools for genotypic analysis and diagnosis.



Rickettsia species infect every organ of the body but never move beyond the endothelial cells lining blood and lymphatic vessels. © CDC

Spotted Fever Group Rickettsia

- *R. aeschlimannii, R. africae, R. akari*, *R. australis*, *R. conorii, R. felis, R. heilongjiangensis, R. helvetica*, *R. honei*, *R. japonica*, *R. massilae, R. parkerei, R. rickettsii, R. sibirica, R. slovaca*
- found on every continent except Antarctica
- transmitted primarily by ticks, also fleas (*R. felis*) and mites (*R. akari*)
- maintained in tick populations by transovarian transmission
- common clinical manifestations include eschar (local dermal/epidermal necrosis at bite site), rash, fever and swollen lymph nodes; symptoms of spotted fever rickettsioses are similar (without species or geographical specificity) and variable in severity
- Effectively treatable with doxycycline, tetracycline or chloramphenicol

Members of the genus *Rickettsia* have small, highly conserved genomes, and not only are the symptoms of most SFG rickettsioses similar, the serologic tests used for diagnosis of spotted fevers are highly cross-reactive; they can diagnose rickettsial infection but are useless in telling the difference between *R. xxx* and *R. yyy*. For species analysis, PCR- and culture-based diagnostic methods – which are not widely used, even in developed countries – are necessary.

The content and synteny of *Rickettsia* genomes are in fact so similar that there is an ongoing debate as to how species should be identified. The official criteria for identification of bacterial species "don't work": the genomes show so much overlap that many defined species of *Rickettsia* would be consolidated as one species (in subspecies) according to normal taxonomic rules. New – and still controversial - guidelines have been proposed, currently defining 25 species in the genus *Rickettsia* based on the genetic diversity of "classical" species.

Some members of the ex-Rickettsia club

In the days before molecular genetics, "Rickettsia" became a term for pretty much any small intracellular bacteria that is difficult to culture. At the same time new species have been identified, others have been kicked out:

- *Bartonella (Rochalimaea) quintana*: lice-borne cause of trench fever
- *Coxiella burnetii*: causes Q-fever (no vector)

Rickettsiales (Order *Rickettsiales*) – sometimes referred to as Rickettsia or Rickettsiae

- genus *Ehrlichia*: tick-borne *E. chaffeensis*, *E. ewingii* cause ehrlichiosis
- genus *Anaplasma*: tick-borne *A. phagocytophilum* causes human granulocytic anaplasmosis
- *Orienta tsutsugamushi*: mite-borne cause of scrub typhus; closely related to Rickettsia (Family Rickettsiaceae)

The old, the new and the possible threats of *Rickettsia*

When you hear "biological weapon", *Rickettsia* probably doesn't immediately come to mind; a tick- or louse-borne disease doesn't exactly seem the most likely candidate for a bioterrorism agent. However, as a number of unfortunate laboratory scientists have demonstrated, aerosolized *Rickettsia* species can cause illness and even death. *Rickettsia* are also easily obtainable in nature, difficult to detect and infectious at low doses, highly desirable characteristics for bioweapons. The Centers for Disease Control and Prevention (CDC) has indeed classified R. prowazekii as a Category B agent (moderately easy to disseminate, moderate morbidity, low mortality), and other *Rickettsia* species - *R. rickettsii*, *R. typhi* and *R. conorii* – may also fit the bill.

Damage to infected endothelial cells causes the characteristic rash of Rocky Mountain Spotted Fever and most of the other clinical manifestations of rickettsial diseases. © CDC

But rickettsioses pose more than a theoretical bioterrorism risk. They exist worldwide and continue to cause epidemics and outbreaks. Epidemic typhus finds its niche where people live under crowded and unsanitary conditions that enable the vector – body lice – to thrive: in 1997 it returned to Europe, with 22 confirmed cases in a Russian hospital, and more than 45,000 cases were diagnosed in Burundi between 1993 and 1997 following the outbreak of civil war. Infection with murine typhus is often thought to go unrecognized and undiagnosed, as are many – if not the majority of – spotted fever infections. Nevertheless, cases of both Rocky Mountain Spotted Fever (*R. rickettsii*) and Mediterranean Spotted Fever (R. conorii) are on the rise, and although mortality is generally low with antibiotic therapy, outbreaks with alarmingly high death rates have recently been reported in Brazil (nearly 30% for RMSF, 1995–2004) and Portugal (>32% for MSF in 1997).

A hundred years later…what we still don't know

The public health risk from *Rickettsia* is still unclear and most likely underestimated. Multiple species of *Rickettsia* are now known to be endemic in specific geographic regions; a recent study found five pathogenic species in southern Germany. And rickettsioses are thought to be second only to malaria in causing fever illnesses in European tourists traveling abroad. New species will almost certainly be identified; in some geographic areas, no *Rickettsia* species are known, but serologic tests indicate that significant portions of the population have been infected. *R. prowazekii* (and perhaps other *Rickettsia* species) will continue to be regarded as potential biological weapons. And while a century of research - since Howard Taylor Ricketts identified R. rickettsii in 1908 – has revealed a great deal about these tiny bacteria, vital information – knowledge that can enable us to better fight both old and emerging rickettsial diseases - is still missing.

The human body louse (*Pediculus humanus humanus*) attaches its eggs to clothing, and epidemics of typhus occur most commonly in winter and at high elevations.
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A short „To Do" list:

- investigate early rickettsial infections in human; do immune responses match those in murine models, how important is oxidative stress?
- check pathogenic mechanisms: *Rickettsia* reactivation in ticks, role of tick saliva in early infection, rickettsial virulence genes
- develop rapid, reliable and easy diagnostic tests (i.e. serologic assays with agent-specific diagnosis)
- establish surveillance of rickettsial diseases
- work on list

Don't mess with a hot tick

The worldwide dog tick *Rhipicephalus sanguineus* is a vector for *R. ricketsii* (RMSF), *R. conorii* (MSF) and the emerging pathogen *R. massiliae* but rarely feeds on humans. While investigating a focus of Rickettsial infections in France, the authors could demonstrate experimentally that when kept at warmer temperatures (40°C vs. room temperature), *R. sanguineus* more readily attaches to human skin.

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Free online: http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=19015724

The brown dog tick (*Rhipicephalus sanguineus*) is the first "global" tick species – it's found worldwide and can transmit a variety of diseases to humans.
© CDC - James Gathany, William Nicholson

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  http://www.euro.who.int/HEN/HTResults?language=English&HTParentPage=30590&HTCode=epidemiology

- More information about bioterrorism agents and diseases can be found on the website of the Centers for Disease Control and Prevention:
  http://www.bt.cdc.gov/agent/agentlist-category.asp