

## Artykuły przeglądowe

# The European problem of spotted fever group rickettsiae, transmitted by ticks: biology, ecology, detection

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**ABSTRACT.** The genus *Rickettsia* is composed of obligatory intracellular gram-negative bacteria associated with arthropods: ticks, mites and insects. The genus was found to comprise the sub-groupings: the spotted fever group (SFG) and the typhus group (TG). Members of the SFG rickettsiae are usually associated with ixodid ticks which transfer them to vertebrates *via* arthropod secretions and between themselves transstadially and transovarially. Rickettsiosis is a complex pathogenic condition which takes on a number of various forms, depending on aetiological factors prevalent locally. Symptoms of rickettsiosis are similar to those occurring in many other tick-borne diseases. The necrotic skin lesion is a typical sign of spotted fever-group rickettsioses. The definition of SFG species has been recommended to use combined methods: rickettsiae detection and identification should be carried out based on serological tests and molecular techniques. Those recommended among the latter include PCR, PCR-RFLP, macrorestriction analysis by pulse-field gel electrophoresis and sequencing. The SFG rickettsiae are present in the Old Continent for example in Italy, France, Sweden, Denmark or Slovakia. Rickettsiae have been detected in patients and ticks from genus *Ixodes* and *Dermacentor*. The bacteria of SFG (*Rickettsia helvetica*) is present in ticks *Ixodes ricinus* from northern Poland creating potential danger for humans and animals.

**Key words:** native and imported rickettsioses, rickettsiae species, vectors of rickettsiae.

### Characteristics of the genus *Rickettsia*

The genus *Rickettsia* is composed of obligatory intracellular gram-negative bacteria associated with arthropods: ticks, mites and insects. The genus was found to comprise the following three sub-groupings: the spotted fever group (SFG), the typhus group (TG), and the scrub typhus group (STG). The rickettsiae belonging to the first two groups are present in Europe, the STG rickettsiae occurring in the Asia-Pacific region [1–3]. It seems, however, that the subdivision is not entirely satisfactory. Phylogenetic studies have demonstrated the evolutionary unity of the SFG and the TG rickettsiae, while those belonging to the third (STG) were transferred from the genus *Rickettsia* to the newly erected genus *Orientia*. The new genus is represented by a single species, *Orientia tsutsugamusi* (earlier known as *R. tsutsugamusi*), classified with the scrub typhus group (STG) [3–5]. The typhus group (TG) rickettsiae include *Rickettsia typhi*, *R. prowazeki*, and *R. canada*, while SFG comprises about 20 dif-

ferent rickettsia species, i.e., *R. helvetica*, *R. sibirica*, *R. conorii*, *R. slovaca* as well as *R. akari*, *R. felis*, and *R. rickettsii*. Some of them are pathogens of humans and domestic animals [1,3].

Rickettsiae are strictly intracellular parasites which require host cells to replicate. Rickettsiae occur within eukaryotic cells, but — unlike e.g., *Anaplasma phagocytophilum* — are not enclosed in vacuoles. The SFG rickettsiae are encountered in host's cell nuclei, while the TG rickettsiae are observed exclusively in the cytoplasm [5, 6]. Pathogens are usually transmitted to vertebrate host when the latter are pricked by arthropods with the vector's saliva or when infected faeces or even the entire crushed body of a vector are rubbed into the host's skin (Table 1). A few cases of human infection *via* exposure to aerosols and *via* blood transfusion were reported as well [5].

### Rickettsiae in arthropods

Arthropods are both important vectors and, col-

lectively, a reservoir of the *Rickettsia* bacteria. In addition, they function as amplifiers in the life cycles of the rickettsia.

Members of the SFG rickettsiae are usually associated with ixodid ticks (Table 1) which transfer them to vertebrates *via* arthropods secretions and between themselves transstadially and transovarially. When in invertebrate hosts, the rickettsiae are present in virtually all the organs. As ovaries and oocytes of an adult female are most often infected, the transovarial transmission of the rickettsiae to the offspring is extremely successful. Transovarial infection of the offspring is reflected in all the remaining stages of the tick's life cycle, transstadial transmission of the SFG rickettsiae being 100% successful [5].

Two tick species: *Ixodes ricinus* and *Dermacentor andersoni* were described as affected by transpermal transmission of the SFG rickettsiae [5, 7]. Such sexual transmission between individuals of different sexes is relatively rare, but important for the persistence and dispersal of rickettsiae. The rickettsia dispersal is associated also with the social behaviour of ticks. Ticks are known to release various pheromones, i.a., assembly pheromones, aggregation and attachment pheromones, and sex pheromones. The pheromones, released mainly through the anus, facilitate aggregation of hungry individuals on host, finding a mating partner, and copulation [8]. A physically close association of the ticks during their feeding on a vertebrate host enhances infection *via* co-feeding.

So far, little is known on adverse effects of rickettsiae on tick functioning. It has been suggested that the bacteria can reduce tick fertility [9]. There is no doubt, however, that the rickettsiae and ticks have been clearly co-evolving. The tick life cycle depends on environmental factors such as, e.g., temperature, humidity, or presence of suitable hosts. They have adapted to a variable environment by evolving a strategy of seasonal activity and are capable of surviving, under unfavourable conditions, long periods of fasting. However, the condi-

tions unfavourable for a tick do not contribute to the elimination of rickettsiae from their bodies, nor do they impair further functioning of the bacteria. Rickettsiae are highly tolerant of adverse environmental conditions and, as soon as the favourable situation is restored, their original virulence is resumed. It seems that their dispersal is basically unhampered. The invertebrate hosts supporting rickettsiae are both vectors and reservoirs of the bacteria. On the other hand, vertebrates may be a significant obstacle for rickettsiae. The short-term rickettsiaemia of vertebrates decidedly restricts the potential for the bacteria transmission to other organisms. Therefore it has been suggested that humans are not good reservoirs for rickettsiae, as a tick infestation is usually short-lived and most often involves a single human, and the rickettsiaemia is short-lived as well and treated with antibiotics, which eliminates the bacteria from their environment [5].

### Rickettsiosis — description of the disease

Rickettsiosis is a complex pathogenic condition which takes on a number of various forms, depending on aetiological factors prevalent locally (Table 2). Symptoms of rickettsiosis are similar to those occurring in many other tick-borne diseases. The symptoms most often include headache, fever, muscle pain, eruptions, rash, local lymphadenopathy, and a "tache noire" (inoculation eschar) at the bite site. This necrotic skin lesion is a typical sign of spotted fever-group rickettsioses [5, 10-12]. In vertebrate hosts, rickettsiae settle in endothelium cells of skin capillaries, lungs, heart, kidneys, and brain, which results in *vasculitis*-type lesions. Damage to vessel endothelium gives rise to necrotic centres and perivascular infiltrations, and slows down blood circulation. Ischaemia and hypoxia are damaging to organs and systems, including the central nervous system and the cardiac muscle. In some infections, e.g., those produced by *R. prowazekii*, falling victim to the disease and recovery is not equivalent with

Table 1. Vectors of *Rickettsia* and *Orientia* to vertebrates host

Arthropods	Rickettsiae species
Hard Ticks from genus <i>Ixodes</i> , <i>Dermacentor</i> , <i>Amblyomma</i> , <i>Rhipicephalus</i> , <i>Haemaphysalis</i>	SFG rickettsiae, <i>R. canada</i> (TG)
Mites	<i>R. akari</i> (SFG), <i>O. Tsutsugamushi</i> (STG)
Lice	<i>R. prowazekii</i> (TG)
Fleas	<i>R. typhi</i> (TG), <i>R. felis</i> (SFG)

elimination of the pathogenic agent from the system. On the contrary, it may persist in cells of the reticular endothelium system for many years, whereby the disease becomes recurrent [11].

### Detection of the *Rickettsia* bacteria

The definition of SFG species has been based on their serotype as determined by the complement fixation test, the toxin neutralisation test in mice, the cross-immunity test in guinea pigs, or the microimmunofluorescence. However, serological identification is rendered difficult due to frequent cross-reactions between individual *Rickettsia* species. Therefore it is recommended to use combined methods: rickettsiae detection and identification should be carried out based on serological tests and molecular techniques. Those recommended among the latter include PCR, RFLP analysis of PCR products, macrorestriction analysis by pulse-field gel electrophoresis and sequencing. Molecular studies most often involve two fast-mutating genes that encode the enzyme citrate synthase (*gltA*) and the outer membrane protein rOmpA (*ompA*) [13-16]. Both genes are extremely sensitive and important tools in

the rickettsia detection and phylogeny studies. The bacteria are detected and identified in blood and skin biopsies, particularly the eschar, from patients [6, 10].

### Areas with endemic rickettsiosis

The SFG rickettsiae are present in the Old Continent; they have been detected in patients suffering of tick-transmitted diseases. Swedish authors concluded that rickettsiae may be an important pathogen in the aetiology of perimyocarditis, which can result in sudden unexpected cardiac death in young people [17]. Rickettsiae, causing various forms of rickettsiosis, have been also reported from, i.a., France, Sweden, Slovakia, Switzerland, Denmark, in the Balkan region, and countries of the former USSR [13, 18-24].

In 1909, the first case of Mediterranean spotted fever (MSF) was described from Tunisia and soon similar cases were reported from other Mediterranean countries, including France, Italy, and Spain (Table 2). Sporadic incidences of the disease were observed in Belgium and Switzerland. The aetiological factor of MSF is *R. conorii* [5].

Table 2. Selected pathogens of the genera *Rickettsia* and *Orientia* and diseases they cause

Bacterium responsible	Disease (first clinical description)	Site	Vector
<i>R. prowazekii</i> (TG)	epidemic typhus	Africa, Asia, South America	African ticks, fleas, lice
<i>R. typhi</i> (TG)	murine typhus	probably in tropical countries	
<i>R. rickettsii</i> (SFG)	Rocky Mountain spotted fever (RMSF)	North, Central and South America	ticks from genus <i>Amblyomma</i> , <i>Dermacentor</i> and <i>Ixodes</i>
<i>R. conorii</i> (SFG)	Mediterranean spotted fever (MSF)	Countries around the Mediterranean, in sub-Saharan Africa, in India, around Black Sea, in the eastern Russia, in France, Spain, Portugal	ticks from genus <i>Rhipicephalus</i> , <i>Dermacentor</i> and <i>Ixodes</i>
<i>R. sibirica</i> (SFG)	Siberian tick typhus	Russia, Pakistan, China	ticks from genus <i>Haemaphysalis</i> and <i>Dermacentor</i>
<i>R. conorii</i> (SFG)	Israeli spotted fever	Israel	ticks
<i>R. japonica</i>	Japanese or oriental spotted fever	Japan	ticks from genus <i>Haemaphysalis</i> , <i>Dermacentor</i> and <i>Ixodes</i>
<i>R. conorii</i> <i>R. africae</i> (SFG)	African tick bite fever	South Africa	ticks from genus <i>Amblyomma</i>
<i>R. helvetica</i> (SFG)	Unnamed	Europe, Japan, Thailand	ticks from genus <i>Dermacentor</i> and <i>Ixodes</i>
<i>R. slovaca</i> (SFG)	Tick-borne lymphadenopathy (TIBOLA) or <i>Dermacentor</i> -borne-necrosis-erythema lymphadenopathy (DEBONEL)	from France to the Crimea	ticks from genus <i>Dermacentor</i> and <i>Ixodes</i>
<i>O. tsutsugamushi</i> (STG)	Scrub typhus	Asian-Pacific region	mites ( <i>Leptotrombidium</i> spp.)

Siberian tick typhus was first described in Primorye (Russia) in the spring-summer 1934-1935. The aetiological factor is *R. sibirica*. Although the bacteria has been most frequently identified in ticks and patients in different parts of northern Asia, documented cases are known also from southern France where the aetiological factor was described as "*R. sibirica mongolotimonae*" [5, 10].

Cases with *R. slovacica* as the aetiological factor have been reported from some European countries, e.g., Slovakia or France. Because the bacteria were first detected in ticks of the genus *Dermacentor*, the disease is known as DEBONEL for "*Dermacentor*-borne-necrosis-erythremalymphadenopathy" or TIBOLA for "tick-borne lymphadenopathy" (Table 2) [10]. The way the disease proceeds has been determined as mild.

*Rickettsia helvetica*, which was originally isolated in 1979 from *I. ricinus* in Switzerland, was shown to have pathologic relevance only in 1999, in two Swedish men [17]. In addition, this bacteria stimulated a specific antibody response in a patient in eastern France [21]. The pathogenicity of *R. helvetica* is still a subject of discussion and requires confirmation by studies conducted in many independent research centres.

### Rickettsioses — a traveller's diseases

Endemic areas for tick-borne diseases are identified from studies on tick populations inhabiting areas known for supporting pathogens. Such information may assist medical and veterinary services in correct diagnosing. Most tick-borne diseases are

characterised by non-specific, flu-like symptoms which render diagnosing difficult. Consequently, all the information on a patient's visits to forest and/or shrubberies and on his/her being bitten by ticks or even on the exposure to potential tick bites facilitates medical treatment. However, in the modern world we are exposed not only to local pathogens, but also to imported ones. It seems that the role of passerine birds in the transmission of tick-borne pathogens is of a minor importance. On the other hand, much more important are human travels, very popular and easy in the recent decade.

Few cases of tick-borne rickettsioses among international travellers were reported in the 1980s. The situation has recently changed. In 1998-2002, rickettsioses caused by *R. africae* were recorded in 131 patients who returned to the UK from a tourist trip to southern Africa [25]. The Astrakhan fever rickettsia, absent from Europe, was reported from a French patient who had visited Chad. A *R. sibirica mongolotimonae* infection was registered in 2004 in Africa [26], while a Japanese traveller returning from Kenya showed the presence of the Mediterranean spotted fever etiological factor [27].

A group particularly risk-prone to imported diseases includes active people preferring ecotourism: a wide spectrum of international travellers, safari tourists, game hunters, film crew members as well as humanitarian workers or deployed soldiers. The imported rickettsioses are dominated by the African tick bite fever, caused by *R. africae*, and the Mediterranean spotted fever, induced by *R. conori* [28]. This is a result of southern Africa, sub-Saharan Africa, and the Mediterranean basin being particu-

Table 3. Levels of similarity (%) between *gltA* sequences *Rickettsia* (Kimura, 1980), PZ-S — *R. helvetica* from Poland (materials sequenced by the present author, GenBank accession number -DQ105664)

	U59723	U59725	U59734	U59414	AJ427878	AJ427879	AJ427880	AJ427889	U59722	PZ-S
U59723	100.0									
U59725	96.8	100.0								
U59734	96.9	99.8	100.0							
U59414	92.0	92.9	92.7	100.0						
AJ427878	100.0	95.0	95.3	91.2	100.0					
AJ427879	95.3	96.2	96.5	92.7	95.3	100.0				
AJ427880	95.6	95.9	96.2	92.4	95.6	99.7	100.0			
AJ427889	95.2	95.2	95.4	91.1	95.6	95.6	95.3	100.0		
U59722	96.8	99.3	99.4	92.8	95.3	96.5	96.2	95.4	100.0	
PZ-S	99.7	95.1	95.3	91.8	100.0	95.3	95.6	95.8	95.3	100.0

U59723 — *R. helvetica*, U59725 — *R. slovacica*, U59734 — *R. sibirica*, U59414 — *R. typhi*, AJ427878 — *R. helvetica*, AJ427879 — *Rickettsia* sp., AJ427880 — *Rickettsia* sp., AJ427889 — *Rickettsia* sp., U59722 — *Rickettsia* sp.

larly attractive to tourists, especially in summer, coincident with increased activity of ticks, the major vector of rickettsiae. The development of new regions for tourism opens the door for, i.a., new tick-borne diseases, which also means diagnostic problems; this should be kept in mind by both the researchers and the relevant medical and veterinary practitioners.

### The presence of *Rickettsia helvetica* in Poland

The presence of *Rickettsia* pathogens in patients' blood directed the attention of the researchers to the infestation prevalence in tick populations which served as vectors in individual countries.

In Poland and in the neighbouring countries, the *Ixodes* ticks were found to carry the SFG *Rickettsia helvetica*. In Scandinavia, where rickettsioses are not known to be endemic or epidemic among humans or animals, the presence of *R. helvetica* DNA was found in 1.7% of the *I. ricinus* population [20]. The presence of the bacteria belonging to that group was recorded in the neighbours of Poland, i.a., in Slovakia. Špitalská and Kocianová [22] found the presence of DNA of *Rickettsia* sp. belonging to the spotted fever group in 10.9% of the *I. ricinus* from south-western Slovakia. An estimated 2-36.8% of the *I. ricinus* ticks in Europe are infected with this rickettsia species [21, 23, 24].

In Poland, DNA of *R. helvetica* was detected in the ticks *Ixodes ricinus* and *Dermacentor reticulatus* in the north-eastern part of the country. The prevalence of infection was 9.9%, 10.5% of nymphs and 8.8% of the imagoes [29]. However, no cases of pathological condition among humans and domestic areas have been so far reported from the areas surveyed.

In Western Pomerania, *R. helvetica* DNA was, too, found in the ticks *I. ricinus* (40% of the population testing positive), but the number of individuals examined was low (10) and they were collected from boreliosis-affected dogs. The DNA isolated from the ticks was analysed by amplifying the *gltA* gene fragment. The homology matrix showed the Western Pomeranian sequence, denoted PZ-S, to be 100% similar to the Italian *R. helvetica* sequence (AJ 427878) and to be 99.7% similar to the Switzerland sequence (U59723). Similarity to other sequences of SFG rickettsiae and to *R. typhi* of TG was 95 and 91%, respectively (Table 3).

Comparison of analogous *gltA* DNA sequence

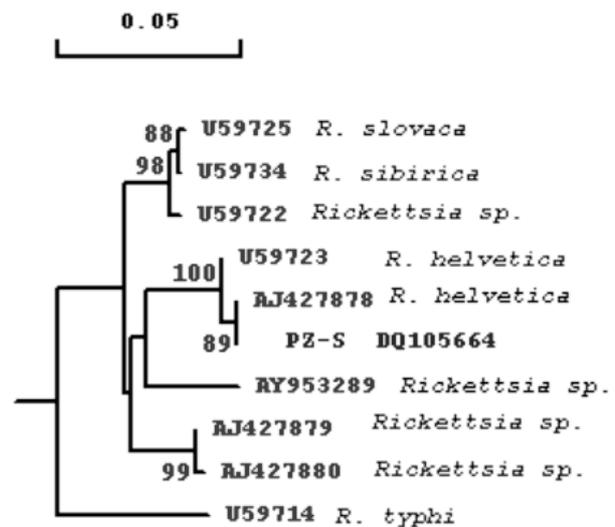


Fig. 1. Phylogenetic tree of rickettsiae based on *gltA* gene (*R. helvetica*, PZ-S, from Poland and various *Rickettsia* spp.); scale bar = 5% difference in nucleotide sequences; the maximum likelihood method was used to construct the phylogenetic tree by using the DNAMAN program (bootstrap 1000)

fragments of the bacteria assigned, in GenBank, to *Rickettsia* sp. and *R. helvetica* produced 26 polymorphic loci; most of them were transitions. On the basis of *gltA* gene fragments, phylogenetic analyses were performed for some rickettsia species, including the rickettsia from Western Pomerania (Fig. 1). The topologies of the *gltA*-based phylogenetic trees demonstrate a high degree of similarity between the Polish rickettsiae and pathogenic populations of *R. helvetica* from Italy and Switzerland (Fig. 1). Bootstrap analysis of the data was performed to measure the reliability of the branching order proposed by each analysis. The values for the nodes were higher than 88% for *R. helvetica* of SFG, which confirms the accuracy of the analysis. Results of the studies discussed demonstrate *R. helvetica* to be present in northern Poland (Western Pomerania and north-eastern part of the country) and to be a potential danger for humans and animals. However, the data from Poland are far from complete; there is no information on the presence of pathogenic *R. helvetica* in central and southern Poland, particularly that *I. ricinus*, the major vector of the bacteria, is one of the most abundant tick species in Poland.

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