

Rickettsia felis, an emerging flea-transmitted human pathogen

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Rickettsia felis was first recognised two decades ago and has now been described as endemic to all continents except Antarctica. The rickettsiosis caused by *R. felis* is known as flea-borne spotted fever or cat-flea typhus. The large number of arthropod species found to harbour *R. felis* and that may act as potential vectors support the view that it is a pan-global microbe. The main arthropod reservoir and vector is the cat flea, *Ctenocephalides felis*, yet more than 20 other species of fleas, ticks, and mites species have been reported to harbour *R. felis*. Few bacterial pathogens of humans have been found associated with such a diverse range of invertebrates. With the projected increase in global temperature over the next century, there is concern that changes to the ecology and distribution of *R. felis* vectors may adversely impact public health.

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The human pathogenicity of the Spotted Fever group (SFG) rickettsiae varies widely between species. In spite of significant phenotypic variability between species, most members of the group are treated as potential human pathogens (1, 2). *Rickettsia felis* is a newly described species of the SFG (3). Previously, *R. felis* was classified as a member of Typhus group (TG) for over 10 years. The main vectors for *R. felis* (as with *R. typhi*) are fleas. Like all rickettsiae, *R. felis* is an obligate intracellular Gram-negative alpha-proteobacterium requiring a vertebrate and invertebrate host to survive and reproduce (4). There are proposals to re-organise the genus *Rickettsia* into four groups, instead of the traditional two, adding an Ancestral group (AG) and Transitional group (TRG) to the widely accepted SFG and TG (5). Should this new form of genotypic classification become generally accepted, *R. felis* would join the TRG alongside the related *Rickettsia akari*.

The geographic distribution of *R. felis* in arthropods, especially the cosmopolitan cat flea, *C. felis*, reinforces the hypothesis that *R. felis* can be found in most, if not all, human populations where domestic animals are kept as pets. The world-wide distribution of *R. felis* is probably due to the co-migration of humans and domestic animals harbouring *C. felis*.

First described by Adams et al. in 1990 (6), *R. felis* was originally named ELB agent after the laboratory from

which it was first isolated, El Labs (ELB) in the United States. Its serendipitous discovery was by electron microscopy, showing a rickettsia-like organism, similar in morphology to *Rickettsia typhi*, the only species of *Rickettsia* known at the time to be flea-borne. Soon after, Azad et al. (7) described this new variant of rickettsiae, reporting on its 17 kDa and citrate synthase genes and classifying it as a TG rickettsia. The demonstration of the presence of the *ompA* gene in *R. felis* by Bouyer et al. (3), resulted in the re-classification *R. felis* as a member of the SFG. Re-analysis of the 17 kDa gene showed greater similarity to the SFG than TG.

The genome of *R. felis* has been sequenced and it was the first rickettsia to be described as having plasmids (8). Together with the two plasmids (pRF and pRF δ), the combined genetic material is the largest among *Rickettsia* sp. to date (5, 8). The plasmids of *R. felis* are highly variable (9).

1. Flea-borne spotted fever/cat-flea typhus

The names used to describe *R. felis* infection (flea-borne spotted fever/cat-flea typhus) may soon be deemed inaccurate with the recognition of other arthropods such as ticks and mites as potential vectors (10–12). However, until this is confirmed, the use of the names flea-borne spotted fever (FBSF) or cat-flea typhus are still warranted.

Clinical manifestations of human *R. felis* infection include fever, fatigue, headache, maculopapular rash, and eschar (13, 14). Observation of cases reported in the literature show a variability of presentation of clinical symptoms that can include a combination of some or all of the listed signs and symptoms (14–17). Thus far there have been no reports of flea-borne spotted fever causing either serious complications or death, and it appears to be milder than other rickettsioses (18). Due to shared symptoms with other rickettsial and viral infections, it is thought that many human cases are currently misdiagnosed.

The gold standard of rickettsial diagnosis is currently serology utilising an indirect immunofluorescence assay (19). There is considerable cross-reactivity between SFG and TG antibodies in human sera. In spite of this, serology remains the diagnostic tool of choice due to its quick turnaround time and ease of use. *R. felis* responds serologically as though it were a TG rickettsiae. This probably contributed to the earlier misdiagnoses of *R. felis* infections as *R. typhi*. There is a need to incorporate additional diagnostic assays such as polymerase chain reaction (PCR), to supplement serology for diagnosing *Rickettsia* infection. PCR as a diagnostic tool is not readily available to clinicians, as few diagnostic laboratories have access to a rickettsial PCR assay. Diagnostic protocols for rickettsiosis continue to rely on serological methods such as immunofluorescence assay (IFA) alongside clinical presentation of symptoms and epidemiological knowledge including a travel history (20).

The self-limiting nature of most rickettsioses can be another reason why these infections, in particular FBSF, are under-reported. This is further exacerbated by the overlapping endemic areas of *R. felis* and *R. typhi* along with shared vectors and hosts (21). The recent appearance in the literature and increasing reporting of cases and locations supports the designation of FBSF as an emerging disease (22). Recently, human infection occurred in Victoria, Australia, where a cluster of five patients between the ages of 4 and 63 years were exposed to fleas (*C. felis*) originating from their pet cat (17). All patients sero-converted to TG antigens. The detection of *R. felis* DNA from the cat fleas supported the FBSF diagnosis.

2. Invertebrate hosts

Infection by *R. felis* has been attributed to flea saliva rather than faeces. In this respect it is unlike *R. typhi* which is usually transmitted by inhalation of dried flea faeces (23, 24). FBSF was first described in 1990 and its main vector was identified as *C. felis*. Since its description, more than 12 flea species have been identified as hosts (Table 1). The expansion of *R. felis* hosts and potential vectors to include mites, lice, and ticks (both

Ixodid and *Argasid*) further highlights the infancy of the field. Much work still needs to be done to fully understand the bacterium's ecology. The sharing of arthropod hosts between several pathogens, especially bacteria, of similar and different genera is well documented (Table 1). This diversity of hosts may have contributed to the earlier misdiagnosis of *R. felis* infection.

Maintenance of *R. felis* in *C. felis* is well documented with transstadial and transovarial transmission (6). The maintenance of *R. felis* within infected populations of *C. felis* has been documented for 12 generations with little adverse affect on the vector's fitness (25), unlike *Rickettsia rickettsii* and *Rickettsia prowazekii* that have been observed to adversely affect their vectors (26, 27).

Even though *R. felis* does not appear to diminish the fitness of *C. felis*, its presence leads to reduced microbiota diversity (28). One may assume that colonisation with *R. felis* limits the diversity of microbiota in the flea thus limiting its effectiveness in transmitting other bacterial pathogens; however, dual infections by *R. felis* and other flea-borne organisms has been reported (29).

In temperate climates, *C. felis* and *Ctenocephalides canis* activity on host animals are influenced mainly by temperature with trends showing peak activity during warm months and periods of high rainfall (30, 31). This was observed with several vector types and species.

The reporting of *R. felis* in *Rhipicephalus sanguineus* ticks points to possible horizontal transmission from flea to tick via a vertebrate host, presumably a dog (32). The global distribution of *R. sanguineus* has been attributed to the geographical spread of the dog. Other intracellular bacteria have also been reported from *R. sanguineus* such as *Rickettsia conorii* and *Coxiella burnetii*, the aetiologic agent for Mediterranean spotted fever and Q fever, respectively (33). *R. sanguineus* has never been implicated as a vector of either *R. felis* or *C. burnetii*. However, due to its world-wide distribution overlapping with that of *C. felis*, it may play the role of an amplifier for horizontal transmission to the more competent vector.

Although *C. felis* has been designated as the main vector of *R. felis*, the competency of all 24 species of fleas, ticks, mites, and lice as transmission vectors has yet to be demonstrated.

3. Human migration

Human migration may have led to the geographical spread of *R. felis* hosts, in particular *C. felis*, *C. canis*, *Pulex irritans*, and *Xenopsylla cheopis*. Occurrence of flea vectors in human settlements world-wide and among animals that are generally associated with human activity such as cats, dogs, and rodents support this view. Increased travel may have played a role in spreading these flea-associated pathogens in recent decades as travellers and their accompanying animals moved between countries (34).

Table 1. Invertebrate hosts of *Rickettsia felis*, some of which carry other potential bacterial pathogens

Invertebrate host	Vertebrate host	Location	Other potential pathogens ^a	Disease	Reference
Fleas					
<i>Ctenocephalides felis</i>	Dog, cat, rodents, monkey, opossums	Argentina, Australia, Brazil, Canada, Chile, Cyprus, France, Gabon, Germany, Israel, Mexico, New Zealand, Peru, Spain, Taiwan, Thailand, UK, United States, Uruguay	<i>Rickettsia typhi</i> , <i>Bartonella</i> sp.	Murine typhus, Cat-scratch disease	(47–66)
<i>Ctenocephalides canis</i>	Dog, cat	Algeria, Brazil, France, Spain, Thailand, Uruguay	<i>Bartonella</i> sp.	Cat-scratch disease	(50, 65–69)
<i>Pulex irritans</i>	Human and mammals	DR Congo, United States	<i>Rickettsia typhi</i> , <i>Yersinia pestis</i>	Murine typhus, Plague	(24, 29)
<i>Xenopsylla cheopis</i>	Rodents, shrew	Indonesia, United States	<i>Rickettsia typhi</i> , <i>Yersinia pestis</i>	Murine typhus, Plague	(21, 70)
<i>Anomiopsyllus nudata</i>	Rodents	United States	–	–	(71)
<i>Archaeopsylla erinacei</i>	Hedgehog, dog, cat	Algeria, France, Germany	–	–	(50, 56, 68)
<i>Echidnophaga gallinacean</i>	Poultry, dog, cat	Australia, DR Congo	<i>Rickettsia</i> sp.	Spotted fever	(29, 49)
<i>Spilopsyllus cuniculi</i>	Cat, rabbit	Australia	–	–	(49)
<i>Ctenophthalmus</i> sp.	Rodent	Portugal	<i>Rickettsia typhi</i> , <i>Bartonella</i> sp.	Murine typhus, Cat-scratch disease	(72)
<i>Xenopsylla brasiliensis</i>	Rodent	Brazil	<i>Yersinia pestis</i>	Plague	(29)
<i>Tunga penetrans</i>	Human, dog, cat, pig	Brazil	–	–	(29)
<i>Polygenis atopus</i>	Dog, cat, opossum	Brazil	–	–	(73)
Ticks					
<i>Haemaphysalis flava</i>	Cat	Japan	<i>Rickettsia japonica</i>	Japanese spotted fever	(11)
<i>Haemaphysalis kitaokai</i>	Cattle, deer	Japan	–	–	(11)
<i>Rhipicephalus sanguineus</i>	Dog, horse	Brazil	<i>Rickettsia</i> sp., <i>Anaplasma</i> sp.	Spotted fever, Anaplasmosis	(32)
<i>Amblyomma cajennense</i>	Dog, horse	Japan	<i>Rickettsia</i> sp.	Spotted fever	(11)
<i>Ixodes granulatus</i>	Shrew	Taiwan	<i>Rickettsia</i> sp., <i>Ehrlichia</i> sp.	Spotted fever, Ehrlichiosis	(74)
<i>Ixodes ovatus</i>	Cat	Japan	<i>Rickettsia</i> sp.	Spotted fever	(11)
<i>Carios capensis</i>	Seabird	United States	<i>Coxiella</i> sp., <i>Rickettsia</i> sp.	Unknown, Spotted fever	(75)
<i>Haemaphysalis sulcata</i>	Sheep, goat	Croatia	–	–	(76)
Mites					
<i>Trombiculid</i>	Wild rodents	South Korea	<i>Orientia tsutsugamushi</i>	Scrub typhus	(10)
<i>Leptotrombidium deliense</i>	Rat	Taiwan	<i>Orientia tsutsugamushi</i>	Scrub typhus	(74)
<i>Mesostigmata</i>	Rat	Taiwan	–	–	(74)
Lice					
<i>Liposcelis bostrychophila</i>	–	Canada	–	–	(77)

^aMultiple bacterial pathogens present in the same host are simplified with genus only. Fields with no bacterial pathogens listed denotes no record in the literature.

During the twentieth-century and the start of the twenty-first century, mass migrations in the form of refugees escaping conflict and persecution were common. A new form of transient migration has arisen with the advent of tourism with fast, low-cost travel. It is not uncommon to see reports of rickettsial infections in travellers returning to their home country (35, 36). Returning infected travellers increase the risk of horizontal transmission of rickettsiae to other endemic arthropods. The rate and efficiency of horizontal transmission of rickettsial organisms, in particular *R. felis*, has yet to be fully understood (22).

4. Climate change

The distribution of vectors and associated pathogen transmission rates can be affected by changes in the ambient temperature and climate. Such changes, whether caused by human activities or not, will cause (a) local vector populations to migrate to more favourable climates alongside vertebrate hosts and (b) alter the life cycle duration of vectors. Evidence has shown an average global temperature increase of 0.3–0.6°C in the last 100 years and that this has affected the hydrological cycle and humidity (37, 38). Arthropod vectors feeding activity, reproduction, and mortality rates are highly sensitive to slight temperature changes. An increase in temperature of 3°C (25 to 28°C) reduced the time needed for hatching, pupation, and development of two *Xenopsylla* flea species (39). The significant time reduction in major stages of the flea life cycle would probably result in an increased population density. As these flea species are potential reservoirs of *R. felis* the risk of human infection is likely to increase.

Fleas harbouring *R. felis* are dependent on hosts directly linked to human habitation (Table 1). Ticks, however, are more widely distributed and most of their vertebrate hosts involve native fauna. Increases in temperature due to climate change would probably see the range of many tick species widening and encroaching further into areas of human activity. Of the several tick species found to potentially transmit *R. felis*, *R. sanguineus* stands out as the most likely to mediate change due to its world-wide distribution and its tendency to harbour other rickettsial organisms (40). *R. sanguineus* prefers a warmer climate in general, thus increased humidity may also enhance the establishment of populations in new areas (41). *R. sanguineus* has been shown to be widely established in the Mediterranean and other similar regions due to adequate humidity and warm temperatures (42). However, populations of *R. sanguineus* have been rarely seen in northern and central Europe. With the projected increase in summer temperatures over the next few decades, there may be a spread of this tick into temperate Europe and the establishment of permanent populations. A recent report reinforces this hypothesis,

where an increase in the affinity of *R. sanguineus* for humans during the warmer months in Europe was noted (43).

5. Conclusion

Long-term surveillance of vector densities and the emergence of diseases associated with those vectors should be established. With evidence of *R. felis* in every human settlement located within temperate zones worldwide, the need to make spotted fever and typhus group rickettsiosis part of diagnostic considerations is crucial for a prompt and proper medical response. As with all zoonotic diseases, overlapping activities between reservoir, vector, and humans would have a significant influence on transmission rates. The *R. felis* vector and reservoir animals have always overlapped with human habitation. Any increase in effective transmission is likely to result in a rise in human cases of FBSF.

There is a need to be vigilant in identifying both current and emerging vector-borne diseases in the environment. A good example to illustrate this is Lyme disease in North America, which was first reported in the literature 27 years ago. Since then it has become the most prevalent vector-borne disease on that continent. However, molecular analysis of specimens that predate the recognition of this major pathogen showed similar prevalences, indicating misdiagnosis and confusion with other illnesses with similar clinical symptoms (44, 45). This observation can be applied to other tick-borne diseases including *R. felis*. Only recently has *R. felis* been considered to be part of an infectious disease differential diagnosis. With the awareness of its human pathogenicity increasing, one would expect to see the number of FBSF cases rise.

With the long list of vector species potentially harbouring and transmitting *R. felis*, the situation is different to other vector-borne pathogens where the vector hosts and reservoir are limited to specific species. The implications of this are that unchecked expansion of vectors would potentially adversely affect human health. It is also of concern that these shared vectors contain other bacterial pathogens such as *Yersinia pestis*, *Ehrlichia* sp., *Bartonella* sp. and *Rickettsia* sp. (Table 1). The competency of implicated invertebrate hosts of *R. felis* listed in Table 1 need proper consideration and investigation. Most, if not all, of the invertebrate hosts are found around and within human populations. Thus, *R. felis* infections are inevitable. The transmission efficiency of this organism by its vectors needs to be investigated further.

Influence of climate change on temperature levels may be far-reaching. Not only could it affect arthropod life cycles but also human activities as well. Use of the land in affected areas will be influenced and long-term activities such as farming and tourism will indirectly affect transmission of arthropod-borne diseases (46).

FBSF poses one of the many challenges to human and veterinary medicine in the twenty-first century. In spite of it being a self-limiting disease with only modest severity, the likelihood of geographical range expansion is a cause for concern. Better understanding of this endemic disease will equip local doctors, veterinarians, and public health officials with the information needed to prevent outbreaks and provide proper treatment.

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