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Rickettsia felis: from a rare disease in the USA to a common cause of fever in sub-Saharan Africa

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Abstract

Rickettsia felis is a spotted fever group rickettsia that has been definitely described in 2002. Within the last 20 years, there have been a growing number of reports implicating *R. felis* as a human pathogen, parallel to the fast-growing reports of the worldwide detection of *R. felis* in arthropod hosts, mainly the cat flea *Ctenocephalides felis felis*. *R. felis* is now known as the agent of the so-called flea-borne spotted fever, with more than 70 cases documented in the literature. Recently, two studies respectively conducted in Senegal and Kenya, have challenged the importance of *R. felis* infection in patients with unexplained fever in sub-Saharan Africa. We focus here on the epidemiological and clinical aspects of *R. felis* infection. More studies are needed, including the study of other arthropod vectors, but it can be speculated that *R. felis* infection might be an important neglected agent of fever in sub-Saharan Africa.

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Rickettsia felis is an obligate intracellular Gram-negative bacterium belonging to the spotted fever group (SFG) of *Rickettsia* [1,2]. It was probably first detected in European cat fleas (*Ctenocephalides felis felis*) in 1918 and tentatively named '*Rickettsia ctenocephali*' [3]. This work was, however, overlooked until 1990, when a *Rickettsia*-like organism (the 'ELB agent', for the Elward Laboratory, Soquel, CA, USA) was found in *C. felis* fleas by electron microscopy [4]. The species *R. felis* was formally validated by molecular criteria in 2001, and the reference strain was isolated and definitely characterized in 2002 [5]. Particularly, it was shown that that this rickettsia can be cultivated at low temperature only. Recent outcomes include the study of the genome of *R. felis* [6]. The presence of up to two plasmid forms has been shown, as well as strain variation of plasmid content [7,8].

A Worldwide-distributed Rickettsia

Since its definitive description, the interest in *R. felis* and its association with fleas has increased [1,9]. The use of molecular assays, including regular and quantitative real-time polymerase chain reaction (qPCR) has provided rapid and reproducible tools to detect *R. felis* in arthropods. *R. felis* has now been described in infected arthropods from more than 20 countries on five continents (Fig. 1). In America, after the USA, Brazil and Mexico, it has been found in fleas from Peru, Uruguay, Chile, Argentina [1,9] and recently Hawaii [10], Canada [11], Panama [12], and the Caribbean Island St Kitts [13]. In Europe, *R. felis* has been detected in fleas from Spain, France, the UK, Portugal, Cyprus [1,9] and recently Germany

FIG. 1. Distribution by 2011 of clinical findings of *Rickettsia felis* infections (yellow stars) and of arthropods infected with *R. felis* (red circles). The numbers in the stars indicate the number of clinical cases. In these countries (but not yet Tunisia, Senegal and Kenya) *R. felis* has also been detected in arthropods. The red circles indicate locations where *R. felis* has been detected in arthropods (mainly fleas) only. Updated from [29].

[14] and Italy [15]. In Asia, it has been detected in Japan, Indonesia, Thailand, Afghanistan, Israel [1,9] and recently Laos [16], Taiwan [17] and Lebanon [18]. It has also been detected in Australia, New Zealand [1,9] and New Caledonia [19]. Finally, in Africa, *R. felis* has been detected in fleas from Algeria, Ethiopia, Gabon [1,9], and recently the Ivory Coast [20] and Morocco (Parola P, unpublished data).

Beside *C. felis*, new arthropods have been found to be infected with *R. felis*, including: other flea species (*C. canis*, *C. orientis*, *Anomiopsyllus nudata*, *Archaeopsylla erinacei*, *Ctenophthalmus* sp., *Xenopsylla cheopis X. brasilliensis, Tunga penetrans, Ceratophyllus gallinae, Spilospsyllus cuniculi* and *Echidnophaga gallinacean*); ticks (*Haemaphysalis flava*, *Rhipicephalus sanguineus*, *Ixodes ovatus,* and *Carios capensis*); and chigger (South Korea) and mesostigmata mites (Taiwan) [1,9,20]. The reported hosts for these vectors were mainly cats, dogs and rodents, and more rarely opossums, hedgehogs, horses, sheep, goats, gerbils and monkeys [1,9].

However, most of the reports state that the cat flea *C. felis* is the most recurrent arthropod in which *R. felis* has been detected. Furthermore, *C. felis* is currently the only known biological vector of *R. felis* [9]. Within the flea, *R. felis* infection is disseminated, having been identified in the midgut, ovaries and salivary glands [21]. Studies examining the transmission of *R. felis* using colonized cat fleas have shown stable vertical transmission (transovarial and trans-stadial) [9,22]. Vertical transmission of *R. felis* persists in *C. felis* for at least 12 generations without the aid of an *R. felis*-infected bloodmeal; however, over successive generations prevalence wanes to low levels (10%) [22]. It has also been recently shown that cat fleas are able to acquire *R. felis* infection from an infectious blood meal [23]. These data further support the wide distribution of *R. felis* in relation to the worldwide distribution of *C. felis*. The cat flea is extremely common on cats and dogs in many temperate and tropical regions, but it also infests opossums, raccoons and rats [24]. It represents the great majority of fleas in human homes. If associated with an infectious agent, the worldwide distribution of *C. felis* represents therefore a threat to the human population because of lack of host specificity of the cat flea, and its ability to bite people.

The Emerging Flea-borne Spotted Fever

In 1994, 'ELB agent' DNA fragments were detected in blood samples obtained from a patient from Texas in 1991 [25]. This became the first evidence of *R. felis'* potential as a human pathogen. More arguments for the pathogenicity of *R. felis* for humans were provided in 2000 in Mexico, when three patients with fever, exanthem, headache and central-nervous system involvement were diagnosed with *R. felis* infection by specific PCR of blood or skin and seroconversion to rickettsial antigens [26]. All the patients had had contact with fleas or animals known to carry fleas. In 2001, high antibody titres to *R. felis* were found in two French patients with clinical signs of rickettsioses and two of 16 Brazilian patients with febrile rash. Moreover, specific sequences of *R. felis* were identified in the serum of one Brazilian patient [27]. In 2002, two cases of typical spotted fever were reported in an adult couple in Germany. Clinical features included fever, marked fatigue, headache, generalized maculopapular rash and a single black, crusted, cutaneous lesion surrounded by a halo, and enlarged, painful lymph nodes in the inguinal region for the man. Serological techniques discriminated *R. felis* infection among several rickettsiae for the woman and this was confirmed by detection of *R. felis* DNA in the woman's sera [28]. Thereafter, within the last 20 years, there have been a growing number of reports implicating *R. felis* as a human pathogen, parallel to the