Fleas and flea-borne diseases of North Africa.

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Abstract

North Africa has an interesting and rich wildlife including hematophagous arthropods, and specifically fleas, which constitute a large part of the North African fauna, and are recognised vectors of several zoonotic bacteria. Flea-borne organisms are widely distributed throughout the world in endemic disease foci, where components of the enzootic cycle are present. Furthermore, flea-borne diseases could re-emerge in epidemic form because of changes in the vector–host ecology due to environmental and human behaviour modifications. We need to know the real incidences of flea-borne diseases in the world due to this incidence could be much greater than are generally recognized by physicians and health authorities. As a result, diagnosis and treatment are often delayed by health care professionals who are unaware of the presence of these infections and thus do not take them into consideration when attempting to determine the cause of a patient's illness. In this context, this bibliographic review aims to summarise the main species of fleas present in North Africa, their geographical distribution, flea-borne diseases, and their possible re-emergence.

Keywords: Fleas, North Africa, flea-borne diseases, vectors

List of abbreviations:

MALDI–TOF MS: Matrix Assisted Laser Desorption Ionisation – Time Of Flight Mass Spectrometry

Introduction

Fleas (Insecta, Siphonaptera) are obligate hematophagous ectoparasites. They are wingless insects which are small (2-10 mm) and generally present a laterally flattened body. Fleas have three thoracic segments, each with a pair of well-developed legs (Beaucournu and Launay, 1990; Bitam et al., 2010) enabling adults to jump long distances (Bitam et al., 2010). They are ectoparasites that usually infest mammals and rodents but rarely birds. Flea species distribution extends to the seven continents, including Antarctica (Whiting et al., 2008). Furthermore, fleas are able to inhabit a very wide range of habitats and hosts (Whiting, 2002). The greatest diversity of species can be observed in the temperate regions of the globe (Lewis, 1993).

Fleas are holometabolous insects that complete their cycle from egg to adult via three larval stages and a pupal stage (Zakson-Aiken et al., 1996). The completion of the entire life cycle varies among species but takes on average three to five weeks depending on the temperature and humidity conditions. Flea larvae are vermiform and legless, with chewing mouthparts (Dryden and Rust, 1994).

Flea species adapt to their hosts but do not do so exclusively. This fact could explain the role of the so-called rat flea *Xenopsylla cheopis* (Rothschild, 1903) in the epidemiology of human plague, or the existence of highly promiscuous fleas species, such as the so-called human flea, *Pulex irritans* (Linnaeus, 1758) or the cat flea *Ctenocephalides felis* (Bouché, 1835) which occur on a wide variety of carnivorous animal species (Gratz, 1999).

Fleas' behaviour towards their hosts makes it possible to classify them in three categories, including i) fleas that live permanently on their host, such as *X. cheopis*, *P. irritans*, *Ctenocephalides canis* and *C. felis,* ii) fleas that permanently live in their hosts' nest or burrows, parasitizing them only during blood meals, such as *Ceratophyllus gallinae*; iii) and the so-called penetrating fleas, such as females of the genera *Tunga* and *Neotunga*, which are able to burrow into their hosts' dermal tissue, where they increase dramatically in size (up to l000-fold) accompanied by an extensive morphological degeneration (Durden and Traub, 2002). Females of *Echidnophaga gallinacea* can also fix themselves around the eyes of poultry after fertilization (Franc, 1994a).

Within Siphonaptera, the Pulicidae family exhibits an interesting diversity of host specificity patterns and ecological habits (Beutel et al., 2008). Within this family, *P. irritans*, *C. felis* and even *X. cheopis* have been the most studied species due to their cosmopolitan distribution together with the fact that these species are closely related to humans (Durden and Traub, 2002).

The importance of fleas in human public health is mostly related to their ability to transmit infectious disease agents during the blood meal. Some fleas are indeed vectors of human infectious diseases, such as bubonic plague, caused by *Yersinia pestis* (Zeppelini et al., 2016), murine typhus, caused by *Rickettsia typhi* (Peniche Lara et al., 2012) and flea-borne spotted fever caused by *Rickettsia felis* (Angelakis et al., 2016) . They are also probably involved in the transmission of *Bartonella henselae* the agent of cat-scratch disease (Bitam et al., 2010; Chomel and Kasten, 2010).

"North Africa" is a collective term including Mediterranean countries and territories situated in the northern-most region of the African continent, including Morocco, Algeria, Tunisia, Libya and Egypt. It is a total area of around five million kilometres, more than 90% of which is desert (Peel et al., 2007). North Africa is vulnerable to various climates, with the coast being characterised by a Mediterranean climate of wet winters and dry summers, while non-coastal areas are characterised by an arid desert climate with generally hot summers, cold winters and little rainfall (Radhouane, 2013). This climatic diversification contributes to the richness of the North African fauna, including fleas.

In this review, we focus on fleas of veterinary and clinical importance from North Africa, particularly those species belonging to the Pulicidae family. We also discuss innovative methods for the identification of fleas and their associated pathogens.

Fleas of medical-veterinary importance in North Africa

The Pulicidae family consists of four tribes, 21 genera and 167 species (Beutel et al., 2008). Some authors (Lewis, 1998) considered Pulicidae as including Tungidae. However, Whiting *et al.* (2008) placed this family as a monophyletic and phylogenetically distant group from Tungidae (Beutel et al., 2008). Most fleas of veterinary importance are grouped in this family since they may act as vectors of some infectious diseases, may play a role as intermediate hosts for several parasites, and many cause allergic reactions in animals and humans, associated with their bloodsucking habits (Dobler and Pfeffer, 2011).

- ***Pulex irritans* (Figure 1.1)**:

This flea has a cosmopolitan distribution and is often referred as the "human flea". However, this species often parasitizes a wide variety of hosts, including large wild mammals and rodents, although rarely found on rats (Gratz, 1999). Under natural conditions, this flea is active throughout the year, with a peak in summer (Beaucournu and Launay, 1990). Its legs are sufficiently developed to jump up to 50 cm and it has the particularity of being able to survive for a year without feeding, since this flea is capable of absorbing quantities of blood equivalent to 20 times its weight (Belthoff et al., 2015).

The presence of this flea in North Africa has been reported several times. *P. irritans* was collected on dogs from Tunisia (Tunis, Maktar, Siliana). *P.irritans* was also found in north-western Libya (Tripoli) on eight farm dogs (Kaal et al., 2006), and in Morocco (Agadir, Casablanca,Tiznit) (Boudebouch et al., 2011). G. Blanc and M. Baltazard (1945) long suspected the role of *P. irritans* in the transmission of the plague in Morocco (Audouin-Rouzeau, 2003).

They conducted nine experiments with naturally infected *P. irritans* on plague victims. In the first eight experiments, all guinea pigs were not infected, even when 240 fleas were used. For their ninth experiment, G. Blanc and M. Baltazard (1945) collected 720 fleas from six plague victims, and one guinea pig bitten by a flea was infected. This experiment enabled the authors to state that infected human fleas could transmit diseases (Audouin-Rouzeau, 2003).

- ***Echidnophaga gallinacea* (Figure 1.2):**

This species is commonly known as the "Stick tight flea" and is about 2 mm long. Females of this species are able to remain attached for up to six weeks to a single host site, causing ulceration at the attachment site. The eggs are then deposited in the ulcers that are formed on the skin of the host. Later, the larvae fall to the ground and feed on any organic debris found (Boughton et al., 2006). In many cases, a large number of fleas can congregate around the eyes and on the bare skin of poultry, which makes it difficult to remove them (Elston, 2001).

E. gallinacea is more active in summer, causing serious trouble with livestock, especially in rural areas. In North Africa, *E. gallinacea* has been reported in Morocco (Rabat, Agadir, Salé, Safi, Essaouira, Casablanca), Algeria (Saïda), in Tunisian islands (Djerba and Zembra) (Beaucournu and Launay, 1990) and has also been isolated from dogs in Libya (Kaal et al., 2006).

Loftis *et al.* (2006) conducted a surveillance study of fleas on mammals and associated pathogens in Egypt, with *E. gallinacea* being the main species collected. In addition, these authors were able to detect spotted fever by *Rickettsia* sp, similar to RF2125, in all collected specimens (Loftis et al., 2006).

- ***Ctenocephalides felis* (Figure 1.3):**

C. felis is commonly known as the "cat flea". *C. felis* originates from Africa and now parasites pets and livestock very easily and regularly in warm and hot climates (Beaucournu and Ménier, 1998). It is considered to be the main flea species infecting domestic carnivores in many countries around the world (Rust, 2016).

This species is cosmopolitan and sedentary on its host and is mainly active in summer. All mammals living in the same biotope are susceptible to be infested by *C. felis* (Beaucournu and Launay, 1990). Its host specificity is low, thus, it can be found on other animals, including small ruminants, cattle, primates, rodents, poultry and even opossums. The direct transmission between individuals is frequent, although it appears to be rarer in dogs than in cats (Dobler and Pfeffer, 2011).

C. felis has been found in Tunisia, and has been collected from cats, dogs, sheep and goats. Several microorganisms have been detected in *C. felis* in Tunisia, including *Bartonella* spp., *R. felis* (Zouari et al., 2017). It has also been collected from hedgehogs in Algeria. These authors reported the presence of *R. felis* DNA in all *C. felis* collected. The results of this study can therefore help human and veterinary clinicians to focus on a broader spectrum of pathogens and take them into consideration during diagnosis (Leulmi et al., 2016).

The presence of this flea has also been reported in Morocco (Casablanca, Tiznit) on domestic animals, and molecular biology demonstrated the presence of *Bartonella clarridgeiae, B. henselae* and *R. felis* in these fleas (Boudebouch et al., 2011). It has also been collected from cats and dogs from a farm in Libya (Kaal et al., 2006). At this point, it should be highlighted the ausence of *Rickettsia asembonensis* in *C. felis* collected from North Africa. This pathogen has been widely detected in *C. felis* and *C. canis* collected from several regions of sub-Saharan Africa such as Rwanda, Zambia or Kenya (Nziza et al., 2018; Moonga et al., 2019), however ; currently, there is no studies which confirm the presence of this bacteriim in the cat flea from North Africa.

This flea can quickly change hosts, which can play a role in the transmission of pathogens. The saliva of *C. felis* has irritating properties, which generally leads to dermatosis due to the bites. It can also cause anemia during a massive infestation (Gaguere and Prelaud, 2006).

- ***Ctenocephalides canis* (Figure 1.4):**

C. canis is also known as the "dog flea". Despite its name, it has been demonstrated that the prevalence of *C. felis* in dogs is higher than that of *C. canis* (Linardi and Santos, 2012). *C. canis* has a very similar morphology to *C. felis* subspecies. Thus, we can easily discriminate between *C. canis* and *C. felis felis* but it used to be difficult to differentiate between *C. canis* and *C. felis strongylus* or *C. felis orientis*. These differences are mainly based on the shape of the frons of the cephalic capsule, the presence and shape of the dorsal incrassation and the number of setae on the occiput (Linardi and Santos, 2012). They also differentiate in the average jump height, which is 15.5 cm in *C. canis* and 13.2 cm in *C. felis* (Beaucournu and Launay, 1990). Although both species are recognised vectors of *R. felis* and several *Bartonella* spp. pathogens, it is important to discriminate between *C. felis* and *C. canis*, since many authors have reported a much lower prevalence of these bacteria in *C. canis* than in *C. felis* (Kumsa et al., 2014; Lawrence et al., 2015).

This is a species that is sedentary on its host and infests mainly domestic and wild canids. The red fox is its primary host, but epidemiological studies have shown that *C. canis* can also be found on cats, albeit with a lower prevalence than *C. felis* (Beaucournu and Ménier, 1998; Linardi and Santos, 2012; Marrugal et al., 2013).

This species of flea is frequent in North Africa, and has been collected from dogs from Tunisia, where molecular analysis showed the presence of *Bartonella* spp. in 23.5% of collected *C. canis* (Zouari et al., 2017). A preliminary study conducted in Egypt on domestic rodents revealed the presence of *C. canis* in the Dakahlia governorate (Soliman and Mikhail, 2011). In northern

Libya, a clinical investigation revealed the presence of *C. canis* on dog farm (Kaal et al., 2006). *C. canis* is also present in Algeria and Morocco, it has been collected from rodents in Oran. The authors also confirmed the presence of *R. felis* for the first time in this species of flea (Bitam et al., 2006b), and in stray dogs in Rabat (Pandey et al., 1987).

- ***Spilopsyllus cuniculi***

This is a specific parasite of wild rabbits, however it can be also found in cats (Pinter, 1999; Visser et al., 2001). The life cycle of the *S. cuniculi* flea is synchronised with that of the wild rabbit, so that eggs are laid after the birth of new-born rabbits (Antonelli and Seymour, 1988).

It is a European flea, but it has already been described in several Moroccan cities (Rabat, Seta, Tangier, Chaouen; Kenitra, Mohammedia and Essaouira) (Beaucournu and Launay, 1990).

It is the vector of the myxomatosis, a viral disease of the rabbit (Shepherd and Edmonds, 1980) and also the vector of *Trypanosoma nabias* (Mead-Briggs and Vaughan, 1975). Some authors have confirmed the involvement of two species of fleas, *S. cuniculi* and *Xenopsylla cunicularis*, in maintaining the *Bartonella alsatica* infection in wild rabbits throughout the year (Márquez, 2015). This flea is also associated with dermatitis in cats, feline and canine leishmaniosis (Harvey, 1990; Otranto et al., 2017).

- ***Xenopsylla cheopis* (Figure 1.5):**

X. cheopis, also known as the "oriental rat flea", is considered to be the main vector in the transmission of *Y. pestis* and *R. typhi* (Peniche Lara et al., 2012; Zeppelini et al., 2016), the agents of plague and murine typhus, respectively.

Its indiscriminant host specificity makes it very dangerous in cases of epidemics. It inhabits all warm and temperate regions of the globe and its synanthropic distribution is often correlated with that of rats (Beaucournu and Launay, 1990). When the temperature is low and when there are few individuals on rats' bodies, they are located at the neck. In dogs and cats, these fleas are most often found in the dorsal-lumbar region (Franc, 1994a).

It is the most common species that infests rodents in Egypt (Loftis et al., 2006) and has been described in many parts of the country, including the governorates of Ismailia (Bahgat, 2013), Dakahlia (Soliman and Mikhail, 2011) and Menoufia (Soliman et al., 2010). In Giza, a study assessing trypanosomiasis in rodents, *X. cheopis* was present in 57.5% of the collected *Rattus norvergicus* (Dahesh and Mikhail, 2016).

The presence of this flea has also been reported in Algeria (Bitam et al., 2006a). Furthermore, in this country, the presence of *B. henselae, B. clarridgeiae* and *Bartonella vinsonii subsp. berkhoffii* was cited in *X. cheopis* collected from dogs using molecular methods. (Bessas et al., 2016).

- ***Archaeopsylla erinacei* (Figure 1.6):**

This flea is known as the "hedgehog flea", but it can also infest dogs (Rehbein et al., 2016). This species has already been described in Morocco and Tunisia (Beaucournu and Launay, 1990). A recent epidemiological study conducted in Algeria reported a prevalence of 72% of *R. felis* in *A. erinacei* collected from hedgehogs (Leulmi et al., 2016).

This flea is the agent of pulicosis, although some authors have already detected other pathogens in this species, such as *Rickettsia helvetica*, a novel rickettsia genotype and *B. henselae* (Hornok et al., 2014).

Flea-borne diseases of North Africa

Current known records are summarized in Table 1, and pathogens are introduced in the following text.

Plague:

Plague is a rodent disease transmitted by fleas to humans and caused by a Gram-negative bacterium, *Y. pestis* (Parkhill et al., 2001; Malek et al., 2017). Plague is the main known disease transmitted by fleas, although lice may have played an important role in historical outbreaks (Drancourt and Raoult, 2016). Three major pandemics have marked human history (Munyenyiwa et al., 2019). The Justinian Plague of 541 began in central Africa and extended to Egypt and the Mediterranean. The Black Death of 1347 originated in Asia and extended to the Crimea then to Europe and Russia. The third pandemic in 1894, began in Yunnan, China, and extended to Hong Kong and India, then to the rest of the world (Butler, 2014; Drancourt and Raoult, 2018). It has long been considered that each of the three pandemics was due to a different biotype of *Y. pestis*. However, Drancourt and Raoult (2018) have recently shown, using a genotyping method based on the sequencing of several intergenic “spacers”, that only one biotype, Orientalis-like *Yersinia pestis*, could have caused the three pandemics (Drancourt and Raoult, 2018).

The vector role of the fleas in plague was first described by Paul-Louis Simond in 1898 (Brossollet, 1990). A key step in the transmission of *Y. pestis* is pro-ventricular blocking. The bacilli ingested by the flea during blood circulation move towards the anterior part of the stomach and the pro-ventricle and thus form a more or less complete wall that blocks the passage of the blood meal. The phenomenon of regurgitation and the hungry flea’s repeated attempts to suck the blood allow the passage of bacteria to the host mammal at the site of bite (Hinnebusch et al., 2017).

Although *X. cheopis* is considered the main vector of plague, approximately 30 flea species are proven vectors of plague (Bitam et al., 2010). For example, *P. irritans* is significantly involved in the transmission of plague, the main reservoir of which is the black rat, *Rattus rattus* (Karimi and Farhang-Azad, 1974; Vadyvaloo et al., 2007; Neerinckx et al, 2008). Furthermore, some authors have highlighted that any flea species might be biologically capable of transmit *Y. pestis* under the appropriate conditions species remarking that this bacteria has been detected in at least 125 species of fleas (Beutel et al., 2008; Bitam et al., 2010).

The remaining natural foci in the world are currently in Africa, Asia and America. The plague is considered to be a re-emerging disease in the world (Guinet and Carniel, 2008; Grácio and Grácio, 2017; D'Ortenzio et al., 2018). This was the case in Oran, Algeria, when, after 60 years of silence, 18 human cases of plague were diagnosed in the south of Oran in 2003 (Bertherat et al., 2007). A year later, rodents were caught in the same areas and *X. cheopis* collected from these rodents were found to carry *Y. pestis* DNA. In 2008, a plague outbreak was detected in Libya which led the authors to believe that it was a reactivation of the organism from neighbouring outbreaks (Cabanel et al., 2013).

In Morocco, an epidemic outbreak took place in Casablanca, Marrakech and Agadir between 1940 and 1945. No further cases were subsequently reported. *P. irritans* and *Pediculus humanus corporis* played an important role in the human-to-human transmission of plague in Morocco (Davis, 1953).

The fact that the plague has reappeared in the same place after decades of absence illustrates the presence of outbreaks of plague in Northern Africa. This presupposes that *Y. pestis* persists in soil under natural and experimental conditions and suggests that plague outbreaks are telluric, where burrowing mammals could be infected by contact with infected soil (Malek et al., 2016).

Flea-borne rickettsial diseases

- Murine typhus:

Murine typhus is a zoonosis with a global distribution. It was clinically described and distinguished from louse-borne typhus epidemic in the 1920s (Houhamdi et al., 2005). Its agent was named *Rickettsia mooseri*, then *R. typhi*, an obligate intracellular bacterium of the typhus group in the genus *Rickettsia* (Raoult and Roux, 1997). It is transmitted from rodents to humans by fleas (via infected flea faeces). Fleas belonging to the *Xenopsylla* genus are considered to be the main vector (*X. astia*, *X. bantorum, X. brasiliensis*). However, other flea species such as *C. felis, P. irritans, Leptopsylla segnis* and *Nosopsyllus fasciatus* may also act as vectors of this disease (Durden and Traub, 2002).

R. typhi infects the endothelial cells of mammalian hosts and the epithelial cells of the midgut of the flea. The bacteria contaminate flea faeces and transmission takes place through contamination in the bite area (Peniche Lara et al., 2012).

The diagnosis of murine typhus is rarely confirmed by lack of laboratory facilities but also by the fact that doctors do not immediately consider murine typhus due to the non-specific signs and lack of diagnostic resources (Houhamdi et al., 2005) .

The disease seems a frequent zoonosis in Tunisia although most of the published cases have been reported in returned travellers (Angelakis et al., 2010; Gastellier et al., 2015). Due to the non-specific nature of the clinical signs, murine typhus should be systematically tested for patients presenting with unexplained fever (Znazen et al., 2013).

Two cases of confirmed *R. typhi* infection have also been reported in Algerian patients, testifying to the presence of this zoonosis in this country (Mouffok et al., 2008).

- *Rickettsia felis* infection and flea-borne spotted fever:

R. felis is an obligate intracellular bacterium, and is a causative agent of a rickettsia disease initially called flea-borne spotted fever (Angelakis et al., 2016; Brown and Macaluso, 2016).

C. felis fleas have been described as the main vector of *R. felis*. The DNA of this bacterium has also been found in many other flea species, such as *P.irritans* (Rolain et al., 2005), *C. canis*, *C. orientis*, *Anomiopsyllus nudata*, *A. erinacei*, *Ctenophthalmus* sp., *X. cheopis X. brasilliensis*, *Tunga penetrans*, *Ceratophyllus gallinae*, *S.cuniculi* and *E. gallinacea* (Parola, 2011). Their role as efficient vectors has not been demonstrated. Flea contamination occurs during a blood meal, once the bacterium have moved to the proventriculus and multiplied in the midgut, then from the intestine to the haemocoel and other tissues to reach the salivary glands (Thepparit et al., 2013). Bacteria remain alive in flea faeces for up to 28 days after the contaminated meal (Reif et al., 2011). The detection of *R. felis* in the salivary glands of *C. felis* suggests a possible transmission during the bite (Macaluso et al., 2008).

Interestingly, *R. felis* has been shown to be transmitted by *Anopheles gambiae* mosquitoes, under laboratory conditions. This might explain why *R. felis* infection is a common cause of fever in sub-Saharan Africa (Dieme et al., 2015).

In Morocco, *R. felis* has been detected with a prevalence of 97.14% in *C. felis* collected from cats in Casablanca (Boudebouch et al., 2011). In Tunisia, *R. felis* was detected in *C. felis* collected from domestic animals (Khrouf et al., 2014).

In Oran, cases of Mediterranean spotted fever were diagnosed clinically. In Marseille, 2 patients initially suspected to suffer tick-borne Mediterranean spotted fever were shown to have murine typhus. (Mouffok et al., 2006).

In Algeria, *R. felis* was detected in 2/87 *C. felis* collected from cats (Leulmi et al., 2016) and in 316 samples out of 316 of *A. erinacei* collected from mountain hedgehogs in northern Algeria (Khaldi et al., 2012). It was also detected in *C. felis* collected from cat in Algiers (Bessas et al., 2016).

R. asembonensis has a remarkable role in this section. This bacterium is considered the most well-characterized rickettsia of the *R. felis*-like organisms (RFLO), however, it is relatively unknown within the vector-borne diseases research community (Maina et al., 2019). *R. asembonensis* is a Gram negative, obligate intracellular bacteria of the order Rickettsiales and family Rickettsiaceae (Maina et al., 2016). *R. felis*, *R. asembonensis*, and "*Candidatus Rickettsia senegalensis*" belong to the spotted fever group rickettsiae (SFGR) that genetically

clusters within the transitional group of rickettsiae (Gillespie et al., 2007). We have just mentioned that *R. felis* is associated with flea-borne spotted fever, however, the pathogenicity of *R. asembonensis* and "*Ca. R. senegalensis*" is currently unknown. These three agents have a worldwide distribution and they have been detected in humans and non-human primates (Tay et al., 2015; Kho et al., 2016). *R. asembonensis* DNA has been detected in fleas from three families of fleas (Pulicidae, Ceratophyllidae and Coptopsyllidae) with highest prevalence rates reported in *C. felis* and *C.canis* (Roucher et al., 2012; Jiang et al., 2013). In spite of that, in North Africa this bacterium only has been detected in *E. gallinacea* collected from Egypt (Loftis et al., 2006).

Bartonelloses

Bartonelloses are zoonosis caused by Gram-negative aerobic bacteria of the genus *Bartonella* (Iannino et al., 2018). Many species have been described. They include recognized pathogens as well as bacteria of unknown pathogenicity. (Stuckey et al., 2017).

- Cat-scratch disease

This disease was first described in 1889 and it is caused by *B. henselae* (Wong et al., 1995). The domestic cat is the main reservoir of this bacterium (Chomel, 1996).

Transmission to humans takes place through a cat scratch or bite, but contamination by *C. felis* flea faeces and transmission by regurgitation have also been demonstrated (Bouhsira et al., 2013b). Infection with *B. henselae* can cause fever, hepatitis, endocarditis, bacillary angiomatosis and bacillary peliosis (Durden and Traub, 2002).

B. henselae has been detected by qPCR in dog blood from Algiers, Algeria (Azzag et al., 2012; Bessas et al., 2016). *B. henselae* has also been detected in *C. canis* and *C. felis,* collected from domestic animals in Sfax, Jendouba and Manouba in Tunisia, (Belkhiria et al., 2017; Zouari et al., 2017). This bacteria was detected using qPCR in *C. felis* collected from sheep, cats and dogs in Casablanca, Morocco (Boudebouch et al., 2011).

- Trench fever:

Trench fever is a zoonosis caused by infection by the bacterium *B. quintana*, a gram-negative bacterium which is considered as a re-emerging human pathogen (Anderson and Neuman, 1997; Faccini-Martínez et al., 2017). This disease was described during the Second World War following several cases of soldiers who suffered from the disease (Kostrzewski, 1949). *B. quintana* may also be responsible for bacillary angiomatosis (Relman et al., 1990), endocarditis (Drancourt et al., 1995) and chronic lymphadenopathy (Raoult et al., 1994).

It is transmitted by body lice (*P. h. humanus*) (Coulaud et al., 2014), but some authors have recently shown the ability of *C. felis* to transmit *B. quintana*, which was found in flea faeces 11 days after an infectious meal (Bouhsira et al., 2013a; Kernif et al., 2014). This bacterium has also been detected in *P. irritans* in Gabon (Rolain et al., 2005).

The presence of this bacterium has often been detected by molecular biology in body lice collected from homeless people in northern Algeria (Louni et al., 2018) and also in patients during an endocarditis study conducted in Casablanca and Marrakech (Morocco) (Boudebouch et al., 2017), and, finally, in 12 endocarditis patients in Sfax (Tunisia) (Znazen et al., 2005).

Parasitic diseases

- *Dipylidium caninum* infection or Dipylidiasis

This is a medium-sized tapeworm which frequently parasitizes the small intestine of dogs and cats. Nevertheless, they can occasionally parasitize humans (Moskvina and Ermolenko, 2016), in which case it causes Dipylidiasis. Its intermediate hosts are *C. felis* and *C. canis* and its final hosts are dogs and cats. These parasites deplete the hosts' nutrients during their presence in the digestive tract and the spoliation of all the nutrients explains the clinical signs (Neira O et al., 2008). The parasite is transmitted to the host by ingestion of contaminated fleas or faeces. Furthermore, lice can, exceptionally, transmit the worm (Franc, 1994b).

This parasite has been reported in three countries of northern Africa. I It was mentioned in a study that targeted wild canids in Tunisia, when the parasite was detected in 55% of foxes and jackals (Lahmar et al., 2014). It was also detected in Egypt, in a study of intestinal parasites from 113 samples of stray cat faeces taken north of the Nile delta (Khalafalla, 2011). Even in Morocco, *D. caninum* has been found in stray dogs in urban and rural areas of Rabat with a percentage of 40.4% of all samples tested (57 dogs) (Pandey et al., 1987).

Flea-borne viral diseases

The biological transmission of viruses by fleas has not been widely studied, the only known virus transmitted by fleas is *Myxomavirus* (myxomatosis virus) (Sobey et al., 1977)(Kerr et al., 2015). This virus is transmitted by the rabbit flea, *S. cuniculi*. This involves mechanical contamination by mouth parts and the virus is released when a bite occurs (Shepherd and Edmonds, 1980). Clinical signs are usually severe and death occurs within 10 to 12 days. However, rabbits with milder signs, including those suffering from the amyxomatous form or those that have been previously vaccinated, may survive with nursing care (Meredith, 2013).The epidemiology of this virus in North Africa has never been studied, but the presence of the flea vector has been reported in several Moroccan cities (Beaucournu and Launay, 1990).

Although several human viral pathogens have been isolated or detected in fleas, the role of fleas in their transmission is either unknown or considered to be incidental. These viruses include those causing lymphocytic choriomeningitis, tick-borne encephalitis and Russian spring-summer encephalitis (Durden and Traub, 2002).

The feline leukaemia virus (FeLV) is a frequent virus in domestic cats and it was still suspected to be transmitted by an arthropod vector. Some authors (Vobis *et al.* 2003) developed an experimental model to study the vector capacity of *C. felis* to transmit the FeLV virus (Vobis et al., 2003). The fleas were fed for 24 hours with blood from a FeLV-infected cat, and FeLV was finally detected in fleas and their faeces. The fleas could even transmit the FeLV virus from one blood sample to another. The results indicate that cat fleas are potential vectors for FeLV RNA in vitro and probably also in vivo (Vobis et al., 2003)

Identification and laboratory rearing

The correct identification of flea species is essential in any research or control project. Current identification methods are mainly based on morphological identification. However, to perform detailed morphological identification, it is necessary to clear flea samples with 10% KOH or NaOH (Lewis, 1993), examine under a stereomicroscope, and then mount and photograph them. Molecular biology has been used over the last 20 years for flea identification and detection of their associated pathogens (Zurita et al., 2015). These approaches are limited by the length of time, the availability of reference sequences in the GenBank database, the cost associated with molecular biology approaches, as well as the small number of entomologists specialised in flea taxonomy (Yssouf et al., 2016). Recently, mass spectrometry has emerged as an innovative identification tool for arthropods, especially fleas (Yssouf et al., 2014). The use of MALDI TOF MS requires the development of an adequate protocol in order to standardise sample preparation methods and to allow for subsequent exchanges using the database between several research laboratories (Nebbak et al., 2017). In addition, MALDI TOF MS has proved its effectiveness in identifying fleas which may or may not be infected by a pathogen and even in distinguishing between fleas infected with two pathogens of the same family (El Hamzaoui et al., 2018). Nevertheless, since MALDI-TOF MS techniques have demonstrated some differences in the MS spectra of specimens preserved in different storage conditions (Nebbak et al., 2017; Zurita et al., 2018), it is still necessary to combine morphological, molecular and proteomics methods in order to carry out an efficient specific identification within the Order Siphonaptera.

Flea rearing is also a key step in the study of the biology of Siphonaptera, their morphology and their vectorial capacity. The cat flea, *C. felis*, is found worldwide and has been reported to parasitize many species of wild and domestic animals (Rust and Dryden, 1997). In addition, *C. felis* has been described as having low host specificity. Indeed, it is a flea that feeds on a variety of animals and rodents, and is therefore the right choice for developing a laboratory breeding programme (Dryden and Rust, 1994). The artificial rearing system described by Wade and Georgi (1988) includes a heated Plexiglas box from which flea chambers are suspended and in which a source of human blood is heated (previously stored at 4°C) (Wade and Georgi, 1988). To maintain the required temperature difference of 10°C, the entire system is housed in a temperature-controlled chamber. The temperature should be maintained between 25°C and 35°C, with a relative humidity of 75 to 80% using a tray filled with water. Fleas are raised in the dark 24 hours a day (Kernif et al., 2015).

Rearing fleas makes it possible to study their vectorial capacity. An experimental model of artificial infection of fleas with a strain of *B. quintana* has shown the ability of *C. felis* to acquire the bacterium and transmit it, alive, in faeces. Several flea groups were fed with blood mixed with the bacterial inoculum at different concentrations. qPCR showed the presence of *B. quintana* in faeces and immunohistochemistry localised the bacterium in the digestive tract of *C. felis* (Kernif et al., 2014).

Control

Insecticides are the most widely-used means of flea control, including powder sprays in nests, burrows, or house walls in infested areas (Rust, 2016). Molt inhibitors are also used to control fleas in their larval stages. It is strongly recommended to control their host in combination with flea control using insecticides, in order to avoid what happened in the case of plague (Franc, 1994a).

Conclusion:

For several decades, we have witnessed the re-emergence of several vector-borne zoonotic pathologies. Metagenomics and molecular biology have revolutionized the epidemiology of these diseases; however, some areas remain poorly explored as North Africa.

Fleas are hematophagous, wingless insects that have the ability to jump. Their ability to transmit pathogens explains their importance in human and animal health. They are spread all over the world and some species do not require the presence of a specific host. This review summarizes the latest data on flea vectors and flea-borne diseases in North Africa (Morocco, Algeria, Tunisia, Egypt and Libya).

For this reason, we have selected disease's vector species described in North Africa in recent years, we have also reported the cases of vector-borne diseases by fleas diagnosed to update the epidemiological situation in this region.

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Figures

Figure 1: 1. *Pulex irritans* female, 2. *Echidnophaga gallinacea* female (Koehler et al., 1991), 3. *Ctenocephalides felis felis* female, 4. *Ctenocephalides canis* female, 5. *Xenopsylla cheopis* male, 6. *Archaeopsylla erinacei* female. Photographs of species (excepting *E. gallinacea* female) were taken using Nikon microscope equipped with a camera lucid system and a photomicroscope at the University of Seville, Seville, Spain

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Table 1. List of main flea-borne microorganisms detected in North Africa.

Pathogen Microorganism (disease in humans)	Flea species	Country	References
Yersinia pestis (Plague)	*P. irritans*	Morocco	Audouin-Rouzeau, 2003; Davis, 1953
	X. cheopis	Algeria	Bertherat et al., 2007.
	E. gallinacea	Egypt	Loftis et al., 2006.
Rickettsia felis (Flea-borne spotted fever)	*C. felis*	Tunisia, Algeria, Morocoo	Kaal et al., 2006; Zouari et al., 2017; Leulmi et al., 2016; Macaluso et al., 2008; Khrouf et al., 2014.
	C. canis	Algeria, Morocco	Bitam et al., 2006; Pandev et al., 1987.
	A. erinacei	Algeria	Leulmi et al., 2016; Khaldi et al., 2012.
Bartonella elizabethae (Endocarditis)	*C. felis*	Tunisia	Zouari et al., 2017.
Bartonella henselae (Cat-scratch disease)	*C. felis*	Tunisia, Morocoo	Kaal et al., 2006, 20, Zouari et al., 2017, Belkhiria et al., 2018.
	C. canis	Tunisia	Zouari et al., 2017; Belkhiria et al., 2018.
	X. cheopis	Algeria	Bessas et al., 2016.
Bartonella clarridgeiae (Cat-scratch disease)	*C. felis*	Tunisia, Morocoo	Kaal et al., 2006; Zouari et al., 2017.
	X. cheopis	Algeria	Bessas et al., 2016.
Bartonella vinsonii (Endocarditis)	*X. cheopis*	Algeria	Bessas et al., 2016.