วารสารสัตวแพทยศาสตร์ มข.
KKU Veterinary Journal
ISSN 0858-2297



REVIEW ARTICLE

Q Fever, re-emerging disease

Kaidi R[1], Mimoune N[2*], Khaled H[1], Khelef D[2]

[1] *Institute of Veterinary Sciences, Saad Dahleb University, Blida, Algeria*
[2]*National High School of Veterinary Medicine, Animal Health and Productions Laboratory, El-Alia, Algiers, Algeria*
[*]***Corresponding author*** *E-mail: nora.mimoune@gmail.com*

Received 4 December 2021, **Revised** 13 April 2022 **Accepted** 28 April 2022, **Published** 17 June 2022

Abstract

Coxiella burnetii is the agent of Q fever in humans and coxiellosis in animals. It causes a range of reproductive diseases, especially abortion in ruminants. These species play a significant role in human infection as they shed *C. burnetii* cells in the fetal membranes, birth fluids and vaginal mucus, as well as in the milk and other excretions. Several studies have been carried out to present an inventory of the prevalence in farms, the risks of Q fever and the possible applicable measures in infected sheep, cattle and goats. Other researches were realized to limit the contamination of the environment and the population. The major current purpose is to determine the best diagnostic approaches and to implement control plans. Vaccination appears to be an essential means of combating Q fever. An inactivated phase I vaccine, of which preventive effectiveness has been demonstrated experimentally, has been developed in France. Ongoing studies will allow an evaluation of this vaccine in farms. In Algeria, few studies have been carried out on the seroprevalence and the genotyping of *C. burnetii* in ruminants which makes the pathology misunderstood, neglected, and underestimated. At the end, Q fever is a challenging disease for all the scientists around the world as significant further investigations are necessary. Great research opportunities are available to reach a better understanding and therefore a better treatment, prevention and control of the infection.

Keywords: *Coxiella burnetii*, ruminants, prevalence, diagnostic, treatment, vaccine

Introduction

Q fever is a zoonosis of worldwide distribution except New Zealand, caused by an intracellular bacterium: *Coxiella burnetii* (Boarbi et al., 2016). This bacterial infection is implicated as a cause of abortions in ruminants (Arricau-Bouvery and Rodolakis, 2005). These species constitute a main reservoir of *Coxiella burnetii*. Contamination occurs through the oral, genital, respiratory routes, or even from infected ticks. Cattle and small ruminants, when infected, shed the bacteria via vaginal excretion and the placenta during parturition as well as in milk, faeces and urine (Muskens et al., 2011). The infectious agent is very resistant in the outdoor environment, since it can survive for seven months in dust (Abeykoon et al., 2021). The seroprevalence varies depending on the country.

Diagnosis of Q fever based on clinical symptoms or post-mortem examination is very difficult or almost impossible due to unspecific or missing symptoms or lesions caused by this disease. Routine diagnosis in aborted ruminants is generally performed by the detection of bacteria in stained smears or impressions of placentas, combined with serological investigations of adult animals using enzyme-linked immunosorbent assay (ELISA), complement fixation test (CFT) or indirect immunofluorescence assay (IFA) (Rousset et al., 2007). However, these methods fail to detect *C. burnetii* shedding animals and show different sensitivities and limitations (Rousset et al., 2009). Moreover, serological diagnosis of Q fever in the early stage of infection can be unsuccessful due to the time-frame of seroconversion spanning 3–4 weeks post infection (Howe et al., 2009). Detection of the etiological agent by PCR or cell culture requires biological material such as placenta, genital swabs or samples from aborted fetuses (liver, lung or abomasum contents). PCR assays provide results within hours rather than weeks as in the case of cell culture methods (Niemczuk, 2014).

With Q fever being a zoonosis, sanitary and prophylactic measures should be applied at herd and human level, in order to limit disease transmission. Human and animal infections must be diagnosed early and treated immediately to prevent the development of infections and complications (Porter et al., 2011). Vaccines, given to animals before their first pregnancy, are used to protect ruminants from clinical signs in some countries. They can reduce but do not eliminate shedding of the organism. Vaccination may need to be carried out for several years to be effective in reducing prevalence (Rousset, 2007; Porter et al., 2011).

In Algeria, the veterinary services are focusing on brucellosis as a cause of abortion in animals (Kardjadj, 2016). This means that other infections involved in abortions such as Q fever are totally neglected. Except little work about the seroprevalence and the genotyping of *Coxiella burnetii* in ruminants in some regions of the country (Rahal et al., 2018), it is difficult to deduce that these studies are representative of the disease situation. In addition, several aspects related to the pathology and the bacteria have not been taken into consideration until now which makes the pathology misunderstood, and underestimated. The lack of diagnostic tools and poor management of livestock complicated the ambiguity. This study is devoted to a review of the literature on Q fever and its different aspects in ruminants. The authors provide some data in Algeria.

Q fever history

Q fever was first observed in humans in 1933. In 1937, Derrick (1937) described the disease found among meat workers in Brisbane in Queensand, Australia. He then called it Q fever. Q being the abbreviation of the English verb “to query: to seek”, because it left a lot of question marks. Derrick inoculated guinea pigs with blood or urine from the “Q” fever patients. The guinea pigs became febrile but he was not able to isolate the agent responsible. Therefore, he sent a saline emulsion of infected guinea pig liver to Macfarlane Burnet in Melbourne (Marrie, 1990). In the same year, Burnet and Freepman (1937) reported the results of their studies on the agent in question which “appeared to be of rickettsial nature”. Derrick proposed the name of Rickettsia burnetii for the Q fever agent (Derrick, 1939). Subsequently, the disease was observed all over the world.

In the Second World War and the movements of troops, the epidemic bronchopneumonia nature of this disease was demonstrated in the Balkans, southern Russia, Greece and Italy (Caminopetros, 1948). In 1944-1965, in The Balkan Peninsula, the disease was known under the name of Balkan influenza. The German and English soldiers of the circummediterranean zone allowed the discovery of the other face of the pathology.

In 1948, major epidemics occurred in Italy and Germany while the disease was identified for the first time in France. In this year, Cornelius B. Philip proposed that R. burnetii be considered as the single species of a distinct genus since it was now apparent that this organism was unique among the rickettsiae. He proposed the name Coxiella (Philip, 1948).

The infection was first reported in Africa in 1947; In Southern Morocco, a focus of Q fever was discovered by Blanc et al. (1947), then the first isolation of *Coxiella burnetii* (old Rickettsia burnetii) was done in Congo from three human subjects, where the organism was also isolated from cows' and goats 'milk, dog and cattle ticks, and human body lice (Ghaoui et al., 2019). In Algeria, coxiellosis has been described for the first time in the Center region for French soldiers, in 1948. After that, outbreaks have been reported in the East between 1955 and 1957, and in the West in 1958 (Bernard et al., 1963). The Outbreak that reported more cases was observed in the region of "Ksar El Boukhari" after transporting soldiers in a freight train that carried livestock.

It was only in 1984 that the first study on animal Q fever was done (Dumas, 1984). However, the twenty first century has observed a resurgence of works on this disease especially in veterinary medicine.

We should therefore not be surprised at the large number of names that this disease took or still take: Derrick and Buren's disease. Q fever, Olympus fever, Crimean fever, 7-day fever, Nine Mile Greeck Fever, Balkan Flu, Crest Pneumonia, Coxiellosis, and abattoir fever.

Causal agent

Coxiella burnetii is a small pleomorphic rod (0.2–0.4 µm wide, 78 0.4–1.0 µm long) (Maurin and Raoult, 1999), exhibiting characteristics similar to those of Rickettsiae: Gram-negative bacteria, very small in the bacterial world, which can be carried by ticks. Nevertheless, phylogenetically, this bacterium is classified in a very distant group of the genus Rickettsia: *C. burnetii* is close to the genus Legionella and is the only species of its genus (Rousset et al., 2007).

The bacterium is intracellular. The main target cells are macrophages located in tissues (lymph and lymph nodes, spleen, liver, lung) and monocytes circulating in the blood (Baca and Paretsky, 1983). *C. burnetii* survives and multiplies in the acidic environment of the phagolysosome, forming a replicative niche, protected from the action of antibiotics (Delaloye and Greub, 2013). The microrganism produces resistant sporelike forms. This ability has been attributed to the existence of *C. burnetii* cycle variants described in *in vitro* studies: largecell variants (LCV), smallcell variants (SCV), and small dense cells (SDC) (McCaul and Williams 1981; Coleman *et al.* 2004). LCV is the infectious intracellular form, characterized by intense metabolic activity and replication rate, but low mechanical resistance (Delaloye and Greub, 2013). The SDC and SCV represent the small morphological variants of the bacteria likely to survive extracellularly as infectious particles, a trait that is important for persistence in the environment and transmission (ECDC, 2010, Kersh et al., 2010; Delaloye and Greub, 2013). The environmentally stable SCV (or endospore) is the form phagocytosed by macrophages during early infection and the form associated to foodborne risk (Pexara et al., 2018). Endospores are released after mother cell lysis and since they are metabolically inactive, they remain stable in soil and dust over many years (Angelakis and Raoult, 2010) and can be spread in dust or windborne aerosols for up to 11 miles (18 km) (Pexara et al., 2018)

Lipopolysaccharide (LPS) exposed on the surface of bacteria is an immunodominant antigen. This LPS is

subjected to a phase variation, observed in vitro and caused by a deletion of genes in the chromosome, therefore irreversible. The complete phase I LPS becomes an incomplete (or truncated) phase II LPS. Only the form carrying a phase I LPS has a high infectivity (Porter et al.,, 2011). A homogeneous population of bacteria in phase II is avirulent and cannot be found in a host organism. This antigen is therefore not used for the serotyping of strains. On the other hand, the search for antibodies can be carried out against one or both antigenic forms (Rousset et al., 2007). *Coxiella burnetii* is considered as a category B biothreat agent (Pearson et al., 2014).

Prevalence of *Coxiella burnetii* infection

Very rare are the countries which have not yet revealed a case of Q fever in their territory. With very few exceptions (Scandinavia. Iceland), the disease therefore has a worldwide distribution (Boarbi et al., 2016).

In Africa, Q fever is frequently reported in humans and many animal species. Depending on species and location, the seroprevalence varies widely (Table 1). Unfortunately, risk factors and incidence estimates are poorly understood. Thus, Q fever is considered an underestimated threat to human and animal health in Africa (Vanderburg et al., 2014).

In Algeria, *C. burnetii* has already been reported in small ruminants and its DNA was detected in 57 samples (21.3%) collected by vaginal swabbing from a total of 267 sheep and goat herds (Khaled et al. 2016). In another study, Aouadi et al (2017) in Eastern Algeria, reported 5.5% of positive qPCR for *Coxiella burnetii* in ticks, 5.8% and 1.7% in sheep and goats blood, respectively. In a recent work, qPCR targeting the *C. burnetii* IS1111 sequence from placental tissues was positive in 19.1% (14 samples) of 73 samples of aborted cows (Rahal et al., 2018).

In table 2, we illustrate the different studies conducted to determine the prevalence of *C. burnetii* in Algeria.

Symptoms

Animal infection with *C. burnetii* is, in most cases, so strikingly asymptomatic that the term Coxiellosis is considered a more appropriate designation than animal Q fever (Angelakis and Raoult, 2010; Pearson et al., 2014). In animals, during the acute phase, *C. burnetii* can be found in the blood, lungs, spleen, and liver whereas during the chronic phase, it is presented as a persistent shedding of *C. burnetii* in feces and urine. Most animals remain totally asymptomatic, including a lack of fever. However, low birth weight animals can occur. Aborted fetuses usually appear normal and the abortion rates can range from 3 to 80% (Angelakis and Raoult, 2010).

Q fever is widespread in livestock, and its seroprevalence is thought to have increased in recent years. Often neglected in the differential diagnosis, Q fever can persist in a herd causing great financial losses on the long term (Porter et al., 2011). Furthermore, ruminants (sheep, goats and cattle) are recognized to be the main sources of human infection (Guatteo et al., 2012; van Engelen et al., 2014). In these species, well-known manifestations of Q fever are abortion, stillbirth, premature delivery, and delivery of weak offspring. However, these dramatic clinical manifestations are generally only expressed in sheep and goats (Porter et al., 2011; van Engelen et al., 2014; Rahal et al., 2018). Cattle and small ruminants, when infected, shed the bacteria via vaginal excretion and the placenta during parturition as well as in milk, feces and urine (Niemczuk et al., 2014; Pearson et al., 2014). Goats and cows mostly shed *C. burnetii* in milk for several months or years. whereas ewes shed the pathogen mostly in feces. *C. burnetii* has been also isolated in bull semen but the role of males in the persistence of infection has not extensively examined (Kruszewska and Tylewska-Wierzbanowska, 1997; Pexara et al., 2018).

Bovine coxiellosis is rarely an overt disease, except for reproductive disorders (such as abortion, infertility, metritis and mastitis) in females (Hassig et Lubsen, 1998). Although high rates of abortions are rarely observed in cattle, shedding of large quantities of germs remains a

Table1. Studies of *Coxiella burnetii* infection prevalence and disease prevalence in humans and animals in Africa according to the origin of the samples (Vanderburg et al., 2014).

Sub-Region	Study Type	Country	Species (n)	Study Year(s)	Sample	Number Positive (%)
Northern	Prevalence	Egypt	Dogs (150)	1998–1999	serum	34 (23%)
		Egypt	Buffalo (45)	2012*	serum	0 (0%)
			Cattle (54)			7 (13%)
			Goats (30)			7 (23%)
			Sheep (55)			18 (33%)
			Humans (92)			15 (16%)
		Egypt	Cattle (100)	2009*	milk	22 (22%)
		Egypt	Humans (883)	1991	serum	285 (32%)
		Sudan	Goats (460)	2010–2011	serum	109 (24%)
	Disease	Morocco	Sheep prior abortion (115) and controls (156)	1986–1987	serum	38 (33%) and 23 (15%)
		Tunisia	Goats & Sheep prior abortion (118) and Sheep controls (517)	1997	serum	22 (12%) and 35 (7%)
		Tunisia	Goats & Sheep abortion (72)	2009*	birth products/ vaginal fluids	14 (19%)[
		Tunisia	Human febrile illness (300)	1993–1994	serum	5 (2%)
		Tunisia	Human febrile illness (47)	2004	serum	4 (9%)
		Tunisia	Human endocarditis (98)	1991–2000	blood	1 (1%)
		Tunisia	Human endocarditis (33)	2008	serum	1 (3%)
		Algeria	Human endocarditis (61)	2000–2003	serum	2 (3%)
Western	Prevalence	Nigeria	Cattle (306) Cattle (84)	1983–1984	serum milk	169 (55%) 44 (52%)
		Nigeria	Cattle (88) Cattle (169)	1983–1984	serum milk	48 (55%) 41 (24%)
		Senegal	Cattle (196)	2007–2008	serum	7 (4%)
		Ghana	Cattle (166)	2012*	serum	30 (18%)
		Cote d'Ivoire	Humans (949)	1965	serum	44 (5%)
		Burkina Faso	Humans (1309)	1975*	serum	100 (8%)
		Niger	Humans, children (177)	1994	serum	17 (10%)
		Ghana	Humans, children (219)	2008*	serum	37 (17%)
	Disease	Niger	Goats prior abortion (75) and controls (47)	1971–1972	serum	24 (32%) and 12 (29%)
		Burkina Faso	Human febrile illness (183)	1995	serum	9 (5%)
Middle	Prevalence	Chad	Cattle (193)	1985*	serum	13 (7%)
		Chad	Camels (142)	1999–2000	serum	114 (80%)

Table1. Studies of *Coxiella burnetii* infection prevalence and disease prevalence in humans and animals in Africa according to the origin of the samples (Vanderburg et al., 2014). (Continued)

Sub-Region	Study Type	Country	Species (n)	Study Year(s)	Sample	Number Positive (%)
			Cattle (195)		serum	8 (4%)
			Goats (134)		serum	18 (13%)
			Sheep (142)		serum	16 (11%)
			Humans (368)		serum	4 (1%)
		Cameroon	Cattle (1377)	2000	serum	431 (32%)
	Disease	Cameroon	Cattle prior abortion (116)	1968*	serum	0 (0%)
		Cameroon	Cattle prior abortion (490) and controls (193)	1985*	serum	14 (3%) and 13 (7%)
		Cameroon	Human pneumonia (110)	1991–1992	serum	6 (6%)
		Cameroon	Human pneumonia (65)	1991–1993	serum	6 (9%)
Southern	Prevalence	South Africa	Cattle (8900)	1985–1986	serum	692 (8%)
	Disease	South Africa	Cattle (6 farms) and sheep (6 farms) abortions	1972–1976	fetal tissue	12 (100%) farms^{+}
		South Africa	Human pneumonia (92)	1987–1988	serum	0 (0%)
Eastern	Prevalence	Tanzania	Humans, pregnant females (150)	1993	serum	7 (5%)
	Disease	Tanzania	Human febrile illness (483)	2007–2008	serum	24 (5%)

reality in the absence of any clinical sign. A retrospective study by Bildfell et al. (2000) demonstrated that *C. burnetii* only sporadically leads to abortion in cattle, but was significantly associated with placentitis. Cattle play an important role in maintaining infection and in dispersing the organism in the environment (Porter et al., 2010; Pexara, 2018).

In cows, placentitis primarily affect the intercotyledonary areas. The placenta is typically leathery and thickened, and it may contain large amounts of mucopurulent or purulent exudates, especially at the edges of the cotyledons and in the intercotyledonary areas. Severe vasculitis is uncommon, but thrombi and some degree of vascular inflammation may be noted. Aborted fetuses tend to be fresh, though they are occasionally autolyzed. Fetal lesions are usually non-specific, although pneumonia and microscopic evidence of hepatic necrosis or granulomatous inflammation have been reported. In representative cases, trophoblasts are distended due to cytoplasmic accumulation of huge numbers of fine, basophilic stained organisms (Agerholm, 2013). Abortions occur principally nearing the end of the pregnancy (Porter et al., 2011; Guatteo et al., 2012; Sidibe et al., 2013).

Sheep have a predisposition for abortion similar to the other ruminants. However, Q fever in sheep seldom causes chronic infections. In naturally infected sheep, the bacterium has been isolated in vaginal discharges long after abortion and can be shed at subsequent pregnancies (Porter et al., 2011). Examination of spontaneous cases of late-term abortions has demonstrated mucopurulent exudates and focal to coalescing necrosis of cotyledons and intercotyledonary placenta. Histologically, a severe necrotising placentitis accompanied by prominent neutrophilic infiltration, oedema and haemorrhage in the stroma and

Table 2. Results about *C. burnetii* in Algeria according to different authors

Species (Individual scale)	Sample	Identification method	Number of positive/Total of samples (%)	Reference
Cows	serum	ELISA	68/180 (29%)	(Dechicha et al., 2010)
Ewes	serum	ELISA	68/184 (36.9%)	(Yahiaoui et al., 2013)
Cows	serum	ELISA	22/92 (23.9%)	(Abdelhadi et al., 2015)
Ewes/goats	serum genital swab	ELISA qPCR	32/227 (14.1%) 57/267 (21.3%)	(Khaled et al., 2016)
Ticks	Tick	PCR	3/18 (15.8%)	(Leulmi et al., 2016)
Cows	serum	ELISA	19/180 (10.6%)	(Agag et al., 2016)
Dromedary	serum	ELISA	131/184 (71.2%)	(Benaissa et al., 2017)
Humans	serum placenta	IFA qPCR	3/725 (0.4%) 4/380 (1.05%	(Ghaoui et al., 2018)
Cows	Placenta	qPCR	14/77 (19.1%)	(Rahal et al., 2018)
Cows	serum	ELISA	31/368 (8.4%)	(Djellata et al., 2019)
Dromedary Ticks	Serum Ticks blood	ELISA qPCR qPCR	139/184 (75.5%) 7/60 (11.7%) 0/184 (0%)	(Bellabidi et al., 2020)
Ewes	serum	ELISA	28/226 (12.4%)	(Hireche et al., 2020)
Horses	serum	ELISA	18/182 (9.9%)	(Ansel et al., 2020)
Cows	serum	ELISA	77/678(11.36%)	(Menadi et al., 2020)

widespread cytoplasmic accumulation of basophilic and IHC or FISH positive bacteria in trophoblasts are seen (Agerholm, 2013).

The frequency of occurrence of Q fever abortions in goats is more important than in sheep with up to 90% of females being affected. Similar to cattle, pregnant animals are more susceptible to infection than nonpregnant animals (Porter et al, 2011). Goats may shed the bacterium in placenta and vaginal mucus in two successive parturitions after a Q fever infection. At their first kidding, young goats shed more *C. burnetii* cells than adults (Pexara et al., 2018). The placental gross morphology and histopathology of spontaneous cases of *C. burnetii* associated abortion in goats resemble the lesions observed in sheep (Agerholm, 2013).

In general, *Coxiella burnetii* localizes in the uterus and mammary glands of infected animals (Marrie, 1990; Porter et al., 2011). Endocarditis, the major form of chronic Q fever in man, does not seem to occur in other animals.

Diagnostic

Since Q fever outbreaks have been recorded in recent years, effective diagnosis is vital for effective eradication and control measures. Due to unspecific or missing symptoms or lesions caused by this disease, the diagnosis based on clinical symptoms or post-mortem lesions is very difficult or almost impossible (Niemczuk et al., 2014).

Serology is still the most used method to test for *C. burnetii* infection (Eldin et al., 2017). Serological tests including indirect immunofluorescence assay (IFA), ELISAs, and complement fixation test (CFT) can be used in this case. The specificity, sensitivity, and positive predictive value vary according to the technique and the antigen (Eldin

et al., 2017).

ELISA test is easy to perform, with results interpretation less subjective than for IFA and CFT, and automation is possible (Rousset et al., 2007; Eldin et al., 2017). The CFT is weakly sensitive and the antigen used in this test frequently fails to detect antibodies in sheep or goats (Horigan et al., 2011; Pexara et al., 2018). The higher sensitivity of ELISA compared to CFT could be due to the detection of the IgG2 subclass of antibodies, which are incapable of binding to the guinea pig complement (Porter et al., 2011).

C. burnetii exists in two antigenic phases, phase I and phase II. Phase I is the virulent, highly infectious form that undergoes a transition to phase II, the avirulent form, during serial laboratory passages in embryonated eggs or cell cultures. In acute infection, the phase II antibody response to *C. burnetii* appears first and is higher than the phase I antibody response (Anderson et al., 2015). Commercially available ELISA kits are frequently coated by phase I and phase II antigens. The antigens present are of two possible origins: antigens of the American Nine Mile strain of *Coxiella burnetii* isolated from an endogenous tick or antigens of a strain originating from infected European domestic ruminants. ELISA kits coated by the latter antigens are more sensitive and are advised for serological diagnosis (Porter et al., 2011).

The serological methods are useful for carrying out preliminary surveys of infection at the herd level but they do not allow for the identification of *C. burnetii* shedding animals. Moreover, serological diagnosis of Q fever in the early stage of infection can be unsuccessful due to the time-frame of seroconversion spanning 3–4 weeks post infection (Sidibe et al., 2013; Niemczuk et al., 2014).

The specific detection of *C. burnetii* by PCR (Polymerase Chain Reaction) is the method of choice for analyzes in veterinary medicine (Delaloye and Greub, 2013). It allows highlighting the bacterium, with a high sensitivity, in various samples, including cell cultures, biopsy samples, blood, arthropods, and serum samples (Rousset et al., 2007; Porter et al., 2011). PCR is very useful for early diagnosis of infection during the period when antibodies are not yet present (Porter et al., 2011). When the positive serological results are found at the herd level, the PCR is the best method to trace shedders. However, in the absence of positive serology and the presence of suspicion of *C. burnetii* infection, the test for pathogen detection should be performed (Niemczuk et al., 2014). Real-time PCR or quantitative PCR (qPCR) is a less time-consuming technique and is able to quantify the amount of bacteria in clinical samples. Therefore, it becomes the most frequently used PCR system for diagnosis (Porter et al., 2011; Eldin et al., 2017). The qPCR system targeting IS*1111* (a repetitive element which is present in about 20 copies in the *C. burnetii* Nine Mile genome) is the most sensitive (Rousset et al., 2007; Eldin et al., 2017). However, the informative value of PCR is still insufficient for dairy products. It is indeed difficult to ensure that the sample has not been contaminated by the environment and the technique detects the presence of DNA from bacteria, both dead and alive (Rousset et al., 2007).

In vitro cell culture of the bacteria is the gold standard for diagnosis of bacterial infections. *Coxiella burnetii* can be cultured efficiently in the yolk sac of chicken embryos and also on diverse cellular specimens, such as human embryonic lung fibroblasts, mosquito cells, greenmonkey kidney (Vero) cells, L cells, tick tissue cultures, and so forth. However, technically, culture of *Coxiella burnetii* remains a difficult process and sensitivity of this diagnostic method is low (Porter et al., 2011).

C. burnetii can be cultured in an axenic medium called Complex Coxiella Medium (CCM). This medium supports axenic metabolic activity by *C. burnetii* for at least 24 h. The medium contains 3 nutrient source complexes; neopeptone, FBS (Fetal Bovine Serum), and RPMI (Roswell Park Memorial Institute medium). This composition was based on an *in silico* genomic analysis of metabolic deficiencies. The authors observed sustained metabolic activity of *C. burnetii* in this medium (Omsland et al., 2009). Recently, another axenic medium, called acidified cysteine citrate medium 2 (ACCM2), was developed. A sample of the heart valve from a patient with *C. burnetii* endocarditis was incubated in 20 ml of ACCM2, and growth was ob-

served after 6 to 8 days of incubation. Inoculation of an ACCM2 agar plate with a sample of the culture positive liquid ACCM2 yielded several colonies at day 5 (170). This new possibility could significantly facilitate the routine cultivation of *C. burnetii* from clinical samples (Eldin et al., 2014).

Another practical limitation to bacterial isolation is that *C. burnetii* is dangerous to laboratory personnel, requiring a Biosafety Laboratory 3 conditions because of its high infectivity. As a result, culture is rarely performed, especially in veterinary medicine (Porter et al., 2011).

Treatment, prophylaxis, and disease's control

With Q fever being a zoonosis, prophylaxis at herd level is fundamental (Porter et al., 2011). The measures target the various potential sources of contamination, especially in the case of abortion or a proven excretory focus (Rodolakis et al., 2007). Sanitary and prophylactic measures should be applied at herd and human level, in order to limit disease transmission. Human and animal infections must be diagnosed early and treated immediately to prevent the development of chronic infections and secondary complications (Porter et al., 2011).

In ruminants, antibiotic treatment generally consist in administering two injections of oxytetracycline (20 mg per kg bodyweight) during the last month of gestation, although this treatment does not totally suppress the abortions and the shedding of *C. burnetii* at lambing (Angelakis and Raoult, 2010). Furthermore, it may promote drug resistance complicating the treatment of clinical cases (Rolain et al., 2003).

Control of the disease in animals will influence the level of disease seen in man. Appropriate tick control strategies and good hygiene practice can decrease environmental contamination (Angelakis and Raoult, 2010).

A Phase II vaccine was developed against Q fever in cattle and sheep in 1982 (Serbezov et al. 1999). However, it has been shown to be non-protective and had no effect on excretion (Rousset et al., 2007).

In animals, vaccines considered the most effective are composed of inactivated whole phase 1 bacteria. Indeed, in goats, the inactivated phase I vaccine (Coxevac, CEVA Santé Animale, Libourne, France) protects efficiently against abortion and has been shown to prevent bacterial shedding in vaginal mucus, feces, and particularly in milk. However, vaccination proved more effective in nulliparous animals than in parous animals. Furthermore, vaccination did not clear infection in previously infected goats and cattle (Porter et al., 2011). No vaccine is available commercially in Algeria.

Conclusions

Q fever is an underestimated disease in Algeria which remains poorly understood to this day and the knowledge of this pathology is limited. Available epidemiological studies consist small samples of animals or humans in few regions regarding a big country like Algeria. In the same context, no available data about the means of control, treatment or prevention to combat coxiollosis in animals. So, important further researches and investigations are necessary to improve the knowledge of the disease itself and of the epidemiological cycle of coxiellosis in this country. Diagnostic tests must be improved to increase their sensitivity and specificity. They must be adapted to the Algerian strain of bacteria with the Algerian conditions. Further research in the field of prevention through the development of new vaccines would allow a maximum control of foci of infection in animals but also in human populations in the future. At the end, Q fever remains a challenge for the veterinary and medical profession around the world and a better knowledge of Q fever would improve diagnostic procedures, control, and prevention of the disease in the future.

References

Abdelhadi FZ, Abdelhadi SA, Niar A, Benallou B, Meliani S, SMAIL NL, Mahmoud D, 2015. Abortions in cattle on the level of Tiaret area (Algeria). Global Vet 14(5), 638-645.

Abeykoon AMH, Clark NJ, Soares Magalhaes RJ, Vincent GA, Stevenson MA, Firestone SM, Wiethoelter AK, 2021. *Coxiella burnetii* in the environment: A systematic review and

critical appraisal of sampling methods. Zoonoses Public Health 68(3), 181 –165.

Agag S, Kaidi R, Khelef D, 2016. Seroprevalence of Q fever in cows in Bejaia area (Algeria). Rev Elev Med Vet Pays Trop 69(4), 155-159.

Agerholm JS, 2013. *Coxiella burnetii* associated reproductive disorders in domestic animals--a critical review. Acta Vet Scand 55(1), 13.

Anderson AD, Szymanski TJ, Emery MP, Kohrs PH, Bjork AC, Marsden-Haug N, Nett RJ, Woodhall DM, Self JS, Fitzpatrick KA, Priestley RA, Kersh GJ, 2015. Epizootiological investigation of a Q fever outbreak and implications for future control strategies. J Am Vet Med Assoc 247(12), 13791386.

Angelakis E, Raoult D, 2010. Q fever. Vet Microbiol 140 (3-4), 297–309.

Ansel S, benfodil K. Cherif AM, Abdelli A, Kaidi R, Miroud K, Aitoudhia K, 2020. *Coxiella burnetii* in Horses of Algeria: Seroprevalence and Associated Risk Factors. World Vet J 10(4), 602-608.

Aouadi A, Leulmi H, Boucheikhchoukh M, Benakhla A, Raoult D, Parola P, 2017. Molecular evidence of tick-borne hemoprotozoan-parasites (*Theileria ovis* and *Babesiaovis*) and bacteria in ticks and blood from small ruminants in Northern Algeria. Comp Immunol Microbiol Infect Dis 50, 34-39.

Arricau-Bouvery N, Rodolakis A, 2005. Is Q fever an emerging or re-emerging zoonosis? Vet Res 36(3), 327–349.

Baca OG, Paretsky D, 1983. Q fever and *Coxiella burnetii*: a model for host-parasite interactions. Microbiol Rev 47(2), 127–149.

Bellabidi M, Benaissa MH, Bissati-Bouafia S, Harrat Z, Brahmi K, Kernif T, 2020. *Coxiella burnetii* in camels (*Camelus dromedarius*) from Algeria: Seroprevalence, molecular characterization, and ticks (Acari: Ixodidae) vectors. Acta Tropica 206, 105443.

Benaissa MH, Ansel S, Mohamed-Cherif A, Benfodil K, Khelef D, Youngs CR, Kaidi R, Ait-Oudhia K, 2017. Seroprevalence and risk factors for *Coxiella burnetii*, the causative agent of Q fever in the dromedary camel (*Camelus dromedarius*) population in Algeria. Onderstepoort J Vet Res 84(1), e1-e7.

Bernard JG, Bereni J, Hainaut J, 1963. Aspect actuel des rickettsioses en Algérie. Bull Soc Pathol Exot 56, 669- 677.

Bildfell RJ, Thomson GW, Haines DM, Mcewen BJ, Smart N, 2000. *Coxiella burnetii* infection is associated with placentitis in cases of bovine abortion. J Vet Diagn Invest. 12(5), 419425.

Blanc G, Martin LA, Maurica A, 1947. Présence du virus de la 'Q fever' dans le Maroc méridional. Bull Acad Natl Med. 131, 138–143.

Boarbi S, Fretin D, Mori M, 2016, *Coxiella burnetii*, agent de la fièvre Q. Can J Microbiol 62(2), 102-122.

Burnet FM, Freeman M, 1937. Experimental studies on the virus of "Q" fever. Med J Aust 2, 299-305.

Caminopetros JP, 1948. La Qfever en Grece: le lait source de l'infection pour l'homme et les animaux. Ann Parasitol Hum Comp 23(1-2), 107-108.

CEVA, 2010. Vaccines. Available from: http://www.ceva.com/en/Products/ Cattle/Vaccines.

Coleman SA, Fischer ER, Howe D, Mead DJ, Heinzen RA, 2004. Temporal analysis of *Coxiella burnetii* morphological differentiation. J Bacteriol 186(21), 7344-7352.

Dechicha A, Gharbi S, Kebbal S, Chatagnon G, Tainturier D, Ouzrout R, Guetarni D, 2010. Serological survey of etiological agents associated with abortion in two Algerian dairy cattle breeding farms. J Vet Med Anim Health 2(1), 001-005

Delaloye J, Greub G, 2013. Fièvre Q : une zoonose souvent méconnue. Rev Med Suisse 383, 879-84.

Derrick EH, 1937. Q fever, a new fever entity: clinical features, diagnosis and laboratory investigation. Med J of Aust 2, 281–299.

Derrick EH, 1939. Rickettsia burneti: the cause of 'Q' fever. Med J Aust 1, 14.

Djellata N, Yahimi A, Hanzen C, Saegerman C. Kaidi R, 2019. Prevalence and factors associated with a higher or lower risk of exposure to *Coxiella burnetii*, Chlamydia abortus and Toxoplasma gondii in dairy cows that have aborted in Algeria. Rev Sci Tech 38(3), 761-786.

Dumas N, 1984. Rickettsioses et chlamydioses au hoggar (République algérienne): sondage épidémiologique. Bull Soc Pathol Exot 77(3), 278-283.

ECDC (European Centre for Disease Prevention and control) 2010. Panel with representatives from the Netherlands, France, Germany, United Kingdom, United States of America. Risk assessment on Q fever. ECDC Technical Report, 40 pp.

Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, Mege JL, Maurin M, Raoult D, 2017. From Q Fever to *Coxiella burnetii* Infection: A Paradigm Change. Clin Microbio Rev 30(1), 115-190.

Ghaoui H, Bitam I, Ait-Oudhia K, Achour N, Saad-Djaballah A, Saadnia FZ, Kedjour S, Fournier PE, Raoult D, 2018. *Coxiella burnetii* infection with women's febrile spontaneous abortion reported in Algiers. New Microbes New Infect

26, 8-14.

Ghaoui H, Achour N, Saad-Djaballah A, Smai A, Temim S, Bitam I, 2019. Between livestock's and humans, Q fever disease is emerging at low noise. Acta Sci Microbiol 2(10), 104-132.

Guatteo R, Joly A, Beaudeau F, 2012. Shedding and serological patterns of dairy cows following abortions associated with *Coxiella burnetii* DNA detection. Vet Microbiol 155(2-4), 430–433.

Hassig M, Lubsen J, 1998. Relationship between abortions and seroprevalences to selected infectious agents in dairy cows. Zentralbl Veterinarmed B 45(7), 435–441.

Hireche S, Agabou A, Bouaziz O, 2020. Seroprevalence of *Coxiella burnetii* among ewes and associated risk factors in Constantine (Northeastern Algeria). J Hellenic Vet Med Soc 71(3), 2383-2390.

Horigan MW, Bell MM, Pollard TR, Sayers AR, Pritchard GC, 2011. Q fever diagnosis in domestic ruminants comparison between complement fixation and commercial enzyme-linked immunosorbent assays. J Vet Diagnost Invest 23(5), 92493.

Howe GB, Loveless BM, Norwood D, Craw P, Waag D, England M, Lowe JR, Courtney BC, Pitt ML, Kulesh DA, 2009. Real-time PCR for the early detection and quantification of *Coxiella burnetii* as an alternative to the murine bioassay. Mol Cell Probes 23(3-4), 127–131.

Kardjadj M, 2016. The Epidemiology of Human and Animal Brucellosis in Algeria. J Bacteriol Mycol 3(2), 16.

Kersh GJ, Fitzpatrick KA, Self JS, Priestley RA, Kelly AJ, Lash RR, Marsden-Haug N, Nett RJ, Bjork A, Massung RF, Anderson AD, 2013. Presence and persistence of *coxiella burnetii* in the environments of goat farms associated with a Q fever outbreak. Appl Environ Microbiol 79(5), 1697–1703.

Khaled H, Sidi-Boumedine K, Merdja S, Dufour P, Dahmani A, Thiéry R, Rousset E, Bouyoucef A, 2016. Serological and Molecular evidence of Q fever among small ruminant flocks in Algeria. Comp Immunol Microbiol Infect Dis 47, 19-25.

Kruszewska D, Tylewska-Wierzbanowska S, 1997. Isolation of *Coxiella burnetii* from bull semen. Res Vet Sci 62(3), 299300.

Leulmi H, Aouadi A, Bitam I, Bessas A, Benakhla A, Raoult D, Parola P, 2016. Detection of *Bartonella tamiae, Coxiella burnetii* and rickettsiae in arthropods and tissues from wild and domestic animals in northeastern Algeria. Parasit Vectors 20(9), 27.

Marrie TJ, 1990. Acute Q fever, In: Marrie TJ (Ed). Q Fever, The disease. CRC Press, Boca Raton, Fla, USA.

Maurin M, Raoult D, 1999. Q Fever. Clin Microbiol Rev 12(4), 518-53.

McCaul TF, Williams JC, 1981. Developmental cycle of *Coxiella burnetii*: Structure and morphogenesis of vegetative and sporogenic differentiations. J Bacteriol 147(3), 1063-1076.

Menadi SE, Mura A, Santucciu C, Ghalmi F, Hafsi F, Masala G, 2020. Seroprevalence and risk factors of *Coxiella burnetii* infection in cattle in northeast Algeria. Trop Anim Health Prod 52(3), 935-942.

Muskens J, van Maanen C, Mars MH, 2011. Dairy cows with metritis: *Coxiella burnetii* test results in uterine, blood and bulk milk samples. Vet Microbiol 147(1-2), 186-189.

Niemczuk K, Szymańska-Czerwińska M, Śmietanka K, Bocian Ł, 2014. Comparison of diagnostic potential of serological, molecular and cell culture methods for detection of Q fever in ruminants. Vet Microbiol 171(1-2), 147–152.

Omsland A, Cockrell DC, Howe D, Fischer ER, Virtaneva K, Sturdevant DE, Porcella SF, Heinzen RA, 2009: Host cell-free growth of the Q fever bacterium *Coxiella burnetii*. Proc Natl Acad Sci U S A 106(11), 4430–4434.

Pearson T, Hornstra HM, Hilsabeck R, Gates LT, Olivas SM, Birdsell DM, Hall CM, German S, Cook JM, Seymour ML, Priestley RA, Kondas AV, Clark Friedman CL, Price EP, Schupp JM, Liu CM, Price LB, Massung RF, Kersh GJ, Keim P, 2014. High prevalence and two dominant host-specific genotypes of *Coxiella burnetii* in U.S. milk. BMC Microbiol 14, 41.

Pexara A, Solomakos N, Govaris A, 2018. Q fever and seroprevalence of *Coxiella burnetii* in domestic ruminants. Vet Ital 54(4), 265279.

Philip CB, 1948. Comments on the name of the Q fever organism. Public Health Rep 63, 58.

Porter SR, Czaplicki G, Mainil J, Guattéo R, Saegerman C, 2011. Q Fever: Current State of Knowledge and Perspectives of Research of a Neglected Zoonosis. Int J Microbiol 2011, 248418.

Rahal M, Tahir D, Eldin C, Bitam I, Raoult D, Parola P, 2018. Genotyping of *Coxiella burnetii* detected in placental tissues from aborted dairy cattle in the north of Algeria. Comp Immunol Microbiol Infect Dis 57, 50–54.

Rodolakis A, Berri M, Héchard C, Caudron C, Souriau A, Bodier CC, Blanchard B, Camuset P, Devillechaise P, Natorp JC, Vadet JP, Arricau-Bouvery N, 2007. Comparison of *Coxiella burnetii* shedding in milk of dairy bovine, caprine and ovine herds. J Dairy Sci 90(12), 53525360.

Rolain JM, Mallet MN, Raoult D, 2003. Correlation between serum doxycycline concentrations and serologic evolution in patients with *Coxiella burnetii* endocarditis. J Infect Dis

188(9), 1322–1325.

Rousset E, Durand B, Berri M, Dufour P, Prigent M, Russo P, Delcroix T, Touratier A, Rodolakis A, Aubert M, 2007. Comparative diagnostic potential of three serological tests for abortive Q fever in goat herds. Vet Microbiol 124(3-4), 286–297.

Rousset E, Berri M, Durand B, Dufour P, Prigent M, Delcroix T, Touratier A, Rodolakis A, 2009. *Coxiella burnetii* shedding routes and antibody response after outbreaks of Q fever-induced abortion in dairy goat herds. Appl Environ Microbiol 75(2), 428–433.

Serbezov VS, Kazár J, Novkirishki V, Gatcheva N, Kovácová E, Voynova V, 1999. Q fever in Bulgaria and Slovakia. Emerg Infect Dis 5(3), 388-394.

Sidibé SS, Coulibaly KW, Dakouo M, Tarnagda Z, Sery A, Niang M, Traoré K, Nantoumé H, Diarra S, Seyni H, 2013. Fièvre Q chez les petits ruminants au Mali. Résultats d'une enquête sérologique. Rev Elev Me. Vet Pays Trop 66 (1), 11-18.

van Engelen E, Schotten N, Schimmer B, Hautvast JL, van Schaik G, van Duijnhoven YT, 2014. Prevalence and risk factors for *Coxiella burnetii* (Q fever) in Dutch dairy cattle herds based on bulk tank milk testing. Prev Vet Med 117(1), 103–109.

Vanderburg S, Rubach MP, Halliday JE, Cleaveland S, Reddy EA, Crump JA, 2014. Epidemiology of *Coxiella burnetii* Infection in Africa: A OneHealth Systematic Review. PLoS Negl Trop Dis 8(4), e2787.

Yahiaoui W-I, Afri-Bouzebda F, Bouzebda Z, Dahmani A, 2013. Sondage sérologique de la fièvre Q chez les ovins par la méthode ELISA et prévalence des avortements dans la région de Ksar El Boukhari (Algérie). Tropicultura 32(1), 22-27.