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Current perspectives on the transmission of Q fever: Highlighting the need for a systematic molecular approach for a neglected disease in Africa

Running Title: Q fever transmission

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Graphical abstract

Q fever is endemic throughout the world, but remains a largely neglected infection in Africa, where there is a need for systematic molecular epidemiological studies.

Highlights

- Q fever is a bacterial zoonotic disease
- Acquired mainly from livestock
- The infection is endemic in Africa but studies are largely restricted to serology
Analysis of bacterial genotype is key to understanding transmission and pathogenesis

There is a need for systematic molecular epidemiological studies in Africa

Abstract

Q fever is a bacterial worldwide zoonosis (except New Zealand) caused by the Gram-negative obligate intracellular bacterium *Coxiella burnetii* (*C. burnetii*). The bacterium has a large host range including arthropods, wildlife and companion animals and is frequently identified in human and livestock populations. In humans, the disease can occur as either a clinically acute or chronic aetiology, affecting mainly the lungs and liver in the acute disease, and heart valves when chronic. In livestock, Q fever is mainly asymptomatic; however, the infection can cause abortion, and the organism is shed in large quantities, where it can infect other livestock and humans. The presence of Q fever in Africa has been known for over 60 years, however while our knowledge of the transmission routes and risk of disease have been well established in many parts of the world, there is a significant paucity of knowledge across the African continent, where it remains a neglected zoonosis. Our limited knowledge of the disease across the African sub-continent have relied largely upon observational (sero) prevalence studies with limited focus on the molecular epidemiology of the disease. This review highlights the need for systematic studies to understand the routes of *C. burnetii* infection, and understand the disease burden and risk factors for clinical Q fever in both humans and livestock. With such knowledge gaps filled, the African continent could stand a better chance of eradicating Q fever through formulation and implementation of effective public health interventions.
Keywords

Coxiella burnetii; Q fever; Zoonosis; Livestock; Africa

1. Introduction

Q fever is a zoonotic disease with a worldwide distribution except for New Zealand and Antarctica. The first identification of Q fever or ‘Query fever’ was published in 1937 (Derrick, 1937). However, Q fever remained a relatively neglected disease, until the recent national outbreak in the Netherlands between 2007 and 2010, which demonstrated the potential of the disease to be a major public health issue (Schneeberger et al., 2014).

The causative agent of Q fever is the bacterium *Coxiella burnetii*, a category B bioterrorism agent. *C. burnetii* has a wide host range including humans, ruminants (goats, sheep, and cattle), as well as companion animals and ticks. In livestock, *C. burnetii* infection remains often clinically inapparent, except in cases of abortion, particularly in goats and sheep (Van den Brom et al., 2015b). In humans, infection can cause an acute form of disease, which typically exhibits itself as pneumonia and a chronic form resulting in endocarditis, which is potentially fatal (Gikas et al., 2010).

In recent years, our understanding of the transmission of Q fever has been transformed by the use of molecular typing techniques. However, our knowledge has remained largely defined by studies in Europe and North America. The presence of Q fever in Africa has been recognised for over 60 years (Kaplan and Bertagna, 1955), however it remains a relatively neglected zoonosis across the continent, and our knowledge of the disease across the continent is largely through serology and sero-epidemiological studies. The purpose of this review is to
provide a general overview of the Q fever bacteriology, pathology, and infection of relevant host, reservoirs and transmission as well as existing genotyping techniques. Most significantly, a special focus is given to revealing the lack of systematic and comprehensive studies of the molecular epidemiology of Q fever in Africa.

2. Clinical Q fever

2.1 Human infection

Clinical manifestation of Q fever occurs as either an acute or a chronic form of disease. Approximately 40% of infected people will develop symptomatic acute Q fever of which, the majority will present as a non-specific, self-limiting illness. More severe clinical symptoms include fever, headache, chills, atypical pneumonia and hepatitis (Derrick, 1973; Maurin and Raoult, 1999; Raoult et al., 2005). Acute episodes are rarely fatal unless the patients also suffered from severe underlying medical conditions (Kampschreur et al., 2010). Approximately 20% of acute Q fever sufferers experience symptoms of long-term fatigue, which frequently lasts beyond a year and more commonly between 5 to 10 years after the initial episode. This is termed post Q fever fatigue syndrome (QFS) and while the symptoms are poorly defined, sufferers experience significant long-term impaired health status and reduced quality of life (Morroy et al., 2016). Chronic Q fever develops in less than 5% of patients in which symptoms may only manifest years after the initial infection. Clinical symptoms include non-specific fatigue, fever, weight loss, night sweats and hepato-splenomegaly as well as endocarditis (Raoult et al., 2005; Wegdam-Blans et al., 2012). After the recent outbreak in the Netherlands, vascular complications appeared to be more common than endocarditis, however due to the relatively short period of time since the outbreak and the slow clinical progression of disease, endocarditis may not have become apparent yet in many chronically infected
individuals (van der Hoek et al., 2012). Chronic Q fever has a wider clinical presentation and has recently been recommended to undergo a nosological refinement to accommodate all probable manifestations, for a better clinical diagnosis (Eldin et al., 2017).

2.2 The role of livestock in the transmission of Q fever

While *C. burnetii* infects a number of animal species, the majority of human infections are thought to be associated with livestock, although infection through contact with wildlife (kangaroos, wallabies and three-toed sloth) (Davoust et al., 2014; Eldin et al., 2015; Maurin and Raoult, 1999), and companion animals (Buhariwalla et al., 1996; Komiya et al., 2003; Kopecny et al., 2013; Kosatsky, 1984; Langley et al., 1988; Laughlin et al., 1991; Malo et al., 2018; Marrie et al., 1988; Pinsky et al., 1991), have been reported. In Infected livestock, the bacteria may be shed in significant quantities in birth products, vaginal mucus, urine, faeces, or milk. The bacterium is highly infectious (1-10 bacteria) therefore this high bacterial load in birth products is a potent source of infection.

In non-pregnant livestock, *C. burnetii* infection is virtually asymptomatic. The most important clinical presentations of Q fever in livestock species are reproductive anomalies such as, abortion, stillbirth, infertility, endometritis, and mastitis. Q fever primarily causes abortion in goats, sheep and less commonly in cattle. The highest concentrations of *C. burnetii* (up to $10^9$ organisms per gram of tissue) are found in the placentas of infected livestock, either after abortion or indeed after livebirth (Berri et al., 2001; Guatteo et al., 2011; Hatchette et al., 2003; Lang et al., 1991; Rousset et al., 2009; van Moll et al., 1993). Abortion occurs most frequently at the end of gestation, without any preceding clinical symptoms (Arricau-Bouvery et al., 2005). In goats, abortion, stillbirth but also the birth of strong and lively kids can occur after Q
fever infection of pregnant animals (Arricau-Bouvery et al., 2005; Roest et al., 2012). The cause of differences in pregnancy outcome between ruminant species is unknown.

The organism is highly stable in the environment, and due to its resistance to desiccation, infectious organisms may be present for many months after shedding, both in the immediate environment but also on the wool of infected animals (Wattiau et al., 2011). In humans, the primary route of infection is via inhalation of contaminated aerosols, and the majority of human infections are primarily the result of contact with infected livestock. Evidence suggests that close proximity to the source (the goat birthing pen) is the major risk factor associated with infection, and that human activity is largely responsible for the transfer of the infective organisms away from the initial source of infection (Kersh et al., 2013a). However, aerosolised transmission between infected and naïve herds, or the human population and are frequent and often associated with specific environmental conditions, which favour dispersal, including wind, and the topography of the landscape (Mori and Roest, 2018). High wind speeds, open landscapes, high animal densities, and high temperatures were identified as risk factors for transmission of Q fever between Swedish dairy cattle herds (Nusinovici et al., 2017). Likewise, in France, a correlation between human cases of Q fever, high sheep densities and the prevailing Mistral wind has been observed (Tissot-Dupont et al., 2004; Tissot-Dupont et al., 1999). Low consistent wind speed in a flat area of the North Brabant region of the Netherlands was identified as favourable towards the dispersal and transmission of \( C.\ burnetii \) to the local population (van Leuken et al., 2015).

While inhalation is the most significant route of \( C.\ burnetii \) infection, given the prevalence of \( C.\ burnetii \) in milk, dietary ingestion has been studied as a potential route of transmission. Mammals shed \( C.\ burnetii \) in milk, and a number of studies have demonstrated the presence of \( C.\ burnetii \) DNA in milk and dairy products from cattle (Bauer et al., 2015; Olivas et al., 2016; Pearson et al., 2014; Velasova et al., 2017), goats (Ceglie et al., 2015; Van
den Brom et al., 2015a) and sheep (Barkallah et al., 2014). A high rate of \textit{C. burnetii} seropositivity was demonstrated in humans consuming raw goat’s milk (Eldin et al., 2013). However, there is an increased likelihood that individuals accessing raw products live in a rural setting, and more likely to be exposed to other potential routes of infection, such as contact with livestock. Despite the widespread shedding of \textit{C. burnetii} in milk, ingestion of dairy products are not seen as a primary route of transmission (Eldin et al., 2013; Gale et al., 2015).

2.3 \textit{Human to human transmission}

\textit{Q} fever is thought to be non-communicable, however human-to-human transmission can occur, albeit rarely. As with livestock, birth products from infected women may be a source of infection, to both hospital staff (Raoult and Stein, 1994), and other pregnant women within the same unit (Amit et al., 2014). There is also evidence for sexual transmission (Milazzo et al., 2001) and transmission via blood transfusion is a potential risk. \textit{C. burnetii} is stable in blood samples for at least six weeks at 1-6°C (Kersh et al., 2013b). In a recipient tracing study of blood donors from the Dutch outbreak of 2009, a transfusion recipient in a highly infected area was found to be seropositive after receiving blood from a \textit{C. burnetii} positive donor (van Kraaij et al., 2013). While in this case, the source of infection cannot be categorically determined and the risks of transmission via blood products has been estimated to be low (Oei et al., 2014), infection via this route cannot be ruled out.

2.4 \textit{The potential role of arthropods in \textit{Q} fever transmission}

\textit{Coxiella burnetii} has been identified in over 40 hard bodied and 14 soft bodied species of tick (Eldin et al., 2017) isolated form a wide range of animal host species. Indeed the Nine Mile strain of \textit{C. burnetii} was first isolated in 1935 from the tick \textit{Dermacentor andersoni} in
Montana (Davis et al., 1938). Experimentally, successful tick to animal transmission of \textit{C. burnetii} has been demonstrated in a guinea-pig model of infection (Siroky et al., 2010). However, it is under debate whether ticks play a significant role in the transmission of \textit{C. burnetii}, or whether the presence of the bacteria in the tick population is simply a reflection for \textit{C. burnetii} prevalence in the tick’s host species. In the Netherlands’ outbreak, ticks were not thought to play a significant role in transmission (Sprong et al., 2012). A recent study of Spanish Ibex suggested that ticks may play a potential role as a vector of infection but modelling suggested a complex interaction between that host, population and environmental factors as drivers of infection in ticks (Varela-Castro et al., 2018).

3. \textbf{Q fever in Africa}

Cases of \textit{Q fever} have been documented in the African continent for over 60 years. \textit{Q fever} is an endemic infection across the continent yet we still know relatively little about the prevalence and routes of infection or the health impact of the disease in both livestock and humans. One of the reasons behind this relative paucity of information, and a major barrier towards understanding the impact \textit{Q fever} is the non-specific nature of symptoms, which are commonly confused for other endemic infections including malaria (Crump, 2014). The was highlighted in a recent ‘OneHealth’ systematic review (Vanderburg et al., 2014) of \textit{Q fever} in Africa, which came to the conclusion that ‘\textit{C. burnetii} presents a real yet underappreciated threat to human and animal health in Africa’.

\textit{3.1 Prevalence in Humans}

In 1955, the first cases of \textit{Q fever} were reported in nine countries across the African continent (Kaplan and Bertagna, 1955). Since then a number of studies have demonstrated that
the infection is endemic across the continent, but with significant variation in prevalence between countries ranging from 1% in Chad (Schelling et al., 2003), to 32% in the Nile Delta in Egypt (Corwin et al., 1993).

Serological evidence of Q fever has been demonstrated in both adults and children; however, rates of C. burnetii seropositivity appear higher among young children. High rates of seropositivity in children were observed in Ghana’s rural Ashanti Region, where 17% of two-year-olds were found to be seropositive (Kobbe et al., 2008). In Niger, 10% of children aged between 1 month old and 5 years of age were seropositive (Julvez et al., 1997). A recent serological survey of 796 children, aged between 1 and 15 years, in Gambia identified C. burnetii antibodies in 8.3% (van der Hoek et al., 2013). Intriguingly, they observed that C. burnetii seroprevalence was highest among young children (under 4 years), compared with other age groups; however, the reasons for this are still unclear.

Several studies have suggested that Q fever is an important cause of acute fever and pneumonia. C. burnetii was identified as the aetiological agent in 5% of 109 severe pneumonia cases in Tanzania (Rubach et al., 2015). Again in Tanzania, an investigation of febrile patients identified bacterial zoonoses as the underlying cause in 26.2% of cases, of which 30% were diagnosed as Q fever (Crump et al., 2013). Within the same patient cohort, malaria was the clinical diagnosis in 60.7% cases, whereas laboratory testing confirmed the diagnosis in only 1.6% of patients. Similarly, Q fever was identified in 8.9% of paediatric febrile admissions in western Kenya (Maina et al., 2016). Q fever was also identified in 2% and 9% of acute hospital admissions across two patient cohort studies of febrile admissions in Tunisia (Kaabia et al., 2006; Omezzine-Letaief et al., 2004), Q fever was diagnosed in 9% of community-acquired pneumonia cases in Cameroon, demonstrating C. burnetii as the second most common etiologic agent of pneumonia, after Streptococcus pneumoniae and of equal prevalence as Mycoplasma pneumonia (Koulla-Shiro et al., 1997). While the effects of acute infection have
been established in several countries, the impact of chronic Q fever in Africa remains largely unexplored. However, in the North African country of Algeria, *C. burnetii* was identified as the cause of 3% (2/77) of infective endocarditis cases analysed (Benslimani et al., 2005).

3.2 Prevalence in Livestock

*Coxiella burnetii* is endemic in cattle, sheep, goats, buffaloes and camels across the African continent, though there are significant regional differences, even within countries. In a recent serological survey of 2,699 animals across Egypt, significant inter-species and regional variation was observed (Klemmer et al., 2018). Significantly, camels exhibited the highest rates of seropositivity (40.7%), followed by cattle (19.3%), buffalo (11.2%), sheep (8.9%) and goats (6.8%). Whereas the highest rates of seropositive animals were observed in the Eastern desert (27%), compared to the Nile Delta (16.4%) or Western Desert (17%). Significantly, pasture based production systems also had lower levels of seropositive animals (9.9%) compared with either Nomadic (19.4%) or stationary husbandry. Similarly, nomadic pastoralism was associated with a higher prevalence of *C. burnetii* seropositivity in small ruminants in Baringo County, Kenya (Muema et al., 2017). Camels appear to consistently exhibit high rates of seroprevalence. In Algeria, *C. burnetii* seroprevalence was determined as 71.2% in camels, with age, increased herd size and tick infestation identified as risk factors (Benaissa et al., 2017). Again, despite a lower overall seroprevalence of 18.6%, camel age was determined to be a significant risk factor for *C. burnetii* infection in Laikipia County in Kenya. A further study in Chad also demonstrated 80% seroprevalence in camels, compared to only 4% in cattle, 13% in goats and 11% in sheep (Schelling et al., 2003).

Serology provides evidence of the exposure of livestock to *C. burnetii* but can only provide limited data on the risk of clinical disease. There are however, few published African
studies that have directly investigated *C. burnetii* in ruminant abortion. In Niger, 32% of goats with prior history of abortion were found to be seropositive for *C. burnetii* compared with 29% of non-randomly selected goats without abortion (Haumesser and Poutrel, 1973). Likewise, *C. burnetii* positivity was a significant risk factor for cattle abortion in Northern Togo (Dean et al., 2013). In South Africa, *C. burnetii* was observed in aborted lamb foetuses by microscopy (Schutte et al., 1976). *C. burnetii* DNA was identified in the placenta and vaginal swab sample from one aborted goat sample in a study of 109 abortions from Egyptian dairy goats, sheep and cattle (Abdel-Moein and Hamza, 2017). In Tunisia, *C. burnetii* DNA was found in the birth products or vaginal secretions of 19% of small ruminants with a history of abortion (Berri et al., 2009).

### 3.3 Livestock and human cross infection

A number of studies have associated livestock production as a significant risk factor for the acquisition of Q fever by humans. Direct evidence was provided in a recent study of small ruminants and humans in Gambia, which identified that the presence of a *C. burnetii* positive animal in a compound was a significant risk factor in human infection (Bok et al., 2017). Exposure to cattle, goats, animal slaughter or the consumption of raw milk products were identified risk factors for *C. burnetii* seropositivity in febrile hospital patients in Northern Kenya (Njeru et al., 2016). In Northern Togo *C. burnetii* seropositivity was found to be higher in Fulani pastoralists (45%) than in non-Fulani (27%) (Dean et al., 2013), and in Chad, working as a Camel breeder was significantly associated with a positive *C. burnetii* antibody titre (Schelling et al., 2003). In a multi-national study across Africa, higher rates of seropositivity were observed in Mali, Burkina Faso, Nigeria and the Central African Republic, which were the countries under study, exhibited highest densities of ruminants (>100/humans).
A study of Egyptians in close contact with animals also reported a high overall seroprevalence (16%) with greater seropositivity among rural (22%) vs. urban (4%) residents (Nahed and Khaled, 2012). Similarly, being a rural inhabitant was a significant risk factor for C. burnetii seropositivity in an agro pastoral region of Algeria (Lacheheb and Raoult, 2009).

4. The importance of Genotype in understanding the epidemiology of infection Q fever

Bacterial genotyping is a key tool in epidemiological investigations, allowing the discrimination of isolates from different sources and thus identify the potential source of infection. Genotyping studies have revealed genetic variability in C. burnetii isolates which may exhibit different degrees of pathogenicity or confer host specificity. Genotyping of human and livestock isolates proved effective in identifying the source of human clinical infections during the Netherlands’ outbreak (Tilburg et al., 2012a; Tilburg et al., 2012b), which allowed the development of strategies to control the transmission of infection to the human population.

4.1 Genotyping in Europe

Multi locus variable-number tandem repeat (VNTR) analysis (MLVA) has become an established typing technique for a number of bacterial species. Up to 17 different genomic target-regions can be used to discriminate between C. burnetii strains, (Arricau-Bouvery et al., 2006; Svraka et al., 2006). MLVA was used to identify a dominant C. burnetii genotype circulating within the goat and sheep population during the Netherlands’ outbreak, initially using a panel of 3-loci, before a 10-loci MLVA panel was developed (Tilburg et al., 2012a). While a study in human clinical samples used a different set of markers (Tilburg et al., 2012b), alleles in the four overlapping markers were identical, implicating goats and sheep as the possible source of the outbreak. While MLVA analysis initially defined goats as the source of
human infection during the Netherlands’ outbreak, it was subsequently confirmed by Multis pecer sequence typing (MST). The MST method is based upon the analysis of the intergenic regions of genomes. These non-coding regions are not subject to the same selection pressures as the coding regions and are therefore considered to be stable elements of the genome.

An MST typing methodology based upon 10 highly variable spacers was first developed in 2005 (Glazunova et al., 2005) and used to separate 173 isolates into 30 discrete genotypes. A modification of the MST method, real-time PCR protocols to analyse of single nucleotide polymorphisms (SNPs) within the MST loci has also been developed, and used extensively in the USA (Hornstra et al., 2011). MST has shown itself to be a useful tool in both the epidemic situation, but also due to its the widespread use the techniques has allowed direct genotypic comparisons of C. burnetii isolates to be made across different host reservoirs throughout the world. In the Netherlands’ outbreak, MST33 was identified in both goats and human clinical cases of infection, demonstrating that goats were the probable source of the epidemic (Tilburg et al., 2012a). Further phylogenetic analysis suggested that MST33 genotype may have originated from Germany and entered the Netherlands via France. Conversely, in cattle where C. burnetii is endemic, the dominant genotype identified in the Netherlands was MST20. The genotype has been identified extensively in cattle populations, particularly in the USA where the ST20 is the dominant genotype and has been identified in 95.9% of genotyped bulk milk samples, and is not thought to pose a risk to human health (Bauer et al., 2015). While apparently being a cattle adapted genotype (Olivas et al., 2016), and not apparently the source of human disease during the Netherlands’ outbreak or in the USA, MST 20 (MLVA I and J) has also been identified in a range of clinical conditions in both humans and animals. These include the presence in human heart valves from France, sheep and goat abortions in the Netherlands (Tilburg et al., 2012a) and UK (Reichel et al., 2012), and cattle abortions in
Hungary (Sulyok et al., 2014b). This apparent discrepancy in pathogenicity and host range between organisms of the same genotype in different geographical locations suggests that despite our current levels of understanding of *C. burnetii* epidemiology, further understanding of local circulating genotypes and/or greater discriminatory power of genotyping analysis is still required to understand the disease causing potential of the organism in different host species.

The complex nature of circulating *C. burnetii* genotypes within different host species has been examined using a different SNP genotyping protocol, which was developed by a Dutch group during the Netherlands’ outbreak (Huijsmans et al., 2011). A total of 10 SNPs were analysed in a total of 14 human and 26 livestock derived samples, using a real-time PCR protocol. This analysis identified 5 distinct genotypes circulating in human and animal populations. The protocol has been used in a number of livestock studies in Belgium and the USA (Boarbi et al., 2014; Mori et al., 2013; Pearson et al., 2014), the results suggesting a greater degree of variability in circulating *C. burnetii* genotypes in goat populations, but much less variability in the genotypes found in cattle. However the significance of this remains to be elucidated.

### 4.2 Coxiella burnetii genotypes in Africa

An investigation of the available literature on current *C. burnetii* genotyping techniques (SNP, MST, VNTR, MLVA), via PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Web of Science (https://wok.mimas.ac.uk/) identified relatively few genotyping studies which have been conducted in Africa (summarised in Figure 1).

Up to 10 distinct MST genotypes have been identified from various hosts (although most are from ticks) and countries. Genotypes MST 2, 6, 16 and 19 have been detected so far in humans
(Hornstra et al., 2011; Mediannikov et al., 2010; Sulyok et al., 2014b). Other hosts include cattle (Rahal et al., 2018), goats (Walter et al., 2014), dogs, rodents (Chitanga et al., 2018) and louse (Louni et al., 2018a; Louni et al., 2018b). While some genotypes (2, 30, and 52) are unique to Africa (Glazunova et al., 2005; Sulyok et al., 2014b), others including MST16 (Sulyok et al., 2014a) and MST20 (Hornstra et al., 2011; Kumsa et al., 2015; Rahal et al., 2018) have been shown to be related to strains from other non-African countries. In addition to the MST data MLVA-typing data is available for two strains from Africa (Morocco and Namibia) showing a distinct pattern with unique regional genotypes (Arricau-Bouvery et al., 2006; Walter et al., 2014).
Figure 1: Various *C. burnetii* genotypes identified in Africa. The different colors indicates different genotypes and the shape of the ribbon is indicative of the host; circle (tick), star (human), square (louse), triangle (dogs/rodents). The Namibian isolate is from a goat.

5. Future directions

There is still a relative paucity of knowledge about *C. burnetii* prevalence and the clinical importance of Q fever in both humans and animals across Africa. The majority of studies to date across the African subcontinent have relied solely on serology. While this data is informative in terms of understanding the exposure of populations to the organism, it is of limited use on its own in terms of epidemiological studies, and source tracking information. Much of our current knowledge on Q fever epidemiology is based upon the experience of the Netherlands’ outbreak. Here, genotyping proved significant and effective in identifying goats as the definitive source of human infection. This data has been subsequently used to model risk factors and transmission. However, it would be naïve for us to assume that such models of risk, based on Northern European farming practices and climate can be extrapolated across the African continent or even between individual African countries. To date there has been limited genotyping of *C. burnetii* samples across Africa, and studies utilizing genotyping have been skewed towards MST analysis of individual human infections and tick populations (see Figure 1). While livestock infections are largely underrepresented in molecular analysis, the presence of MST20 in Algerian cattle abortions is an important observation (Rahal et al., 2018). However, on its own this is an important observation, but as previously highlighted will only be of limited value unless put into a wider regional context in human and animal health. Given our knowledge of the transmission of *C. burnetii* and differences in the apparent pathogenicity of different genotypes in human and animal populations, the long-term focus must be on
integrating serological and molecular genotypic data. Only then will we be able to differentiate between the transmission of *C. burnetii* and the risks of Q fever.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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