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Comprehensive literature review of the sources of infection and transmission routes of *Coxiella burnetii*, with particular regard to the criteria of "evidence-based medicine"

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ABSTRACT

The present review aims to compile the currently available literature since 1936 according the sources of infection of the Q fever pathogen (*Coxiella (C.) burnetii*) as well as the transmission from animal to man and also from human to human. In terms of quality and validity, the existing publications were reviewed systematically. For this purpose, firstly a structured literature search was carried out using various databases and search engines supplemented by a manual literature search. For critical appraisal, 1444 relevant publications were identified for the moment and evaluated. A total of 73 publications describing a transmission of *C. burnetii* from animals to man or a human-to-human transmission were discovered. The identified publications are 29 case series, two case reports, 21 cohort studies and 21 case-control studies. With regard to the sources of infection, 25 publications describing the transmission of *C. burnetii* from sheep to humans could be identified.

1. Introduction

Q-fever, a human disease caused by *Coxiella (C.) burnetii,* was known as a classic zoonotic disease. The pathogen has a broad host range, but is predominantly detected in sheep, goats, cats and cattle in often asymptomatic infections [1,2]. If clinical disease symptoms occur, fertility disorders and / or abortions are mainly found [3–5]. The main transmission route of *C. burnetii* to humans is aerogenic [6]. Incorporation of contaminated dust or aerosols from an animal-contaminated environment e.g. placental membranes, or birth fluids/vaginal discharges of aborted ewes lead to human infections. The exposed person may develop Q-fever clinical symptoms or remain asymptomatic. The symptoms start as flu like syndrome associated with pneumonia and hepatitis in acute courses. In some cases neurological manifestations may occur. However, in chronic forms endocarditis is usually the major disease symptom, which may be accompanied with hepatic cirrhosis and interstitial pulmonary fibrosis [7].

The disease represents a great threat to public health as the *C. burnetii* is an extremely resistant pathogen against environmental influences. It resists drying, heat, and common disinfectants. It can survive as spore stage for up to 10 months on the wool of the sheep and for up to 40 months in milk powder at room temperature [7]. In 2007, an outbreak of Q-fever occurred among humans in Noord Brabant, Holland [8]. Between 2007 and 2012 about 4162 infections and 25 deaths were reported [9,10]. In Germany, also many Q-fever outbreaks in human were recorded. They occur in Germany with an incidence of 200 to 500 cases annually [11]. Some cases received special attention in public health. In 1997 for example, near Stuttgart, following the abortion of 71 female deer, 13 persons showed signs of Q-fever. In 1998, in Freiburg, 101 cases were reported. The source of infection was a close lying sheep grazing area located near a settlement. The largest Q-fever outbreak in Germany occurred in 2003, in North Rhine Westphalia with 277 patients, who visited a farmer's market and an exhibition of a lambing sheep [12]. As a zoonotic occupational disease, Q-fever affects mainly farmers, foresters, veterinarians or livestock holders [13]. The prevalence of *C. burnetii- antibodies* among humans in close contact with animals varies in different countries. The ratio ranged from 0.4 to 2.1% in Netherlands, from 6.4 to 8.7% in Poland and from 16.3 to 25.7% in Egypt [14,15]. The aim of the present study is to evaluate the significance of these identified studies with emphasis on the description of all previously known infection pathways for *C. burnetii* described in the scientific literature.

One possibility of qualitative evaluation and classification of existing publications concerning the transmission pathways of *C. burnetii*

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are criteria of the evidence-based medicine. "Evidence-based medicine" has been the subject of scientific discussion in human medicine since the early 1990s, but also in veterinary medicine the claim of conscientious, explicit, and rational use of the current best external scientific evidence as the basis for medical care decisions for individual patients was increasingly articulated [16].

In the present study, the structured search for available scientific publications on the subject of "Transmission of *Coxiella burnetii*" was followed by a thorough evaluation of identified scientific publications in the form of a systematic review.

2. Material and methods

After formulating an initial question, a systematic search was carried out to identify relevant publications from the years since 1936 until 2011. This search was carried out via free text search and so-called Thesauri (MeSH: Medical Subject Headings) in the databases "Medline", "Web of Knowledge / Web of Science" and "Veterinary Science CAB Abstracts". Existing literature was additionally reviewed by means of a "hand search" on the library and on the basis of the literature appendices. The literature search in the databases was carried out in 2009 from May to October; hand search extended to the end of December 2011. Only German- and English-language publications were considered. The systematic search was carried out with the help of synonyms and terms for transmission or transmission paths and connections with the terms of the study design.

Inclusion and exclusion criteria (presence of one prevalence study on only one species / human, secondary literature, thematically misleading publications) were defined and applied. The Critical Appraisal was carried out according to the rules of evidence-based medicine in such a way that the publications / studies identified by the search were first integrated into study designs and an evidence hierarchy. The evidence hierarchy was modeled on the evidence pyramid developed by Cardwell [17], based on (low evidence) case reports and series, with randomized controlled trials (high evidence, less confounding in the study) at the top.

In order to assess the quality of the study, a valuation schedule was developed as a decision support, which weighted individual evaluation criteria in the identified studies. The evaluation criteria included the design of the introduction, the methodology used and the exact indication of the subjects described, as well as the experimental procedure and the study design of the publication. To further explain the method described above, here we provide some examples from literature clarifying the used approach in the present study. Applying the inclusion and exclusive criteria, the four studies below [18–21] could be selected after searching in the above mentioned databases. All of these were identified as cohort studies, which according to the classification of Cardwell [17] are altogether to be located at the mean level of evidence. The subsequent weighting of individual evaluation criteria by means of an evaluation plan as a decision attempt showed that in the cohort studies of Benenson and Tigertt [18], Fishbein and Raoult [19], Kaufmann et al. [20] and Komiya et al. [21] a clear expressiveness is given. That means in these four studies [18–21], both a temporal and a geographical context can be seen. An antibody and pathogen (genome) / antigen detection by guinea pig inoculation test or PCR was also performed in these exemplary studies. The internal validity of the study by Benenson and Tigertt [18] can only be assessed to a limited extent since it does not provide information on methodology and implementation the tests. On the other hand, dealing with the study by Komiya et al. [21] the validity is reduced by a too small study population (only five subjects). With the exception of one, all identified cohort studies can provide a connection between source of infection and Q fever disease in humans here for example via the detection of antibodies (sero-conversion). An aerogenic transmission path is assumed by the authors.

It was judged whether a statistical method was performed and how meaningful it appeared; the composition and comprehensibility of the publication were also assessed. Concluding criteria were used as evaluation criteria as well as the practical benefits of the study. Assessment criteria that could not be evaluated for the study were not included in the scoring scheme for this study. The scores were distributed according to quality, the statement of the studies and the avoidance of bias (systematic errors). Different evaluation criteria were weighted with different scores. Criteria relevant to the validity of a study were rated -1, +1, -2, +2, -3, and +3, respectively, according to their relevance. The sum of the scores correlates with the quality of the study.

Finally, the meaningfulness of the identified study was assessed, i.e. how likely a transmission of *C. burnetii* may have taken place. For this statement at least the proof of the serological response to the pathogen and a temporal and geographical relationship between infection and source of infection were decisive.

A peer review procedure was performed on 21 randomly selected publications. Additional reviewers assessed these publications according the evaluation scheme.

The possible bias was in addition to Reader Bias (subjective assessment [22], Personal Bias, Language Bias and Retrieval Bias (retrieval of literature).

3. Results

A total of 1444 citations (studies / publications) could be determined. However, most of them are double entries and publications that could not be assigned to the formulated initial question. Others excluded publications are secondary literature or non-thematically relevant publications. There were also many studies that deal with the prevalence of *C. burnetti* in individual species or in humans. Only one publication was not accessible.

Concerning the "hand search" based on the literature annexes 19 relevant publications could be additionally identified.

Finally, 73 studies remained, which could be checked for quality by means of the evaluation scheme established in the present work.

The search method with best results was the search by the utility "MeSH" in the database "Medline" (Fig. 1).

Thirty-one of them are case reports (2) or series (29), 21 cohort studies and 21 case-control studies.

The highest publication rate per year with a total of 4 publications could be observed in 1988. Most of the publications included in the present study dated from the last 15 years.

Regarding the journals, in which the publications were published, most appeared in "The Lancet" (7). In total, the 73 publications were published in all together 44 journals.

Sixty publications are written in the English language, 13 were in German, but most of them (n = 19) are from the Federal Republic of Germany.

In the identified studies, there were strongly differing case numbers and examination methods. Only in one study authors reported the sensitivity and specificity of the methodology they used.

Sheep were identified or suspected as the main source of infection (n = 25) in the investigated and considered publications. The

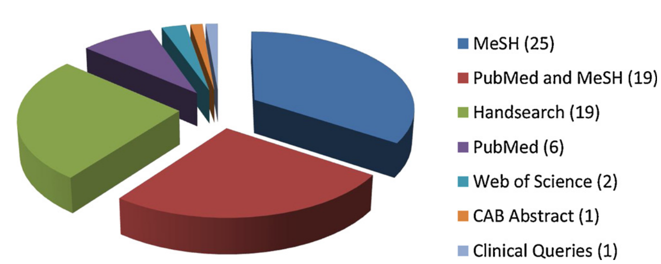

Fig. 1. Distribution of identified and evaluated studies on search in different databases.

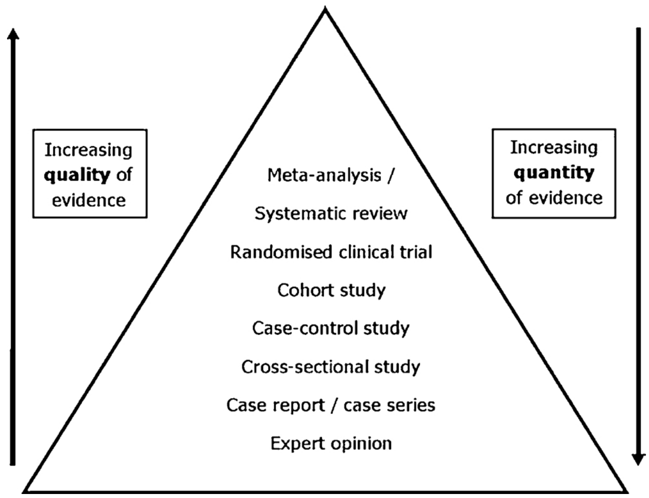

Fig. 2. Evidence pyramid according Cardwell [17].

distribution of the identified species in the 73 evaluated publications is summarized in the following diagram (Figs. 1–3).

In the considered literature, the source of infection was discussed in 25 publications dealing with a transmission of *C. burnetii* from sheep to man (4 case series, 1 case report, 8 case-control-studies and 12 cohort studies), in another 13 studies dealt with cattle as a source of infection (5 case series, 1 case report, 4 case control-studies and 3 cohort studies). The role of goats in disease epidemiology was discussed in 8 publications (2 case series, 4 case-control-series and 2 cohort studies). Pets like dogs and cats were also reported as a source of infection in few publications (n = 8, 5 case series, 2 case-control-studies and 1 cohort study). Other animal species like pigeons (n = 1), rodents (n = 1), deer (n = 1), and wild rabbits (n = 1) were also objects of description in five publications (2 case series, 2 case-control-studies and 1 cohort study). To lesser extent, swallows, Guinea pigs, and Rhesus monkeys were also reported as a source of infections. Finally, 13 studies and reports described man-to-man transmission and accidental laboratory infection was also reported in about 7% of the cases (4 case series and 2 cohort studies).

As an occupational zoonotic disease, Q-fever affects mainly people who work in close contact with animals. In USA, the seroprevalence of the disease-causing agent ranged from 3.1% among normal population to 22% among veterinarians compared to 41.6% (in goats), 16.5% (sheep) and 5% in cattle according to Barberio [23]. Analysis of the collected data referred to aborted ewes as the main threat for public health. This is attributed to the shedding nature of the pathogen from infected sheep which occurs mainly through the feces and vaginal secretions of aborted ewes. In goat, *C. burnetii* was also found to be excreted mainly in vaginal mucus, followed by feces and to less extent in milk of both aborted and normally delivered ewes. Even seronegative herds of cattle, sheep and goats were also found to shed the pathogen [5]. Cows, in opposite to sheep and goats, excrete the pathogen mostly in the milk [24]. As a result, cow milk is usually more loaded with *C. burnetii* than that of sheep and goat regardless of the nature of the milk as pasteurized, unpasteurized or thermized milk [25,26].

The literature reviewed confirmed the differential role of aerosol, oral contact, animal contact and intradermal injection (via ectoparasites) in disease transmission. The major sources of human infection are summarized in Fig. 4. Considered publications determined aerosol exposure as the most common route of the infection. Therefore, people working in close contact with animals and their products especially at parturition or slaughtering time are at greater risk [27–29]. Aerosol infection in other population groups, who have less contact with animals, may be attributed to the long term persistence of *C. burnetii* in the soil, due to its heat resistance in the environment, and to its ability to be transmitted by the wind for more than 30 km which makes the aerosol route of infection ideal in infecting man and animals even far away from the source of infection [30].

The role of oral transmission (especially via drinking raw milk) in the involved studies is still strongly controversial [5,31,32]. Analysis of the involved studies in the present work showed a debate about possible role of milk in disease transmission. While some studies showed the limited epidemiological role of raw milk in disease transmission [33–44], others described the role of milk in disease induction in human consumers [45–51]. As a compromise, many researchers

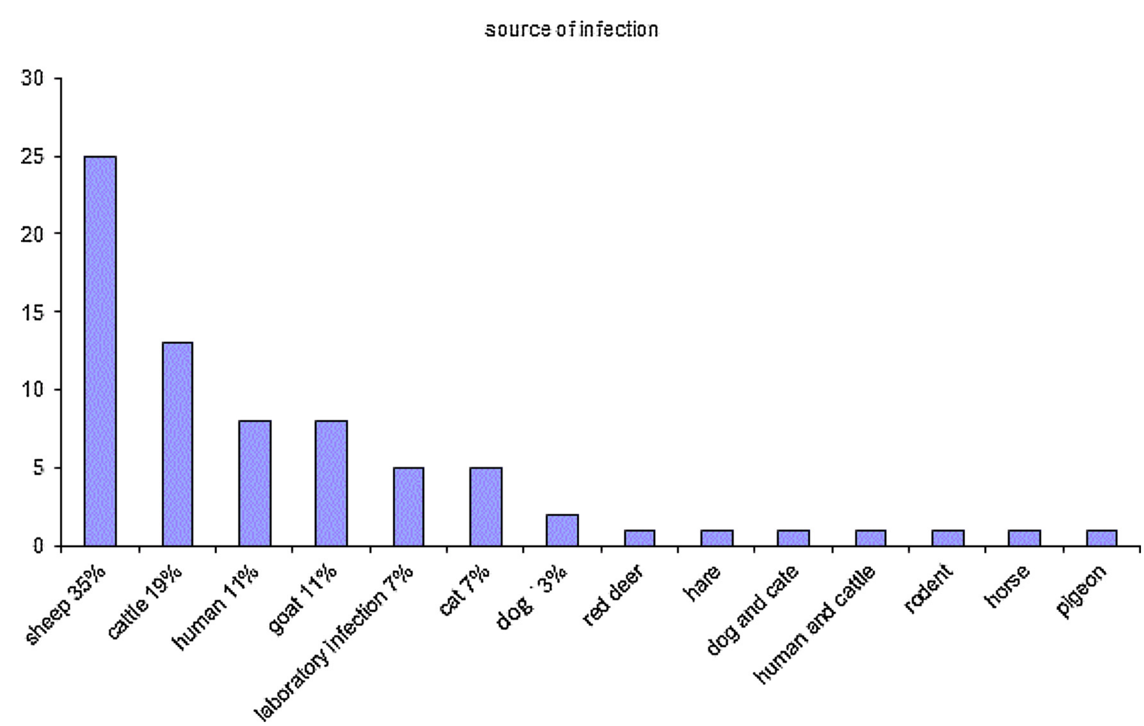

Fig. 3. Distribution of animal species in the evaluated publications (n = 73).

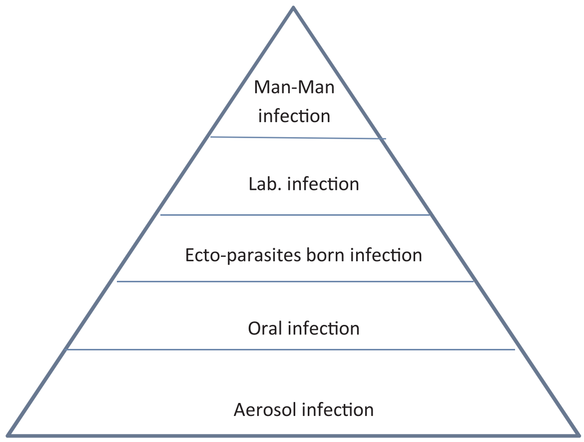

Fig. 4. Major sources of human infections with Q fever.
The main sources are shown in the graphic, however, there could be some differences according to the situation of every country according to the prevalence of the pathogen in animals, hygienic measures taken to control ectoparasites, and the safety measures undertaken in the laboratories. N.B. intradermal inoculation of the pathogen by insect bites results in 100% seroconversion, compared with 27% and 20% of oral and aerosol exposure persons, respectively [59].

attributed the high seroprevalence of raw milk consumers to their lifestyle in close contact with farm animals which makes them at higher risk for aerosol infections rather than due to the consumption of contaminated milk [48,52,53]. This opinion was strongly supported by data delivered from the experimental infection of 34 volunteers consuming contaminated raw milk without developing any seroconversion or clinical signs of Q fever [54].

Beside inhalation and ingestion, ectoparasites were also reported to play an epidemiological role in disease spread. Most related publications focused on the role of different species of ticks in disease transmission where more than 40 tick species were found to be naturally infected with *C. burnetii* [55,56]. In Germany, the ticks play a major epidemiological role in disease maintenance in wild life [12]. In Italy, *C. burnetii* could be detected from 5% to 21% of ticks collected from a public park in Rome according to tick species [57]. Similarly, in Cyprus, between 25.2% up to 48% of 1315 ticks from 10 different tick species isolated from different wildlife animals and birds were positive for *C. burnetii* [56]. The ticks can infect their victims either through intradermal inoculation of the pathogen or through shedding contaminated feces on their broken skin [58]. Humans may be get infected through the inhalation of contaminated tick feces especially of sheep ticks (*Dermacentor marginatus*) harboring *C. burnetii* [12].

Following infection of ticks with *C. burnetii*, the pathogen can persist in the ticks for up to 3 years and even up to 10 years in certain tick species. Certain species of ticks can even transmit the pathogen transstadially and transovarially [59–62]. The overall results of investigated research papers agree with the data delivered by an old study which was carried out in Portugal in 1950 and still has a high scientific impact for the determination of the mode of infections with *C. burnetii* in humans. In this study, the experimental infection of human volunteers (10 intranasal, 11 orally, 29 intra-dermally inoculation) resulted in 100% seroconversion rate in intradermal inoculation, 27% following oral infection and 20% in aerosol challenged volunteers [63].

Human-to-human transmission of *C. burnetii* rarely happens [27,64]. In the present work, 13 studies and reports describing human-to-human transmission were analyzed. The various human-to-human transmission pathways involved sexual transmission of infected males to their females, pathogen-loaded blood transfusions and bone marrow transplants, infected breast milk, Infections following autopsies, familial cases, inhalation of vaginally-secreting infectious particles, nosocomial infections during delivery and nosocomial infection of the respiratory tract [26,64–66].

Laboratory infections were reported in about 7% of the cases involved in the present work. Up to 1976, the number of Laboratory infected cases with *C. burnetii* was the second highest number among all laboratory infections. Outbreaks with more than 15 affected persons in several institutions were reported and were responsible for 278 cases and 1 death. This is attributed to the need of using embryonated eggs or tissue culture assays for the cultivation of *C. burnetii* [67–72].

Using the evaluation scheme the highest quality study was that of [51], in which goats were considered a source of infection, but no comparison was made of the genome sequences of *C. burnetii*. A comparison was made only in the study of [73], in which cat and dog were identified as a source of infection. Homologies could be found in the COM-1 region of the isolates of 99.9%.

4. Discussion

Due to the topicality of the Q fever epidemic in the Netherlands from 2007 to 2012 and the relevance of the data collected so far, a literature review was carried out on the topic "Transmission of *C. burnetii to humans*". This collection was written in the style of a systematic review. The chosen systematic search by linking synonyms in selected databases showed that searching through Pubmed is effective, but a "hand search" helps to increase the sensitivity of the study. The search engine "Pubmed" was chosen as it has the highest evidence in the field of medicine and veterinary medicine according to Sackett et al [16]. However, Korwitz [74] believes that the search alone, even with a suitable combination of search terms, finds only half of all relevant publications in the database (Table 1).

Moher [75] mentioned that finding libraries is an important additional method. This is the only way to find as many relevant publications as possible on the chosen question. Obtaining all the relevant literature, however, is a time-consuming and costly task.

The fact that most of the studies are found in the area of a low level of evidence (case reports / series, base of the pyramid) supports the statement by Holmes and Cockcroft [76] that in veterinary medicine mainly case reports and / or series can be observed. Case reports and / or series are important sources of information, but not generally valid [77]. For ethical reasons, humans cannot be experimentally exposed to *C. burnetii*, so no randomized controlled study (highest level of evidence hierarchy, top of the evidence pyramid) can be found in the selection of this work.

In order to assess the quality of a study, all relevant points should be considered [78]. The quantification of evaluation criteria is controversial [79–82]. In the present work it was also found that a classification according to evaluation points as well as the handling of the determined total score turns out to be problematic. The evaluation scheme can only assess whether the study was planned in a structured manner and the facts of the study were presented transparently [83]. The particular difficulty of the overall evaluation resulted from the sometimes unavoidable, subjective consideration of the evaluation points. Nevertheless, it can be assumed that the sum of the evaluation points correlated with the transparency and the basic information of the

Table 1
Applied terms to search for "transference" and "excretion" in the different databases transmission paths.

transmission paths	transmission	excretion	routs of excretion
"way of transmission"	communication	excretion	"process of elimination"
"way of passing on" "route of infection" "mode of transmission" "source of infection" "way of communication"	contamination transfer spreading transmission	shedding exsudation	"route of elimination"

study. In addition, therefore, the validity of the study was also determined in relation to the initial question.

Above all as quality defects of the studies the respective study structure and the partly lack of detailed descriptions were identified. Thus, less well-described studies are associated with a poorly-planned study design because the presentation of the study design occurs through the publication [84,85].

With regard to the transmission routes, no summarized presentation of the risk factors could be presented. In addition, the results of the individual studies are too inhomogeneous and the transmission paths are not clearly represented. A sequence comparison of the pathogen genomes of the isolated field strains was carried out exclusively in one cohort study in which obviously dogs and cats were the source of *C. burnetii* infection.

Further investigations are necessary to shed light on the role of the infection host. Studies on the individual susceptibility of humans are long overdue. When conducting the study, the "Good Clinical Practice" should be adhered to, transparency should be ensured and meaningful planning should be carried out.

5. Conclusion

C. burnetii seems to represent an underestimated threat to public health worldwide. The animal contact especially sheep at time of parturition or slaughtering is the main source of infection. The inhalation of the pathogen contaminated particles represents the major route of infection even miles away from the infected animals. Man to man infection may occur, however, remains rare. Ingestion, even of raw milk, seems to play a minor role in disease epidemiology. Using the evaluation scheme developed the assessment of the investigated studies is very different. Only 14 out of the 73 publications to be rated could be awarded a clear statement. The evaluation of the 21 randomly selected studies by two reviewers also gave different ratings.

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Conflict of interest

The authors declare no competing interests.

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