APHIS Info Sheet

Veterinary Services
Centers for Epidemiology and Animal Health
Center for Animal Health Information and Analysis

October 18, 2010

Emerging Disease Notice

Q Fever: An Emerging Disease in the Netherlands

Summary
During the spring of 2007 there was a steady increase in the number of reported cases of Q fever in humans in the Netherlands, causing this disease to become a major public health concern. Q fever outbreaks and abortion waves on dairy goat farms were the primary source of infection of humans. One hypothesis to explain the increase in human cases is the intensive goat farming practices along with high population densities. Another hypothesis is that of mutation to a more virulent strain by the bacteria that causes Q fever. The outbreak differs from previous outbreaks in that human infections have occurred over consecutive years and some victims were not occupationally related to domestic ruminants. These changes, coupled with the unusually high number of human infections, suggest that Q fever may be regarded as an emerging disease. The purpose of this emerging disease notice is to provide the most recent facts about the epidemic of Q fever in the Netherlands and general background information about the disease.

Historical background of Q fever
The phrase "Q fever" was first used to describe a febrile illness in abattoir workers in Brisbane, Queensland, Australia in 1937. The letter Q was a reference to "query" because the causative agent had not been identified.[1] This terminology was proposed by Edward Derrick of the Queensland Health Department.[2] Derrick was assigned in 1935 to investigate the outbreak of febrile illnesses. He described the epidemiology of the disease and concluded that wild animals were the natural reservoir of Q fever, and that the disease could be transmitted by ticks.

Taxonomy
The etiological agent of Q fever was given the name *Rickettsia burnetii* originally; it was renamed *Coxiella burnetii* to honor the researchers who identified the pathogen as a new rickettsial species.[3] *C. burnetii*, a gram negative, obligate intracellular coccobacillus, is a highly virulent organism (i.e., only one bacterial organism is sufficient to cause infection in a human). It resides in the host's macrophages and monocytes, and exists in two variant forms, a large-cell and small-cell form. The large-cell variant is the vegetative intracellular form; the small-cell variant is the infectious form found extracellularly in body secretions. The small-cell form is also resistant to heat, desiccation, and some disinfectants. *C. burnetii* may remain viable in the environment for weeks to years.[4] It can survive in contaminated butter and milk as long as 3 months.[5] Recent investigation into the phylogeny of *C. burnetii* showed that it belongs to a subdivision of Proteobacteria with the genera *Legionella* and *Francisella* as its closest relatives, not the genus *Rickettsia*.[3,4]

Transmission
There are two major patterns of transmission of *C. burnetii*.[4] The first pattern of transmission is completely independent of wild animals, and it involves spread among domesticated ruminant species. Cattle, sheep, and goats are the primary reservoirs of *C. burnetii*. The bacteria do not usually cause overt disease in these animals; however sporadic, late-term abortions in ruminants have been linked to *C. burnetii*. The bacteria are shed intermittently in milk, urine, and feces of infected animals. The high number of bacteria in amniotic and placental fluids during birth is of great importance (10^9 bacteria per gram of placenta).[3,4,7]

The second pattern involves vector transmission from ticks to rabbits, rodents, and other wild animals.[6] Ixodes and Argasid ticks have been found to be naturally infected with *C. burnetii*. Nymphs and adult

ticks may transmit the bacteria in saliva during feeding, and female ticks may also pass the bacteria transovarially. Argasid ticks can also disseminate the bacteria through infectious coxal fluids. *C. burnetii* may survive in tick feces for as long as 6 years, which promotes spread to humans and animals. *C. burnetii* can remain in an enzootic cycle between domestic ruminants, wildlife, and their associated ticks; however transmission to humans via ticks is extremely rare.[5]

Humans become infected with *C. burnetii* primarily due to inhalation of infected particles.[3,5] Contaminated aerosols can arise from birth fluids which may then contaminate the fleece of newborn animals. Inhalation of aerosolized particles from contaminated animal excreta may also result in human infection, as can handling materials contaminated with tick feces.[5] Ingestion of contaminated, unpasteurized milk is an uncommon mode of transmission, and remains a controversial issue. Other modes of transmission such as tick bites and human-to-human exposure are very rare.[7]

Geographical distribution

Q fever is found in every country with the exception of New Zealand.[9] The disease has been endemic in large parts of Europe for several decades. Seroprevalence studies from 1970 to 2009 show that 10 to 30% of rural populations in different parts of Europe have antibodies against *C. burnetii*. The prevalence is higher in farmers of domesticated ruminant, and is highest in people who encounter afterbirth and aborted tissues. Other high-risk groups are veterinarians and laboratory personnel who work with animals.[8] Because many countries are still not required to report Q fever to health officials, scientists have not been able to reliably assess the global incidence. In addition to the mild signs and symptoms in ruminants and humans, Q fever may be under-reported.[7]

Bioterrorism agent

C. burnetii is a class B bioterrorism agent. Class B bioterrorism agents are moderately easy to disseminate, cause moderate morbidity and low mortality, and require enhanced disease surveillance by the CDC. Other qualities that contribute to its proposed use as a bioterrorism agent are its persistence in the environment and the small infectious dose. Q fever infections are rarely fatal, but the disease is incapacitating.[7,10]

Clinical disease in domesticated ruminants and humans

Domesticated ruminants usually develop a subclinical infection. *C. burnetii* has been implicated as a cause of infertility and sporadic late-gestation abortions due to necrotizing placentitis. Gross lesions are nonspecific, and differential diagnoses should include both infectious and noninfectious abortifacients.[4] Nearly 50% of all humans infected with Q fever show signs of clinical illness. About 30% to 50% of those who are clinically ill will develop pneumonia, and most people will develop hepatitis. Generally, most humans recover within several months without any therapy, and very few (1 to 2%) die from acute disease. Chronic Q fever is characterized by an infection that persists for more than 6 months. While chronic infections are uncommon, they are more serious. Endocarditis involving the aortic valve is a complication of chronic Q fever, but most people who develop chronic disease have pre-existing valvular abnormalities.[7] The percent case-fatality of chronic Q fever in humans is 30 to 65%.[5,7]

Reports indicate a risk of adverse pregnancy outcomes in women with Q fever, but the particular mechanism remains unclear. Transplacental transmission appears to be possible, but its association with adverse pregnancy outcomes is understood poorly. *C. burnetii* has been found in breast milk from infected humans, but transmission to the breastfed child has not been reported. One incident of transmission to obstetrical personnel has been reported.[8]

Because a single bacterium in one monocyte or macrophage is sufficient to cause infection, all blood products (including plasma) can become contaminated due to the degradation of monocytes and macrophages in the blood. The bacteria can even remain viable during the storage and preparation of blood or blood-derived products. *C. burnetii* can remain viable in cells, tissues, and organs destined for transplantation. However, it is not current practice to screen large groups of blood donors, and donors of organs, cells, or tissues are not routinely screened for *C. burnetii*.[8]

Q fever epidemic in the Netherlands, 2007

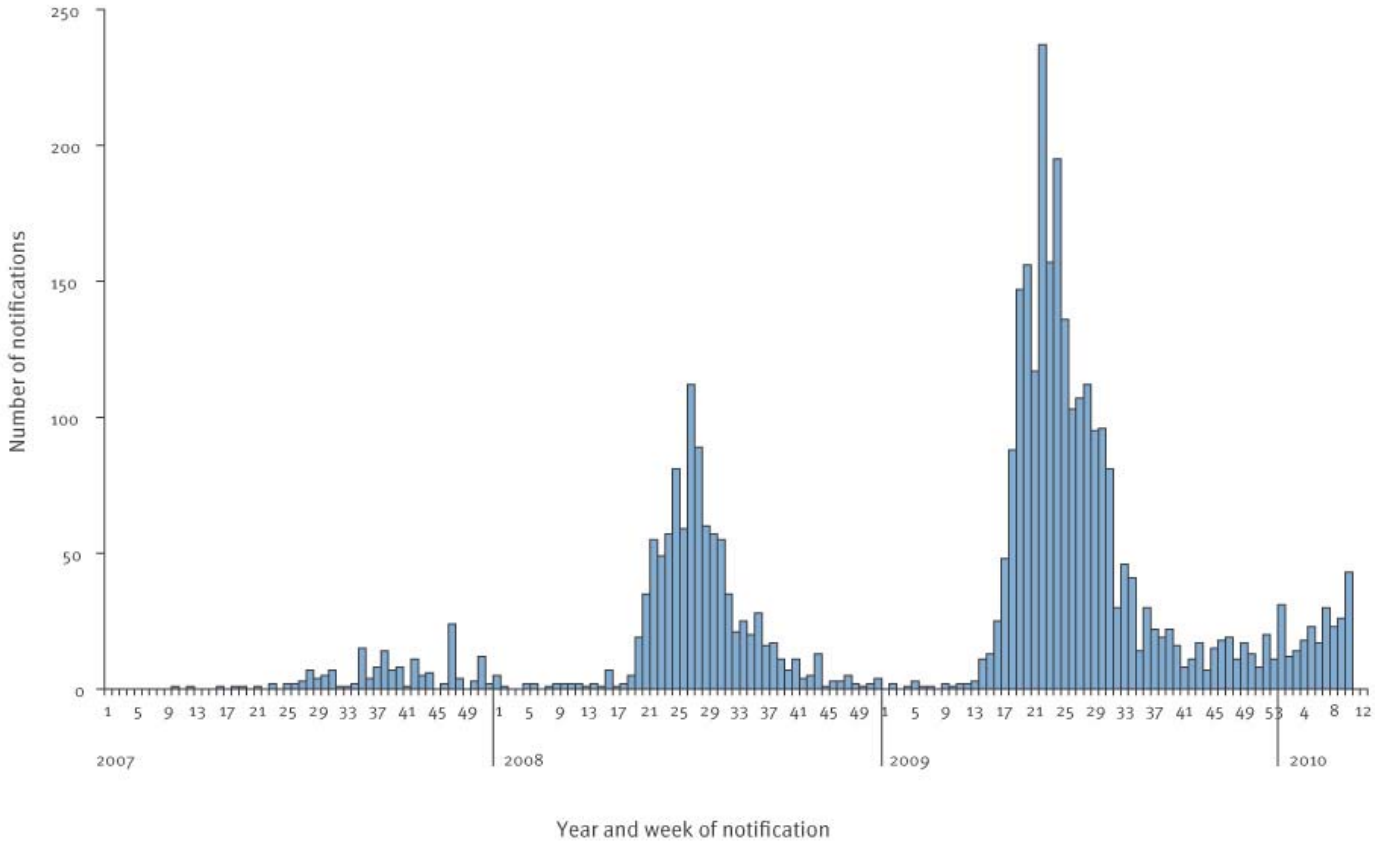
Incidence

Q fever became a reportable disease in humans in the Netherlands in 1978. During 1978 to 2006, the average number of reported cases was 17 per year.[11]

During 2007, 190 human cases were reported. That number increased to 1,000 cases during 2008 and 2,356 cases during 2009 (Figure 1).[12] Most cases occurred in the province of Noord-Brabant, which is located in the southern region of the Netherlands (Figure 2). During 2009 six deaths were reported among cases, with all fatalities having underlying medical conditions.[12] There were 247 reported cases as of March 18, 2010.[9]

FIGURE 1

Q fever notifications by year and week



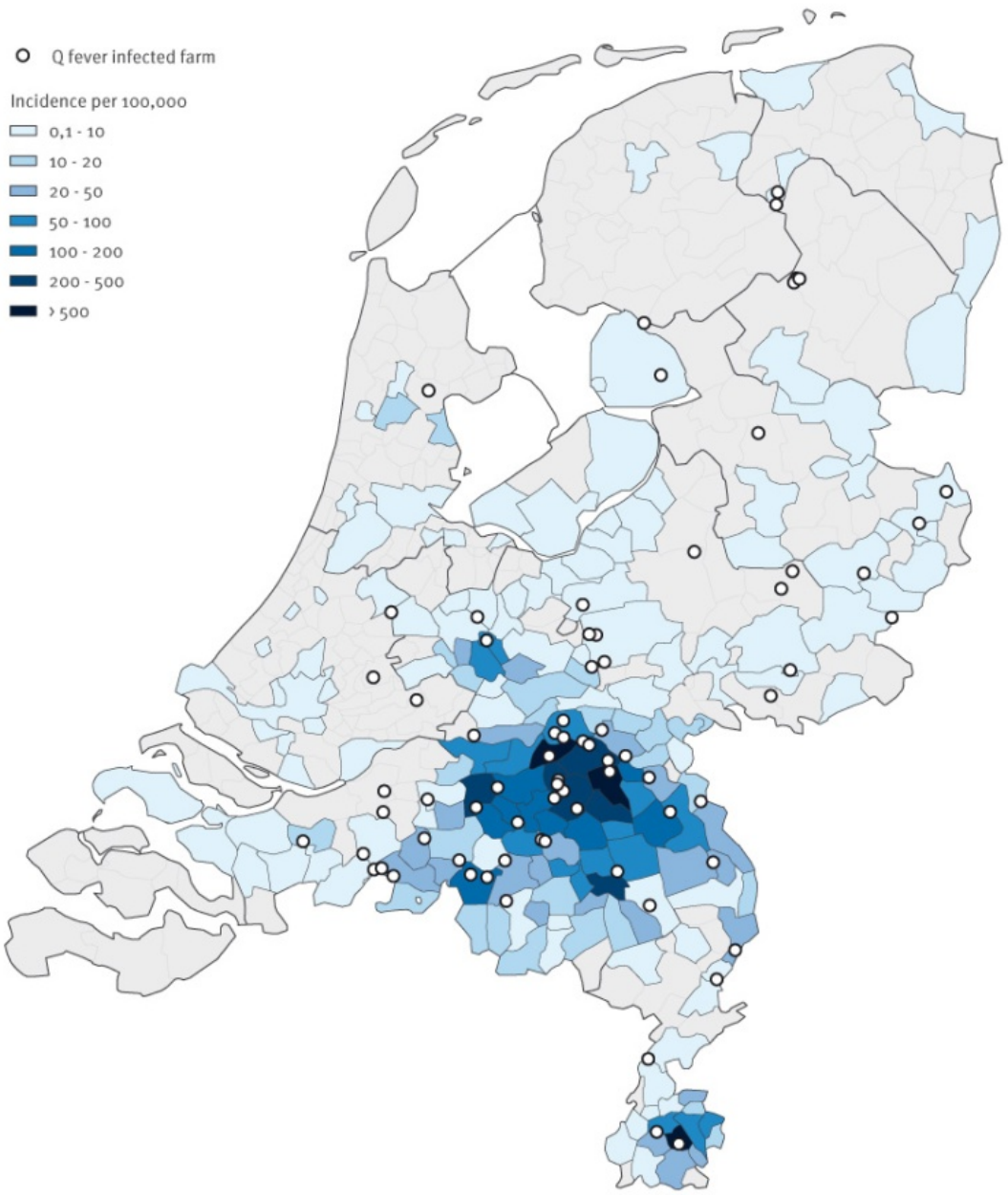
The epidemic curve (by week of onset of illness) is updated weekly and is publicly accessible at http://www.rivm.nl/cib/themas/Q-koorts/

The notification criteria for an acute infection were clinical presentation with fever, pneumonia, or hepatitis and laboratory confirmation, which included a fourfold increase in IgG antibodies against *C. burnetii* in paired sera, or the presence of IgM antibodies against a phase II antigen. During 2008 the median age of infected patients was 49 years and 61% were male; during 2009 the median age was 50 years and 64% were male. The predominant clinical presentation in human cases was pneumonia. Clinical follow-up of patients that were diagnosed with an acute infection in 2007 showed that Q fever was not always a mild disease of short duration; many patients continue to suffer from fatigue several months after initial symptoms.[12]

The epidemic consisted of at least 10 separate outbreaks with multiple sources. While most of the outbreaks were linked to goat farms that were experiencing abortions, other outbreaks had less obvious associations. Data collected in 2009 showed that 59% of the reported human cases lived within a 5-kilometer radius of an infected dairy goat or sheep farm. There is also evidence that direct contact with non-dairy sheep caused some human infections in 2009.[12] At least 28 laboratory-confirmed cases occurred in patients and staff of a psychiatric institution who had direct contact with newborn lambs on a farm located adjacent to the institution.[13] Another report noted as many as 46 human cases after they visited a sheep farm during lambing season in February and March.[12]

FIGURE 2

Incidence of human Q fever by municipality (n=2,357) and locations of Q fever infected dairy goat and dairy sheep farms, the Netherlands, 2009



Map compiled by Ben Bom, Expertise Centre for Methodology and Information Services, RIVM.

Vaccination

After November 2008 all owners of non-pregnant sheep and goats in high incidence areas were given the opportunity to vaccinate voluntarily. The goal was to decrease shedding of *C. burnetii* into the environment and in turn, decrease human exposure. In February 2009, a nationwide vaccination protocol was mandated by the Dutch government for professional dairy goat and dairy sheep farms in the provinces of Noord-Brabant, Gelderland, Utrecht, and Limburg.[15] Approximately 250,000 small ruminants were vaccinated during April to November 2009, including those on farms in the high-incidence areas, farms with a recent diagnosis of Q fever, and farms that offered recreational activities to the public.[12]

Evaluation of Bulk Milk

In October 2009, diagnostic screening of bulk milk became mandatory on farms with more than 50 dairy goats or dairy sheep. Bulk milk that was PCR-positive became an additional criterion for veterinary notification of Q fever. In December 2009, the frequency of bulk milk testing increased from

bimonthly to biweekly. The most recent data from bulk milk samples collected in February 2010 declared 74 dairy goat and 2 dairy sheep farms as infected. A list of positive farms became available publicly on the Web site of the Food Consumer Product Safety Authority.[12]

Culling Program

A culling campaign was proposed by the Ministry of Agriculture to begin at the end of 2009 and involved 55 infected farms with 64,000 goats. The goal was to remove all pregnant does and all bucks on these farms, sparing only the open does. The open does were permanently prohibited from breeding. No actions were taken to distinguish between infected and non-infected animals. Also, a general ban on breeding for all farms with 50 or more dairy goats or sheep was proposed for July 2010.[15]

Biosecurity

As of June 2008 infected farms were prohibited from receiving human visitors, and as of October 2009 the movement of animals from infected farms onto farms which supply milk was prohibited. This measure was expanded to state that all farms were restricted to introducing animals that had been vaccinated against *C. burnetii*. On the farms where animals had been culled due to a suspect infection, manure was prohibited from removal from the farm for 30 days after the culling. All farms were then required to store manure under cover for 90 days prior to removal from the premises. Finally, all farmers, farm workers, and veterinarians were required to notify authorities of any suspicious signs that indicated a possible Q fever infection in farm animals.[15] Q fever officially became a reportable disease of animals in 2008.[16]

Environmental Factors

Acute Q fever cases in Europe are reported more frequently during spring and early summer, which coincides with the outdoor kidding and lambing season. Consequently this also corresponds to heavy contamination of the environment with *C. burnetii*.[3] An association between transmission to humans and environmental factors (e.g., wind speed, dry weather, vegetation density) has been established. Likewise, the airborne spread of *C. burnetii* in the vicinity of an infected farm has been clearly established. However, the distance that the bacteria can spread and the duration of spreading is under investigation.[8] Initial experiments show that *C. burnetii* can be detected shortly after an outbreak at distances of 500 to 1,000 meters around an infected farm.[17]

Goat Industry in the Netherlands

The goat industry in the Netherlands is relatively small with fewer than 250,000 breeding does.[14] However, during the past decade the dairy goat population in the Netherlands, especially in Noord-Brabant, has increased nearly 10-fold.[17] Of the 50,000 registered small ruminant farms, there are approximately 360 professional dairy goat farms with 200 to 1,000 adult goats per farm.

Genetic Evaluation

The first comprehensive genotyping of *C. burnetii* was completed in 2006. Current research is evaluating whether one particularly virulent strain of the bacteria is causing human cases of the disease. Analyses of 12 strains of *C. burnetii* found on infected Dutch dairy farms revealed one strain (CbNL01) that seemed to be universally present in infected animals.[19]

Control

Short-term control methods such as culling pregnant animals, and imposing a ban on breeding and transport of animals are expected to reduce shedding into the environment.[14] Longer-term control methods include preventive vaccination, manure management, shearing management, segregated birthing areas, and improved farm hygiene. A ban on public visitation should be considered in areas where there is a risk to public health. Control methods to reduce the proximity between humans and small ruminants during the kidding and lambing period should play one of the most important roles in decreasing spillover from animal populations to humans. There is a need to strengthen awareness among goat farmers and veterinarians regarding disease transmission, zoonotic potential, and risk factors for human infection.[14]

Implications of the Epidemic

The European Food Safety Authority identified several shortcomings of the investigations of Q fever outbreaks[14]: (1) currently there are no EU rules regarding notification, monitoring or surveillance of *C. burnetii* infection in domestic ruminants; (2) in many European countries Q fever is not a reportable/notifiable disease in ruminants; (3) there are no rules regarding control options, intra-community trade, or importation of stock; (4) the

epidemiological investigations were executed using a variety of methods, and the published literature about associated risk factors for the disease was incomplete.

The epidemic in the Netherlands was remarkably divergent from previous epidemics in the EU. Infections occurred during consecutive years, and the disease was more widespread in humans following initial notification of an outbreak.[14] Infections also occurred following direct contact with non-dairy sheep, and in persons not involved in animal occupations.[12,14] The factors thought to contribute to the unique situation in the Netherlands are a more virulent bacterial strain of *C. burnetii* and expansion to high-intensity goat production in the densely populated country. At this time, no single factor has proven to be the primary reason for the surge in human infections.[12]

Incidence of Q fever in the United States

Prior to 1978 there was little national surveillance information available regarding human Q fever in the United States. From 1948 to 1977, each State reported numbers of cases that occurred, but no information on disease trends or epidemiology existed. The interest in *C. burnetii* as a possible agent of bioterrorism highlighted the need to accurately understand the disease burden of Q fever. Thus, in 1999 Q fever became a reportable disease in humans. Between 1978 and 1999, 436 cases of Q fever in humans were reported by State health departments in the United States, with a mean of 20 cases per year. That number increased to 51 cases per year from 2000 to 2004, when Q fever became a reportable disease. Annual incidence during that time period was 0.28 cases per million persons, and the incidence increased with age. Cases appeared to be seasonal, with 39% occurring mostly during spring and early summer, but cases were also reported year-round. Like cases in the Netherlands, most were male with a mean age of 50.5 years.[18]

The average annual incidence in the United States ranks much lower than other countries such as France and Australia where small ruminants make up an important aspect of the agricultural industry. However the epidemiologic features of human Q fever in the United States for the period 2000 through 2004 were similar to those reported in other countries.[18]

Conclusions

Persons at risk of contracting Q fever in the United States usually have been those with an occupational relationship to livestock. However, changes are occurring in the demographic characteristics of goat producers and consumers, and these changes may place these groups at higher risk of infection. An increase of hobby farmers older than 55 years is noteworthy, given that the mean age of reported cases of Q fever infections in the United States is approximately 50 years.[19] Likewise, the increase in female goat farmers raises the question of the possibility of an increase in adverse pregnancy outcomes. The increase in the number of goats at Federal inspection facilities may increase the risk to inspectors and some slaughterhouse personnel. Immigrant populations in the United States are increasing, and some of these immigrants perform private slaughter for religious reasons. Finally, with the increasing trend of raw milk consumption are individuals who may be at greater risk of infection. Although there are no documented human cases confirmed from consumption of raw milk, serological conversion has occurred among these consumers, raising the concern that an infective dose exists.

Other countries continue to learn from the Dutch outbreak of 2007–2009. Passive surveillance methods for monitoring Q fever in the Netherlands failed to prevent a significant increase in human cases. Strengthening systems to promote rapid identification and disease notification, and promoting early exchanges of information between veterinarians and public health officials will be vital to identify Q fever outbreaks promptly.

Credits and Inquiries

This publication is a revision of a paper that was written by Ms. Laura Kotinsley of the University of Florida's College of Veterinary Medicine, graduating class of 2011. The original paper was prepared during a summer internship at the Centers for Epidemiology and Animal Health to partially fulfill the requirements for the Master of Public Health degree. Patti R. Rosenfelder provided editorial support.

Inquiries: Dr. Reginald Johnson
USDA:APHIS:VS:CEAH
2150 Center Avenue
Bldg. B, MS 2W4
Fort Collins, CO 80526-8117
(970) 494-7001

Bibliography

1. Derrick E. "Q Fever, A New Fever Entity: Clinical Features, Diagnosis, and Laboratory Investigation". Medical Journal of Australia. 1937;11(2):281-299.
2. McDade, J. (1990). Historical Aspects of Q Fever. In T. Marrie (Ed.), *Q Fever, Volume I: The Disease* (p. 8). Boca Raton: CRC Press.
3. Maurin M. & Raoult D. "Q fever". Clinical Microbiology Reviews. 1999 Oct;12(4):518-553.
4. Merck Veterinary Manual. Fact sheet: Q Fever: Introduction. <http://www.merckvetmanual.com/mvm/index.jsp?cfile=htm/bc/52000.htm&word=Q%2cfever>. 2008; Accessed 07 June 2010.
5. Mullen, G. & Durden, L. (2002). *Medical and Veterinary Entomology*. San Diego: Elsevier Science.
6. University of Pittsburgh. Institutional Animal Care and Use Committee: Q Fever. <http://www.iacuc.pitt.edu/occhealth/qfever.htm>. Accessed 07 June 2010.
7. Centers for Disease Control and Prevention. Fact Sheet: Q Fever. <http://www.cdc.gov/ncidod/dvrd/qfever/index.htm>. 2009: Accessed 10 June 2010.
8. European Centre for Disease Prevention and Control. Technical Report: Risk Assessment on Q Fever. <http://www.ecdc.europa.eu/en/publications/Publications/1005_TER_Risk_Assessment_Qfever.pdf>. 2010: Accessed 15 June 2010.
9. Centers for Disease Control and Prevention. Travel Notice: Q Fever in the Netherlands. <http://wwwnc.cdc.gov/travel/content/in-the-news/q-fever-netherlands.aspx>. 2010; Accessed 10 June 2010.
10. Rascoe, B. & Bledsoe, G. (2005) *Bioterrorism and Food Safety*. Boca Raton: CRC Press.
11. Schimmer B., Dijkstra F., Vellema P., Shneeberger P., Hackert V., Schegget R., Wijkmans C., van Duynhoven Y. & van der Hoek W. "Sustained Intensive Transmission of Q Fever in the South of the Netherlands, 2009". Eurosurveillance. 2009 May;14(19):pii=19210.
12. Van der Hoek W., Dijkstra F., Schimmer B., Shneeberger P., Vellema P., Wijkmans C., Schegget R., Hackert V. & van Duynhoven Y. "Q Fever in the Netherlands: An Update on the Epidemiology and Control Measures". Eurosurveillance. 2010 Mar;15(12):pii=19520.
13. Koene R.P., Schimmer B., Rensen H., Biesheuvel M., De Bruin A., Lohuis A., Horrevorts A., Verduyn Lunel F., Delsing C. & Hautvast J. "A Q Fever Outbreak in a Psychiatric Care Institution in the Netherlands". Epidemiology and Infection. 2010 Feb;9:1-6.
14. EFSA Panel on Animal Health and Welfare. "Scientific Opinion on Q fever". European Food Safety Authority Journal. 2010 May;8(5):1595-1709.
15. Factsheet. Q fever in the Netherlands. Ministry of Agriculture, Nature and Food Quality. Directorate for Food, Animal Health and Animal Welfare and Consumer Policy. The Hague Netherlands. <http://www.dyr.is/assets/greinar/factsheet_Q-fever_LNV-VB_versie_1.0%5B1%5D.pdf>. Accessed 13 June 2010.
16. Delsing C. & Kullberg B. "Q Fever in the Netherlands: A Concise Overview and Implications of the Largest Ongoing Outbreak." The Netherlands Journal of Medicine. 2008 Oct;66(9):365-367.
17. Shimshony, A. (2010, January 1). Q fever: The Dutch Experience. *Infectious Disease News*. <http://www.infectiousdiseasenews.com/article/60015.aspx>. Accessed 21 June 2010.
18. McQuiston J., Holman R., McCall C., Childs J., Swerdlow D. & Thompson H. "National Surveillance and the Epidemiology of Human Q fever in the United States, 1978-2004". The American Journal of Tropical Medicine and Hygiene. 2006;75(1):36-40.
19. United States Department of Agriculture Food Safety and Inspection Service. Fact Sheet: Goat From Farm to Table. < http://origin-www.fsis.usda.gov/Fact_Sheets/Goat_from_Farm_to_Table/index.asp>. 2008: Accessed 29 June 2010.
