

Chapter 12

Q FEVER

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SUMMARY

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INTRODUCTION AND HISTORICAL PERSPECTIVES

Q fever is a zoonotic infection with almost worldwide distribution, characterized by sudden fever, headache, and atypical pneumonia, and which, in some cases, results in chronic disease. The causative agent of Q fever is the gram-negative bacterium *Coxiella burnetii*. In two separate but concurrent instances, a new disease and the causative agent were discovered on different continents. An illness of unknown etiology struck slaughterhouse workers in Queensland, Australia, in 1933.^{1,2} Symptoms included fever, headache, and malaise, but serological tests for all suspected infectious agents were negative. This led to the designation as query, or “Q,” fever. Attempts to culture the agent on bacterial medium proved fruitless; however, scientists were able to demonstrate the transmissibility of the agent by inoculating guinea pigs with blood and urine from infected patients. It seemed likely that the causative agent was viral.

Around the same time in the United States, scientists in Montana were investigating a filter-passing agent isolated from ticks collected in the Nine Mile Creek area near Missoula, Montana. Initially looking for the agent of Rocky Mountain Spotted Fever, they found something new that did not cross-react with sera from patients infected with *Rickettsia rickettsii*: the causative agent of Rocky Mountain Spotted Fever, or any other known rickettsial agents.^{3,4} When placed on guinea pigs, the ticks infected with this unknown agent caused febrile illness, which was transmissible to other guinea pigs by injection of blood from the infected animals. Examination of the inflammatory cells revealed that the agent was rickettsia-like.⁴ Although the researchers in Montana were also unable to culture their agent on traditional bacterial media, they discovered that they were able to culture it in chicken embryos.⁵ This discovery was a significant breakthrough not only for studying the Nine Mile agent, but also for the study of all rickettsial organisms. The scientists in Montana now had a Rickettsia-like microorganism that they

had demonstrated to be infectious, but whether it caused disease in humans remained unknown until a researcher from the National Institutes of Health visited the public health laboratory in Hamilton, Montana, and became ill after working with the isolate from Nine Mile Creek. When blood from the researcher was injected into guinea pigs, the same febrile illness that resulted from the infected ticks was produced. After considerable effort by researchers in Montana and Washington, DC, a correlation was made between the agent found in the Nine Mile ticks and the disease that manifested in the visiting scientist. Serum from the visiting scientist was found to protect against infection by Nine Mile ticks in guinea pigs.²

The similarities between Q fever and the disease caused by the filter-passing agent found in the ticks from Nine Mile did not go unnoticed. In 1938, Dr Frank Macfarlane Burnet, who, along with Doctors Edward Holbrook Derrick and Mavis Freeman, published on Q fever in Australia, sent mouse spleens infected with Q fever agent to the National Institutes of Health in Washington, DC. The spleens were used to pass the infection to guinea pigs; the guinea pigs infected with Q fever were subsequently immune to the Nine Mile agent, but not the agents of Rocky Mountain Spotted Fever.² After issues arose with its source, Burnet’s Q fever sample was lost before any further comparisons could be made; however, the similarities between the infections and immunity observed against the Nine Mile in guinea pigs that had recovered from Q fever infection indicated these two agents were one and the same.

Due to the similarities between the Q fever agent and members of the *Rickettsia* genus, it was originally classified as *Rickettsia diaporica*,⁶ and then later *Rickettsia burnetii*,⁷ in honor of Dr Burnet. In 1948, *R burnetii* was reclassified to its own genus named in honor of Dr Cox and became known as *Coxiella burnetii*.⁸ Q fever’s prevalence in the world was soon discovered; to date, it has been found in every country except New Zealand.

MILITARY RELEVANCE

Fevers of unknown origin and atypical pneumonia have plagued troops throughout history. Even as late as World War II (WWII), it was common for infectious disease to sideline significant numbers of troops and impact the outcome of battles. Because Q fever was identified just prior to WWII, it was during this war that the impact of the disease was first noted, though likely not understood to the full extent because of the nonspecific nature of the symptoms. While Q fever

does not have a high mortality rate, it has the potential to debilitate large numbers of troops for extended periods of time.

World War II

Service members from both the Allied and the Axis forces sustained Q fever outbreaks during WWII. German troops were plagued with outbreaks of an atypical

pneumonia they called “balkengrippe” in northern Yugoslavia, Serbia, Bulgaria, Italy, Crimea, Greece, Ukraine, and Corsica in 1941.⁹ The outbreaks were not well contained and a single consulting physician for the German army saw over 1,000 cases of balkengrippe. Although the mortality rate of Q fever is not high, the impact of these outbreaks was not insignificant; the minimum absence from duty for infected individuals was more than 6 weeks. Similar outbreaks occurred in 1942, 1943, and 1944, including a very severe outbreak in Swiss troops during which half of the soldiers in two battalion subunits developed pneumonia. As the balance of power shifted and Germany was pushed out of its previously conquered territories, the Allied troops now occupying these areas began to experience outbreaks of the same atypical pneumonia that had been sidelining German troops in previous years. From February to April 1945, there were 511 cases of “primary atypical pneumonia” admitted to British and New Zealand military hospitals near Naples, Italy. From winter 1944 to spring 1945, there were nine significant outbreaks of atypical pneumonia reported in Allied troops in Greece, Italy, and Corsica.⁹ Although most of the outbreaks of atypical pneumonia were never confirmed to be Q fever during the acute stage of infection, serological analysis of select individuals up to 2 years after infection revealed high antibody titers against *C burnetii*.⁹

In the years following WWII, there were several small outbreaks of Q fever in military personnel. Between 1951 and 1958, there were three outbreaks of Q fever in Libya, Algeria, and the Isle of Man that impacted US, French, and British units, respectively. There were no further reports until an outbreak among British soldiers in Cyprus in 1974 that affected 78 soldiers.^{10,11}

INFECTIOUS AGENT

C burnetii is classified phylogenetically within the gamma subdivision of proteobacterium in the *Legionellales* order, with several unique properties.²⁶ It is a pleomorphic coccobacillus with a gram-negative cell wall and replicates within phagolysosome-like parasitophorous vacuoles (PVs) of eukaryotic cells. Replication depends on trafficking to a PV with low pH; this “biochemical stratagem” as an acidophile²⁷ involves developmental cycle forms with metabolically active large cell variants and metabolically quiescent small cell variants.^{28–30} The type isolate, Nine Mile (RSA493), was found to contain few highly degraded genes but a large accumulation of point mutations, leading to the hypothesis that *C burnetii* is in an early stage of reductive evolution.³¹ This is in contrast to other obligate

Gulf War

There were very few confirmed cases of Q fever in American service members during the Persian Gulf War. Only one case of acute illness was attributed to Q fever during this campaign: a severe case of meningoencephalitis associated with acute Q fever in a soldier following deployment.^{12,13} Three additional soldiers within the same battalion as the afflicted soldier seroconverted during the same period, as evidenced by subsequent testing.¹⁴ This small number of confirmed cases should not be taken as an indication that Q fever did not affect other military personnel or that it was absent in the environment. The nondescript nature of the symptoms associated with Q fever generally lead to gross under estimations of the disease.

Operation Enduring Freedom and Operation Iraqi Freedom

The impact of Q fever on military personnel in Iraq was realized starting in 2003.¹⁵ To date, there have been over 150 cases of Q fever in US military personnel in Iraq and Afghanistan.^{16–23} An evaluation of pre- and post-deployment sera of US military personnel hospitalized with symptoms consistent with acute Q fever between April 2003 and December 2004 revealed a seroconversion rate of 10%.²⁴ In addition to pneumonia, the infected personnel also presented with hepatitis, high fever, cholecystitis, and meningoencephalitis. In May of 2010, the Centers for Disease Control and Prevention issued an official health advisory detailing the potential for Q fever in travelers returning from Iraq.²⁵

intracellular pathogens, like *Rickettsia* and *Chlamydia*, that appear to have undergone massive genome fragmentation and reduction since their separation from free-living organisms. *Coxiella* genomes are composed of one chromosome and one large plasmid or plasmid-related sequences integrated into the chromosome.^{32–34} Sequencing genomes of four isolates identified approximately 2,150 to 2,300 open reading frames per genome and a high degree of homology among phylogenetically distinct isolate groups, with most major genetic variation resulting from transposon-mediated rearrangements.³⁵

C burnetii undergoes a phase variation population shift where virulent phase I converts to avirulent phase II upon serial passage in a nonimmunologically

competent host.³⁶ Phase I organisms have “smooth” lipopolysaccharides (LPS) with complete O antigen, while phase II have a “rough” LPS, missing, at a minimum, O-antigen sugars. Two clonal isolates of the Nine-Mile-type strain—phase I, RSA493 (clone 7) and phase II, RSA439 (clone 4)—have been used for comparative analysis to demonstrate the requirement for O-antigen expression for virulence. The phase II isolate has a well-defined genetic deletion (~ 20 Kbp),³⁷ which encodes O-antigen LPS biosynthesis and will not revert to wild-type. This clone 4 has been exempted from Centers for Disease Control and Prevention’s select agent regulation and requires only biosafety level 2 biocontainment.

C burnetii are primarily found in cells of the reticuloendothelial lineage, especially monocytes, macrophages, and polymorphonuclear cells during infection. Intracellular interactions have been modeled in vitro in a variety of continuous and primary cell lines, including L929 mouse fibroblasts, Vero (African green monkey kidney), J774 mouse macrophages, THP-1 human monocytes/macrophages, primary human peripheral blood mononuclear cells, and mouse bone-marrow-derived macrophages. The following models of the essential stages of uptake and survival have emerged from these studies.³⁸ *C burnetii* is taken up via complement receptor 3 and alpha V beta 3 integrin-mediated mechanisms into human macrophages.³⁹ The adhesins recognized by the host receptors are uncharacterized, but complement receptor 3 uptake appears dependent on loss of LPS O antigen.³⁹ An actin-dependent, endocytic mechanism of uptake leads to trafficking through an early endosome, progressing to a late endosome/phagolysosome PV.⁴⁰ The trafficking appears slightly delayed compared to latex bead uptake⁴¹ and membrane markers for Rab5, Rab7, Rab24, LC3, lysosomal-associated membrane protein (LAMP)-1, LAMP-2, and LAMP-3, and flotillin 1 and 2 progressively decorate the PV.^{42–45} Connection to the autophagosome compartment appears essential to support a productive replication compartment, and PV membrane development to a spacious vacuole requires access to continual cholesterol biosynthesis.⁴⁶ The PV biogenesis process requires de novo synthesis of *C burnetii* proteins, suggesting actively expressed bacterial factors in the modulation of host processes.⁴⁴ Infection of activated macrophages appears to favor pro-survival stimulation through Akt and extracellular signal-regulated kinases (Erks) 1 and 2 and restriction of proapoptotic events in a caspase-dependent manner.⁴⁷ Alternatively, the interaction with pro- and antiapoptotic host factors appears to be additionally complicated based on the observations that infected monocytic THP1 cells undergo a caspase-independent

apoptosis soon after infection that may be mediated, in part, by tumor necrosis factor and require protein synthesis by *C burnetii*.^{48,49} Infection of monocytes or macrophages does not result in subsequent activation, and several pathogen-associated common molecules appear modified to avoid serving as agonists for toll-like receptor recognition, including the lipid A of LPS that contains a tetraacylated structure with antagonistic activity for toll-like receptor 4.⁵⁰ When taken up by polymorphonuclear leukocytes, an incompletely defined, secreted acid phosphatase prevents release of reactive oxygen intermediates through the nicotinamide adenine dinucleotide phosphate-oxidase pathway.^{51,52} This avoidance of activating macrophages appears to be a key pathogenic strategy, and hypersensitivity to oxidative stress suggests avoidance of reactive oxygen intermediates as well as detoxification as evolutionary pressures.^{53,54} Through reductive evolution, several virulent isolates have lost expression of a functional catalase or secreted superoxide dismutase without a loss of virulence, and the organism requires very low iron levels, in part, as a strategy to avoid Fenton chemistry.^{53,55}

The model of pathogen–host interaction suggests that *C burnetii* actively remodels the host cell to establish a productive intracellular niche, and two secretion systems are likely key to the effector molecule release that mediates this remodeling. Virulent isolates with acute disease-causing potential appear to encode a functional type IV pilus-structured, type II secretion system to release several enzymes, including acid phosphatase, phospholipases D and A1, copper/zinc superoxide dismutase, chitin, and a family of enhanced entry proteins.⁵⁵ *C burnetii* also encode and express a type IVB secretion system with striking similarity to the defective in organelle trafficking/intracellular multiplication (dot/icm) system (type IV secretion system [T4SS]) of *L pneumophila*.^{31,56} It encodes 23 of the 26 dot/icm proteins, lacking homologs of the chaperone IcmR and the inner membrane proteins DotJ and DotV.^{31,56,57} *C burnetii* dotB, icmS, icmW, and icmT are able to complement these mutations in *Legionella*,^{58,59} while icmX, icmQ, dotM, dotL, dotN, and dotO do not complement.⁵⁹ These results suggest strong functional similarities as well as unique properties associated with each system. The *Legionella* dot/icm system has identified over 300 substrate effector proteins using a variety of approaches, and most of these effectors have been shown to subvert some step in the host cell process connected with replication in its unique niche.⁶⁰ Interestingly, although not surprising given the PV of *Legionella* and *Coxiella* are so dramatically distinct, *C burnetii* encodes relatively few homologs of the *Legionella* effectors. This suggests that although

C burnetii has maintained a functional dot/icm-related T4SS, the effectors, which are substrates for this secretion system, are almost entirely unique to *C burnetii*.

Pursuit of molecular pathogenesis studies for *C burnetii* has dramatically advanced with the development of the extracellular growth media acidified citrate cysteine media under microaerophilic conditions and the advent of genetic tools to randomly and site-specifically mutagenize and rescue mutant phenotypes using complementation methods.^{61–66} Using these techniques, the isolation of T4SS mutants verified that, like *Legionella*, the dot/icm system of *Coxiella* is essential for intracellular replication but not growth in artificial media.^{67,68} The identification of specific effectors released via T4SS has begun to determine which effectors are essential for this replication and potentially many additional *Coxiella*-unique virulence properties. Among potential type IV secreted effector molecules are a diverse family of pathotype-specific ankyrin repeat-containing proteins.^{57,69} Ankyrin repeat domains (Anks) are commonly found in eukaryotic systems to mediate protein-to-protein and protein-to-DNA interactions and may be involved in host modulation events. Like *Legionella*, some redundancy appears to exist among *Coxiella* secretion substrates, as three substrates, ankyrin repeat-containing protein G (AnkG), *C burnetii* anti-apoptotic effector A protein (CaeA), and *C burnetii* anti-apoptotic effector B protein (CaeB), appear to act to promote host cell viability by modulating apoptosis. Recent studies suggest that AnkG binds the proapoptotic protein p32 to inhibit apoptosis.⁷⁰ Either redundantly or in support of AnkG, CaeB inhibits apoptosis through a mitochondrial pathway, whereas the nuclear effector CaeA was also noted to block apoptosis.⁷¹ A variety of essential host manipulations via T4SS substrate/effectors released into the host cytoplasm will likely be identified to elucidate the intimate relationship between host and pathogen in this exquisitely adapted agent.

Pathogenesis

The pathogenesis of Q fever in humans is not well studied, and knowledge of acute *C burnetii* infection has been elucidated primarily in animal models. Upon inoculation, *C burnetii* are engulfed by resident macrophages and transported systemically. Alveolar macrophages have been identified as the resident cells that are primarily infected upon aerosol infection.^{38,72,73} *C burnetii* grows and replicates within these macrophages and then bursts the cell, resulting in release and the subsequent infection of other phagocytic cells. In mice and guinea pigs, the spleen and liver are the most heavily burdened organs, and it is

assumed that this is the same in human infection.⁷⁴ Chronic Q fever is far more complex. In chronic infection, reactivation of the microorganisms is possible years after the initial infection. Studies in guinea pigs and mice have demonstrated that these animals remain infected throughout their lives, but growth is uncontrolled during parturition and other periods of immunosuppression. Immunosuppressed animals have also been used to model chronic infection,⁷⁵ as have mice that are altered genetically to over produce the cytokine interleukin 10.⁷⁶ The early prediction that phylogenetic groups are uniquely virulent to cause either acute or chronic disease in humans is supported by studies that demonstrate in acute disease animal models that pathotypes are distinct in their ability to cause acute inflammatory disease.⁷⁷ Yet, there remains much to learn about chronic infection, including where the microorganisms persist during periods of latency and if the microorganisms are ever cleared from the body.

Epidemiology

Q fever is a worldwide zoonotic infection found in every country, with the exception of New Zealand. *C burnetii* is able to infect a wide range of species, but symptomatic infection is only found in humans. Occupational exposure is the primary source of human infection, with the vast majority of cases occurring in abattoir (slaughter house) workers, farmers/ranchers, and veterinarians. Although Q fever is primarily a problem in rural areas with domestic animals such as cattle, sheep, and goats as the primary sources, domestic pets can spread infection in urban areas, though at a much lower rate.^{78,79} Infected animals shed *C burnetii* in urine, feces, milk, and, in highest concentration, in the placenta and other materials that are released during birth. *C burnetii* is incredibly stable in the environment and can persist as dried infectious particles for months or even years, perpetuating the infectious cycle.^{80,81} This can also result in infections in individuals indirectly associated with the infected animals, such as those living in the area, because infectious particles can be carried by the wind. Although infectious aerosols are the most common source of infection in humans, bites by infected ticks and consumption of contaminated milk are also associated with infection⁸² (though it is possible that long-term consumption of contaminated milk may result in seroconversion without causing disease).

C burnetii is one of the most infectious organisms known, with an infectious dose of fewer than 10 microorganisms, and possibly as low as 1 microorganism.^{83,84} Routes of infection include aerosol, ingestion, and, rarely, human to human. The route of infection impacts

the manifestation of the disease; ingestion generally results in granulomatous hepatitis, while pneumonia is more common with aerosol transmission.⁸⁵ *C burnetii* is ubiquitous in the environment, yet there has been little work done to estimate its seroprevalence around the world. In the United States, the estimated seroprevalence is around 3% but the number of reported cases is very low, indicating that the majority of cases do not produce clinical disease.¹⁹ Extensive studies were completed in Nova Scotia before 1990 that revealed a 14% seropositivity rate, but significantly fewer reported cases.^{86,87}

Between 2007 and 2010, the Netherlands experienced one of the most significant Q fever outbreaks known. Approximately 4,000 cases of human Q fever were reported during this 3-year period, an exponential increase from the 1 to 32 cases per year that the country experienced in the years prior to the outbreak.^{88,89} The outbreak resulted in the culling of millions of domestic animals, which was a devastating loss to the farming industry. This outbreak highlights the potential for large-scale Q fever outbreaks even in highly developed countries.

DISEASE

Humans (Q Fever)

Q fever is a zoonotic infection that produces symptomatic infection only in humans. Even in humans, only approximately 50% of infected individuals develop clinical disease, and the mortality rate is less than 1%.¹ Typically, Q fever presents as an acute, self-limited, systemic infection after an incubation period ranging from a few days to several weeks; there is evidence that disease severity is directly related to the infectious dose.^{83,90,91} Symptoms, although acute, are typically nonspecific and may include fever, chills, severe headache warranting lumbar puncture,¹⁹ fatigue, pneumonia, myalgia, nausea, vomiting, diarrhea, chest pain, weight loss, and abdominal pain. Of infected individuals, 30% to 50% develop pneumonia, and it is not uncommon for patients to develop hepatitis. Less common clinical manifestations include acalculous cholecystitis, acute respiratory distress syndrome, gastroenteritis, myelitis, orchitis, epididymitis, pericarditis and myocarditis, and rhabdomyolysis, among others.^{12,17-20} In many cases, patients clear the infection without antibiotic intervention.

In addition to acute infection, Q fever is also capable of inducing chronic infection. Chronic Q fever has the potential to manifest in excess of 20 years after the initial exposure and can persist for 6 or more months at a time. In its chronic form, Q fever is especially dangerous in patients with heart disease, as endocarditis is known to develop in conjunction with chronic disease. Immunocompromised patients, such as those undergoing immunosuppressive therapy, suffering from diseases such as AIDS, or receiving antirejection therapy after organ transplant are particularly at risk for developing chronic Q fever.^{92,93} The most common disease associated with chronic Q fever is endocarditis of the aortic and mitral valves, though it is not uncommon to see chronic hepatitis.⁹⁴⁻⁹⁷ A preexisting heart disease is a major risk factor for chronic Q fever.

It is estimated that of those individuals that develop Q fever endocarditis, close to 90% have preexisting valvular disease⁹⁶; as many as one third of all chronic Q fever patients with cardiac valve abnormalities go on to develop Q fever endocarditis.⁹⁷ In patients with chronic Q fever, the immune responses necessary to fight the infection, such as T-cell responses, are not present. Patients have been observed to produce increased immunosuppressive cytokines, including tumor necrosis factor⁹⁸ and interleukin 10.^{76,99} Immune response suppression is responsible for the persistence of the microorganism.

Animals (Coxiellosis)

As a zoonosis, infection with *C burnetii* is termed "coxiellosis" and infects both wild and domestic animals. Q fever is especially common in domestic ruminants such as cattle, sheep, and goats. Unlike infection in humans, coxiellosis does not produce overt symptoms, and pathological changes are generally limited to the genital tract, manifesting as spontaneous abortion and fertility issues.¹⁰⁰ Sheep appear to have only transient infection while the infection persists in other mammals.¹⁰¹ Infection reactivates in female mammals during pregnancy. As with infection in humans, animals are infected by aerosol transmission, tick bites, and milk (nursing). A 2005 study demonstrated that over 90% of dairy cows in the northeastern United States are infected with *C burnetii*,¹⁰² but pasteurization prevents human infection via consumption of contaminated milk. Although exposure via contaminated milk can be prevented by simply pasteurizing milk, infection by the aerosol route (ie, inhalation of dried infectious particles shed by infected animals) cannot be prevented. Without obvious symptoms, it is difficult to identify infected animals and therefore next to impossible to eradicate *C burnetii* from domestic animals.

DIAGNOSIS

Q fever cannot be diagnosed based on clinical symptoms because of the nonspecific presentation of symptoms; instead, diagnosis is made based on the combination of clinical signs and serological testing. History of exposure to animals or time spent on farms bolsters what is usually a presumptive diagnosis. Humoral responses are more consistently activated during Q fever infection than cellular responses and, as such, serological testing is considered the more reliable immunoassay for Q fever. The most commonly used assays are indirect immunofluorescence assay (IFA), complement fixation, microagglutination, and enzyme-linked immunofluorescence assay (ELISA).^{19,103}

The gold standard for Q fever serological diagnosis is the IFA because it is highly sensitive and very specific, and does not require purified antigen.^{103,104} This method is very convenient for laboratories with limited space for equipment, but it is not feasible for testing large numbers of samples. Complement fixation is one of the most specific assays for diagnosing Q fever, but it lacks sensitivity and cannot detect specific antibody early in the course of an infection.¹⁰⁵ Microagglutination is sensitive, but its use is hindered by the requirement for large amounts of antigen.^{103,106} ELISA rivals IFA in specificity and sensitivity, and is a platform conducive for analyzing large numbers of samples. Unlike IFA, however, ELISA requires highly purified antigen to achieve sensitivity and specificity.^{103,104,107}

Phase variation plays an important role in serodiagnosis of Q fever. Acute and chronic Q fever produce characteristic, yet distinct, antibody profiles.¹⁰⁸⁻¹¹¹ During acute infection, antibody to the phase II, nonpathogenic organism is detectable before antibody to the phase I, pathogenic organism. Phase II antibody titers peak much

higher than phase I antibody and remain elevated for years after infection, while phase I antibody titers wane shortly after infection. Individuals with chronic infection have an antibody profile exactly opposite the profile of individuals with acute infection. Chronic infection produces and sustains high titer phase I antibody, but much lower phase II antibody titers.

Although it is possible to diagnose Q fever based on bacterial culture, this method is not widely used. *C burnetii* is highly infectious and must be grown under biosafety level 3 conditions, a requirement that is not feasible at most medical treatment facilities. Culturing *C burnetii* from patient samples can be done by using the sample to infect research animals such as mice, or by infecting a monolayer of cells and subsequently staining and visualizing the cocci. These methods are very time consuming and are not conducive for large numbers of samples.¹⁰³ The advent of the use of acidified citrate cysteine media⁶⁵ for axenic culture of *C burnetii* will likely make culturing patient samples easier, but it seems unlikely that this will become the primary method for diagnosing Q fever. Detection by quantitative polymerase chain reaction is also a viable method and can be used to detect the bacteria in the infected individual much earlier than methods that rely on the production of antibody.^{112,113} Most of the information on the use of PCR for diagnosis have come from animal studies, but there has also been success detecting *C burnetii* in the buffy coat of citrated or ethylenediaminetetraacetic acid (EDTA)-treated blood.¹⁰³ In the spring of 2011, the US Food and Drug Administration cleared the first test to diagnose Q fever in military personnel serving overseas. The nucleic acid amplification test by Idaho Technologies produces results within 4 hours.¹¹⁴

TREATMENT

Acute Q fever is easily treated. The treatment of choice is doxycycline, 100 mg twice daily for 14 days.¹¹⁵ This treatment is not effective for chronic Q fever; instead, drug combinations such as doxycycline plus hydroxychloroquine are considered the most efficacious treatment in chronic cases. In cases with endocarditis, an 18-month regimen of 100 mg of doxycycline twice per day and 200 mg of chloroquine three times per day is effective.¹¹⁷ When chloroquine is not an option for a particular patient, a combination of 100 mg doxycycline twice per day and 200 mg

ofloxacin three times per day is recommended for a period of 3 years.¹¹⁶ There is evidence of reactivation of disease when the drug regimens are shortened or not completed. Doxycycline is not bactericidal, but is an effective treatment for intracellular bacteria such as *C burnetii* and *Chlamydia*. The effectiveness of doxycycline is improved when used in combination with hydroxychloroquine and it is hypothesized that the hydroxychloroquine increases the pH of the phagolysosome, which would decrease the metabolic activity of *C burnetii*.¹¹⁷

VACCINE

The ability to create an efficacious vaccine has never been a problem in the field of Q fever research. The failure of most of these vaccines has been the inability to uncouple the protection and the accompanying adverse reactions. Within a few years of identifying *C burnetii*, researchers had successfully developed an effective vaccine.¹¹⁸ The composition of the vaccine was crude and consisted of formalin-inactivated *C burnetii* extracted with ether from egg culture and was contaminated with 10% yolk sack. Knowledge of the phase variation that occurs in *C burnetii* came after this early vaccine was developed. It was later determined that vaccines consisting of phase I antigen are 100- to 300-fold more protective than those consisting of phase II antigen in guinea pigs.¹¹⁹ Whole cell vaccines (WCVs) consisting of formalin inactivated phase I *C burnetii* have been studied extensively. There is no question that these vaccines are highly protective against Q fever, but the side effects that occur in a specific population of people has prevented their wide-spread use. Individuals that have been exposed to *C burnetii* prior to vaccination, such as those who have had Q fever or have spent significant time in close proximity to livestock, are very likely to have adverse reactions at the site of injection.^{120,121} The reactions can range from mild redness and swelling to painful granulomas and sores. The same can be seen after multiple vaccinations. To circumvent the adverse reactions to the WCV, alternative antigen sources have been, and continue to be, investigated.

M-44

The Soviet Union developed a live attenuated oral vaccine using phase II organisms from the M-44 strain.^{122,123} The vaccine was tested in Soviet volunteers

with great success, but studies in guinea pigs revealed that the organisms persisted in the animals and led to lesions in the heart, spleen, and liver, suggesting either reactivation or low-level contamination with phase I organisms.¹²⁴

Chloroform:Methanol Residue

Another attempt to prevent the side effects of vaccination in the previously exposed individuals was to vaccinate with an extraction from phase I organisms, rather than the WCV. Scientists at the United States Army Medical Research Institute of Infectious Diseases vaccinated with the residue from chloroform and methanol extracted from phase I organisms that had been formalin inactivated. They have demonstrated that the vaccine is protective in animals, nontoxic, and immunogenic in humans.^{125,126} However, at high doses the residue is reactive, though to a lesser extent than whole cell vaccine. Studies using a low-dose prime-boost scheme have shown success in animals and induce protection without reaction.¹²⁷

Q-Vax

Q-Vax (short for Q fever vaccine) is a WCV that is licensed for use in Australia from CSL Limited, a company based in Victoria, Australia; it is the most widely studied Q fever vaccine.¹²⁸ Studies have demonstrated that this vaccine is 100% effective for more than 5 years in individuals who are considered extremely at risk due to their occupation.¹²⁸ Q-Vax, however, is hampered by the need for pretesting to determine prior immunity. It is currently not licensed for use in the United States.

SUMMARY

Q fever is a worldwide zoonotic disease with one of the most highly infectious causative agents known, *C burnetii*. Q fever significantly impacted wartime efforts as recently as the past few years, and as evidenced by the recent outbreak in the Netherlands, can produce prolific disease even in areas with sufficient preparation. The ubiquitous nature of *C burnetii* in the environment indicates that Q fever will be a concern for years to come; not only does it have the potential to produce disease in humans, it can also result in devastating losses to domestic ani-

mals. Extremely resistant to environmental stresses, *C burnetii* can persist for long periods of time in the environment.

Q fever is easily treated by antibiotics of the tetracycline class, though diagnosis can be difficult based on the nonspecific symptoms observed in Q fever patients. Physicians must rely on a combination of clinical presentation and serological testing to diagnose Q fever. Although the vaccine used in Australia is not available for use in the United States, efforts continue to find a safe and efficacious alternative.

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