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Q Fever Briefing Note — Dr Paul B Bartley 15th November 2010

Client : Minter Ellison Lawyers
PO Box 7844
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Matter: Real Property Consultants Pty Ltd v Logan City Council & Teys Bros (Holdings) Pty Ltd
Planning and Environment Appeal No. 648 of 2010-08-13

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Reference: AJM 40-6432697

Summary
Q fever is a bacterial infection of humans that is transmitted by aerosol of the organism from infected animals. Both acute and chronic forms of infection occur with measurable mortality rates.

Infection is widespread in livestock and companion animals. Large quantities are aerosolised at both parturition and defecation.

Q fever is an occupational hazard for meat workers, veterinarians and others in animal industries.

Community-based outbreaks have been reported where infection occurs from often trivial if any direct animal contact – and often facilitated by windborne carriage of aerosols.

Risk of non-occupational infection is greatest in those living or working close to animal facilities – especially if climatic conditions favour windborne aerosol transmission.

Q Fever

Q fever is a disease of humans caused by infection with the bacterium *Coxiella burnettii* (*C. burnettii*).

The Organism

C. burnettii is a gram-negative bacterium that cannot be culture in routine axenic laboratory media. It multiplies within the phagloysosome of host eukaryotic cells[1].

C. burnettii is a member of the gamma subgroup of proteobacteria, most closely related to *Legionella pneumophila* and *Wolbachia persica* based on 16S-ribosomal RNA (16S-rRNA) genotyping[1]

Laboratory Isolation & Cultural Characteristics

C. burnettii is best grown in the yolk-sac of chicken embryos, or in cultures of chicken fibroblast cell lines or Vero cells[1]. A shell vial technique is used in most reference laboratories. Physical Containment Level 3 (PC-3) laboratory facilities are required to safely culture, manipulate and store this organism.
It has been demonstrated that one organism is a sufficient inoculum to establish infection within cell culture systems[2]. One organism was sufficient induce infection in both mice and guinea pigs in controlled laboratory circumstances [2]. These data support the highly infectious nature of this organism.

Morphology and Genetics
C. burnettii genomic DNA contains 37 open reading frames (ORF) encoding genes for structural and non-structural proteins. The G+C content is 42%. Restriction-Fragment Length Polymorphism (RFLP) analysis has demonstrated 14 distinct RFLP patterns in the organism's genomic DNA[1]. Plasmids have been discovered in *C. burnettii*, however, they are not known to encode virulence factors. A high degree of genetic conversation within plasmids suggests they are essential to the survival of the organism.

Morphology and Cell Wall Structure
C. burnettii has adapted to multiple within the acidic phagolysosome with a simple developmental cycle that includes binary fission and sporogenesis. Two phase-variants of surface lipopolysaccharide (LPS) molecules are evident. LPS structural changes between Phase-1 and Phase-2 antigens are incompletely understood. It appears as though the change is mediated by truncation of the O-side polysaccharide. Phase-1 cells are infectious for animals and are able to survive in an acidic environment when the pH is 5 or lower. Phase-2 cells are elicited following repeat cultures in yolk-sacs of chicken embryos and are unable to survive in macrophages[1].
Structural cell wall composition and antigenic properties formalin treated Phase-1 whole cell vaccines have been used extensively in animals and in humans. Whilst efficacious, these vaccines can produce significant reactions including erythema, induration, granulomas and sterile abscesses in some individuals. In individuals previously infected by *C. burnettii*, severe local and systemic reactions can occur - such that testing by both serology and skin tests are necessary before routine vaccination. Vaccines based on Phase-2 antigens are not effective[1].

Environmental Habitat
C. burnettii is stable within the natural environment, facilitating its transmission between animals and from animals to humans (zoonotic transmission) primarily by aerosol[1]. Environmental contamination and asymptomatic animal infection has been reported from every part of the world. Some natural infections may be spread by ticks. The organism is most abundant in the placenta of parturient animals.

Disinfection and Sterilisation
C. burnettii is resistant to elevated temperatures, desiccation, osmotic shock, ultraviolet light and chemical disinfection. Highly effective disinfectants include 70% ethanol and 5% chloroform kill the organism. Low- level disinfectants including benzalkonium and sodium hypochlorite are ineffective[1].

Human Illness

Edward Derek first described the illness in Australian meatworkers in 1935. Derek was able to infect guinea pigs with material from infected meatworkers. MacFarlane Burnet established an animal model of infection in guinea pigs. Simultaneously Davis and Cox from Montana USA, identified the same agent in guinea pigs (referred to as the "Nine-mile Agent") following investigation of an outbreak of spotted fever. Later the agent of Q fever and the Nine-mile Agent were demonstrated to be identical – *C. burnettii.*

Q Fever is usually transmitted by the inhalation of small particle aerosols that originate from infected animals. Q Fever is enzootic amongst domestic animals particularly in livestock such as sheep, cattle and goats[3,4]. Small, domestic, companion-like animals such as cats can be asymptomatically infected. The organism is found in high concentrations within the placenta of infected females and is shed readily at the time of parturition. The organism is extremely stable under environmental conditions and is easily disseminated in dust, from dry manure or from other materials[3,4]. Consumption of warm milk from infected animals has also been responsible for transmission. The organism can also been shed in animal faeces.

Outbreaks have been reported particularly in abattoir workers. Other reported outbreaks included transient contact with cattle, sheep or from cats given birth.

ACUTE Q FEVER. The incubation period (time from infection to disease onset) ranges from nine to twenty-eight days, averaging eighteen to twenty-one. The incubation period is inversely proportional to the infecting inoculum. Illness onset is abrupt with fevers, severe headaches, myalgias, chills, malaise, sore throat and often confusion. Occasionally a patient may complain of chest pain. Fever can often be as high as 40°C and may persist for longer than three weeks. Widely reported clinical syndromes include pneumonitis, occasionally lobar consolidation, and acute hepatitis. More protean manifestations have been reported in those without occupational risk factors[5]. Morality rate for acute Q Fever is approximately 1-2%. Most patients if untreated can recover to full health within three months.

Patients that recover from acute Q fever have life-long immunity.

CHRONIC Q FEVER. Chronic Q Fever occurs in two forms, either chronic granulomatous hepatitis or endocarditis. By definition the infection has been present for greater than six months. A minority of patients (approximately 1-2%) with acute Q fever can progress to develop chronic Q fever within one year or as long as twenty years after initial infection. Endocarditis typically involves infection of the aortic valve of the heart and less frequently the mitral valve. Those with pre-existing valvular abnormalities or endovascular prosthetic grafts are at greater risk of endocarditis from Q fever. Those who are immunosuppressed as a consequence of malignancy and its treatment, or organ transplantation are also at risk of chronic Q Fever. Mortality rates have been reported as high as 65% from chronic Q fever.

Laboratory Diagnosis

There are significant hazards associated with direct culture of *C. burnettii* outlined above, and so is only performed in major reference laboratories. Routine documentation of infection is usually achieved by serological methods. Most routine diagnoses are based on retrospective serological techniques originally based on an immunofluorescent assay employing Phase-1 and Phase2 antigens.

Acute Q fever is demonstrated by the presence of IgM and IgG antibodies to Phase-2 antigens which are usually detectable in the second week of illness. Chronic Q fever is usually diagnosed by the presence of high levels of IgG Phase-1 antibodies. Typically this is associated with complement fixation titres of greater than 128, or IFA anti Phase-1 titres of greater than 1:800. PCR of peripheral blood may be useful within the first two weeks of infection before an opportunity for detectable antibodies is achieved.

Treatment – Susceptibility to Antibiotics

As *C. burnettii* does not reproduce on axenic media, a variety of animal inoculation methods have been used in the past to demonstrate antibiotic efficacy. Essentially all methods demonstrate that *C. burnettii* is relatively resistant to Chloramphenicol, Erythromycin and Streptomycin. Whereas Rifampicin, Trimethoprim, Dicloxacillin and Tetracycline antibiotics are bacteriostatic.

Cure of acute Q fever is usually with 100mg of Doxycycline twice daily for two to three weeks. Chronic Q fever has historically been treated with two antibiotics, typically Doxycycline and a quinolone antibiotic such as Ciprofloxacin in combination for at least four to five years. More modern protocols are usually a combination of Doxycycline along with Hydroxychloroquine. Hydroxychloroquine, whilst possessing no antimicrobial activity itself, is able to modify the pH of the parasitophorous vacuole to facilitate a bactericidal effect from Doxycycline, thereby killing the organism. Treatment durations are believed to be at least two to three years, however final recommendations of treatment durationremain the subject of ongoing research.

Epidemiology and Control for Q fever

The only known important inoculation for humans is that of inhalation of aerosols[3,4,6,7]. The infecting dose in humans has been reported as low as ten organisms with an incubation period of seventeen days. Increasing the inoculum to 100,000 organisms is associated with an incubation period of ten days.

There is an extensive environmental reservoir of *C. burnettii* infection in mammals, birds and arthropods. Humans are usually infected by contact with aerosols from cattle, sheep, goats and occasionally household pets[3,4,6,7]. The organism is shed in animal faeces, milk and birth products. *C. burnettii* cannot be eradicated from soil [3,4,6].

Workers involved in animal husbandry, dairy farming or abattoirs are well known to be at significant risk of this infection. Other outbreaks involving occupational exposure have been reported in veterinarians, livestock farmers and researchers[3,4,6,7].

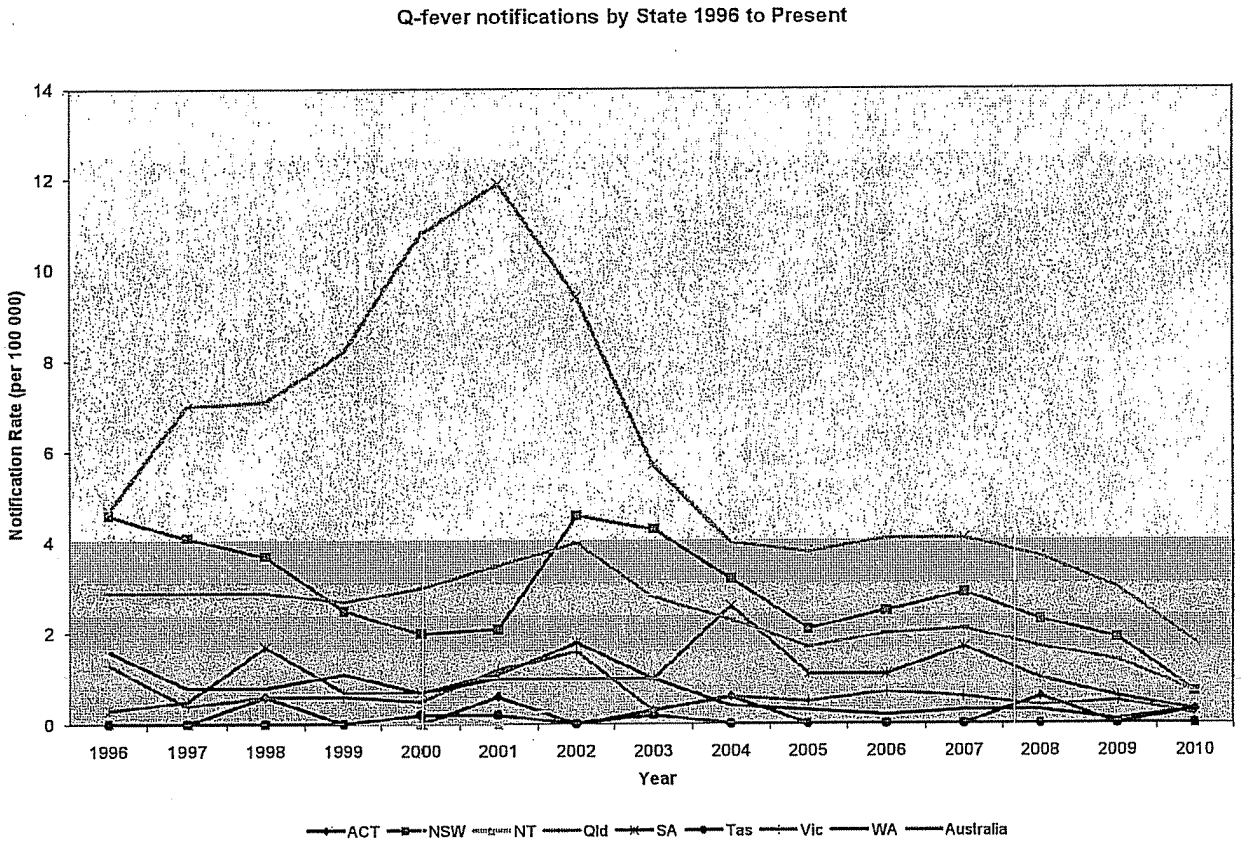

Figure 1. Q fever Notification rate per 100000 population by State 1996 to July 2010. Source- National Notifiable Diseases Surveillance System Database - Accessed August 2010.

Figure 1 above displays the notification rate of Q fever per 100000 population in Australia for the last 15 years. The peak notification rate I Queensland provided impetus for a large-scale Public Health intervention based on the vaccination of Meatworkers[7].

A comprehensive review of all Q fever notifications to Brisbane South Public Health Unit (BSPHU) from January 2000 to September 2006 was recently published[7]. 191 notifications were received in that period. 56% of cases (n=106) arose from occupational infection. 36% of cases (n=69) were a consequence of non-occupational infection without direct livestock contact (i.e. community acquired). In 16 cases, there was insufficient information to determine exposure risk.
The majority of the community acquired cases were in those who lived or worked in close proximity to high risk industries[7]. They argued therefore that since C. burnettii aerosol transmission may be facilitated by suitable environmental conditions and can occur within a wide radius of the source, buffer zones should be an important consideration around high risk industries[7].

Large community outbreaks of Q fever have been reported from The United Kingdom[8,9], Italy [10], Germany [11,12], France [13], Switzerland [14]and The Balkans Region [15,16]. The majority of cases reported in these outbreaks occurred in those living adjacent to, and downwind from animal pastures and along stock routes. Many cases were reported in workers from factories immediately adjacent to, and downwind from livestock pastures. Windborne transmission in appropriate climatic conditions was demonstrated in all of these reported outbreaks – particularly so in France[13], Germany[11,12] and the

United Kingdom[9,17]. Seasonality of these outbreaks has coincided with spring summer and the lambing season [18].

Attack rates have been demonstrated to be greater in those living closer to animal facilities - as high as 11.8% [12] for those who lived within 50m of a sheep meadow and decreased to 1.3% at living distance of over 400m. Other investigators have come to similar conclusions from other regions of Europe[9,17].

Buffer zones ranging from 1000m to 5000m have been recommended b y the respective Victorian[19] and Western Australian[20] Environmental Protection Agencies between cattle feeding lots and surrounding developments.

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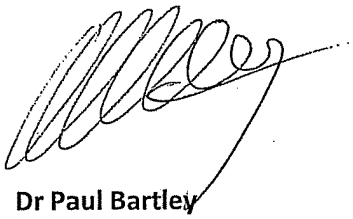
Yours sincerely



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