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Q FEVER IN JAPAN: AN UPDATE REVIEW

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ABSTRACT

As neglected zoonosis for many years, Q fever is now ubiquitous in Japan. Similarly to elsewhere in the world, domestic animals are considered to be important reservoirs of the causal agent, *Coxiella burnetii*, a resistant intracellular bacterium. Infected animals shed bacteria in milk, feces, urine, vaginal mucous and birth products. Inhalation of bacteria present in the environment is the main route of animal and human infection. Shedding of *C. burnetii* in milk by domestic ruminants has a very limited impact as raw milk is seldom ingested by the Japanese population. The clinical expression of Q fever in Japan is similar to its clinical expression elsewhere. However clinical cases in children are more frequently reported in this country. Moreover, *C. burnetii* is specified as one of the causative organisms of atypical pneumonia in the Japanese Respiratory Society Guideline for the management of community-acquired pneumonia. In Japan, *C. burnetii* isolates are associated with acute illness and are mainly of moderate to low virulence. Cats are considered a significant source of *C. burnetii* responsible for human outbreaks in association with the presence of infected parturient cats. Since its recognition as a reportable disease in 1999, 7 to 46 clinical cases of Q fever have been reported by year. The epidemiology of Q fever in Japan remains to be elucidated and the exact modes of transmission are still unproven. Important further research is necessary to improve knowledge of the disease itself, the endogenous hosts and reservoirs, and the epidemiological cycle of coxiellosis in Japan.

Keywords: Q fever, *Coxiella burnetii*, zoonosis, Epidemiology, Clinical aspects, Animals, Birds, Humans, Cats

48 **TABLE OF CONTENTS**

60

61 **1. INTRODUCTION**

62 Q fever was first described in 1937 (Derrick, 1937). Q fever is a ubiquitous neglected
63 zoonosis caused by a resistant intracellular bacterium, *Coxiella burnetii* (Derrick, 1937;
64 Mitscherlich & Marth, 1984; Babudieri, 1959; Maurin and Raoult, 1999; Rousset *et al.*,
65 2009). Ignored for many years, Q fever is now thought to be ubiquitous in Japan since the
66 reservoirs are present throughout the country (Hirai & To, 1998). Similarly to elsewhere in
67 the world, domestic animals are considered to be important reservoirs of *C. burnetii* (Hirai &
68 To, 1998). However Q fever is known to infect a large variety of hosts, mammals (humans,
69 caprids, bovids, ovids, small rodents, dogs, and cats) but also birds, fish, reptiles and
70 arthropods (Hirai & To, 1998; Maurin & Raoult, 1999; Bildfell *et al.*, 2000; Berri *et al.*, 2007;
71 Rousset *et al.*, 2007; Okimoto *et al.*, 2007; Hartzell *et al.*, 2008). It is a highly infectious
72 disease (Ormsbee *et al.*, 1978). Infected mammals shed bacteria in milk, feces, urine, vaginal

mucous and very importantly in birth products. Inhalation of resistant bacteria present in the environment is the main route of animal and human infection. The main characteristic of Q fever is its clinical polymorphism (Kuroiwa *et al.*, 2007; Hartzell *et al.*, 2008; Million *et al.*, 2009; Pape *et al.*, 2009). After an incubation period of 1 to 3 weeks (Maurin & Raoult, 1999; Watanabe & Takahashi, 2008), Q fever can cause either an acute or a chronic disease.

This manuscript describes the epidemiological situation of Q fever in Japan. The authors' choice of country was based firstly on the peculiar role of cats and additionally of wild birds in the epidemiology of Q fever in Japan and secondly the limited epidemiological investigation and awareness of Q fever in Japan incited further research on the subject.

2. CLINICAL EXPRESSION

2.1. In humans

Since April 1999, the management of infection control and prevention in Japan has changed drastically and Q fever was designated as a national reportable disease. Q fever occurs almost all over the country. Under the revised surveillance system, clinical cases of Q fever have been reported 7-46 cases since 1999 for a total of 127 million inhabitants (Mahara, 2006). The clinical expression of Q fever in Japan is similar to its clinical expression elsewhere (Ejercito *et al.*, 1993; Htwe *et al.*, 1993). In the acute form, infections can be totally asymptomatic or can lead to self-limiting 'influenza-like" illness, pneumonia or hepatitis (To *et al.*, 1998b; Sampere *et al.*, 2003; Setiyono *et al.*, 2005; Berri *et al.*, 2007; Kuroiwa *et al.*, 2007; Delsing & Kullberg, 2008; Hartzell *et al.*, 2008; Schimmer *et al.*, 2008; Frangoulidis *et al.*, 2009; Million *et al.*, 2009; Pape *et al.*, 2009; Ughetto *et al.*, 2009). Pneumonia is typically mild but progression to acute distress syndrome can occur (Hartzell *et al.*, 2008; Watanabe & Takahashi, 2008). Indeed a study found Q fever to be involved in 2.5% of patients with an

acute infection/exacerbation of a chronic lower respiratory tract disease state (Okimoto *et al.*, 2007). In Japan, pneumonia is a common clinical presentation of acute Q fever. The prevalence of *C. burnetii* infection as causative agent for atypical pneumonia differs between different countries. Indeed, To *et al.* (1996) found that 39.7% of Japanese patients with atypical pneumonia were infected by *C. burnetii*. On the other hand, in the rural areas of Nova Scotia, a province of Canada, only 20% of patients admitted to hospital with atypical pneumonia were infected by Q fever (Marrie, 1990). In France, Tissot Dupont *et al.* (1992) reported a prevalence of atypical pneumonia caused by *C. burnetii* of 45.8%. The variability in prevalence between countries is most probably due to differences in incidence of Q fever in domestic ruminants (goats, sheep, and cattle). On the other hand, variability in occurrence of clinical illness could be explained by differences between local strains and their respective virulence, and/or by physiological differences in the host (To et al., 1996). Alimentary habits could also play a role. In France, for example, farmers and stock breeders are known to drink unpasteurized milk. Moreover, 61.9% of French patients infected by Q fever presented clinical signs of hepatitis (Tissot Dupont *et al.*, 1992; Maurin & Raoult; 1999). However, currently, bacterial genotype and not route of infection is thought to determine clinical presentation. Furthermore transmission of infection by oral route remains a matter of debate (Marmion & Stoker, 1958; Benson *et al.*, 1963; Krumbiegel & Wisniewki, 1970; AFSSA, 2004; Dorko *et al.*, 2008; Natale *et al.*, 2009).

In Japan, *C. burnetii* isolates are mainly associated with acute illness and of moderate to low virulence (Oda and Yoshiie, 1989; Hirai & To, 1998). *C. burnetii* is specified as one of the causative organisms of atypical pneumonia in the Japanese Respiratory Society Guideline for the management of community-acquired pneumonia (Okimoto *et al.*, 2004; Watanabe & Takahashi, 2008).

In Japan, on the contrary to other countries, clinical expression of the disease has frequently been observed in children (Hirai & To, 1998) (Table I). The study by To *et al.* (1996) suggested that Q fever was an important cause of atypical pneumonia in Japanese children. Cases of hepatitis have also been reported and can potentially be fatal (Kuroiwa *et al.*, 2007). The difference in prevalence of infection in Japanese children compared to children from other countries could be due to: (1) a more frequent clinical expression (as mentioned here above) due to a different virulence of the bacterial strain or to a greater sensitivity of the host, increasing the probability of diagnosis; (2) to a greater awareness of physicians of the possibility of Q fever infection in atypical and/or non-specific clinical cases.

In pregnant women, clinical expression of Q fever, initially asymptomatic, consists in abortions, intrauterine growth retardation, fetal and neonatal death, oligoamnios or premature delivery (Peter et al., 1987; Numazaki *et al.*, 2000; Desling & Kullberg, 2008; Hartzell *et al.*, 2008; Schimmer *et al.*, 2008; Vaidya et al., 2008b; Frangoulidis *et al.*, 2009). Sporadically other clinical signs have been reported (such as osteomyelitis, septic arthritis, pericarditis, myocarditis, arteritis, hemolytic anemia, granulomatous hepatitis, lymphadenopathy, Guillain-Barré, optic neuritis, paralysis of the oculomotor nerve, meningitis, encephalitis, polyradiculonevritis, peripheral neuropathy, cranial nerve deficiency, and exanthema) (Hirai & To, 1998; Frangoulidis *et al.*, 2009; Million *et al.*, 2009; Pape *et al.*, 2009).

In Japan, such as other countries, chronic infection leads commonly to endocarditis (Yuosa et al., 1996). Chronic hepatitis, osteomyelitis, septic arthritis, interstitial lung disease (Berri *et al.*, 2007), and infection of aneurysm and vascular grafts (Delsing & Kullberg, 2008; Ughetto *et al.*, 2009) have also been reported in chronic cases of Q fever (Frangoulidis *et al.*, 2009; Pape *et al.*, 2009). Individuals with underlying valvulopathy or other cardiovascular abnormalities are predisposed to the development of endocarditis (Maurin & Raoult, 1999; Kuroiwa *et al.*, 2007; Delsing & Kullberg, 2008; Harzell *et al.*, 2008; Million *et al.*, 2009;

Pape *et al.*, 2009; Ughetto *et al.*, 2009). Furthermore, chronic fatigue syndrome has been diagnosed in previously infected individuals (Berri *et al.*, 2007; Million *et al.*, 2009).

2.2. In farm animals

C. burnetii is widespread among cattle population in Japan (4.4 millions of heads). Bovine coxiellosis is rarely an overt disease, except for reproductive disorders (such as abortion, infertility, metritis and mastitis) in females likewise to other parts of the world (To *et al.*, 1995, 1998a; Vaidya et al., 2008a). Although high rates of abortions are rarely observed in cattle (Palmer et al., 1983), shedding of large quantities of germs remains a reality in the absence of any clinical sign. A retrospective study by Bildfell *et al.* (2000) demonstrated that *C.burnetii* only sporadically leads to abortion in cattle, but was significantly associated with placentitis. Some studies have reported an increase in seroprevalence of Q fever in Japanese cattle in recent years (Hirai & To, 1998). Cattle play an important role in maintaining infection and in dispersing the organism in the environment (Beaudeau *et al.*, 2006; Guatteo *et al.*, 2006; Rodolakis *et al.*, 2007) They are one of the major reservoirs of *C. burnetii* in Japan (To *et al.*, 1998a). The controversy associated to transmission of Q fever through milk ingestion is of minor importance for the Japanese population. Indeed shedding of *C. burnetii* in milk has a very limited impact as raw milk is seldom ingested by the native population (Okimoto *et al.*, 2004). Raw milk is commonly pasteurized at 63°C for 30 minutes or more therefore no problem is expected (Watanabe & Takahashi, 2008).

The rarity of sheep (10,000 heads) and goats (32,000 heads) populations renders these animals non significant for the spread of the disease (Hirai & To, 1998). Q fever has not been reported in pigs as yet but available data remains scarce (Hirai & To, 1998).

2.3. In pet animals

Dogs and cats have been found to be positive for *C. burnetii* by serology and bacteriology throughout the Japanese territory (Hirai & To, 1998; Komiya *et al.*, 2003). Nagaoka *et al.* (1998) isolated *C. burnetii* in swabs of feline vaginal mucosa and suggested that the organism could be associated with reproductive disorders or abortions in the feline species. Further epidemiological study about the relationship between feline disorders and *C. burnetii* infection are suggested by the authors (Nagaoka *et al.*, 1998). Small human outbreaks of coxiellosis associated with the presence of infected parturient cats have been reported in several studies (Marrie *et al.*, 1988a; Marrie *et al.*, 1988b; Marrie *et al.*, 1989; Pinsky *et al.*, 1991). Cats are thus considered as a potential source for human infections in this country. However premature conclusions must not be made and supplementary evidence of feline to human transmission of Q fever is necessary with special attention to potential confounding factors. Outbreaks associated to infected dogs have not yet been reported to our knowledge. The dogs' role as reservoir of the pathogen remains poorly explored.

3. EPIDEMIOLOGICAL DATA

The epidemiology of Q fever in Japan remains to be elucidated and the exact modes of transmission are still unproven (Hirai & To, 1998). The review by Hirai and To (1998) attempted to explain the epidemiology of Q fever in Japan. Figure 1 illustrates their hypotheses. Environment and ticks would be responsible for infection of domestic animals; infected domestic animals hereafter leading to human infections. Transmission directly from infected wild animals to humans would also be possible. Ticks could play a role in transmission of disease from the environment to domestic animals. Tick transmission from domestic and wild animals to humans (Hirai & To, 1998) is considered minor.

3.1. Prevalence of Q fever in animals

Hirai and To (1998) reported the seroprelavence of Q fever in domestic and wild animals present in Japan (Table I). Several authors contributed to these estimations. In domestic animals, cattle with reproductive disorders had the highest percentage of seroprevalence of coxiellosis. A significant level of seropositivity was detected in wild animals but the results must be interpreted with care as the sample size is often limited. Crows (seroprevalence of 36%) could be involved in transmission of *C. burnetii* from infected areas to non infected areas.

In a study performed by To *et al.* (1998b) many wild birds were found to be seropositive against *C. burnetii* by monoclonal antibody assay (MA). The polymerase chain reaction (PCR) also used in this study confirmed the serological results by detecting the bacterial DNA. Furthermore areas where infected livestock was present were associated with a higher seroprevalence of Q fever in birds. The authors suggested that wild birds could be used as indicators of foci of infection (To *et al.*, 1996). Domestic birds were also found to be seropositive for Q fever and capable of infecting humans (Hirai & To, 1998) rendering additional investigation necessary, especially to determine the eventual role as natural reservoir of *C. burnetii* (dejection, soil). In 2006, chicken products were highly suspected as responsible for Q fever infections in humans (Muramatsu *et al.*, 2006). *C. burnetii* was detected in market eggs and mayonnaise (Tatsumi *et al.*, 2006). Initially the probability that the bacteria were alive was considered high (Tatsumi *et al.*, 2006). However, the results of further investigations remain non precise and incomplete. PCR-based detection of *C. burnetii* DNA in dead bacterial fragments was reported but there are no reports demonstrating contamination with viable bacteria (Watanabe & Takahashi, 2008). No data is available concerning the extent of transmission of *C. burnetii* from wild animals and birds to humans and domestic animals (Hirai & To, 1998). Its epidemiological importance, however, is considered minor (Hirai & To, 1998). A previous study reported that four out of 11 Japanese

wild species had a prevalence of infection higher to 50%, two had a prevalence of infection lesser to 50%, and five species were free from infection (Ejercito *et al.*, 1993). Three hypotheses could explain absence of infection in the five species: the species were either isolated in a area free from Q fever, or they had an innate resistance to infection, or were false negative animals due to a lack of sensitivity of the laboratory diagnostic method (Ejercito *et al.*, 1993). Further epidemiological studies are necessary to explain this apparent or real resistance to infection.

To *et al.* (1998a) studied the seropositivity rate in herds of dairy cattle with reproductive disorders in Japan. The three main reproductive problems studied were infertility, metritis and mastitis. The rates of positivity were assessed by indirect immunofluorescence assay (IFA) (with a distinction for phase 1 antibodies and phase 2 antibodies), by PCR (in sera and milk samples) and by isolation (in milk samples). Phase 2 antibodies and phase 1 antibodies are associated with acute and with chronic infections, respectively. The study showed that 60.4% of the cows considered were seropositive by IFA towards phase 2 bacteria. In addition, 3.9% and 24.6% were seropositive by PCR on sera and milk respectively. All PCR-positive samples were confirmed by isolation. Whatever the laboratory method, a positive result was always obtained. This study by To *et al.* (1998a) demonstrated that in herds with reproductive disorders the prevalence of Q fever was far from nil.

In studies on feline seroprevalence, stray cats were found to have a higher incidence of infection than domestic cats (Nagaoka *et al.*, 1998; Komiya *et al.*, 2003) (Table I). In this species it is suspected that Q fever could be responsible for breeding disorders (Nagaoka *et al.*, 1998).

3.2. Prevalence of Q fever in the Japanese population

Table I reports the seroprevalence in humans in Japan (Hirai & To, 1998). It is interesting to notice that many healthy humans are seropositive to Q fever. In this study, the seroprevalence of infection was relatively high in children with respiratory disorders, flu-like symptoms, atypical pneumonia and in adults with chronic respiratory disease (Hirai & To, 1998). Sample size is a problem for interpretation in certain categories of human beings. Table II reports the estimated number of cases of community-acquired pneumonia in Europe and the USA from 1989 to 2001. In Japan, the incidence rate of Q fever has significantly increased between 2000 and 2004. However, Q fever has been underdiagnosed for many years in Japan and increased awareness and recognition of the illness might be responsible for the increase observed in this study (Watanabe & Takahashi, 2008).

3.3. Isolation of *C. burnetii* from animals and humans

Hirai and To (1998) reported the isolation rates of *C. burnetii* in different animals present in Japan (Table I). Fetuses of healthy cattle had a high content in bacteria. Ticks of the *Ixodes* order were significantly infected by *C. burnetii*. Indeed 75% of the sampled *Ixodes* ticks in the Toyama prefecture were infected by the bacteria.

As mentioned previously, cats are considered a significant source of *C. burnetii* in Japan (Marrie *et al.*, 1988a; Marrie *et al.*, 1988b; Marrie *et al.*, 1989; Pinsky *et al.*, 1991). In the study by Nagaoka *et al.* (1998) bacteria were isolated from vaginal swabs of asymptomatic cats as well as of cats with respiratory disorders, with fever or with fever and abortion. The bacteria were also isolated in cats with atypical clinical manifestations (compared to human clinical manifestations) such as peritonitis and mammary tumors.

Table I reports the isolation rates of *C. burnetii* in humans with various clinical signs (Hirai & To, 1998). The rate of isolation in children is particularly high compared to those observed in other parts of the world (To *et al.*, 1996; Maurin & Raoult, 1999). Positive serologies,

occasionally associated to bacterium isolation, were a relative frequent finding in adults with fever of unknown origin (Knockaert et al., 2003; Arnow and Flaherty, 1997; Hirschman, 1997; Lozano et al., 1996). In consequence, Q fever serology should be included in the standard work-up of fever of unknown origin in Japan. To confirm these results a second study with larger samples of humans would be necessary.

4. DIAGNOSIS OF Q FEVER AND VACCINATION

Q fever is rarely mentioned in Japanese medical text books and many physicians are unaware of its existence (Watanabe and Takahashi, 2008). Similarly, Japanese veterinarians are insufficiently informed about the risks associated to manipulations of infected animals or infected biological matter (Abe *et al.*, 2001). Thus the recognition of Q fever infections remains limited throughout the country (Watanabe & Takahashi, 2008). Reported clinical cases are rare with the first clinical case reported dating from 1989 (Watanabe & Takahashi, 2008). Increasing the physicians' awareness of the possibility of Q fever infections is essential as rapid diagnosis is known to improve prognosis (To *et al.*, 1996). Table III reports the different aspects of the illness to facilitate diagnosis by a clinician (Watanabe & Takahashi, 2008). To reach definite diagnosis IFA, complement fixation test (CFT), enzyme linked immunoassay (ELISA) and PCR are available (e.g., Field et al., 2000; Ughetto et al., 2009). Imported IFA and ELISA kits present problems when used on Japanese individuals. Indeed, it has been observed that the increase in IgM antibodies in many Japanese patients infected in Japan is slow; whereas the increase in IgM antibodies is very rapid in Japanese patients infected abroad. This suggests that *Coxiella* strains vary between different countries (Watanabe & Takahashi, 2008). Moreover, the Japanese population might have a different physiological response to infection compared to Caucasians. Currently, results obtained with

imported IFA and ELISA kits remain difficult to interpret. Furthermore, ELISA kits require a retest with the standard IFA before evaluating a patient (Watanabe & Takahashi, 2008). In conclusion, new rapid diagnostic tests specifically using the Japanese strain of *C. burnetii* are indispensable. In addition, a larger number of Japanese institutions and laboratories should be equipped with the diagnostic tests (Watanabe & Takahashi, 2008). Vaccination is uncommon in Japan because of the limited recognition of the disease (Watanabe & Takahashi, 2008).

5. CONCLUSION AND PERSPECTIVES

Q fever is a newly discovered disease in Japan. Previously it was considered completely absent. Knowledge of the illness is thus limited. Available epidemiological data consists frequently of small samples of animals or humans rendering the interpretation poorly accurate. The lack of knowledge of the epidemiological and geographical situation in certain areas of the country also causes problems. The estimation of the prevalence or incidence of Q fever is difficult due to the recent awareness of the illness, to the absence of previous data and to seroprevalences estimated on sampled individuals that are not necessarily representative of the endogenous population. Recently differential diagnoses are including Q fever and cases are being diagnosed and reported. Important further research is however necessary to improve knowledge of the disease itself, of the endogenous hosts and reservoirs (e.g., the role of domestic birds should be more investigated), and of the epidemiological cycle of coxiellosis in this country. Diagnostic tests must be improved to increase their sensitivity and avoid the necessity of retesting. They must be adapted to the Japanese strain of bacteria and to the Japanese conditions. The multidisciplinary approach needed would involve a large variety of scientists. To this day, Q fever remains a challenge for the veterinary and medical profession.

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Figure and table legends

Figure 1. Epidemiology of Q fever in Japan (from Hirai and To, 1998)

Table I. Seroprevalence and isolation of *Coxiella* in animals and humans from Japan, through 1990 to 2008 (from Hirai and To, 1998; Hirai, 1999; Nagaoka *et al.*, 1998 and various sources)

Table II. Incidence of Q fever as a cause of community-acquired pneumonia in Japan, Europe, Asia, Africa and America (from Watanabe and Takahashi, 2003 and 2008 and varied sources)

Table III. Diagnostic points of acute Q fever (from Watanabe and Takahashi, 2008)

Table I. Seroprevalence and isolation of *Coxiella* in animals and humans from Japan, through 1990 to 2008 (from Hirai and To, 1998; Hirai, 1999; Nagaoka *et al.*, 1998 and various sources)

Parameter	Kingdom	Species	Number of samples	% of positive	Reference
Seroprevalence	Animal	Healthy cattle	329	29.2	Yoshiie *et al*. (1991)
			562	46.6	Htwe *et al.* (1992)
			1501	25.4	Htwe *et al.* (1992)
			619	16.9	Nguyen *et al.* (1997)
		Reproductive disorder cattle	102	84.3	Htwe *et al.* (1992)
			166	78.9	To *et al*. (1995)
			207	60.4	To *et al*. (1996)
		Sheep	256	28.1	Htwe *et al.* (1992)
		Goat	85	23.5	Htwe *et al.* (1992)
		Dog	635	15	Htwe *et al.* (1992)
			589	10.2	Nguyen *et al.* (1997)
			81	9.9	Nagaoka *et al*. (1996)
			301	16.6	Hirai (1999)
		Cat	274	0	Htwe *et al.* (1992)
			100	16	Morita *et al*. (1994)
			150	15.3	Nguyen *et al.* (1997)
			101	6.7	Nagaoka *et al.* (1996)
			304	18.8	Hirai (1999)
		Pig	396	0	Htwe *et al.* (1992)
		Chicken	1589	2	To *et al*. (1996)
		Quail	174	2.9	To *et al*. (1996)
		Duck	158	2.2	To *et al*. (1996)
		Bear	36	77.8	Ejercito *et al.* (1993)
		Deer	133	61.7	Ejercito *et al*. (1993)
		Hare	8	62.5	Ejercito *et al*. (1993)
		Monkey	54	27.7	Ejercito *et al.* (1993)
		Nutria	32	12.5	Ejercito *et al*. (1993)
		Wild rodent	129	24.1	Hirai *et al.* (1998)
		Crow	431	36	To *et al*. (1996)
		Rock Dove	201	6	To *et al*. (1996)
	Human	Veterinarians	9	22.2	Yoshiie *et al.* (1991)
		Healthy humans (adults)	60	3.3	Htwe *et al.* (1992)
			275	22.2	Htwe *et al.* (1992)
		Meat-processing workers	107	11.2	Htwe *et al.* (1992)
		Adults with respiratory disorders (in general)	184	15.2	Htwe *et al.* (1992)
		Adults with atypical pneumonia	284	1.4	Okimoto *et al.* (2004)
			120	4.17	Watanabe and Takahashi (2008)
		Children with flu-like symptoms	55	32.7	Nagaoka *et al.* (1996)
		Children with atypical pneumonia	56	35.7	To *et al*. (1996)
			58	46.55	Maurin and Raoult (1999)
		Hospitalized patients (adults)	3000	5.2	Nguyen *et al.* (1997)
		Veterinary students	275	35.64	Htwe *et al.* (1993)
		Adults with acute exacerbation of chronic respiratory disease	80	2.5	Okimoto *et al.* (2007)

		Adults with acute exacerbation of COPD*	240	0.4	Lieberman *et al.* (2001)
Isolation	Animal	Cattle with reproductive disorder (raw milk)	207	24.6	To *et al*. (1995)
		Healthy cattle (raw milk)	47	36.3	Nagaoka *et al.* (1996)
		Healthy cattle (fetus)	4	50.0	To *et al*. (1995)
		Tick (Ixodes spp.)	15	26.7	To *et al*. (1995)
		Dogs (sera)	5	100	To *et al*. (1996)
		Cat (sera, uterus swabs)	5	100	To *et al*. (1996)
	Human	Acute Q fever (adults)	1	100	Oda *et al.* (1989)
		Atypical pneumonia (children)	58	36.2	To *et al*. (1996)
		Hospitalized patients (adults)	17	76.5	Hirai *et al.* (1997)
		Chronic Q fever endocarditis (adults)#	56	7.1	Yuosa *et al.* (1996)

Legend: *: COPD: chronic obstructive pulmonary disease; #: Light microscopic observation.

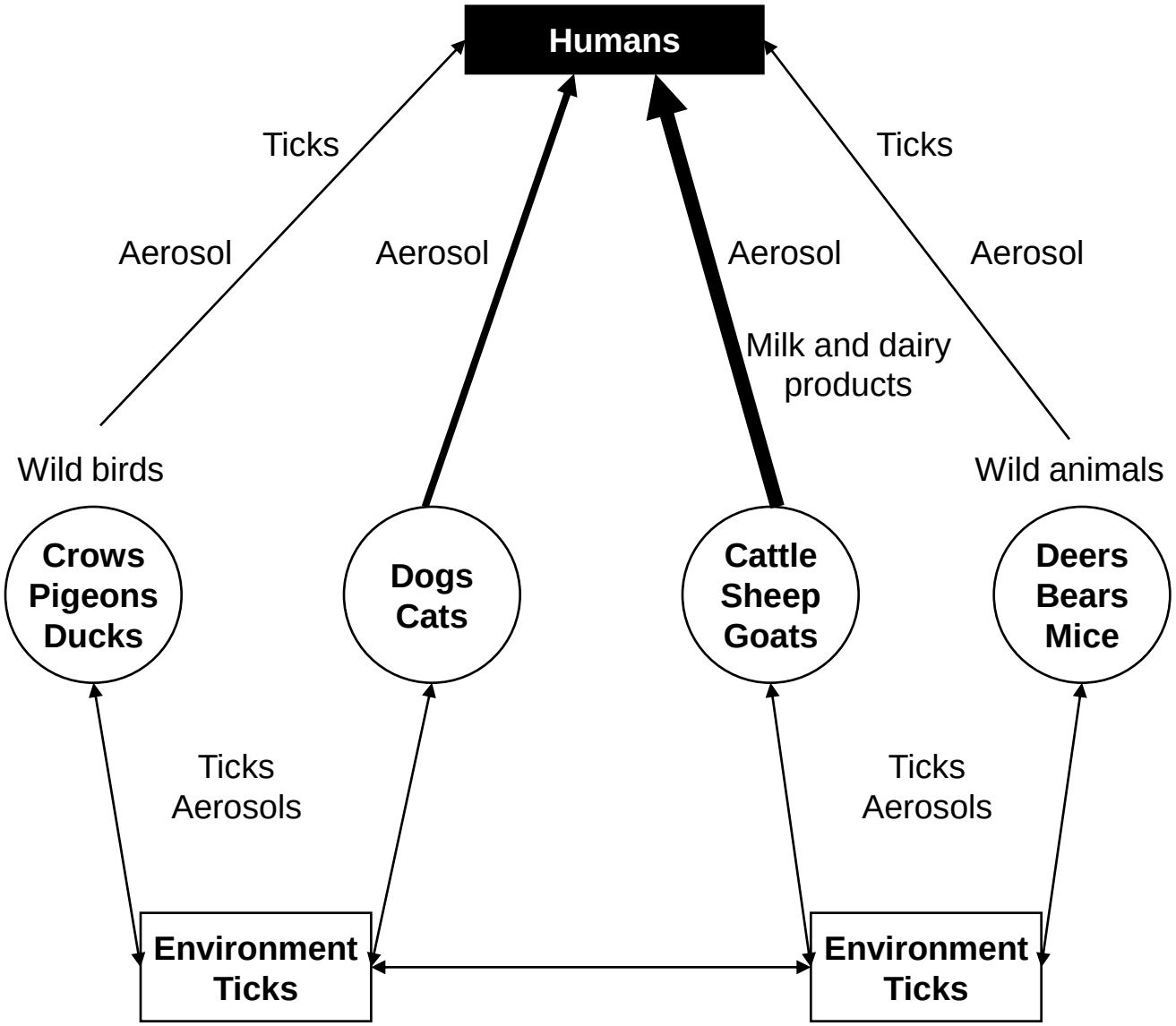
Table II. Incidence of Q fever as a cause of community-acquired pneumonia in Japan, Europe, Asia, Africa and America (from Watanabe and Takahashi, 2003 and 2008 and varied sources)

Area	Report year	No of patients	No of Q fever cases	Incidence (%)	Reference
Africa	1997	65	6	9.2	Koulla-shiro *et al.* (1997)
America (USA)	1996	149	4	2.7	Marrie *et al.* (1996)
	2001	170	4	2.4	Bochud *et al.* (2001)
Asia	1997	346	20	5.8	Lieberman *et al.* (1996)
Europe	1991	225	18	8.0	Albornoz *et al.* (1991)
	1996	124	3	2.4	Torres *et al.* (1996)
	1997	106	19	17.9	Zalacain *et al.* (1997)
	1998	173	4	2.3	Sopena *et al.* (1998)
	1999	395	11	2.8	Ruiz *et al.* (1999)
Japan	2000	232	2	0.9	Saito *et al.* (2006)
	2004	284	4	1.4	Okimoto *et al.* (2004)
	2004	400	10	2.5	Takahashi *et al.* (2004)

Table III. Diagnostic points of acute Q fever (from Watanabe and Takahashi, 2008)

Area	Criteria	Key points
Clinical viewpoint	Opportunities for contact with animals	▪ It should be noted that even slight contact may lead to an infection ▪ The risk of mass exposure is high around an animal after delivery ▪ An epidemic outbreak is possible at home or in an office
	Subjective and objective symptoms	▪ Systemic symptoms such as high fever, arthralgia, and malaise are significant ▪ Influenza-like symptoms in the "off-season"
	Responsiveness to antimicrobial drugs	▪ ß-Lactam antibiotics are basically ineffective (spontaneous remission during treatment is possible) ▪ Tetracyclines, macrolides and quinolones are effective
Etiological diagnosis	Measurement of antibody titers to phase II Coxiella	▪ It is often impossible to evaluate antibody titers based only on acute phase serum samples ▪ It may take a few months for antibody titers to increase ▪ It is important to monitor antibody titers even after recovery from the disease
	PCR-based detection of the Coxiella gene	▪ It is often necessary to use a nested PCR technique ▪ Detection is also possible in various samples from outside the respiratory system ▪ For suspected cases, acute phase samples should be kept in a freezer ▪ At present PCR should be considered as an adjunct diagnostic technique
	Overall evaluation	▪ The clinical picture changes in antibody titers and PCR results should be integrated into the evaluation ▪ It is necessary to differentiate the pathogen from *Mycoplasma*, *Chlamydia*, and *Legionella*

Figure 1.


Humans
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Milk and dairy products
Wild birds
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Crows
Pigeons
Ducks
Dogs
Cats
Cattle
Sheep
Goats
Deers
Bears
Mice
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Aerosols
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