

# Q fever in the Netherlands: a concise overview and implications of the largest ongoing outbreak

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## ABSTRACT

Two outbreaks of Q fever were reported in the Netherlands in 2007 and 2008. The ongoing 2008 outbreak in the south-eastern part of the Netherlands is the largest community outbreak ever described, with 808 cases reported until August 2008. The changing epidemiology of Q fever is most likely related to intensive goat farming, and has important implications for the clinical care of patients in endemic areas. Treatment of community-acquired pneumonia has to take possible Q fever into account, and the high incidence of Q fever endocarditis and other manifestations of chronic Q fever require a specific diagnostic and therapeutic approach.

## INTRODUCTION

In 2007, an outbreak of Q fever was reported in the Netherlands, in particular around the town of Herpen. In 2008, a remarkable further increase in Q fever cases was noted around the city of Nijmegen, in the provinces of Noord-Brabant and Gelderland, causing considerable morbidity and a high number of hospital admissions. Until 13 August 2008, 808 cases were notified, constituting the largest community outbreak of Q fever reported in the literature.<sup>1</sup>

Q fever is an ubiquitous zoonosis, caused by *Coxiella burnetii*, an obligate intracellular coccobacillus. Q stands for query, dating from the period when the causative agent was still unknown. The first confirmed cases were described in 1937 as a febrile illness in abattoir workers in Brisbane, Australia. Subsequently, the pathogen was isolated by Cox and Davis from ticks in Montana and by Burnet from Derrick's patients, and named *Coxiella burnetii*.

## ACUTE ILLNESS

The incubation period varies from two to six weeks, depending on the infective dose. Most cases are asymptomatic (60%) or have mild flu-like symptoms. Only 20% of infected patients seek medical attention, and 2 to 3% are admitted to a hospital. The mortality rate is 1 to 2%.<sup>2</sup> Symptomatic patients present with a sudden onset of high fever, chills, severe headache and dyspnoea. Laboratory results show acute-phase reaction and often mild hepatitis. Chest X-rays usually reveal nonspecific infiltrates.<sup>3</sup> In some patients, the clinical course is complicated by pericarditis, myocarditis, pancreatitis or haemolytic anaemia. The recent epidemic around Nijmegen has led to a considerable number of hospital admissions, including patients in need of intensive care and ventilatory assistance.

## CHRONIC Q FEVER

A small proportion of infected patients develop chronic Q fever. Endocarditis is the most frequent manifestation, occurring in approximately 1% of patients following Q fever.<sup>4</sup> Conversely, Q fever represents 3 to 5% of all cases of endocarditis.<sup>5</sup> Q fever endocarditis usually occurs in patients with preexisting valvulopathy. Echocardiography reveals vegetations in only a small percentage of these patients, which makes diagnosis difficult. Modified Duke criteria have been developed for the diagnosis of Q fever endocarditis.<sup>6</sup> Recent data suggest that endocarditis may develop in up to 40% of patients with pre-existing valvular defects.<sup>4</sup> Graft infection may occur in patients with vascular prostheses. A high level of suspicion is crucial to diagnose patients with possible vascular infection in endemic areas. Other factors predisposing to Q fever endocarditis are immunosuppression, pregnancy, liver cirrhosis or cancer.

## Q FEVER AND PREGNANCY

Pregnant women are especially prone to infection with Q fever. Q fever infection during pregnancy is almost always asymptomatic, but may result in obstetric complications such as spontaneous abortion, intrauterine growth retardation, foetal and neonatal death, or premature delivery.<sup>7,8</sup> Complications have been described in over 80% of women with Q fever during pregnancy. This percentage seems to be markedly reduced in women receiving long-term therapy with cotrimoxazole, but still remains considerably high (44%).<sup>7</sup> Adverse outcome of pregnancy occurs in particular after infection during the first trimester. In addition, pregnancy may lead to reactivation of previous infection. After infection during pregnancy, breast feeding is considered contraindicated. This has major consequences for mother and child. The recent epidemic has raised the question whether pregnant women living in areas with high incidence of Q fever should be offered screening for Q fever.

## LONG-TERM SEQUELAE

Following acute infection with Q fever, patients frequently report long-lasting fatigue, often for more than six months. Ten years' follow-up of patients after an outbreak in the UK revealed a high percentage of persisting fatigue, with almost 20% of patients fulfilling the criteria of chronic fatigue syndrome at ten years after acute infection, compared with 5% in controls.<sup>9</sup> In Australia, courts have granted large compensation for abattoir employees with chronic fatigue syndrome. Chronic fatigue after acute Q fever infection may be reported more frequently in the Netherlands following the recent epidemic and will result in considerable costs for the society.

## DIAGNOSIS OF Q FEVER

Serology is the most important diagnostic tool for Q fever. Indirect immunofluorescence (IF) is the reference method.<sup>5</sup> Complement fixation is also available, but more laborious and less specific and sensitive than IF. Serological cross reactions with other micro-organisms occur, including *Legionella* and *Leptospira* species. *Coxiella burnetii* displays a unique antigenic variance in surface polysaccharides, which can be used to distinguish between acute and chronic infection. In acute infection, phase 2 antibodies develop, whereas chronic infection is characterised by high titres of phase 1 antibodies. Polymerase chain reaction (PCR) is highly specific and, although still in an experimental phase, can be useful in early diagnosis, since antibody response may not develop until a few weeks after onset of symptoms. It can become positive again in chronic Q fever. Culture of *C. burnetii* is difficult, as it is an obligate intracellular bacterium. Special

precautions need to be taken because of high infectivity and handling is restricted to specialised laboratories.

## EPIDEMIOLOGY

The most important reservoir is formed by sheep, goats and cattle. Domestic animals such as dogs, cats, rabbits and birds can also carry the disease. Ticks are thought to spread the disease among animals. Infected animals excrete the bacteria in milk, faeces, urine, and in high concentrations in amniotic fluid and the placenta. The animals are often asymptomatic except for increased incidence of spontaneous abortion. Infection in humans occurs through inhalation of contaminated aerosols or ingestion of unpasteurised milk. *Coxiella* is resistant to chemical and physical disinfectants. A small inoculum is sufficient to cause clinical illness. Human-to-human transmission does not usually occur, although it has been described following contact with infected parturient women.

A sero-epidemiological survey in the Netherlands performed in 1983 using immunofluorescence showed a seroprevalence of 24% in blood donors and 84% in veterinarians.<sup>10</sup> Results of serosurveillance as part of a case-control study during the 2007 outbreak around the town of Herpen have not yet been published. Until 2007, 10 to 20 cases of *Coxiella* infection were reported to the health authorities in the Netherlands each year, and no seasonal fluctuation was observed. These cases predominantly involved patients with occupational risk (farmers, veterinarians, slaughterhouse personnel). In 2007 a total of 167 cases were reported, most of whom had no occupational risk, but lived in a distinct area in the south-eastern part of the Netherlands. The outbreak correlated with the density of goat farms in this area, and the veterinary authorities had reported Q fever in local goat farms in 2006 and 2007.<sup>11</sup> In 2007 and 2008, a seasonal variation has been observed with peak incidence from December to May, correlating with spread of manure from goat stables. In 2008, a marked increase in reported cases of Q fever has occurred. Since most patients are asymptomatic, the true number of infections is probably much higher than the more than 800 cases reported until now. Recently, a mandatory notification of Q fever in ruminants, including compatible symptoms, such as abortion, has been instituted. Also, restriction for visitors to infected farms and a ban on spreading manure for three months have been imposed.<sup>1</sup>

## TREATMENT

Increased awareness in areas with a high incidence of Q fever is crucial. Most patients with acute Q fever are asymptomatic or have only mild symptoms, and therefore will not seek medical attention. Patients presenting with

acute illness should be treated with doxycycline 100 mg twice daily for two to three weeks. Antibiotic treatment shortens the duration of fever and accelerates the recovery in case of pneumonia.<sup>3</sup> Treatment with fluoroquinolones is an alternative. Cotrimoxazole is advised for treatment of children.

In endemic areas, these recommendations should overrule the standard guidelines for treatment of community-acquired pneumonia, such as the national guidelines in the Netherlands issued by the Dutch Working Party on Antibiotic Policy (SWAB) and the Dutch College of General Practitioners (NHG), which do not routinely cover *Coxiella burnetii* in moderately ill patients.<sup>12</sup>

Long-term treatment of endocarditis with combination therapy of doxycycline (100 mg twice daily) and hydroxychloroquine (200 mg twice daily) for at least 12 to 18 months have yielded favourable results.<sup>13</sup> Because of the high incidence of endocarditis following acute Q fever in patients with pre-existing valvulopathy, some experts recommend 12 months of combination therapy with doxycycline and hydroxychloroquine for this selected group.<sup>4</sup>

Q fever during pregnancy is treated with long-term therapy with cotrimoxazole (960 mg twice daily), at least until delivery. Further treatment with doxycycline and hydroxychloroquine may prevent persistence of Q fever.<sup>8</sup> Mothers should be instructed to refrain from breast feeding, and serological screening is needed during subsequent pregnancies.

## PREVENTIVE MEASURES

Effective vaccines have been developed but are currently not available in the Netherlands. Pregnant women are advised to avoid contact with cattle farms that are suspect of being infected with Q fever.

A conference held by the Dutch Health Council and the National Institute for Public Health and Environment (RIVM) in July 2008, attended by international experts on the subject, addressed the usefulness of screening pregnant women for Q fever, and the possible transmission of Q fever by blood transfusion. It was concluded that the currently available diagnostic tests for Q fever are not suitable for screening of large groups. Moreover, the efficacy and possible disadvantages of long-term use of antibiotics is still unknown. Further epidemiological research of the risks of Q fever during pregnancy will be conducted. Based on international data, the risk of transmission by blood transfusion seems negligible and the policy for blood donors should not be changed. The necessity of taking further measures to prevent transmission of Q fever from animals to humans will be investigated. Since 12 June 2008, Q fever has been designated by the Dutch government to be a reportable

disease in goats and sheep. Spread of manure of infected goat farms is prohibited for at least 90 days after suspicion of infection.

## CONCLUSIONS

Q fever is an emerging epidemic disease in the Netherlands with considerable morbidity and serious long-term complications. Further increase in reported cases is likely in the coming years. Physicians need to be aware of the increased incidence of chronic Q fever, and of the appropriate diagnostic procedures and empirical therapy. More effort will have to be taken to prevent infections. New guidelines for general practitioners and gynaecologists are under construction. When treating a community-acquired pneumonia, a possible infection with Q fever should be taken into account, resulting in a deviation from the national SWAB treatment guidelines for community-acquired pneumonia.

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