



## WIDE-RANGING OVERVIEW OF RESEARCH DURING SYMPOSIUM ON Q FEVER

On Thursday June 7, 2012, the *Trippenhuis* (headquarters of the Royal Netherlands Academy of Arts and Sciences) in Amsterdam was packed to the rafters for an international symposium on Q fever. National and international experts told 200 attendees about the results of diverse scientific, mainly PhD studies and about the lessons that had been learned from the Dutch epidemic of 2007-2009. At the end of the day, the importance of collaboration between all sectors involved in combatting zoonoses was emphasized once again by the signing of a covenant between the Dutch Food & Consumer Product Safety Authority (NVWA), the Netherlands Municipal Health Services (GGD), the Netherlands Animal Health Service (GD), and the National Institute for Public Health and the Environment (RIVM).

The symposium was organized by the RIVM in cooperation with the Central Veterinary Institute (CVI), the GD, the Jeroen Bosch hospital, the Canisius Wilhelmina hospital and the Netherlands Organization for Health Research and Development (ZonMw). The program was very full indeed: even before the coffee break, twelve PhD candidates had given presentations on epidemiological, immunological, financial and patient-related aspects of Q fever. These studies examine some of the many questions that arise during an outbreak, such as dissemination from the focus of infection, the localization of the source of a large-scale outbreak, the risk and protective factors related to infection in man and animal, the dosage-response relationship and the manner of the spread of *Coxiella burnetii* as well as the effects on the health and quality of life of the patients. These studies sometimes delivered unexpected results. For instance, people in the vicinity of an infected farm appeared to be more often affected than was initially apparent: on a goat farm in Limburg that became infected in March 2009, almost all the employees were infected. Half of the farm visitors and other contacts also proved to be infected. In the neighboring village, the prevalence of antibodies to the bacteria was 12 percent indicating that there was high regional dissemination from the farm. Another surprising preliminary finding was that the more it rained the more *Coxiella* DNA was

found in air samples; there is no explanation for this yet. Air measurements were taken at eight sites in Brabant varying between 100 to 600 meters from goat farms. Further investigations are to take place on the farms, at varying points in time around the lambing season. Investigations will also be done on pig and sheep farms.

### **Complex**

Immunological findings are the starting points for the development of new diagnostic tests and vaccines. Interferon-gamma (IFN- $\gamma$ ) and interleukin-2 (IL-2) both play a role in the immune response to *Coxiella burnetii*. When compared with the results from people who have had Q fever in the past, IFN $\gamma$  has been shown to be strongly elevated in people who have chronic Q fever even though IL-2 is actually very low in this group. At the St. Radboud University Medical Center in Nijmegen and the CVI in Lelystad, *in vitro* models have been developed to expose immune cells to the bacteria. Also genes that play a role in the recognition of *Coxiella* have been found. This development also provides diagnostic possibilities.

The GGD in the Dutch province of Brabant, has carried out research into aspects of health and of the costs related to Q fever. Almost half of those affected have long-term fatigue and a poorer quality of life. The cost to the human sector has not yet peaked, but during the years 2007-2009 the costs incurred by both the veterinary and the human sectors has been estimated at 600 million euro. Around 85 percent of these costs are due to absence from work through illness and the lowered quality of life of those affected. However, this type of research, which is mainly carried out through patient questionnaires, is rather complex. Professor Didier Raoult (Université de la Méditerranée, Marseille) warned that conclusions should be drawn only cautiously. "The answers given in questionnaires are culturally determined. For example, the percentages of fatigue were found to be different depending on the country where the research took place. Moreover, people always try to explain away their symptoms with something that had happened before - an outbreak of a disease for example."

## **Staying alert**

There was a separate session on the diagnosis and treatment of Q fever. An accurate diagnosis is of course enormously important to patients, but acute episodes of Q fever are usually asymptomatic. At 15 to 20 percent, the death rate among people with chronic Q fever is high. The message is to remain alert to chronic Q fever and possibly to screen high-risk groups in areas where there is a lot of Q fever. One study in Groningen, however, found nothing to support the screening of pregnant women in high-risk areas.

Dr. Robert Massung (National Center for Emerging and Zoonotic Infectious Diseases, CDC, USA) compared the situation in Europe with that in the US, where new guidelines are due to be published this fall. With a seroprevalence of around three percent, theoretically there are about ten million people in the US who have had the infection. However, there are only about two hundred notifications a year. In Massung's opinion this situation has been brought about by a lack of awareness and the asymptomatic nature of the infection. He also pointed out that awareness of the disease is now increasing in the medical world. In diagnosis, the Indirect Fluorescent Antibody Test (IFAT) remains the gold standard. PCR can be used within the first two weeks after the symptoms arise but it is not completely reliable: a negative test does not exclude Q fever. In the US, recommendations for treatment are not much different than in the Netherlands.

One difference is that the US in contrast to the European Centre for Disease Prevention and Control (ECDC) uses different diagnostic criteria and case definitions that differentiate between acute and chronic Q fever, while a single case definition is provided by the ECDC, most resembling an acute infection.

## **Criticism**

As was expected, Professor Didier Raoult of the Université de la Méditerranée, Marseille, which is the French national reference center for Q fever, expressed some criticism of the Dutch approach to the Q fever epidemic. Q fever is endemic in the South of France and Raoult has been working on the disease for three decades. By his own account, years ago he published research on much of what

is now being studied. "For example, that the bacteria cause abortion. This happens in goats, sheep and mice and also in humans. This has been known for years. It surprises me that people are now frightened of this." Raoult also said that there is no difference between acute and chronic Q fever. "The term 'chronic' is misleading and we should no longer use it."

Raoult has proposed new diagnostic criteria for the chronic infections, based on culture results, PCR or immunochemistry, and heart valve problems. However, when Raoult's criteria were applied to 97 chronic patients from the Dutch databank, it appeared that 25 percent fewer patients would have been traced with this method. And this was not the only rebuttal of the vision of the French professor. Roel Coutinho (RIVM) responded: "In 2008 we were required to provide recommendations when not much was known about Q fever. In your lecture essentially you are saying 'follow the leader', but at that time you did not respond to an invitation to give recommendations. The literature had very little to offer in the way of evidence-based information. We really wanted to use this unique situation to gather as much knowledge as possible on a disease about which we knew very little."

### **Difficult aspects**

During the afternoon program which concentrated on risk management, it became clear that vaccination against Q fever has many difficult aspects. When should vaccination be started? When should it be stopped? How can it be determined if a herd is free of infection? And, in fact shouldn't every goat in the world be vaccinated? Answering these questions is not easy. There are still sticking points concerning serology, clinical symptoms and the detection of pathogens – not to mention the cost aspect. In addition, vaccination in humans requires complicated logistics. In Australia between 2001 and 2004, 50,000 people were vaccinated. So far, follow-up of vaccinated people in the Netherlands shows disappointing results in terms of biological markers of protection.. More research into adverse effects, real protection and into cost versus benefit is necessary. At an interactive session where the audience was invited to respond to a number of questions, opinion on various vaccination strategies also proved to be divided. Most people favored vaccination of animals rather than humans as this

appears to be more successful. Many people supported offering vaccinations to high-risk groups for severe infections during a future epidemic.

Another way to reduce the risk of infection is to disinfect farms. Currently there is no protocol for this. If it is carried out then it is generally done with soap and water but this method does not appear to be very effective. The Netherlands Organization for Applied Scientific Research (TNO), the CVI and RIVM are collaborating on research into various disinfection methods and means. Dry disinfection (with a very fine spray mist) appears more promising than wet disinfection (spraying).

There has also been a lot of discussion, particularly at the start of the epidemic, about the role of manure in dissemination of Q fever. However, it has been shown that the bacteria do not survive for long in manure heaps, partially due to the high temperatures found there. "In spite of the fact that sometimes even placentas can be found in manure, we do not think that manure plays a role in the spread of *Coxiella*", said Piet Vellema from the Animal Health Service.

### **Collectively**

The Q fever epidemic has also had an effect on blood transfusions and tissue transplantation in the Netherlands. Donated blood from high-risk areas was tested for the bacteria from May to August 2009, and since October 2010 post-mortem tissue has been screened for *Coxiella* antibodies. As far as is known, there is only a very small risk of infection; one publication (1977) reported one case of transfer of the bacteria by transfusion. And despite a seroprevalence of three percent among tissue donors, the presence of *Coxiella* DNA in tissue has not been demonstrated. Most of those present did not think there was any indication for testing all donors for *Coxiella* or chronic Q fever. Half thought that there should be targeted screening for donors from high-risk groups.

The lesson that has been learned from the Q fever epidemic is that all parties involved should follow one strategy - this includes

veterinarians, advisors from industry and patient groups. Following the publication of the Van Dijk Committee report, a new identification and consultative structure was put in place which has already been implemented in the Schmallenberg virus outbreak. The signals were quickly picked up, information was shared and available to all and there were intensive discussions with national and international experts. "In a good strategy it is important that people know and trust one another", concluded Laurent de Vries, Director of GGD Nederland. "We have confirmed this today by the signing of the collective agreement."

### **Very satisfied**

Looking back on the Q fever symposium, Yvonne van Duynhoven (RIVM) is very satisfied with how it went: "It was an excellent mixture of clinical, veterinary and public health - the much-discussed 'One Health' concept being carried out in practice! Interaction with the audience provided insight into the differences in views and priorities and gave us the opportunity to discuss them. The symposium was an effective way to share knowledge with other disciplines and in particular with people from other countries. The presence of around fifty international guests exceeded our expectations!"

Van Duynhoven is also positive about the scientific presentations: "I take my hat off to the PhD candidates who were able to deliver their latest results in such a short time but so effectively. It bodes well for the future: these scientific researchers and new insights into Q fever and their application in the practice of combatting the disease. During and after the symposium I received very positive reactions - both in person and by email. This shows that at the end of that day I was not the only very satisfied participant."