



## RAPID RISK ASSESSMENT

# Human cases of Q fever and 'fresh cell therapy' in Germany

15 October 2015

### Main conclusions and options for response

- Six human cases of Q fever were associated with a so-called 'fresh cell therapy' performed in Germany on 28 May 2014. An additional case was reported by the Paul Ehrlich Institute in Germany linked to the same practice in October 2014. These cases reconfirm the risk of infectious disease transmission through xenotransplantation. Infectious disease risks, including Q fever transmission, depend on the local epidemiology of disease in the animal population, the strategy for laboratory screening donor animals and xenotransplant products, and the clinical severity of the disease. As the majority of Q fever cases are mild and self-limiting, similar events may remain undetected.
- The potential recipients of fresh cell therapy or other products of animal origin, should be informed of the risks. Organisations that are active in donation and transplantation of substances of human origin should be aware that instances of fresh cell therapy occur, because potential donors who have received animal cells as part such therapy should be rejected for donation. Countries may consider regulating such practices by establishing the national systems for vigilance and traceability of xenotransplantation.

### Source and date of request

Following the Morbidity and Mortality Weekly Report (MMWR) on 2 October 2015 [1], the European Centre for Disease Prevention and Control decided on 5 October 2015 to produce a rapid risk assessment.

### Public health issue

Assessment of the risk of Q fever associated with 'fresh cell therapy' in international and European patients in Germany.

### Consulted experts

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## Disease background information

### Q fever disease

Q fever is a zoonosis caused by the intracellular bacterium *Coxiella burnetii*. This bacterium has been identified in a wide range of wild and domestic animals, including arthropods, birds, rodents, carnivores, ungulates and livestock [2]. The most common reservoirs are cattle, sheep and goats. Humans are primarily infected by contact with an infected animal, most commonly sheep, goats and cattle. In sheep and cattle, *C. burnetii* can grow in large numbers in the uterus and udder. Therefore, humans can become infected when they come into contact with the foetus, placenta or fluids of animal births. As the bacteria can survive for months in dry dust, indirect transmission after exposure to wool, straw or hay has also been documented [3].

Q fever has been endemic in large parts of Europe for several decades. Seroprevalence studies from the period 1970–2009 show that 10–30% of rural populations in different parts of Europe have antibodies against *C. burnetii*. The seroprevalence is higher among farmers working with cattle or sheep, and highest in persons who are in contact with the products of animal births or abortions. Other high-risk groups for infection are veterinarians and personnel in abattoirs and research laboratories working with animals.

The course of human infection ranges from asymptomatic (in about 50% of cases) to severe, but typically results in a mild, self-limiting, influenza-like disease in the event of acute infection. However, about 1.5 to 2% of patients develop a more serious chronic infection, including endocarditis and other complications (e.g. vascular or osteo-articular infections). Estimates of the case–fatality ratio for chronic Q fever vary between 5 and 50% [4]. During the recent outbreak in the Netherlands (2007–2010) the overall mortality rate was 19.1%, while that related to chronic Q fever was 13.0%, with mortality rates of 9.3% among endocarditis patients and 18% among patients with a vascular focus of infection [5]. Infection with *C. burnetii* during pregnancy can also result in spontaneous abortion, premature delivery, low birth weight and the development of chronic *C. burnetii* infection [6]. Doxycycline is the treatment of choice for acute Q fever, but chronic Q fever endocarditis is much more difficult to treat effectively and often requires the use of multiple drugs.

### Xenotransplantation

Xenotransplantation includes any procedure that involves the transplantation, implantation, or infusion into a human of either (a) live cells, tissues, or organs from a nonhuman animal source or (b) human bodily fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs [7]. Besides the ethical, legal and animal welfare issues, xenotransplantation raises serious public health concerns about the potential transmission of both known and emerging infections through xenotransplantation products to recipients. Additionally, such xenogenic infectious agents could be subsequently transmitted from the xenotransplantation product recipient to close contacts and then to other human beings.

### 'Fresh cell' therapies

'Fresh cells'-based 'therapy', despite unproven efficacy and numerous associated risks, continues to be offered and used. Therapies using fresh cells were developed by the Swiss physician Paul Niehans (1882–1971) in the 1930s [8]. The fresh cells are usually isolated from the homogenised organs and tissues of sheep foetuses and placentas, and prepared as cell suspensions. Within two hours of collection and processing, the buffered cell suspension is usually injected intragluteally. Today, living cells are increasingly replaced by cell fragments or extracts from frozen or lyophilised cells. The live cells or extracts are injected into the recipient in order to obtain a purported revitalising effect. Often, these therapies are promoted as anti-aging treatments, treatment for chronic diseases, age-related disorders (such as arteriosclerosis) or as an alternative treatment for cancer. Several deaths have been reported following treatment using fresh cells due to anaphylaxis, and also other complications such as vasculitis, encephalitis, polyradiculitis or clostridial infections [9–13]. These treatments are not accepted by professional medical associations and a number of European countries are in the process of regulating the practice [13,14].

## Event background information

In September 2014, in the context of the International Health Regulations, Canadian health authorities informed the Robert Koch Institute in Germany about a case of Q fever in a Canadian resident. The person probably acquired the infection in Germany after receiving intramuscular injections containing material from sheep foetuses and sheep placenta (so-called fresh cells) in a treatment facility in the Federal state of Rhineland-Palatinate, south-western Germany on 28 May 2014 [15]. Since the beginning of August 2014, the public health authorities in that federal state had been investigating a Q fever outbreak with 12 laboratory-confirmed human cases who lived or worked in close proximity to affected sheep flocks.

After receiving this information, the German physician notified patients treated with fresh cells during the period January–July 2014 of their potential Q fever exposure. This prompted testing for Q fever of five patients in New

York who travelled in a group of 10–15 people to the state of Rhineland-Palatinate in Germany to receive the same injections of foetal sheep cells on 28 May 2014.

In December 2014, the Paul Ehrlich Institute reported in the Bulletin for Drug Safety (*Bulletin Zur Arzneimittelsicherheit*) one additional case of Q fever in Germany [16]: a patient from Munich who received foetal and placental cells of sheep to treat degenerative changes in the cervical spine on 22 October 2014.

No other Q fever cases with positive antibody titre and history of travel to Germany to be treated with fresh cell injections have been identified in the United States or Canada to date. The identities and nationalities of the other persons in the travel group are unknown to US and Canadian public health authorities. It is therefore not known whether the other persons did not get ill, did not get tested for Q fever, tested negative, or did not report an exposure to foetal sheep cell injections [1].

## ECDC threat assessment for the EU

Reported cases of Q fever transmission to the recipients of fresh cell therapies [1,15] show that such xenotransplantation products may pose a threat to health in the EU. Besides this considerable risk of Q fever transmission through such products, *C. burnetii* can be further transmitted from the recipient of the fresh cell products to other human beings through close contact [17] or donated substances of human origin [9-11]. Furthermore, the threat has international significance as potential recipients are not only German or EU citizens but also individuals from the USA, Canada and possibly other countries.

*C. burnetii* infection in cattle, sheep and goats is widely distributed in the EU, but infection is usually subclinical with very few clinically affected herds reported by the countries [12]. Its seroprevalence among sheep in Germany is estimated at 8.7%, with higher values in some rural German regions [18]. Although data on laboratory screening of individual donor sheep involved in reported cases are not available, it is clear that an inappropriate screening or lack of screening of donor sheep in areas with higher prevalence of Q fever in herds might result in contamination of fresh cell products. As the products are given to recipients within two hours after preparation, the results of cell product screening by a bacterial culture or universal PCR would be only available after the fresh cell product was administered. Fresh cells prepared from one donor sheep are injected into several recipients, which may generate a cluster of infections. Fresh cells contaminated with *C. burnetii*, which is an intracellular pathogen, can transmit Q fever to human recipients. *C. burnetii* has been transmitted to humans by transfusion, bone marrow transplantation and xenotransplantation (liver, thymus, and lymph nodes) [9-11].

The primary infection with *C. burnetii* through fresh cell therapy may be undetected because 50 to 60% of those infected remain asymptomatic, while others may develop a flu-like illness, which is mostly self-limiting.

Strategies for early detection, identification and containment of possible infections need to be developed in order to manage the infectious disease risks of xenotransplantation. In this respect, monitoring for adverse effects and reporting to a regulatory authority is essential.

A quantitative risk assessment of Q fever transmission through fresh cell treatment in this incident is limited by a number of uncertainties: the lack of data on the number of individuals treated with the same product; the total number of diseased individuals; the period of exposure; and the type and results of screening donor sheep and final products. Although data on the number of fresh cell treatments are not available, it is likely that the fresh cell therapy is not a common event due to the considerable financial investment needed and its scientifically unproven effects.

## Conclusions and options for response

Cases of Q fever in Canadian and US citizens treated with the fresh cell products in Germany reconfirm the risk of Q fever linked to xenotransplantation, as has been demonstrated in the past. The risk is not limited to Q fever. The use of foetal and other products of animal origin in humans poses potential transmission risks of a variety of infectious diseases. These risks, including Q fever transmission, are dependent on the local epidemiology of disease in the animal population, strategies for screening donor animals and xenotransplant products, and the clinical severity of the transmitted disease. As the majority of Q fever cases are mild and self-limiting, similar events may remain undetected.

Organisations that are active in the donation and transplantation of substances of human origin should be aware that these treatments occur, because donors who have received these therapies should be rejected for donation. The potential recipients of fresh cell therapy or similar products of animal origin, should be informed about the risks. Furthermore, countries may consider regulating such practices and establishing national systems for vigilance and traceability of xenotransplantation.

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