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Q fever: new insights, still many queries

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When Edward Derrick named the illness he described in 1937 as Q (query) fever – 'until fuller knowledge should allow a better name' [cited in 1] – little did he know how well the name fits. Some 75 years later, the illness still deserves the name as, in spite of major advances in knowledge about the causative bacterium, reservoirs, routes of transmission and the clinical manifestations of the disease, many queries continue to puzzle clinicians, microbiologists, public health experts as well as veterinarians. Q fever is a worldwide zoonosis caused by the intracellular bacterium *Coxiella burnetii*. The most common clinical presentation is an influenza-like illness with varying degrees of pneumonia and hepatitis [1]. Acute disease is usually self-limiting. However, chronic presentations, most often endocarditis, are life-threatening. Infections in pregnancy may lead to spontaneous abortions or premature delivery, even if the infected pregnant woman herself remains asymptomatic [2].

In Europe, the number of reported cases is low and is in contrast to results of seroprevalence studies, which suggest that between 2% and 14 % of the general population have been previously infected by *C. burnetii* [3]. This discrepancy can be explained by the large proportion of subclinical cases, estimated be about 50%. Also, the diagnosis of symptomatic cases is often missed as symptoms are non-specific. Laboratory confirmation is essential for diagnosis, but is often not sought due to low awareness of Q fever among patients and practitioners outside high-incidence areas. Nevertheless, Q fever outbreaks are regularly reported throughout Europe as well as in other parts of the world. Most often the source is infected livestock and there are a limited number of cases in the vicinity of the affected farms. However, from 2007 to 2009, an outbreak of unprecedented scale occurred in the Netherlands, involving 3,523 notified human cases [4]. The Dutch health authorities faced many challenges regarding the identification and control of the source of contamination, the risk for pregnant women and other groups likely to develop chronic Q fever, the strategies to be used for diagnosis, follow-up and treatment regimens of acute and chronic Q fever, and the safety of blood transfusion and organ transplantation. Consequently, the outbreak sparked a large number of research studies to address these questions. The outbreak setting created the opportunity to study several issues difficult to address in a low-incidence setting.

In 2010, given the increase in the number of cases in the Netherlands, a number of questions arose, related to the safety of blood transfusions, the need to strengthen surveillance for new cases, the impact on health of chronic Q fever and the impact on health for people in risk groups, such as pregnant women. These issues were tackled in a risk assessment carried out by the European Centre for Disease Prevention and Control (ECDC) [3], at the request of the European Commission. The ECDC assessed whether an evidence-based approach, comparable to the methodology used in clinical medicine, was appropriate for giving public health advice on Q fever control strategies under the time constraints of an outbreak. In this issue of *Eurosurveillance*, Forland et al. present a summary of their findings [5]. The most striking finding was the lack of scientific evidence for the screening and treatment regimens for Q fever in pregnant women. Although a retrospective hospital-based study from France and a Canadian study emphasise that *C. burnetti* is a potential threat to pregnant women, the risk is difficult to quantify [6,7]. The retrospective design and selection bias of these studies may have led to overestimation of the risk.

The risk of acute Q fever patients developing chronic Q fever was estimated to be 2% [3]. Both symptomatic and asymptomatic infected patients with previous cardiac valve pathology, aneurysms or vascular grafts, with malignancies or who are immunocompromised are most at risk for developing chronic Q fever. On the basis of the findings of observational studies, ECDC recommended to consider targeted case-finding among these risk groups and long-term follow-up of acute and chronic cases. However, the need to initiate prospective cohort studies and trials with control groups was emphasised, to obtain more robust evidence on how to diagnose and treat acute and chronic disease.

Because of the theoretical possibility that *C. burnetii* can be transmitted through blood transfusion, ECDC recommended that active screening of blood and tissue products be considered, although only a few blood-borne infections have been clearly documented.

The inhalation of contaminated aerosols originating from the faeces and birth products of infected animals, most often cattle, sheep and goats, is the main route of transmission in humans. In the literature, estimates of the distance infectious particles can spread by air range from 400 m to 40 km. The ECDC risk assessment team concluded that the most sound data were from a Dutch study using a geographic information system, which demonstrated that the highest risk of infection was within a radius of 5 km from the source [8].

Since the ECDC risk assessment, results of the large portfolio of ongoing multidisciplinary research in the Netherlands are gradually becoming available and contribute new insights and evidence. In this issue, three papers present recent findings.

Munster et al. examine the evidence base for routine *C. burnetii* screening among pregnant women in high-risk areas for Q fever [9]. A recent population-based study in the Dutch outbreak area showed no evidence of adverse pregnancy outcome among women who had antibodies to *C. burnetii* during early pregnancy [10]. On the basis of this study and because of the potential biases in earlier retrospective studies reporting adverse pregnancy outcomes, the authors judged that there still is much uncertainty about the consequences of untreated *C. burnetii* infection during pregnancy. There is also no consensus about the screening method or treatment. Therefore, they conclude that at this stage, there is no evidence on the effectiveness of a *C. burnetii*-screening programme in the present Dutch setting.

Van der Hoek et al. describe how, in the aftermath of the outbreak in the Netherlands, the priorities are shifting from detection and management of acute cases and control of transmission to the follow-up of acute Q fever patients, screening of groups at risk for chronic Q fever, screening of blood and tissue, and human vaccination [11]. Although there seems to be an international consensus on the groups most at risk for chronic Q fever, the optimal follow-up strategy of acute Q fever patients for the early detection and treatment of chronic Q fever and the strategy for screening of people in risk groups for chronic Q fever are points of controversy. There is an ongoing debate about the validity of serological profiles as predictors of chronic Q fever, which serological cut-off values should be used, the exact timing and frequency of examinations and serological follow-up, and the duration of treatment [12-16]. The wide variation in serological and PCR results during the follow-up of patients with acute Q fever implies that the diagnosis of chronic Q fever must be based primarily on clinical grounds [15,17]. Van der Hoek proposes different serological follow-up strategies for patients with and without known risk factors for chronic Q fever [15].

Another article by van de Hoek et al. in this isssue sheds light on the problem of under-diagnosis and under-reporting [18]. The authors estimate that only 7.9 % of incident infections of *C. burnetii* that occurred in the affected area of the Netherlands were notified, and that the 3,522 acute Q fever cases that were notified in the country from 2007 to 2009 correspond to more than 44,000 infections in the same period. The proportion of under-diagnosed and under-reported cases is likely to vary by region and is expected to be even higher in low-incidence areas because of a lack of awareness of patients and physicians. These high numbers of undiagnosed infections constitute an additional challenge for the detection of chronic Q fever.

Adoption of an evidence-based approach is challenging in infectious disease epidemiology, especially during an outbreak. Forland et al. point out that in many situations, observational studies, often retrospective, or natural experiments are the only studies available [5]. Such studies provide evidence at the lower level of the evidence hierarchy in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [19]. However, such studies can still be of good quality and yield important information. Clearly stating the strengths and limitations of such studies not only enables the best available evidence to be used for preliminary recommendations, but also ensures transparency regarding uncertainties and allows knowledge gaps and priorities for further research to be clearly identified. The evidence base for public health policy and strategies should be continuously reassessed, whenever new evidence is made available through new studies.

An evidence-based approach and continuous updates are time- and resource-consuming. However, considering the consequences for health, the enormous resources that are often needed for the implementation of the selected strategies and the resulting higher quality of public health advice, it is beyond doubt that the investment is worth it.

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Applicability of evidence-based practice in public health: risk assessment on Q fever under an ongoing outbreak

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With reference to the Q fever outbreak in the Netherlands in 2009–10, we tested if an evidence-based approach, comparable to the methodology used in clinical medicine, was appropriate for giving public health advice under time constrains. According to the principles of evidence-based methodologies, articles were retrieved from bibliographic databases and categorised by type and size, outcome, strengths and limitations. The risk assessment was conducted in two months and involved six staff members. We retrieved and read 559 abstracts and selected approximately 150 full text articles. The most striking finding was the lack of sound scientific evidence behind standard treatment regimes for Q fever in pregnancy. Difficulties in applying existing evidence rating systems and in expressing uncertainties were identified as problems during the process. By systematically assessing the evidence on several questions about Q fever, we were able to draw new conclusions and specify earlier statements. We found it difficult to grade the mostly observational studies with the known evidence-based grading systems. There is need to develop new methods for grading evidence from different sources in the field of public health. We conclude that an evidence-based approach is feasible for providing a risk assessment within two to three months.

Introduction

The European Centre for Disease Prevention and Control (ECDC) may be requested by the European Commission, the Member States of the European Union (EU), third countries and international organisations to provide scientific or technical assistance in any field within its mandate. Regarding the Q fever outbreak in the Netherlands in 2009 and 2010 [1], ECDC was asked by the European Commission to assess the following questions: (i) What is the risk and safety of blood transfusions, especially from donors who are asymptomatic or still in the incubation phase of the disease? (ii) What is known on the impact on health of chronic Q fever disease? (iii) What is the impact on health for risk groups like pregnant women? (iv) Is it advisable to strengthen the surveillance of new cases?

After a short-term risk assessment had been conducted within a few days, we tested if an evidence-based approach, comparable to the methodology used in clinical medicine, was appropriate for giving more in-depth public health advice on Q fever to policy makers and public health practitioners. Evidence-based methodologies are increasingly discussed and applied in public health practice and health promotion. There is a growing consensus that scientific and technical advice in the field of public health should rely on evidence-based science and technology and should aim to support evidence-based decision making [2]. During this process, we addressed two questions: Does an evidence-based approach work when advice has to be given in an outbreak situation, i.e. under time constraints? And if so, does change the conclusions compared with more traditional, expert-based approaches?

In this paper we summarise the risk assessment and discuss our experiences with applying evidence-based methodology in its production.

Background

Q fever is a zoonotic disease caused by the intracellular bacterium *Coxiella burnetii*. A wide range of wild and domestic animals (including arthropods, birds, rodents, cats, and livestock) serve as a natural reservoir for the pathogen [3]. Acute Q fever most often presents with non-specific influenza-like symptoms, and the infection is asymptomatic in approximately 50% of cases. A subset of the patients develops chronic Q fever, a potentially life-threatening condition. Since 2007, the Netherlands has been experiencing the largest Q fever outbreak ever reported in the literature. As of the end of 2010 approximately 4,000 people have been affected and at least 14 of these patients, nearly all of them with severe underlying conditions, have died.

Methods

On the basis of a rapid risk assessment in the beginning of 2010, a more comprehensive risk assessment was performed according to the principles of evidence-based medicine (EBM) [4]. In March 2010, a working group was established at the ECDC including one medical librarian and five reviewers with broad epidemiological experience. Reviews and original research articles were retrieved from PubMed and Embase bibliographic databases. The search strategies covered different aspects of Q fever: blood, pregnancy, chronic diseases, occupational exposure, transmission and surveillance of the disease. The concepts used in the search were taken from the controlled vocabulary available in the bibliographic databases (i.e. MeSH and Emtree terms). These were complemented with multiple field search combinations by using natural vocabulary (i.e. keywords). The results were limited to records published from 1970 onwards. The search was not restricted to articles written in English. Studies were selected according to relevance for the different questions, using inclusion criteria agreed upon before the review process started. When in doubt about inclusion of a paper, it was discussed with the group of reviewers. We included only studies reporting on outbreaks and having primary results from research. Excluding commentaries, editorials, single case reports.

The studies were categorised according to the following study designs: reviews, trials and observational studies. The observational studies were sub-classified into the following categories: cohort studies, case series, case–control studies, case studies, cross-sectional studies, time series, 'before and after' studies. The following sections were included in the evidence table: bibliographic citation, type of study, number of patients or size of population, study outcome, strengths of study and limitations of study. The results were presented to, and discussed with, an expert panel with 18 representatives from the Netherlands, France, Germany, the United Kingdom, the United States (US), the European Food Safety Authority and the European Commission.

The applicability of the EBM methods was assessed during the process of preparing the risk assessment in discussions with the panel of experts and the advisory forum of ECDC, and after publication of the risk assessment in discussion among the team of reviewers.

Results

The risk assessment was conducted within two months (mid-March to mid-May 2010), and involved six staff members (at approximately half of their working time). A total of 559 abstracts were retrieved and read, and approximately 150 full text articles were selected for inclusion in the evidence base. A meeting with experts from Europe and the US was held in Paris in April 2010. The full report describing the exact methodology including search strategies, evidence tables and recommendations has been published [5].

The following results regarding the four questions were obtained by the risk assessment:

Blood

Q fever can be transmitted through direct contact to blood, and cases have been reported among laboratory personnel and pathologists [6]. The exact duration of bacteraemia is unknown. To date there has been only one documented case of human-to-human transmission via blood transfusion [7]. One case of transmission from a bone marrow transplant in an immunosuppressed patient has also been reported [8]. Q fever has also been transmitted via organ transplantation in animals [9]. Donors of organs, cells or tissues are not routinely screened for *C. burnetii* [10]. Blood donors have been examined for Q fever mainly in epidemic settings [11].

The following recommendations were made, based on the evidence as described in the full report [5], and bearing the precautionary principle in mind:

- During an outbreak, the affected area should be defined and safety precautions should be considered, such as screening of blood and tissue products, active surveillance among blood and tissue recipients, and screening of donors.
- It should be considered to defer travellers returning from an epidemic area from donating blood for six weeks after their arrival in a low-prevalence area.
- An antibiotic course could be considered for blood transfusion recipients at particularly high risk of chronic disease, such as patients with heart valve defects, in an epidemic area.
- Donors who have had an acute Q fever infection should be deferred from giving blood for two years following the date of confirmed cure from acute infection (absence of phase 1 antibodies).

Chronic Q fever

A cumulative point estimate calculated from all the studies included in this assessment, gave an overall average prevalence for chronic Q fever of 1.9% of acute cases. Chronic Q fever can develop after, or appear as an asymptomatic infection [12,13]. The fatality rate for chronic Q fever may vary from 5% to 60% [14]. Risk factors for developing chronic disease are mainly connected to the host and include heart valve defect, heart valve prosthesis or arterial graft, aneurisms, malignancies, and immunosuppression. Medical treatment for chronic Q fever should be at least one year with more than one drug. The optimal treatment of chronic Q fever is still debated and the recommended duration of treatment varies from one year up to a lifespan [15]. Most authors today recommend broad-spectrum tetracyclines, preferably doxycycline in combination with hydroxychloroquine for at least 18 months [16]. During an outbreak, three possible strategies are described in the risk assessment for population-wide, targeted case finding and individual follow-up to identify patients at risk in the outbreak area: (i) Serological testing, during

an outbreak, of all patients with known heart valve disease or vascular grafts, in order to identify them early and refer them for treatment. (ii) Testing of all patients with acute Q fever with echocardiography for heart valve lesions. (iii) Individual serological follow-up after acute Q fever infection and raising awareness among the general population and physicians. An effective whole-cell vaccine is used for defined risk groups in Australia but is not licensed or used in any other country [3].

The recommendations below are based mainly on evidence from observational studies and the judgements from the expert panel:

- Acute and chronic cases need to be followed up individually by primary and secondary healthcare services.
- Special attention should be paid to risk groups, i.e. people with valvular heart disease, vascular diseases, cancer or a compromised immune system.
- Among these risk groups, targeted case-finding should be considered as an option.
- People with known risk factors should not visit farms infested with Q fever.
- The formalin-inactivated whole-cell Q fever vaccine is effective, but pre-vaccination testing is necessary due to high reactogenicity in persons who have earlier been infected with *C. burnetii*, making the vaccine more suitable for defined risk groups than for general vaccination.
- Making the vaccine available for defined risk groups should be considered.
- There is need to initiate good prospective cohort studies and trials with control groups when ethically feasible, to obtain more robust evidence on how to prevent and control outbreaks of Q fever, and on how to diagnose and treat acute and chronic disease at the clinical level.

Pregnancy

The available evidence with regard to effects of Q fever infection in pregnant women is limited [17]. There are indications for severe disease and progress towards chronic infection/disease in pregnant women. To what extent the risk of pregnant women for severe Q fever outcomes differs from the risk of the general (female) population and in comparison to other well-known risk groups cannot be quantified based on the current available evidence. The presence of *C. burnetii* in fetal tissue after abortion or intrauterine fetal death has been reported, but also in healthy children delivered from infected mothers with placentitis. Transplacental transmission seems to be possible but its association with adverse obstetrical outcomes remains incompletely understood as well as the consequences for the child in case of live birth. Several case reports on adverse pregnancy outcomes associated with maternal Q fever exist [15,16,18,19]. The largest published case series summarising the serological profiles and pregnancy outcomes of 53 women during a period of 15 years in southern France, found obstetric complications in 70% of all observed pregnancies, and in 81% of the non-treated pregnancies [17]. So far, this case series also provides some indication that long-term antibiotic therapy with co-trimoxazole has the potential to prevent the most severe pregnancy outcomes [17].

The evidence led to the following conclusions and recommendations:

- There is some indication that long-term antibiotic therapy with co-trimoxazole has the potential to prevent severe pregnancy outcomes associated with Q fever, but the evidence is based on a case series without randomisation and without controlling for potential biases.
- As long as no further evidence from high quality treatment studies is available, pregnant women with diagnosed Q fever infection should be treated with antibiotics until the end of the pregnancy. However, the scientific basis for this recommendation is weak, and ECDC would strongly recommend that randomised controlled trials are performed to obtain more reliable evidence. Pregnant women should be advised not to visit farms in affected areas.
- ECDC does not recommend against breastfeeding by mothers with proven *C. burnetii* infection, except in cases of chronic disease that need long-term treatment of the mother.

Transmission and surveillance

There is scientific evidence (experimentally, epidemiologically and by use of statistical models) that airborne transmission of *C. burnetii* is the principal mode of transmission to humans [1-3]. Airborne transmission includes long-distance (indirect) transmission of the aerosolised bacteria and direct transmission through inhalation of droplets, aerosols and dust during contact with infected animals, contaminated animal products (e.g. wool or straw) and contaminated clothing [20-23]. An association between transmission to humans and environmental factors, i.e. wind speed, dry weather conditions and vegetation density, has also been established [21,24,25]. The distance infectious particles can spread by air is a point of controversy. Several estimates ranging from 400 m to 40 km are provided in the literature from different outbreak investigations [21,26,27]. More sound data was provided from a Dutch study on a Geographical Information System, which demonstrated that the risk of infection is highest within a 5 km radius from the source [28].

There have only been a few studies that describe foodborne transmission of *C. burnetii*. These indicated that consumption of contaminated food may lead to seroconversion, but not to clinical disease [29]. Data from experiments in which contaminated milk was fed to healthy volunteers gave no clear evidence about transmission [30]. Single case reports indicate a low rate of human-to-human transmission during birth or through

breastfeeding, sexual transmission, transplacental transmission and spread after autopsies [31-33]. Active surveillance (i.e. active serological targeted case finding for Q fever independent of clinical symptoms) helped to detect cases of acute Q fever in the general population, in patients with valvular heart diseases or vascular grafts, and in pregnant women [34-37]. In epidemic situations, awareness campaigns addressing both the general public and medical care providers were successfully used to enhance case finding [27,36,38].

We derived the following conclusions and recommendations from the reviewed evidence:

- Available evidence suggests an effective range of airborne spread of *C. burnetii* from infested farms in the Netherlands of less than 5 km. The risk of airborne spread is therefore limited to areas close to outbreak sources.
- Active surveillance or case finding for acute Q fever in risk groups on a local level and for a defined period of time is reported feasible and an efficient method for detecting acute infections.
- In areas adjacent to epidemic settings (≤5 km from the source), awareness campaigns among healthcare providers should be initiated.
- If the area also affects other Member States, the responsible public health authorities need to inform their cross-border counterparts.
- Sharing of information between public health and veterinary authorities would facilitate early recognition of an outbreak.

Discussion

By systematically assessing the evidence for the four questions from the European Commission related to the Q fever epidemic in the Netherlands, we explored the applicability of an evidence based methodology in a medium-term (i.e. two to three months) public health risk assessment. When compared with the earlier short-term risk assessment which had been conducted within a few days by the ECDC, the use of EBM allowed us not only to refine some of the previous statements, but also to draw some new conclusions. The most remarkable finding was the lack of sound evidence behind some standard treatment regimes (e.g. long-term co-trimoxazole treatment for pregnant women). This should be an incentive for the research community to initiate high quality studies on the effects of different clinical and public health interventions on Q fever and pregnancy. This knowledge gap has also been recognised by research institutes in the Netherlands, and a first well designed study about screening strategies for Q fever among pregnant women in risk areas has recently been launched [39]. We were also able to provide more accurate information on the risk for chronic disease, and on the risk for possible spread of *C. burnetii* to neighbouring countries.

While conducting this risk assessment, we identified several potential problems that could make it difficult to conduct an EBM approach in a public health setting, including logistical and managerial problems, difficulties in applying existing evidence rating systems, and difficulties in expressing uncertainties.

After reviewing the process of developing the risk assessment, we found that endorsement by the top management is essential to promote EBM as a core part of public health practice, and several steps might be considered by the management to foster EBM as part of daily working routine. It should be expected that recommendations and decisions for any scientific advice are based on the best available evidence and that appropriate methods are employed to search and analyse the evidence. We think there is a need to incorporate EBM as part of the goals and objectives for project managers and programme leaders in public health, and continuous EBM training should be established in organisations and institutes which are involved in producing general public health recommendations and assessments. To support the use of EBM in public health, ECDC has established a one-week training course, held for the first time in November 2010, which has been open also to external participants since May 2011. To work on a medium-term evidence-based risk assessment within an organisation where everybody is preoccupied with other assignments, turned out to be logistically difficult. The Q fever risk assessment was developed within a time frame of approximately two months, and six experts were actively involved in the process. A group of experienced people should be clearly assigned to the task and share the work to be able to deliver in the short time frames. We found that discussions with a panel of experts are mandatory, but the questions to be addressed and the evidence should be prepared by the review team. Experts should be selected in a transparent way, i.e. by using an existing database of experts with well defined profiles and conflict of interest declaration.

An evidence-based approach normally includes grading of the quality of the studies and thereafter grading of recommendations. In many settings of infectious disease epidemiology, however, observational studies or natural experiments are the only feasible study designs, i.e. evidence at the lower level of the evidence hierarchy when referring to the GRADE system [40]. That was also the case in this situation. Nevertheless, we found that such studies can still be judged according to their quality. A study can be of high quality even if its design does not fulfil the strict criteria for 'high quality evidence'. Existing grading systems, however, were perceived as not appropriate since almost all studies which were included for our risk assessment would have been graded very low. To enhance the information level with regard to study quality the group decided instead to indicate strengths and limitations. We found that there is a need to develop new tools and methods for grading evidence from different sources (especially

from observational studies) in the field of public health and infectious diseases.

To conduct comprehensive, evidence-based risk assessments is time and resource consuming and may not be feasible for all the assessments required when threats emerge. A rapid assessment, conducted within few days of the occurrence of an event, is often needed to provide immediate guidance. It relies on review of easily assessable evidence from different sources, including review articles, websites of internationally recognised organisations and textbooks, which might be outdated, not transparent on conclusions and presenting diverging views. It is hardly possible, however, to apply the classical evidence-based methodology on a two-day risk assessment, and EBM was not designed to do so. On the other hand, these constraints are no justification for disregarding the principles of EBM when conducting rapid risk assessments: transparency, reproducibility and validity of all scientific advice given to the public, to professionals or to other stakeholders. Following these principles under pressure of time will probably reveal a higher level of uncertainty about the conclusions and recommendations when compared to medium- or long-term risk assessments. We are aware that it is difficult, especially for public health agencies, to translate scientific uncertainty into policy advice. Stakeholders expect certainty and clear answers. However, we also believe that public health advice and policy is most consistent if scientific uncertainty is included in the assessment and the decision-making process as information, not ignorance. The decision of starting a full assessment should balance the expected benefits against the resources needed and the time it will take to produce it. There is need to define indications for doing evidence-based risk assessments under different time constraints.

In this assessment we tested whether an evidence-based approach, comparable to the methodology used in clinical medicine is appropriate for giving public health advice under an ongoing outbreak. We found that an evidence-based approach is feasible for providing an intermediate-term risk assessment within two to three months. Working explicitly and transparently with methods, evidence and experts will result in higher quality of public health advice.

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Relation between Q fever notifications and *Coxiella burnetii* infections during the 2009 outbreak in the Netherlands

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Large outbreaks of Q fever in the Netherlands from 2007 to 2009 were monitored using notification data of acute clinical Q fever. However, the notification system provides no information on infections that remain subclinical or for which no medical attention is sought. The present study was carried out immediately after the peak of the 2009 outbreak to estimate the ratio between *Coxiella burnetii* infections and Q fever notifications. In 23 postcode areas in the high-incidence area, notification rates were compared with seroconversion rates in blood donors from whom serial samples were available. This resulted in a ratio of one Q fever notification to 12.6 incident infections of *C. burnetii*. This ratio is time and place specific and is based on a small number of seroconversions, but is the best available factor for estimating the total number of infections. In addition, as subclinical *C. burnetii* infection may lead to chronic Q fever, the ratio can be used to estimate the expected number of chronic Q fever patients in the coming years and as input for cost–benefit analyses of screening options.

Introduction

Q fever is a zoonosis caused by *Coxiella burnetii*. The bacterium has a worldwide distribution in domesticated and wild animals, but transmission to humans is mostly associated with sheep and goats [1]. Most patients with Q fever recover after mild febrile illness; others may experience pneumonia, hepatitis or, more rarely, myocarditis or central nervous system complications [2]. Because the clinical presentation of acute Q fever is rather non-specific, laboratory confirmation is essential. *C. burnetii* has two antigenic phases (I and II) and with serological assays, IgM II, IgG II, IgM I and IgG I antibodies are used to distinguish between acute infection and chronic infection.

From 2007 to 2009, the Netherlands faced large seasonal outbreaks of Q fever, with the highest peak in 2009 [3]. Surveillance of Q fever is mandatory in European Union (EU) countries. In 2009, a total of 370 Q fever cases were reported in 24 EU countries, apart from the 2,317 cases from the 2009 outbreak in the Netherlands [4]. The low number of notifications is in contrast to results from seroprevalence studies, which suggest that 2–10% of the general population in EU countries have previously been infected with *C. burnetii* [1]. People with a *C. burnetii* infection will only be notified as Q fever cases to the national public health authorities if: (i) they have symptoms; (ii) they seek medical attention; (iii) have been tested with a Q fever diagnostic laboratory test; (iv) the test is sensitive and shows a positive result; (v) the physician or laboratory notifies the case to the local public health authorities; and (vi) the local public health authorities confirm that the notification criteria are fulfilled and reports the case to the national public health authorities. Each of these steps has an influence on the difference between the true number of infections and the number of notifications. However, little is known about the relative importance of the various steps.

An estimate much cited in the international literature is that 40% of *C. burnetii* infections are symptomatic [2,5]. However, this estimate is based on just one original study, from an outbreak in Switzerland in 1983, in which 191 (46%) of 415 serologically confirmed cases were symptomatic [6]. Hardly any information is available on the health-seeking behaviour of symptomatic patients. Symptomatic *C. burnetii* infection (Q fever) may resemble influenza-like illness, for which only an estimated 20% in the Netherlands seek medical care [7] and for which most general practitioners will not request a laboratory test. Low sensitivity of the

laboratory test and failure to report a diagnosis of Q fever are probably of minor importance during a period in which there is a high number of incident cases and both the physician and laboratory are legally required to notify cases.

Before the recent Q fever epidemic in the Netherlands, the seroprevalence of 2.4% in the general population was relatively low in comparison with that in other countries [8]. The epidemic resulted in an unprecedented number of 3,522 laboratory-confirmed Q fever cases notified from 2007 to 2009 [9]. Policy decisions on veterinary interventions were to a large extent based on close monitoring of these human Q fever notifications. With the declining number of Q fever notifications in 2010, attention has shifted to the increasing number of patients with long-term effects of acute Q fever, especially Q fever fatigue syndrome and chronic Q fever. The number of asymptomatic infections is relevant in this context, because asymptomatic infections can also lead to chronic Q fever, mostly in people with risk factors such as cardiac valve disease, aneurysm, vascular graft or pregnancy [10]. Knowing the total number of persons infected, including those with asymptomatic infections, would allow better estimates of the expected number of chronic disease cases. There are also other remaining public health policy questions that pertain to screening of blood, semen, tissue and organ donors, pregnant women and patients with cardiac valve or vascular disease for asymptomatic infection. For these reasons, having an estimate of the number of infections is important for public health policy. The present study therefore focuses on the ratio of the incidence of *C. burnetii* infection to that of notified Q fever cases during the 2009 outbreak in the Netherlands by relating the number of blood donors with seroconversion to figures from the national infectious diseases notification system.

Methods

Notifications

We used data on notifications for 1 June 2009 to 31 January 2010 from the 23 postcode areas in the south of the Netherlands that had the highest incidence of notified Q fever cases between weeks 26 and 37 of 2009 (22 June to 13 September) [11]. According to Dutch legislation, the attending physician and the head of the medical microbiology laboratory must notify any diagnosis of acute Q fever to the municipal health service. Of the 23 postcode areas, 21 were under the municipal health service 'Hart voor Brabant' and two were under a neighbouring municipal health service. The municipal health services interviewed the notified patients and entered information on those who fulfilled the notification criteria into the national infectious diseases surveillance database. Notification criteria of acute Q fever were a clinical presentation with fever or pneumonia or hepatitis, in combination with a positive laboratory result indicating acute *C. burnetii* infection. The laboratory criteria were a fourfold IgG titre rise or more measured by immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA) or complement fixation test, a positive IgM phase II antibody test or detection by polymerase chain reaction (PCR) of *C. burnetii* DNA in blood or respiratory material.

Blood donors

Sanquin Blood Supply Foundation is the only organisation in the Netherlands authorised to manage the supply of blood and blood products. To assess the safety of donated blood, samples of blood donations from people living in the most affected area were collected by Sanquin over a one-year period from 20 May 2009. From this collection, donations from people living in the 23 postcode areas with the highest incidence were tested for the presence of antibodies against *C. burnetii*. Details of the study have been reported elsewhere [11]. Briefly, serological data were generated of the 543 donors who donated more than once in the first eight months of the study (20 May 2009 to 15 January 2010). The donor's last donation was screened for the presence of IgG antibodies to phase II of *C. burnetii* using a commercial ELISA (Serion, Clindia Benelux, the Netherlands). All ELISAs that gave borderline results (IgG levels of 20–30 international units (IU)/ml) or positive (>30 IU/ml) sera were confirmed by IFA (Focus Diagnostics, United States). An IgG II antibody titre of ≥1:64 was considered positive in the IFA. If the last donation tested positive, the donor's previous donation was also tested in the same way.

The mean age of the 543 donors was 49.5 years (range: 19–70 years) and 60.4% were male (n=328). Due to Sanquin privacy regulations, information on age and sex at the individual donor level was not available.

Data analysis

The incidence of infection was calculated by dividing the number of blood donors with seroconversion by the person-time of follow-up. As population figures by postcode area were available by five-year age groups [12], we used the age range 20–69 years instead of 19–70 years.

The incidence of notified acute Q fever cases was calculated by dividing the number of notifications of persons aged 20–69 years with a date of symptom onset between 1 June 2009 and 31 January 2010 by the total number of people aged 20–69 years living in the 23 postcode areas on 1 January 2010 (n=55,715).

Results

Notifications

The number of acute Q fever notifications (all ages) in the 23 postcode areas was 75 in 2007, 323 in 2008 and 570 in 2009 (Figure). There were 167 notifications of cases aged 20–69 years who had a date of symptom onset between 1 June 2009 and 31 January 2010.

The mean age of the 167 notified cases was 45.6 years and 53.9% (n=90) were male. With a population size of 55,715, the incidence of notified cases was 4.5 (95%

confidence interval (CI): 3.9–5.2) per 1,000 persons per year.

Infections

Of the 543 people who donated blood more than once during 20 May 2009 to 15 January 2010, 66 tested positive or borderline for *C. burnetii* IgG antibodies in the last donation [11]. All 66 ELISA-reactive sera had a phase II IgG antibody titre ≥1:64 in the confirmatory IFA. The phase II IgG seroprevalence in the 23 postcode areas was therefore 12.2% (95% CI: 9.7–15.2). When the previous donation of the 66 seropositive donors was tested, 10 of the 66 sample pairs were identified as seroconversions for IgG phase II. In two of the 10 donors, the seroconversion was from a weak antibody response to at least a fourfold higher titre in the IFA in the last donation; for the other eight donors, no antibodies were detected at all in the previous donations.

The cumulative follow-up period for the 487 (543 minus 56) donors without *C. burnetii* IgG antibodies in the previous donation was 64,135 days. With 10 seroconversions observed, the *C. burnetii* infection incidence was 56.9 (95% CI: 31.2–101.4) per 1,000 person-years. This point estimate translates into 2,113 (95% CI: 1,159–3,766) new infections among those aged 19–70 years in the study area over the eight-month study period.

On the basis of the notifications and seroconversions, there was a ratio of one Q fever notification to 12.6 incident infections of *C. burnetii* – i.e. 7.9% of the infections that occurred in the area were notified.

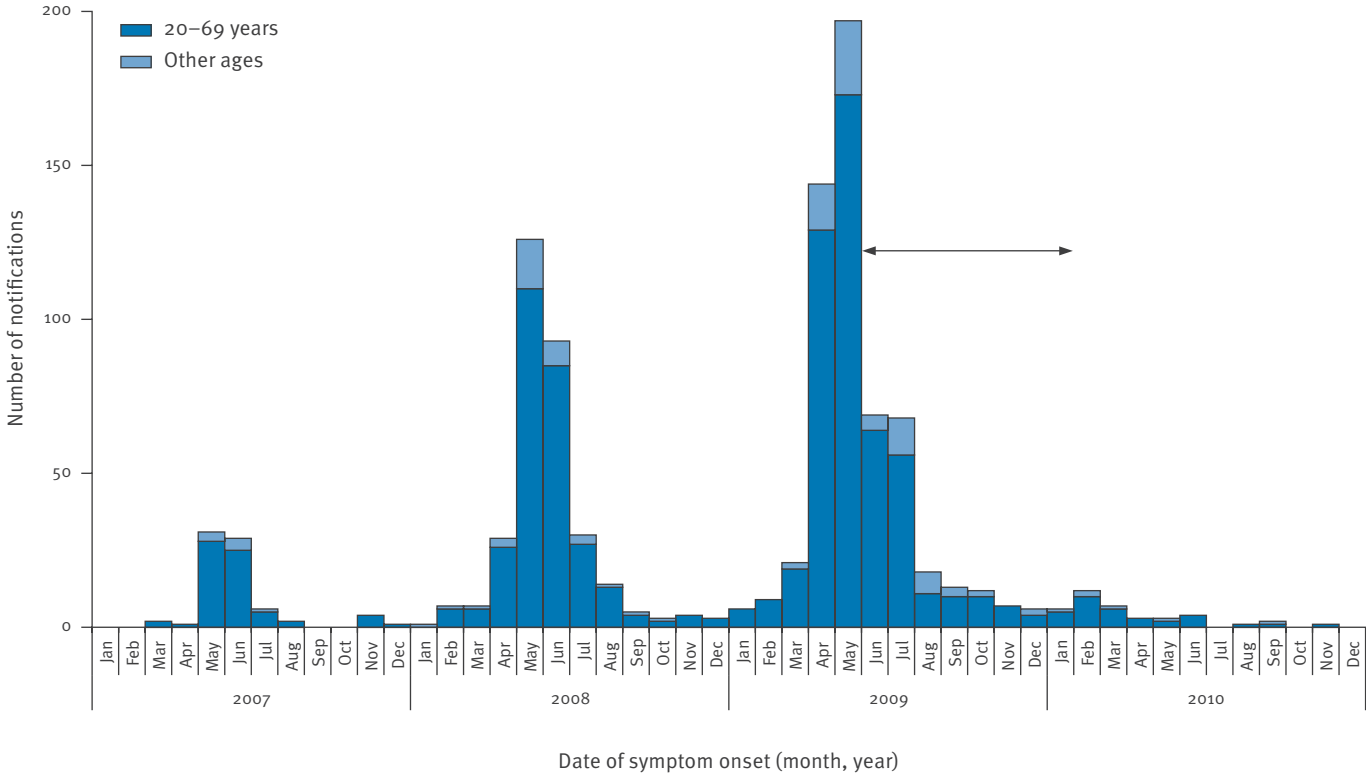
Discussion

The study provides an estimate of incidence of infection with *C. burnetii* in relation to incidence of notified acute Q fever cases. It suggests that the 3,522 acute Q fever cases that were notified in the Netherlands from 2007 to 2009 correspond to more than 44,000 infections in the same period. This rough estimate is likely to be an underestimation as underreporting outside the high-incidence study area was probably higher. However, our study pertains to a particular time and area: the estimate for the entire epidemic is indicative only and should be interpreted with caution.

In the village where the first outbreak in 2007 occurred, 443 inhabitants provided a blood sample, of which 73 (16.5%) showed a recent infection [13]. Of these 73 people, 48 had symptoms that could be attributed to Q fever. This suggests that 66% were symptomatic infections. However, the actual percentage of symptomatic infections is likely to be lower, as symptoms are non-specific and could easily have been misclassified as Q fever-related.

Figure

Notifications for acute Q fever in 23 postcode areas in the high-incidence area of the Netherlands, 2007–2010



The arrowed line indicates the study period for collection of notification data (1 June 2009 to 31 January 2010).

Even if we accept the prevailing estimate from the international literature that 40% of *C. burnetii* infections are symptomatic, it is clear that a large proportion of symptomatic cases do not seek medical attention or are not diagnosed as acute Q fever patients. It is a common finding that surveillance systems have low reporting efficiency for infectious diseases with mild or non-specific symptoms [14].

The proportion of infections that is not notified because patients do not seek medical attention or a diagnostic test is not requested, is neither fixed nor random, but is highly affected by certain factors, such as media attention or physicians' awareness that a particular pathogen is circulating. At the time of study in the second half of 2009, awareness of Q fever among patients and general practitioners in this area was at a high level [15]. In combination with easy availability of diagnostic facilities in the area, we can expect that a larger proportion of symptomatic *C. burnetii* infections were diagnosed as acute Q fever compared with areas with lower awareness and where laboratory tests for *C. burnetii* infection were not routinely available to general practitioners. Raoult et al. showed a high incidence of Q fever around the French National Reference Centre for Rickettsial Diseases (in Marseille, France) [16], suggesting high levels of awareness and testing in this area. Conversely, in a low-incidence situation, the absolute number of cases that are not notified would be low, while the proportion of infections that is not notified could be high. This will especially be the case when the beginning of an outbreak passes largely unnoticed. This happened in 2007 in the Netherlands, when increasing numbers of pneumonia cases were first thought to be due to *Mycoplasma pneumoniae* infection. Retrospectively, a number of clusters of hospital admissions for respiratory tract infections were identified that occurred in 2005 to 2007 – earlier than the recorded Q fever outbreaks – which could have been Q fever because there was a Q fever-affected farm nearby and there was no alternative explanation for the cluster [17].

A limitation of our study is that in general, healthy adult blood donors poorly represent the general population. However, Q fever is an airborne infection, thus reducing biases caused by the comparison of donors with the general population [11]. The age and sex distribution of the donors in the study population was very similar to those of the notified Q fever cases in the Netherlands (mean age of 50 years, 62% male) over the entire epidemic period from 2007 to 2009 [3]. We had no information on addresses of blood donors and could therefore not correct for possible differences between donors and notified Q fever patients in the proximity of their places of residence to infected farms.

The 12.2% seroprevalence among blood donors suggests that approximately 6,800 people in the age group 20–69 years in the study area had been infected at the time of the study, i.e. after the 2007 and 2008 outbreaks and half-way through the 2009 outbreak. This estimated number of prevalent cases seems low in comparison with the number of notifications and the estimated incident infections. It illustrates that in relating incidence to prevalence, other parameters have to be taken into account such as the decay rates of antibody titres.

In conclusion, our study suggests that during the peak of the epidemic in the Netherlands, every notification of clinical Q fever represented more than 12 infections with *C. burnetii*. Despite uncertainties surrounding the clinical significance of asymptomatic seroconversion, this ratio could be used as one factor to estimate the number of chronic Q fever patients that could be expected in the coming years and as input for cost–benefit analyses of screening options.

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Shifting priorities in the aftermath of a Q fever epidemic in 2007 to 2009 in the Netherlands: from acute to chronic infection

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From 2007 to 2009, the Netherlands faced large seasonal outbreaks of Q fever, in which infected dairy goat farms were identified as the primary sources. Veterinary measures including vaccination of goats and sheep and culling of pregnant animals on infected farms seem to have brought the Q fever problem under control. However, the epidemic is expected to result in more cases of chronic Q fever among risk groups in the coming years. In the most affected area, in the south of the country, more than 12% of the population now have antibodies against *Coxiella burnetii*. Questions remain about the follow-up of acute Q fever patients, screening of groups at risk for chronic Q fever, screening of donors of blood and tissue, and human vaccination. There is a considerable ongoing research effort as well as enhanced veterinary and human surveillance.

Introduction

Acute Q fever was made mandatorily notifiable in the Netherlands in 1975, but was rarely reported from 1975 to 2006 (with between one and 32 notifications per year). In 2005, Q fever was diagnosed on two dairy goat farms with unusually high numbers of abortions and two years later, in 2007, it emerged in the human population in the south of the Netherlands. This was the start of an exceptionally large epidemic that showed a marked seasonality and expanded both geographically and in size in 2008 and 2009. From 2007 to 2009, more than 3,500 human cases were notified. The observation that human cases mainly occurred in the same area as dairy goat farms with Q fever-induced abortion waves provided circumstantial evidence that dairy goat farms were the most plausible source of human infection in this epidemic. The patients most affected were men, smokers and aged 40–60 years, while children were rarely affected [1]. Acute Q fever mainly presents as febrile illness, pneumonia or hepatitis, but clinical presentation may vary from one area to another [2]. More than 92% of notified patients in the Netherlands with onset of illness in 2007 and 2008 had fever, while 62% presented with pneumonia [1]. Hepatitis was reported in less than 1% of notified patients but is a common presentation of acute Q fever in some countries such as France [2]. The diagnosis Q fever can only be made after confirmation with a laboratory test. Serological methods can detect antibodies against phase I and phase II antigens of *Coxiella burnetii*, the causative agent of Q fever, and thereby distinguish acute from chronic disease. Annual updates on the Q fever epidemic in the Netherlands have been published in this journal [3-5]. We now report on the current situation in the aftermath of the epidemic, focusing on the challenges and remaining questions, especially with respect to chronic Q fever.

Decreasing incidence of acute Q fever, increasing seroprevalence

The epidemiological situation in the aftermath of the epidemic can be characterised by a decreased incidence of notifications of acute Q fever and an increased prevalence of antibodies to *C. burnetii* in the general population, particularly in the most affected area in the south of the country. The number of notified acute Q fever patients fell from 2,354 in 2009 to 504 in 2010 (Figure). From January to November 2011, 81 patients were notified, which is far fewer than the same period in the epidemic years, despite the exceptionally warm and dry weather conditions in the spring of 2011, which are considered conducive to airborne spread of *C. burnetii*.

It is difficult to attribute the decrease in incidence in 2010 and 2011 to any particular control measure because several veterinary interventions were implemented at the same time. In April 2009, vaccination of sheep and goats on dairy farms with more than 50 animals and on farms with public functions in the high-incidence area became mandatory and was extended to the entire country in January 2010 [6]. In addition, stringent hygiene measures were implemented, such as safe manure management and hygiene during lambing. In October 2009, mandatory monitoring of bulk tank milk was implemented. In addition, from December 2009 to June 2010, more than 50,000 pregnant goats and sheep were culled on 87 farms in which bulk tank milk was positive for *C. burnetii*.

Increasing immunity and thereby a smaller population at risk among the general population in the high-incidence area might also have played a role in the decrease in incidence of acute Q fever. Seroprevalence among the general population of the Netherlands was only 2.4% during February 2006 to May 2007, before the first outbreak in June 2007 [7]. More recent nationwide figures are not available, but in the high-incidence area, seroprevalence estimates are available for pregnant women in 2007 to 2009 (9.0%) [8] and for blood donors in 2009 (12.2%) [9].

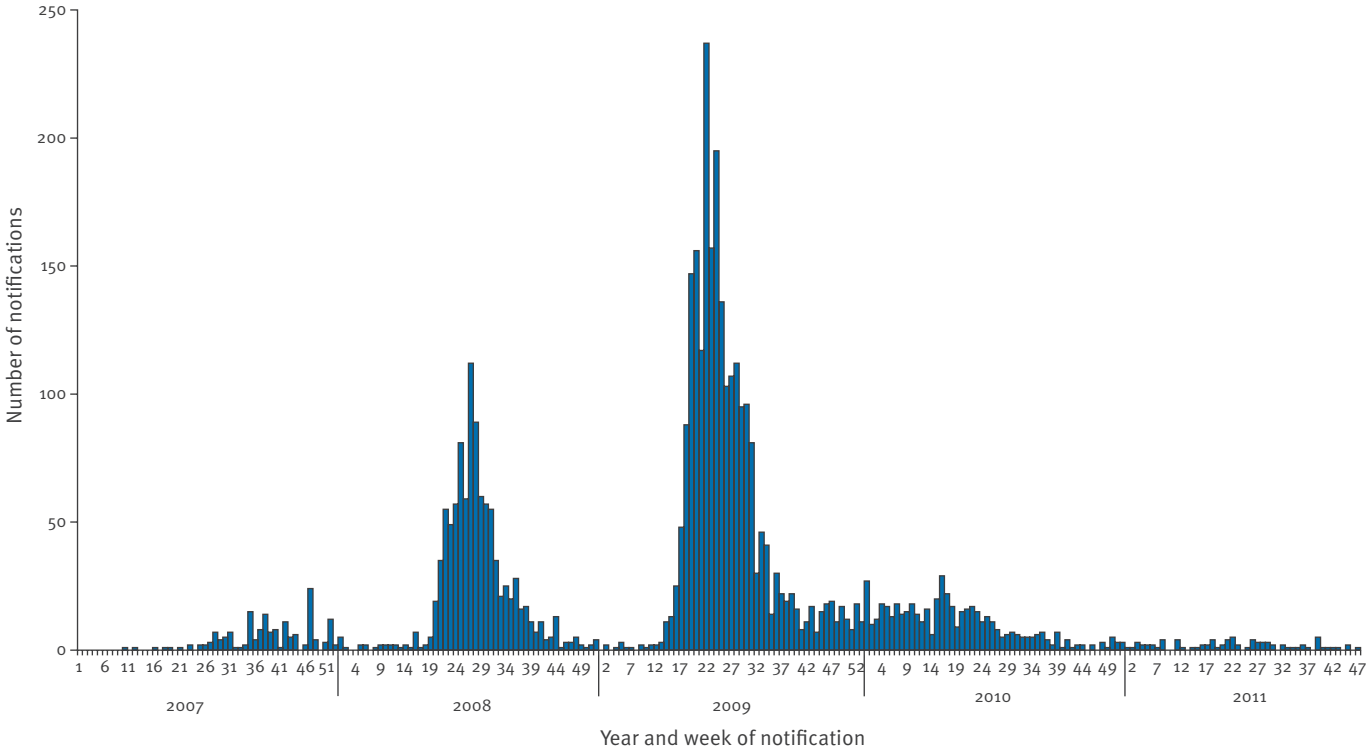
Chronic Q fever

Despite the decreasing incidence of acute Q fever, the Q fever problem is not over: a rising number of chronic Q fever patients are seen. An estimated 2% of acute Q fever patients develop chronic Q fever months to years after the acute infection [10]. Chronic Q fever mainly presents as endocarditis or vascular infection and carries a high morbidity and mortality. Infected patients with previous cardiac valve pathology, aneurysms or vascular grafts or who are immunocompromised and women who are infected during pregnancy are most at risk of developing chronic Q fever [2]. Diagnosis of chronic Q fever is based on a combination of the following: PCR analysis positive for *C. burnetii* in blood or tissue in the absence of an acute infection, an IgG phase I antibody titre of ≥1:1,024, presence of clinical risk factors, presence of clinical signs, and radiological imaging results including echocardiography and positron emission tomography-computed tomography (PET-CT) [11]. There is no notification system for chronic Q fever in the Netherlands, but based on personal communications from various Dutch hospitals in September 2011, we estimate that a total of over 250 patients have been diagnosed since the start of the epidemic.

The major challenge in the Netherlands is therefore early detection and treatment of patients who are at risk for chronic Q fever. The following issues are of particular relevance: (i) the follow-up strategy of acute Q fever patients, for the early detection and prompt treatment of chronic Q fever; (ii) the screening of people in risk groups for chronic Q fever; (iii) the protection of people in risk groups through vaccination; and (iv) the possibility of person-to-person transmission through infected blood or tissue.

Figure

Acute Q fever notifications, the Netherlands, 1 January (week 1) 2007–30 November (week 48) 2011



It is expected that the number of patients with chronic infection will increase in the Netherlands the coming years. In order to diagnose and treat chronic Q fever patients in a consistent way, new guidelines are currently being developed for the diagnosis of chronic Q fever in the country.

Follow-up of acute Q fever patients

In the early stages of the epidemic, the internationally recommended follow-up strategy was followed, consisting of at least three consecutive serological tests in the first year after the diagnosis of acute Q fever and echocardiography for all patients diagnosed with acute Q fever [12]. However, of 134 Dutch Q fever patients from the 2007 and 2008 outbreaks who had undergone screening echocardiography and were followed up for one year after diagnosis of acute infection, none progressed to a chronic infection and echocardiographic screening was discontinued [13]. However, the policy of discontinuing echocardiographic screening has been challenged by Raoult et al., on the basis of data from France that show that clinically silent valvulopathies predispose to chronicity [14]. Considerable uncertainties also exist about the value of serology to identify chronic cases during follow-up. At the regional laboratory of the Jeroen Bosch Hospital (in ´s-Hertogenbosch), located at the epicentre of the Dutch outbreaks, the serological profiles of 686 patients diagnosed with acute Q fever in 2007 and 2008 were evaluated at three, six and 12 months after diagnosis [15]. The results differ from data provided by others, as high IgG phase I antibody titres at the three-month follow-up were not predictive for chronic Q fever and IgG phase I antibody titres greater than IgG phase II antibody titres were rarely seen. The study confirmed that a cut-off value of ≥1:1,024 for IgG phase I titres is suitable for screening in the commercially available immunofluorescence assay used (Focus Diagnostics, United States), at a follow-up between six and 12 months after the acute Q fever episode. For patients with clinical risk factors, however, a more stringent follow-up scheme is required. Wide variation in serological and PCR test results during the follow-up of acute Q fever [15] implies that the diagnosis of chronic Q fever – necessitating long-term antibiotic treatment – must be based on a combination of laboratory results, radiological imaging and clinical grounds. On the basis of the experience gained since 2007, the follow-up strategy is now generally one serological analysis nine months after an episode of acute Q fever. For patients with specific risk factors, the previous serological follow-up strategy at three, six and 12 months is maintained, with use of PCR if high IgG I titres are obtained.

Screening of risk groups for chronic Q fever

Chronic Q fever has been diagnosed in the Netherlands in patients who had no history of acute Q fever, suggesting that chronic Q fever can develop after asymptomatic infection or symptomatic infection with only mild aspecific symptoms. The incubation period of a chronic infection is largely unknown and may be different in patients with vascular disease compared with those who have valvular disease. Some hospitals in the high-incidence area are now implementing screening programmes for the detection of chronic Q fever in patients with known cardiac valve or vascular pathology. The risk of chronic Q fever in other risk groups, such as pregnant women, is probably too low to warrant a targeted screening strategy.

Human vaccination

Q fever can be prevented by a vaccine that is produced and licensed in Australia to protect abattoir workers [16]. For this and other occupational risk groups, such as sheep shearers and farmers of ruminants, the vaccine has proved to be successful and is still in use in Australia [17]. From the notification data, it is clear that occupational exposure did not play an important role in the epidemic in the Netherlands [1]. The prevalence of antibodies against *C. burnetii* in dairy goat farmers and practising veterinarians is greater than 80%, but very few seem to develop clinical disease (unpublished data). Vaccination – a one-off campaign during the epidemic – was therefore primarily considered for persons at risk for chronic Q fever. Implementing vaccination was difficult, however, because the vaccine is not registered in any European country and its effectiveness has only been shown in healthy young adults, not in persons with cardiovascular risk factors or patients with severe underlying disease [18]. Moreover, the logistics are cumbersome: the vaccine can only be given to those who have not previously been in contact with *C. burnetii*, as vaccinating people who have already mounted an immune response against the pathogen may lead to serious adverse reactions such as sterile abscesses and systemic symptoms of inflammation. Therefore, serology and skin testing are mandatory before vaccination. In the absence of a licence, the vaccine can only be administered after the patients' physician has signed a medical awareness statement and the patient has signed an informed consent form. Nevertheless, the Health Council of the Netherlands advised vaccination of people in specific risk groups in the high-incidence area who have an increased risk of developing complications following acute infection [19]. The groups included patients:

- who have had endocarditis
- with prosthetic heart valves
- with important congenital heart anomalies, including those that required grafts
- with structural defects of the aortic or mitral valve
- with known aneurysm of the aorta
- with vascular grafts
- with severe peripheral vascular disease (such as Buerger's disease).

General practitioners selected all patients from these groups from their patient registration systems. In total, 1,781 patients were screened: 394 (22%) could not be vaccinated because of a positive skin test or the presence of antibodies against *C. burnetii*. After

screening, 21 eligible patients declined vaccination or did not attend the vaccination session: eventually 1,366 patients were vaccinated from 28 January to 27 June 2011. There is a routine follow-up of vaccinated individuals for vaccine-related adverse events – the results should be available by the end of 2011. The vaccination campaign has also been followed by a post-vaccination immune-response study in which humoral and cell-mediated immunity will be investigated.

Transmission of *C. burnetii* by infected blood and tissue

Although only few cases have been clearly documented, there is a theoretical possibility that *C. burnetii* can be transmitted through blood transfusion, and semen, tissue and organ donation [20]. Active screening was therefore recommended by the European Centre for Disease Prevention and Control (ECDC) in their risk assessment in 2010 [10]. Sanquin Blood Supply Foundation tested blood donated from people living in the area with highest Q fever incidence in the south of the Netherlands for the presence of *C. burnetii* DNA by PCR from 20 May 2009 – in 2009 as part of a research project, then in 2010 as a screening instrument [9]. In 1,004 blood donations, there were three positive PCR results and in one recipient, there was evidence of seroconversion. However, the recipient lived in the high-incidence area and it is therefore possible that the infection was caused by environmental exposure. The screening programme was discontinued on 1 November 2010, when it was clear that the incidence of the disease had fallen dramatically. With the decreasing incidence and the expected increasing numbers of chronic infections in the coming years, the issue of protecting recipients of blood, semen, tissue and organs is shifting towards detecting asymptomatic persons harbouring *C. burnetii* months to years after their acute infection. However, there are important logistic and financial constraints in using PCR on a large scale. Capacity for PCR testing at Sanquin is limited to 100 samples per day, while close to a million blood component transfusions are given annually. Alternatively, donors could be screened for the presence of IgG phase I antibodies against *C. burnetii*. For large-scale screening purposes, an automated ELISA would have to be used, but the performance of ELISAs for IgG phase I antibodies have yet to be evaluated.

In August 2011, the Health Council of the Netherlands advised that a detailed cost-effectiveness analysis of serological testing of blood donors be carried out and, should the incidence of acute Q fever increase again, screening of blood donors be resumed [20]. Concerning tissue donations, no screening is needed for tissues that carry a low risk of transmission such as cornea, coagulants and other treated blood products or tissues collected before 2007. Otherwise, nationwide serological testing is recommended. In certain circumstances, such as organ transplantation or use of stem cells, the responsible physician and patient might decide to use infected material anyway, when a considerable improvement in quality of life or even the saving of life is anticipated. Knowing that the donor's serological status is positive can then make appropriate antibiotic prophylactic treatment of the recipient possible.

Persistent fatigue after acute Q fever

While relatively few patients who have had acute infection develop chronic Q fever, a much larger group suffers from persistent fatigue and other long-term effects of acute infection. Unlike chronic Q fever, this is not a life-threatening condition, but the fatigue can be debilitating and seriously affect the person's quality of life [21]. In an ongoing study, the effectiveness of antibiotic treatment is being compared with cognitive behavioural therapy for post acute Q fever fatigue.

Outlook

We expect that the sustained mandatory vaccination of goats and sheep will control transmission of Q fever to humans. The veterinary vaccine seems effective in reducing shedding of *C. burnetii* and in preventing abortion [22]. However, the bacteria are widespread in the environment and in other animal reservoirs, such as wild rats [23]. Enhanced surveillance in animal populations as well as in humans will remain essential. To fill the remaining knowledge gaps, there is an extensive ongoing research agenda, covering fields such as as host–pathogen characteristics, transmission and risk factors, chronic Q fever and treatment of post acute Q fever fatigue.

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Screening for *Coxiella burnetii* infection during pregnancy: pros and cons according to the Wilson and Jungner criteria

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In Europe the incidence of human Q fever has dramatically increased over the previous years. Untreated infections with *Coxiella burnetii*, the causal agent of Q fever, have been associated with both obstetric and maternal complications. The majority of pregnant women with a *C. burnetii* infection remain asymptomatic, hence screening could be of value to prevent unwanted outcomes in this high-risk group. We applied the updated Wilson and Jungner criteria to review the evidence for routine screening for *C. burnetii* infection during pregnancy. Since much uncertainty remains about the incidence, clinical consequences, diagnostics and treatment of *C. burnetii* infection during pregnancy, routine screening for *C. burnetii* infection during pregnancy should not be recommended. Rigorous studies to assess the effectiveness of *C. burnetii* screening are warranted.

Introduction

Infections during pregnancy may cause a threat to both maternal and foetal health, even if the infected pregnant woman herself remains asymptomatic [1]. Therefore, routine screening at 12 weeks of gestation is being offered to all Dutch pregnant women for human immunodeficiency virus (HIV), *Treponema pallidum* and hepatitis B virus (HBV). The incidence of human Q fever, a zoonosis caused by *Coxiella burnetii*, showed an enormous increase in the Netherlands and other European countries over the past few years [2]. Since there is evidence for infection-associated obstetric and maternal complications, *C. burnetii* infection poses a potential risk to pregnant women and their (unborn) children [3]. Most of the pregnant women with a *C. burnetii* infection remain asymptomatic [4]. Therefore routine screening has been put forward for early detection and treatment in this group, but scientific evidence about the usefulness of such an intensive program is lacking. In this review we applied the Wilson and Jungner criteria according to the World Health Organization to scrutinise the available evidence for routine screening for *C. burnetii* infection during pregnancy. These criteria were developed over 40 years ago but are still of great value in decision making around screening policies [5]. The criteria centre on the problem caused by the infection or disease, the screening population, the test and the treatment, and the costs. As newer policy tools, especially concerning genetic screening, have been suggested [6], we also integrated the emerging criteria which are applicable to our research question. A review of the literature was done by searching PubMed and the references of included papers. Our search was limited to studies in English or Dutch. The search strategy included the keywords 'Q fever' or '*Coxiella burnetii*' and keywords related to the criteria ('incidence' or 'prevalence' or 'pregnancy' or 'risk factors' or 'diagnosis' or 'treatment' or 'costs'). Our overall aim was to examine the evidence base for routine *C. burnetii* screening among pregnant women in high-risk areas for Q fever all over Europe.

The problem

Terminology used in the scientific literature concerning 'Q fever' is diverse and therefore direct comparisons of epidemiological studies should be performed with caution. 'Q fever' is commonly referred to the symptomatic disease, including symptoms such as fever, hepatitis or pneumonia in combination with positive antibody titres or polymerase chain reaction (PCR). The terms '*C. burnetii* infection' and 'presence of antibodies' are more often used in the context of asymptomatic disease, for example, in prevalence studies.

Is *Coxiella burnetii* infection during pregnancy an important health problem?

Prior to 2007 Q fever was uncommon in Europe [2], except from some local outbreaks such as the outbreak

in Germany in spring 2005, causing 331 cases [7]. In the Netherlands around 10 to 30 cases have been notified each year since 1977. Between 2007 and 2009 the numbers briskly increased to over 2,300 cases in 2009, the highest number ever reported in the literature [8]. Veterinary outbreaks on several dairy goat and sheep farms in the southern parts of the Netherlands are held responsible for this increase. In 2009 and 2010 it was decided to implement extensive measures such as vaccinating and culling of thousands of animals [8]. As a result, the number of human Q fever cases decreased rapidly to around 500 cases by the end of 2010, which is still considerable and may indicate an endemic stage [9]. Also other European countries, such as Belgium, Cyprus and Germany have reported an increasing number of cases since 2007, albeit to a smaller extent [2].

The prevalence of Q fever among pregnant women is unknown. Recently published data from the Netherlands showed a prevalence of immunoglobulin (Ig)M, suggesting recent infection with *C. burnetii*, in 3.4% of 1,646 tested serum samples from pregnant women in Q fever high-risk areas [10]. In a cohort study from Canada, 3.8% of parturient women had evidence of previous exposure to *C. burnetii* (presence of IgG phase I and/or II). These women had, in contrast to the Dutch seropositive women [10], a higher risk for adverse pregnancy outcomes, in terms of premature delivery and prior or current neonatal death, compared with seronegative women [11]. A milestone hospital-based study from France showed that 81% of the pregnant women with untreated Q fever had a miscarriage, premature delivery, intrauterine growth restriction or foetal death. Furthermore, chronic Q fever occurred in 50% of the cases, of whom 10% developed *C. burnetii* endocarditis [3]. These figures are alarming, but need to be cautiously interpreted as the retrospective design covering many years may have led to some overestimation of risks. Certainly, this study together with the prevalence studies emphasise that *C. burnetii* infection is a potential threat to pregnant women.

Is there a latent or early symptomatic stage?

Up to 90% of infected pregnant women remain asymptomatic [4]. Therefore, early detection, before obstetric complications and maternal chronic Q fever have occurred, enables treatment that may prevent complications due to *C. burnetii* infection [3].

Is the natural history of *Coxiella burnetii* infection adequately understood?

C. burnetii is a small gram-negative intracellular living bacterium. The main route of transmission is the respiratory route, in which alveolar macrophages in the lungs are the first cells to be infected [12]. Furthermore, the placenta seems to be a target organ since placentitis has been described in both animals and humans [3,13]. After the primary infection, *C. burnetii* has the ability to induce chronic infections. It is hypothesised that, besides the liver, bone, heart valves and mural endocardium [14], the uterus could be a site of latent infection, hence reactivation during pregnancy can occur [3,11].

The pathogenesis of obstetric complications following infection is not completely understood; immune complexes may cause vasculitis and vascular thrombosis, which in turn may lead to the placental insufficiency and subsequent obstetric complications [15]. Also, direct transplacental transmission by *C. burnetii* may cause foetal death [16]. Obstetric complications occur significantly more often in patients who are infected during the first trimester of pregnancy than in those infected later [3].

Not only have acute infections been associated with obstetric complications, but also previous infections seem to increase the risk [11]. There is no good explanation for this association besides the hypothesis of intrauterine latency of the infection [11]. In all, the natural history of *C. burnetii* infection among pregnant women is not completely understood.

The screening population

Since the Q fever incidence largely varies between regions (see for example the situation in the Netherlands, figure), the population for routine screening should be limited to pregnant women living in high-risk Q fever areas. Women living within a five-kilometre zone around a dairy goat or dairy sheep farm affected by *C. burnetii*-related abortion waves have the highest risk of contracting an infection, however, still 41% of the Dutch cases in 2009 lived outside of these areas [8]. Whether these cases visited the five-kilometre zones is unclear. Therefore, if introduced, routine screening of all pregnant women would be advisable in areas with a high incidence (e.g. >50/100,000 inhabitants). So, with a good surveillance system, the screening population can be accurately defined. Screening of specific groups at risk, e.g. pregnant women with occupational hazard for Q fever or with complicated pregnancies can also be considered, but is beyond the scope of this study discussing routine screening of a total population.

Similar to other screening programs during pregnancy, eligible women have to be counselled about the benefits and possible consequences of the screening (i.e. long-term antibiotic treatment and hospital birth instead of home birth in case of an acute infection, stress induced by awareness of infectious diseases during pregnancy) to be able to make an informed choice about participation.

Is there an agreed policy on whom to treat as patients? All phases of *C. burnetii* infection during pregnancy have been associated with adverse pregnancy outcome. However, evidence for the benefits of antibiotic treatment is only available in patients with acute and chronic Q fever [3]. Whether antibiotic treatment prevents complications in women with asymptomatic seropositivity needs to be investigated.

Is case finding a continuing process and not a 'once and for all' project?

If introduced, screening for *C. burnetii* infection should be performed during each pregnancy since the infection can be contracted at any moment and reactivation during pregnancy of a previous infection may occur [3,11]. Therefore case finding is a continuing process.

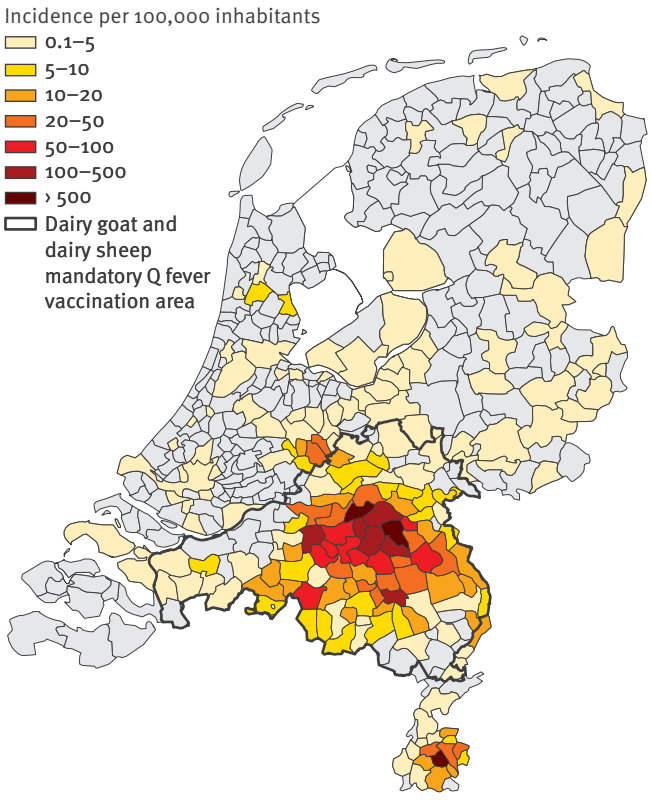
The test and the treatment

Is there a suitable test?

There are several accurate methods to diagnose *C. burnetii* infection, including culture, PCR and serology, of which serology is most suitable for screening [17]. However, the performance of these tests during pregnancy is unknown. In the general population, indirect immunofluorescence assay (IFA) is the reference method [17,18]. Since one of the characteristics of *C. burnetii* is antigenetic phase variation, antibodies against two phases of antigens can be detected. All types of antibodies have their own timeframe of appearance, therefore distinguishing previous, acute and chronic infections is possible [12,18]. As already mentioned, test characteristics during pregnancy are unknown. From other infectious diseases we know that false-positive serological results occur quite often during pregnancy [19]. Furthermore, with respect to sensitivity and specificity, there is an ongoing debate about which cut-off values to use, especially because there are many different commercial and in-house methods. In all, more research needs to be performed with respect to serological screening for *C. burnetii* during pregnancy before routine screening can be implemented.

Figure

Human Q fever incidence per 100,000 inhabitants per municipality in the Netherlands, 1 January–12 August 2009



Incidences are based on symptomatic (fever, pneumonia and/or hepatitis), laboratory-confirmed Q fever cases.

Source: National Institute for Public Health and the Environment (RIVM).

Is the test acceptable to the population?

Acceptance of the test can be expected since only one blood sample is necessary, which can be obtained by venepuncture combined with the screening for other infectious diseases around 12 weeks of pregnancy. An advantage of testing in the first trimester is the possibility of early counselling and treatment during the most vulnerable phase of pregnancy [3]. However, with early screening, infections later in pregnancy would be missed. Timing of the screening needs to be further investigated, also taking into account a seasonal variation in *C. burnetii* spreading [9].

Is there an accepted treatment for patients with recognised disease?

First choice treatment for Q fever among the general population is a 14-day antibiotic treatment with doxycycline or fluoroquinolone [12]. However, both agents are contraindicated during pregnancy. Long-term treatment with cotrimoxazole has been suggested to be the treatment of choice during pregnancy [3]. However, use of cotrimoxazole during pregnancy has not been fully investigated yet. Pharmacological activity of this drug could cause folic acid depletion in the foetus [20]. Furthermore, neonatal hyperbilirubinemia has been described when used prior to delivery. However, these risks turned out to be small in large groups of pregnant women with HIV who received prophylactic cotrimoxazole therapy during pregnancy [21]. In all, more evidence for the best treatment option during pregnancy is needed.

Are there facilities for diagnosis and treatment available?

Since screening for other infectious diseases during pregnancy is already routinely performed, adding *C. burnetii* screening will be relatively straightforward. In the Netherlands, as in other Western countries, several laboratories have facilities to perform *C. burnetii* serology. Quality assessments should be performed on a regular basis. Treatment and follow-up of positively screened women should be performed by obstetricians, infectious disease specialists and medical microbiologist, who should receive additional training on diagnostics and treatment of *C. burnetii* infection during pregnancy.

The costs

Are the costs of case finding economically balanced in relation to possible expenditure on medical care as a whole?

Outcomes of cost-effectiveness models are not available yet and input data are required. Screening with IFA and antibiotic treatment are relatively cheap, though referral for treatment and hospital birth may induce high costs since around 25% of the deliveries in the Netherlands normally take place at home [22].

The adapted Wilson and Jungner criteria, addressed in this study are summarised in the table.

Conclusion

According to the adapted Wilson and Jungner criteria (Table), the currently available evidence is insufficient to promote routine screening for *C. burnetii* infection during pregnancy in high-risk Q fever areas. Because of potential bias in the studies reported so far, there is too much uncertainty about the consequences of untreated *C. burnetii* infection during pregnancy. There is also no consensus about the screening method and treatment. Furthermore, Q fever incidence rates highly affect the effectiveness of screening. Therefore the candidate populations for screening are not static and should be identified based on epidemiological criteria. Finally, besides screening, there are other methods to prevent *C. burnetii* related complications, for example human vaccination [23]. Overall, more evidence about the effectiveness of a *C. burnetii* screening program, in addition to other Q fever prevention and control measures taken by the European countries, is needed before this infection will become a candidate for routine screening during pregnancy.

Disclosure statement

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Table

Wilson and Jungner criteria and emerging criteria for disease screening

Wilson and Jungner criteria and emerging criteria for disease screening	Criteria fulfilled?
The problem	
The condition sought should be an important health problem.	Not certain
There should be a latent or early symptomatic stage.	Yes
The natural history of the condition should be adequately understood.	Not certain
The screening program should respond to a recognised need.	*Not certain*
The objectives of screening should be defined at the outset.	*Yes*
The screening population	
There should be an agreed policy on whom to treat as patients.	Not certain
Case finding should be a continuing process and not a 'once and for all' project.	Yes
There should be a defined target population.	*Yes*
The program should ensure informed choice, confidentiality and respect for autonomy.	*Yes*
The program should promote equity and access to screening for the entire target population.	*Not applicable*
The test and the treatment	
There should be an accepted treatment for patients with recognised disease.	Not certain
Facilities for diagnosis and treatment should be available.	Yes
There should be a suitable test or examination.	Not certain
The test should be acceptable to the population.	Yes
There should be quality assurance, with mechanisms to minimise potential risks of screening.	*Not certain*
The costs	
The costs of case finding should be economically balanced in relation to possible expenditure on medical care as a whole.	Not certain
Overall	
There should be scientific evidence of screening program effectiveness.	*No*
The program should integrate education, testing, clinical services and program management.	*Not applicable*
Program evaluation should be planned from the outset.	*Not applicable*
The overall benefits of screening should outweigh the harm.	*Not certain*

Wilson and Jungner criteria for disease screening adopted by the World Health Organization [5], combined with the emerging screening criteria proposed over the past 40 years [6] (*italic*).

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According to recent data, health information seeking is now the third most popular activity for all users over 18 years old [1]. Health professionals, one of *Eurosurveillance*'s target audiences, are also increasingly finding their way online. In order to keep better in touch with our audience, *Eurosurveillance* has now entered the world of social media and set up a Twitter account.

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