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.

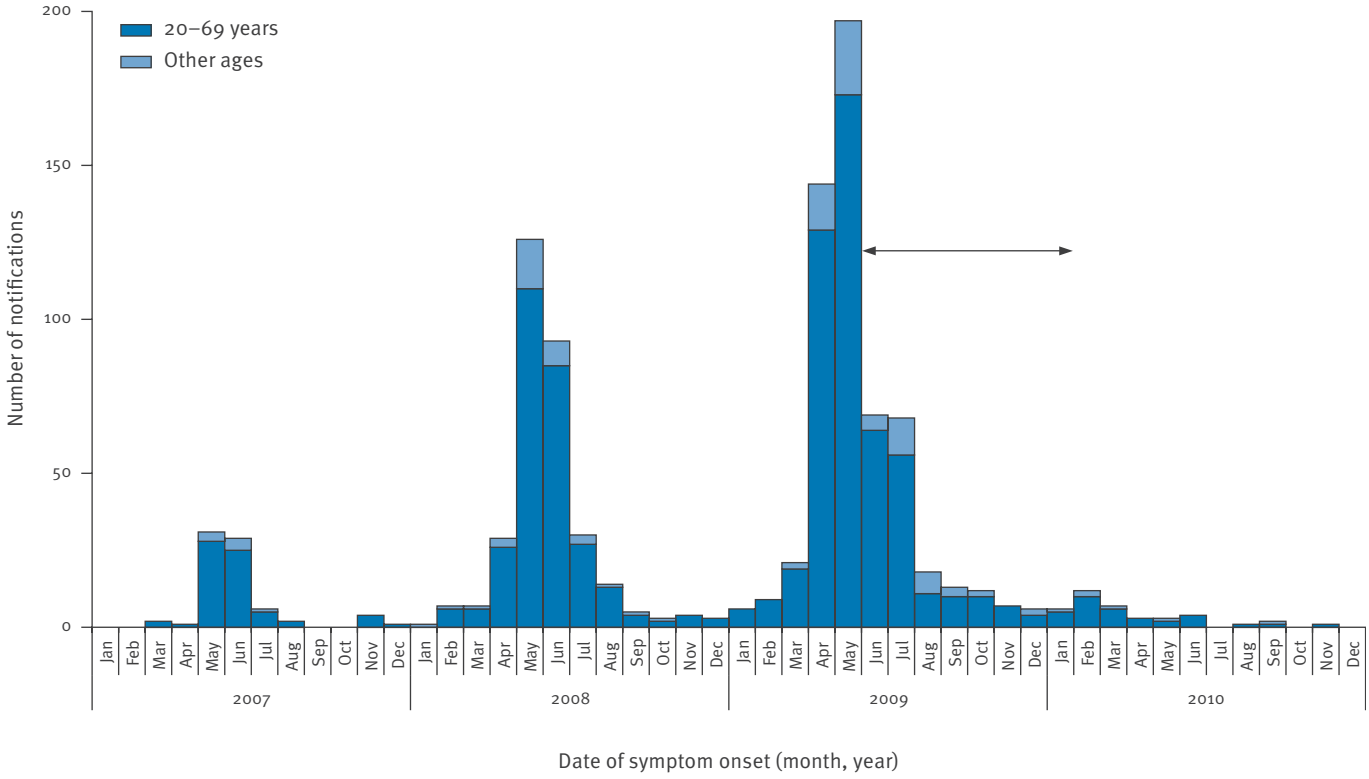
Discussion

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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