Large Regional Differences in Serological Follow-Up of Q Fever Patients in The Netherlands

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Abstract

Background: During the Dutch Q fever epidemic more than 4,000 Q fever cases were notified. This provided logistical challenges for the organisation of serological follow-up, which is considered mandatory for early detection of chronic infection. The aim of this study was to investigate the proportion of acute Q fever patients that received serological follow-up, and to identify regional differences in follow-up rates and contributing factors, such as knowledge of medical practitioners.

Methods: Serological datasets of Q fever patients diagnosed between 2007 and 2009 (N = 3,198) were obtained from three Laboratories of Medical Microbiology (LMM) in the province of Noord-Brabant. One LMM offered an active follow-up service by approaching patients; the other two only tested on physician’s request. The medical microbiologist in charge of each LMM was interviewed. In December 2011, 240 general practices and 112 medical specialists received questionnaires on their knowledge and practices regarding the serological follow-up of Q fever patients.

Results: Ninety-five percent (2,226/2,346) of the Q fever patients diagnosed at the LMM with a follow-up service received at least one serological follow-up within 15 months of diagnosis. For those diagnosed at a LMM without this service, this was 25% (218/852) (OR 54, 95% CI 43–67). Although 80% (162/203) of all medical practitioners with Q fever patients reported at least one serological follow-up within 15 months of diagnosis. For those diagnosed at a LMM without this service, this was 25% (218/852) (OR 54, 95% CI 43–67). Although 80% (162/203) of all medical practitioners with Q fever patients reported informing patients of the importance of serological follow-up, 33% (67/203) never requested it.

Conclusions: Regional differences in follow-up are substantial and range from 25% to 95%. In areas with a low follow-up rate the proportion of missed chronic Q fever is potentially higher than in areas with a high follow-up rate. Medical practitioners lack knowledge regarding the need, timing and implementation of serological follow-up, which contributes to patients receiving incorrect or no follow-up. Therefore, this information should be incorporated in national guidelines and patient information forms.


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Funding: The authors have no support or funding to report.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

In the Netherlands, more than 4,000 patients were notified with acute Q fever during seasonal outbreaks between 2007 and 2010 [1,2]. However, at least ten times as many people might have been infected with Coxiella burnetii in this period and had either asymptomatic or non-diagnosed infections [3,4]. Acute Q fever may progress to chronic Q fever in about 2% of cases [5]. Chronic Q fever is not notifiable. There are no estimates for the proportion of asymptomatic acute C. burnetii infections that develop into chronic infection. The most common presentations of chronic Q fever are endocarditis and vascular infections, conditions with high morbidity and mortality [6]. The diagnosis of chronic Q fever is based on clinical presentation, presence of risk factors, diagnostic imaging techniques, detection of C. burnetii DNA in blood or tissue, and serological test results. Detection of an IgG antibody titre against phase I of C. burnetii of ≥1:1,024 in a commercially available immunofluorescence assay during follow-up screening is considered an important marker of chronic infection [7]. Serological follow-up of acute Q fever patients is advised in order to identify and ensure timely treatment of chronic Q fever [8–10]. Follow-up is especially important for patients with valvulopathy, vascular prosthesis/abnormalities, pregnant women, and immunocompromised patients, as they have a higher risk of developing chronic Q fever after acute infection [8,11].

A common but non-validated recommendation in the international literature was to offer all patients at least two serologic tests (at three and six months) in the first year after the diagnosis of acute Q fever [12,13]. In 2008 the advice to test all Q fever
patients at three, six, and twelve months after diagnosis was published in a Dutch microbiology journal [9]. Two years later, in 2010, new advice was published in another Dutch medical journal proposing one follow-up serologic test at nine months for low-risk patients, while the recommendation for high-risk patients was to test at three, six, nine, and twelve months [14]. During the Dutch Q fever outbreak, apart from these recommendations in scientific journal articles, there were no national guidelines on the serological follow-up of Q fever patients.

In the province of Noord-Brabant, one Laboratory of Medical Microbiology (LMM) used an automatic patient recall system for the serological follow-up of patients with acute Q fever. The other two LMMs depended on medical practitioners to request serological Q fever follow-up. The Municipal Health Service (MHS) Hart voor Brabant received information from both patients and health professionals that indicated poor serological follow-up of Q fever patients with regional differences. Therefore the question arose, if and to what extent the serological follow-up rates of Q fever patients differed per LMM catchment area. Are chronic Q fever cases potentially missed due to a lack of proper follow-up? The aim of this study was to investigate the extent to which acute Q fever patients received serological follow-up, identify regional differences and contributing factors and study the differences in knowledge and practices regarding serological follow-up among medical practitioners.

Methods

Ethics Statement
According to Dutch legislation, written consent from patients for the use of anonymised information from laboratory databases is not necessary, therefore ethical review was not required.

Study population and data collection

Laboratories of Medical Microbiology (LMMs). Three LMMs (A, B, and C, see Figure 1) performed the majority of Q fever serology in the province of Brabant. LMM-A in ’s-Hertogenbosch provided active follow-up by contacting every diagnosed Q fever patient for serological follow-up through an automated system. All patients received an explanatory letter and a laboratory form. The other two LMMs, LMM-B in Tilburg and LMM-C in Veldhoven, performed serological follow-up only upon request of a medical practitioner.

All three LMMs provided anonymous serological datasets from all patients that were diagnosed with acute Q fever between January 2007 and December 2009. Follow-up samples up to 15 months after diagnosis of Q fever were analysed for timing and frequency. Samples that were taken within 60 days of diagnosis were not considered as follow-up samples. Follow-up periods were divided into 60–135 days (2.5–4.5 months), 136–255 days (4.5–8.5 months) and 256–450 days (8.5–15 months) in order to include the 3-, 6-, and 12-month follow-up, respectively. The 9-month follow-up started in 2010; therefore these data are not presented as a separate follow-up moment in this study but are included in the follow-up period 256–450 days (8.5–15 months). Patients that were present in the dataset of more than one LMM were only included once by checking gender, date of birth and the postal code. These patients were then allocated to the LMM that requested the Q fever serology. We conducted semi-structured interviews with the head medical microbiologist of each laboratory regarding perceived role and responsibility of serological follow-up of Q fever patients.

Information from general practitioners and medical specialists

In December 2011, questionnaires were posted to all 240 general practices (with 501 general practitioners) and all internists (N = 42), cardiologists (N = 46), and pulmonologists (N = 24) from all hospitals (N = 6) in the MHS region Hart voor Brabant (MHS HvB), the epicentre of the Q fever outbreaks (see Figure 1). We used the term medical practitioners to refer to both general practitioners (GPs) and medical specialists. Non-responders received a reminder after two and four weeks. Reminders were not sent to GPs when one out of three GPs from the medical practice responded.

The questions posed were: work location (postal code), LMM used, the number of Q fever patients treated and the knowledge and practices regarding serological follow-up of Q fever patients. Practice questions included informing the patient about the importance of serological follow-up (never/sometimes/often/always); requesting Q fever follow-up serology for patients (never/sometimes/often/always); and differentiating between high- and low-risk patient groups when offering follow-up (never/sometimes/often/always). Never and sometimes were regarded as inadequate practice. Knowledge questions (multiple-choice) focused on identification of high-risk groups for developing chronic Q fever i.e. “people with valvulopathy, vascular abnormalities, pregnant women, and the immunocompromised”. The possibility to add another perceived risk group was offered as an open question. The same method was used for the follow-up, timing and differences in follow-up between high- and low-risk group patients. Not being able to identify three high-risk groups, and making no distinction in frequency or timing of serological follow-up between high- and low-risk groups were regarded as incorrect answers.

Medical practitioners were divided in groups with zero (<10) and many (>10) Q fever patients and the Q fever incidence area where they worked. These Q fever incidence areas were based on the cumulative Q fever notification data from 2007 up to December 2010 in the area of the MHS HvB and were defined as low (<150 cases per 100,000 residents), medium (150–300/100,000) and high (>300 up to 2,425/100,000) (see Figure 1).

Data analysis

All data were analysed using SPSS (v. 19) 2010. Proportions were compared with the Mantel-Haenzel chi square and Fishers exact test. P-values were based on two-tailed tests, defining P<0.05 as significant.

Results

Laboratories of Medical Microbiology

We received serological datasets of 3,198 patients diagnosed by three LMMs between 2007 and 2009 with serology indicative of acute Q fever (Figure 1). The difference in percentage of patients without serological follow-up within 15 months of diagnosis, differed greatly between LMMs with an active or passive follow-up approach (Table 1); 5% (120/2,346) versus 74% (634/852) respectively (OR 54, 95% CI 43–67). The percentage of patients that did not receive serological follow-up was comparable for the two LMMs without active follow-up (74%). Overall, 24% (754/3,198) of Q fever patients did not receive any follow-up.

During the interviews, one of the heads of an LMM (without a follow-up service) stated that both the medical practitioner and the MHS were responsible for the serological follow-up of Q fever patients. The other two microbiologists perceived this to be a shared responsibility between medical practitioners, patients, and
Figure 1. Cumulative Q fever incidence in the Netherlands from 2007 up to and including 2010, marking the Municipal Health Service regions, highlighting the Municipal Health Service region Hart voor Brabant and the Laboratories of Medical Microbiology, A in ’s-Hertogenbosch, B in Tilburg, and C in Veldhoven.

doi:10.1371/journal.pone.0060707.g001

Table 1. Diagnosis and serological follow-up up to 15 months (450 days) after diagnosis of Q fever for three Laboratories of Medical Microbiology (LMM).

<table>
<thead>
<tr>
<th>Provision follow-up service and location LMM</th>
<th>No</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>’s-Hertogenbosch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total diagnosis Q-fever</td>
<td>2,346 (100)</td>
<td>527 (100)</td>
<td>3,198 (100)</td>
</tr>
<tr>
<td>Diagnosis by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>1,786 (76.2)</td>
<td>320 (60.7)</td>
<td>2,197 (68.7)</td>
</tr>
<tr>
<td>Specialist</td>
<td>536 (22.8)</td>
<td>207 (39.3)</td>
<td>880 (27.5)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>24 (1.0)</td>
<td>0 (0.0)</td>
<td>121 (3.8)</td>
</tr>
<tr>
<td>No follow-up</td>
<td>120 (5.1)</td>
<td>392 (74.4)</td>
<td>754 (23.6)</td>
</tr>
<tr>
<td>Received follow-up in days after diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*60–135</td>
<td>2,077 (88.5)</td>
<td>67 (12.7)</td>
<td>2,144 (68.5)</td>
</tr>
<tr>
<td>136–255</td>
<td>2,015 (85.9)</td>
<td>57 (10.8)</td>
<td>2,112 (66.0)</td>
</tr>
<tr>
<td>256–450</td>
<td>1,926 (82.1)</td>
<td>61 (11.6)</td>
<td>2,087 (62.9)</td>
</tr>
<tr>
<td>Follow-up requested by</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>NA</td>
<td>86 (46.5)</td>
<td>129 (45.6)</td>
</tr>
<tr>
<td>Specialist</td>
<td>NA</td>
<td>99 (53.5)</td>
<td>154 (54.4)</td>
</tr>
<tr>
<td>Total</td>
<td>185 (100)</td>
<td>98 (100)</td>
<td>283 (100)</td>
</tr>
</tbody>
</table>

*A sample taken within 60 days after diagnosis was not considered as a follow-up sample.

†For 13 samples the applicant was unknown (request by an external laboratory).

NA: not applicable.

doi:10.1371/journal.pone.0060707.t001
the LMM. The microbiologist in charge of LMM-A, the LMM that provided active follow-up, chose a proactive approach at the beginning of the outbreak. The heads of the two LMMs without active follow-up stated that in their opinion an active recall of patients by an LMM was not an option because they regarded this as interfering with the responsibility of the medical practitioner.

Response questionnaires and interviews medical practitioners

The response rate of general practices was 70% (167/240), and included 42% (209/501) of GPs. The response rate of specialists was 29% (32/112); highest for pulmonologists 37% (9/24) and internists 33% (14/42), and lowest for cardiologists 15% (6/46). The most frequently mentioned reasons for not participating in the study by non-responders who gave reasons (N=70) were no Q fever patients (38%) or time constraints (25%).

Knowledge and behaviour of medical practitioners regarding serological follow-up

Although 80% (162/203) of all medical practitioners with Q fever patients reported informing patients of the importance of serological follow-up, 33% (67/203) stated never to request follow-up. Information on knowledge and practice questions for medical practitioners with Q fever patients that do (sometimes/often/always) offer follow-up is provided in table 2. Outcomes were comparable for different incidence areas and type of medical practitioner (GP or medical specialist). Medical practitioners with one to five Q fever patients (mainly found in the low and middle incidence areas) seemed less likely to request serological follow-up, as 47% (27/58) stated never. There was no significant difference compared to those with more patients. Overall, there was no difference in reported practice of requesting follow-up serology between GPs in an area with or without an automatic recall system (Table 3). GPs with many patients (>10) and working in the catchment area of a LMM without active follow-up requested follow-up significantly more often than those with few patients (≤10).

The ability to differentiate between high- and low-risk patient groups was comparable for GPs and specialists. The knowledge question; “are patients with a heart valve defect a high-risk group for chronic Q fever” was answered ‘yes’ by 88% of GPs and 100% of specialists. For stents and vascular abnormalities this was 85% and 86%, for the immune compromised 85% and 79%, and for pregnant during the initial infection 74% and 61%, respectively. When looking at individual medical practitioners, 67% correctly identified all high-risk groups. When offering serological follow-up, 35% of GPs and 22% of medical specialists never consider the risk category of the patient. Medical practitioners with many (>10) patients scored significantly worse for identification of the correct high-risk groups, discussing the importance of serological follow-up with the patient, and requesting follow-up serology for high-risk groups (Table 2).

Both GPs (63%) and specialists (45%) assumed that the LMM requests follow-up. GPs with few Q fever patients indicated that they were not acquainted with the procedure and referred patients to specialists. The main reason for not requesting serological follow-up, mentioned by GPs with many Q fever patient cases, was the assumption that the LMM or the MHS would take responsibility for this.

### Table 2. Answers to knowledge and practice questions of medical practitioners (MPs) comparing those with few (≤10) and many (>10) Q fever patients.

<table>
<thead>
<tr>
<th>Knowledge questions</th>
<th>Number* of Q fever patients per medical practitioner</th>
<th>MP category</th>
<th>N (%)</th>
<th>Total MPs</th>
<th>Answered Yes</th>
<th>N (%)</th>
<th>Total MPs</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifies all high-risk groups</td>
<td>&gt;10</td>
<td>35 (53.7)</td>
<td>69 (100)</td>
<td>62 (100)</td>
<td>68 (100)</td>
<td>44 (34)</td>
<td>131 (100)</td>
<td>0.9 (0.4–1.8)</td>
</tr>
<tr>
<td>Makes distinction of risk groups</td>
<td>&gt;10</td>
<td>28 (41.1)</td>
<td>68 (100)</td>
<td>65 (100)</td>
<td>44 (34)</td>
<td>133 (100)</td>
<td>2.1 (1.0–4.5)</td>
<td></td>
</tr>
<tr>
<td>Requests follow-up Q fever patients without distinction of risk groups</td>
<td>&gt;10</td>
<td>32 (46.2)</td>
<td>70 (100)</td>
<td>65 (100)</td>
<td>66 (100)</td>
<td>121 (88)</td>
<td>137 (100)</td>
<td>3.6 (1.1–11.8)</td>
</tr>
<tr>
<td>Requests serology at least once for low-risk groups</td>
<td>&gt;10</td>
<td>34 (50.2)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>52 (40)</td>
<td>133 (100)</td>
<td>0.7 (0.2–2.7)</td>
</tr>
<tr>
<td>Requests serology at least three times for high-risk groups</td>
<td>&gt;10</td>
<td>34 (50.2)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>52 (40)</td>
<td>133 (100)</td>
<td>3.1 (1.4–7.0)</td>
</tr>
<tr>
<td>Identifies all high-risk groups</td>
<td>≤10</td>
<td>33 (53.2)</td>
<td>68 (100)</td>
<td>65 (100)</td>
<td>44 (34)</td>
<td>133 (100)</td>
<td>2.1 (1.0–4.5)</td>
<td></td>
</tr>
<tr>
<td>Makes distinction of risk groups</td>
<td>≤10</td>
<td>16 (24.6)</td>
<td>65 (100)</td>
<td>44 (34)</td>
<td>133 (100)</td>
<td>2.1 (1.0–4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requests follow-up Q fever patients without distinction of risk groups</td>
<td>≤10</td>
<td>18 (27.3)</td>
<td>63 (100)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>52 (40)</td>
<td>133 (100)</td>
<td>0.7 (0.2–2.7)</td>
</tr>
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<td>133 (100)</td>
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<td>63 (100)</td>
<td>65 (100)</td>
<td>65 (100)</td>
<td>52 (40)</td>
<td>133 (100)</td>
<td>0.7 (0.2–2.7)</td>
</tr>
</tbody>
</table>

*Excluded are medical practitioners without Q fever patients (n = 30), those who never request serological follow-up (n = 70) or gave not applicable (NA) answers.

doi:10.1371/journal.pone.0060707.t002
Table 3. Regional differences in reported serological follow-up practices by GPs in regions with a Laboratory of Medical Microbiology (LMM) with or without an automatic follow-up system.

<table>
<thead>
<tr>
<th>Frequency serology request GP</th>
<th>LMM with automatic follow up; GPs N = 123 (100%)</th>
<th>LMM without automatic follow-up GPs; N = 47 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Few patients ≤10</td>
<td>52 (49.2)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Many patients &gt;10</td>
<td>71 (60.8)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>123 (100)</td>
<td>47 (100)</td>
</tr>
</tbody>
</table>

Municipalities in the service area of a LMM with follow-up: Heusden, Oss, Maasdonk, Uden, Bernebeke, Landerd, Vught, ’s-Hertogenbosch (Den Bosch), Sint Michielsgestel, Veghel, Schijndel, Boekel, Boxtel.

Municipalities in the service area of a LMM without follow-up: Dongen, Waalwijk, Tilburg, Oisterwijk, Gilze Rijen, Loon op Zand, Sint Oedenrode, Cuijk, Boxtel, Mill en Sint Hubert, Hilvarenbeek, Sint Anthonis, Haaren, Grave.

doi:10.1371/journal.pone.0060707.t003

Discussion

Laboratory follow-up of Q fever: Recent developments and experiences

Most data on the serological follow-up of Q fever patients is relatively outdated. The recent Q fever epidemic in the Netherlands led to a renewed interest in the efficacy and efficiency of serological follow-up. The Dutch Q fever outbreak was essentially caused by contaminated meat derived from sheep with chronic Q fever. The rapid spread of the disease and the high infection rate in the Dutch population indicate that the disease is underdiagnosed. In the light of this, the follow-up of Q fever patients becomes even more important.

The follow-up of Q fever patients is crucial for the prevention of chronic disease. A recent study in the Netherlands showed that approximately 1% of patients with acute Q fever develop chronic disease. The follow-up of Q fever patients should therefore be considered a public health priority.

The follow-up of Q fever patients is not only important for the prevention of chronic disease, but also for the early detection of chronic Q fever. Chronic Q fever is characterized by a persistent antibody response, which can be detected by various serological tests. The detection of chronic Q fever is important for the management of patients, as it can lead to an early diagnosis and treatment.

In the Netherlands, follow-up of Q fever patients is mainly done by general practitioners (GPs). However, the follow-up of Q fever patients is not standardized and there is a lack of guidelines for the follow-up of Q fever patients. This lack of standardization and guidelines can lead to a variable follow-up rate among different regions.

The follow-up of Q fever patients is also influenced by the availability of laboratories with active recall systems. In regions with a laboratory with an active recall system, the follow-up rate is higher compared to regions without a laboratory with an active recall system.

The follow-up of Q fever patients is an essential part of the management of patients with Q fever. The follow-up should be standardized and based on guidelines to ensure effective and efficient follow-up. The availability of laboratories with active recall systems is also important for the follow-up of Q fever patients.

Chronic Q fever is a chronic, non-communicable disease that is characterized by a persisting antibody response (IgG phase I) to C. burnetii. The diagnosis of chronic Q fever is challenging, as the infection is often asymptomatic or with mild symptoms. The diagnosis of chronic Q fever is based on the detection of chronic antibodies, which can be detected by various serological tests.

The diagnosis of chronic Q fever is often based on the detection of chronic antibodies in a follow-up sample. The detection of chronic antibodies is essential for the diagnosis of chronic Q fever, as it can lead to an early diagnosis and treatment.

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The follow-up of Q fever patients is an essential part of the management of patients with Q fever. The follow-up should be standardized and based on guidelines to ensure effective and efficient follow-up. The availability of laboratories with active recall systems is also important for the follow-up of Q fever patients.

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Conclusion and recommendations

The serological follow-up of Q fever patients poses logistical challenges. Our results clearly indicate that a LMM based follow-up system with active patient approach achieves high patient compliance compared with systems that rely on referral by medical practitioners. Also, the current registration systems of medical practitioners are not suited to follow-up Q fever patients. Medical practitioners hold others, including the patient, responsible for follow-up and often lack knowledge on the indication for and implementation of serological follow-up of Q fever. A lesson learned from this outbreak, is that recommendations on best practices regarding the serological follow-up of acute Q fever patients should be translated into practical guidelines for medical practitioners early on during an outbreak. The recommendation on serological follow-up should also be incorporated in patient information leaflets. Recalling selected high risk patients that received incomplete or no serological follow-up should be considered. Additional information, on conversion to chronic Q fever per patient category in time, is needed in order to decide which patient groups should be recalled and up to what time after initial infection. Organising such a recall needs to be a joint action by medical practitioners, the LMM, the Q fever patient association and the MHS.

Acknowledgments

The authors thank Paula Schreurs who assisted in data gathering and interviewing medical microbiologists during her internship in Biomedical Sciences at the MHS Hart voor Brabant. We are grateful for the assistance and advice during data analysis of the bio statistician Hans Bor of the Academic Collaborative Centre AMPHI, Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, who assisted with data analysis. Figure 1 was compiled by Ben Bom, of the National Institute for Public Health and the Environment, Bilthoven, the Netherlands.

Author Contributions

Revised the manuscript critically for important intellectual content and approved the final document: GM CCHW MJBK. Performed the experiments: GM CCHW MJBK. Contributed reagents/materials/analysis tools: JHM MCAWB. Wrote the paper: GM CCHW.

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