Chronic Q Fever: Different Serological Results in 3 Countries—Results of a Follow-up Study 6 Years After a Point Source Outbreak

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Background. Acute and chronic Q fever/Coxiella burnetii infection is diagnosed principally by serology. The management of patients who have serological evidence of chronic Q fever but no other manifestation of chronic infection is challenging.

Methods. This paper describes a follow-up study of individuals 6 years after a point source outbreak. The study compares serological and polymerase chain reaction (PCR) results between 3 international reference laboratories in a well-defined cohort of Q fever patients.

Results. Concordance in microimmunofluorescence result interpretation from the 3 centers was only 35%. Australian and UK results had the greatest concordance and French and UK results the lowest. Serological testing revealed no chronic serological profiles when tested in either France or Australia but 10 when tested in the UK. Serological results from a patient with treated Q fever endocarditis suggested treated (France), chronic (UK), and borderline chronic (Australia) infection. PCR results on blood were universally negative.

Conclusions. This study has shown that the results from Q fever micro-immunofluorescence vary according to the center in which they are carried out. This has implications for the interpretation of such tests, raises questions regarding the validity of using serological criteria alone as a means of diagnosing chronic Q fever, and affects the interpretation of epidemiological studies. We recommend that all results are interpreted according to the clinical picture and particular caution is applied in the interpretation of chronic serological profiles. In order to further our understanding of Q fever infection we propose that an international standard of Q fever serological investigation be developed.

Q fever is an infection caused by an obligate intracellular bacterium Coxiella burnetii. It causes acute Q fever, the most frequent manifestations of which are a self-limiting febrile illness, hepatitis, or pneumonia. In some instances the infection is entirely asymptomatic.

The presentation of chronic Q fever is heterogeneous. The most common manifestation is Q fever endocarditis in patients with preexisting valvular heart disease [1].

Difficulties in diagnosing chronic Q fever infection clinically have led to the development of diagnostic serological criteria. These criteria are based on studies that mostly compare acute Q fever patients with those that have Q fever endocarditis. The most commonly quoted criteria [2], developed in France, are used on a worldwide basis to interpret Q fever serology.

The management of patients who only partially meet the diagnostic criteria for chronic Q fever is challenging. Although not widely published in the literature, this
phenomenon—patients with raised *Coxiella burnetii* antibody titres, no other clinical features of chronic infection and who do not fulfill modified Dukes criteria for endocarditis—is well recognized [3]. PCR has been proposed as a means of distinguishing those patients in this category that have Q fever endocarditis or vascular infection [4]. The significance of a negative PCR result has not been evaluated prospectively nor has PCR been evaluated on a cohort of patients with raised Q fever antibody levels (UK testing) but no other signs of chronic infection.

This paper describes a follow-up study of individuals 6 years after a point source outbreak in a cardboard box manufacturing plant in Newport, Gwent, 2002 [5]. The original outbreak consisted of 106 cases of acute Q fever (84% symptomatic) from a factory of 250 employees [5]. All infected individuals were invited to a follow-up clinic. The clinic identified 1 case of endocarditis [6] (by modified Dukes criteria) and 38 individuals with phase 1 IgG titres $>800$, consistent with chronic Q fever, but with no other manifestations of infection. They were afebrile, with normal C reactive protein, erythrocyte sedimentation rate (ESR), and white cell counts and did not have valve lesions diagnostic of endocarditis. The optimal management of these individuals is uncertain. This study examines the relationship between serological results and clinical features and compares serological and PCR results between 3 international reference laboratories in a well-defined cohort of Q fever patients.

### Aims

The aims of this study were as follows:

1. To describe the spectrum of long-term consequences of Q fever infection in the South Wales outbreak population 6 years after exposure to point source
2. To assess the relationship between clinical symptoms and serological results 6 years after initial infection in 4 subgroups: (i) those with raised phase 1 IgG antibodies to *Coxiella burnetii*, (consistent with chronic Q fever), (ii) individuals with apparent recovery from *Coxiella burnetii* (as defined by low or absent phase 1 IgG antibodies), (iii) individuals who were potentially exposed but apparently uninfected, and (iv) 1 patient with proven Q fever endocarditis who had completed treatment.

3. To compare serological tests undertaken by 3 international reference laboratories in a well-defined cohort of Q fever patients.
4. To compare the use of PCR with serological tests in the diagnosis of chronic Q fever and examine its role in differentiating patients into groups that have (i) active infection, (ii) those that have recovered clinically, and (iii) those who have quiescent infection.
5. To determine whether Q fever infection results in chronic persistence of the organism in the blood, as defined by PCR.

### METHODS

Individuals from the exposed cohort were categorized into 4 groups, differentiated on the basis of serological tests for Q fever antibodies (UK reference laboratory results, Table 1).

Informed consent was taken prior to entry into the study and ethical approval was granted by South East Wales Research Ethics Committee Panel C. Eighty of the 95 uninfected controls were selected using a random number generator (group 3).

Blood was taken for a full blood count, urea and electrolytes, liver function tests, CRP, ESR, rheumatoid factor, thyroid function tests, thyroid peroxidase antibodies, immunoglobulin, *Coxiella burnetii* microimmunofluorescence and PCR. Serum samples were sent to 3 separate reference laboratories in the UK (Special Pathogens Reference Unit SPRU), France (Unite des Rickettsies, Marseille), and Australia (Australian Rickettsial Pathogens Reference Laboratory, ARR).

### Table 2. Information on MIF and PCR Tests

| Reference laboratory         | Phase 2          | Phase 1          | PCR target (reference)          |
|------------------------------|------------------|------------------|---------------------------------|
| ARRL, Australia              | Nine mile (clone 4) | Henzerling strain | Com 1 and IS1111a [7]          |
| SPRU, UK                     | Patient strain “Lane”—ST12 group | Patient strain “Lane”—ST12 group | IS1111a, COM1, and 16sRNA [8] |
| Unite des Rickettsies, Marseille, France | Nine mile (ATCC VR615) (2) | Nine mile (ATCC VR615) (2) | IS1111a x 2 targets [4] |
Reference Laboratory) for microimmunofluorescence and PCR tests (in house assays) (Table 2) [2, 4, 7–9]. Participants were asked to complete a questionnaire containing a number of validated health measures (not reported in this paper).

A serological status was assigned to each individual based on the results from each center using the most commonly accepted interpretation rules (Table 3) [2]. A “borderline” category was added as there is uncertainty in managing patients with a phase 1 immunoglobulin G (IgG) of between 400 and 800, as Q fever endocarditis has been recognized in at least 1 patient with a phase 1 IgG < 800. It is recognized that these thresholds are not universally adopted. For example, in France a serological titre of 800 would be considered borderline (D. Raoult, oral communication, 2010).

RESULTS

Of 212 individuals invited to take part in the study, 52 attended for blood testing (see Table 1) and 50 completed questionnaires.

The results from the 3 centers interpreted using recognized criteria [2] are shown in Table 4. Table 5 shows the results according to original status groups 1–4. The concordance between the test results from the 3 laboratories was 35% (18/52) overall, 35% (18/52) France cf UK, 42% (22/52) France cf Australia, and 71% (37/52) Australia cf UK (Table 6).

Concordance was greatest between Australian and UK laboratories and lowest between French and UK laboratories.

**Discordant Results**

Discordant results are shown in Table 7 (18 out of 52 results, 35%).

Four participants had a different status assigned by all 3 centers (Table 7, bold type, nos. 2, 3, 4, 35).

If borderline is considered as a separate category there are a further 6 participants with different serological results in each center (Table 7, italics, nos. 1, 5, 6, 12, 13, 14).

Eighteen participants had the same serological status assigned by all 3 centers, 10 negative results, 8 past infections (although 3 of these results from the UK gave a borderline chronic serological profile, nos. 15, 16, 17).

**Table 3. Q Fever Infection Definitions Devised by Dupont et al [2] With a Borderline Category Added for Results Within One Serial Dilution of a Chronic Definition**

| Status          | Serological criteria                      |
|-----------------|------------------------------------------|
| Chronic         | Phase 1 IgG > 800 or Phase 1 IgA > 25    |
| Past            | Phase 2 IgG detected and Phase 1 IgG < 800|
| Negative        | No antibody detected                     |
| Acute           | Phase 2 IgM > 50                         |
| Borderline      | Phase 1 IgG > 400 and < 800              |

**Table 4. Serological Status According to Testing Center [2]**

| Status   | France | UK  | Australia |
|----------|--------|-----|-----------|
| Negative | 34     | 11  | 17        |
| Past     | 18 (1) | 29 (7) | 32 (2) |
| Chronic  | 0      | 9   | 0         |
| Acute    | 0      | 3   | 3         |
| Total    | 52     | 52  | 52        |

**NOTE.** Figures in brackets are “borderline chronic” serological results—ie, phase 1 IgG within 1 serial dilution of being >800 (400 or 640).

**Chronic/Borderline Serological Profile**

A chronic serological profile was present in 10 individuals when tested in the UK (Table 7) but not in any tests performed in either France or Australia. Eight individuals had borderline results for chronic Q fever when tested in the UK. There were 3 borderline results from Australia (Table 6, nos. 5, 6, 15) and one borderline result from France (Table 6, no. 1).

**Follow-Up Results of Serologically Negative Participants (Group 3)**

Of the 12 participants from group 3 (asymptomatic and serologically negative at the time of the outbreak), 4 were serologically positive by the UK reference laboratory test, 3 by the Australian, none by the French, and 5 by any of the 3 labs (table 5). It is not possible to determine whether this represents late seroconversion, subsequent infection, or false positive serological results. The rate of seroconversion, 5 of 12 cases in 6 years, is high for a background rate of new infections, however.

**Patient With Treated Endocarditis**

One patient was diagnosed with endocarditis in March 2004 [6] and treated for 22 months with doxycycline and hydroxychloroquine. She was asymptomatic prior to treatment, and so treatment response was judged by a fall in her C-reactive protein (CRP) and serological titres (when tested in France). Her results from this study would suggest past/treated infection (France, Phase 1 IgG 50), chronic infection (UK, Phase 1 IgG >1280), and borderline chronic (Australia, Phase 1 IgG 400). The patient stopped treatment in July 2006 but remains under regular follow-up. Since stopping treatment, there has been no increase in her CRP and no further deterioration in her valve function.

**PCR Results**

PCR results on blood were universally negative in this study.

**Biochemical Blood Test Results**

The majority of blood results were within normal limits. There are no results from routine blood tests that suggest those patients with a chronic serological profile have ongoing infection/inflammation greater than those who have evidence of past infection serologically or those who have been consistently seronegative. Three people had mildly elevated CRP. None of these
Chronic Q fever endocarditis can be entirely asymptomatic [6], and normal routine haematological studies [11]. Present in individuals who are afebrile [6, 11, 12], have a normal ESR [12, 13], and normal routine haematological studies [11]. The clinical diagnosis of chronic Q fever infection is challenging. The presentation is heterogeneous and typical markers of infection frequently absent. Q fever endocarditis, the commonest manifestation of chronic Q fever, is a slow indolent disease, and endocarditis is often only diagnosed after significant valvular damage has occurred [10]. Chronic Q fever endocarditis can be present in individuals who are afebrile [6, 11, 12], have a normal ESR [12, 13], and normal routine haematological studies [11]. Chronic Q fever endocarditis can be entirely asymptomatic [6] and can be both clinically and histologically silent [11–14].

A study by Raoult et al [15] has demonstrated that Q fever infection of heart valves does not produce the typical histological findings of endocarditis. In that study, valves removed because of infection with Coxiella burnetii resembled valves removed because of degenerative valve disease in almost every regard. The presence of small vegetations and focal inflammatory changes in the infected valves were the only distinguishing features. These changes however were subtle and could be easily overlooked by routine histological examination. In addition, 3 individuals had no obvious infection on histology, no vegetations, and only a slight inflammatory reaction. These findings in part explain why even transoesophageal echocardiograms perform so poorly in the diagnosis of Q fever endocarditis [1]. The long-term sequelae of these indolent infections has never been prospectively evaluated, nor has the impact of treatment of these individuals been assessed. A cohort study carried out by Swiss investigators, however, has suggested that the long-term (12 year) risk of endocarditis in a group of individuals acutely infected with Coxiella burnetii is no different to a noninfected control population [16]. Equally, follow-up of patients with echocardiographic evidence of valvulopathy has suggested the short-term risk of endocarditis is low [17].

Because chronic Q fever infection is extremely difficult to diagnose, the optimal management of individuals with raised titres but no other evidence of ongoing infection is uncertain. The management is further complicated by the duration and potential toxicity of the recommended treatment regimen, doxycycline and hydroxychloroquine for a minimum of 18 months.

Although local serological thresholds should ideally be developed (using Bayes theorem) and interpreted in the light of clinical information, in clinical practice published criteria are often used in isolation to interpret serological results. A variety of serological criteria to diagnose chronic Q fever infection have been published [2, 18–22] resulting in the following (sometimes contradictory) recommendations:

**DISCUSSION**

The main finding of this study is the discrepancy between serological tests from different reference laboratories and the consequent challenges that this presents in the interpretation of serological results.

The clinical diagnosis of chronic Q fever infection is challenging. The presentation is heterogeneous and typical markers of infection frequently absent. Q fever endocarditis, the commonest manifestation of chronic Q fever, is a slow indolent disease, and endocarditis is often only diagnosed after significant valvular damage has occurred [10]. Chronic Q fever endocarditis can be present in individuals who are afebrile [6, 11, 12], have a normal ESR [12, 13], and normal routine haematological studies [11]. Chronic Q fever endocarditis can be entirely asymptomatic [6] and can be both clinically and histologically silent [11–14].

had a chronic serological profile, and all had serological profiles that were either negative or suggestive of past infection (UK 3/29 past infection, 0/11 negative, France 1/18 past, 2/34 negative, Australia 2/32 past, 1/17 Negative).

**Table 5.**

|a) Results on Patients From Group 1; Infected With Phase 1 IgG Titre ≥ 800 at Any Stage N = 18 |
|---|---|---|---|---|
|Negative| Acute| Past| Chronic|
|UK| 0| 0| 11 (4)| 7|
|France| 5| 0| 13 (1)| 0|
|Australia| 0| 2| 16 (1)| 0|

|b) Results on Patients From Group 2; Infected With Phase 1 IgG Titre Consistently < 800 N = 19 |
|---|---|---|---|---|
|Negative| Acute| Past| Chronic|
|UK| 1| 2| 14 (3)| 2|
|France| 15| 0| 4| 0|
|Australia| 6| 0| 13| 0|

c) Results on Patients From Group 3; Serologically Negative N = 14 |
|---|---|---|---|---|
|Negative| Acute| Past| Chronic|
|UK| 10| 0| 4| 0|
|France| 14| 0| 0| 0|
|Australia| 11| 1| 2| 0|

d) Results on Patient From Group 4; Q Fever Endocarditis—Treated N = 1 |
|---|---|
|Phase 1 IgG Interpretation|
|UK| >1280| Ongoing treatment required|
|France| 50| Cured|
|Australia| 400| Ongoing treatment required|

**NOTE.** Figures in brackets are “borderline chronic” serological results—ie, phase 1 IgG within 1 serial dilution of being >800 (400 or 640).
proposed that development of phase 1 IgG antibodies is part of the normal response to Q fever infection [24].

In one study, cases of Q fever endocarditis were compared with cases of acute Q fever that had been followed up for between 8 and 88 months [18]. Phase 1 IgG was present in all of the control subjects and was >800 in 2 of them. Two also had phase 1 IgA of 320 and CFT of 64.

The Duke criteria have been modified to permit improved diagnosis of Q fever endocarditis, and phase 1 IgG antibody titre >800 to Coxiella burnetii is now considered a major criterion for the diagnosis of endocarditis [25, 26]. In many countries the diagnosis of chronic Q fever will be suspected if an immunofluorescence phase 1 IgG antibody >800 is detected, and physicians may consider starting treatment based on serological results alone.

The optimal management of patients with raised phase 1 IgG levels but no other markers of chronic infection, however, is not clear [3]. It has been proposed that PCR on blood of patients with phase 1 IgG serological titres <1:25600 can identify those with active endovascular infection [4]. In that study, overall sensitivity of PCR was 27% (13/48), 39.4% (13/33) in patients with titres <1:25600, 64% (7/11) in those samples tested prospectively, and 100% (7/7) in patients with titres <1:25600 tested prospectively [4]. One hundred patients with endocarditis caused by other organisms were used as a control group. The significance of a negative PCR result has not been evaluated prospectively, nor has PCR been evaluated on a cohort of patients with raised Q fever antibody levels (UK testing) but no other signs of chronic infection.

The follow-up of patients following Q fever infection is further complicated by the finding that 88% of individuals from a previous UK outbreak [27] had bone marrow samples that were positive by PCR for Q fever 12 years after their acute infection and regardless of their clinical state at the time the samples were taken [9]. Some of these patients had ongoing fatigue, but others had made a complete clinical recovery. All attempts at culture of the bone marrow were unsuccessful [9] including PCR positive marrow/peripheral blood cell homogenates from 10 patients that were inoculated into SCID mice [28]. Although no coxiella were isolated, coxiella antigen-LPS complexes were detected by immunofluorescence in SCID mice spleens. The authors propose that noninfective, nonbiodegradable antigen-LPS complexes persist in the host, and these can provoke aberrant humoral and cell mediated immunity responses [28, 29].

This study has shown that there is discordance in the serological results generated by 3 reference laboratories in UK, France, and Australia. A similar disparity between American and French test results has been found in the United States [3]. It is not possible to determine the sensitivity or specificity of the results from each center as Q fever is frequently
asymptomatic and all the individuals in the factory were potentially exposed. Any detectable titre could therefore represent past infection or exposure. In addition, it is not possible to ascertain from this study the sensitivity and specificity of the chronic serological profile in each country as Chronic Q fever is difficult to diagnose and requires more detailed investigation than carried out here.

However, it is possible to compare the results and it is apparent that the UK test produced the fewest negative results (11 cf 17 [Aus] cf 34 [France]), the most chronic serological profiles (9 cf 0 cf 0) and the most “borderline” chronic serological profiles (8 cf 3 cf 1).

The discrepancy in the results obtained by the different centers has clear implications for the interpretation of serological results.

1. The indiscriminate application of cut off points or criteria for interpretation of serological results (including the indiscriminate use of the phase 1 IgG ≥800 cut off proposed in the modified Duke criteria) is questioned.

2. Serological evaluation of treatment response using microimmunofluorescence will vary according to the testing center being used.

3. Sero-epidemiological studies will produce different results according to the center in which the testing is carried out. As the diagnosis of Q fever infection is based primarily on serological profiles, this discrepancy hampers our understanding of the natural history of Q fever infection.

The differences in the results are surprising given that all 3 centers were using the same microimmunofluorescence method. Strain differences (Table 2), growth substrate, manufacturing technique, and use of different antigenic material are possible explanatory factors.

This study has not provided any additional evidence on the utility of Q fever PCR in establishing a diagnosis of chronic Q fever endocarditis or vascular infection. While a positive PCR in blood is undoubtedly helpful, the long-term outcome of patients with negative PCR results and a chronic serological profile (when tested in the UK) has not been established.

**CONCLUSIONS**

This study has shown that the results from Q fever microimmunofluorescence vary according to the center in which they are carried out. This has implications for the interpretation of such tests, raises questions regarding the validity of using serological criteria alone as a means of diagnosing Chronic Q fever and affects the interpretation of epidemiological studies. We recommend that all results are interpreted according to the clinical picture and that particular caution is applied in the interpretation of chronic serological profiles since the results from this study show that the serological diagnosis of chronic Q fever varies according to where the test is performed. In order to further our understanding of Q fever infection, we propose that an international standard of Q fever serological investigation is developed.

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