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Original article

The prognostic value of serological titres for clinical outcomes during treatment and follow-up of patients with chronic Q fever

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ABSTRACT

Objectives: We assessed the prognostic value of phase I IgG titres during treatment and follow-up of chronic Q fever.
Methods: We performed a retrospective cohort study to analyse the course of phase I IgG titres in chronic Q fever. We used a multivariable time-varying Cox regression to assess our primary (first disease-related event) and secondary (therapy failure) outcomes. In a second analysis, we evaluated serological characteristics after 1 year of therapy (fourfold decrease in phase I IgG titre, absence of phase II IgM and reaching phase I IgG titre of ≤1:1024) with multivariable Cox regression.
Results: In total, 337 patients that were treated for proven ($n = 284$, 84.3%) or probable ($n = 53$, 15.7%) chronic Q fever were included. Complications occurred in 190 (56.4%), disease-related mortality in 71 (21.1%) and therapy failure in 142 (42.1%) patients. The course of phase I IgG titres was not associated with first disease-related event (HR 1.00, 95% CI 0.86–1.15) or therapy failure (HR 1.02, 95% CI 0.91–1.15). Similar results were found for the serological characteristics for the primary (HR 0.97, 95% CI 0.62–1.51; HR 1.12, 95% CI 0.66–1.90; HR 0.99, 95% CI 0.57–1.69, respectively) and secondary outcomes (HR 0.86, 95% CI 0.57–1.29; HR 1.37, 95% CI 0.86–2.18; HR 0.80, 95% CI 0.48–1.34, respectively).
Discussion: *Coxiella burnetii* serology does not reliably predict disease-related events or therapy failure during treatment and follow-up of chronic Q fever. Alternative markers for disease management are needed, but, for now, management should be based on clinical factors, PCR results, and imaging results.
Sheila B. Buijs, Clin Microbiol Infect 2021;27:1273

Introduction

After primary infection with *Coxiella burnetii*, chronic Q fever or persistent focalized infection develops in 1–5% of patients, usually causing endocarditis or vascular infection [1]. In general, long-term treatment with at least two antibiotic agents is indicated for patients with proven and probable chronic Q fever, typically for a duration of 18–24 months [2]. Serological follow-up is recommended for 5 years after discontinuation of therapy [3]. Assessment of the effect of treatment and determination of the duration of treatment is based on clinical factors, imaging results, and microbiological tests, including *C. burnetii* phase I IgG antibody titres [4–6].

Criteria for safe discontinuation of antibiotic therapy are based on expert opinion and limited medical literature [3,5]. The role of serological titres was assessed in only one study, which showed higher mortality rates among patients that failed to reach a fourfold decrease in phase I IgG titre after 1 year of therapy [3]. Also, the persistence of phase II IgM after 1 year of therapy was associated

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with higher mortality. As a result, Dutch guidelines for the treatment of chronic Q fever recommend to strive for a fourfold decrease in phase I IgG titres and/or a titre of 1:1024 or below before discontinuing antibiotic treatment [5].

However, serology might not be an adequate marker for disease activity. For example, a quarter of patients have possible chronic Q fever without a focus of chronic infection nor a disease-related event [7,8]. Nevertheless, they have persistent, high phase I IgG titres after their primary infection. In addition, the clinical observation of chronic Q fever experts is that titres vary within patients, also because titration of titres is susceptible to measurement errors, and do not always seem to reflect the course of the disease. Moreover, antibodies might not be adequate markers for disease activity as the protective immune response against *C. burnetii* is largely T-cell driven [9,10].

As a result, basing the duration of therapy on serological titres may potentially lead to an inadequate therapy duration. Since the most objective and evident way to measure disease activity is evaluating the occurrence of disease-related events, the aim of this study is to investigate whether serological titres can predict such events in a large cohort of patients during and after treatment for chronic Q fever.

Materials and methods

Patient selection and data collection

We used data from the Dutch Chronic Q Fever Database, containing data of patients diagnosed with chronic Q fever from January 2007 until November 2018 in one of the 45 participating hospitals [7,8]. We excluded possible chronic Q fever patients, since they are not at risk for disease-related events [7,8]. We based the diagnosis of chronic Q fever on predefined criteria (please see supplementary material) [11]. Data on patient and disease characteristics were collected from medical records.

Laboratory testing

Indirect immunofluorescence assay (IFA) for *C. burnetii* phase I and II IgM and IgG was used for serological testing (Focus Diagnostics, Inc., Cypress, CA, USA or Fuller Diagnostics, LLC, Anchorage, AK, USA). Titration of antibody levels was performed at local hospital sites and a titre of $\geq$1:32 was considered positive. PCR was performed for detection of *C. burnetii* DNA in blood or tissue samples (in-house, real-time PCR targeting IS1111) [12].

Definitions

The primary outcome was first chronic Q fever-related event (new complication or chronic Q fever-related mortality after initial presentation). Only the first event was taken, because multiple consecutive events are not independent of each other. The secondary outcome was therapy failure, defined as a new chronic Q fever-related complication or chronic Q fever-related mortality after >12 weeks of therapy and/or a new positive PCR on serum/blood after having been negative for at least 3 months and/or a persistent positive PCR on serum/blood for more than 6 months. Definitions of disease-related complications and mortality are listed in the Supplementary text. Cause of death was reviewed by two investigators (S.B.B. and C.P.B.-R.) in all cases and differences were discussed until consensus was reached.

Statistical analysis

We performed a multivariable time-varying Cox regression analysis with repeated measurement of serological titres modelled as the determinant of interest [13]. The difference between subsequent *C. burnetii* phase I IgG titre measurements every 3 months during and after treatment was analysed as a continuous time-varying determinant. The difference was chosen to account for trends in patients (supplementary material). In a second analysis, we evaluated previously reported serological characteristics after 1 year of therapy [3].

The model for the primary outcome included the following other prognostic factors that were chosen based on pathophysiology or their previously found association: age at diagnosis, sex, immunocompromised state at diagnosis, presence of prosthetic material at diagnosis, focus of infection, positive *C. burnetii* PCR on serum/blood at any time during disease, level of phase I IgG at diagnosis, serum doxycycline concentration measurement, antibiotic therapy (as categorical time-varying covariate) and surgery (as categorical time-varying covariate) [3,7,14,15]. As a proxy for intensity of patient care, the number of phase I IgG antibody titre measurements per year during serological follow-up was added. Patients were stratified based on the presence of complications before the start of treatment to account for left-censoring. To account for clustering of patients that were treated in the same hospital and differences between hospitals, a random effect for hospital was included by fitting shared frailty terms in the model (assuming a Gaussian distribution for the frailty parameter). The model for the secondary outcome consisted of the same covariates except for *C. burnetii* PCR serum positivity, since it is part of the definition. Since the probability of PCR serum positivity increases with each increasing phase I IgG titre, we excluded PCR serum positivity from the model for the primary outcome in an additional analysis to evaluate if the effect of phase I IgG titres changed [16].

For the second analysis, titres were analysed as binary variables, and thus not time-varying, in patients that had reached 1 year of therapy: fourfold decrease in phase I IgG titre at 1 year of therapy, phase I IgG titre $\leq$1:1024 within 1 year of therapy, and absence of phase II IgM at 1 year of therapy. These determinants were analysed in six separate Cox regression models for both outcomes, because of presumed collinearity.

Hazard ratios were calculated. The Cox proportional hazards models were fit with the “survival” package in R, version 3.5.1. The proportional hazard assumption was verified and confirmed with formal tests and graphically using Schoenfeld residuals. Descriptive data were generated using SPSS, version 25.0.0.2.

Missing data

Due to the retrospective nature of this study, serological titres were not measured every 3 months during treatment and follow-up as is recommended [3]. Titres were assumed to be missing at random, i.e. related to observed variables. Multiple imputation was used to create and analyse 50 imputed datasets (supplementary material). Additionally, as titres change slowly over time, a last observation carried forward analysis for missing titres was performed as a sensitivity analysis to evaluate the plausibility of imputed titres. Multiple imputation was performed with the “mice” package in R, version 4.0.0 and last observation carried forward with the “zoo” package in R, version 3.5.1.

Ethics statement

The local Medical Ethics Committee of the University Medical Centre Utrecht declared that the study was exempt from ethics review. The internal review board from participating hospitals approved the anonymous processing of data and waived the need for informed consent from patients.

Results

In total, data of 519 patients with chronic Q fever were available. After exclusion of patients with probable chronic Q fever, that did not receive antibiotic therapy, or with a positive *C. burnetii* PCR result only, 337 patients remained (Fig. 1). Of these, 284 (84.3%) had proven and 53 (15.7%) probable chronic Q fever (Table 1). Most patients (n = 314, 93.2%) received the first choice antibiotic regimen of doxycycline and hydroxychloroquine [3,5]. Median duration of follow-up was 4.2 (IQR 1.6–6.8) years.

Missing data

In total, 3908 phase I IgG titres were measured with a median of 12.0 (IQR, 6.0–20.0) measurements per patient. Additionally, 1847 (/5755, 32.1%) phase I IgG titres were missing at different time points: 38 (2.1%) before start therapy, 558 (30.2%) during therapy and 1251 (67.7%) after stopping therapy. Of 264 patients that reached 1 year of therapy, phase II IgM measurements were missing in 126 patients (47.7%). These patients had less often experienced a chronic Q fever-related event (73.0% vs. 89.2%, p < 0.001, Table S1).

Treatment and serology

In total, 264 patients (/337, 78.3%) were treated for at least 1 year of whom 251 patients (/264, 95.1%) with doxycycline and hydroxychloroquine at some point. Fourteen patients (/337, 4.2%) had not yet reached 1 year of therapy at the time of analysis and 45 (/337, 13.4%) died before reaching 1 year of therapy. In 14 patients (/337, 4.2%) treatment duration was less than 1 year. A fourfold decrease of phase I IgG titre after 1 year of therapy was observed in 99 patients (/264, 37.5%): in 34 patients (/264, 12.9%) this decrease resulted in a phase I IgG of ≤1:1024 (Table 2). Phase II IgM titres were measured in 138 patients (/264, 52.3%) and were negative in 93 (/138, 67.4%) after 1 year of therapy.

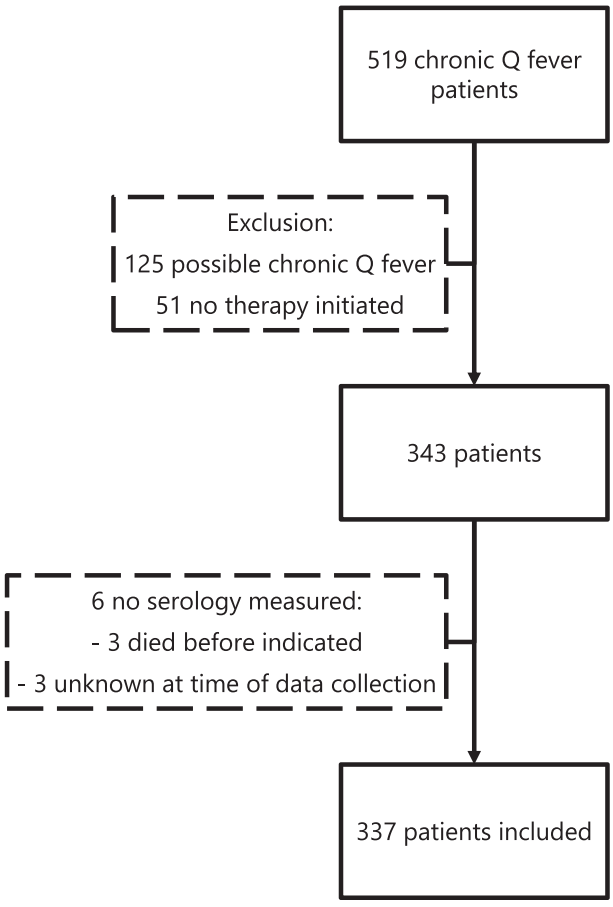

Fig. 1. Flowchart of patient inclusion.

Clinical outcomes

Chronic Q fever-related complications occurred in 190 patients (56.4%) and chronic Q fever-related mortality in 71 patients (21.1%). Therapy failure occurred in 142 patients (42.1%). An increase or decrease in phase I IgG titres was not associated with first disease-related events or therapy failure during treatment or follow-up (Table 3, and Table S2 for the results of univariable analyses). PCR serum positivity was a prognostic factor for first disease-related events (HR 1.57, 95% CI 1.10–2.25, p 0.01). Also, a higher phase I IgG at the start of therapy was a prognostic factor for therapy failure (HR 1.11, 95% CI 1.03–1.21, p 0.01). After removing *C. burnetii* PCR serum positivity from the model, the hazard ratio for the difference between phase I IgG titres did not change (HR 1.00, 95% CI 0.86–1.15, p 0.98). Sensitivity analyses with a last-observation-carried-forward analysis for missing values did not change the hazard ratios for either outcome (Table S3). In the second analysis, an association between both outcomes and before mentioned serological characteristics was also not found (Table 4 and Table S4).

Discussion

An increase or decrease in phase I IgG titres was not associated with first chronic Q fever-related events or therapy failure. Moreover, a fourfold decrease in phase I IgG titre, absence of phase II IgM, and reaching a phase I IgG titre of 1:1024 or lower, were also not associated with the outcomes.

These results are not in line with previous findings. One prior study included 104 patients with Q fever endocarditis and found that an absence of a fourfold decrease of phase I IgG and IgA at 1 year (HR 5.69, 95% CI 1.00–32.22, p 0.005) and the presence of phase II IgM at 1 year (HR 12.08, 95% CI 3.11–46.8, p 0.005) were associated with mortality [3]. This discrepancy may be explained by several differences in the study design and analysis. First, we performed a time-varying Cox regression analysis, which optimally takes into account the repeated measurements during therapy and follow-up, whereas Million et al. dichotomized serological factors [3]. Second, median follow-up period of our study was shorter (4.2 vs. 8.3 years) because we did not request a follow-up duration of at least 3 years. However, this did not limit the number of occurring events. Also, the study from Million et al. suffers from potential survival bias, because it was performed in a tertiary referral centre. Patients that died early in the course of the disease would not have been referred [17,18].

A hypothetical explanation for the lack of the prognostic value of titres could be that clinicians are likely to take action in patients with increasing phase I IgG titres and in doing so improve the patient's prognosis. Therefore, we included surgery and therapy as time-varying covariates and added the number of titres measured per follow-up year as a proxy for intensity of care. Moreover, if serological titres would actually predict outcomes, we would have found the prognostic effect of decreasing titres following action taken by clinicians. Additionally, we previously showed that treatment regimens or intensification were not associated with mortality or therapy failure [2]. Therefore, we believe this is an unlikely explanation for the lack of an effect.

Although the course of serology was the scope of this study, we found that PCR serum positivity was a prognostic factor for first

Table 1
Baseline characteristics of patients with proven and probable chronic Q fever

Characteristic	All patients	Proven chronic Q fever	Probable chronic Q fever
n (%)	337 (100)	284 (84.3)	53 (15.7)
Male sex (%)	269 (79.8)	226 (79.6)	43 (81.1)
Mean age at diagnosis (SD)	68.0 (11.7)	68.4 (11.6)	65.9 (11.9)
Median follow-up, years (IQR)	4.2 (1.6–6.8)	4.0 (1.5–6.8)	5.6 (2.6–6.9)
Focus of chronic Q fever (%)			
Vascular (prosthesis) infection	180 (53.4)	154 (54.2)	26 (49.1)
Endocarditis	79 (23.4)	70 (24.6)	9 (17.0)
Both vascular (prosthesis) infection and endocarditis	49 (14.5)	47 (16.5)	2 (3.8)
Other focus[a]	9 (2.7)	8 (2.8)	1 (1.9)
No focus	20 (5.9)	5 (1.8)	15 (28.3)
PCR serum/blood positivity (%)			
PCR positive any time during disease	156 (46.3)	156 (54.9)	NA
PCR positive for more than 6 months	15 (4.5)	15 (5.3)	NA
PCR relapse after 3 months of being negative	30 (8.9)	30 (10.5)	NA
Chronic Q fever-related complications (%)			
Number of patients with complication	190 (56.4)	183 (64.4)	7 (13.2)
Complication before start of therapy	123 (36.5)	120 (42.3)	3 (5.7)
Deceased (%)	128 (38.0)	111 (39.1)	17 (32.1)
Related to chronic Q fever	71 (21.1)	68 (23.9)	3 (5.7)
Weeks to death, median (IQR)	96.5 (29.5–221.0)	91.0 (24.0–209.5)	138.0 (88.0–289.0)
Weeks to chronic Q fever-related death, median (IQR)	55.0 (10.5–127.0)	46.0 (9.5–119.5)	134.0 (–)

SD, standard deviation; IQR, interquartile range; PCR, polymerase chain reaction; NA, not applicable;
[a] Other foci: 3 lung (2 with PET positive scan and PCR positive lung tissue, 1 with PCR positive scan and PCR positive sputum), 2 pregnancy (1 with PCR positive placenta and amniotic fluid), 2 spondylodiscitis (1 with PET positive scan, 1 with PCR positive pus from paraspinal abscess), 1 pleuritis with PCR positive pleural effusion, 1 pericarditis.

Table 2
Overview of serological titres of chronic Q fever patients

	All patients ($n = 337$)	Proven chronic Q fever ($n = 284$)	Probable chronic Q fever ($n = 53$)
Serology details			
Median number of titres measured during follow-up (IQR)	12.0 (6.0–20.0)	12.0 (5.0–20.0)	13.0 (8.0–20.0)
Median number of titres measured during therapy (IQR)	7.0 (4.0–12.0)	7.0 (4.0–12.0)	7.0 (5.0–9.0)
Median phase I IgG titre at start of therapy (IQR)	4096 (2048–16 384)	4096 (2048–16 384)	4096 (1024–8192)
Details at 1 year of therapy			
Number of patients reaching 1 year of therapy (%)[a]	264 (78.3)	218 (76.8)	46 (86.8)
Median phase I IgG titre at 1 year of therapy (IQR)[b]	4096 (1024–8192)	4096 (1024–8192)	1024 (512–4096)
Fourfold decrease in phase I IgG titre at 1 year of therapy (%)[b]	65 (24.6)	59 (27.1)	6 (13.0)
Phase I IgG titre ≤1:1024 within 1 year of therapy (%)[b]	45 (17.0)	32 (14.7)	13 (28.3)
Both fourfold decrease in phase I IgG titre at 1 year of therapy and phase I IgG titre ≤1:1024 within 1 year of therapy (%)[b]	34 (12.9)	23 (10.6)	11 (23.9)
Phase II IgM negative at 1 year of therapy (%)[c]	93 (35.2)	78 (35.8)	15 (32.6)
Follow-up details			
Years of serological follow-up, median (IQR)	3.1 (4.4)	3.1 (4.4)	3.2 (4.2)
Therapy			
Ongoing therapy (%)	75 (22.3)	71 (25.0)	4 (7.5)
Ongoing follow-up after end of therapy (%)	84 (24.9)	65 (22.9)	19 (35.8)
Reached 5 year follow-up after end of therapy (%)	50 (14.8)	37 (13.0)	13 (24.5)
Died during therapy (%)	79 (23.4)	74 (26.1)	5 (9.4)
chronic Q fever-related death (%)	58 (17.2)	57 (20.1)	1 (1.9)
Died during follow-up after end of therapy (%)	49 (14.5)	37 (13.0)	12 (22.6)
chronic Q fever-related death (%)	13 (3.9)	11 (3.9)	2 (3.8)

IQR, interquartile range.
[a] Fourteen patients (4.2%) had not yet reached 1 year of therapy at the time of analysis, 45 (13.4%) died before reaching 1 year of therapy, 14 patients (4.2%) were treated for less than 1 year, because of pregnancy as focus (n = 1), unknown (n = 1), non-adherence to national guidelines (n = 2), refusal by the patient (n = 3) or due to side effects (n = 7);
[b] Determined for patients that reached 1 year therapy;
[c] Phase II IgM determined in 138/264 (52.3%) patients at 1 year of therapy.

disease-related events. As PCR serum positivity was included as a binary covariate in the model while in reality patients are not continuously PCR positive, it would be interesting to investigate whether this effect remains in a time-varying analysis.

To date, this is the largest cohort of chronic Q fever patients in which the prognostic value of serological titres has been evaluated in a multivariable time-varying model. A limitation of this study is due to the retrospective nature, missing values were introduced, mostly occurring after the end of therapy. We have dealt with this consequence with the best method possible and evaluated plausibility of imputed titres by comparing its results to a last observation carried forward analysis, but it remains a limitation. Also, defining complications and mortality as chronic Q fever-related was based on data collected from routine clinical care. We dealt with this by

Table 3
Hazard ratios from time-varying Cox regression analyses for primary and secondary outcomes

Variable	Number of events	HR	95% CI	p value
First disease-related event	152			
Phase I IgG titres, time varying[a]		1.00	0.86–1.15	0.96
Age at diagnosis		1.03	1.02–1.05	<0.001
PCR serum ever positive		1.57	1.10–2.25	0.01
Serum doxycycline concentration measured		0.64	0.43–0.95	0.03
Ratio titre measurements per follow-up year		1.03	1.01–1.04	<0.001
Therapy				
Ongoing		1.14	0.64–2.02	0.67
Finished		1.25	0.58–2.71	0.57
Surgery				
Vascular		0.89	0.55–1.43	0.63
Valvular		0.52	0.15–1.78	0.30
Other		1.12	0.57–2.19	0.74
Vascular And Valvular		0.96	0.13–7.89	0.99
Female sex		1.28	0.84–1.97	0.25
Immunocompromised		1.02	0.62–1.68	0.93
Presence of prosthetic material		0.92	0.63–1.33	0.64
Phase I IgG titre at start of therapy		1.03	0.95–1.12	0.49
Vascular focus of infection		1.23	0.51–2.99	0.65
Endocarditis		0.84	0.34–2.08	0.70
Both vascular focus and endocarditis		1.57	0.62–3.96	0.34
Therapy failure	142			
Phase I IgG titres, time-varying[a]		1.02	0.91–1.15	0.74
Age at diagnosis		1.03	1.00–1.03	0.04
Phase I IgG titre at start of therapy		1.11	1.03–1.21	0.01
Ratio titre measurements per follow-up year		1.03	1.00–1.06	0.02
Therapy				
Ongoing		2.58	0.78–8.58	0.12
Finished		2.53	0.69–9.35	0.16
Surgery				
Vascular		0.79	0.48–1.30	0.35
Valvular		0.43	0.15–1.26	0.12
Other		1.08	0.56–2.06	0.83
Vascular And Valvular		0.54	0.07–4.18	0.55
Female sex		1.16	0.74–1.80	0.52
Immunocompromised state		1.36	0.83–2.23	0.22
Presence of prosthetic material		0.85	0.58–1.25	0.42
Serum doxycycline concentration measured		0.93	0.60–1.45	0.76
Vascular focus of infection		1.67	0.61–4.53	0.32
Endocarditis		1.83	0.67–4.98	0.24
Both vascular focus and endocarditis		2.31	0.82–6.51	0.11

Abbreviations: HR, hazard ratio; CI, confidence interval; PCR, polymerase chain reaction;
[a] The difference between subsequent phase I IgG titre measurements at every 3-month interval.

using predefined and previously reported criteria [7,15]. By using complications and mortality as the primary outcome, we did not evaluate clinical improvement in patients.

Although serology has shown to be a sensitive method for diagnosing *C. burnetii* infection, the same cannot be said for its role in monitoring the disease during therapy and follow-up [16]. This phenomenon is also seen in Lyme disease, where high levels of antibodies can be observed after recovery and treatment success should be assessed based on clinical signs and symptoms [19]. On the other hand, serology is used to monitor treatment response in syphilis [20]. For now, we recommend basing the decision to discontinue antibiotic therapy on other factors, such as improvement of signs and symptoms, PCR serum negativity, and complete recovery of the focus of infection confirmed with radiologic

Table 4
Hazard ratios from the second analyses for primary and secondary outcomes with serological variables at 1 year of therapy

Variable		Number of events	HR	95% CI	p value
First disease-related event					
1.	Fourfold decrease phase I IgG titre at 1 year of therapy[a]	105	0.97	0.62–1.51	0.88
2.	Phase I IgG titre ≤1:1024 within 1 year of therapy[a]	105	0.99	0.57–1.69	0.96
3.	Phase II IgM present at 1 year of therapy[a]	105	1.12	0.66–1.90	0.67
Therapy failure					
4.	Fourfold decrease phase I IgG titre at 1 year of therapy[a]	116	0.86	0.57–1.29	0.46
5.	Phase I IgG titre ≤1:1024 within 1 year of therapy[a]	116	0.80	0.48–1.34	0.40
6.	Phase II IgM present at 1 year of therapy[a]	116	1.37	0.86–2.18	0.18

HR, hazard ratio; CI, confidence interval; PCR, polymerase chain reaction;
[a] All other covariates entered in the analyses and their respective hazard ratios with 95% confidence intervals can be found in Table S3.

techniques [5]. Future research should focus on the prognostic value of these factors or identify other markers. As *C. burnetii* is an intracellular bacterium, the immune response is predominantly an interferon-γ-mediated T-helper 1 response. Searching for a marker of disease activity in this pathway instead of the B-cell-derived humoral immune response might yield a better prognostic factor for disease activity [21]. Host-derived biomarkers and transcriptomic profiling, such as nowadays investigated for monitoring response in *Mycobacterium tuberculosis* treatment, may be needed to improve chronic Q fever management [22]. Continued follow-up of our cohort, with an increasing amount of patients finishing therapy, is being performed [8].

Conclusions

We showed that *C. burnetii* serology has no prognostic value for first disease-related complications or mortality, or therapy failure during and after treatment for chronic Q fever. We recommend searching for alternative markers to monitor treatment efficacy and basing the decision of discontinuation of antibiotic therapy on clinical factors, PCR, and radiologic results for now.

Transparency declaration

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Author contributions

S.B.B. and S.E.v.R. extracted the data. S.E.v.R. devised the methodology. S.B.B. and C.H.v.W. did the formal analysis. S.B.B., S.E.v.R. and J.J.O. acquired funding. J.J.O., C.P.B.-R. and P.C.W. conceived the study. J.J.O., C.P.B.-R., P.C.W. and A.I.M.H. supervised the study. S.B.B. prepared the figures. S.B.B. wrote the original draft of the manuscript. J.J.O., C.P.B.-R., P.C.W., C.H.v.W., S.E.v.R. and A.I.M.H. reviewed and edited the manuscript. All authors contributed to the final version of the manuscript and approved it for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.03.016.

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