

Cost-effectiveness of Screening Program for Chronic Q Fever, the Netherlands

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In the aftermath of a large Q fever (QF) epidemic in the Netherlands during 2007–2010, new chronic QF (CQF) patients continue to be detected. We developed a health-economic decision model to evaluate the cost-effectiveness of a 1-time screening program for CQF 7 years after the epidemic. The model was parameterized with spatial data on QF notifications for the Netherlands, prevalence data from targeted screening studies, and clinical data from the national QF database. The cost-effectiveness of screening varied substantially among subpopulations and geographic areas. Screening that focused on cardiovascular risk patients in areas with high QF incidence during the epidemic ranged from cost-saving to €31,373 per quality-adjusted life year gained, depending on the method to estimate the prevalence of CQF. The cost per quality-adjusted life year of mass screening of all older adults was €70,000 in the most optimistic scenario.

Chronic Q fever (CQF) is a potentially lethal condition that develops in 2% of Q fever (QF) patients (1). QF is caused by infection with *Coxiella burnetii*, a gram-negative bacterium that has its main reservoir in livestock and can infect humans by airborne transmission. CQF can become apparent months to years after infection and usually manifests as endocarditis or vascular infection (2). Risk factors for CQF include heart valve disorders, aortic aneurysms, vascular prostheses, older age, and a compromised immune system (3–5). Prognosis is poor despite long-term antimicrobial drug

treatment; 28% of patients need surgery, and 15% die from CQF-related complications (6).

During 2007–2010, the Netherlands faced the world's largest QF epidemic ever documented. More than 4,000 patients with acute QF were notified. However, QF often occurs asymptotically (1), and the total number of infections has been estimated at 50,000 (7). Through May 2016, a substantial number of CQF infections occurred, and at least 74 patients died (8). Because early detection of CQF might result in a better prognosis, local hospitals initiated multiple targeted screening studies for clinical risk groups living in areas affected by the epidemic. These studies revealed that 7%–20% of screened patients had serologic evidence of *C. burnetii* infection, of whom 5%–31% had CQF (9–11).

In 2017, new diagnoses of CQF continued to appear in the Netherlands, often with severe complications, and led to a call from multiple concerned parties, including politicians, the QF patient association, and medical doctors for a national CQF screening program. One aspect considered for such a screening program is whether its costs are economically balanced with the expenditure (12,13). To answer this question, we assessed the cost-effectiveness of a screening program for CQF in the Netherlands.

Methods

Overview

We developed a health-economic decision model to compare estimated costs and effects of a 1-time screening program for CQF with no such screening program (Figure 1). The screening was assumed to occur in 2017, seven years after the epidemic. We estimated comparative outcomes of the model in terms of clinical events, quality-adjusted life years (QALYs), and costs from a societal perspective. We used a lifetime time horizon. Costs were annually discounted at 4% and QALYs at 1.5% (14).

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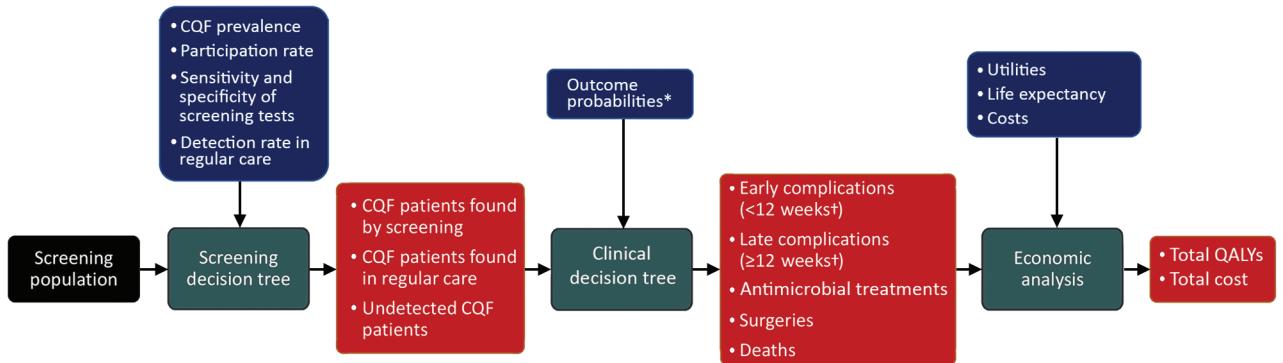


Figure 1. Schematic overview of the health-economic model in a study of the cost-effectiveness of screening for CQF, the Netherlands, 2017. Black square represents model input; green squares are model processes; blue squares are model parameters; and red squares are model outputs. Individual decision trees for screening and clinical outcomes are shown in Appendix Figure 1 (<https://wwwnc.cdc.gov/EID/article/26/2/18-1772-App1.pdf>). *Outcome probabilities differed among patients found by screening, patients found in regular care, and patients who remained undetected. †Weeks after diagnoses. CQF, chronic Q fever; QALY, quality-adjusted life year.

Screening Population

The analysis focused on adults ≥ 18 years of age. Because the prevalence of CQF is not uniformly distributed in the population (most QF patients resided in the south of the Netherlands; patients can have risk factors for CQF), we considered different subgroups for screening. We used the Netherlands population data from 2017 (15). First, we stratified the population on the basis of residence area between high, middle, and low QF incidence areas. For this stratification, we used spatial data on QF notifications and farms with QF outbreaks during the epidemic period (2007–2010). Next, we further divided these subgroups on the basis of a risk factor for CQF between persons with a cardiovascular risk factor, an immunocompromised status, or an unknown risk

status. The last group was labeled as unknown because the prevalences of heart valve disorders and aortic aneurysms are underreported. Because these cardiovascular prevalences increase with age, the unknown subgroup was split between persons < 60 years and ≥ 60 years of age. Thus, we considered 12 (3×4) subgroups (Table 1). We obtained prevalences of diagnosed and undiagnosed risk factors from the literature (16–21) (Appendix Table 1, <https://wwwnc.cdc.gov/EID/article/26/2/18-1772-App1.pdf>).

Model

We used a decision-tree model that consisted of 2 parts: a screening part and a clinical part (Appendix Figure 1). CQF is usually characterized by persistent high IgG against *C. burnetii* phase I, often in the

Table 1. Subgroup criteria in a study of the cost-effectiveness of screening for CQF, the Netherlands, 2017*

Category	Condition
Area of residence	
High incidence	≥ 50 acute QF notifications/100,000 inhabitants <i>and</i> > 2 acute QF notifications OR presence of a farm with QF abortion waves† within a 5-km range during the epidemic period.
Middle incidence	10–49 acute QF notifications/100,000 inhabitants <i>and</i> > 2 acute QF notifications OR presence of a farm that tested positive in the mandatory bulk tank milk monitoring initiated during the QF epidemic.
Low incidence	< 10 acute QF notifications/100,000 inhabitants OR < 2 notifications during the epidemic period.
Preexisting risk factor	
Diagnosed cardiovascular risk factor	Heart valve disorder (all types of defects), heart valve prosthesis, aortic aneurysm, prosthesis/stent, history of endocarditis and congenital heart anomalies.
Immunocompromised patients	HIV infection, asplenia, spleen disorder, malignancy or bone marrow transplantations and patients using immunosuppressant drugs. As proxy for patients using immunosuppressant drugs, prevalence data were used of rheumatoid arthritis patients and patients with inflammatory bowel disease, assuming these patients frequently use immunosuppressant medication.
Unknown, ≥ 60 y	Age ≥ 60 y AND no or undiagnosed cardiovascular risk factor, e.g., heart valve disorder, aortic aneurysm.
Unknown 18–59 y	Age 18–59 y AND no or undiagnosed cardiovascular risk factor, e.g., heart valve disorder, aortic aneurysm.

*The epidemic period was 2007–2010. QF, Q fever.

†Abortion of $> 5\%$ of pregnant goats in a farm over a 4-week period.

presence of high IgG against phase II (2,3). In the current clinical setting in the Netherlands, patients suspected of having CQF are tested with immunofluorescence assay (IFA) for IgG against phase I. However, IFA is a nonautomated and subjective test, and its use might not be feasible for a large-scale screening program (22). Therefore, we proposed an initial screening round with the ELISA for IgG against phase II, and positive samples were tested with IFA for IgG against phase I. In the sensitivity analysis, we explored a scenario with direct testing with IFA for IgG against phase I.

In the clinical part, patients were first classified among proven, probable, or possible CQF, according to the guideline of the Dutch Q Fever Consensus Group (23). This classification ranks the probability of having CQF based on PCR, serology, clinical parameters, imaging techniques, and pathologic findings (Appendix Table 2). Next, patients were divided by focus of infection and whether CQF led to an early complication (before diagnosis or within 12 weeks after diagnosis). Complications considered were heart failure, symptomatic aneurysm, arterial embolic complication, and other complications. After diagnosis, antimicrobial treatment can be initiated, possibly combined with a surgical procedure. Then, patients may have a late complication (≥ 12 weeks after diagnosis) and can die of CQF.

CQF Prevalence

The prevalence of CQF 7 years after the QF epidemic is uncertain because the average duration between infection and development of CQF is unknown. Therefore, we considered 2 scenarios, a low CQF prevalence scenario and a high CQF prevalence scenario. For both scenarios, we estimated the prevalence of CQF in 3 consecutive steps: 1) define the risk for *C. burnetii* infection per QF incidence area, 2) multiply by the risk for CQF given infection per risk group,

and 3) adjust the CQF prevalence from directly after the epidemic to the year of screening 7 years later. This final step accounts for a decrease of CQF prevalence over time, for instance, because of death or earlier diagnosis.

We selected parameter values for the low and high CQF prevalence scenarios (Table 2). In the low CQF prevalence scenario, we assumed that only patients with a *C. burnetii* infection during the epidemic period were at risk for CQF. We divided them among high, middle, and low QF incidence areas using small geographic areas (4-digit postal code) and used incidence rates of QF notifications during the epidemic period for each incidence area. To adjust for underreporting, we multiplied the incidence rates by 12.6 (7). In the high CQF prevalence scenario, we assumed that all patients who seroconverted after the epidemic can develop CQF. For this scenario, we used larger geographic areas (3-digit postal code areas) and *C. burnetii* seroprevalences for each incidence area from the literature (24,25). In the second step, we estimated the risk for CQF using targeted screening studies for CQF conducted during or immediately after the epidemic (Appendix Table 4) (9–11,26,27). In the third step, we based the adjustment of the CQF prevalence from directly after the epidemic to the year of screening for the low CQF prevalence scenario on the reduction of CQF patients in the national CQF database over time (28). For the high prevalence scenario, we estimated this adjustment factor on the risk for CQF among patients with a heart valve disorder in studies conducted immediately after the outbreak (9,10) and a study conducted in 2016–2017 (29) (Appendix).

Detection Rate of Screening and Regular Care

We assumed a participation rate in the screening program of 50%, which is the lower bound of previous targeted screening programs for CQF in the Netherlands (10,27,30). The prevalence of CQF was assumed

Table 2. Prevalence scenarios explored in a study of the cost-effectiveness of screening for CQF, the Netherlands, 2017*

Parameter	Low CQF prevalence scenario	High CQF prevalence scenario
Risk for <i>Coxiella burnetii</i> infection	Based on incidence rates of new infections during the epidemic period, adjusted for underreporting	Based on overall seroprevalences from the literature (24,25)
High incidence area, %	2.15	10.7
Middle incidence area, %	0.15	2.30
Low incidence area, %	0.027	1.00
Risk for CQF after <i>C. burnetii</i> infection	Equal for low and high CQF prevalence scenarios. Risk for CQF after infection is 7% for patients with heart valve disorders/prostheses, 29.3% for patients with vascular disorders/prostheses, and 6.9% for immunocompromised patients (probable or proven CQF). Risk for possible CQF in patients without risk factor is 0.2%.	
Adjustment factor to account for reduction of CQF prevalence from directly after epidemic (2010–2012) to year of screening (2017)	0.25	0.52

*The epidemic period was 2007–2010. CQF, chronic Q fever.

to be equal between participating and nonparticipating persons; hence, the participation rate affects only the number of CQF patients detected but not the cost-effectiveness of screening. We obtained sensitivity and specificity of ELISA from the literature; these values accounted for decreasing sensitivity over time after infection (31) (Appendix Table 5). CQF patients with high IgG against phase I were assumed to also have high IgG against phase II (C.C.H. Wielders, unpub. data [32]), which implies that all CQF patients test positive with ELISA. In the second screening round using IFA, patients with an IgG $\geq 1:512$ against phase I were clinically evaluated. The detection rate of CQF in regular care is unknown; we used a detection rate of 80% for proven CQF, 50% for probable CQF, and 10% for possible CQF.

Outcome Probabilities

We estimated outcome probabilities using data from the national CQF database (Appendix Table 6). This database contains information about 439 CQF patients in the Netherlands, of whom 249 had proven, 74 had probable, and 116 had possible CQF (6). To estimate the effectiveness of screening, we stratified outcome data between CQF patients detected by regular healthcare (358 patients) and CQF patients detected by screening (78 patients). Proven CQF patients detected through screening had a 4.0 (95% CI 3.3–4.7) times lower risk for an early complication, 2.8 (95% CI 2.2–3.3) times lower risk for surgery, and 1.8 (95% CI 1.1–2.5) times lower risk for CQF-related death compared with proven CQF patients detected through regular care. The risk for a late complication did not differ significantly (risk ratio 0.7 [95% CI 0.1–1.4]) and was assumed to be equal between screening and regular care. For probable CQF patients, outcome probabilities were not significantly lower for screened patients than for patients identified through regular care. To avoid overestimation of the effect of screening, we conservatively assumed no effectiveness of screening for probable CQF patients and explored a scenario in which probable CQF patients benefit from screening in the sensitivity analysis. No clinical events were assumed in possible CQF patients (6). For undetected CQF patients, we used a higher risk for a late complication and death than for patients found through regular care.

QALYs and Costs

We estimated QALYs by multiplying the utility value associated with a certain health status by the years lived in that status. We obtained utility data for CQF-related complications from the literature (33–36) (Appendix

Table 7). We applied a disutility for antimicrobial treatment (37,38). Average life expectancies of patients with premature CQF-related death were obtained from the national CQF database (6) (Appendix Table 8). For patients without premature CQF-related death, we assumed life expectancy to be half the life expectancy of a person at that age from the general population (39). We also obtained utility values for the general population from the literature (40) (Appendix).

We calculated costs in 2016 Euros (Appendix Table 9). Direct healthcare costs include costs of screening, diagnostic procedures, surgical procedures, antimicrobial drugs, specialist consultations, and lifelong costs of chronic complications. According to the national cost-effectiveness guideline (41), indirect healthcare costs (healthcare costs unrelated to CQF in life-years gained) should be taken into account, which we estimated using a prespecified tool (42). Because guidelines from other countries do not consider indirect healthcare costs, we show results without including indirect healthcare costs in the sensitivity analysis. Direct nonhealthcare costs include travel costs, and indirect nonhealthcare costs include productivity losses resulting from work absence (Appendix).

Cost-effectiveness and Sensitivity Analysis

We calculated the incremental cost-effectiveness ratio (ICER) of screening versus no screening by dividing the difference in costs by the difference in QALYs. We conducted a multivariate probabilistic sensitivity analysis using 10,000 simulations in which we varied a set of parameters at the same time within their uncertainty distributions. We conducted univariate sensitivity analyses, in which we varied several parameters one by one.

Results

CQF Prevalence

Depending on the size of the areas, 12% of the population (3-digit postal codes) or 16% of the population (4-digit postal codes) live in high QF incidence areas (Figure 2; Appendix Table 10). For the low CQF prevalence scenario, we estimated the number of *C. burnetii* infections at 42,143, resulting in 414 CQF patients directly after the epidemic and 102 CQF patients in the year of screening. For the high CQF prevalence scenario, the number of *C. burnetii*-infected persons was estimated to be 391,188, resulting in 3,842 CQF patients directly after the epidemic and 1,844 CQF patients in 2017. We also stratified the population by risk factor (Appendix Table 11). The prevalence of CQF varied substantially among risk groups and by

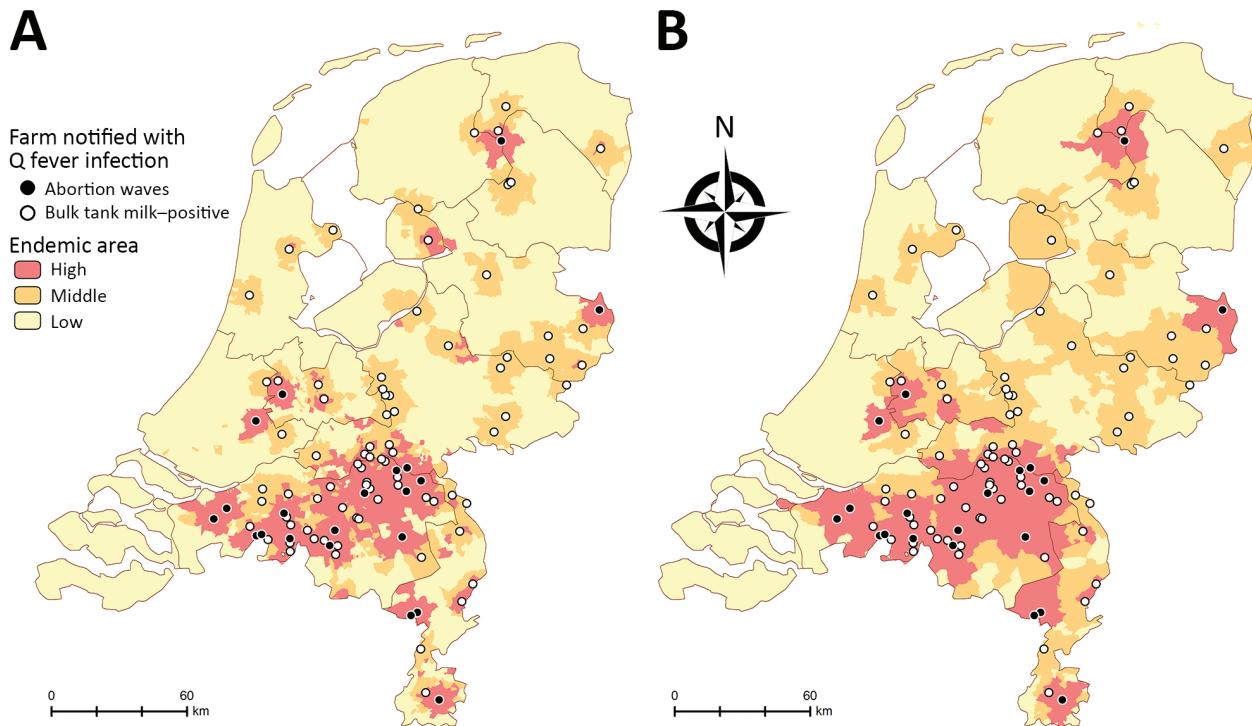


Figure 2. Geographic categorization of high, middle, and low Q fever incidence in the Netherlands using (A) 4-digit postal code areas and (B) 3-digit postal code areas. Incidence level was based on acute Q fever notifications and the proximity of farms with Q fever during the epidemic period (2007–2010).

residence area (Table 2); the highest prevalence occurred in cardiovascular risk patients living in high incidence areas (Appendix Table 12).

Clinical Impact

We determined the number of CQF patients and prevented clinical events for each subgroup (Table 3, <https://wwwnc.cdc.gov/EID/article/26/2/18-1772-T3.htm>; Appendix Tables 13, 14). Most CQF-related events are prevented by screening of cardiovascular risk groups living in high incidence areas. At an assumed participation rate of 50%, 8 complications, 4 surgeries, and 2 premature deaths are prevented for the low CQF prevalence scenario and 105 complications, 54 surgeries, and 26 premature deaths for the high CQF prevalence scenario. Screening of immunocompromised patients or all adults ≥ 60 years of age living in high-risk incidence areas, or screening of cardiovascular risk groups in middle-incidence areas, also could prevent a substantial number of clinical events.

Cost-effectiveness

We determined the incremental costs, incremental QALYs, and ICERs for each subgroup (Table 3; Appendix Tables 15–17). The ICER of screening of

cardiovascular risk groups living in high QF incidence areas was €31,737 per QALY for the low CQF prevalence scenario and cost-saving for the high CQF prevalence scenario. The next most cost-effective strategy would be screening of immunocompromised patients living in high incidence areas; ICERs were €66,145 per QALY for the low CQF prevalence scenario and €2,312 per QALY for the high CQF prevalence scenario. The ICER of screening for cardiovascular risk groups would increase substantially outside the high QF incidence area. For the high CQF prevalence scenario, the ICER increased from cost-saving to €12,929 per QALY in middle QF incidence areas and to €34,912 per QALY in low QF incidence areas. The ICER of screening for adults >60 years of age with an unknown risk factor living in high QF incidence areas was €679,136 per QALY in the low CQF prevalence scenario and €69,208 per QALY in the high CQF prevalence scenario. Screening of adults 18–59 years of age with an unknown risk factor was at least €8 million per QALY.

Sensitivity Analysis

We conducted a multivariate probabilistic sensitivity analysis (Figure 3; Appendix Figure 2). In the low

CQF prevalence scenario, screening of cardiovascular risk patients living in high incidence areas had a 3.1% chance of an ICER <€20,000 per QALY and 92.5% chance of an ICER <€50,000 per QALY (Figure 3, panel A). In the high CQF prevalence scenario, screening had a 54.4% chance of being cost-saving and 100% chance of an ICER <€20,000 per QALY (Figure 3, panel B) for this subgroup.

The ICER was most sensitive to the lifetime costs of complications, the life expectancy of CQF patients, and the effectiveness of the screening program. For the low CQF prevalence scenario, the ICER varied from €17,561 to €63,449 per QALY (Figure 3, panel C). Adding the effectiveness of screening for probable CQF patients changed the ICER from €31,737 to €29,585 per QALY. Exclusion of indirect healthcare costs reduced the ICER to €25,681 per QALY (ICERs without the inclusion of indirect healthcare costs of other subgroups are shown in Appendix Table 18). Adding additional program costs of €11.36 per participant increased the ICER to €53,639 per QALY. For the high CQF prevalence scenario, the ICER remained cost-saving in most scenarios explored, and the highest ICER found was €1,903 per QALY (Figure 3, panel D).

Discussion

We assessed the cost-effectiveness of a 1-time screening program for CQF in the Netherlands 7 years after a large QF epidemic. Cost-effectiveness varied substantially among areas and risk groups, and the results are highly sensitive to the prevalence of CQF. In a high CQF prevalence scenario, screening of cardiovascular risk patients living in high QF incidence areas during the epidemic was estimated cost-saving, whereas in a low CQF prevalence scenario the ICER was €31,737 per QALY for this subgroup. We found substantially higher ICERs for screening in areas with lower QF incidence during the epidemic or for screening of adults with an unknown risk factor for CQF.

A limitation is that the true prevalence of CQF 7 years after the epidemic is unknown. This prevalence can be affected by many factors, such as death from CQF or other causes, earlier diagnosis in regular care, and the background QF incidence after the epidemic. To account for uncertainty in CQF prevalence, we conducted a low and high CQF prevalence analysis. The estimated 42,000 new *C. burnetii* infections and 411 CQF patients during or after the epidemic low

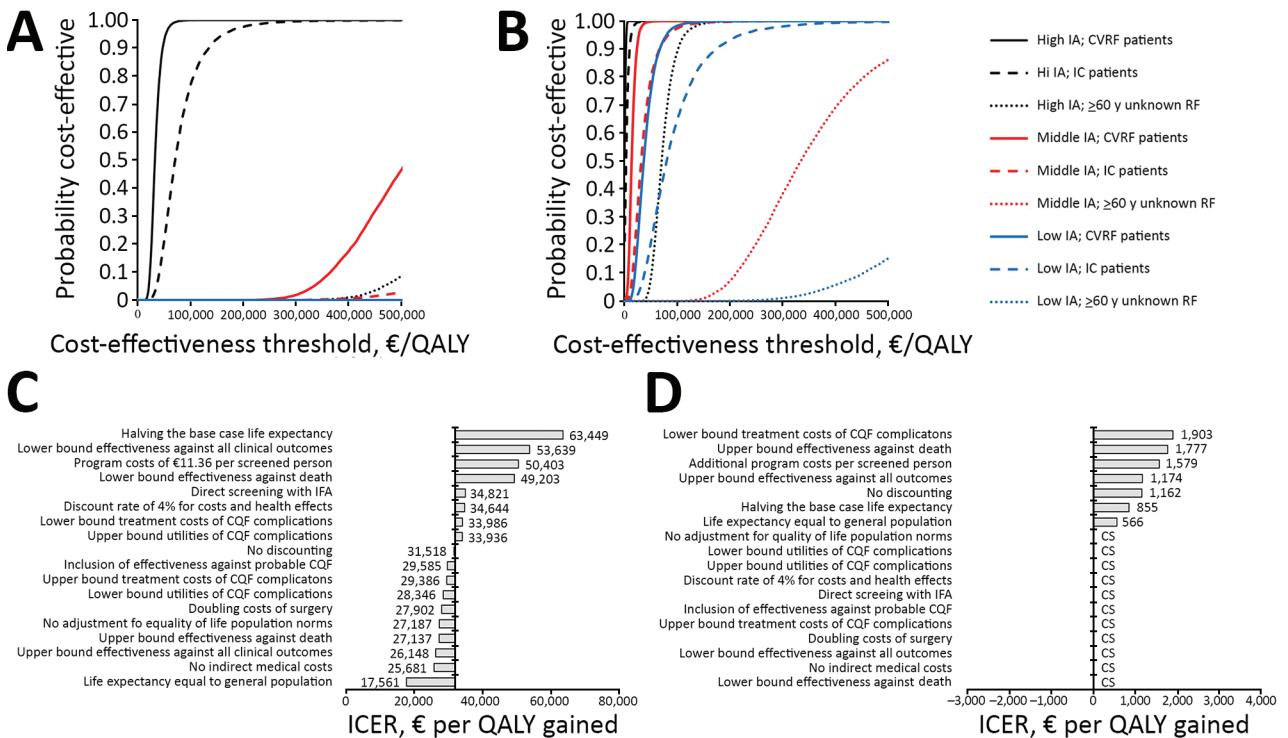


Figure 3. Sensitivity analysis of a screening program for CQF 7 years after the 2007–2010 epidemic, the Netherlands. A, B) Results of the multivariate probabilistic sensitivity analysis of screening in various target groups for a low CQF prevalence scenario (A) and a high CQF prevalence scenario (B). C, D) Results of a univariate sensitivity analysis of screening for chronic Q fever in patients with CVRFs living in high incidence areas for a low CQF prevalence scenario (C) and a high CQF prevalence scenario (D). CQF, chronic Q fever; CVRF, cardiovascular risk factor; IA, incidence area; IC, immunocompromised; ICER, incremental cost-effectiveness ratio; IFA, immunofluorescence assay; QALY, quality-adjusted life year; RF, risk factor.

CQF prevalence scenario estimated correspond with previous estimates from the literature (7) or CQF patients included in the national database until May 2016 (6). However, these numbers are thought to be the absolute minimum. Only 23% of the proven CQF patients had a diagnosed acute QF episode (6), and a postmortem study among patients with a history of heart valve surgery in the epidemic area indicates that CQF possibly contributed to the death in 15% of the patients (9). The high CQF prevalence scenario could be the upper range because it does not account for preexisting immunity from before the epidemic. It is therefore likely that the true prevalence falls within the reported ranges.

Recent seroprevalence studies performed outside high QF incidence areas are lacking. Underreporting of QF could be higher in these areas because medical doctors are less familiar with QF symptoms (7). Furthermore, the geographic division between high, middle, and low QF incidence areas is arbitrary. Persons could be infected while traveling, and the extent to which farms with positive bulk milk samples contribute to disease spread is uncertain because 1 infected goat could yield a positive result.

The effectiveness of screening on the prevention of CQF-related complications and premature death is not well documented. We estimated the effectiveness by comparing outcome data between patients detected by screening and by regular care. We did this comparison separately for different CQF categories (proven, probable, or possible), but the effectiveness of screening can still be biased by uncontrolled confounders, such as age and presence of underlying conditions. The effectiveness of antimicrobial treatment for CQF has never been assessed in a randomized clinical trial. Surgery is known to have a positive effect on survival of CQF patients with vascular infection (3).

Our cost-effectiveness analysis is based on data from several sources in the Netherlands, such as spatial data on notifications of acute QF, seroprevalence data of *C. burnetii* infections, risk factor-specific probabilities of CQF given infection, and clinical data from a large number of CQF patients. However, combining data from different sources could also introduce biases when study populations do not exactly overlap or screening studies are conducted at different time-points.

Results of our study could also be relevant for other countries, where CQF also might be underreported. For instance, the seroprevalence of *C. burnetii* infection in the United States was estimated

at 3.1% (43), representing millions of infections and potentially thousands of CQF cases, but no high numbers of CQF have been reported. An explanation may be that *C. burnetii* infections in the United States originate from cattle. The *C. burnetii* strains circulating in cattle differ from and are considered less pathogenic than the strains in small ruminants (3). In France, however, *C. burnetii* causes 5% of all endocarditis (44), and in Israel, *C. burnetii* infection was found in 9% of patients undergoing valve surgical procedure caused by endocarditis (45).

Cost-effectiveness is not the only criterion in deciding whether a screening program is justified (12). Screening for CQF is based on an antibody profile suggesting a chronic infection but cannot always be linked to a focus of infection (probable or possible CQF patients). Therefore, physicians must make difficult decisions about whether long-term antimicrobial treatment should be initiated when the outcome is uncertain and adverse events frequently occur. Raoult (46) has recently proposed alternative definition criteria for CQF from the consensus guideline in the Netherlands; these criteria could exclude most probable and possible CQF patients from follow-up but also may be less sensitive in the diagnosis of proven CQF (47).

When screening for CQF would be limited to subgroups for which screening is most cost-effective, a substantial proportion of CQF patients will remain undetected. Serologic follow-up for patients with acute QF is therefore recommended, even in absence of a risk factor for CQF (32). However, compliance with this recommendation was suboptimal during the epidemic (48), and many patients experience an acute infection asymptotically or do not have the infection diagnosed. Alongside a standalone screening program, case finding could be implemented in regular care, in which the physician decides whether a patient should be screened according to a risk profile. Also, a combination of case-finding and screening programs among high-risk groups could be initiated; this approach has also been suggested for hepatitis B and hepatitis C (49).

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Cost-Effectiveness of Screening Program for Chronic Q Fever, the Netherlands

Appendix

Supplemental Methods

Prevalence of Risk Factors for Chronic Q Fever

Prevalence rates of risk factors are shown in Appendix Table 1. Prevalence rates of cardiovascular risk factors by age group were based on data from a general practice research database in the Netherlands (1). We used prevalence data of patients with heart valve defect, aortic aneurysm/prosthesis, congenital heart anomaly, and endocarditis. As patients can have >1 risk factor, we used prevalence rates of any of these diagnosed cardiovascular risk factors and assigned these patients to the individual cardiovascular risk factors in proportion with the prevalence rates of the risk factor–specific prevalence rates. As the prevalence of aortic aneurysms and heart valve disorders are underreported, we also considered people with undiagnosed cardiovascular risk factors to be at increased risk of chronic Q fever (CQF). Prevalence rates of these undiagnosed cardiovascular risk factors were based on screening studies in the general population, and prevalence rates of diagnosed risk factors were then subtracted from these. For heart valve disorders, we used prevalence rates of clinically relevant heart valve disorders in ≥ 65 -year-olds from the UK (2), and for aortic aneurysms, we used prevalence rates of abdominal aortic aneurysms in ≥ 55 -year-olds from the Netherlands (3).

The prevalence of patients being immunocompromised due to an underlying disease by age was obtained from a study in the UK and includes patients with HIV infection, asplenia, spleen dysfunction, malignancy (e.g., leukemia), or bone marrow transplant (4). As proxy for the prevalence of immunosuppressive drug users, we used prevalence rates by age of rheumatoid arthritis and inflammatory bowel disease (5,6). These are the largest patient groups that use immunosuppressive drugs, and we assumed that all these patients use these drugs continuously or have used these drugs at least temporarily. To avoid counting patients twice, we adjusted the

prevalence rates of immunocompromised patients for the probability of having a cardiovascular risk factor. As the risk of developing CQF in patients with cardiovascular risk factors is thought to be higher than in immunocompromised patients (7), we considered patient with both a cardiovascular risk factor and an immunocompromised status in our model as a patient with cardiovascular risk factor.

Appendix Table 1. Prevalence of risk factors for chronic Q fever (per 10,000 persons)

Population	Age group, y								
	18–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	≥90
Diagnosed cardiovascular risk factor	74	66	60	132	171	476	948	1,666	1,845
Heart valve disorders or =prosthesis	14	19	28	87	122	373	793	1,375	1,760
Aortic aneurysm or -prosthesis	5	4	0	11	34	85	222	339	172
Congenital heart anomaly	70	51	34	39	25	31	7	35	0
Endocarditis	0	2	6	6	13	27	21	28	0
Undiagnosed cardiovascular risk factor									
Heart valve disorder*	0	0	0	0	0	57	251	941	1,220
Aortic aneurysm†	0	0	0	0	10	101	120	194	255
Immunocompromised									
Underlying disease‡	90	90	90	90	90	158	230	230	230
Medication use									
Rheumatoid arthritis	21	39	68	115	177	273	353	465	507
Inflammatory bowel disease	14	39	32	35	46	81	119	95	95

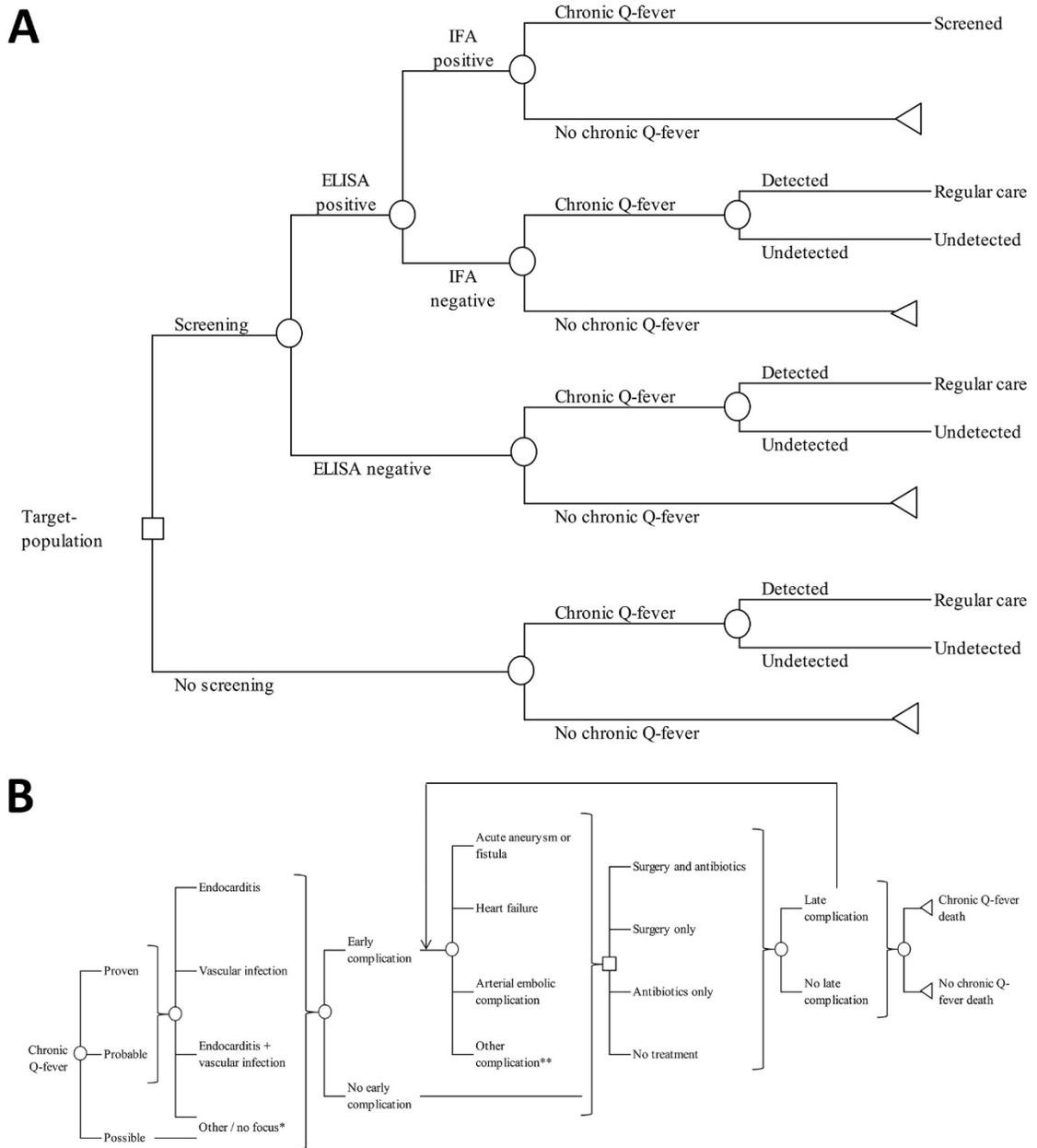
*Only clinically relevant heart valve disorder.

†Abdominal aortic aneurysms only.

‡Includes HIV infection, asplenia, spleen dysfunction, malignancy (e.g., leukemia), or bone marrow transplant.

Model Design

Appendix Figure 1 shows the decision tree of the screening part (panel A) and the clinical part (panel B).



Appendix Figure 1. Decision tree model. A) Decision tree for detection of chronic Q fever in presence or absence of a screening program. A square represents a decision node, a circle represents a chance node, and a triangle represents a terminal node. IFA, Immunofluorescence assay. B) Decision tree for the clinical outcomes of chronic Q fever after screening, regular care, or undetected (outcome of the decision tree of screening). * contains less prevalent presentations, i.e., osteomyelitis, pericarditis, and spondylodiscitis. ** includes non-cardiac abscess, spondylodiscitis and osteomyelitis.

Definition of Chronic Q Fever

Appendix Table 2 shows the definition of chronic Q fever according to the Dutch Q fever consensus group (8).

Appendix Table 2. Diagnostic criteria for CQF as defined by the Dutch Q Fever Consensus Group*

Category	Criteria
Proven CQF	1) Positive <i>Coxiella burnetii</i> PCR in blood or tissue in absence of an acute Q fever infection OR 2) IFA $\geq 1:1,024$ for <i>C. burnetii</i> phase I IgG, AND ≥ 1 of the following criteria: - Definite endocarditis according to the modified Duke criteria (9) OR - Proven large vessel or prosthetic infection, confirmed by imaging studies (e.g., PET-CT).
Probable CQF	IFA $\geq 1:1,024$ for <i>C. burnetii</i> phase I IgG AND ≥ 1 of the following criteria: - Valvulopathy not meeting the major criteria of the modified Duke criteria (9). - Known aneurysm or vascular or cardiac valve prosthesis without signs of infection (by means of TEE/TTE, PET-CT, other imaging studies). - Suspected osteomyelitis, pericarditis or hepatitis as manifestation of CQF. - Pregnancy. - Symptoms and signs of chronic infection, such as fever, weight loss and night sweats, hepato-splenomegaly, persistent raised ESR and CRP. - Granulomatous tissue inflammation proven by histologic examination. - Immunocompromised state.
Possible CQF	IFA $\geq 1:1,024$ for <i>C. burnetii</i> phase I IgG without meeting the criteria for proven or probable CQF

*CQF, chronic Q fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFA, immunofluorescence assay; PET-CT, positron emission tomography-computed tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Prevalence of Chronic Q Fever

We estimated the prevalence of CQF in 3 steps:

1) Estimating the number of patients with a *Coxiella burnetii* infection. This was done separately for high, middle, and low QF incidence areas during the epidemic.

2) Estimating the number of patients that develop CQF after *C. burnetii* infection. This was separately done for risk groups (heart valve disorder, aortic aneurysm, compromised immune system, or none of the aforementioned risk factors).

3) Estimating the number of CQF patients that are still alive and undetected in the year screening 7 years after the epidemic.

Given the uncertainty around the prevalence of CQF 7 years after the epidemic, we analyzed 2 scenarios: 1) a low prevalence scenario and 2) a high prevalence scenario.

Estimating the Number of Patients with a *C. burnetii* Infection

The low prevalence scenario assumes that only patients infected with *C. burnetii* during the epidemic (period 2007–2010) are able to develop CQF; hence, individuals that were seroconverted before the epidemic only had an immune boost but no risk of developing CQF.

These boosted individuals are treated as seronegative in the model. The risk of a *C. burnetii* infection during the epidemic is based on Dutch incidence rates of QF notifications for areas that were qualified as high, middle, and low incidence area. The distribution of the population between high, middle, and low incidence areas was estimated using the incidence of QF notifications and the proximity of a farm with QF abortion waves or the proximity of a farm that tested positive in the mandatory bulk tank milk monitoring within a range of 5 km during the epidemic (Table 1 in the main article for more details). To account for underreporting because of asymptomatic infections or symptomatic infections that were not medically attended or diagnosed, we multiplied these notification rates by 12.6. This multiplication factor was based on a study from the Netherlands that compared QF notification rates with seroconversion rates in blood donors from whom serial samples were available (10). The adjusted risk of *C. burnetii* infection during the epidemic was then estimated at 2.15% in high incidence areas, 0.15% in middle incidence areas, and 0.027% in low incidence areas.

In the high prevalence scenario, the risk of *C. burnetii* infection was based on Dutch seroprevalence studies. This scenario assumes that all patients tested seropositive after the epidemic are able to develop CQF, independent whether they were already infected before the epidemic and immune during the epidemic or not. The seroprevalence in high incidence areas was estimated at 10.7%. This estimate was based on a large seroprevalence study in areas with high QF incidence during the epidemic in 2014–2015 finding a seroprevalence of 6.0%. However, the used ELISA test for IgG phase II is known to decrease over time and the seroprevalence study was conducted 5 years after the epidemic in 2007–2010. Follow-up data over 4 years showed a decreasing trend of ELISA sensitivity after *C. burnetii* infection over time (C.C.H. Wielders, unpub. data from [10]) and, after extrapolation of this decreasing to 5 years after *C. burnetii* infection using a lognormal curve, we found that 55.9% of the patients test would still test positive after 5 years. We adjusted the seroprevalence to 10.7% using longitudinal data on sensitivity of. In absence of serologic studies in middle and low incidence areas, we used data from a study that measured the seroprevalence of *C. burnetii* using IFA for IgG phase II in an area that covered high, middle, and low incidence areas in 2008 (before the epidemic in this part of the country) and in 2010 (the final year of the QF epidemic). The seroprevalence of 3.2% after the epidemic was used for middle incidence areas and the

seroprevalence of 1.0% before the epidemic was used for low incidence areas. More details of the studies are listed in Appendix Table 3.

Not relevant for the cost-effectiveness within a specific incidence area, but relevant for the absolute number of cases, is the size of the areas that are divided between high, middle, and low incidence areas. For the low prevalence scenario, we based this division based on 4-digit postal code areas and for the high prevalence scenario we used 3-digit postal codes (larger areas). Use of 4-digit postal code areas result in a lower number of infections, as the areas that are assigned to high or moderate incidence areas due to the proximity of an infected farm are smaller.

Estimating the Number of Patients that Develop CQF after *C. burnetii* Infection

The second step of estimating the risk of developing CQF after *C. burnetii* infection was assumed to be equal for the 2 prevalence scenarios. The risk of CQF given *C. burnetii* infection in risk groups was based on targeted screening studies for CQF from the Netherlands that were conducted during or directly after the epidemic (Appendix Table 4). Most of these studies defined CQF as an IgG titer of 1:512 or 1,024 against *C. burnetii* phase I or a positive PCR not related to acute QF. The risk of CQF differs by pre-existing risk factor, estimated at 8.7% for patients with heart valve disorders/prostheses (11,12), 29.3% for patients with vascular disorders/prostheses (11,13), and 6.9% for immunocompromised patients (14). In accordance with the Dutch consensus guideline, detected CQF patients in these studies are by definition proven or probable CQF patients because they have a risk factor (15). We applied the same risk of CQF for diagnosed and undiagnosed cardiovascular risk factors. For people without a risk factor, we estimated that 0.2% had possible CQF based on a Dutch screening study in the general population (16).

Appendix Table 3. Prevalence of *Coxiella burnetii* infection by CQF prevalence scenario and incidence area*

Area	Deterministic	SD†	Distribution†	Source
Low CQF prevalence scenario				
High incidence area	0.0215	95% CI 0.0208–0.0223	Lognormal	Based on the incidence of QF notifications in areas with low QF incidence (see main article Table 1 for criteria) during the period 2007–2010, adjusted for underreporting by multiplying with 12.6 (10).
Middle incidence area	0.00152	95% CI 0.00137–0.00168	Lognormal	Based on the incidence of QF notifications in areas with middle QF incidence (see main article Table 1 for criteria) during the period 2007–2010, adjusted for underreporting by multiplying with 12.6 (10).
Low incidence area	0.000275	95% CI 0.000243–0.000311	Lognormal	Based on the incidence of QF notifications in areas with low QF incidence (see main article Table 1 for criteria) during the period 2007–2010, adjusted for underreporting by multiplying with 12.6 (10).
High CQF prevalence scenario				
High incidence area	0.107	95% CI 0.088–0.131	Lognormal	Pijnacker, 2017 (17). The seroprevalence of QF was adjusted from 6.0% to 10.7% to account for a decreasing sensitivity of ELISA over time (unpub. data from [13]).
Middle incidence area	0.0230	95% CI 0.0140–0.0380	Lognormal	Brandwacht, 2010 (18). Based on seroprevalence data of 2010 in areas of the Netherlands that covered high, middle, and low incidence areas.
Low incidence area	0.0100	95% CI 0.0050–0.0190	Lognormal	Brandwacht, 2010 (18). Based on seroprevalence data of 2008 from before the area was affected during the epidemic.

CQF: Chronic Q fever; QF, Q fever.

†Used for the multivariate probabilistic sensitivity analysis.

Appendix Table 4. Dutch screening studies on the risk of chronic Q fever among individuals tested seropositive for *Coxiella burnetii**

Risk condition	Study	Population	Incidence area	Study period	Test and cutoff value	CQF given seropositive for <i>C. burnetii</i> infection	% CQF	SD†	Distribution†	Additional information
Screening studies conducted directly after the QF epidemic of 2007–2010										
Aortic aneurysm/prosthesis	Hagenaars, 2014 (13)	Patients with abdominal aortic- or ileac aortic aneurysm, or reconstruction of abdominal aortic aneurysm or vascular prosthesis	High	2009–2012	IFA IgG phase I \geq 1:512	40/130	30.8			
	Wegdam-Blans, 2013 (12)		High	2010–2011	IFA IgG phase I \geq 1:1.024 or positive PCR	7/30	23.1			
	Total					47/160	29.3	0.02	Beta	All proven or probable CQF ^a
Heart valve disorder/prosthesis	Wegdam-Blans, 2013 (12)	Patients with heart valve prosthesis	High	2010–2011	IFA IgG phase I \geq 1:1.024 or positive PCR	3/22	13.8			
	Kampschreur, 2012 (11)	Patients with history of heart valve surgery	High	2010–2011	IFA IgG phase I \geq 1:512	9/116	7.8			
	Total					12/138	8.7	0.04	Beta	All proven or probable CQF ^a
Immunocompromised patients	Schoffelen, 2014 (14)	Patients with rheumatoid arthritis	High	2011–2012	Not reported	7/102	6.9	0.03	Beta	All proven or probable CQF ^a
Non-risk patients	Morroy, 2015 (16)	All adults	High	2014	IFA IgG phase I \geq 1:512	1/491 ^b	0.2	0.001	Beta	All possible CQF
Screening studies conducted close to the year of the screening in 2017										
Heart valve disorder/prosthesis	De Lange, 2019 (19)	Patients with heart valve disorder	High	2016–2017	IFA IgG phase I \geq 1:512	6/133	4.5			All proven or probable CQF ^a

*IFA, Immunofluorescence assay; QF, Q fever.

†According to the Dutch consensus guideline patients with risk factors and titer IgG phase I \geq 1:512 automatically qualify for probable or proven CQF (8). ^b: Patients with a cardiovascular risk factor or immunocompromised status were excluded.

Estimating the Prevalence of CQF Patients in the Year of Screening

The targeted screening studies referred to in the second step were conducted during or directly after the epidemic (2010–2012), while the screening program was assumed to take place in 2017. As the prevalence of CQF is expected to decline over time due to CQF-related mortality or mortality from another cause and due to detection via regular care, we adjusted the prevalence downwards. This adjustment factor was different in the low and high CQF prevalence scenario. In the low prevalence scenario, we based this adjustment factor on the numbers of CQF patients in the Dutch national CQF database over time. This database includes all diagnosed CQF patients in the Netherlands and shows a high number of proven CQF patients reported in 2010–2011, which drops substantially in the year 2012 and remains relatively stable after 2012 (20). The adjustment factor was the division of the average annual number of proven CQF cases in the period 2012–2017 by the average annual number of CQF cases in the period 2010–2011, resulting in an adjustment factor of 0.25. For the high prevalence scenario, we compared the risk of proven or probable CQF given *C. burnetii* infection among people with heart valve disorders between screening studies conducted during or directly after the epidemic (17,18), and a recent screening study conducted in 2016–2017 (19). This resulted in an adjustment factor of 0.52 (4.5%/8.7%; see Appendix Table 4).

Sensitivity and Specificity of Testing

Sensitivity of ELISA for IgG phase II and IFA for IgG phase II and phase I are shown in Appendix Table 5. Sensitivity of ELISA 7 years after the epidemic was estimated by extrapolating longitudinal data on sensitivity of ELISA over the first 4 years after infection (C.C.H. Wielders, unpub. data from [21]). The specificity was based on a study from Germany (22). Cutoff for ELISA positivity was according to the manufacturer's instruction, considering borderline samples as positive. We assumed that all CQF patients had high IgG phase II titers (C.C.H. Wielders, unpub. data from [21]), hence testing positive for ELISA. In the second screening round using IFA, patients were tested for having an IgG titer of $\geq 1:512$ against phase I and clinical examined. As patients with an IgG titer of $\geq 1:512$ against phase I do not necessarily have CQF according to the Dutch consensus guideline (the guideline uses an IgG titer threshold of $\geq 1:1,024$ against phase I). Targeted screening studies in patients with heart valve disorder showed that 8 of 234 patients had an IgG titer of 512 but no CQF (19,23), resulting in a

specificity of IFA of 0.966. Similarly, in individuals with no risk factor 2/512 patients had an IgG titer of 512, resulting in a specificity of 0.996 (16).

Appendix Table 5. Sensitivity and specificity of ELISA IgG phase II and IFA IgG phase I*

Diagnostic test	Deterministic	SD†	Distribution†	Source
ELISA IgG phase II				
Historic QF only				
Sensitivity	0.50	95% range: 0.39–0.63	Lognormal	Extrapolation of sensitivity data of first 4 y after infection to 7 y after infection (C.C.H. Wielders, unpub. data from [10]) Frosinski, 2016 (18)
Specificity	0.980	0.014	Beta	
CQF				
Sensitivity	1			
IFA IgG phase I titer 1:512				
Proven / probable CQF				
Sensitivity	1			Estimated from Kampschreur 2013 and De Lange 2019 (19, 23)
Specificity	0.966	0.012	Beta	
Possible CQF				
Sensitivity	1			Estimated from Morroy, 2016 (16)
Specificity	0.996	0.003	Beta	

*CQF, chronic Q fever; QF, Q fever.

†Used for the multivariate probabilistic sensitivity analysis.

Outcome Probabilities of CQF

The outcome probabilities of CQF are listed in Appendix Table 6. The outcome probabilities are stratified by CQF category (proven and probable) and by outcome of the screening decision tree (detected by screening, detected in regular care, not detected at all). Clinical outcome probabilities are obtained from the Dutch national CQF database. Proven and probable patients were stratified between patients detected via screening and patients detected in regular care. We found that proven CQF patients detected by screening had a significantly reduced risk of an early complication, surgery, and CQF-related mortality as compared to patients detected in regular care, but not a significantly reduced risk of a late complication. For probable CQF patients, we found no significant reduction in any clinical outcome. Therefore, we conservatively assumed that screening had no effectiveness against probable CQF. In the sensitivity analysis, we included a scenario in which screening had effectiveness against an early complication. No complications, surgeries, or mortality was reported for possible CQF patients in the national CQF database.

Appendix Table 6. Outcome probabilities of proven or probable CQF*

Parameter	Deterministic	SD†	Distribution‡	Scenario	Reference and comments
Classification of proven/probable CQF					
Proven CQF	0.689	0.054	Beta		CQF database (20), distribution based on 74 proven and probable CQF patients found via screening. Calculated as 1-proven CQF
Probable CQF	0.311				
Type of infection					
Proven CQF					
Endocarditis	0.273	0.028	Dirichlet		CQF database (20), distribution based on 249 proven CQF patients.
Vascular infection	0.502	0.032	Dirichlet		
Endocarditis & vascular infection	0.161	0.023	Dirichlet		
Other /no infection focus	0.064	0.016	Dirichlet		
Probable CQF					
Endocarditis	0.216	0.048	Dirichlet		CQF database (20), distribution based on 74 probable CQF patients.
Vascular infection	0.378	0.056	Dirichlet		
Endocarditis & vascular infection	0.041	0.023	Dirichlet		
Other /no infection focus	0.365	0.056	Dirichlet		
Early complication					
Proven CQF					
Late detected by regular care or not detected	0.548	0.04	Beta		CQF database (20). Early complication detected in 108/197 patients detected via regular care. Not detected was assumed equal to late detected, as late detected will usually be diagnosed after a complication occurred.
RR due to early detection by screening	3.99	95% CI 3.30–4.69	Lognormal	Lower and upper bound of 95% CI	CQF database (20). Early complication in 7/51 patients detected via screening (RR 4.0 [95% CI 3.3–4.7] as compared to detected via regular care)
Early detected by screening	0.137				Probability late detected divided by RR
Probable CQF					
Late detected by regular care or not detected	0.095	0.034	Beta	0.118	CQF database (20). Early complication detected in 8/73 patients. Not detected was assumed equal to late detected, as late detected will usually be diagnosed after a complication occurred.
RR due to early detection by screening	1			2.7	No significant difference between patients detected via screening or regular care. (RR 2.7 [95% CI 0.6–4.8])
Early detected by screening	0.095			0.043	Probability late detected divided by RR
Type of complication					
Proven CQF					
Acute aneurysm / fistula	0.542	0.04	Beta		CQF database (20). On the basis of 153 complications. Other complications include spondylodiscitis/osteomyelitis and non-cardiac abscess.
Heart failure	0.327	0.04	Beta		
Arterial embolic complication	0.124	0.03	Beta		
Other complication	0.248	0.04	Beta		
Probable CQF					
Acute aneurysm / fistula	0.364	0.15	Beta		CQF database (20). On the basis of 11 complications. Other complications include spondylodiscitis/osteomyelitis and non-cardiac abscess.
Heart failure	0.455	0.15	Beta		
Arterial embolic complication	0.091	0.09	Beta		
Other complication	0.091	0.09	Beta		
Surgery					
Proven CQF					CQF database (20). Surgery at 107/197 patients detected via regular care and at 10 of 51 detected via screening (RR 2.8 [95% CI 2.2–3.3]).
Late detected by regular care or not detected	0.543				

Parameter	Deterministic	SD†	Distribution†	Scenario	Reference and comments
RR due to early detection by screening	2.77	95% CI 2.20–3.34	Lognormal	Lower and upper bound of 95% CI	
Early detected by screening Probable CQF	0.196				Probability late detected divided by RR
Late detected by regular care or not detected RR due to early detection by screening	0.081 1				CQF database (20). Surgery at 6/74 patients No significant difference between patients detected via screening or regular care (RR 0.5 [95% CI 0–2.0]) Probability late detected divided by RR
Early detected by screening Antibiotic treatment initiated	0.081				
Proven CQF	0.912	0.02	Beta		CQF database (20), 227/249 patients.
Probable CQF	0.662	0.05	Beta		CQF database (20), 49/74 patients.
Possible CQF	0				Assumption based on current standard work-up of possible CQF patients (C.P. Bleeker-Rovers, pers. comm.)
Late complication Proven CQF					
Not detected	0.452				Assuming that all undetected patients will have a CQF complication; calculated as (1 – probability of early complication)
Late detected by regular care RR due to early detection by screening	0.153 1	0.02	Beta		CQF database (20). Late complication in 38/249 patients CQF database (20). No significant difference between patients detected via screening or regular care (RR 0.7 [95% CI 0.1–1.4]). Probability late detected divided by RR
Early detected by screening Probable CQF	0.153				
Not detected	0.095				Assumed equal to early complication.
Late detected by regular care	0.054	0.03	Beta		CQF database (20). Late complication in 38/249 probable CQF patients
RR due to early detection by screening	1				CQF database (20). No significant difference between patients detected via screening or regular care (RR 1.4 [95% CI 0–3.6]). Probability late detected divided by RR
Early detected by screening CQF-related mortality Proven CQF	0.054				
Not detected	0.497				CQF database (20). CQF-related mortality at 55/197 proven CQF patients detected via regular care. Assumed that the RR between non-detected and regular care was equal to between regular care and non-detected. This approximates a 60% death rate among CQF patients in the 1970s, when effective antibiotic treatment was not available and there was a large diagnostic delay (24).
Late detected by regular care	0.279	0.032	Beta		CQF database (20). CQF-related mortality at 55/197 proven CQF patients detected via regular care.
RR due to early detection by screening	1.78	95% range 1.11–2.45	Lognormal	Lower and upper bound of 95% CI	CQF database (20). CQF-related mortality in 8/51 patients detected via screening (RR 1.78 [95% CI 1.11–2.45] as compared to late detected).
Early detected by screening Probable CQF	0.157				Probability late detected divided by RR
Late detected by regular care or not detected	0.041	0.023	Beta		CQF database (20). CQF-related mortality in 3/74 probable CQF patients
RR due to early detection by screening	1				No significant difference between patients detected via screening or regular care (RR not given due to small numbers)
Early detected by screening	0.041				Probability late detected divided by RR

*CQF, chronic Q-fever; RR, risk ratio.

†Used for the multivariate probabilistic sensitivity analysis.

Quality-Adjusted Life Years

The number of quality-adjusted life years (QALYs) for CQF patients was calculated by multiplying the utilities (preference based measure of health-related quality of life) for each health state with the time spent in that health state.

Utilities

Utilities of the different health states used in this model are shown in Appendix Table 7. As the average age of CQF patient in the national CQF database is 65 years (25), we used population norms of ≥ 50 -year-olds for the general population (26). In a sensitivity analysis we also explored a scenario in which the utility of the general population is 1. Utility data of CQF patients is lacking. Before a complication occurs, CQF is usually asymptomatic or it presents as influenza-like symptoms. We assumed that for proven or probable CQF, the utility is equal to the utility of a patient with a heart valve prosthesis (27). We based the utilities of the different health states on quality of life data of the complications. The utility of an aneurysm or fistula was based on patients in need of a surgery for a symptomatic abdominal aortic aneurysm (28). The utility of heart failure was based on patients with New York Heart Association class III or IV heart failure (29). The utility of patients with an embolic complication was based on patients with a stroke with mild impairment (30). We assumed that long-term antibiotic use leads to a reduction of the utility. According to data from France, long-term antibiotic use to treat CQF led to gastrointestinal adverse events in 7% (24) of the patients. The disutility of this adverse event was assumed to be 0.105 (31). Possible CQF patients were assumed to have no reduction of the utility.

Appendix Table 7. Utilities of the different health states*

Health state	Input	SD†	Distribution†	Scenario	Source
Utilities					
General population	0.857	0.0086	Beta	1	Versteegh, 2016 (26)
Proven or probable CQF (uncomplicated)	0.855	0.0051	Beta		Franklin, 2016 (27)
Symptomatic aneurysm or fistula	0.690	0.048	Beta		Timmers, 2013 (28)
Heart failure	0.610	0.015	Beta		Calvert, 2005 (29)
Arterial embolic complication	0.640	0.063	Beta		Stouthard, 1997 (30)
Dead	0				
Utility adaption					
Gastroenteritis due to antibiotic use	-0.007	0.0028	Beta		Million, 2010 (24), WHO, 2004 (31)

*CQF, chronic Q fever.

†Used for the multivariate probabilistic sensitivity analysis.

Time Spent in Each Health State

Time spent in each health state is shown in Appendix Table 8. It is assumed that patients with a complication remain in the indicated health state for the rest of their lives. The life

expectancy of proven or probable CQF patients with premature CQF-related death was based on survival data of patients included in the Dutch national CQF database (25). The life expectancy of patients not dying prematurely due to CQF was based on the life expectancy of a comparable person at that age from the general population. We obtained the average age at diagnosis of proven and probable CQF patients from the national CQF database, being 69 years and 64 years, respectively (25). Using lifetables of the Netherlands, the life expectancies in the general Dutch population at these ages are 16.8 years and 20.8 years (32). However, the life expectancy of proven and probable CQF patients is expected to be lower than the life expectancy of an average person at that age due to the presence of a cardiovascular risk condition. Based on the comparison of the life expectancy of patients with heart valve prosthesis at the age of 60 years (33) with the life expectancy of patients in the general population at that age from the literature, we halved the life expectancy of proven and probable CQF patients to 8.4 years and 10.4 years, respectively. In the sensitivity analysis we explored life expectancies of the general population or halving the base case life-expectancies to 4.2 years for proven CQF and 5.2 years for probable CQF.

For those receiving antibiotic treatment, the duration of treatment was obtained from the national Dutch CQF database for proven and probable CQF patients (25).

Appendix Table 8. Time spent in health state*

Outcome	Input	SD†	Distribution†	Scenario	Source
Life expectancy					
CQF-related mortality					
Proven CQF	0.6				Van Roeden, 2018 (25)
Probable CQF	2.6				Van Roeden, 2018 (25)
No CQF-related mortality					
Proven CQF	8.4			16.8 and 4.2	Average age of diagnosis Van Roeden, 2018 (25), life expectancy from Statistics Netherlands (32), adjustment factor for co-morbidity from Van Geldorp, 2009 (33)
Probable CQF	10.4			20.8 and 5.2	Average age of diagnosis from Van Roeden, 2018 (25), life expectancy from Statistics Netherlands (32), adjustment factor for co-morbidity from Van Geldorp, 2009 (33)
Duration of antibiotic treatment (weeks)					
Proven CQF	96	7.8	Gamma		Van Roeden, 2018 (34)
Probable CQF	83	9.1	Gamma		Van Roeden, 2018 (34)

*CQF, chronic Q fever.

†Used for the multivariate probabilistic sensitivity analysis.

Costs

In accordance with the Dutch guideline on health economic evaluation in healthcare, we adopted a societal perspective. Costs considered in our analysis are:

- Direct healthcare costs: blood collection, diagnostic tests, surgeries, antibiotics, specialist visits.

- Indirect healthcare costs: costs unrelated to CQF in gained life years of averted premature CQF-related deaths.

- Direct non-healthcare costs: travel costs.

- Indirect non-healthcare costs: Productivity losses due to work absence.

Appendix Table 9 shows the costs inputs presented in 2016 euros (€). Costs from other years were converted to the 2016 price year using the Dutch consumer price index (35). A positive ELISA test will be followed by an IFA test for IgG titer of $\geq 1:512$ against phase I (IFA screen) and a positive IFA screen test will be confirmed with a IFA titration to determine the exact titer. Patients with IgG titer of $\geq 1:512$ against *C. burnetii* phase I will then be clinically evaluated by a medical specialist using different serologic tests and imaging techniques (initial diagnostic procedure) whether the patient has proven, probable, or possible CQF. In the base case analysis, we ignored program costs because the screening of risk groups may also occur during routine visits. In the sensitivity analysis, we explored a scenario in which we assumed that the program costs would be €1.36 per screened person for selecting and inviting patients. We based these program costs on the tariff a GP currently receives for the selection, invitation and administration of influenza vaccination within the national influenza immunization program.

Cost of a surgery is the weighted average of vascular surgeries, heart valve surgeries and other kind of surgeries (according to surgery data from S.E. van Roeden, pers. comm., and cost data from the literature [36,37]). Surgeries gathered under “other surgeries” mostly consist of the drainage of a non-cardiac abscess and we used the cost of a pulmonary drainage for this parameter. The cost of antibiotics is based on a treatment with doxycycline and hydroxychloroquine and includes also costs of blood tests to determine the antibiotic levels. The duration of antibiotic treatment is shown in Appendix Table 8. During treatment, patients visit the medical specialist every 3 months for serologic follow up, and CQF patients with a vascular infection have a PET scan every year. Follow-up of proven and probable CQF patients is life-long and consists of medical specialist visits and serologic tests of which the frequency reduces over time. Possible CQF patients are followed until the IgG titer against *C. burnetii* phase I has been decreased to $< 1:1,024$. We assumed that the average follow-up of possible CQF patients is

1 year. Concerning CQF-related complications, we assumed that the treatment of acute aneurysm, heart failure, and arterial embolic complication would be lifetime. Treatment costs are obtained from the literature and include annual treatment costs, as well as costs of future complications. For an arterial embolic complication we used costs of a stroke.

Indirect healthcare costs, also referred to as healthcare costs unrelated to CQF in gained life years, were estimated by using the remaining life-expectancy at the age of death (Appendix Table 8) and age-specific healthcare costs from a specifically developed tool labeled Practical Application to Include Disease Costs (PAID) (38). This tool distinguishes healthcare costs incurred in the last year of life and costs incurred in other years by sex, age and healthcare provider. To avoid a possible double count of influenza-related costs, we excluded healthcare costs of the disease category heart failure and diseases of arteries. We included costs of all healthcare providers available in the tool, and the weighted average of men and women was estimated using age-specific sex distributions of the Dutch population. The total indirect healthcare costs in the remaining life years was estimated using lifetables, attributing the cost incurred in a final life year to a person that died in the lifetable and cost incurred in other years to a person that survives in the lifetable. As the inclusion of indirect healthcare costs is specific for the Dutch guideline, we present results without the inclusion of indirect medical costs in the sensitivity analysis.

Direct non-medical costs include travel costs to the medical doctor, hospital, and pharmacy. We assumed that blood collection for screening was conducted at the medical doctor. Average distances to the different healthcare facilities and travel costs per kilometer were obtained from the Dutch guideline for economic evaluations in healthcare.

Indirect non-medical costs included productivity losses due to work absence were counted for screening, clinical evaluation, and complications. The duration of absence was adjusted for age-specific labor participation rates and age-specific working hours per week from Statistics Netherlands of 2016 (39). The duration of absence was assumed to be half an hour for blood collection and 1.5 day for clinical evaluation. Given the seriousness of CQF-related complications, we assumed permanent work absence after developing a symptomatic aneurysm, heart failure, or arterial embolic complication. In accordance with the Dutch guideline on economic evaluations in healthcare, we used the friction approach. This method assumes that

work absence is limited to a certain friction period, as an unemployed person has replaced the deceased person after this period. We used a friction period of 85 days (40). Productivity loss per absent working hour was €35.07 (40).

Appendix Table 9. Costs in 2016 euros

Cost unit	Input	SD†	Distribution†	Scenario	Source and additional details
Direct healthcare costs					
Selection and invitation	0			11.36	Assumption: Screening occurs during routine visits
Blood collection	10.71				Dutch cost-effectiveness guideline, 2016 (40)
ELISA	7.00				Assumption based on (41)
IFA screen	9.90				List price JBH (P.M. Schneeberger, pers comm.)
IFA titration	19.80				List price JBH (P.M. Schneeberger, pers comm.)
Initial diagnostic procedure after positive IFA	1,299				Blood collection, IFA titration, PCR, CRP/standard blood tests, PET scan, TTE (all once); TEE (half of the patients); specialist consultations (3 times) (C.P. Bleeker-Rovers, pers. comm.)
Surgery	14,717			30,000	Based on 76% vascular surgeries, 19% heart valve surgeries, and 5% other kind of surgeries (S.E. van Roeden, pers. comm.) with average cost of 10,639 (36), 16,124 (37), and 8,803 (36).
Antibiotic treatment, per year					
First year	343				Based on treatment with doxycycline (1 dd 200 mg) and hydroxychloroquine (3 dd 200 mg) (42), pharmacy dispensing fee (6 times, at the assumption of delivery per 2 mo) and additional fee for first delivery (2 times), serologic antibiotic level determination (2 times) (C.P. Bleeker-Rovers, pers. comm.)
Consecutive years	297				Doxycycline and hydroxychloroquine, pharmacy dispensing fee (see first year)
Costs routine visits during treatment, per year	1,440				PCR, IFA, specialist visit, CRP/standard blood tests (all 4 times per year). A PET scan in the first year for vascular infections (C.P. Bleeker-Rovers, pers. comm.)
Follow-up					
Year 1	912				PCR, IFA, specialist visit, CRP/standard blood tests (4 times per year) (C.P. Bleeker-Rovers, pers. comm.)
Year 2	864				PCR, IFA, specialist visit, CRP/standard blood tests (3 times per year) (C.P. Bleeker-Rovers, pers. comm.)
Year 3	456				PCR, IFA, specialist visit, CRP/standard blood tests (2 times per year) (C.P. Bleeker-Rovers, pers. comm.)
Year 4 and after	228				PCR, IFA, specialist visit, CRP/standard blood tests (1 time per year) (C.P. Bleeker-Rovers, pers. comm.)
Complications, per year					
Heart failure	3,176				Van Giessen, 2016 (43)
Vascular prosthesis or aneurysm	2,430	358	Gamma		Prinssen, 2007 (44)
Embolus complication					
Year 1	12,352	1897	Gamma		Van Eeden, 2015 (45)
Year 2 and after	4,997	2038	Gamma		Van Eeden, 2015 (45), costs of the second half of the year extrapolated to a year
Other complications	0				Assumption
Indirect healthcare costs, lifelong					
Proven CQF	60,301			Excluded	
Probable CQF	47,183				PAID toolkit (38), based on the difference between life expectancy of CQF-related death and non-CQF-related death. Costs of heart

Cost unit	Input	SD†	Distribution†	Scenario	Source and additional details
					failure and vascular infections were excluded, because these costs could be related to CQF.
Direct non-healthcare costs					
Screening travel cost	0.42				Assumption travel costs to hospital
Initial diagnosis travel cost	11.42				Travel costs to hospital, including parking fee (2 times) (40)
Surgery travel cost	11.42				Travel costs to hospital, including parking fee (2 times) (40)
Antibiotics travel cost, per year	2.99				Travel costs to pharmacy (2 times) (40)
Travel cost of routine visits during treatment or follow-up	5.71				Travel costs to hospital, including parking fee (40)
Indirect non-healthcare costs					
Productivity loss screening	4.36–12.57				Half an hour of productivity loss (Assumption). Cost depends on age due to differences in net labor participation rates and average working hours per week.
Productivity loss initial diagnostics	105–302				1.5 d of lost productivity (Assumption). Cost depends on age due to differences in net labor participation rates and average working hours per week.
Productivity costs complication	5,936–17,089				We assumed that a CQF complication was leading to long-term work absence. Given that the friction method is the recommended approach in the Netherlands to value productivity losses, we limited the work absence of a complication to a standardized friction period of 85 d (40). Cost depends on age due to differences in net labor participation rates and average working hours per week.

*CQF, chronic Q fever; CRP, C-reactive protein; IFA, immunofluorescence assay; JBH, Jeroen Bosch hospital; PAID, Practical Application to Include future disease costs; PET, positron emission tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.
†Used for the multivariate probabilistic sensitivity analysis.

Supplemental Results

Appendix Table 10. Subdivision of the Dutch 2017 adult population (N = 13,678,496) to Q fever incidence area using 4-digit postal codes and 3-digit postal codes

Incidence area	4-digit postal codes, no. (%)	3-digit postal codes, no. (%)
High	1,650,873 (12.07)	2,135,169 (15.61)
Middle	2,637,196 (19.28)	3,637,843 (26.60)
Low	9,390,427 (68.65)	7,905,484 (57.79)

Appendix Table 11. Subdivision of the Dutch 2017 adult population (N = 13,678,496) to specific risk groups

Population	Size (%)
Persons with diagnosed risk factor	908,248 (6.64)
Cardiovascular risk factor	462,512 (3.38)
Heart valve disorder or –prosthesis	329,112 (2.41)
Aortic aneurysm or vascular prosthesis	77,323 (0.57)
Congenital heart anomaly	40,968 (0.30)
Endocarditis	15,109 (0.11)
Immunocompromised status	445,736 (3.26)
Underlying disease*	158,858 (1.16)
Medication use	286,878 (2.10)
Rheumatoid arthritis	217,764 (1.59)
Inflammatory bowel disease	69,115 (0.51)
Persons without diagnosed risk factor	12,770,248 (93.36)
Age ≥60 y	3,633,184 (26.56)
Undiagnosed cardiovascular risk factor	141,221 (1.03)
Heart valve disorder	96,311 (0.70)

Population	Size (%)
Aortic aneurysm	44,911 (0.33)
No risk factor†	3,491,963 (25.53)
Age 18–59 y	9,137,064 (66.80)
Undiagnosed cardiovascular risk factor	2,379 (0.02)
Heart valve disorder	– (0.00)
Aortic aneurysm	2,379 (0.02)
No risk factor†	9,134,685 (66.78)

*Includes HIV infection, asplenia, spleen dysfunction, malignancy (e.g., leukemia) or bone marrow transplant.

†No risk factor is defined here as patients without a cardiovascular risk factor or compromised immune system.

Appendix Table 12. Estimation of the prevalence and number of *Coxiella burnetii*-infected individuals and CQF patients*

Screening population	Prevalence scenario	Population size	Seroprevalence	<i>C. burnetii</i> infections	CQF prevalence after epidemic	CQF patients after epidemic	CQF prevalence at screening	CQF patients at screening	Proven CQF patients at screening	Probable CQF patients at screening	Possible CQF patients at screening
High incidence area											
CVRF patients	Low	55,821	215	1,202	26.2	146	6.4	36	25	11	—
	High	72,197	1,070	7,725	130.1	939	62.4	451	311	140	—
IC patients	Low	53,796	215	1,159	14.8	80	3.6	20	13	6	—
	High	69,578	1,070	7,445	73.4	511	35.2	245	169	76	—
Age ≥60 y, unknown RF	Low	438,493	215	9,444	1.7	74	0.4	18	10	4	4
	High	567,128	1,070	60,683	8.4	477	4.0	229	119	54	56
Age 18–59 y, unknown RF	Low	1,102,763	215	23,750	0.4	49	0.1	12	0	0	12
	High	1,426,266	1,070	152,610	2.2	317	1.1	152	4	2	146
Middle incidence area											
CVRF patients	Low	89,172	15	135	1.8	16	0.5	4	3	1	—
	High	123,007	230	2,829	28.0	344	13.4	165	114	51	—
IC patients	Low	85,937	15	131	1.0	9	0.3	2	2	1	—
	High	118,545	230	2,727	15.8	187	7.6	90	62	28	—
Age ≥60 y, unknown RF	Low	700,473	15	1,064	0.1	8	0.0	2	1	0	1
	High	966,258	230	22,224	1.8	175	0.9	84	44	20	21
Age 18–59 y, unknown RF	Low	1,761,614	15	2,677	0.0	6	0.0	1	0	0	1
	High	2,430,034	230	55,891	0.5	116	0.2	56	1	1	54
Low incidence area											
CVRF patients	Low	317,519	2.7	87	0.3	11	0.1	3	2	1	—
	High	267,308	100	2,673	12.2	325	5.8	156	108	48	—
IC patients	Low	306,002	2.7	84	0.2	6	0.0	1	1	0	—
	High	257,613	100	2,576	6.9	177	3.3	85	58	26	—
Age ≥60 y, unknown RF	Low	2,494,218	2.7	685	0.0	5	0.0	1	1	0	0
	High	2,099,798	100	20,998	0.8	165	0.4	79	41	19	19
Age 18–59 y, unknown RF	Low	6,272,687	2.7	1,724	0.0	4	0.0	1	0	0	1
	High	5,280,764	100	52,808	0.2	110	0.1	53	1	1	51
Total	Low	13,678,496	31	42,143	0.3	414	0.1	102	57	26	19
	High	13,678,496	286	391,188	2.8	3,842	1.3	1,844	1,032	465	347

*CQF, chronic Q fever; CVRF, cardiovascular risk factor; IC, immunocompromised; RF, risk factor.

Appendix Table 13. Screening outcomes at a screening participation rate of 50%*

Screening population	Prevalence scenario	Persons screened	ELISA positive	IFA positive	CQF patients detected	NNS CQF	Proven CQF patients detected	NNS proven CQF
High incidence area								
CVRF patients	Low	27,911	856	28	18	1,552	12	2,252
	High	36,098	2,689	288	225	160	155	232
IC patients	Low	26,898	821	20	10	2,750	7	3,990
	High	34,789	2,544	184	123	284	85	412
Age ≥60 y, unknown RF	Low	219,247	6,656	21	9	24,020	5	46,141
	High	283,564	20,292	190	86	3,281	60	4,760
Age 18–59 y, unknown RF	Low	551,381	16,731	29	6	90,913	0	3,585,959
	High	713,133	50,927	225	3	254,977	2	369,966
Middle incidence area								
CVRF patients	Low	44,586	925	3	2	22,002	1	31,924
	High	61,503	1,950	105	83	745	57	1,081
IC patients	Low	42,969	891	2	1	38,980	1	56,559
	High	59,273	1,862	67	45	1,320	31	1,915
Age ≥60 y, unknown RF	Low	350,237	7,261	2	1	340,477	1	654,042
	High	483,129	15,017	70	32	15,263	22	22,146
Age 18–59 y, unknown RF	Low	880,807	18,259	3	1	1,288,685	0	50,830,867
	High	1,215,017	37,728	82	1	1,186,195	1	1,721,146
Low incidence area								
CVRF patients	Low	158,759	3,197	2	1	121,642	1	176,499
	High	133,654	3,354	100	78	1,713	54	2,486
IC patients	Low	153,001	3,081	1	1	215,509	0	312,699
	High	128,807	3,216	64	42	3,036	29	4,405
Age ≥60 y, unknown RF	Low	1,247,109	25,107	2	1	1,882,392	0	3,615,996
	High	1,049,899	26,057	66	30	35,104	21	50,936
Age 18–59 y, unknown RF	Low	3,136,344	63,141	2	0	7,124,742	0	281,028,271
	High	2,640,382	65,495	78	1	2,728,249	1	3,958,636

*CQF, chronic Q fever; CVRF, cardiovascular risk factor; IC, immunocompromised; NNS, number needed to screen; RF, risk factor.

Appendix Table 14. Clinical and health impact of the analyzed screening strategies as compared to no screening at a screening participation rate of 50%*

Screening population	Prevalence scenario	Additional antibiotic courses	Complications averted	Surgeries averted	CQF-related deaths averted	Life years saved	QALYs gained
High incidence area							
CVRF patients	Low	4.1	-8.4	-4.3	-2.1	15.2	17.1
	High	51.5	-104.7	-53.9	-25.8	190.2	214.9
IC patients	Low	2.2	-4.5	-2.3	-1.1	8.3	9.3
	High	28.0	-56.9	-29.3	-14.0	103.4	116.9
Age ≥60 y, unknown RF	Low	1.6	-3.2	-1.6	-0.8	5.8	6.6
	High	19.8	-40.1	-20.7	-9.9	72.9	82.4
Age 18–59 y, unknown RF	Low	0.1	-0.1	-0.1	-0.0	0.2	0.2
	High	0.6	-1.3	-0.7	-0.3	2.4	2.7
Middle incidence area							
CVRF patients	Low	0.5	-0.9	-0.5	-0.2	1.7	1.9
	High	18.9	-38.3	-19.7	-9.4	69.6	78.7
IC patients	Low	0.3	-0.5	-0.3	-0.1	0.9	1.1
	High	10.3	-20.9	-10.7	-5.1	37.9	42.8
Age ≥60 y, unknown RF	Low	0.2	-0.4	-0.2	-0.1	0.7	0.7
	High	7.2	-14.7	-7.6	-3.6	26.7	30.2
Age 18–59 y, unknown RF	Low	0.0	-0.0	-0.0	-0.0	0.0	0.0
	High	0.2	-0.5	-0.2	-0.1	0.9	1.0
Low incidence area							
CVRF patients	Low	0.3	-0.6	-0.3	-0.1	1.1	1.2
	High	17.8	-36.2	-18.7	-8.9	65.8	74.4
IC patients	Low	0.2	-0.3	-0.2	-0.1	0.6	0.7
	High	9.7	-19.7	-10.1	-4.9	35.8	40.5
Age ≥60 y, unknown RF	Low	0.1	-0.2	-0.1	-0.1	0.4	0.5
	High	6.8	-13.9	-7.2	-3.4	25.2	28.5
Age 18–59 y, unknown RF	Low	0.0	-0.0	-0.0	-0.0	0.0	0.0
	High	0.2	-0.4	-0.2	-0.1	0.8	0.9

*CQF, chronic Q fever; CVRF, cardiovascular risk factor; IC, immunocompromised; QALY, quality-adjusted life year; RF, risk factor.

Appendix Table 15. Incremental costs of the analyzed screening strategies as compared to no screening at a screening participation rate of 50%*

Screening population	Prevalence scenario	Screening costs, €	Direct HC costs, €	Non-HC costs, direct and indirect, €	Total societal costs, excluding indirect HC costs, €	Indirect HC costs, €	Total societal costs (including indirect HC costs, €)
High incidence area							
CVRF patients	Low	503,270	-144,557	81,542	440,256	103,818	544,074
	High	671,548	-1,892,276	-155,227	-1,375,955	1,301,471	-74,484
IC patients	Low	484,832	-73,132	148,657	560,358	56,473	616,831
	High	644,881	-993,980	-88,602	-437,702	707,956	270,255
Age ≥60 y, unknown RF	Low	3,948,773	-52,244	527,743	4,424,273	39,806	4,464,079
	High	5,226,068	-679,387	657,153	5,203,834	499,016	5,702,850
Age 18–59 y, unknown RF	Low	9,930,185	9,116	6,290,432	16,229,733	1,288	16,231,021
	High	13,136,941	113,863	8,142,174	21,392,977	16,148	21,409,125
Middle incidence area							
CVRF patients	Low	798,757	-16,291	163,934	946,400	11,700	958,100
	High	1,110,506	-693,011	123,447	540,942	476,640	1,017,582
IC patients	Low	769,765	-8,242	273,324	1,034,847	6,364	1,041,211
	High	1,069,382	-364,027	266,486	971,841	259,276	1,231,117
Age ≥60 y, unknown RF	Low	6,273,987	-5,888	846,345	7,114,444	4,486	7,118,930
	High	8,705,394	-248,813	1,157,466	9,614,047	182,756	9,796,803
Age 18–59 y, unknown RF	Low	15,778,334	1,027	10,047,828	25,827,189	145	25,827,334
	High	21,890,903	41,700	13,862,862	35,795,465	5,914	35,801,379
Low incidence area							
CVRF patients	Low	2,843,033	-10,492	591,186	3,423,727	7,535	3,431,262
	High	2,401,947	-654,782	398,729	2,145,894	450,347	2,596,241
IC patients	Low	2,739,902	-5,308	981,177	3,715,771	4,099	3,719,870
	High	2,314,029	-343,946	719,500	2,689,583	244,973	2,934,557
Age ≥60 y, unknown RF	Low	22,332,648	-3,792	3,014,362	25,343,218	2,889	25,346,107
	High	18,851,093	-235,088	2,528,039	21,144,045	172,674	21,316,719
Age 18–59 y, unknown RF	Low	56,164,141	662	35,777,732	91,942,535	93	91,942,628
	High	47,406,356	39,400	30,122,503	77,568,258	5,588	77,573,846

*CQF, chronic Q fever; CVRF, cardiovascular risk factor; HC, healthcare; IC, immunocompromised; RF, risk factor.

Appendix Table 16. Costs of screening of 50% of all adults in the Netherlands as compared to no screening at all*

Cost component	Without screening, € million	Screening, € million	Difference, € million
Direct healthcare costs			
Screening	—	123.43	123.43
Blood sampling	—	73.24	73.24
ELISA	—	47.87	47.87
IFA	—	2.32	2.32
Treatment of CQF	33.43	31.84	-1.59
Diagnostic procedures	1.39	2.18	0.79
Surgeries	8.80	6.17	-2.64
Antibiotics	0.51	0.61	0.09
Follow-up during treatment	1.78	2.10	0.32
Follow-up after treatment	2.57	3.26	0.69
Complications	18.37	13.20	-5.17
Indirect healthcare costs	—	4.32	4.32
Direct non-healthcare costs	0.15	3.07	2.92
Travel costs screening	—	2.89	2.89
Travel costs treatment of CQF	0.15	0.18	0.03
Indirect non-healthcare costs	4.20	59.01	54.82
Productivity loss screening	—	55.92	55.92
Productivity loss treatment of CQF	4.20	3.09	-1.10
Total societal costs	37.77	217.35	179.58

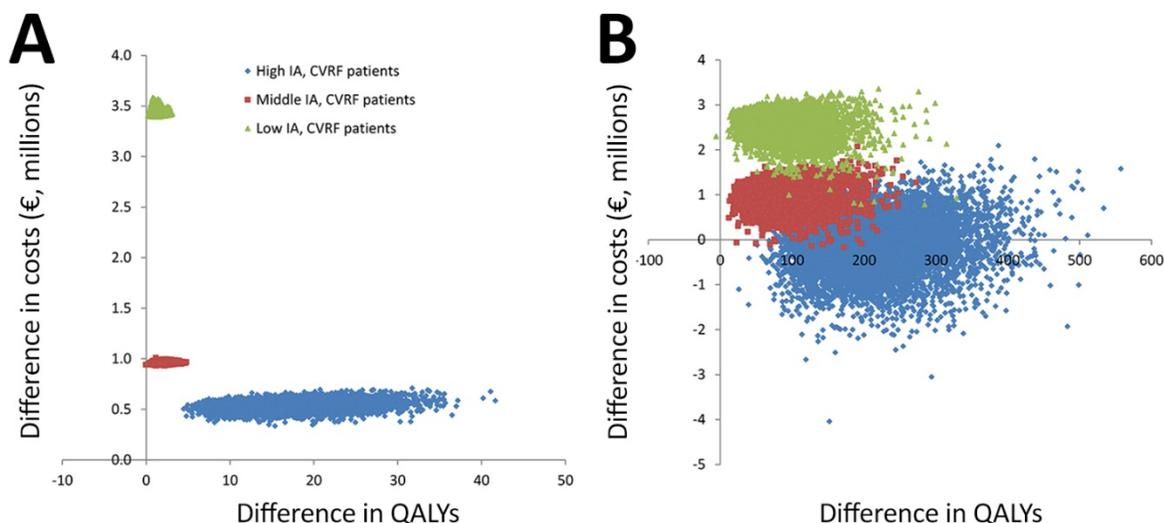
*CQF, chronic Q-fever; IFA, immunofluorescence assay.

Appendix Table 17. Cost-effectiveness of screening strategies as compared to no screening at a screening participation rate of 50%*

Screening population	Prevalence scenario	Screening		No screening		Difference		ICER, €/QALY gained
		Costs, €, million†	QALYs†	Costs, €, million†	QALYs†	Costs, €, million†	Total QALYs†	
High incidence area								
CVRF patients	Low	1.44	174.9	0.89	157.8	0.54	17.1	31,737
	High	11.11	2,192.7	11.19	1,977.8	-0.07	214.9	Cost-saving
IC patients	Low	1.15	95.1	0.53	85.8	0.62	9.3	66,145
	High	6.94	1,192.8	6.67	1,075.9	0.27	116.9	2,312
Age ≥60 y, unknown RF	Low	4.78	165.5	0.32	158.9	4.46	6.6	679,136
	High	9.70	2,074.8	4.00	1,992.4	5.70	82.4	69,208
Age 18–59 y, unknown RF	Low	16.25	259.7	0.02	259.5	16.23	0.2	76,308,665
	High	21.62	3,255.4	0.21	3,252.8	21.41	2.7	8,029,064
Middle incidence area								
CVRF patients	Low	1.06	19.7	0.10	17.8	0.96	1.9	495,918
	High	5.11	803.0	4.10	724.3	1.02	78.7	12,929
IC patients	Low	1.10	10.7	0.06	9.7	1.04	1.1	990,755
	High	3.67	436.8	2.44	394.0	1.23	42.8	28,755
Age ≥60 y, unknown RF	Low	7.15	18.7	0.04	17.9	7.12	0.7	9,610,222
	High	11.26	759.9	1.47	729.7	9.80	30.2	324,632
Age 18–59 y, unknown RF	Low	25.83	29.3	0.00	29.2	25.83	0.0	1,077,459,984
	High	35.88	1,192.2	0.08	1,191.3	35.80	1.0	36,661,479
Low incidence area								
CVRF patients	Low	3.50	12.7	0.06	11.5	3.43	1.2	2,757,608
	High	6.47	758.7	3.87	684.4	2.60	74.4	34,912
IC patients	Low	3.76	6.9	0.04	6.2	3.72	0.7	5,495,846
	High	5.24	412.7	2.31	372.3	2.93	40.5	72,544
Age ≥60 y, unknown RF	Low	25.37	12.0	0.02	11.5	25.35	0.5	53,126,291
	High	22.70	717.9	1.38	689.4	21.32	28.5	747,603
Age 18–59 y, unknown RF	Low	91.94	18.8	0.00	18.8	91.94	0.0	5,955,497,518
	High	77.65	1,126.5	0.07	1,125.6	77.57	0.9	84,075,394

*CQF, chronic Q-fever; CVRF, cardiovascular risk factor; IC, immunocompromised; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RF, risk factor.

†In CQF patients only, except costs of screening.



Appendix Figure 2. Results of the multivariate sensitivity analysis using 10,000 simulations for screening of patients with a cardiovascular risk factor in high, middle, and low incidence areas for the (A) low CQF prevalence scenario and (B) high CQF prevalence scenario. CQF, chronic Q fever; CVRF, cardiovascular risk factor; IA, incidence area; QALY, quality-adjusted life year.

Appendix Table 18. Cost-effectiveness of screening without the inclusion of indirect medical costs

Screening population	CQF prevalence scenario	Difference in QALYs	Difference in costs, without indirect HC costs	ICER, €/QALY gained, without indirect HC costs
High incidence area				
CVRF patients	Low	17.1	440,256	25,681
	High	214.9	-1,375,955	-6,402
IC patients	Low	9.3	560,358	60,090
	High	116.9	-437,702	-3,744
Age ≥ 60 y, unknown RF	Low	6.6	4,424,273	673,080
	High	82.4	5,203,834	63,152
Age 18–59 y, unknown RF	Low	0.2	16,229,733	76,302,609
	High	2.7	21,392,977	8,023,009
Middle incidence area				
CVRF patients	Low	1.9	946,400	489,862
	High	78.7	540,942	6,873
IC patients	Low	1.1	1,034,847	984,699
	High	42.8	971,841	22,699
Age ≥ 60 y, unknown RF	Low	0.7	7,114,444	9,604,166
	High	30.2	9,614,047	318,576
18–59 y, unknown RF	Low	0.0	25,827,189	1,077,453,928
	High	1.0	35,795,465	36,655,423
Low incidence area				
CVRF patients	Low	1.2	3,423,727	2,751,552
	High	74.4	2,145,894	28,856
IC patients	Low	0.7	3,715,771	5,489,790
	High	40.5	2,689,583	66,488
Age ≥ 60 y, unknown RF	Low	0.5	25,343,218	53,120,236
	High	28.5	21,144,045	741,547
Age 18–59 y, unknown RF	Low	0.0	91,942,535	5,955,491,462
	High	0.9	77,568,258	84,069,338

*CQF, chronic Q-fever; CVRF, cardiovascular risk factor; HC, healthcare; IC, immunocompromised; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RF, risk factor.

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