Signs and symptoms do not predict, but may help rule out acute Q fever in favour of other respiratory tract infections, and reduce antibiotics overuse in primary care

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Abstract

Background From early 2009, South Limburg, Netherlands, experienced a massive outbreak of Q fever, overlapping with the influenza A(H1N1)pdm09 pandemic during the second half of the year and affecting approximately 2.9% of the regional population. Acute Q fever shares clinical features with other respiratory conditions. Most symptomatic acute infections are characterized by mild symptoms, or an isolated febrile syndrome. Pneumonia was present in a majority of hospitalized patients during the Dutch 2007-2010 Q fever epidemic. Early empiric doxycycline, guided by signs and symptoms and patient history, should not be delayed awaiting laboratory confirmation, as it may shorten disease and prevent progression to focalized persistent Q fever. We assessed signs' and symptoms' association with acute Q fever to guide early empiric treatment in primary care patients.

Methods In response to the outbreak, regional primary care and hospital-based specialty physicians tested a total of 1228 subjects for Q fever. Testing activity was bimodal, a first "wave" lasting from March to December 2009, followed by a second "wave" which lasted into 2010 and coincided with peak pandemic influenza activity. We approached all 253 notified acute Q fever cases and a random sample of 457 Q fever negative individuals for signs and symptoms of disease. Using data from 140/229(61.1%) Q fever positive and 194/391(49.6%) Q fever negative respondents from wave 1, we built symptom-based models predictive of Q-fever outcome, validated against each other and against our wave 2 data.

Results Our models had moderate AUC scores (0.68% to 0.72%), with low positive (4.6-8.3%), but high negative predictive values (91.7-99.5%). Male sex, fever, and pneumonia were strong positive predictors, while cough was a strong negative predictor of acute Q fever in these models.

Conclusion Whereas signs and symptoms of disease do not appear to predict acute Q fever, they may help rule it out in favour of other respiratory conditions, prompting a delayed or non-prescribing approach instead of early empiric doxycycline in primary care patients with non-severe presentations. Signs and symptoms thus may help reduce the overuse of antibiotics in primary care during and following outbreaks of Q fever.

Background

From March 2009, South Limburg, the southernmost region of the Netherlands, experienced a massive outbreak of human Q fever related to an abortion storm on a local dairy-goat farm. Laboratory-confirmed symptomatic human Q-fever cases were first reported in April, peaked in May, and then steadily declined over subsequent months. Culling of infected goats took place around the turn of the year. By April 2010, no more new cases were reported to the regional Public Health Service (PHS), and the number of notified human cases reported to the regional PHS had totalled 253, whereas the number of infections was estimated to run into thousands.(1)

A majority of acute Q fever infections is understood to be asymptomatic or only mildly symptomatic. Symptomatic patients usually present with a febrile syndrome or flu-like illness frequently said to be associated with myalgia and headache. During the Dutch Q fever epidemic, which lasted from 2007 to 2010, pneumonia was present in as many as 86% of hospitalized patients. Although most cases of acute Q fever are self-limiting, early antibiotic treatment with doxycycline within the first days of symptoms may shorten duration of disease, and may prevent progression to persistent focalized infection, commonly referred to as chronic Q fever, in cases with known or unknown underlying risk factors, including vascular and valvular anomalies.(2, 3) Definite diagnosis usually relies on laboratory testing. While polymerase chain reaction (PCR) may provide timely outcomes, serological assays still are the mainstay of laboratory testing, resulting in diagnostic delay and foregone or inappropriate treatment.(2)

During the Dutch epidemic of Q fever, general practitioners (GP's) with experience in treating Q fever patients tended to start empiric antibiotic therapy ahead of laboratory confirmation, which had a median delay of 20 days from onset of illness in 2009.(4, 5) While doxycycline was the most commonly prescribed initial antibiotic, a substantial proportion of subjects were treated with a penicillin, which is considered to be ineffective in Q fever.(6) A complicating factor in the diagnostic workup of cases was the influenza A(H1N1)pdm09 pandemic which overlapped with the regional outbreak for several months during the second half of the year.

Several studies have assessed the diagnostic potential of signs and symptoms in respiratory disease, including influenza and Q fever.(7–10) However, evidence regarding the predictive usefulness of signs and symptoms in patients with suspected Q fever has remained scarce, and has been limited to hospital settings. A Dutch study performed during the 2007–2010 Q fever epidemic in the Netherlands, for example, found that signs and symptoms did not differentiate between acute Q fever and other respiratory infections in hospitalized patients.(11) However, it is the primary care setting where signs and symptoms of disease are essential in the initial diagnostic workup and in guiding early clinical decision-making. Our study, which used data from a cohort of subjects a majority of whom were tested by general practitioners, aimed to assess whether signs and symptoms could support decision-making in primary care. Specifically, we assessed whether signs and symptoms could accurately identify acute Q fever in suspect cases prior to laboratory confirmation, or help rule out the diagnosis in favour of other respiratory infections where, depending on national guidelines, treatment with amoxicillin as a first-line antibiotic or a delayed or non-prescribing approach would be considered more appropriate.

Methods

Study area. The study area was the catchment area of one of the largest Dutch general hospitals, located in South Limburg, Netherlands (346 km^2, 12 municipalities, 308000 inhabitants).

Study period. In March 2009, the regional Food and Consumer Product Safety Authority notified the South Limburg PHS of a large dairy-goat farm where 220 out of 450 pregnant goats had aborted due to laboratory-confirmed Q fever. The study period was defined by the time of veterinary notification (March 2009) and the time when the outbreak source had been eliminated through culling of infected goats and vaccination of remaining goat populations, and new community cases were no longer reported (April 2010).

Study design. We performed a retrospective case-control study assessing the association of acute Q fever case status with signs and symptoms of disease in a sample of questionnaire respondents from the cohort of all individuals tested for acute Q fever by GP's or specialty physicians in the period from March 2009 through April 2010 (n = 1218). All notifiable community cases (n = 253) were reported to the regional PHS by the affiliated regional testing laboratory. Disease onset in community cases was physician-reported. The testing laboratory also provided data on all other individuals tested for Q fever in the study period, including date of birth, gender, zip code as a proxy for residential address, name and address of GP, testing dates, and testing results. Promptly following notification, all notified community cases were approached with a questionnaire assessing the presence or absence of individual presenting signs and symptoms of disease preceding testing, underlying medical conditions, risk exposure activities, among others. Response in this group was 64.4% (163/253). A random selection of seronegative individuals who did not meet criteria for notification and had not been reported to the PHS by name were approached with the same questionnaire via their GP's (response: 67.2%(307/457).

Laboratory investigation. The entire cohort of subjects was tested for IgG- and IgM-type antibodies to phase-I and phase-II C. burnetii antigen by Serion ELISA classic, according to manufacturer's instructions (Serion ELISA classic, Institut Virion\Serion GmbH, Würzburg, Germany). The presence of phase-II IgM (absorbance > 10% above extinction of the cut-off control) in a single serum sample, or presence of C. burnetii DNA in PCR ($Ct \leq 36$), routinely performed on all samples seronegative on initial testing, was considered diagnostic of acute Q fever.(12–14)

Study population. Overall, 20.8% (253/1218) of all patients tested were confirmed with a diagnosis of acute Q fever by serology or PCR. Testing activity followed a bimodal distribution over time. A larger first testing wave from March to December 2009 was followed by a second smaller one from December 2009 through April 2010 (Fig. 1). The larger first wave, including subjects tested from week 13 (March 2009) until week 49 (December 2009), contained 72% of all tested patients, with a Q fever positive rate of 26%, thus yielding 91% of all notifiable patients with a laboratory-confirmed diagnosis of acute Q fever in the study period. By contrast, the second wave, although it counted more than a quarter of all tested patients, had a positive rate of only 7% and identified just 9% of all notified patients. Characteristics of tested subjects are summarized in Table 1.

Table 1
Characteristics of the total population of subjects tested in the study period, by testing wave

	Q fever positive		Q fever negative		Total	Positive rate
Wave 1						
Subjects tested, n	229		644		873	26.2%
Test ordered by						
GP, n (%)	155	(67.7)				
Specialty physician, n (%)	72	(31.4)				
Unknown	2	(0.9)				
Age in years (week 13 2009)						
Mean (range)	49.0	(0.9–85.5)	45.1	(0.5–92.4)		
0–19, n (%)	11	(4.8)	87	(13.5)		
20–39, n (%)	46	(24.9)	154	(37.4)		
40–59, n (%)	113	(49.3)	235	(36.5)		
≥60, n (%)	59	(25.8)	168	26.1)		
Sex, n female (%)	83	(36.2)	346	(53.7)		
Residential farm distance, mean km	5.1		6.1			
Wave 2						
Subjects tested, n	24		321		345	7.0%
Test ordered by						
GP, n (%)	19	(79.2)	237	(79.2)		
Specialty physician, n (%)			61	(19.0)		
Unknown	5	(20.8)	23	(7.2)		
Age in years (week 13 2009)						
Mean (range)	46.7	(20.8–71.7)	46.8	(0–88.5)		
0–19, n (%)	0	0	42	(13.1)		
20–39, n (%)	4	(16.7)	60	(18.7)		
40–59, n (%)	17	(70.8)	125	(38.9)		
≥60, n (%)	3	(12.5)	94	(29.3)		
Sex, n female (%)	10	(41.7)	184	(57.3)		
Residential farm distance, mean km	5.1		5.7			

Table 1. Characteristics of the total population of subjects tested in the study period, by testing wave

Data selection and analysis. Statistical analyses were performed using SPSS

Statistics 21.0 (IBM corporation, New York, USA). For derivation and cross-validation of our symptom-based prediction, we used questionnaire data from the first wave of testing. This dataset included all subjects from the age of 20 years who had been testing in the weeks before week 49 and who had answered all questions about presenting signs and symptoms of disease which preceded testing (n = 338). Children and adolescents under the age of 20 were excluded since the association of signs and symptoms with Q fever in this age group is known to be less clear-cut than in adults.(15, 16) Questionnaire data from the second wave were set aside as a holdout sample for additional validation of the models derived from our first wave data. Characteristics of questionnaire respondents are summarized in Table 2.

Table 2
Characteristics of questionnaire respondents, by testing outcome (positive vs. negative) and wave (wave 1 vs. wave 2)

	Q fever positive		Q fever negative	
Wave 1				
Questionnaire recipients, n (% of tested)	229	(100)	391	(60.7)
Respondents, n (response rate)	143	(62.4)	198	(50.6)
Respondents, complete response, n (rate)	140	(97.9)	194	(98.0)
Test ordered by				
GP, n (%)	102	(72.9)	177	(91.2)
Specialty physician, n (%)	38	(27.1)	16	(8.2)
Unknown	0	(0)	1	(0.5)
Age in years (at beginning of study period)				
Mean (range)	49.7	(5.9–85.5)	46.7	(0.8–92.4)
0–19, n (%)	7	(5.0)	28	(14.4)
20–39, n (%)	23	(16.4)	40	(20.6)
40–59, n (%)	72	(51.4)	64	(33.0)
≥60, n (%)	38	(27.1)	62	(32.0)
Sex, n female (%)	51	(36.4)	106	(54.6)
Residential farm distance, mean km (range)	4.7	(1.9–13.1)	4.8	(1.1–11.6)
Active smoking, n (%)	49	(35.0)	47	(24.2)
Wave 2				
Questionnaire recipients, n (% of tested)	24	(100)	95	(29.6)
Respondents, n (response rate)	19	(79.2)	94	(98.9)
Respondents, complete response, n (rate)	18	(94.7)	91	(96.8)
Test ordered by				
GP, n (%)	13	(72.2)	73	(80.2)
Specialty physician, n (%)				
Unknown	5	(26.3)	18	(19.8)
Age in years (at beginning of study period)				
Mean (range)	47.7	(20.8–71.7)	49.1	(4.4–82.3)
0–19, n (%)	0	0	9	(9.9)
20–39, n (%)	3	(16.7))	11	(12.1)
40–59, n (%)	12	(66.7)	43	(47.3)
≥60, n (%)	3	(16.7)	28	(30.8)
Sex, n female (%)	8	(44.4)	56	(61.5)
Residential farm distance, mean km (range)	4.3	(1.6–7.4)	5.1	(1.2–13.1)
Active smoking, n (%)	4	(22.2)	17	(18.7)

Table 2. Characteristics of questionnaire respondents, by testing outcome (positive vs. negative) and wave (wave 1 vs. wave 2)

Variable selection. We assessed association of Q fever status with sex, age, smoking habits, test ordered by GP versus specialty physician, and presence or absence of individual presenting signs and symptoms of disease in subjects pertaining to the first wave of testing using both univariate binary logistic regression and stepwise backward multivariate logistic regression. Variables that were statistically significantly associated with Q fever outcome ($p < 0.10$) in univariate and/or multivariate regression were used for derivation of our predictive models, as were sex, age, active smoking habits, and test ordered by GP versus specialty physician regardless of their association with outcome, given their role as potential confounders. Distance of residential address from the

outbreak farm was not included in model derivation, since this parameter would usually be unavailable to physicians at the time when patients present to their office, or may be unknown altogether in situations where no outbreak source has been identified.

Predictive model derivation. The first-wave dataset was randomly subdivided into four subsets containing equal numbers of questionnaire respondents each. One subset was set aside for cross-validation, while data from the remaining three subsets were used for derivation of our prediction model. To build the model, all variables selected according to the procedure described above were entered into backward stepwise binary logistic regression, retaining all variables with p values < 0.10 in the final model. Coefficients from the final model were used to calculate a sum score. To test and assess performance of our model, the sum score was applied to the validation subset, using the Area Under the Curve (AUC) of the Receiver Operating Characteristics (ROC). For additional validation, the same score was applied to the holdout sample from the second wave, again using AUC to assess performance of the model. The entire process was iterated for all four subsets, resulting in four cross-validated predictive models. Models were assessed and compared in terms of AUC, sensitivity and specificity (based on cut-points specific to each model, calculated according to the Youden index), and their positive and negative predictive values (based on an estimated regional seroprevalence of 2.9%, derived from comparison of two regional population samples, one pre-outbreak (2008) and the second one post-outbreak (2010).(1, 17) Areas under the ROC curves were assessed for statistical differences using a bivariate approach.(18, 19)

Results

Predictors of acute Q fever. Outcomes of univariate and multivariate binary logistic regression applied for the purpose of variable selection are summarized in Table 3 and 4, respectively.

Table 3
Univariate associations with Q fever outcome for adult respondents with complete questionnaire response

	B	S.E.	Wald	P	OR	95% CI	
						Lower	Upper
Signs and symptoms							
Fever	1.50	0.31	23.22	< 0.001	4.47	2.43	8.23
Pneumonia	1.42	0.30	22.43	< 0.001	4.12	2.29	7.41
Confusion	0.85	0.37	5.20	0.023	2.33	1.13	4.83
Flu-like illness	0.78	0.28	7.85	0.005	2.19	1.27	3.79
Night sweats	0.76	0.25	9.35	0.002	2.14	1.31	3.48
Weight loss	0.72	0.27	7.37	0.007	2.05	1.22	3.45
Severe fatigue	0.69	0.25	7.61	0.006	1.99	1.22	3.24
Headache	0.52	0.24	4.65	0.03	1.67	1.05	2.68
Chest pain	0.51	0.26	3.87	0.05	1.67	1.00	2.77
Abdominal pain	-0.81	0.28	8.13	0.004	0.45	0.26	0.78
Shortness of breath	0.40	0.25	2.64	0.10	1.49	0.92	2.41
Arthralgia	0.33	0.23	1.93	0.17	1.39	0.88	2.19
Stiff neck	0.12	0.24	0.24	0.62	1.12	0.71	1.79
Exanthema	0.06	0.28	0.04	0.84	1.06	0.62	1.82
Diarrhea	0.00	0.25	0.00	0.99	1.00	0.62	1.63
Jaundice	-0.65	0.70	0.85	0.36	0.52	0.13	2.07
Earache	-0.51	0.34	2.22	0.14	0.60	0.31	1.17
Ocular symptoms	-0.36	0.40	0.82	0.37	0.70	0.32	1.52
Cough	-0.31	0.24	1.66	0.20	0.74	0.46	1.17
Myalgia	-0.06	0.23	0.08	0.79	0.94	0.59	1.48
Demographics							
Age 40–59 vs. 20–39	0.67	0.31	4.60	0.03	1.96	1.06	3.61
Age ≥60 vs. 20–39	0.06	0.33	0.04	0.85	1.07	0.56	2.05
Sex	0.83	0.24	12.00	0.001	2.30	1.43	3.67
Residential farm distance	-0.02	0.05	0.17	0.68	0.98	0.90	1.08
Others							
Active smoking	0.42	0.25	2.77	0.10	1.52	0.93	2.48
Specialty physician vs. GP	1.35	0.34	15.57	< 0.001	3.85	1.97	7.53

Table 4
Multivariate associations with Q fever outcome for adult respondents with complete questionnaire response

	B	S.E.	Wald	P	OR	95%CI	
Sex	0.56	0.32	3.01	0.083	1.75	0.93	3.30
Age 20–39 vs. 40–59	0.82	0.33	6.33	0.012	2.26	1.20	4.27
Fever	1.56	0.41	14.71	< 0.001	4.77	2.15	10.59
Pneumonia	1.25	0.41	9.45	0.002	3.47	1.57	7.69
Confusion	1.14	0.56	4.14	0.04	3.12	1.04	9.32
Abdominal pain	-0.75	0.38	3.82	0.05	0.47	0.22	1.00
Cough	-0.62	0.35	3.09	0.08	0.54	0.27	1.07
Earache	-0.99	0.47	4.46	0.04	0.37	0.15	0.93
Constant	-1.80	0.46	15.24	< 0.001	0.17		

Table 3. Univariate associations with Q fever outcome for adult respondents with complete questionnaire response

Table 4. Multivariate associations with Q fever outcome for adult respondents with complete questionnaire response

Prediction models. Four cross-validated prediction models were derived from multivariate logistic regression on our dataset of questionnaire respondents from the first wave of testing. The final models, their coefficient-based sum scores, and the scores´ performance on the retained cross-validation samples from the first wave and the holdout sample from the second wave are summarized and compared in Table 5 and Fig. 2.

Table 5
Prediction estimates derived from multivariate logistic regression

	Model 1				Model 2				Model 3				Model 4			
	B	P	SE	OR	B	P	SE	OR	B	P	SE	OR	B	P	SE	OR
Variable																
Sex	1.13	< 0.001	0.33	3.09	0.66	0.04	0.32	1.94	0.56	0.08	0.32	1.75	0.91	0.01	0.32	2.48
Age 40–59 yrs					0.83	0.01	0.31	2.29								
Age ≥60 yrs	-0.91	0.01	0.37	0.40					0.82	0.01	0.33	2.26	-0.57	0.10	0.34	0.57
Active smoking					0.77	0.03	0.35	2.16	-0.62	0.08	0.35	0.54	0.87	0.01	0.34	2.39
Fever	0.83	0.07	0.46	2.30	1.24	< 0.001	0.38	3.45	1.56	< 0.001	0.41	4.77	1.25	< 0.001	0.38	3.48
Flu-like illness	0.98	0.02	0.41	2.66												
Pneumonia	1.24	0.00	0.38	3.45	1.02	0.01	0.40	2.78	1.25	0.00	0.41	3.47	1.43	0.00	0.42	4.16
Confusion	0.99	0.06	0.53	2.68												
Severe fatigue	0.59	0.10	0.36	1.81												
Abdominal pain	-1.15	0.01	0.42	0.32	-0.76	0.05	0.38	0.47	-0.75	0.05	0.38	0.47	-0.88	0.02	0.37	0.42
Earache	-1.02	0.04	0.49	0.36												
Chest pain					0.61	0.08	0.35	1.84								
Cough					-0.63	0.05	0.32	0.53	-0.99	0.04	0.47	0.37	-0.86	0.01	0.33	0.42
Headache									1.14	0.04	0.56	3.12	0.64	0.06	0.35	1.90
Constant	-2.42	< 0.001	0.56	0.09	-2.15	< 0.001	0.47	0.12	-1.80	< 0.001	0.46	0.17	-1.55	< 0.001	0.50	0.21
χ^2			71.00				52.00				65.00				67.00	
df			9.00				8.00				8.00				8.00	
P			< 0.001				< 0.001				< 0.001				< 0.001	
Nagelkerke R^2			0.37				0.28				0.34				0.33	
Hosmer & Lemeshow			0.69				0.46				0.81				0.71	
Classification accuracy			75.1%				71.8%				73.1%				73.1%	

Table 5. Prediction estimates derived from multivariate logistic regression

Figure 2 (legend)

[1]at cut-point calculated according to Youden index

[2]based on cut-point calculated according to Youden index and an estimated regional prevalence of 2.9%

The difference between model performance in terms of AUC was statistically significant between the least- and best-performing model in cross-validation (model 1 versus model 2, P = 0.02), but not between the least- and best-performing model applied to the holdout sample (model 4 versus model 3, P = 0.73). Comparing performance of each model on the cross-validation dataset versus the holdout sample (rows in Fig. 5) showed no statistically significant differences either.

Discussion

Our study suggests that signs and symptoms of disease do not predict acute human Q fever in GP patients, confirming earlier results from a Dutch study in hospitalized patients.(11) However, signs and symptoms may be useful in ruling out acute Q fever in favour of other acute lower respiratory tract infections. This is especially relevant in cases where pneumonia is not suspected and a non-prescribing or delayed prescribing approach would seem more appropriate, helping reduce the overuse of antibiotics. In the cohort of patients tested in our region, this would have been particularly relevant in the immediate post-outbreak phase where the number of tests for acute human Q fever remained high but the proportion of seropositive cases was very low (7%), and prevalence of pneumonia was also low (12%). Even during the outbreak phase, only 26.2% of tested individuals were positive, and ruling out acute Q fever by symptoms would likely have reduced overuse of antibiotics.

Male sex, fever, and pneumonia were positive predictors of acute Q fever across all four of our models, in accordance with other studies.(2, 20) Cough was a negative predictor in three models, suggesting that cough as a symptom may be particularly useful in ruling out Q fever in suspected cases. Cough is considered a common symptom in upper respiratory tract infections. Its presence, according to our findings, may point to respiratory conditions other than Q fever.(21) Specifically, cough has been described as a symptom suggestive of influenza, rather than, for example, common cold.(7) Overall, in our sample cough was the most prevalent symptom – second only to flu-like illness – in questionnaire respondents from the second wave, both in Q fever positive and Q fever negative subjects. This, combined with the low rate of Q fever positive findings during the second wave, may suggest that the rise in Q fever testing activity by GP's and specialty physicians during the second half of 2009 and the early months of 2010 may – at least to some degree – have resulted from patients presenting with respiratory symptoms due to increasing pandemic influenza A(H1N1)pdm09 activity in that period. Moreover, due to long persistence of anti-Coxiella phase II IgM following infection, some of the subjects who tested positive during the second wave may have been misclassified as acute Q fever. While abdominal pain was a negative predictor of acute Q fever across all four models, gastrointestinal symptoms such as abdominal pain and diarrhoea were much less prevalent than cough in both Q fever positive and Q fever negative subjects from both waves, and the nature of the observed negative association of abdominal pain with Q fever remains unclear. Studies on the gastrointestinal symptoms in patients with influenza report prevalence rates ranging from 0.6 to 6.6% for influenza A(H1N1) infections, and 9.8 to 57.5% for influenza A(H1N1)pdm09 infections, suggesting a possible association of gastrointestinal symptoms in our study with the 2009 swine flu.(22)

Use of signs and symptoms of disease to rule out acute Q fever would be most appropriate in patients with non-severe lower respiratory tract infections, i.e., in cases where pneumonia is not suspected clinically. In such cases, use of antibiotics has been shown to provide little benefit in primary care, both overall and in patients aged 60 years and above, but may cause slight harms.(23, 24) In cases with clinical suspicion of pneumonia, however, the benefit of antibiotics would outweigh potential harms. Whereas doxycycline is recommended only as a second line treatment for empiric management of community-acquired pneumonia (CAP) in several national guidelines, it is a first-line antibiotic in others, and generally considered to be safe and effective. Thus, in cases of lower respiratory tract infections where acute Q fever is included in the differential diagnosis and pneumonia is suspected, use of doxycycline would seem a perfectly justifiable choice.

Predictive values are greatly impacted by prevalence of the disease in the base population. Positive predictive values (PPV) tend to be low in situations where prevalence in the base population is low, as was the case in our study, where post-outbreak seroprevalence of prior exposure to C. burnetii in the base population was estimated a mere 2.9%.(1) With PPV ranging between 4.6% and 8.3%, mirrored by low areas under the Receiver Operator Curves, our models had no use as a diagnostic tool for acute Q fever. Conversely, negative predictive values (NPV) tend to be high under circumstances of low disease prevalence. With NPV ranging between 91.7–99.5%, our models were able to rule out the presence of acute Q fever with a relatively high degree of confidence. Nevertheless, decisions favouring a delayed or non-prescribing approach should ideally be corroborated by other clinical findings supporting such approach. In other contexts, for example in a well-circumscribed population of patients with high-risk exposure to a known source, prevalence may be (much) higher, with resulting decline in NPV.

To the best of our knowledge, ours is the first study to use post-outbreak data to validate prediction models for acute Q fever derived from outbreak data, thus enhancing the generalisability of our findings. Moreover, our study is first to assess the predictive potential of signs and symptoms for the diagnosis of acute Q fever in a large population of subjects most of whom were GP patients. Other studies attempting to predict Q fever by signs and symptoms, including a retrospective case-control study from the Netherlands, were performed in hospital settings. The Dutch study reported that clinical signs and symptoms were not helpful in differentiating adult hospital-referred patients with acute Q fever from a hospital-referred control group.(11) A second study aimed to predict Q fever in patients presenting with community-acquired pneumonia to the hospital. The only symptom independently associated with Q fever in this study was headache. The prognostic score derived from multivariate logistic regression included male sex, age 30–60 years, a low leukocyte count and a high C-reactive protein (CRP) level, along with headache, as predictors of Q fever pneumonia.(10) A third study attempted to predict acute Q fever in febrile patients from rural Kenya, based on parameters including a range of clinical signs and symptoms. The study identified acute lower respiratory infection, abdominal pain, diarrhoea and a history of fever lasting > 14 days as independent significant positive predictors of acute Q fever. A prediction score derived from a modelling approach similar to ours was reported to reliably identify acute Q fever in febrile patients with undifferentiated illness.(9)

Our study had a number of limitations. Selection of subjects for inclusion in our study was based on laboratory Q-fever testing outcomes rather than random sampling, with a potential for selection bias, e.g., due to variations in diagnostic strategies between individual physicians. Laboratory confirmed cases of acute Q fever and patients who were Q fever negative were both selected based on signs and symptoms leading to addition of Q fever in the differential diagnosis, possibly resulting in some weakening of the association under study. Our laboratory data were strictly limited to outcomes of Q fever testing, precluding us from assessing signs and symptoms in relation to possible alternative outcomes. As mentioned above, misclassification of positive laboratory results as acute Q fever infection cannot be entirely ruled out, since phase-II IgM antibodies to C. burnetii, which at the time of the outbreak were considered to be reliable markers of acute Q fever infection, have been shown to persist for longer periods in individual patients, thus complicating the differentiation between past Q fever infections and acute respiratory infections with different etiologies.(25) Cross-validation and testing of our models were performed on samples from the same base population, potentially compromising generalizability of our findings. Lack of external validation of our models, however, may

have partly been offset by the fact that we performed validation against a holdout sample, i.e., data from the second wave of Q fever testing. Testing during the second wave took place in what may be described as a immediate post-outbreak transition period where Q fever was increasingly replaced by other aetiologies of clinical respiratory disease, thus distinguishing the population of individuals tested during the second wave from those included in the first wave. Splitting our first-wave dataset for internal cross-validation may have resulted in loss of power, and may have contributed to discrepancies between our four models in terms of predictors included in each model. Nevertheless, all four models performed equally well in terms of their negative predictive value, suggesting they may be equally useful as predictive tools. Whereas the Youden index is a commonly used method for cut-point selection in ROC analysis, there a several other approaches, whose application may have led to different results.(26)

Conclusions

Our study suggests that signs and symptoms have no use as a diagnostic tool for acute Q fever, but may help rule it out. Classifying patients as Q fever negative, based on cut points from any of our models, may prompt a delayed or non-prescribing approach in primary care patients with non-severe presentation, and reduce overuse of antibiotics. We recommend further validation of our findings in different independent cohorts.

Abbreviations

AUC: Area Under the Curve, CAP: Community-Acquired Pneumonia, CRP: C-Reactive Protein, GP: General Practitioner, NPV: Negative Predictive Value, PCR: Polymerase Chain Reaction, PHS: Public Health Service, PPV: Positive Predictive Value, ROC: Receiver Operator Characteristic

Declarations

Ethics approval and consent to participate

This study was ethically approved by the medical ethics committee of the Maastricht University Medical Centre (number 104034).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

VH conceptualised and designed the study, collected, analysed and interpreted the patient data, and wrote the manuscript. ND and CH were major contributors in designing and conceptualising the study, and in writing the manuscript. All authors read and approved the final manuscript.

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Figures

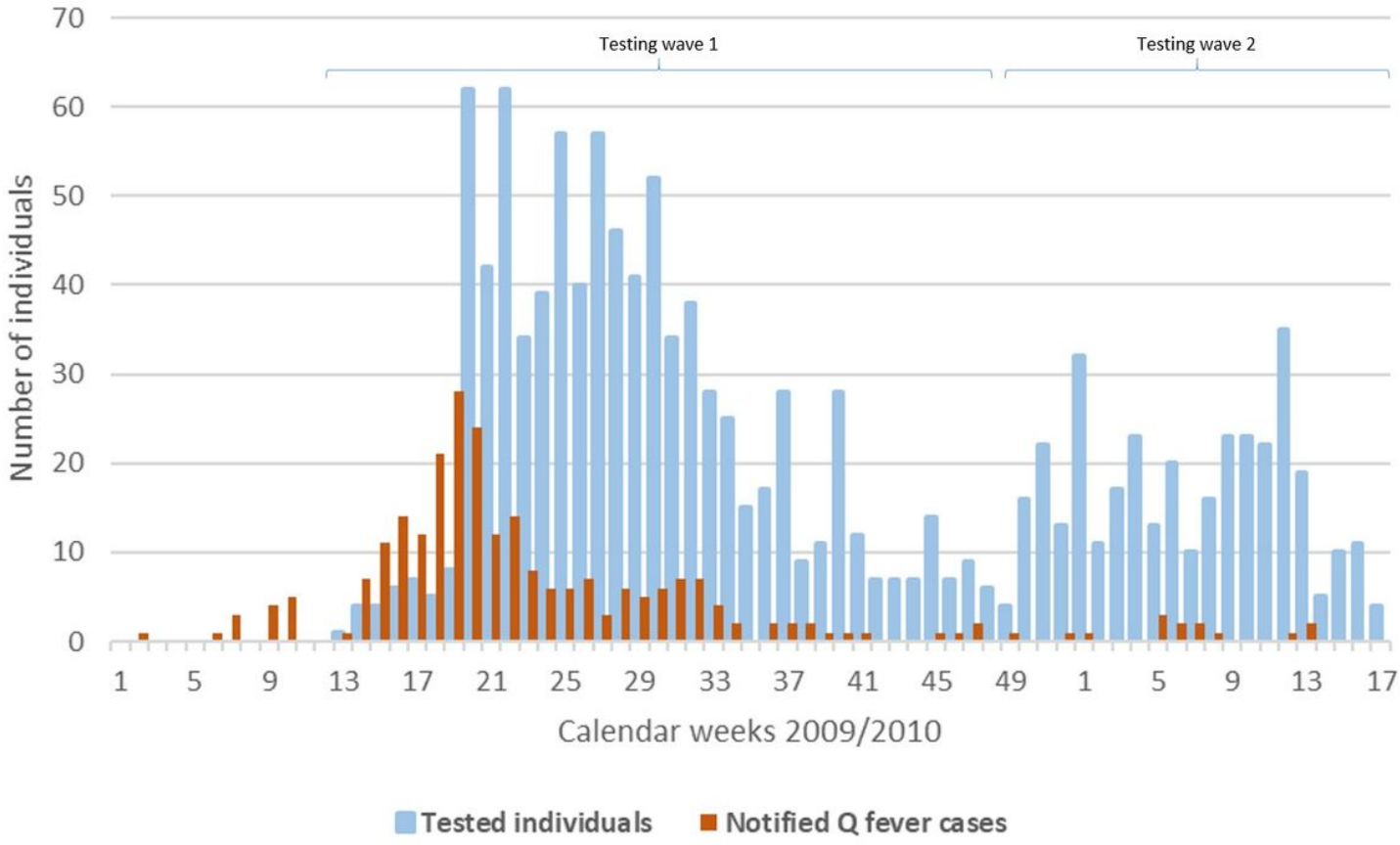


Figure 1

Weekly counts of all individuals tested for Q-fever by South Limburg GP's and specialist physicians, along with weekly counts of notified Q-fever cases (by GP-reported week of disease onset)

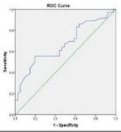
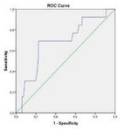
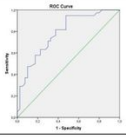
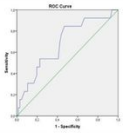
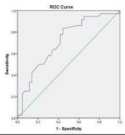
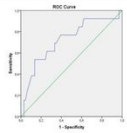
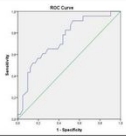
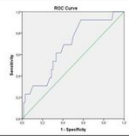
Cross-validation samples (wave 1)	Holdout sample (wave 2)
	
Model 1	
AUC = 0.671 (95%CI = 0.548-0.793) Sensitivity[1] = 55.6% Specificity[1] = 80.5% Positive predictive value[2] = 7.8% Negative predictive value[2] = 92.2%	AUC = 0.680 (95%CI=0.520-0.841) Sensitivity[1] = 69.2% Specificity[1] = 77.3% Positive predictive value[2] = 8.3% Negative predictive value[2] = 91.7%
	
Model 2	
AUC = 0.784 (95%CI = 0.683-0.885) Sensitivity[1] = 71.1% Specificity[1] = 70.0% Positive predictive value[2] = 6.6% Negative predictive value[2] = 93.4%	AUC = 0.683 (95%CI = 0.527-0.839) Sensitivity[1] = 84.6% Specificity[1] = 53.0% Positive predictive value[2] = 5.1% Negative predictive value[2] = 94.9%
	
Model 3	
AUC = 0.713 (95%CI = 0.599-0.827) Sensitivity[1] = 83.3% Specificity[1] = 55.8% Positive predictive value[2] = 5.3% Negative predictive value[2] = 94.7%	AUC = 0.719 (95%CI=0.558-0.880) Sensitivity[1] = 76.9% Specificity[1] = 60.6% Positive predictive value[2] = 5.5% Negative predictive value[2] = 94.5%
	
Model 4	
AUC = 0.743 (95%CI = 0.618-0.868) Sensitivity[1] = 91.3% Specificity[1] = 53.7% Positive predictive value[2] = 5.6% Negative predictive value[2] = 99.5%	AUC = 0.678 (95%CI = 0.527-0.830) Sensitivity[1] = 92.3% Specificity[1] = 42.4% Positive predictive value[2] = 4.6% Negative predictive value[2] = 95.4%

Figure 2

Predictive performance for the retained wave 1 cross-validation samples and the wave 2 holdout sample (legend) 1at cut-point calculated according to Youden index 2based on cut-point calculated according to Youden index and an estimated regional prevalence of 2.9%