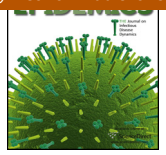
Epidemics 11 (2015) 1–6

Epidemics

journal homepage: www.elsevier.com/locate/epidemics



Exposure to low doses of *Coxiella burnetii* caused high illness attack rates: Insights from combining human challenge and outbreak data

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ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form
28 November 2014
Accepted 19 December 2014
Available online 31 December 2014

Keywords:
Q-fever
Coxiella burnetii
Outbreak
Dose response
Exposure estimates

ABSTRACT

Background: As a major zoonotic pathogen, characterization of the infectivity and pathogenicity of *Coxiella burnetii* is essential to understand Q-fever epidemiology.
Objectives: We want to extend a recently published human dose response model based on experimental challenge of young adult males to include other age groups and both genders. Additionally, we can estimate the spatial distribution of exposure based on observed outbreak data.
Methods: Dose response assessment based on human challenge, is extended by including outbreak data, using location of cases as a proxy for exposure. This allows estimation of the influence of age and gender on the probability of developing symptoms of acute respiratory illness.
Results: In an outbreak in Switzerland, in 1983, exposure to *C. burnetii* was shown to depend strongly on distance from the source. The susceptibility of males to develop Q-fever decreases with age, while in females, middle-aged women appear to have the lowest risk.
Conclusions: The published dose response model for Q-fever, based on experimental challenge of a small group of human volunteers, has been updated with data from a well studied outbreak. Infectivity estimates remain high, and even low doses (of 10 or fewer organisms) cause a high risk of illness.

Introduction

From 2007 to 2010, an epidemic of Q-fever in the Netherlands caused more than 3000 cases, due to *Coxiella burnetii* spreading from infected goat farms (Schimmer et al., 2010). Such large numbers of notified cases imply that a much higher number of infections must have occurred (van der Hoek et al., 2012), and that exposure may have been widespread. A recently published dose response relationship estimated the dose required for fifty percent of the exposed population to become infected (infd50) at 1.5 bacteria (0.75–38.7 95% credible interval (CI)), indicating high infectivity of *C. burnetii* via aerosol exposure (Brooke et al., 2013). These predictions were based on experimental challenge of adult male volunteers. Outbreak data from the Netherlands indicate that both age and gender may affect the risk of developing acute Q-fever (Schimmer et al., 2008). This is reflected in the published literature where males are 1.5–2.5 times as likely to be notified than females (van der Hoek et al., 2010; Karagiannis et al., 2009; Maurin and Raoult, 1999) and incidence increases with age and peaks in the 50–60 year age group (Schimmer et al., 2008; Maurin and Raoult, 1999). Therefore, the effects of age and gender on susceptibility for infection and acute illness must be quantified.

For every symptomatic case of Q-fever, there are many infections that are not notified. Published estimates of the incidence of seroconversion to notified cases ranges from 1.5 (Maurin and Raoult, 1999) to 62.5 (Kampschreur et al., 2013). During the outbreak in the Netherlands, a serological study in a high incidence region quantified the rate ratio between seroconversion in blood donors to the number of notified cases in the outbreak area at 12.6 seroconversions for each notified case (van der Hoek et al., 2012). However, the ratio of seropositives to notified cases may depend on the dose. Human challenge study results indicate that at lower doses individuals can become infected but, once infected, they are more likely to remain asymptomatic (Brooke et al., 2013).

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http://dx.doi.org/10.1016/j.epidem.2014.12.004

To quantify the effects of age and gender, a study should include individual patient data with information about infection status, illness status, age, and gender, as well as the applied dose. It would be impossible to implement such a design as a clinical trial. However, a well studied outbreak could provide a natural experiment, where health effects can be studied in a defined population exposed to *C. burnetii*. In the fall of 1983 a large outbreak of Q-fever took place in the Val de Bagnes, in the canton of Valais in Switzerland. During this outbreak 191 symptomatic cases and 224 asymptomatic cases were identified (Dupuis et al., 1987). This Swiss outbreak is the first documented point source outbreak of Q-fever as well as one of the most comprehensively studied outbreaks (Dupuis et al., 1987). Effort was undertaken to identify asymptomatic infections by means of a serosurvey. Serological screening of a major fraction (approximately 50%) of the exposed population identified many asymptomatic cases; demographic characteristics were collected by questionnaire, completed by all surveyed subjects. Direct observations of exposure are not available from this outbreak. However, because this was a point source outbreak, distance from the source could be used as a proxy for dose. We will show how this allows us to quantify exposure by village.

Combined epidemiological and serological data from the Swiss outbreak can be used to update the dose response model based on the human challenge study, to include age and gender in order to allow predictive studies of infection and illness in humans after exposure to *C. burnetii*.

Methods

On October 8 and 9, 1983 there was a market for alpine sheep on the soccer field of the Val de Bagnes high school in Le Châble, in the canton of Valais in Switzerland. The animals were brought down from the hills, auctioned and then sent to the new owners, about half of which were in different districts outside the study area. At the market and adjacent slaughterhouse 30 sheep were slaughtered (a known risk event), which was believed to be the primary source of *C. burnetii* in the valley. The outbreak was identified after eight concurrent hospitalized acute Q-fever cases had been notified. A large scale screening program was started 4–8 weeks later, after the peak of the epidemiological curve, approximately 2–3 months after the sheep market had been held. The community was approached and everyone in the valley was asked to provide a blood sample as well as fill in an epidemiological survey. The blood samples were screened for IgM phase 1 and 2 and IgG phase 1 and 2 using indirect micro-immunofluorescence (IF) as described in the original outbreak report (Dupuis et al., 1987). The IF test for IgM tested for the presence of phase 1 and 2 antibodies at levels of 1:20, 1:40, 1:80 and 1:160 while IgG was tested at levels of 1:40, 1:80 and 1:160.

Archived original data records from the outbreak were electronically entered at the regional hospital in Sion, Switzerland and cross-checked for errors, see Table 2. The data consist of birth year, gender, village of residence and location data, illness status, and serological markers. A symptomatic case is defined as any individual living in the valley, who was notified to the public health authorities and who had a known date for the onset of illness after the date of the animal market. Note that this includes any notified cases among the screened population.

Among screened subjects who were not notified cases, infection may be identified by serology. Two different categories of infected subjects were defined, based on serum antibody titers measured from the time of exposure until one year later:

- IgM positive (IgM^+) at least one observed titer of 1:20 or higher, for IgM phase I or IgM phase II.
- IgM positive or IgG positive (IgX^+) either IgM positive, or at least one observed titer of 1:40 or higher for IgG phase I or IgG phase II.

So that IgX^+ is a more inclusive definition of infection than IgM^+, see Fig. 1 (Table 1).

Table 1
Numbers exposed, infected and ill. Eight cases with missing age or gender information were excluded.

Age	Total	Sero-positive		Combined		Ill
		IgM^+	IgX^+	IgM^+	IgX^+	
0–19	601	3	8	33	38	30
20–39	630	10	26	92	108	82
40–59	428	10	28	48	66	38
> 60	253	6	15	28	37	22
	1912	29	77	201	249	172

Data overview: the numbers exposed (village residents), numbers screened and numbers classified as infected by serology: IgM positive (IgM^+), IgM and IgG positive (IgX^+). Also shown, right hand side: screened numbers combined with population data, including numbers notified with acute Q-fever, as used for the dose response assessment.

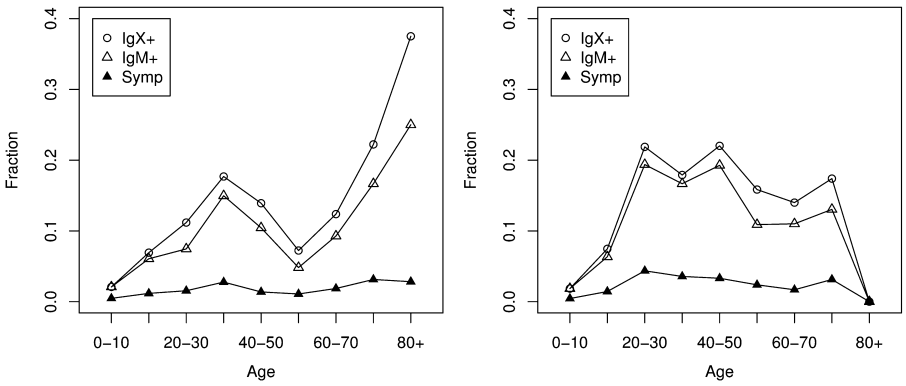
A negative screened case is an individual who is not a notified case and does not have a serological profile indicative of infection. Note that any resident of the valley who was not a notified case could have been asymptomatically infected. Demographic data for the entire valley were obtained from the 1980 census data from the Swiss Federal Statistics Office (S.F.S. Office, 2013).

Though dose was not quantified during the outbreak, the location of a resident can be used as a proxy for exposure. Increasing distance from the source of contamination is associated with decreasing exposure (Schimmer et al., 2010) as is suggested when viewing attack rates by village as a function of Euclidian distance from the presumed source (Fig. 2). Spatial kernel calculations used the locations of the center of gravity for each village, using building density as a proxy for population density. Required data were obtained from OpenStreetMap (www.openstreetmap.org) hosted by GeoFabrik (www.geofabrik.de) on November 11, 2013. The buildings in the valley were cross referenced with survey maps, which were gathered during the original outbreak, to ensure that all buildings were accounted for. Increase in population since 1980 has been predominantly in the valley's ski resort with no large development elsewhere in the valley. The Swiss national coordinate system CH1903 (SRID/EPSG 21781) was used for all spatial maps and calculations.

Based on the literature and exploratory logistic regression, effects of age and gender were included for illness but not for infection. The beta-Poisson dose response model for infection assumes that a volume V inhaled from a suspension of pathogens of concentration c results in exposure to a discrete random number of bacteria that is Poisson distributed with an expected value of cV. Heterogeneity in the host–pathogen interaction is taken into account by assuming a beta distributed conditional probability of infection (Teunis and Havelaar, 2000). The resulting dose response relation is

$$P_{\text{inf}}(cV|\alpha,\beta) = 1 - {}_1F_1(\alpha, \alpha+\beta; -cV) \quad (1)$$

where ${}_1F_1$ is a confluent hypergeometric function (Abramowitz and Stegun, 1965) and (α, β) are the parameters of the beta distribution describing heterogeneity. Infection may remain asymptomatic: a fraction of those infected may develop symptoms of acute illness, which may again depend upon dose (Teunis et al., 1999). To account for a dose dependent probability of symptoms we used the conditional dose response model proposed by Teunis et al. defining the



(a) Females (b) Males

Fig. 1. Fraction infected and symptomatic. Fraction of the screened population classified infected by serology: IgM positive (IgM$^+$), IgM or IgG positive (IgX$^+$). Also shown: fraction of the exposed population with symptoms of acute Q-fever (Symp).

probability of illness among those that are infected (Teunis et al., 1999).

$$P_{\text{ill}|\text{inf}}(cV|\eta,\rho) = 1-(1+\eta cV)^{-\rho} \tag{2}$$

with shape parameter ρ and scale parameter η (Teunis et al., 1999). Further, it is assumed that the scale parameter η is stratified by age and gender as

$$\log(\eta[i,j]) = \gamma_{a,s}[i,j] + \gamma_s[j]; \quad i=1,2,3,4; \quad j=1,2 \tag{3}$$

where $\gamma_{a,s}[i,j]$ represent scale parameters for age category i (0–19, 20–39, 40–59, 60 years and older), and gender j (female and male); $\gamma_s[j]$ is a gender specific offset term.

The spatial variation in exposure is modelled using a distance kernel that is proportional to a bivariate normal distribution with mean vector $\boldsymbol{x}_0 = (x_0, y_0)$ and covariance matrix

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_x^2 & \rho_{x,y}\sigma_x\sigma_y \\ \rho_{x,y}\sigma_x\sigma_y & \sigma_y^2 \end{pmatrix} \tag{4}$$

The mode at (x_0, y_0) is the estimated location where the highest exposure occurred, presumably near the source of the outbreak. Anisotropic exposure can occur because the two axes (σ_x, σ_y) may be different, and the orientation of the axes may be adjusted by the correlation coefficient $\rho_{x,y}$. The logarithm of the dose then changes with location as

$$\log(\text{dose}) = h_0 - \left(\frac{(X-x_0)^2}{\sigma_x} + \frac{(Y-y_0)^2}{\sigma_y} - 2\rho_{x,y}\frac{(X-x_0)}{\sigma_x}\frac{(Y-y_0)}{\sigma_y}\right) \tag{5}$$

where log(dose) is the (log) of the dose: the average number of bacteria inhaled by a subject at location (X, Y), h_0 is the peak dose at location (x_0, y_0).

Serological screening was not performed on all inhabitants of the valley. Therefore the probability of sampling an infected subject depends on the probability that that subject is screened. The probability of sampling an asymptomatically infected subject, P_{inf} from Eq. (1), is

$$P_{\text{inf,smpl}} = P_{\text{inf}}\frac{N_{\text{scrn},i}}{N_{\text{pop},i}} \tag{6}$$

where $P_{\text{inf,smpl}}$ is the fraction of asymptomatically infected (not notified) subjects in the screened population of a village, $N_{\text{scrn},i}/N_{\text{pop},i}$ is the fraction screened in any village i. For notified cases we assume that they do not depend on screening: the probability of observing a notified case is the same for screened subjects and subjects who were not screened.

Simultaneous estimation of parameters of the dose response relations for infection and illness including the effects of age and gender, and the spatial relation between village location and dose, was done by means of Markov chain Monte Carlo (MCMC).

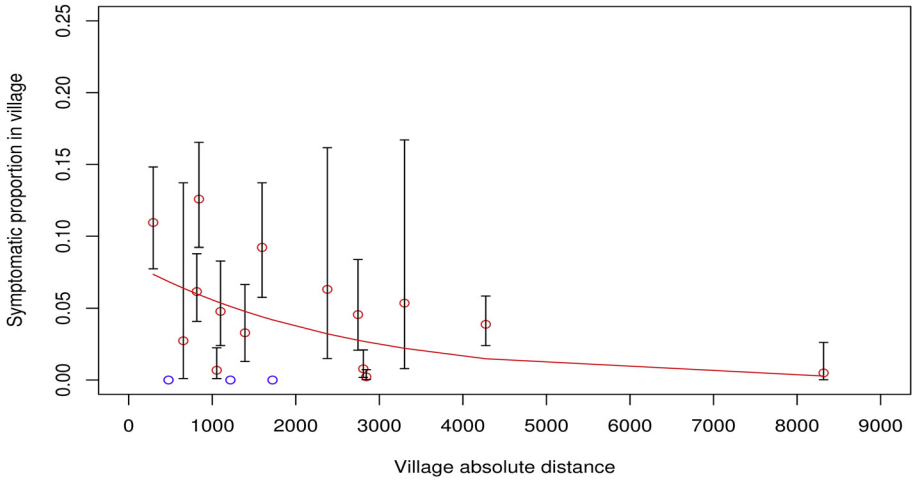


Fig. 2. The proportion symptomatic decreases with increasing distance from the putative source of exposure. The regression line is the fitted values of a logistic regression model with a significant ($p < 0.0001$) distance term. To indicate village size, 95% binomial confidence intervals are included except for villages with no cases, which are indicated in purple. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Outbreak data by village.

Village	Population	Screened		Symptomatic	
		All	<20	All	<20
Bruson	247	160 (65%)	24	2 (0.8%)	0
Le Châble	401	289 (72%)	81	25 (6%)	5
Champsec	169	60 (36%)	24	8 (5%)	1
Le Cotterg	173	120 (69%)	28	6 (3%)	1
Fionnay	140	2 (1%)	1	1 (0.7%)	0
Fontenelle	70	6 (9%)	3	0 (0%)	0
Le Fregnoley	32	3 (9%)	0	2 (6%)	0
Lourtier	482	302 (63%)	71	19 (4%)	7
Le Martinet	26	15 (58%)	6	1 (4%)	0
Medieres	117	6 (5%)	6	0 (0%)	0
Montagnier	299	127 (42%)	29	31 (10%)	2
La Montoz	43	5 (12%)	0	3 (7%)	0
Prarreyer	203	91 (45%)	31	10 (5%)	4
Sarreyer	343	136 (40%)	17	3 (0.9%)	0
Le Sappey	63	4 (6%)	4	0 (0%)	0
Versegeres	203	128 (63%)	49	19 (9%)	2
Verbier	772	176 (23%)	163	2 (0.3%)	0
Villette	316	290 (92%)	64	40 (13%)	8
	4099	1920 (47%)	601	172 (4%)	30

Data from outbreak in Val de Bagnes, Switzerland: Population exposed, population screened, and numbers notified with symptoms of acute Q-fever. For the screened population, total numbers and those younger than 20 years are shown.

The model was implemented in JAGS (v3.4.0) and run using rjags (v3-13) in R (v3.0.3), for source code see online supplement. Based on slow convergence of the human challenge model (Brooke et al., 2013), three chains were run for 10^7 iterations, after checking for convergence thinned chains (thinning factor 10^4) were merged and the resulting 3000 parameter samples used for further calculations. Calculations of spatial coordinates were performed with Quantum GIS (v1.8).

Results

The coverage of screening in all villages is 1920 out of 4099 (47%) across all age groups, see online supplement, Fig. S1. Among children, the proportion screened is an impressive 93% of all 10–15 year olds. Details on the numbers screened and infected are given in Table 1. The screened population is equally divided between men (664/1319 adults, 322/601 children) and women (647/1319 adults, 279/601 children). Median age of the included adult population was 40 years, mean age of 43 years, and range 20–99 years. Of the combined village population of 4099, 172 (3.5%) were notified cases, see Table 2.

Initially exploratory analysis was performed, using logistic regression, to test if age, gender, and distance along the two main axes (North–South and East–West) were predictive for infection or illness. Two interaction terms were included: age × gender and latitude × longitude. Backward selection for infection, interaction terms first, found no significant predictors for infection, see Table 3.

Table 4
Estimated maximum dose and location of peak exposure for two definitions of infection by serology.

	Peak exposure e^{h_0}	Latitude x_0 (km)	Longitude y_0 (km)
IgM^+	0.16 (0.13–0.25)	−0.31 (−3.67 to 4.14)	0.94 (−3.62 to 4.48)
IgX^+	0.27 (0.20–0.45)	−1.43 (−4.96 to 3.98)	1.39 (−3.38 to 4.71)

Median estimates of peak exposure (average number of infectious bacteria) and spatial coordinates of the exposure peak, and 95% interval.

Backward selection for illness, interaction terms first, found that both interaction terms were significant predictors for illness.

The full model therefore includes a spatial kernel to estimate exposure by village (location). Infection dose response is assumed independent of age and gender, but given infection, dose response for illness depends on age (category) and gender.

The exposure estimates by village show a clear dependence on distance from the source, see Fig. 4. The spatial kernel estimate for peak exposure is low, around 1 infectious bacterium or smaller, while the location of peak exposure is offset from the approximate location of the animal market where the source was located (Table 4). The contours of exposure are shown in Fig. 4.

The estimated 50% infectious dose of the combined outbreak and human challenge data is 0.71 (95% CI 0.70–0.74), independent of the definition of infection. The estimated dose causing 50% probability of (acute) illness increases with increasingly inclusive definitions of infection as explained below (Fig. 5). The IllD50 also depends on age and sex: in children it is highest; in female subjects the IllD50 increases with age, but in females above 60 it decreases again. In males the IllD50 increases from age 20 onwards.

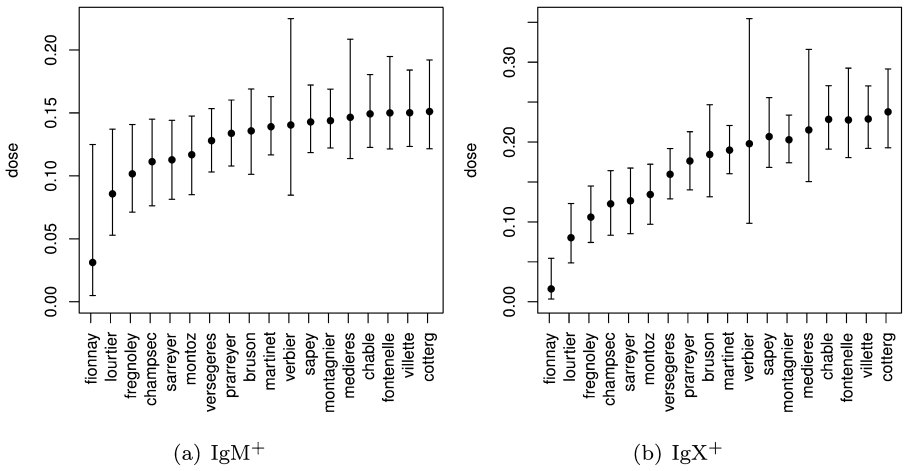
For children who may have been in a nursery or at school at the time of exposure, the location of their residence is not a suitable proxy for exposure as the animal market was held on the field next to the school. Therefore, in an initial analysis, all subjects under 20 years of age (601) were excluded, leaving 1319 screened subjects. Subsequently, all children were allocated to the village of Montagnier, near the location where the exposure occurred. The estimated doses by village, and the estimated infectivites and illness risks remained the same. Therefore, here only the results of the combined analysis including all children, are shown.

The size of the infected population is based on the results of serological screening. To investigate the sensitivity of the model to the screening criteria, two different definitions of infection were used (see Methods section). Using the more inclusive definition leads to a higher number of infected subjects, and thus the estimated doses increase (Fig. 3). Given the observed numbers of acute cases, the 50% infectious dose does not depend on the criteria for infection, but the dose required for 50% illness does, because the same numbers of acute symptomatic cases appear to occur at higher estimated doses (Fig. 5).

Table 3
Logistic regression results.

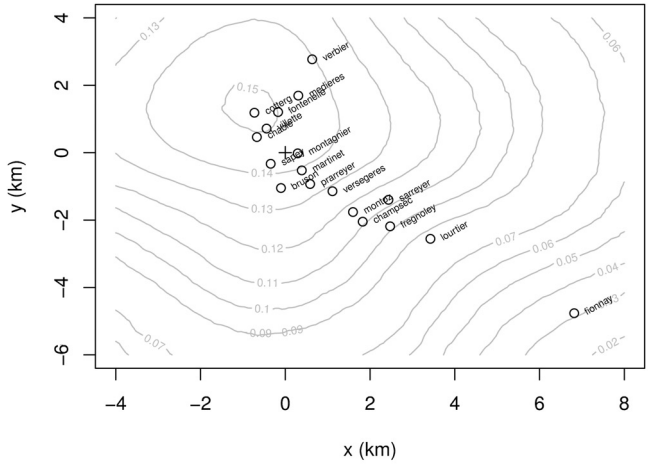
Parameter	Infection coefficients		Illness coefficients	
(Intercept)	−2.83	(−3.08 to −2.60)	−2.52	(−3.34 to −1.74)
Gender	–		1.61	(0.60–2.64)
Age	–		0.00	(−0.01 to 0.02)
Latitude	–		0.02	(−0.13 to 0.18)
Longitude	–		−0.30	(−0.65 to 0.05)
Gender × age	–		−0.03	(−0.05 to 0.00)
Latitude × longitude	–		0.27	(0.03–0.51)

GLM logistic regression coefficients with 95% confidence intervals of screened population 20 years and older. Backward selection of parameters indicated no age or gender effects on infection while illness GLM indicated significant effects for both age and gender.

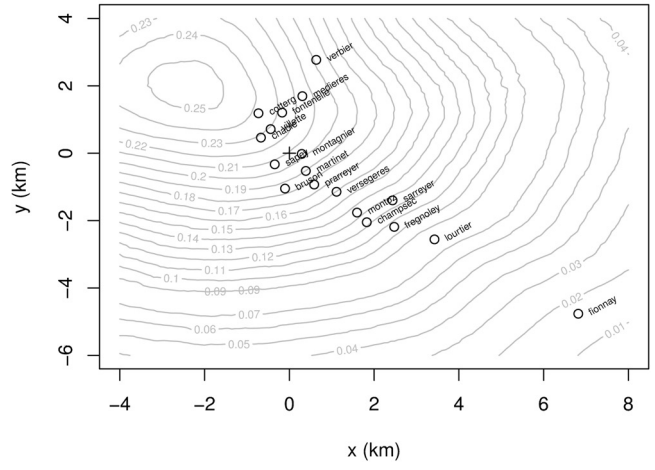


(a) IgM$^+$ (b) IgX$^+$

Fig. 3. Exposure estimates by village for different definitions of infection. Estimated median dose and 95% range. Villages are sorted by dose estimated for IgM$^+$ in both graphs, illustrating how both IgM$^+$ and IgX$^+$ produce the same ordering of doses, but with different magnitudes. For reference: distance from estimated source location to Cotterg 0 km (IgM$^+$); 2.3 km (IgX$^+$), and distance to Fionnay 9 km (IgM$^+$); 11.4 km (IgX$^+$).



(a) IgM$^+$

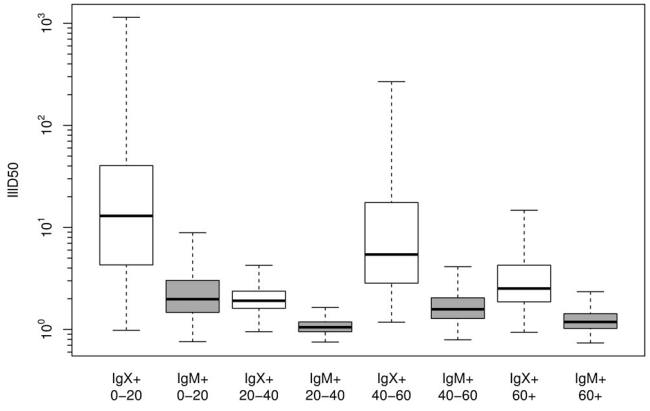


(b) IgX$^+$

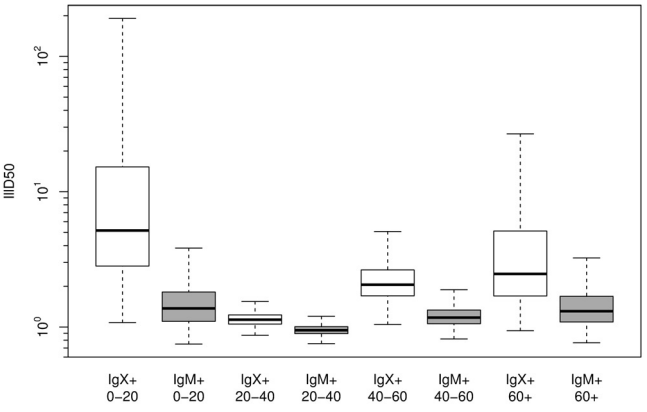
Fig. 4. Spatial distribution of exposure. Based on the distance kernel, infections defined as IgM$^+$ or IgX$^+$. The location of highest exposure is offset from the animal market (indicated by "+" at $(x, y) = (0, 0)$) see Table 4. Predicted doses were obtained by averaging from a posterior sample of parameter estimates, and shown as contours of equal individual exposure (average number of infectious bacteria inhaled by an individual at location (x, y)).

Discussion

To our knowledge this is the first quantification of *C. burnetii* exposure during an outbreak using epidemiological data and dose response modelling. It is also the first characterization of the effect of age and gender on human susceptibility to infection and illness.



(a) Females



(b) Males

Fig. 5. Boxplot of illness dose 50% by age and gender groups. (a) Age groups females; (b) age groups males. From left to right are the illd50% for the Swiss outbreak by age category with white boxes representing the IgX$^+$ scenario and the grey boxes representing the IgM$^+$ scenario.

Compared to the published studies on *C. burnetii* dose response relations (Tamrakar et al., 2011), the present results are better grounded in empirical data. Due to the inclusion of subjects from a wide range of ages, and both sexes, these new results are more generalizable than the published dose response relations in experimentally challenged young adult males (Brooke et al., 2013).

The risk of acute illness appears to depend on age and gender, Fig. 5. Males tend to be slightly more susceptible than females, who have a higher illD50%. In males, the illD50 increases with age, which is contrary to Dutch literature that identified the age group between 50 and 60 years as having the highest incidence. Females between 40 and 60 years of age appear to have a higher illD50 than younger women, but in women older than 60 the susceptibility increases again. The gender difference may be due to a protective effect of the female sex hormone beta-estradiol, which controls host responses to *C. burnetii* (Leone et al., 2004). Studies in blood donors show equal numbers of seropositives in both genders implying Q-fever infectivity may be equal in males and females, but the occurrence of clinical symptoms depends upon gender (Maurin and Raoult, 1999).

The comprehensive nature and quality of the 1983 Swiss outbreak data makes this analysis possible. Nonetheless, quantifying the number of asymptomatic (non-notified) infections remains difficult because these can only be observed using invasive methods like sampling of blood, which is especially difficult given the limited time available.

Different inclusion criteria for infected cases were tested, because of observations that some notified cases during the Dutch outbreak had only IgG positive serology after three months from onset of symptoms (Teunis et al., 2013). The infection estimates in the more inclusive scenario (IgX^+), provide higher doses that we consider more realistic than the highly selective scenario (IgM^+). The IgM^+ scenario is based on diagnostic protocols for acute Q-fever where high specificity is desired to reduce the probability of false positives. Both scenarios lead to similar age patterns of the illD50%, and to similar spatial exposure patterns.

Comparing the previously published dose response relations to the present results shows the effect of updating the dose response model with the Swiss outbreak data. The infD50% of the original study is 1.18 (95% CI 0.76–40.2) and the updated model changes this estimate to 0.71 (0.70–0.74). The median value is slightly lower, and the estimate is less uncertain than the previously reported estimate, see online supplement, Figs. S2 and S3.

The estimated location of the highest exposure is close to the known location of the animal market, supporting the assumption that this is the source that caused the outbreak. The small offset from the exact location of the market may be due to the effects of wind in the valley. A Western wind, following the direction of the valley South-Eastwards, is known to have been the predominant wind direction during the exposure period. In the Netherlands distance has been shown to be a predictor for the illness risk (Schimmer et al., 2010; van Leuken et al., 2013). Studies working on environmental effects on aerosol dispersion could provide additional information regarding the relationship between aerosol exposure, environmental factors and infection rates.

The current analysis does not include any environmental determinants regarding the dispersion of airborne particles in the valley. The spatial distribution of exposure has been determined from the spatial distribution of infected and symptomatic subjects only. The results are consistent with the assumption that the slaughter house and market are the main source of exposure but there might be residual exposure resulting from the herding of infected animals from the fields. The wind in the valley may affect the dispersion; altitude may also play a factor as villages higher up the sides of the valley might be less likely to be exposed compared to villages at the base of the valley. It is interesting that the estimated spatial dispersion parameters (σ_x and σ_y, in Table 4) are of the same order of magnitude as parameter values used in atmospheric dispersion modelling Hanna et al. (1982).

The results from this study may be used in risk studies, to translate exposure estimates into risk of infection and acute respiratory illness, and to define acceptable levels of exposure near environmental sources of *C. burnetii*.

Acknowledgments

This work is funded by ZonMW (http://www.zonmw.nl) project number 205520010. We thank Jeroen van Leuken for assistance in calculations of spatial coordinates.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2014.12.004.

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