Received: 17 January 2018 | Accepted: 8 October 2018

DOI: 10.1111/zph.12534

REVIEW

WILEY

# A systematic knowledge synthesis on the spatial dimensions of Q fever epidemics

Myrna M. T. De Rooij[1*] | Jeroen P. G. Van Leuken[2*] | Arno Swart[2] | Mirjam E. E. Kretzschmar[2,3] | Mirjam Nielen[4] | Aline A. De Koeijer[5] | Ingmar Janse[2] | Inge M. Wouters[1] | Dick J. J. Heederik[1]

[1]Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands

[2]Centre for Infectious Disease Control (CIb), National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[3]Julius Centre, University Medical Centre Utrecht (UMCU), Utrecht, The Netherlands

[4]Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

[5]Central Veterinary Institute, Wageningen University and Research Centre, Lelystad, The Netherlands

**Correspondence**
Myrna M. T. De Rooij, Institute for Risk Assessment Sciences (IRAS), Utrecht University, Utrecht, The Netherlands.
Email: m.m.t.derooij@uu.nl

**Funding information**
ZonMW, Grant/Award Number: 50-51800-98-035

## Abstract

From 2007 through 2010, the Netherlands experienced the largest Q fever epidemic ever reported. This study integrates the outcomes of a multidisciplinary research programme on spatial airborne transmission of *Coxiella burnetii* and reflects these outcomes in relation to other scientific Q fever studies worldwide. We have identified lessons learned and remaining knowledge gaps. This synthesis was structured according to the four steps of quantitative microbial risk assessment (QMRA): (a) Rapid source identification was improved by newly developed techniques using mathematical disease modelling; (b) source characterization efforts improved knowledge but did not provide accurate *C. burnetii* emission patterns; (c) ambient air sampling, dispersion and spatial modelling promoted exposure assessment; and (d) risk characterization was enabled by applying refined dose–response analyses. The results may support proper and timely risk assessment and risk management during future outbreaks, provided that accurate and structured data are available and exchanged readily between responsible actors.

**KEYWORDS**
airborne exposure, *Coxiella burnetii*, epidemiology, Q fever, risk assessment, spatial analysis

## 1 | INTRODUCTION

From 2007 through 2010, the Netherlands experienced the largest Q fever epidemic ever reported with over 4,000 identified human cases and 74 deaths (Dijkstra et al., 2012; Rijksinstituut voor Volksgezondheid en Milieu, 2017). Q fever is mainly caused by a respiratory infection with *Coxiella burnetii* bacteria (Angelakis & Raoult, 2010). Health effects include mild respiratory symptoms, pneumonia, hepatitis, endocarditis and fatigue (Dijkstra et al., 2012). Besides the epidemic in the Netherlands, outbreaks have occurred worldwide, including other European countries (Brouqui, Badiaga, & Raoult, 2004; Gilsdorf et al., 2008; Gyuranecz et al., 2014; Jorm, Lightfoot, & Morgan, 1990; King et al., 2011; Lyytikäinen et al., 1998; Manfredi Selvaggi et al., 1996; Martinov, 2007; Medic et al., 2005; Porten et al., 2006; Tissot-Dupont, Amadei, Nezri, & Raoult, 2005; Wallensten et al., 2010), the United States (Biggs et al., 2016) and Australia (Bond et al., 2016; O'Connor, Tribe, & Givney, 2015).

In the Netherlands, dairy goats (and sheep) were associated with human infections (Roest et al.., 2010). It was suggested that mutations in the predominant *C. burnetii* strain led to a changed antigenic profile, which increased virulence and—as a consequence—led to increased susceptibility of the human population (D'Amato et al., 2014; Tilburg et al., 2012).

[a]These first authors contributed equally to this article.

The number of Q fever notifications recurrently peaked in spring and expanded both geographically and temporally over years (Dijkstra et al., 2012). From December 2009, >50,000 pregnant goats and sheep from 88 bulk tank milk positive commercial farms were culled; all other goats and sheep from commercial farms were vaccinated, resulting in a sharp decrease of case notifications (Roest et al., 2010). The epidemic caused approximately 5,800 Disability Adjusted Life Years (DALYs), mainly because of the Q fever fatigue syndrome (Brooke, Lier, Donker, Hoek, & Kretzschmar, 2014). Clearly, the impact on society and farmers was major. The epidemic drew considerable media attention with national and regional public health authorities being viewed as largely unprepared (Van Dijk et al., 2010).

From 2011 through 2015, a multidisciplinary research programme was conducted to increase knowledge on airborne *C. burnetii* transmission in the outdoor environment. It included air sampling, atmospheric dispersion modelling and dose–response analyses (Figure 1).

**Impacts**

- Insights on the spatial aspects of *Coxiella burnetii* (bacterium that causes Q fever) have increased as a result of synthesis of studies focusing on transmission during Q fever outbreaks.
- More effective risk assessment tools have been developed in response to the largest Q fever epidemic ever reported which occurred in the Netherlands.
- Results support proper and timely risk management and risk communication during future Q fever outbreaks.

This study aims at (a) synthesizing the outcomes of the multidisciplinary programme and other studies performed worldwide on airborne transmission of *C. burnetii*; (b) providing a synopsis of

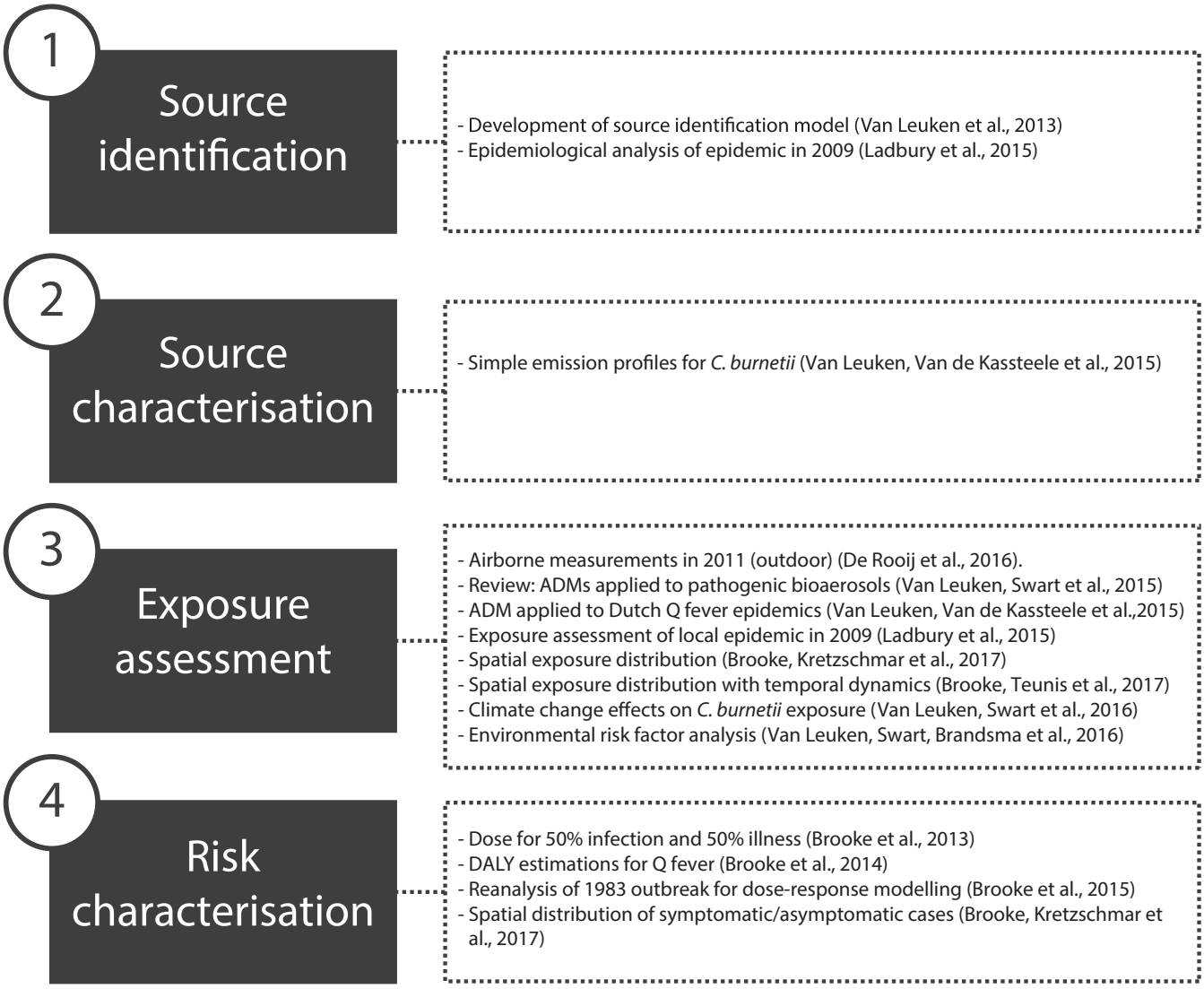


**FIGURE 1** Overview of publications of studies performed as part of the multidisciplinary research programme following the four steps of quantitative microbial risk assessment (QMRA)

obtained knowledge and remaining knowledge gaps with respect to airborne transmission, exposure and dose–response modelling; and (c) presenting recommendations to improve rapid and informed decision-making and initiation of efficient investigations during future Q fever outbreaks.

## 2 | METHODS

The findings of the various studies within the multidisciplinary research programme were structured following the approach of Quantitative Microbial Risk Assessment (QMRA), with sections on source identification, source characterization, exposure assessment and risk characterization (see Figure 1 for all publications of this programme). In order to reflect the outcomes with other publications on the Dutch Q fever epidemic of 2007–2010, two systematic literature reviews were conducted. The focus of the first literature search was specifically on papers of the Dutch Q fever epidemic. The focus of the second literature search was on airborne spread of *C. burnetii* during Q fever epidemics that have occurred in other parts of the world, in order to obtain a full overview of knowledge on spatial aspects of *C. burnetii* transmission. This was then combined with the outcomes of the QMRA of the Dutch epidemic to synthesize current knowledge and discuss insights gained.

All articles obtained via the systematic literature searches were scanned regarding title, abstract and keywords. See Supporting Information Data S1 and S2 for a full description of the search queries and criteria. The first search strategy yielded 234 publications (see Supporting Information Data S1 and Table S1). The majority of the peer-reviewed publications were published from 2011 onwards in the aftermath of the epidemic (88.0%) (Supporting Information Figure S1). Most peer-reviewed publications included microbiological or epidemiological analyses (71.8%) (Supporting Information Figure S2).

The second search strategy provided 258 publications, of which 52 publications remained for full-text screening. The majority of these (67%) described various (small-scale) outbreaks amongst humans that had occurred worldwide, of which half discussed the Dutch Q fever outbreak (see Supporting Information Data S2).

## 3 | QUANTITATIVE MICROBIAL RISK ASSESSMENT OF THE DUTCH Q FEVER EPIDEMIC

### 3.1 | Source identification

#### Early investigations

Until 2007, Q fever cases were notified sporadically in the Netherlands (Karagiannis et al.., 2009). Annually, there were about 5–20 registrations, the size of the Dutch population stayed in the same order of magnitude over time (11.5 million inhabitants in 1960 – 16.4 million inhabitants in 2007). In 2007, two atypical clusters of pneumonia cases were observed in the province of Noord-Brabant. Most cases were later diagnosed with acute Q fever (178 cases that year) (Karagiannis et al., 2009). A causal link with dairy goats was suspected, since *C. burnetii* infections were observed in goats at nearby farms (Van den Brom & Vellema, 2009). An investigation amongst 515 persons in 2008 revealed that airborne *C. burnetii* spread from a nearby farm was likely (Karagiannis et al., 2009). This was later confirmed by epidemiological investigations linking cases to large dairy goat farms (Brandsen-Schreijer et al., 2010; Hackert et al., 2012; Schimmer et al., 2010). A major predictor was the distance between cases' residential addresses and infected farms (Karagiannis et al., 2009). This was also concluded in other studies: (a) serum samples of 2,004 pregnant women living in the Q fever area confirmed a relation between positive antibody titre and proximity (Van der Hoek, Meekelenkamp, et al., 2011); (b) a risk factor analysis based on goat serum samples from 123 farms showed that presence of another positive dairy goat farm within 8 km was a risk factor (Schimmer et al., 2011); (c) a human population-based study with medical record data resulted in a clear distance–response relationship for Q fever (Smit et al., 2012); (d) humans living within 2 km from a positive farm had much higher risks of developing disease than those living further than 5 km from a positive farm (relative risk 31.1; Schimmer et al., 2010); and (e) spatial analyses detecting clusters of both infected farms and human cases (Commandeur, Jeurissen, Hoek, Roest, & Hermans, 2014). A radius of 5 km was later adopted in several scientific studies and policy advices (Dijkstra et al., 2012), despite a considerable residual risk at larger distances (Smit et al., 2012).

#### Genome sequencing and modelling techniques

The usual approach for assessing links between potential sources and infectious disease occurrence is based on isolation and characterization of cultivated strains from cases and suspected sources. Microbiological and molecular testing has the potential to reveal similarities between environmental or veterinary samples and human isolates. Examples of molecular typing techniques include multispacer sequence typing (MST) and multiple locus variable number of tandem repeats analysis (MLVA). These techniques are developing rapidly and increasingly facilitate rapid source identification. However, molecular testing can still be time-consuming in the case of many suspected sources. A (probable) link to goats and sheep based on MLVA genotyping was not established until the aftermath of the Dutch epidemic (Tilburg et al., 2012).

Rapid decision-making during outbreaks might be improved by using modelling techniques to gain more insight into the likelihood of putative sources being positive. Modelling techniques can help narrowing down the involved source type (e.g., goats or cattle) and by constricting the area in which sampling should be performed. This has been illustrated by Van Leuken et al. (2013), who retrospectively showed that source identification could have been facilitated by relating Q fever incidence to farm proximity based on six-digit zip codes of notified cases and a population density database. The authors retrospectively analysed three distinct Q fever outbreaks in 2009, all with suspected exposure from one large dairy goat farm.

An exponential incidence-distance model was fitted on a spatial grid. The model predicted the likelihood that a source was located at each individual grid cell based on the spatial distribution of cases and non-cases. The three suspected goat farms all ranked first amongst all regional commercial dairy goat farms. This indicates that the number of putative sources to be investigated by microbial testing can be rapidly reduced by modelling. Major advantages of this method include its statistical robustness as compared to attack rate analyses (Brandsen-Schreijer et al., 2010; Hackert et al., 2012; Schimmer et al., 2010), and the limited amount of data and calculation time required. Nevertheless, it should be noted that these strong findings resulted partly from the spatial distribution of infected cases in both rural and urban areas. The present model is not applicable in urban areas when the number of cases is low. Therefore, the model should be tested in different outbreak situations and with other airborne pathogens to explore its applicability under different circumstances.

Van der Hoek, Kassteele, et al. (2012) developed a technique which rapidly produced high-resolution Q fever incidence maps based on six-digit zip code observations adjusted for population clusters (cities and villages) by smoothing. These clearly showed Q fever hotspots around infected dairy goat farms. Such maps could be very useful to detect separate clusters and to (roughly) attribute cases to putative sources.

### Manure as a potential source

Application of goat manure was suggested as another potential source of exposure. From June 2008, it was prohibited to remove manure from stables of positive farms, and from 2009, a stringent hygiene protocol became mandatory for manure handling (Roest et al., 2010). *C. burnetii* DNA has been detected in manure samples (De Bruin et al., 2012; Van den Brom et al., 2015), likely as a result of contamination by birth products (Roest et al., 2012; Van den Brom et al., 2015). Its association with Q fever in humans was investigated as well (Hermans, Jeurissen, Hackert, & Hoebe, 2014; Van den Brom et al., 2015). However, convincing evidence for the contribution of manure to the occurrence of Q fever was not found in particular because of methodological limitations of the performed studies, including lack of adjustment for sources other than manure (presence of farms keeping goats) and limited statistical power.

## 3.2 | Source characterization

### Investigations at farms during the epidemic

*Coxiella burnetii*-infected ruminants may excrete up to one billion bacteria per gram of placenta during parturition (Arricau Bouvery, Souriau, Lechopier, & Rodolakis, 2003). Clinical signs of *C. burnetii* in animals include abortion and other reproductive disorders (Angelakis & Raoult, 2010). Data collection on farms was non-systemic during the whole epidemic until the very end. Q fever became a notifiable animal disease only from June 2008 onwards (Van Dijk et al., 2010). Then, reporting of occurrence of abortion waves (defined as ≥5% of births aborted in a herd) became mandatory. In the period from 2005 to 2008, abortion waves were reported 23 times (thus voluntarily made notifications; Van den Brom & Vellema, 2009; Wouda & Dercksen, 2007).

In 2008, a study was performed collecting vaginal and stable swabs at 29 commercial dairy goat farms (7.4% of total number commercial dairy goat farms in 2008) (De Bruin et al., 2011). Approximately 50% of the collected samples contained *C. burnetii* DNA as detected by qPCR (De Bruin et al., 2011).

Infrequent bulk tank milk screening based on voluntary participation of farmers started in 2008 (Van den Brom et al., 2012). Then, 74% of all commercial dairy goat farmers (defined as more than 200 dairy goats) and 40% of all dairy sheep farmers participated (Van den Brom et al., 2012). Approximately 30% of the 392 bulk tank milk samples were positive. Less than 5% of the farms contained high levels of *C. burnetii* DNA (defined as more than 10,000 bacteria per ml) in the bulk tank milk sample based on the qPCR results. These results contributed to the implementation of a national mandatory bulk tank milk screening programme starting October 2009, the start of systemic data collection on all farms. Results of this screening showed that many farms (55) were positive (Van Dijk et al., 2010). These results, that became available at the beginning of December, led to the start of the culling of goats at infected farms at the end of December 2009.

### Sampling in the aftermath

Sampling of stables and the outdoor environment started only at the end of the epidemic. Results from stable and indoor dust samples collected at 19 dairy goat farms, further supported the hypothesis that contaminated dust and aerosols from positive farms played a role in human exposure (De Bruin et al., 2012). In 2010, shortly after implementation of mandatory culling and vaccination, *C. burnetii* DNA was detected at affected farms in settled dust samples and airborne dust samples (inhalable fraction and particulate matter smaller than 10 μm [PM10]; duration of sampling 4 hr; Hogerwerf et al., 2012).

In 2012, a study was performed at five goat farms of which three were affected by the culling measures 2 years earlier (see Supporting Information Data S3). Weekly averaged (sampling for 15 min of each hour during 7 days) indoor and outdoor PM10 samples were collected repeatedly during 3–4 months beginning prior to the kidding season. The percentage of positive samples ranged from 36%–100% (indoor) and 10%–27% (outdoor) in farms affected by culling. At the farms where no culling had taken place, these percentages were lower: 7%–22% (indoor) and 0%–23% (outdoor). However, the concentrations were too low to make inferences about the number of bacteria, and no clear temporal patterns and associations with kidding numbers were found.

Thus, even though all farms had a negative bulk tank milk status during the measurement period and despite vaccination of goats for 2 years, *C. burnetii* was still detected in indoor and outdoor air. As bulk tank milk tests were developed to detect within-herd

prevalence of minimally 15% (van den Brom et al., 2012), *C. burnetii* positive animals could have been present on bulk tank milk negative farms, thus possibly explaining these findings.

### Intraherd transmission modelling

A dynamic compartmental herd transmission model, containing multiple infectious states, was developed to simulate infection dynamics within a goat herd (Hogerwerf et al., 2013). The model was based on an infection dynamics model of *C. burnetii* in a French cattle herd (Courcoul et al., 2011; Courcoul, Vergu, Denis, & Beaudeau, 2010; Taurel, Guatteo, Joly, Seegers, & Beaudeau, 2011). The occurrence of abortion waves was largely explained by the herd's demographic characteristics. The model generated relative amounts of bacteria emitted to the bulk tank milk and the stable environment.

However, neither this modelling attempt nor the sampling campaign within goat farms resulted in quantified emission rates, which are required to predict exposure levels and infection risks based on dispersion models. Therefore, Van Leuken, Swart, et al. (2015) defined three simple emission profiles to model exposure (see Section 2.1.3). These included two steady-state (constant in time) profiles and a log-normally shaped profile based on the epidemic curves of outbreaks.

### Attempts to assess inter-herd transmission

Attempts were made to identify risk factors for transmission of *C. burnetii* between goat herds (Schimmer et al., 2011), sheep herds (Schimmer, Lange, Hautvast, Vellema, & Duijnhoven, 2014) and dairy cattle herds (Van Engelen et al., 2014). Efforts were made to gain insight in direct transmission, via direct contact (e.g., via exchange of infected animals/materials) as well as indirect transmission. Proxies for direct transmission were identified (e.g., number of animal supply addresses; Schimmer et al., 2014; Van Engelen et al., 2014), origin of straw (Schimmer et al., 2011) and indirect transmission (e.g., distance to nearest infect farm (Schimmer et al., 2011), farm region (Schimmer et al., 2014) and animal density (Schimmer et al., 2011).

No further retrospective insight was gained due to a lack of data on top of a complex situation involving various transmission routes. Not only indirect transmission played a role in the epidemic, but also direct transmission was able to contribute until October 2009, as then a transport ban of animals from infected farms was implemented (Van Dijk et al., 2010). There is a lack of data availability on source level during the whole epidemic, except for the very end (see the aforementioned section on "Investigations at farms during the epidemic"). Until the end of 2009, *C. burnetii* screening in bulk tank milk was not standard and unnoticed infection of animals is known to occur.

Likely transmission of *C. burnetii* between herds already took off four years before the peak of the epidemic. In 2005, remarkable abortion waves amongst goats linked to *C. burnetii* were observed on two farms (Wouda & Dercksen, 2007). This was endorsed by findings of Van den Wijngaard et al. (2011) who concluded that *C. burnetii* was a plausible cause for four human clusters of lower respiratory infections in the period 2005—beginning of 2007.

## 3.3 | Human expose assessment

During the epidemic, most studies focussed on source identification and/or characterization of sources. After the epidemic, the research focus shifted to the assessment of human exposure assessment and risk characterization. Several initiatives were launched to assess the exposure of humans to *C. burnetii*, namely exposure sampling, atmospheric dispersion modelling and spatial statistics.

### Environmental sampling

*Coxiella burnetii* DNA was observed in 63% of the aerosol samples (unspecified dust fraction) taken at distances of 500–2,000 m from positive goat farms in 2009 and 2010 (De Bruin et al., 2013). Quantitative PCR analyses using single and multicopy targets (varying number of copies per strain) were performed; however, the majority of positive samples were below the limit of quantification. Furthermore, the limited number of samples, unspecified dust fraction and short averaging times (10 min) hampered quantitative assessment of exposure to *C. burnetii* DNA. Outdoor air samples collected from June through November 2010 (which was at the end of the epidemic) were retrospectively analysed to assess *C. burnetii* levels. Weekly averaged (sampling for 15 min of each hour during 7 days) air samples (particulate matter 10) were collected at six locations, at distances ranging from 1.4 to 7.6 km of goat farms (Heederik et al., 2011). *C. burnetii* DNA was present in 15% of the collected air samples.

In 2011, a large sampling campaign was performed in order to assess *C. burnetii* exposure in ambient air (De Rooij et al., 2016). Weekly averaged (sampling 30 min per hr, during 7 days) PM10 samples were collected from March through September 2011 at eight locations, each within 600 m from a goat farm. *C. burnetii* DNA was detected in 28% of all samples, albeit in the non-quantifiable range. Occurrence of positive samples was mostly in spring, corresponding with the kidding season. The nearby goat farm was spatially associated (distance to that nearby farm combined with numbers of goats on that farm) to the detection of *C. burnetii* in air samples. These findings thus suggested that goat farms still contributed to the *C. burnetii* load in the ambient air in 2011, thus after the nation-wide implementation of measures like culling and vaccination. Looking at the findings from a more general perspective, then these imply that a timely and well-designed airborne sampling campaign may contribute to source identification.

### Atmospheric dispersion modelling

An atmospheric dispersion model (ADM) is a mechanistic model simulating particle, including bioaerosol and gas dispersion through the atmosphere as a function of meteorological conditions, either retrospectively with observational meteorological data or prospectively

with weather forecast data (Van Leuken, Kassteele, et al., 2015; Van Leuken, Swart, et al., 2015). Three local Dutch outbreaks were retrospectively analysed to assess the correlation between observed incidence rates and ADM modelled *C. burnetii* exposure. Annual cumulative exposure levels were correlated to spatial information on incidence rates at the six-digit zip code level, based on two steady-state emission profiles and a log-normal emission profile related to the observed epidemic curves. Exposure levels based on the meteorological model were compared to a null model (with no spatial predictive information) and a model with decreasing concentrations as a function of distance to the source. The modelled ADM-concentrations based on steady-state emission profiles correlated better to the incidence rate data than the concentrations of the two simple non-meteorological models. Moreover, modelled cumulative concentrations appeared to be correlated to timing of disease (Ladbury et al., 2015).

In addition, Van Leuken, Swart, Brandsma, et al. (2016) investigated in a simulation study the effects of climate change on airborne *C. burnetii* concentrations under non-outbreak conditions. Five climate scenarios to wind speed, temperature, precipitation and global radiation were included for the periods 2016–2045 and 2036–2065. Modelled future concentrations were compared to concentrations based on meteorological data from 1981 to 2010. Results suggest that due to climate change, the dispersion profile altered, resulting in on average decreased modelled concentrations at a single receptor point, but with large hourly variation. Changed wind speed and global radiation (related to horizontal and vertical dilution, respectively) contributed most.

### Spatial epidemiological analyses

Next to atmospheric dispersion modelling, the spatial exposure distribution of *C. burnetii* and its impact on the distribution of symptomatic and asymptomatic cases were calculated by a novel spatial statistical model (Brooke, Kretzschmar, et al.,2017 ). The spatial distribution of 200 notified cases in an at-risk population was translated into a smooth spatial field of dose.

The Q fever hotspot area was situated in the south of the Netherlands. However, a considerable number of goat farms in other parts of the country were positive too, whereas the number of notified human cases in these regions was limited. Therefore, several hypotheses arose including a high heterogeneity in shedding rates amongst farms (Schimmer et al., 2011), regional diversity in Q fever awareness (Dijkstra et al., 2012), presence of multiple *C. burnetii* strains with different virulence and/or the effect of environmental conditions on *C. burnetii* transmission.

Van der Hoek, Hunink, Vellema, and Droogers (2011) assessed the role of environmental conditions on *C. burnetii* transmission in analyses of a limited number of Q fever clusters. Higher vegetation density values and relatively shallow groundwater conditions were identified as limiting factors for transmission. An ecological study showed an association of human Q fever incidence with regional annual average PM10 concentrations; however, no adjustment was made for the geographical distribution of goat farms making interpretations of the findings difficult (Reedijk, Leuken, & Hoek, 2013). A statistical risk factor analysis at a national scale was performed by Van Leuken, Swart, Droogers, et al. (2016). Spatial incidence distribution was predicted as a function of modelled *C. burnetii* concentrations (based on assumed emission patterns), vegetation density, soil moisture, soil erosion sensitivity and land use, using a zero-inflated regression model. Modelled airborne concentration was the most important predictor for Q fever incidence, followed by a protective effect of vegetation density.

## 3.4 | Risk characterization

### Dose–response modelling

Exposure to one or more pathogenic microorganisms may lead to colonization and subsequently to infection, but not always to disease. A dose–response model quantifies the probability of an outcome (e.g., infection or illness) as a function of the dose and, possibly, other covariates.

Brooke, Kretzschmar, Mutters, and Teunis (2013) developed a dose–response relation to predict infection after exposure to aerosolized *C. burnetii*. A Bayesian statistical framework (using non-informative priors) was used to scale *C. burnetii* doses applied to human volunteers in the 1950s (Tigertt & Benenson, 1956) into numbers of bacteria using results of a guinea pig study (Russell-Lodrigue, Zhang, McMurray, & Samuel, 2006). The dose for infection in 50% of human subjects was estimated at 1.18 bacteria (95% credible interval: 0.76–40.2) and the 50% illness dose at 5.58 bacteria (0.89–89.0). The probability of a single viable bacterium causing human infection was estimated at 44% (4%-59%). As a result, *C. burnetii* should be considered highly infectious.

Next, a large Q fever outbreak in Switzerland in 1983 was reanalysed to extend the dose–response model (Brooke, Mutters, Péter, Kretzschmar, & Teunis, 2015). Data included serological information on symptomatic and asymptomatic cases as a function of age, gender and distance between residential addresses and the source. The interaction effect of age and gender and the main effect of gender on the probability of (symptomatic) illness was (borderline) significant (gender × age OR: 0.97 (95% confidence interval 0.95–1.00), gender OR: 5.00 (1.82–14.01). The ratio of symptomatic to asymptomatic cases decreased with distance from the source.

By using the improved dose–response model in combination with the smoothed exposure model, Brooke, Kretzschmar, et al. (2017) predicted a median of 611 asymptomatic infections next to 220 symptomatic cases (i.e., 26.5% being symptomatic). Although this number was only based on observations at short distances to a source, it differs from the generally accepted number of 40% in the international literature (Dijkstra et al., 2012) and the value of 7% reported in an earlier study based on a much larger area (Van der Hoek, Hogema, et al., 2012).

Finally, Brooke, Teunis, et al. (2017) extended the smoothed exposure model with temporal exposure dynamics. They showed that,

while modelled exposure increased over time during 2006–2009, the spatial patterns of exposure remained unchanged, thus implying that contamination likely occurred by the same sources with increasing intensity resulting in wider spread.

### Health impact

For the complete duration of the epidemic (2007–2010), the mean number of Disability Adjusted Life Years (DALYs) per year was estimated to be approximately 2,625 (Brooke et al., 2014). The impact during the peak of the epidemic (2009) was calculated to be 5,800 DALYs, corresponding to 497 DALYs per 1,000 symptomatic cases (Brooke et al., 2014). This was primarily due to long-term sequelae including the Q fever fatigue syndrome. To put this in perspective, the influenza A(H1N1)pdm09 infections in 2009 caused more DALYs in total (almost 25,000); however, the impact per 1,000 symptomatic cases was only 60 DALYs.

## 4 | SYNTHESIS AND CONCLUSIONS

The Dutch Q fever epidemic is the best documented and most extensively studied Q fever epidemic worldwide and consequently has provided valuable insights. The findings of the multidisciplinary research programme on the Dutch Q fever epidemic further elucidated aspects of airborne transmission of *C. burnetii*. The programme included *C. burnetii* detection in aerosol samples, atmospheric dispersion modelling and dose–response analyses. Mathematical diseases modelling showed that incidence rates were related to meteorological and environmental conditions, and that infection risks were highest within several kilometres from a source farm. The dose–response relation for *C. burnetii* was quantified and further refined.

### 4.1 | Studies on worldwide Q fever epidemics

Q fever outbreaks have occurred in many countries worldwide. Studies on these epidemics mainly used ad hoc investigations (affected area/suspected cases sampling; Bond et al., 2016; Gilsdorf et al., 2008; Gyuranecz et al., 2014; Lyytikäinen et al., 1998; Medic et al., 2005; Wallensten et al., 2010) or classical epidemiological study designs, including cross-sectional studies (Biggs et al., 2016; Jorm et al., 1990; King et al., 2011; Martinov, 2007; Porten et al., 2006) and case–control studies (Manfredi Selvaggi et al., 1996; O'Connor et al., 2015; Porten et al., 2006; Tissot-Dupont, Torres, Nezri, & Raoult, 1999) to identify associated risk factors.

Numerous studies suggested the role of the wind, particularly when either cases without contact with ruminants were observed and/or *C. burnetii* infections on a nearby farm were detected, but in depth analyses were lacking (Biggs et al., 2016; Bond et al., 2016; Brouqui et al., 2004; Gyuranecz et al., 2014; Jorm et al., 1990; King et al., 2011; Lyytikäinen et al., 1998; O'Connor et al., 2015; Tissot-Dupont et al., 1999). Tissot-Dupont, Amadei, Nezri, and Raoult (2004) went into further detail with respect to the effect of wind in relation to a cluster of Q fever cases in France. Monthly variations of Q fever incidence and sheep births over multiple years in relation to meteorological data appeared to be associated. Wallensten et al. (2010) found support for windborne spread during a British outbreak in 2007 by means of an atmospheric dispersion model (NAME: Numerical Atmospheric-dispersion Modelling Environment). However, only 30 cases were included and no information on *C. burnetii* status of surrounding farms was available.

### 4.2 | Insights in source characterization

During the Dutch epidemic, source characterization appeared to be challenging. Air samples collected in goat stables in 2012 (2 years after the end of the epidemic) contained *C. burnetii* DNA, although too low for quantification. As a result, quantified emission profiles were not established and thus modelling attempts were performed with arbitrary emission rates.

Rapid source characterization in a future outbreak could contribute to better establish *C. burnetii* emission profiles. To this end, air samples should be taken at farms both indoor and outdoor at close distances. A similar strategy is described by Jonges et al (2015) in their attempts for assessment of an avian influenza outbreak. Measurements should start shortly after a source is identified and, preferably, performed repeatedly over longer periods in order to obtain insight in variation over time. A within-herd infection model (Hogerwerf et al., 2013) can then be used to supplement results. See Supporting Information Data S4 for further recommendations on this.

During and after the Dutch epidemic, studies mainly focused on transmission from farms to humans and to a lesser extent on transmission between farms. Due to a lack of information on top of a complex situation, retrospective assessment of herd-to-herd transmission during the Dutch Q fever outbreak was hampered (See Supporting Information Data S4 for recommendations on data collection). Studies performed in other countries on inter-herd transmission of ruminants also showed relevance of transmission via direct contact as well as indirect transmission. Direct transmission was mainly studied by assessing trade data (Nusinovici et al., 2014; Nusinovici, Hoch, Brahim, Joly, & Beaudeau, 2015) and by assessing proxies like proper quarantine procedures (Cardinale, Esnault, Beral, Naze, & Michault, 2014). Indirect transmission was suggested by identified crude risk factors like animal density (Lambton, Smith, Gillard, & Horigan, 2016; Nusinovici et al., 2015, 2014 ) and spatial clustering (Alvarez et al., 2012; Nogareda et al., 2013). Pandit, Hoch, Ezanno, Beaudeau, and Vergu (2016) further researched transmissions by first combining the intraherd dynamic model of Courcoul et al. (2011) with cattle trade data to assess direct transmission, then with a Gaussian dispersion model to assess airborne transmission. Findings indicated that airborne transmission had the ability to introduce *C. burnetii* in a large number of cattle herds, but the size of generated outbreaks was predicted to be small; for animal trade, opposite results were found.

Nusinovici et al. (2015) linked information on temporal data of bacterial loads at herd-level with local wind direction and wind speed data. A synergistic effect was shown of strong winds and high bacterial load in source herds on the infection risk of a naive herd. Since both studies assessed transmission between cattle herds, it would be interesting to apply this for goat herds. A major limitation of the aforementioned methods is that availability of data on concentrations of bacteria at source level is a prerequisite. However, since these are often lacking, modelling of airborne transmission between farms with only input of inter-farm distance (spatial kernel) and information on farm status (positive/negative) is an option (e.g., Boender, Meester, Gies, & Jong, 2007). These kernel models estimate the probability of transmission as a function of the inter-farm distance assuming that each infected farm can infect neighbouring farms, this approach has been proven useful for various infectious diseases (Boender et al., 2014; Boender, Hagenaars, et al., 2007; Nassuato et al., 2013).

### 4.3 | Exposure assessment opportunities

By measuring airborne concentration levels, knowledge is gained on the role of airborne transmission and sources could be detected more rapid than in epidemiological studies that need a sufficient number of cases. Preferentially, a real-time environmental surveillance network is established to continuously monitor signals of airborne zoonotic pathogens. Networks should then be strategically located in livestock dense areas for rapid detection; this is however currently unfeasible. Therefore, we recommend to collect, as soon as there is suspicion of an outbreak within a farm, besides veterinary samples also already environmental samples (see also Supporting Information Data S4).

In the Netherlands, outdoor air sampling to assess the presence of *C. burnetii* DNA in PM10 samples was performed in 2010, 2011 and 2012. The locations measured differed per year. Sites included in 2010 had the largest distances to the nearest goat farms and measurements were, in contrast to the years 2011 and 2012, performed outside the peak of the kidding season. However, the proportion of samples containing *C. burnetii* DNA in the year 2010 was not markedly below that of the years 2011 and 2012. These results may hint towards higher exposure levels during the epidemic, but comparisons were difficult as not only different sites were measured but also the number of sites was limited. The measurements performed after the end of the epidemic showed a considerable proportion of samples to be positive, while the number of notified human cases in 2011 and 2012 was much lower (81 and 66, respectively).

Bacterial viability and actual concentrations could not be assessed as only DNA was measured in levels too low for quantification. This hampers firm conclusions on (temporal) exposure levels and health implications. There is no information on viable/unviable ratios of *C. burnetii* in the environment; however, the bacteria's potential to survive in the environment outside farms was stressed by findings of Kersh et al. (2010). They found *C. burnetii* bacteria in environmental dust samples collected outside ruminant farms to be still viable and infectious (Kersh et al., 2010). To increase knowledge on viability, combination of qPCR analyses with methods to assess viability is recommended (see Supporting Information Data S4). Promising for application on environmental samples are viability qPCR methods using dyes to assess viability of *Coxiella* bacteria (Mori et al., 2013); however, viability status is assessed of the bacteria in the sample and thus cannot account for dying of bacteria during the sampling period/due to sampling methods.

### 4.4 | Risk characterization improvements

Movement patterns of humans (and animals) are known to complicate spatial risk estimations. Knowledge on movement patterns and methods to take these into account are increasing. For instance, Schrödle, Held, and Rue (2011) showed the added value of applying movement network information in modelling spatio-temporal spread of *C. burnetii* infection in Swiss cattle. Information on cattle trade was used for this, unfortunately obtaining data on human movement patterns is more complicated. Klous et al. (2017) assessed mobility by means of GPS data collected in 2014–2016 of participants living in the region affected most by Q fever during the epidemic. It is expected that in the near future data on movement patterns will contribute to improved risk assessment.

### 4.5 | Conclusions

During the Dutch Q fever epidemic, risk assessors and risk managers mainly focused on source identification and characterization. Tools included sampling of (suspected) sources (predominantly of animals and animal products) and epidemiological methods. Environmental source characterization was virtually lacking. In the aftermath, the suspected link between Q fever in humans and infected goats and sheep became more firmly established. However, because of the prolonged search and identification of individual sources, implementation of systematic surveillance programmes was delayed. Moreover, observational data were not systematically collected and not readily available for research. As a result, exposure assessments and risk characterizations were hampered. It would thus be highly recommendable protocolling data collection and exchange.

The number of microbiological and modelling techniques that are of use during an outbreak has increased since the Q fever epidemic. Mathematical disease models may predict infection risks at locations and times for which data are unavailable. The newly developed techniques give the opportunity to better comprehend microbiological, meteorological and livestock-related processes. Furthermore, the framework of methods described in this study may be applied to outbreaks with other (zoonotic) airborne pathogens (e.g., the avian influenza virus, or *Legionella* spp.), although adjustments to aspects like inactivation rates and dose–response functions should be considered.

The Dutch Q fever epidemic intensified collaboration of multiple organizations. The research work enabled enhancement of a

quantitative microbial risk assessment focussed on Q fever. With the current knowledge, the Dutch Q fever epidemic might have been controlled in an earlier stage. During possible future epidemics, focus should be on rapid source identification, quantification of emissions, accurate data collection, and smooth data exchange amongst relevant actors to enable effective risk assessment and risk management.

## ACKNOWLEDGEMENTS

We thank Dr. Christianne Bruschke, Prof. Dr. Roel Coutinho, Dr. Hendrik-Jan Roest, Dr. Yvonne van Duijnhoven, Dr. Wim van der Hoek, Drs. Stasja Valkenburgh and Drs. Stephanie Wiessenhaan for their critical input. The study was financially supported through a research grant of ZonMW (project number 50-51800-98-035).

## CONFLICT OF INTEREST

No conflict of interests to declare.

## ORCID

*Myrna M. T. De Rooij* http://orcid.org/0000-0002-6560-4839

## REFERENCES

Alvarez, J., Perez, A., Mardones, F. O., Pérez-Sancho, M., García-Seco, T., Pagés, E., … Dominguez, L. (2012). Epidemiological factors associated with the exposure of cattle to *Coxiella burnetii* in the Madrid region of Spain. *The Veterinary Journal*, *194*, 102–107.

Angelakis, E., & Raoult, D. (2010). Q Fever. *Veterinary Microbiology*, *140*, 297–309. https://doi.org/10.1016/j.vetmic.2009.07.016

Arricau Bouvery, N., Souriau, A., Lechopier, P., & Rodolakis, A. (2003). Experimental *Coxiella burnetii* infection in pregnant goats: Excretion routes. *Veterinary Research*, *34*, 423–433.

Biggs, H. M., Turabelidze, G., Pratt, D., Todd, S. R., Jacobs-Slifka, K., Drexler, N. A., … Anderson, A. (2016). *Coxiella burnetii* infection in a community operating a large-scale cow and goat dairy, Missouri, 2013. *American Journal of Tropical Medicine and Hygiene*, *94*, 525–531. https://doi.org/10.4269/ajtmh.15-0726

Boender, G. J., Hagenaars, T. J., Bouma, A., Nodelijk, G., Elbers, A. R. W., De Jong, M. C. M., & Van Boven, M. (2007). Risk maps for the spread of highly pathogenic avian influenza in poultry. *PLoS Computational Biology*, *3*, e71.

Boender, G., Hagenaars, T. J., Elbers, A., Gethmann, J. M., Meroc, E., Guis, H., & DeKoeijer, A. A. (2014). Confirmation of spatial patterns and temperature effects in Bluetongue virus serotype-8 transmission in NW-Europe from the 2007 reported case data. *Veterinary Research*, *45*, 75. https://doi.org/10.1186/s13567-014-0075-x

Boender, G. J., Meester, R., Gies, E., & De Jong, M. C. M. (2007). The local threshold for geographical spread of infectious diseases between farms. *Preventive Veterinary Medicine*, *82*, 90–101.

Bond, K. A., Vincent, G., Wilks, C. R., Franklin, L., Sutton, B., Stenos, J., … Firestone, S. M. (2016). One Health approach to controlling a Q fever outbreak on an Australian goat farm. *Epidemiology and Infection*, *144*, 1129–1141. https://doi.org/10.1017/S0950268815002368

Brandsen-Schreijer, A. J. M., Rump, B. O., Schimmer, B., Cox, C. P. G. E., Van den berg, J. P. A. M., Hulshof, F., … Woonink, F. (2010). Q-koortsuitbraak in de provincie Utrecht in 2009. *Infectieziektenbulletin*, *21*, 334–341.

Brooke, R. J., Kretzschmar, M. E. E., Hackert, V., Hoebe, C. J. P. A., Teunis, P. F. M., & Waller, L. A. (2017). Spatial prediction of *Coxiella burnetii* outbreak exposure via notified case counts in a dose – Response model. *Epidemiology*, *28*, 127–135.

Brooke, R. J., Kretzschmar, M., Mutters, N., & Teunis, P. (2013). Human dose response relation for airborne exposure to *Coxiella burnetii*. *BMC Infectious Diseases*, *13*, 488. https://doi.org/10.1186/1471-2334-13-488

Brooke, R. J., Mutters, N. T., Péter, O., Kretzschmar, M. E. E., & Teunis, P. F. M. (2015). Exposure to low doses of *Coxiella burnetii* caused high illness attack rates: Insights from combining human challenge and outbreak data. *Epidemics*, *11*, 1–6. https://doi.org/10.1016/j.epidem.2014.12.004

Brooke, R. J., Teunis, P. F. M., Kretzschmar, M. E. E., Wielders, C. C. H., Schneeberger, P. M., & Waller, L. A. (2017). Use of a dose – Response model to study temporal trends in spatial exposure to *Coxiella burnetii*: Analysis of a multiyear outbreak of Q Fever. *Zoonoses Public Health*, *64*, 118–126.

Brooke, R. J., Van Lier, A., Donker, G. A., Van der Hoek, W., & Kretzschmar, M. E. E. (2014). Comparing the impact of two concurrent infectious disease outbreaks on The Netherlands population, 2009, using disability-adjusted life years. *Epidemiology and Infection*, *142*, 1–10. https://doi.org/10.1017/S0950268813003531

Brouqui, P., Badiaga, S., & Raoult, D. (2004). Q fever outbreak in homeless shelter. *Emerging Infectious Diseases*, *10*, 1297–1299. https://doi.org/10.3201/eid1007.031020

Cardinale, E., Esnault, O., Beral, M., Naze, F., & Michault, A. (2014). Emergence of *Coxiella burnetii* in Ruminants on Reunion Island? Prevalence and risk factors. *PLoS ONE*, *8*, e3055. https://doi.org/10.1371/journal.pntd.0003055

Commandeur, M., Jeurissen, L., van der Hoek, W., Roest, H.-J., & Hermans, T. C. M. L. (2014). Spatial relationships in the Q fever outbreaks 2007–2010 in the Netherlands. *International Journal of Environmental Health Research*, *24*, 37–41. https://doi.org/10.1080/09603123.2013.800963

Courcoul, A., Monod, H., Nielen, M., Klinkenberg, D., Hogerwerf, L., Beaudeau, F., & Vergu, E. (2011). Modelling the effect of heterogeneity of shedding on the within herd *Coxiella burnetii* spread and identification of key parameters by sensitivity analysis. *Journal of Theoretical Biology*, *284*, 130–141. https://doi.org/10.1016/j.jtbi.2011.06.017

Courcoul, A., Vergu, E., Denis, J.-B., & Beaudeau, F. (2010). Spread of Q fever within dairy cattle herds: Key parameters inferred using a Bayesian approach. *Proceedings of the Royal Society B: Biological Sciences*, *277*, 2857–2865. https://doi.org/10.1098/rspb.2010.0575

D'Amato, F., Rouli, L., Edouard, S., Tyczka, J., Million, M., Robert, C., … Raoult, D. (2014). The genome of *Coxiella burnetii* Z3055, a clone linked to the Netherlands Q fever outbreaks, provides evidence for the role of drift in the emergence of epidemic clones. *Comparative Immunology, Microbiology and Infectious Diseases*, *37*, 281–288. https://doi.org/10.1016/j.cimid.2014.08.003

De Bruin, A., de Groot, A., de Heer, L., Bok, J., Wielinga, P. R., Hamans, M., … Janse, I. (2011). Detection of *Coxiella burnetii* in complex matrices by using multiplex quantitative PCR during a major Q fever outbreak in the Netherlands. *Applied and Environment Microbiology*, *77*, 6516–6523. https://doi.org/10.1128/AEM.05097-11

De Bruin, A., Janse, I., Koning, M., de Heer, L., van der Plaats, R. Q., van Leuken, J. P., & van Rotterdam, B. J. (2013). Detection of *Coxiella burnetii* DNA in the environment during and after a large Q fever epidemic in the Netherlands. *Journal of Applied Microbiology*, *114*, 1395–1404.

De Bruin, A., Van der Plaats, R. Q. J., De Heer, L., Paauwe, R., Schimmer, B., Vellema, P., … Van Duynhoven, Y. T. H. P. (2012). Detection of

*Coxiella burnetii* DNA on small-ruminant farms during a Q fever outbreak in the Netherlands. *Applied and Environment Microbiology*, *78*, 1652–1657.

De Rooij, M. M. T., Borlée, F., Smit, L. A. M., De Bruin, A., Janse, I., Heederik, D. J. J., & Wouters, I. M. (2016). Detection of *Coxiella burnetii* in ambient air after a large Q fever outbreak. *PLoS ONE*, *11*, e0151281. https://doi.org/10.1371/journal.pone.0151281

Dijkstra, F., Van der Hoek, W., Wijers, N., Schimmer, B., Rietveld, A., Wijkmans, C. J., … Schneeberger, P. M. (2012). The 2007–2010 Q fever epidemic in The Netherlands: Characteristics of notified acute Q fever patients and the association with dairy goat farming. *FEMS Immunology and Medical Microbiology*, *64*, 3–12. https://doi.org/10.1111/j.1574-695X.2011.00876.x

Gilsdorf, A., Kroh, C., Grimm, S., Jensen, E., Wagner-Wiening, C., & Alpers, K. (2008). Large Q fever outbreak due to sheep farming near residential areas, Germany, 2005. *Epidemiology and Infection*, *136*, 1084–1087. https://doi.org/10.1017/S0950268807009533

Gyuranecz, M., Sulyok, K. M., Balla, E., Mag, T., Balázs, A., Simor, Z., … Dán, A. (2014). Q fever epidemic in Hungary, April to July 2013. *Eurosurveillance*, *19*(30), 20863. https://doi.org/10.2807/1560-7917.ES2014.19.30.20863

Hackert, V. H., Van der Hoek, W., Dukers-Muijrers, N., De Bruin, A., Al Dahouk, S., Neubauer, H., … Hoebe, C. J. P. A. (2012). Q fever: Single-point source outbreak with high attack rates and massive numbers of undetected infections across an entire region. *Clinical Infectious Diseases*, *55*, 1591–1599. https://doi.org/10.1093/cid/cis734

Heederik, D. J. J., Opstal-van Winden, A. J. W., Smit, L. A. M., Wouters, I. M., Hooiveld, M., IJzermans, C. J., …Van Rotterdam, B. (2011). Mogelijke effecten van intensieve-veehouderij op de gezondheid van omwonenden: onderzoek naar potentiële blootstelling en gezondheidsproblemen [Potential Effects of Intensive Livestock Farming on Neighboring Residents' Health],Utrecht, Netherlands:Netherlands Institute for Health Services Research [in Dutch].

Hermans, T., Jeurissen, L., Hackert, V., & Hoebe, C. (2014). Land-applied goat manure as a source of human Q-fever in the Netherlands, 2006–2010. *PLoS ONE*, *9*, e96607. https://doi.org/10.1371/journal.pone.0096607

Hogerwerf, L., Borlée, F., Still, K., Heederik, D., Van Rotterdam, B., de Bruin, A., … Wouters, I. M. (2012). Detection of *Coxiella burnetii* DNA in inhalable airborne dust samples from goat farms after mandatory culling. *Applied and Environment Microbiology*, *78*, 5410–5412. https://doi.org/10.1128/AEM.00677-12

Hogerwerf, L., Courcoul, A., Klinkenberg, D., Beaudeau, F., Vergu, E., & Nielen, M. (2013). Dairy goat demography and Q fever infection dynamics. *Veterinary Research*, *44*, 28.https://doi.org/10.1186/1297-9716-44-28

Jonges, M., Van Leuken, J., Wouters, I., Koch, G., Meijer, A., & Koopmans, M. (2015). Wind-mediated spread of low-pathogenic avian influenza virus into the environment during outbreaks at commercial poultry farms. *PLoS ONE*, *10*, e0125401. https://doi.org/10.1371/journal.pone.0125401

Jorm, L. R., Lightfoot, N. F., & Morgan, K. L. (1990). An epidemiological study of an outbreak of Q fever in a secondary school. *Epidemiology and Infection*, *104*, 467–477. https://doi.org/10.1017/S0950268800047476

Karagiannis, I., Schimmer, B., VanLier, A., Timen, A., Schneeberger, P., VanRotterdam, B., … VanDuynhoven, Y. (2009). Investigation of a Q fever outbreak in a rural area of The Netherlands. *Epidemiology and Infection*, *137*, 1283–1294. https://doi.org/10.1017/S0950268808001908

Kersh, G. J., Wolfe, T. M., Fitzpatrick, K. A., Candee, A. J., Oliver, L. D., Patterson, N. E., … Massung, R. F. (2010). Presence of *Coxiella burnetii* DNA in the environment of the United States, 2006 to 2008. *Applied and Environment Microbiology*, *76*, 4469–4475. https://doi.org/10.1128/AEM.00042-10

King, L. A., Goirand, L., Tissot-Dupont, H., Giunta, B., Giraud, C., Colardelle, C., … DeValk, H. (2011). Outbreak of Q fever, Florac, Southern France, Spring 2007. *Vector-Borne and Zoonotic Diseases*, *11*, 341–347.

Klous, G., Smit, L. A. M., Borlée, F., Coutinho, R. A., Kretzschmar, M. E. E., Heederik, D. J. J., & Huss, A. (2017). Mobility assessment of a rural population in the Netherlands using GPS measurements. *International Journal of Health Geographics*, *16*, 1–13. https://doi.org/10.1186/s12942-017-0103-y

Ladbury, G. A. F., Van Leuken, J. P. G., Swart, A., Vellema, P., Schimmer, B., Ter Schegget, R., & Van der Hoek, W. (2015). Integrating interdisciplinary methodologies for One Health: Goat farm re-implicated as the probable source of an urban Q fever outbreak, the Netherlands, 2009. *BMC Infectious Diseases*, *15*, 372. https://doi.org/10.1186/s12879-015-1083-9

Lambton, S. L., Smith, R. P., Gillard, K., & Horigan, M. (2016). Serological survey using ELISA to determine the prevalence of *Coxiella burnetii* infection (Q fever) in sheep and goats in Great Britain. *Epidemiology and Infection*, *144*, 19–24.

Lyytikäinen, O., Ziese, T., Schwartländer, B., Matzdorff, P., Kuhnhen, C., Jäger, C., & Petersen, L. (1998). An outbreak of sheep-associated Q fever in a rural community in Germany. *European Journal of Epidemiology*, *14*, 193–199.

Manfredi Selvaggi, T., Rezza, G., Scagnelli, M., Rigoli, R., Rassu, M., De Lalla, F., … Binkin, N. (1996). Investigation of a Q-fever outbreak in Northern Italy. *European Journal of Epidemiology*, *12*, 403–408. https://doi.org/10.1007/BF00145305

Martinov, S. (2007). Contemporary state of the problem Q fever in Bulgaria. *Biotechnology and Biotechnological Equipment*, *21*, 353–361. https://doi.org/10.1080/13102818.2007.10817473

Medic, A., Dzelalija, B., Polic, V., Margan, I. G., Turkovic, B., & Gilic, V. (2005). Q fever epidemic among employees in a factory in the suburb of Zadar, Croatia. *Croatian Medical Journal*, *46*, 315–319.

Mori, M., Boarbi, S., Michel, P., Bakinahe, R., Rits, K., Wattiau, P., …Fretin, D. (2013). In vitro and in vivo infectious potential of coxiella burnetii: A study on Belgian livestock isolates. *PLoS One*, *8*, e67622.https://doi.org/10.1371/journal.pone.0067622

Nassuato, C., Boender, G. J., Eble, P. L., Alborali, L., Bellini, S., & Hagenaars, T. J. (2013). Spatial transmission of Swine vesicular disease virus in the 2006–2007 epidemic in Lombardy. *PLoS ONE*, *8*, 1–7. https://doi.org/10.1371/journal.pone.0062878

Nogareda, C., Jubert, A., Kantzoura, V., Kouam, M. K., Feidas, H., & Theodoropoulos, G. (2013). Geographical distribution modelling for *Neospora caninum* and *Coxiella burnetii* infections in dairy cattle farms in northeastern Spain. *Epidemiology and Infection*, *141*, 81–90. https://doi.org/10.1017/S0950268812000271

Nusinovici, S., Hoch, T., Brahim, M. L., Joly, A., & Beaudeau, F. (2015). The effect of wind on *Coxiella burnetii* transmission between cattle herds: A mechanistic approach. *Transboundary and Emerging Diseases*, *64*, 585–592.

Nusinovici, S., Hoch, T., Widgren, S., Joly, A., Lindgren, A., & Beaudeau, F. (2014). Relative contributions of neighbourhood and animal movements to Coxiella burnetii infection in dairy cattle herds. *Geospatial Health*, *8*, 471. https://doi.org/10.4081/gh.2014.36

O'Connor, B. A., Tribe, I. G., & Givney, R. (2015). A windy day in a sheep saleyard: An outbreak of Q fever in rural. *Epidemiology and Infection*, *143*, 391–398.

Pandit, P., Hoch, T., Ezanno, P., Beaudeau, F., & Vergu, E. (2016). Spread of *Coxiella burnetii* between dairy cattle herds in an enzootic region: Modelling contributions of airborne transmission and trade. *Veterinary Research*, *47*, 48 https://doi.org/10.1186/s13567-016-0330-4

Porten, K., Rissland, J., Tigges, A., Broll, S., Hopp, W., Lunemann, M., … Buchholz, U. (2006). A super-spreading ewe infects hundreds with

Q fever at a farmers' market in Germany. *BMC Infectious Diseases*, *6*, 147. https://doi.org/10.1186/1471-2334-6-147

Reedijk, M., van Leuken, J. P., & van der Hoek, W. (2013). Particulate matter strongly associated with human Q fever in The Netherlands: An ecological study. *Epidemiology and Infection*, *141*, 2623–2633. https://doi.org/10.1017/S0950268813000460

Rijksinstituut voor Volksgezondheid en Milieu (2017). *Q-koorts (Q fever)*. Retrieved from https://www.rivm.nl/Onderwerpen/Q/Q_koorts

Roest, H.-J., van Gelderen, B., Dinkla, A., Frangoulidis, D., van Zijderveld, F., Rebel, J., & van Keulen, L. (2012). Q fever in pregnant goats: pathogenesis and excretion of *Coxiella burnetii*. *PLoS ONE*, *7*, e48949. https://doi.org/10.1371/journal.pone.0048949

Roest, H. I., Tilburg, J. J., van der Hoek, W., Vellema, P., van Zijderveld, F. G., Klaassen, C. H., & Raoult, D. (2010). The Q fever epidemic in The Netherlands: History, onset, response and reflection. *Epidemiology and Infection*, *139*, 1–12. https://doi.org/10.1017/S0950268810002268

Russell-Lodrigue, K. E., Zhang, G. Q., McMurray, D. N., & Samuel, J. E. (2006). Clinical and pathologic changes in a guinea pig aerosol challenge model of acute Q fever. *Infection and Immunity*, *74*, 6085–6091. https://doi.org/10.1128/IAI.00763-06

Schimmer, B., De Lange, M. M. A., Hautvast, J. L. A., Vellema, P., & Van Duijnhoven, Y. T. H. P. (2014). *Coxiella burnetii* seroprevalence and risk factors on commercial sheep farms in The Netherlands. *The Veterinary Record*, *175*, 1–14.

Schimmer, B., Luttikholt, S., Hautvast, J. L. A., Graat, E. A. M., Vellema, P., & Van Duynhoven, Y. T. H. P. (2011). Seroprevalence and risk factors of Q fever in goats on commercial dairy goat farms in the Netherlands, 2009–2010. *BMC Veterinary Research*, *7*, 81.

Schimmer, B., Ter Schegget, R., Wegdam, M., Züchner, L., De Bruin, A., Schneeberger, P. M., … Van Der Hoek, W. (2010). The use of a geographic information system to identify a dairy goat farm as the most likely source of an urban Q-fever outbreak. *BMC Infectious Diseases*, *10*, 1–7. https://doi.org/10.1186/1471-2334-10-69

Schrödle, B., Held, L., & Rue, H. (2011). Assessing the impact of a movement network on the spatiotemporal spread of infectious diseases. *Biometrics*, *68*, 736–744. https://doi.org/10.1111/j.1541-0420.2011.01717.x

Smit, L. A., van der Sman-de Beer, F., Opstal-van Winden, A. W., Hooiveld, M., Beekhuizen, J., Wouters, I. M., … Heederik, D. (2012). Q fever and pneumonia in an area with a high livestock density: A large population-based study. *PLoS ONE*, *7*, e38843.

Taurel, A. F., Guatteo, R., Joly, A., Seegers, H., & Beaudeau, F. (2011). Seroprevalence of Q fever in naturally infected dairy cattle herds. *Preventive Veterinary Medicine*, *101*, 51–57.

Tigertt, W. D., & Benenson, A. S. (1956). Studies on Q fever in man. *Transactions of the Association of American Physicians*, *69*, 98–104.

Tilburg, J. J. H. C., Roest, H. J. I. J., Buffet, S., Nabuurs-Franssen, M. H., Horrevorts, A. M., Raoult, D., & Klaassen, C. H. W. (2012). Epidemic genotype of *Coxiella burnetii* among goats, sheep, and humans in the Netherlands. *Emerging Infectious Diseases*, *18*, 887–889.

Tissot-Dupont, H., Amadei, M. A., Nezri, M., & Raoult, D. (2004). Wind in November, Q fever in December. *Emerging Infectious Diseases*, *10*, 1264–1269. https://doi.org/10.3201/eid1007.030724

Tissot-Dupont, H., Amadei, M. A., Nezri, M., & Raoult, D. (2005). A pedagogical farm as a source of Q fever in a French city. *European Journal of Epidemiology*, *20*, 957–961. https://doi.org/10.1007/s10654-005-2336-5

Tissot-Dupont, H., Torres, S., Nezri, M., & Raoult, D. (1999). Hyperendemic focus of Q fever related to sheep and wind. *American Journal of Epidemiology*, *150*, 67–74. https://doi.org/10.1093/oxfordjournals.aje.a009920

Van den Brom, R., Roest, H. I. J., De Bruin, A., Dercksen, D., Santman-Berends, I., Van der Hoek, W., … Vellema, P. (2015). A probably minor role for land-applied goat manure in the transmission of *Coxiella burnetii* to humans in the 2007–2010 Dutch Q fever outbreak. *PLoS ONE*, *10*, e0121355. https://doi.org/10.1371/journal.pone.0121355

Van den Brom, R., Van Engelen, E., Luttikholt, S., Moll, L., van Maanen, K., & Vellema, P. (2012). *Coxiella burnetii* in bulk tank milk samples from dairy goat and dairy sheep farms in The Netherlands in 2008. *The Veterinary Record*, *170*, 310.

Van den Brom, R., & Vellema, P. (2009). Q fever outbreaks in small ruminants and people in the Netherlands. *Small Ruminant Research*, *86*, 74–79. https://doi.org/10.1016/j.smallrumres.2009.09.022

Van den Wijngaard, C. C., Dijkstra, F., Van Pelt, W., Van Asten, L., Kretzschmar, M., Schimmer, B., … Koopmans, M. P. (2011). In search of hidden Q-fever outbreaks: Linking syndromic hospital clusters to infected goat farms. *Epidemiology and Infection*, *139*, 19–26. https://doi.org/10.1017/S0950268810001032

Van der Hoek, W., Hogema, B. M., Dijkstra, F., Rietveld, A., Wijkmans, C. J., Schneeberger, P. M., & Zaaijer, H. L. (2012). Relation between Q fever notifications and *Coxiella burnetii* infections during the 2009 outbreak in the Netherlands. *Eurosurveillance Weekly*, *17*, 20058.

Van der Hoek, W., Hunink, J., Vellema, P., & Droogers, P. (2011). Q fever in The Netherlands: The role of local environmental conditions. *International Journal of Environmental Health Research*, *21*, 441–451. https://doi.org/10.1080/09603123.2011.574270

Van der Hoek, W., Meekelenkamp, J. C. E., Leenders, A. C. A. P., Wijers, N., Notermans, D. W., & Hukkelhoven, C. W. P. M. (2011). Antibodies against *Coxiella burnetii* and pregnancy outcome during the 2007–2008 Q fever outbreaks in The Netherlands. *BMC Infectious Diseases*, *11*, 44. https://doi.org/10.1186/1471-2334-11-44

Van der Hoek, W., Van de Kassteele, J., Bom, B., De Bruin, A., Dijkstra, F., Schimmer, B., … Schneeberger, P. M. (2012). Smooth incidence maps give valuable insight into Q fever outbreaks in The Netherlands. *Geospatial Health*, *7*, 127–134. https://doi.org/10.4081/gh.2012.111

Van Dijk, G., Van Dissel, J. T., Speelman, P., Stegeman, J. A., Vanthemsche, P., De Vries, J., & Van Woerkum, C. M. J. (2010). *Van verwerping tot verheffing; Q-koortsbeleid in Nederland 2005–2010*. The Hague, The Netherlands: Evaluatiecommissie Q-koorts.

Van Engelen, E., Schotten, N., Schimmer, B., Hautvast, J. L., Van Schaik, G., & Van Duijnhoven, Y. T. H. P. (2014). Prevalence and risk factors for *Coxiella burnetii* (Q fever) in Dutch dairy cattle herds based on bulk tank milk testing. *Preventive Veterinary Medicine*, *117*, 103–109. https://doi.org/10.1016/j.prevetmed.2014.08.016

Van Leuken, J. P. G., Havelaar, A. H., Van der Hoek, W., Ladbury, G. A. F., Hackert, V. H., & Swart, A. N. (2013). A model for the early identification of sources of airborne pathogens in an outdoor environment. *PLoS ONE*, *8*, 1–9.

Van Leuken, J. P. G., Swart, A. N., Brandsma, J., Terink, W., Van de Kassteele, J., Droogers, P., … Van der Hoek, W. (2016). Human Q fever incidence is associated to spatiotemporal environmental conditions. *One Health*, *2*, 77–87. https://doi.org/10.1016/j.onehlt.2016.03.004

Van Leuken, J. P. G., Swart, A. N., Droogers, P., Van Pul, A., Heederik, D., & Havelaar, A. H. (2016). Climate change effects on airborne pathogenic bioaerosol concentrations: A scenario analysis. *Aerobiologia (Bologna)*, *32*, 607–617.

Van Leuken, J. P. G., Swart, A. N., Havelaar, A. H., Van Pul, A., Van der Hoek, W., & Heederik, D. (2015). Atmospheric dispersion modelling of bioaerosols that are pathogenic to humans and livestock – A review to inform risk assessment studies. *Microbial Risk Analysis*, *1*, 19–39.

Van Leuken, J. P., van de Kassteele, J., Sauter, F. J., van der Hoek, W., Heederik, D., Havelaar, A. H., & Swart, A. N. (2015). Improved correlation of human Q fever incidence to modelled *C. burnetii* concentrations by means of an atmospheric dispersion model. *International Journal of Health Geographics*, *14*, 14.

Wallensten, A., Moore, P., Webster, H., Johnson, C., van der Burgt, G., Pritchard, G., … Oliver, I. (2010). Q fever outbreak in Cheltenham,

United Kingdom, in 2007 and the use of dispersion modelling to investigate the possibility of airborne spread. *Eurosurveillance*, *15*, 19521. https://doi.org/10.2807/ese.15.12.19521-en

Wouda, W., & Dercksen, D. P. (2007). Abortus en doodgeboorte op melkgeitenbedrijven ten gevolge van *Coxiella burnetii* [Dutch]. *Tijdschrift Voor Diergeneeskunde*, *132*, 908–911.

**How to cite this article:** De Rooij MMT, Van Leuken JPG, Swart A, et al. A systematic knowledge synthesis on the spatial dimensions of Q fever epidemics. *Zoonoses Public Health*. 2019;66:14–25. https://doi.org/10.1111/zph.12534

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.