Preventive Veterinary Medicine 123 (2016) 71–89

Contents lists available at ScienceDirect

Preventive Veterinary Medicine

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

Analysis of Q fever in Dutch dairy goat herds and assessment of control measures by means of a transmission model

D.M. Bontje[a], J.A. Backer[a,1], L. Hogerwerf[b,1], H.I.J. Roest[a], H.J.W. van Roermund[a,*]

[a] Central Veterinary Institute of Wageningen UR, P.O. Box 65, 8200 AB Lelystad, The Netherlands
[b] Department of Farm Animal Health, Faculty of Veterinary Medicine, Utrecht University, P.O. Box 80.151, 3508 TD Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 20 December 2014
Received in revised form 30 October 2015
Accepted 1 November 2015

Keywords:
Stochastic simulation model
Coxiella burnetii
Dairy goats
Control measures
Control strategies
Preventive vaccination

ABSTRACT

Between 2006 and 2009 the largest human Q fever epidemic ever described occurred in the Netherlands. The source of infection was traced back to dairy goat herds with abortion problems due to Q fever. The first aim of control measures taken in these herds was the reduction of human exposure. To analyze Q fever dynamics in goat herds and to study the effect of control measures, a within-herd model of *Coxiella burnetii* transmission in dairy goat herds was developed. With this individual-based stochastic model we evaluated six control strategies and three herd management styles and studied which strategy leads to a lower Q fever prevalence and/or to disease extinction in a goat herd. Parameter values were based on literature and on experimental work. The model could not be validated with independent data.

The results of the epidemiological model were:

(1) Vaccination is effective in quickly reducing the prevalence in a dairy goat herd. (2) When taking into account the average time to extinction of the infection and the infection pressure in a goat herd, the most effective control strategy is preventive yearly vaccination, followed by the reactive strategies to vaccinate after an abortion storm or after testing BTM (bulk tank milk) positive. (3) As *C. burnetii* in dried dust may affect public health, an alternative ranking method is based on the cumulative amount of *C. burnetii* emitted into the environment (from disease introduction until extinction). Using this criterion, the same control strategies are effective as when based on time to extinction and infection pressure (see 2). (4) As the bulk of pathogen excretion occurs during partus and abortion, culling of pregnant animals during an abortion storm leads to a fast reduction of the amount of *C. burnetii* emitted into the environment. However, emission is not entirely prevented and Q fever will not be eradicated in the herd by this measure. (5) A search & destroy (i.e. test and cull) method by PCR of individual milk samples with a detection probability of 50% of detecting and culling infected goats – that excrete *C. burnetii* intermittently – will not result in eradication of Q fever in the herd. This control strategy was the least effective of the six evaluated strategies.

Subject to model limitations, our results indicate that only vaccination is capable of preventing and controlling Q fever outbreaks in dairy goat farms. Thus, preventive vaccination should be considered as an ongoing control measure.

1. Introduction

The bacterium *Coxiella burnetii* is the causative agent of Q fever (Cox et al., 1947; Burnet and Freeman, 1983). *C. burnetii* can survive very long outside a host (Welsh et al., 1958) but needs host cells for reproduction. In goats, *C. burnetii* colonizes the trophoblast cells of the placenta of pregnant female hosts leading to necrotic purulent placentitis (Van Moll et al., 1993; Bildfell et al., 2000; Sanchez et al., 2006), and subsequent premature birth or abortion of goat kids. Excretion products like abortion- or parturition products, urine and faeces of infected goats contain *C. burnetii* and can dry and mix with dust leading to exposure of humans. Q-fever is primarily an airborne infection. The alimentary route by consumption of dairy products is debated but until now not proven for acute infection of humans and clinical disease (EFSA Scientific Opinion on Q fever: EFSA, 2010).

The Dutch dairy goat industry developed since 1984, and 25 years later, total annual goat milk production grew from almost

* Corresponding author.
E-mail address: herman.vanroermund@wur.nl (H.J.W. van Roermund).
[1] Present address: National Institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands.

http://dx.doi.org/10.1016/j.prevetmed.2015.11.004
0167-5877/

Table 1
Chronology of Q fever control measures in the Netherlands (VWZ, 2010; Roest et al., 2011c).

Date	Control measure
June 2008	Q fever in goats and sheep becomes a notifiable disease: when during a 30 day period 5% or more of pregnant goats abort, it must be reported.
	Up to 90 days after a suspicion of Q fever, a visitors ban is in place and it is not allowed to move manure from the stable.
October 2008	It is allowed to use Coxevac vaccine on a voluntary basis within a 45 km zone around a Q fever affected farm.
February 2009	Mandatory hygiene measures on commercial dairy farms with more than 50 small ruminants.
April 2009	Mandatory vaccination (before January 2010) of all dairy goats and sheep in a "vaccination zone" in the high incidence area in the South of the Netherlands on farms with more than 50 ruminants, which are open to the public.
October 2009	Transport ban for small ruminants to and from infected farms, although vaccinated animals are allowed to be added to the herd.
	Bi-monthly bulk milk monitoring becomes mandatory for farms with more than 50 dairy goats or dairy sheep.
	Visitor ban on infected farms.
December 2009	Ban on herd size increase for all dairy goat or sheep farms.
	Breeding ban.
	Ban on adding animals to any dairy goat or sheep herd.
	Mandatory bi-weekly bulk milk monitoring
	Culling of all pregnant goats on farms that were considered infected based on a positive PCR in bulk tank milk.
	Ban on moving manure out of the stable up to 30 days after the end of the lambing season.
	Manure must remain on the farm site for at least 90 days.
January 2010	Mandatory nationwide vaccination of small ruminants.
May 2010	Mandatory bulk milk monitoring relaxed to bi-monthly schedule.
January 2013	Besides mandatory hygiene measures, vaccination and bulk milk monitoring there are no other obligations or restrictions on negative farms.

zero to over 150,000 tons of milk (Van den Brom and Vellema, 2009). The total number of 98,080 dairy goats in 2000 increased to 274,060 in 2009 (CBS, http://statline.cbs.nl, query 2011). In the 1980s, Q fever apparent seroprevalence in Dutch goats was lower than 1% (Roest et al., 2011c).

Between 2006 and 2009 the largest human Q fever epidemic ever described occurred in the Netherlands. In 2007, 168 human cases were confirmed, 1000 in 2008, 2355 in 2009 and 208 cases in 2010 (Roest et al., 2011c). Since the start of the human epidemic in total 4160 humans were affected (RIVM, 2012). Based on a retrospective analysis, Q fever may have already infected humans in 2005 and 2006 (Van der Hoek et al., 2010). The source was traced back to dairy goat herds with abortion problems due to Q fever. Twenty eight dairy goat farms and two dairy sheep farms were confirmed Q fever positive with abortion problems. In addition, 102 dairy goats farms and three dairy sheep farms were confirmed Q fever positive but without reported abortion storms during the epidemic (see Table 10.1 in Roest (2013)). Analysis of the first 13 goat farms with abortions showed an average of 900 goats per farm of which 20% aborted (Van den Brom and Vellema, 2009). The average number of sheep on the two affected dairy sheep farms was 400 with an average abortion rate of 5% (Van den Brom and Vellema, 2009). In 2008, during the second year of the Dutch epidemic, Q fever apparent seroprevalence in goats was 7.8% at animal level (Van den Brom and Vellema, 2009; Van den Brom et al., 2012a). Average apparent seroprevalence on positive farms was 46.6%, ranging between 4.8 and 95.2% (Schimmer et al., 2011).

Infected placentas contain many *C. burnetii* bacteria (Welsh et al., 1951; Sanchez et al., 2006). Excreted *C. burnetii* can aerosolize ((Welsh et al., 1958; Tigertt et al., 1961; Marrie et al., 1996; Stein et al., 2005; EFSA, 2010; Jones et al., 2011) leading to environmental contamination and thus to human health risks as a few inhaled bacteria can lead to infection and illness in humans (Brooke et al., 2013). The *C. burnetii* isolated from Dutch infected goat farms since 2007 were genetically near identical, suggesting a single introduction event followed by between-herd transmission (Roest et al., 2011b,c). *C. burnetii* isolated from Dutch diagnosed humans were also genetically similar (Klaassen et al., 2009). The dominant genotype found in goats was similar to the one found in infected humans in the Netherlands (Roest et al., 2011c; Tilburg et al., 2012). An increase in Q fever incidence in humans was observed with increasing proximity to goat farms with abortion storms (Schimmer et al., 2010). These two observations make it likely that infected goat farms were the cause of human infections during the Dutch epidemic. Control measures on dairy goat farms which were implemented in 2008 were a breeding ban on bulk tank milk positive goat farms and culling of pregnant does. Table 1 provides a chronological overview of the control measures applied in the Netherlands (VWZ, 2010; Roest et al., 2011c).

Eventually the human Q fever incidence decreased, indicating that the combined control measures had an effect. However, it remains unclear which of the individual control measures can effectively control Q fever in a dairy goat herd. In order to support decision making, an economic cost-benefit analysis for each control measure separately is needed. This can be done by modelling the effect of each control measure on disease dynamics in a dairy goat herd.

Q fever disease dynamics has been modelled to investigate the effectiveness of three vaccination strategies in a recently infected dairy cattle herd (Courcoul et al., 2011). Hogerwerf et al. (2013) showed that the model structure for dairy cattle of Courcoul et al. (2011), but adapted for herd size and reproductive pattern of goats, could not capture the dynamics of the abortion storms in Dutch dairy goat herds. In that model goats were similar to cows with goat abortion rates derived from observed bovine abortion rates and goats could have only once an abortion. Therefore, in the present study a Q fever within-herd transmission model was developed to describe the disease dynamics in goat herds with abortion storms and to evaluate the effect of control measures. Parameter values were based on literature and experimental work. First, a deterministic version of the model was developed, consisting of a system of Ordinary Differential Equations (ODEs). With this deterministic version, an elasticity analysis of the input parameters was studied. Then, an individual-based stochastic version of the model was developed, to evaluate the effect of six control strategies and three herd management styles. The output of the individual-based stochastic model was used in another study to perform an economic analysis of the control- and herd management strategies (Van Asseldonk et al., 2015).

2. Material and methods

2.1. Dairy goat farming

In dairy goat herds, the breeding season entails conception, gestation and partus. To produce milk a dairy goat needs to give birth at least once. Goats produce milk during pregnancy, and milking of goats during gestation is very common. So in a dairy herd all goats

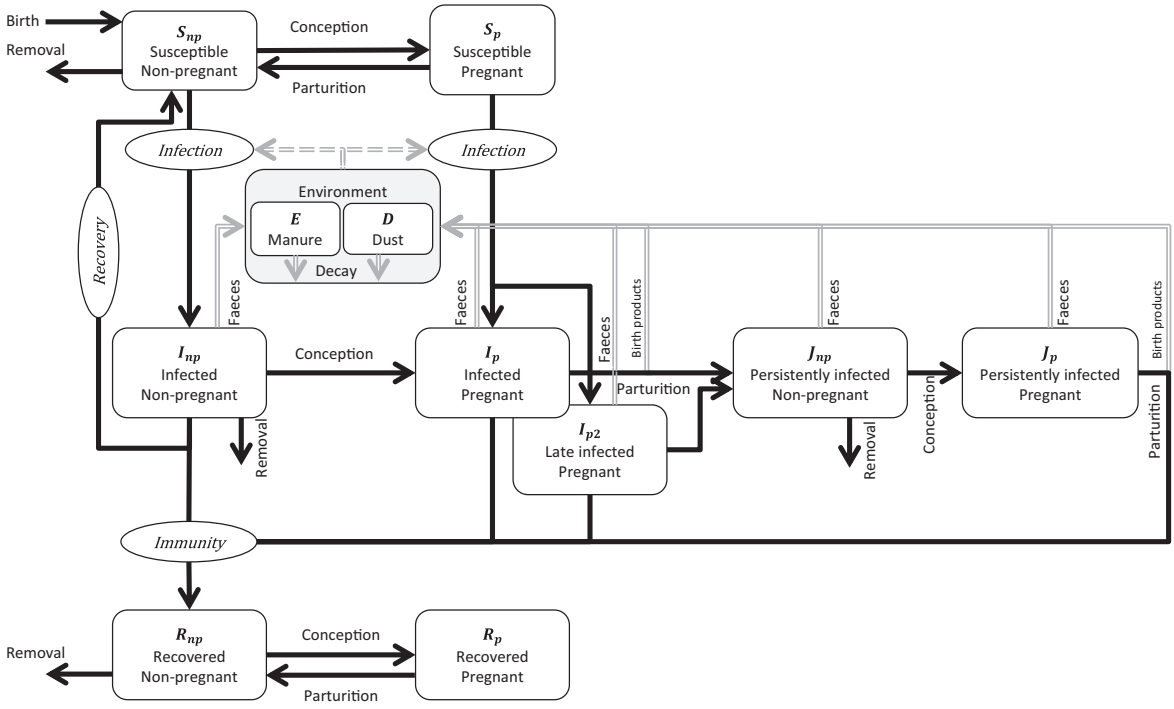


Fig. 1. Schematic overview of the Q fever within-herd transmission model. Variables are in rounded boxes, black arrows represent state transitions for the goat, and grey arrows depict *C. burnetii* excretion routes resulting from faeces and from birth products (at partus or abortion). *C. burnetii* decays in each environmental compartment. The transmission of the bacteria from the stable environment E and dust D to susceptible goats is denoted with dashed grey arrows. The processes of infection, recovery and development of immunity are indicated with ovals. The model includes conception, partus, abortion and influx of young animals in the herd. In the figure partus and abortion is taken together and labelled 'parturition' in the black arrows leaving the infected pregnant goats (I_p and J_p). Only non-pregnant goats can be removed from the population. Equations and modelling details are given in Appendix 1.

produce milk, except the first time pregnant females. Adult goats which do not conceive and thus will not lactate are culled from the herd. Only a few male goats are kept in the herd for breeding or none when insemination is done artificially. Effectively, a herd consists of young females which have never conceived yet, of first time pregnant females (nulliparous) and older pregnant and older non-pregnant females (multiparous). In the Dutch dairy goat industry, nearly all young goats do not drink from their mother, but they are housed separately and drink processed cow-milk. This is done to prevent disease spread between doe and kids.

The peak of conception in most Dutch dairy goat herds occurs during September–October, and kidding occurs ca 22 weeks later in February–March. After the kidding season, the young are kept separate from the main herd and those young that are kept for production are introduced into the herd two months after the kidding season.

Many farmers restock their goat population with a yearly birth cycle, but it is possible to continue with milking and skipping one or more mating seasons, effectively prolonging the lactation period of all goats. Prolonged lactation is on the rise in the Netherlands as it results in fewer animal losses, less labour, a larger total milk production and leads to a better spread of the milk production over the year (Schuiling, 2007). However, it does lead to fewer offspring to breed with.

2.2. The Q fever within-herd transmission model

We first derived a conceptual model from the biology, pathology and epidemiology of Q fever as found in the literature, taking a default susceptible-infected-recovered (SIR) model as starting point (Keeling and Rohani, 2008). The literature overview used to derive the conceptual model can be found in Appendix 2 (Choice of parameter values), as it is too elaborate to present here. Fig. 1 shows the resulting flow diagram of the model. In the model a goat can be susceptible, infected or recovered and pregnant or non-pregnant. These combinations lead to the following six state variables: susceptible non-pregnant goats [S_{np}], susceptible pregnant goats [S_p], infected non-pregnant goats [I_{np}], infected pregnant goats [I_p], recovered non-pregnant goats [R_{np}] and recovered pregnant goats [R_p]. Besides these six states, adult goats can be in three additional disease states, namely the late infected pregnant goats [I_{p2}], persistently infected non-pregnant goats [J_{np}] and the persistently infected pregnant goats [J_p].

In the model, when a non-pregnant susceptible animal [S_{np}] is infected, it will follow an acute disease course: it becomes infected [I_{np}] and will shed bacteria in faeces for assumingly a month, after which a fraction (p) clears the infection and acquires immunity and recovers [R_{np}] and a fraction ($1-p$) clears the infection but does not acquire immunity and thus returns to the state of non-pregnant susceptible animal [S_{np}]. The largest source of *C. burnetii* bacteria are infected birth products such as placentas, so infected pregnant animals play an important role in transmission. The group of infected pregnant animals [I_p] arises when non-pregnant infected animals [I_{np}] become pregnant or when pregnant susceptible animals [S_p] are infected. A fraction (f_I) of these animals [I_p] will abort before their due time, and the rest ($1-f_I$) will have a normal parturition. Infected pregnant animals cannot clear the infection. At abortion and parturition equally large amounts of bacteria are shed via birth products. Animals that become infected in the last month of gestation enter the infectious state I_{p2} and are assumed to not shed bacteria at parturition. A fraction (α) of infected pregnant animals [I_p and I_{p2}] will recover to R_{np} after abortion or parturition; the complementary fraction ($1-\alpha$) will become persistently infected [J_{np}]. While these animals are not pregnant anymore they

will shed bacteria via faeces. Once pregnant again [J_p], they have probability (f_J) of having an abortion or ($1-f_J$) of having normal birth, similar to the first infected gestation. We assume that persistently infected individuals will always recover after the second birth, thus a third infected pregnancy cannot occur in the model. Non-pregnant recovered animals [R_{np}] can only move to the state of pregnant recovered animals [R_p] and vice-versa.

There is no conclusive information on shedding of *C. burnetii* in faeces for acutely infected goats [I_{np}], for animals infected during pregnancy [I_p] and for animals still infected between pregnancies [J_{np}] (chronically infected goats). Around the partus infected pregnant goats shed *C. burnetii* [I_p and J_p]. We will assume that there is a daily shedding via faeces for all infectious states [I_{np}, I_p, I_{p2}, J_{np} and J_p], but at an extremely low level of excretion compared to bacterial load in abortion- or parturition products. In short, acutely infected and chronically infected animals shed daily equal amounts of *C. burnetii* in faeces. The *C. burnetii* bacteria in faeces and abortion- or parturition products are deposited on the manure (litter) of the stable or settle on dust particles (which can spread via aerosol formation), leading to environmental bacterial load [E] in manure and bacterial load [D] in dust. A fraction ρ of the excreted bacteria will settle on dust, the complementary fraction $1-\rho$ will enter the manure.

The *C. burnetii* bacterial load in manure decays over time. Also in dust the bacterial load decreases, albeit slower. The infection pressure for the goats depends on the amount of *C. burnetii* in both the environments [E] and [D]. The infection pressure resulting from a bacteria is equal in each environmental compartment but the decay rate of the bacterial load differs per environmental compartment. N_{tot} is the total number of goats in the herd and β the constant transmission rate from environment to goat, the *per capita* infection rate is $\beta(E+D)/N_{tot}$, which describes frequency dependent mixing (Keeling and Rohani, 2008).

In the model male goats are excluded, because they are unlikely to play an important role in Q fever transmission after disease introduction in the herd. The route of introduction is not considered in this model. Q fever is introduced into the herd by introducing an infected pregnant goat at the average day of conception. After the kidding season, the young [Y] are kept separate from the main herd and those young that are kept for production are introduced into the herd two months after the kidding season. We assumed a best case-scenario in which the young remain uninfected (and thus susceptible) until being introduced in the herd. The young do not drink from their mother, which excludes vertical transmission of Q fever via milk. Non-pregnant goats which fail to conceive or become unproductive are removed from the population (for slaughter) at a constant rate.

The above conceptual model was first used to construct a deterministic version of the model based on ordinary differential equations (ODEs) to study the Q fever dynamics in the herd without control measures. Appendix 1 details the equations of the model. Parameter values of the model are summarized in Table 2, and Appendix 2 details the underpinning of the chosen parameter values based on literature. An elasticity analysis of the deterministic model was performed to study which parameters have the most influence on model predictions.

2.3. Elasticity analysis

To find which parameters affect the quantitative output of the deterministic model the most, elasticity calculations were performed for each parameter separately. As output variable of interest E_{cum} six years after the disease introduction was selected. E_{cum} is the cumulative *C. burnetii* excretion in the environment since the moment of disease introduction (without control measures).

The elasticity of a parameter, L(P), is the relative change of model outcome E_{cum} (evaluated at the default parameter value P_0) divided by the relative change of the single parameter of interest (P):

$$L(P) = \frac{\Delta E_{cum}}{\Delta P}\frac{P_0}{E_{cum}} \quad (1)$$

Numerically L(P) was calculated as in the equation below with $d = 0.1$. If P is a fraction (e.g. as for parameter φ) and it may become larger then unity, then a value for d was taken such that P reaches unity.

$$L(P) = \frac{\Delta E_{cum}((1+d)P) - \Delta E_{cum}((1-d)P)}{2dP}\frac{P_0}{E_{cum}(P_0)} \quad (2)$$

2.4. Stochastic model

When infected animals in a herd are controlled to very low numbers, stochastic processes such as disease extinction become important, and a stochastic version of the model was needed to study output like time until extinction. In this model, the transmission events follow a Poisson distribution with the transmission rate depending on the number of susceptible animals and the bacterial load in E and D. The Poisson process was implemented using Gillespie's First Reaction Method (Keeling and Rohani, 2008) in which at each time point the time to the next event is randomly drawn according to the respective rate of each stochastic process. Only the earliest event takes place and time is progressed to the event time. Each simulation covered a 10 year period since disease introduction. When an individual becomes infected it will subsequently move via different states to R_{np} as is prescribed in the flow chart in Fig. 1. The time the individual spends in a state was drawn from the parameter distributions in Table 2, e.g. a gamma distribution for the period to remain in I_{np}. Each time a state transition occurred for an individual in the population, the *C. burnetii* excretion to the environmental compartments E and D from all animals was updated, leading to a dynamic infection pressure. Non-pregnant individuals were removed with a constant rate, vacancies due to removal were filled during the period of influx of young after the kidding season. The model was coded in Mathematica 8.0 (Wolfram Research Inc, 2012).

2.5. Parameter values

Parameter values of the model are summarized in Table 2, and Appendix 2 details the underpinning of the chosen parameter values based on literature. The average day of kidding is set at calendar day 55 (February 24th) based on Chapter SI 1 of the Supplementary Information. Given an average gestation time of 150 days, the average day of conception is at calendar day 270 (September 27th). Q fever is introduced into the herd by changing a pregnant goat (S_p) into an infected pregnant goat (I_p) at the average day of conception (t_c).

The parameters values for β (the transmission rate), α (fraction of infected pregnant animals to become persistently infected) and ρ (the fraction of *C. burnetii* excretion targeted to dust) could not be estimated with certainty from literature data. Therefore, the infection dynamics in the model was studied for a range of values to find for which combination of parameter values the abortions patterns as observed in 13 Dutch dairy goat herds in 2006–2007 could be reproduced (high abortion percentage of >5%, see Appendix 2). The reason for this approach is further explained in the Section 4.

The timing of state transitions in the stochastic model was done as follows. Life expectancy has an exponential distribution with mean μ_t. Date of partus has a normal distribution with mean t_p and standard deviation T_p. Date of conception has a normal distribution with mean t_c and standard deviation T_c. The assigned

Table 2
List of variables and parameters in the Q fever model. The choice of each parameter value was based on literature (see Appendix 2). The goat demographic data were derived from the Small Animal Database of the Dutch Animal Health Service (see Chapter SI 1 of the Supplementary Information).

Symbol	Value	Units	Description
Variables			
S_{np}		Animals	Susceptible non-pregnant animals
S_p		Animals	Susceptible pregnant animals
I_{np}		Animals	Acutely infected non-pregnant animals
I_p		Animals	Infected pregnant animals
J_{np}		Animals	Persistently infected non-pregnant animals
J_p		Animals	Persistently infected pregnant animals
R_{np}		Animals	Immune non-pregnant animals
R_p		Animals	Immune pregnant animals
E		Scaled unit	*C. burnetii* load in manure
D		Scaled unit	*C. burnetii* load in dust
Demography parameters			
φ	0.95	n.a.	Fraction of animals to conceive
t_p	55	Day of year	Average day of parturition (February 24th)
T_p	46	Day	Standard deviation for day of parturition
$T_c = T_p$		Day	Standard deviation for day of conception
T_g	150	Day	Average duration of gestation (~22 weeks)
$t_c = 356 + t_p - T_g$		Day of year	Average day of conception (September 27th)
μ_t	1/2.7	Day^{-1}	Total birth rate to keep population constant, on average a goat reach an age of 2.7 years.
μ	Varies	Year^{-1}	Removal rate of non-pregnant animals, see Chapter SI 1 of the Supplementary information.
n_{max}	600	Animals	Maximal herd size
t_{in}	112	Day of year	Average day of introduction of new (young) animals in the herd
$t_{in,s}$	0.00523		Scale parameter for logistic distribution for day of introduction
Infection parameters			
f_I	0.75	n.a.	Fraction of infected pregnant animals in I_p to abort
f_J	0.25	n.a.	Fraction of infected pregnant animals in J_p to abort
T_i	14.4	Day	Infectious period of infected non-pregnant animals
n_i	4	n.a.	Number of infectious stages for non-pregnant animals
$\gamma = n_i/T_i$		Day^{-1}	Recovery rate for each infectious stage
T_l	28	Day	Last period of pregnancy when infection does not lead to abortion
α	0.7	n.a.	Fraction of infected pregnant animals to become persistently infected
β	1.0	Day^{-1} scaled unit^{-1} [a]	Transmission rate per equivalent *Coxiella* excretion
p	0.5	n.a.	Probability to gain immunity after acute infection
T_a	50	Day	Last period of pregnancy when abortion can occur
r_i=-log [1-f_i]/T_a		Day^{-1}	Specific rate of abortion, i∈ (I,J)
Shedding parameters			
1-ρ		n.a.	Fraction of *C. burnetii* excretion targeted to manure
ρ	0.01	n.a.	fraction of *C. burnetii* excretion targeted to dust
ε_p	1	Scaled unit/part.	*C. burnetii* excretion in partus material (per parturition)
ε_f	2.7×10^{-6}	Scaled units/day	*C. burnetii* excretion in faeces and urine per day
C. burnetii survival parameters			
μ_E	1/20	Day^{-1}	Mortality rate for *C. burnetii* in manure
μ_D	1/200	Day^{-1}	Mortality rate for *C. burnetii* in dust
Additional parameters for the stochastic simulations			
v_e	90%	n.a.	Vaccination efficacy
S_{SD}	50%	n.a.	Detection probability of the search & destroy strategy
Forcing functions for the deterministic model (see Appendix 1)			
Φ_a (t)		n.a.	Forcing function for abortion: 95% of abortions occur between day 100 of gestation and day 150 of gestation.
Φ_c (t)		n.a.	Logistic function: 95% of animals conceive during the breeding season with duration T_p centred on t_c
Φ_p (t)		n.a.	Logistic function: 95% of animals give birth during a period of T_p centred on t_p
Φ_{in} (t)		n.a.	Forcing function for influx of young in the herd
Φ_4 (t)		n.a.	Forcing function for late infections
$\kappa_c = \kappa_p$		n.a.	Shape parameter for logistic function Φc
κ_{in}	1.91	n.a.	Shape parameter for logistic function Φ_{in}
κ_p	11.06	n.a.	Shape parameter for logistic function Φ_p

n.a: Not applicable.
[a] Per day per scaled infectious unit in the environment.

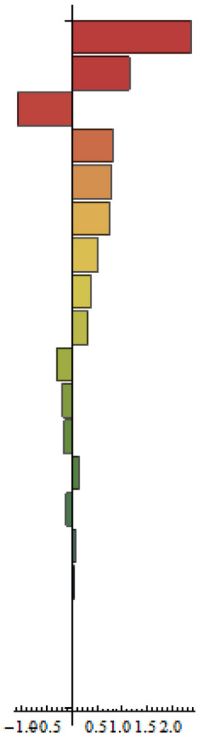
date of partus is T_g days after conception. The date of abortion is x days before the assigned date of partus, x has an uniform distribution with width T_α. The day of introduction of new (young) animals into the herd has a logistic distribution with mean t_{in} days and its scale parameter $t_{in,s}$ is taken such that 95% of the introductions occur in a 14 day period. Introduction of young animals takes place until the maximum group size (600) is reached. This is to replenish the adult animals that have died over the preceding year (and is independent of herd management style). The day of recovery from an acute infection is z days past the day of infection, z has a gamma distribution with mean T_i and shape parameter N_i.

2.6. Sensitivity analysis of key parameters

Based on the results of the elasticity analysis, three parameters were identified as key parameters having a large uncertainty and a high elasticity: α (fraction of infected pregnant animals to become persistently infected), β (the transmission rate), and T_l (which denotes the late period of pregnancy in which infection

Table 3
Elasticity analysis of the deterministic model. As output variable of interest E_{cum} six years after the disease introduction was selected. E_{cum} is the cumulative *C. burnetii* excretion in the environment since the moment of disease introduction (without control measures). See Eqs. (1) and (2).

Parameter P	Value P_0	Elasticity $L(P)$	Visualized Elasticity
ϕ	0.95	2.36	
T_a	50	1.14	
T_l	28	−1.07	
β	1	0.81	
α	0.7	0.78	
f_I	0.75	0.74	
T_p	46	0.51	
T_g	150	0.37	
T_{in}	112	0.32	
$1/\mu_t$	2.7	−0.31	
p	0.5	−0.18	
μ_D	0.005	−0.15	
f_J	0.25	0.14	
μ_E	0.05	−0.11	
ρ	0.01	0.08	
T_i	14	0.06	
ϵ_f	$2.74 \cdot 10^{-6}$	0.00	
t_p	55	0.00	
t_i	300	0.00	



Elasticities are ranked by absolute value.

does not lead to abortion). These parameters were varied in a sensitivity analysis without control measures, tracking the pattern and number of abortions in the goat herd during a 10 year period after disease introduction. In the sensitivity analysis, the effect of T_l was studied by changing its value from its default value (28 days) to 21 days and 35 days. As α and β were calibrated together (to reproduce the abortions patterns as observed in 13 Dutch dairy goat herds, see above), they were also studied in combination here. α was changed from its default value (0.7) to 0.5 and 0.9, and β was changed from its default value (1.0) to 0.67 and 1.5. All 9 combinations were studied. The parameter ρ (the fraction of *C. burnetii* excretion targeted to dust) was also calibrated in combination with α and β (see above), but this parameter was not subjected to the sensitivity analysis, as its elasticity L(P) in the elasticity analysis was very low (see Section 3).

2.7. Detection and subsequent control strategies

C. burnetii-infected lactating goats excrete bacteria in their milk, in varying numbers over time (Arricau-Bouvery et al., 2003; Berri et al., 2005; Hogerwerf et al., 2014). The presence of *C. burnetii* DNA in milk can be detected at herd level with PCR of bulk tank milk (BTM), with a detection probability close to 100% (Van den Brom et al., 2012b). Q fever infection in a herd may lead to high abortion percentages (≥5%), the so called abortion storms (Van den Brom and Vellema, 2009). Abortion storms and positively tested BTM are both herd level indicators for Q fever infection in a herd. For modelling purposes BTM is considered positive when two subsequent conditions are met. Firstly, at least one goat must excrete *C. burnetii* at parturition in the herd during the kidding season (infected pregnant goats I_p and J_p). Secondly, after the kidding season is completed (so in absence of pregnant goats) and goats are lactating, the milk must test positive (which is then only possible by persistently infected non-pregnant goats J_{np}). When Q fever is detected in a herd, for example by one of these herd level indicators, reactive control strategies may be implemented, with the aim to minimize the impact of the infection, for instance impact on public health, economics costs and animal health. In addition to the reactive control strategies, it is also possible to implement preventive control strategies, such as vaccination, hygiene measures, rodent control, having a closed herd without introduction of animals from other herds, etc.

The effect of seven strategies were evaluated with the stochastic model. These include one strategy without control measures (1), one preventive vaccination control strategy (2) and five reactive control strategies (3–7):

1. No control
   - No control measures are implemented and the disease runs its course without simulated interventions.
2. Preventive vaccination
   - When vaccinated before infection, most abortions are prevented (Arricau-Bouvery et al., 2005). In the model, calendar day 162 (June 11th) is in between the peak of the kidding season and the peak of the conception period. Therefore on day 162 it is the least likely to have pregnant goats in the herd. All animals (including newly introduced animals) are vaccinated on day 162 with a 90% efficacy (meaning here that nine of ten animals were vaccinated correctly and also developed an effective immune response). Vaccination is repeated every year. In the model animals recovered from a *C. burnetii* infection and vaccinated animals are identical in their response to

exposure. Thus, we assume that only animals in state S_{np} can benefit from vaccination and are moved to R_{np}. See Appendix 2 for the derivation of vaccination parameter values and timing of vaccination.

3. Vaccination after BTM positive kidding season
   - In this strategy, after a kidding season with a positive BTM, the animals on the farm are vaccinated yearly as in Strategy 2. The detection probability of the PCR test (BTM) in the model is 100%. This assumes that the bulk tank monitoring program sampling frequency is high enough to detect intermittent shedding lactating goats (lactating infected goats are: I_p, J_{np} and J_p, and not I_{p2}).
4. Vaccination after kidding season with abortion storm
   - In this strategy, after a kidding season with an abortion rate above 5%, the animals on the farm are vaccinated yearly as in Strategy 2.
5. Breeding ban after BTM positive kidding season
   - After a kidding season with a positive BTM all animals present are permanently banned from breeding. Newly introduced animals are allowed to conceive. If the BTM is positive again after the next breeding season, the breeding ban is prolonged.
6. Search & destroy (i.e. test and cull) after BTM positive
   - After a kidding season with a positive BTM any lactating infected animal is detected with PCR with a 50% probability (due to intermittent shedding in milk) and is consequently culled. So the detection probability of the PCR test in the model is 100% at farm level (BTM), but 50% at individual level (individual milk sample) to account for intermittent shedding in milk in practice (please note that shedding in milk is not part of the model). Culling of detected animals is only done on day 162 (June 11th). This is repeated in any subsequent kidding season when the BTM is found positive again. The value of 50% of shedding/non-shedding is based on (Courcoul et al., 2010). For five dairy cattle herds in a different model structure, they found a ratio between (point estimates of) time spent in shedding compartments and time spent in non-shedding compartments of 0.19, 0.52, 0.18, 0.71 and 0.64.
7. Culling of pregnant animals after abortion storm
   - If since the start of the kidding season 5% or more of all conceived goats have aborted, all remaining pregnant animals are culled instantly and new arrivals are postponed for one year. This is repeated any time an abortion storm occurs.

Each simulation was done for a period of ten years. The day that the last infected animal became disease free (i.e. fully recovered) is considered as the day of disease extinction. If after ten years infected animals are still present, then time until disease extinction is given as '>10' in the table with results (Table 4).

2.8. Dairy goat management style

Each farmer decides individually when and how often a goat is bred to induce pregnancy, leading to a range of dairy goat herd management styles. In all herd management styles a goat gives its first birth approximately 12 months after its own birth. Dairy goats have an average life span of 2.7 years (see Chapter SI 1 of the Supplementary Information). Three strategies for different breeding management styles are implemented in the stochastic model, namely:

1. Every year pregnant
   - Every goat is selected for breeding each year.
2. Every two years pregnant
   - Goats give birth on their odd years of age, e.g. when aged one-year, three-year, five-year, etc. This reduces the number of pregnant goats and resulting kids in a herd per year in comparison with the first management style.
3. First two years pregnant
   - Only the one- and two-year-old goats are selected for breeding. After the second birth the goat is milked until removal. This lowers the number of pregnant goats and resulting kids in a herd per year in comparison with the first management style.

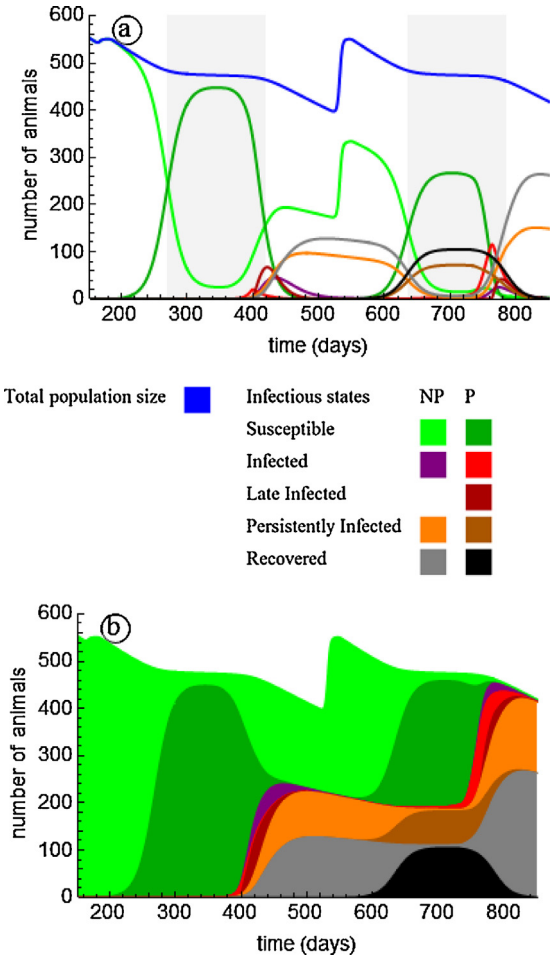


Fig. 2. Model results of an outbreak starting on day 270 with one infected pregnant goat. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
All susceptible animals are green, all recovered animals are dark (grey and black) and all infected animals are reddish, with the first-time infected states I_{np} (purple) and I_p (red), late infected I_{p2} (dark red) and the persistently infected states J_{np} (orange) and J_p (brown). (a) Number of individuals per infectious state during two breeding seasons. Blue indicates total population size. The steep upward part of the "saw-tooth" pattern results from the seasonal introduction of young into the herd during a short period. The two gradual downward parts of the curve result from removal of the non-pregnant goats. Vertical grey columns indicate each annual period from average time of conception till average time of birth. (b) Same as (a) but stacked figure.

For comparison purposes the strategy No disease is included to provide baseline values for productive animals (lactating goats) and surplus of healthy kids (number of female goats born minus goats kept for replacement) for the three herd management styles. These data are needed for the economic analysis of the control- and herd management strategies (Van Asseldonk et al., 2015).

The combination of seven control strategies (including the "no control") and three herd management styles lead to 21 different scenarios to be simulated. For each scenario, 200 simulations were executed, which was sufficient as mean values were stable across repeated runs. The following model output was generated, and

Table 4
Summary of results of stochastic simulations for seven control strategies and three goat herd management styles, style 1: every year pregnant, 2: every two years pregnant, 3: first two years pregnant. The average numbers are 10 year averages (needed for the economical evaluation by Van Asseldonk et al. (2015). Values between parentheses are the lower and upper bound of the 5–95% percentiles interval. Infected placentas leads to environmental contamination and thus to human health risks.

Control strategy	Management style	Duration (years)		Average number of vaccinated animals per year		Average number of culled animals per year		Average number of infected placentas per year		Average number of abortions per year	
No control measures	1	>10	(>10–>10)	0	(0–0)	0	(0–0)	99	(90–110)	56	(50–64)
	2	>10	(>10–>10)	0	(0–0)	0	(0–0)	68	(58–76)	42	(35–48)
	3	>10	(>10–>10)	0	(0–0)	0	(0–0)	78	(68–86)	46	(40–51)
Preventive vaccination	1	2.1	(0.9–3.9)	578	(576–581)	0	(0–0)	0	(0–1)	0	(0–0)
	2	1.2	(0.8–5.2)	581	(579–583)	0	(0–0)	0	(0–0)	0	(0–0)
	3	1.9	(0.8–3.3)	581	(578–583)	0	(0–0)	0	(0–1)	0	(0–0)
Vaccination after BTM positive	1	5.3	(4.2–8.0)	578	(576–580)	0	(0–0)	28	(10–45)	15	(5–24)
	2	5.5	(3.4–8.3)	581	(578–583)	0	(0–0)	8	(2–17)	4	(1–10)
	3	4.1	(2.3–6.0)	581	(578–583)	0	(0–0)	6	(1–13)	4	(1–8)
Vaccination after abortion storm	1	5.8	(4.2–7.4)	578	(521–581)	0	(0–0)	30	(14–45)	16	(7–26)
	2	6.2	(4.3–9.2)	580	(521–582)	0	(0–0)	10	(4–21)	6	(2–12)
	3	4.2	(3.1–6.3)	581	(521–583)	0	(0–0)	9	(4–18)	5	(2–10)
Breeding ban after BTM positive	1	5.2	(1.5–9.5)	0	(0–0)	0	(0–0)	13	(4–26)	10	(3–19)
	2	3.3	(1.4–8.4)	0	(0–0)	0	(0–0)	5	(1–12)	4	(1–9)
	3	3.3	(1.3–8.4)	0	(0–0)	0	(0–0)	4	(1–12)	3	(1–9)
Search & destroy after BTM positive	1	>10	(>10–>10)	0	(0–0)	25	(23–29)	82	(74–93)	52	(46–60)
	2	>10	(>10–>10)	0	(0–0)	26	(22–30)	51	(22–30)	36	(29–43)
	3	>10	(>10–>10)	0	(0–0)	23	(20–26)	66	(57–74)	43	(37–49)
Culling after abortion storm	1	>10	(6.2–>10)	0	(0–0)	111	(66–146)	13	(7–16)	10	(6–12)
	2	>10	(9.0–>10)	0	(0–0)	96	(62–125)	12	(9–14)	9	(7–10)
	3	>10	(2.2–>10)	0	(0–0)	57	(8–98)	8	(2–13)	6	(2–9)

summarized as median value and 5–95% percentiles interval for each scenario in a 10-year period:

- time until extinction or still present at the end of the simulated period (i.e. not extinct)
- number of vaccinated animals per year
- number of culled animals per year
- number of infected placentas excreted per year
- number of abortions per year
- average number of productive animals per year
- surplus of healthy female kids per year
- surplus of healthy male kids per year

The above output for each of the 21×200 simulation runs, was used as input for the economic analysis (Van Asseldonk et al., 2015).

2.9. When to end with preventive vaccination?

Given that a herd is yearly preventively vaccinated and currently free of *C. burnetii* (or free of symptoms), what would be the effect of ending this preventive vaccination on disease incidence in case of Q fever introduction now, in the near future or in the recent past? This was investigated by simulating different moments of disease introduction in a herd for each of the three herd management styles, namely from five years before until four years after the last round of vaccination. As a measure of disease incidence the total number of infected animals (pregnant infected animals and persistently infected animals) over time is followed.

3. Results

3.1. Deterministic model simulations

In the model, an infected pregnant goat is introduced on September 27th (day 270) which is the average day of conception. The resulting outbreak without control measures is presented until day 850 in Fig. 2. In chapter SI 2 of the Supplementary Information, we show the disease dynamics over a 10-year period. Fig. 2 indicates that around day 550 all goats are non-pregnant and that the majority of the goats is either uninfected (light green), recovered (light grey) or persistently infected (orange). The introduction of Q fever into the herd first leads to an increase in the number of infected pregnant goats towards the end of the same gestation period (red), but mostly to late infected pregnant goats (dark red, I_{p2} in the flow diagram of Fig. 1) and some infected non-pregnant goats (purple). Fraction α of the infected goats (red) and late infected pregnant goats (dark red) become persistently infected (orange) and they can carry the infection to the next breeding season. These persistently infected goats (orange) become pregnant and subsequently abort or give birth, leading to an environmental bacterial load which in turn can infect the pregnant susceptible goats (dark green). This latter group consists of goats that had escaped infection so far, and of younger goats which did not encounter the disease yet because they were newly introduced in the previous season. The combination of persistently infected goats and the influx of new susceptibles prevents the infection from going extinct in the herd.

3.2. Elasticity analysis

We calculated the elasticity for all parameters in the deterministic model with Eq. (1) given the default parameter values of Table 2. Results are summarized in Table 3. A high elasticity value indicates that a small change in parameter value causes a relatively large change in the value for the cumulative *C. burnetii* excretion since the moment of disease introduction. Therefore, the parameters with a large elasticity should be known with a fair amount of certainty. Below, we will summarize the 11 most elastic parameters and their range of uncertainty. The other parameters with a low elasticity can have a large uncertainty, but they will not affect the quantitative model behaviour much.

The most elastic parameter is the fraction of animals which conceive (φ). However, the value for φ is unlikely to be lower than 0.95

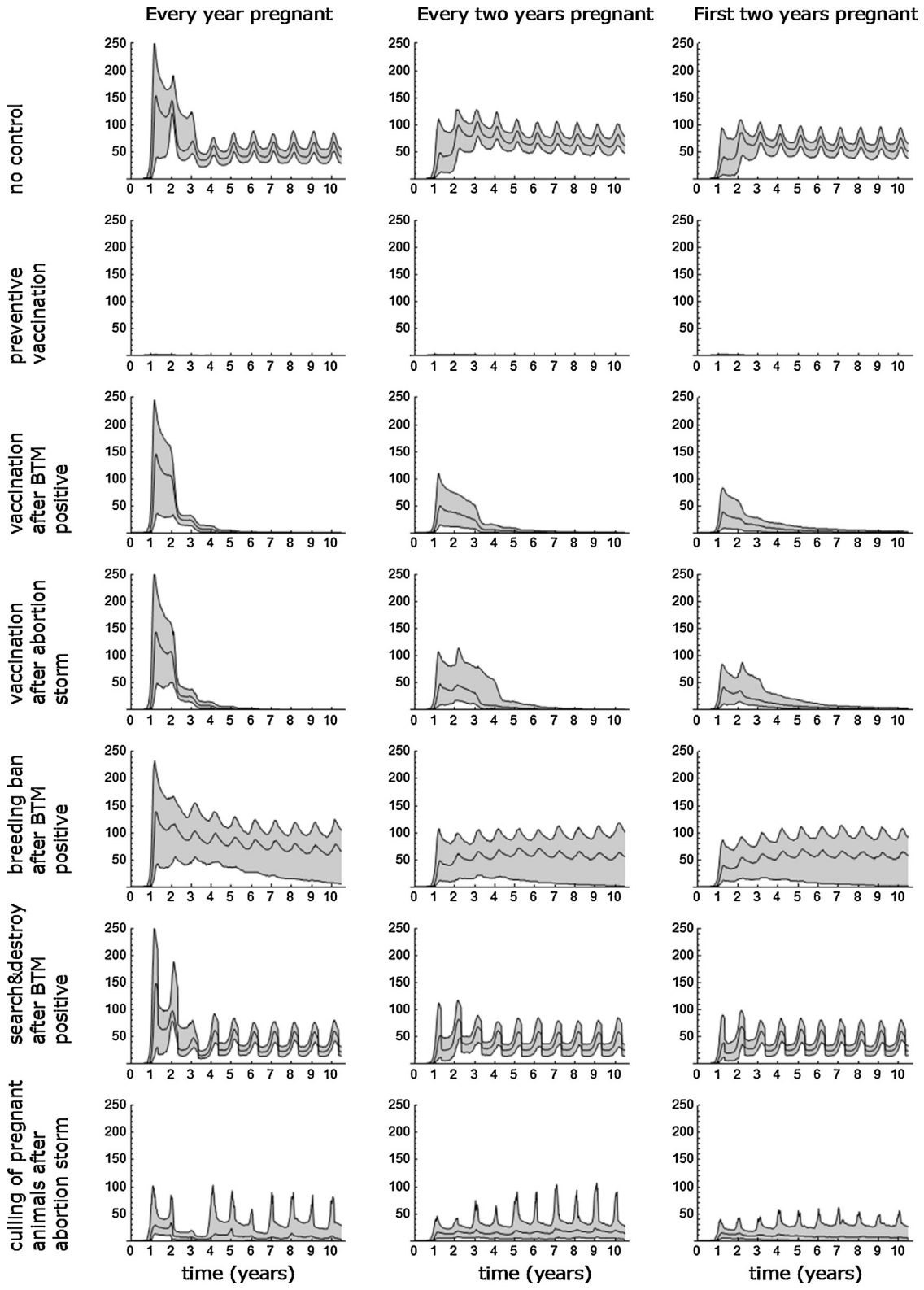


Fig. 3. The total number of infected animals for each combination of control strategy and herd management style over time. The total number of infected animals is the sum of the number of animals in their first infected gestation, after their first infected gestation (the persistently infected animals) and in the second infected gestation. The grey area denotes the 5–95% percentiles interval and the centre line the median value of all simulations.

and impossible to be larger than unity. Thus, the uncertainty of this parameter value is low (i.e. within a factor of 1.1 as a guideline).

T_a denotes the period of the gestation when a pregnant infected goat can abort (i.e. from day 100 till the end of gestation at day 150 after conception). Given that an abortion occurred on day 102 (Arricau-Bouvery et al., 2003) and abortions were not observed in the field before day 100 during the Dutch epidemic (P. Vellema, pers. com.), the uncertainty of this parameter value is low.

T_l denotes the late period of pregnancy (last 28 days) in which infection does not lead to abortion. Increasing or decreasing T_l with

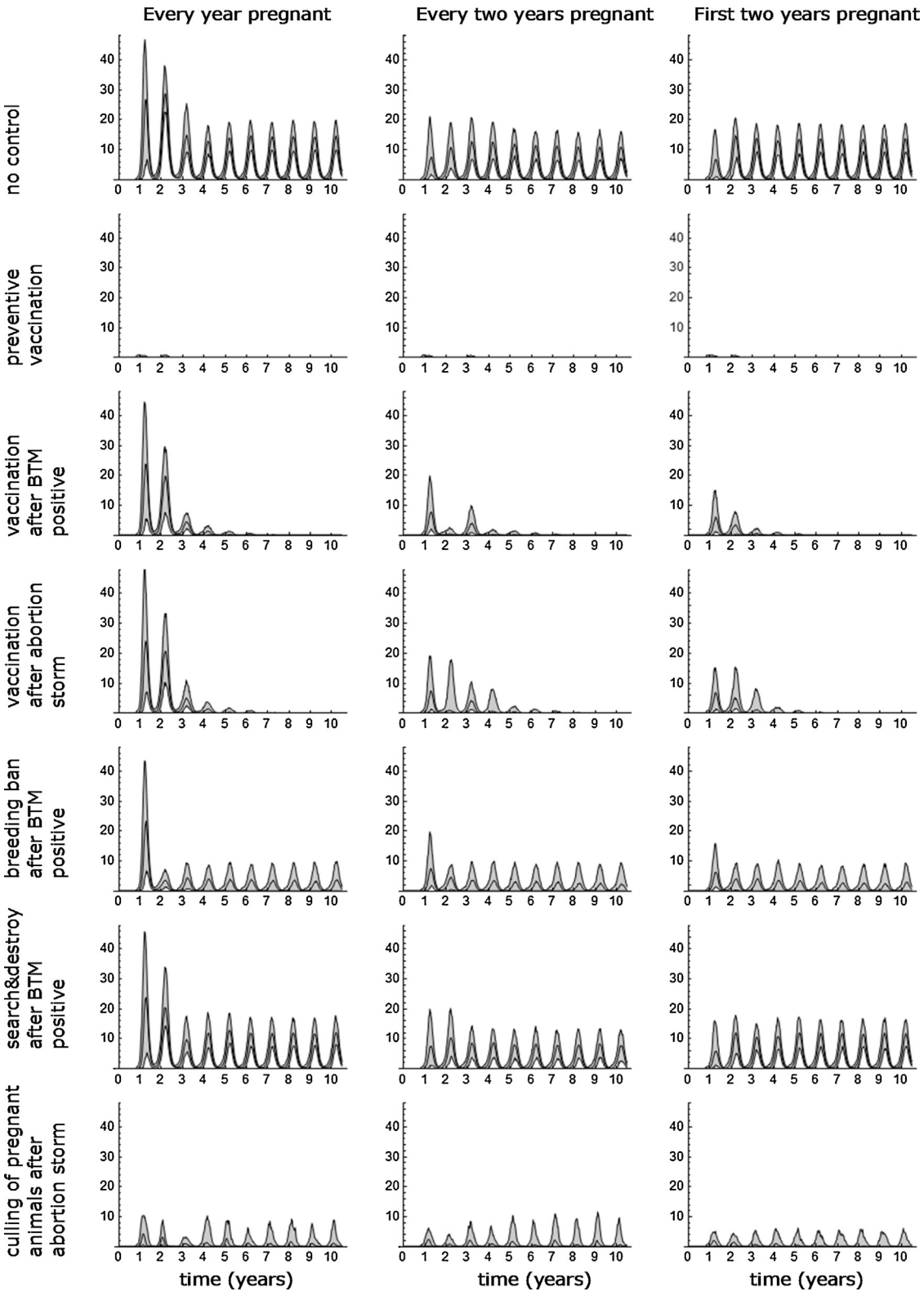


Fig. 4. Number of scaled *Coxiella burnetii* units in environment (E and D compartments) over time, for each combination of control strategy and herd management style. The viable *C. burnetii* bacteria in manure and dust are summed; their combined infection pressure is expressed in units of excreted *C. burnetii*. The grey area denotes the 5–95% percentiles interval and the centre line the median value of all simulations.

7 days affects the abortion peak in the first season noticeably and slightly affects the endemic incidence. Due to a lack of data the value of 28 days is indirectly derived from Roest et al. (2012), as explained in Appendix 2. The uncertainty of this parameter value is medium (i.e. within a factor of 1.25).

The transmission rate β has a high elasticity, and a large uncertainty (i.e. within a factor of 1.5) as its value was selected to reproduce the abortion patterns as observed in problem herds (see also Table A2-1 in Appendix 2). No other data exist to estimate this parameter.

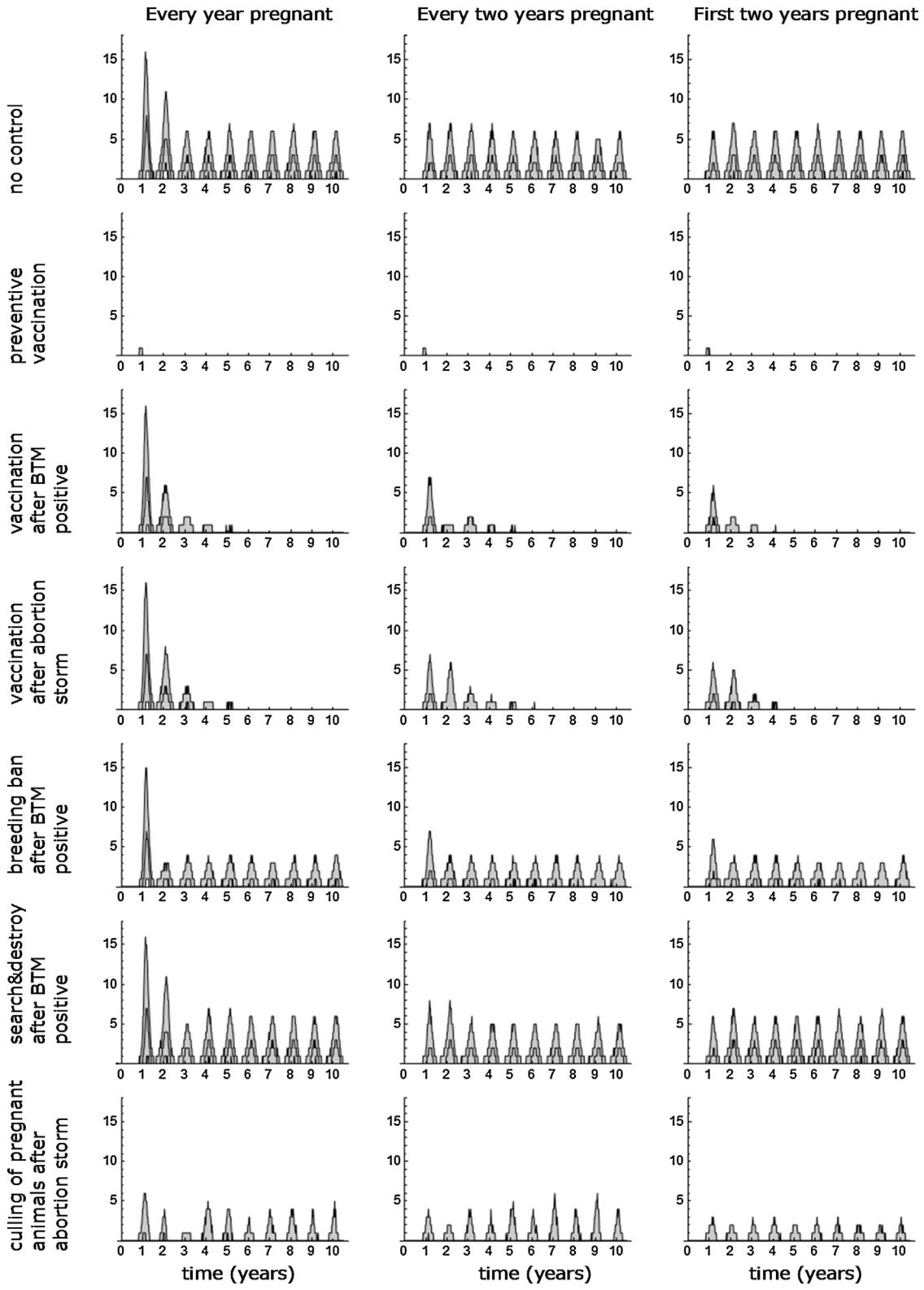


Fig. 5. The number of abortions per week over time, for each combination of control strategy and herd management style. The grey area denotes the 5–95% percentiles interval and the centre line the median value of all simulations.

α is the fraction of the infected goats which will not recover but will have an infected placenta again during the next gestation and this parameter has a medium elasticity. We took 0.7 for α given the information available, but values of 0.6 or 0.8 or more extreme cannot be excluded. The uncertainty of this parameter value is large.

The fraction of aborting goats during the first infected pregnancy (f_1) has a medium elasticity. We took 0.75 for f_1 based on experimental data from (Arricau-Bouvery et al., 2003, 2005; Roest et al., 2012), giving a proper indication of the value of f_1. The uncertainty of this parameter value is medium.

T_p denotes the standard deviation of the kidding season. This standard deviation is based on the observed birth date of nearly 9000 kids (see Chapter SI 1 of the Supplementary Information), so the uncertainty of this parameter is low. However, based on choices made by the farmer, the value for T_p for specific farms might differ.

The average gestation period T_g is 150 days, and this value is very certain.

T_{in} is the period between the average day of partus (t_p) and the average day of influx of young animals into the herd (t_{in}). This parameter is very variable as it differs per farmer, from two months until almost a year. We took 4 months. As farmers differ in management style, any choice for the parameter value of T_{in} remains arbitrary.

The parameter for average life expectancy of a goat ($1/\mu_t$) has a medium elasticity, but it is a very certain value, as it is based on data of nine Dutch dairy goat farms (see Chapter SI 1 of the Supplementary information).

The parameter p, the probability for a goat to gain immunity after an acute infection while not being pregnant, has a low elasticity, but a very high uncertainty as no literature data are available. With the difference between innate and acquired immunity in mind, a value of 0.5 for p was selected to obtain a hybrid SIS and SIR model formulation for the acute infection of non-pregnant goats.

Three of the model parameters described above, are characterized by a combination of a large uncertainty and a high elasticity. Therefore, these parameters α, β and T_l were subjected to a sensitivity analysis with the stochastic model, to study their effect on the abortion pattern in the goat herd during a 10 year period after disease introduction, and on the mean number of abortions during that period. Detailed results can be found in Chapter SI 4 of the Supplementary information. Despite considerable changes in the key parameters (up to 50%), the effect on the mean number of abortions is limited, ranging from −14% to +9%. The abortion pattern in the first two years after disease introduction is affected to some extent, mostly by β and least by α. After this period the infection is sustained at a comparable endemic level for all studied parameter combinations, demonstrating the need for control strategies. So although the parameter values are uncertain, the results for the control strategies are expected to be valid over a large range of values.

3.3. Stochastic model simulations

3.3.1. Effect of control strategies

Output of 200 ten year simulations of six control strategies and one scenario without control measures were summarized by looking at five model outputs, namely the time until disease extinction, average number of animals vaccinated per year, average number of culled animals per year, average number of infected placentas per year and the average number of abortions per year. Table 4 summarizes these outputs for each control strategy per herd management style (every year pregnant, every two years pregnant or first two years pregnant) for a herd of 600 animals. The time course during 10 years of some outputs are given in Figs. 3–5. Fig. 3 shows the total number of infected animals per year for each combination of control strategy and herd management style. Fig. 4 shows the infection pressure per year and Fig. 5 shows the number of abortions per year. The most significant findings in these figures will be described below, together with the results summarized in Table 4. For many control strategies, the model output during the second infected kidding season has a narrow 5–95% percentiles interval compared to that during the first infected kidding season (Figs. 3–5).

When implementing the strategy "No control measures" the disease remains in the herd for the whole simulated period. Herd management style "Every two years pregnant" leads to the fewest average number of infected placentas per year and the average number of abortions per year in comparison to the two other herd management styles (Table 4). Fewer infected placentas would reduce environmental contamination and thus reduce risks to human health. Fewer abortions would also help the farm economics.

Control strategy "Preventive vaccination" leads to the shortest average time until disease extinction, the lowest number of infected placentas and the lowest number of abortions (Table 4), of all control strategies irrespective of herd management style. The number of infected animals, the infection pressure and abortions over time is always at a very low level, without a peak over time (Fig. 3). The disease goes extinct after approximately 2 years (median). Herd management style "First two years pregnant" has the lowest upper bound of time to disease extinction (Table 4).

Control strategies "Vaccination after BTM positive" and "Vaccination after abortion storm" show similar results when compared and have the capability to halt the disease. A BTM positive herd is also likely to have had an abortion storm, making the group of farms with abortion storms and with positive BTM largely overlapping, which can explain the slight differences between these two control strategies. The disease goes extinct after approximately 5 years (median). When looking at the number of infected placentas and number of abortions, the herd management style "Every year pregnant" is much worse than the other two (Table 4). The number of infected animals, infection pressure and number of abortions over time peak between year 1–3, where after they decline rapidly as shown in Figs 3–5.

The control strategy "Breeding ban after BTM positive" hardly has the capability to halt the disease within 10 years (Table 4). The number of infected animals over time peaks between year 1–3, where after they do not decline to values close to 0 as shown in Fig. 3.

Similarly, the control strategy "Culling of pregnant animals after abortion storm" hardly has the capability to halt the disease within 10 years. The number of infected placentas and abortions is much lower than that of "Breeding ban after BTM positive" (Table 4), meaning that next breeding season there will still be infected placentas and a human health risk. Interestingly, the number of infected animals, the infection pressure and abortions over time is always at a similar level, without a peak over time (Figs. 3–5). The herd management style "First two years pregnant" is better than the other two, when using this control strategy.

Independent of herd management style, the control strategy "Search & destroy (i.e. test and cull) after BTM positive" fails to let Q fever go extinct, as the disease remains in the herd for the whole simulated 10-year period for all simulations. This control strategy results in the highest number of infected placentas and the highest number of abortions (Table 4). The number of infected animals, the infection pressure and abortions over time peak between year 1–3, but they do not decline to low numbers (Figs. 3–5).

3.3.2. Effect of ending preventive vaccination

The average life span of a Dutch commercially held dairy goat is 2.7 years (see Chapter SI 1 of the Supplementary information). This average life span means that each year 37% of the herd size is restocked, and that percentage of the population has not encountered the pathogen and thus has no immunity against Q fever. As a result, a large pool of susceptible goats arises with the potential to become infected (simultaneously, persistently infected goats will not remain long in the stable). Our simulations show that herd immunity can wane fast: even when the last vaccination was 0.7 year before disease introduction (i.e. only one batch of new imports of young goats is not vaccinated at the time of infection), all disease introductions develop into an endemic situation. For details see Chapter SI 3 of the Supplementary Information. When the herd is vaccinated at the time of infection, a large outbreak is prevented in the first season (see last vaccination at 0.3 year in Chapter SI

3). Infections can flare up when vaccination is stopped too early (see last vaccination at 2.3 years in Chapter SI 3). Herd management style 2 ("Every two years pregnant") is affected to the largest extent by ending the vaccination. If vaccination is continued for 4.3 years after disease introduction, then it is unlikely that Q-fever will persist, independent of herd management style.

4. Discussion

4.1. Disease dynamics and effect of control strategies

Due to the synchronised lambing season in combination with most *C. burnetii* being excreted at partus or abortions, simulated Q fever prevalence shows a 'saw-tooth' pattern during the year, with the highest prevalence shortly after lambing. From year to year, a peak is observed in number of infected animals, abortions and infection pressure in year 1–2 after introduction of Q fever in the herd. *C. burnetii* can survive from breeding season to breeding season as intracellular bacterium in the goat (persistent infection). According to the model, the presence of persistently infected goats is sufficient for the bacterium to survive from year to year in the herd; no other survival mechanisms are needed for persistence.

When the disease goes extinct in the goat herd we can assume that there is no human health risk anymore. When looking at the average time to extinction of the infection and at the infection pressure in a goat herd, the best control strategy is "Preventive vaccination" (i.e. yearly), followed by the reactive vaccination strategies "Vaccination after abortion storm" and "Vaccination after BTM positive" (see Table 4).

As *C. burnetii* in dried dust may affect the public health, an alternative ranking method is based on the cumulative amount of *C. burnetii* emitted into the environment (from disease introduction until extinction). Using this criterion, the same three control strategies are effective, as when aiming at disease extinction and infection pressure (see Table 4).

As the bulk of the pathogen excretion occurs during partus and abortion, the strategy of "Culling of pregnant animals after abortion storm" leads to a fast reduction of the amount of *C. burnetii* emitted into the environment. Then, no peak is observed anymore in number of infected animals, abortions and infection pressure in the goat herd. However, Q fever will not be eradicated in the herd by this measure.

We assumed that the bulk tank milk (BTM) turns positive for *C. burnetii* DNA when even one infected milk producing dairy goat is present in the herd. This assumption of a perfect detection probability of the BTM test (on the farm level) is close to reality, based on (Van den Brom et al., 2012b) where only very few excreting animals are needed for a positive BTM result. These few animals appeared to be infected before the vaccination became mandatory in the Netherlands, so even these old infections generated a positive BTM result. So the detection probability of the PCR test in the model is 100% at farm level (BTM), but 50% at individual level (individual milk sample) to account for intermittent shedding in milk. Shedding in milk is not simulated explicitly in the model, but only implicitly by reducing the detection probability of the PCR test (milk) to detect individual goats. When during the kidding season the BTM turns positive, then each infected milk producing dairy goat has a 50% chance to be found and destroyed in the model. With this assumed efficacy of 50% for detection and subsequent cull, the Search & destroy (i.e. test and cull) control strategy is not viable, as it does not lead to disease extinction and does not reduce the infection pressure sufficiently. If it was possible to increase this efficacy to 100%, then all persistently infected goats would be removed from the population after the kidding season.

Given an average life span of a Dutch commercially held dairy goat of 2.7 years, each year 37% of the herd size is restocked. Then herd immunity will wane fast as this fraction of the herd has no immunity against Q fever. Only if vaccination is continued for several years after disease introduction, then it is likely that the herd becomes free of Q fever.

Next to the control strategies, Q fever can be controlled by manipulating the frequency of pregnancy (and thus lambing) of goats. The herd management style "Every year pregnant" always performs worse than the herd management styles "Every two year pregnant" and "First two years pregnant". Thus, a herd management style in which fewer births per goat occur is better than one in which a goat gives birth every year. The herd management styles "Every two year pregnant" and "First two years pregnant" do not differ much.

4.2. Model uncertainties and assumptions made

During the modelling study, gaps in knowledge were identified and assumptions had to be made. One of these assumptions is recently verified by an animal experiment. Non-vaccinated nulliparous non-pregnant goats were experimentally infected with *C. burnetii*. First results indicate that they recovered from infection, and after insemination all gave birth to healthy kids without infected partus material (Roest et al., in prep). These results support our model assumption where non-pregnant goats cannot develop a persistent infection.

In the model we used a calibrated value for β (the within-herd transmission rate), for α (fraction of infected pregnant animals to become persistently infected) and for ρ (the fraction of *C. burnetii* excretion targeted to dust), using the observed abortion patterns in problem herds. The reason for this was that field data of infected goat farms at the time of the epidemic were still confidential. Furthermore, longitudinal data from the same farm, so at more than one point in time, were not available. So data were far from complete. We decided to aim at problem herds, where abortion storms take place with a peak in the second year after introduction of Q fever in the herd, because these herds are most relevant when considering human health risks. The goal of the model is to evaluate different control strategies in problem herds, and this can very well be done with calibrated values for the three parameters.

The consequence of using calibrated values is that independent field data were not available to validate the model. However, even if they existed, a serious complication of the Dutch Q fever outbreak data is that multiple control measures were implemented at the same time, making it impossible the determine the effect of an individual measure. The simulations are done for each control strategy separately (to be able to compare them). This makes validation of the simulation results with the Dutch field data very complicated, if not impossible.

As stated above, the parameters values for β, α and ρ could not be estimated with certainty from literature data. Therefore, the infection dynamics in the model was studied for a range of values to find for which combination of parameter values the abortions patterns observed in the field could be reproduced. The abortion percentages of 13 Q fever affected Dutch dairy goat farms in 2006–2007 were very heterogeneous (Animal Health Service, 2008) (see also Table A2-1 in Appendix 2). If we compare the subsequent kidding seasons of 2006 and 2007, five farms showed a high abortion percentage in 2006 followed by a low percentage in 2007, two farms showed equal abortion percentages for both years and six farms had a low abortion percentage in 2006 followed by a high abortion percentage in 2007. Information for the years 2005 and 2008 is absent, so it cannot be determined whether these two subsequent kidding seasons were the first and second year of herd infection, or the second and third year. In the model, to be able to achieve an abortion peak in the second kidding season (as compared to only a peak in the first year), the presence of persistently infected goats

was a prerequisite. To achieve this high abortion peak in the second season and a lower disease incidence in following years, the parameters α and ρ must be non-zero, and β must be approximately 1, as is chosen in the model.

As the parameters α, β and T_I are characterized by a combination of a large uncertainty and a high elasticity, these parameters were subjected to a sensitivity analysis with the stochastic model. The simulated abortion pattern in the first two years after disease introduction is affected to some extent, mostly by β and least by α. After this period the infection is sustained at a comparable endemic level for all studied parameter combinations, demonstrating the need for control strategies. So although the parameter values are uncertain, the results for the control strategies are expected to be valid over a large range of values. The parameter ρ (the fraction of *C. burnetii* excretion targeted to dust) was also calibrated in combination with α and β (see above), but this parameter was not subjected to the sensitivity analysis, as its elasticity L(P) in the elasticity analysis was very low.

The value for parameter p, the probability for a goat to gain immunity after an acute infection while not being pregnant, could not be estimated from literature. With the difference between innate and acquired immunity in mind, we chose that half of these goats will become susceptible again and the other half immune.

The fraction of aborting goats during the first infected pregnancy (f_I) could be estimated from literature data, but not the fraction during the second infected pregnancy (f_J). In the model, a lower value of 0.25 was chosen, reflecting an increased immunity.

The infection pressure caused by the latent stage of *C. burnetii* bacteria on dust particles is also unknown. *C. burnetii* can survive from breeding season to breeding season in the form of a small cell variant (SCV), i.e. like a spore (McCaul and Williams, 1981). However, the fraction of infectious SCVs after one year is unknown, and so is their contribution to the infection pressure from stable environment to the goat herd. To solve this problem, in the model the decay rate in dust (μ_D) is assumed to be 10 times smaller than in manure (μ_E), meaning a 10-times longer survival time of the bacterium in dust.

The length of the infectious period of non-pregnant goats in the model (T_i) of 28 days was derived from the time to build up immunity in vaccinated goats and from time to clearance in goats born from infected mothers. Also the level of excretion of *C. burnetii* in faeces (ε_f) was not quantified, as it was in infected placentas (expressed in infectious units). In the model a much lower value was chosen for manure, and this excretion rate was taken equal for all infected goats, either pregnant or non-pregnant.

4.3. Comparison with other Q fever models

Q fever disease dynamics has been modelled to investigate the effectiveness of three vaccination strategies in a dairy cattle herd (Courcoul et al., 2011). Hogerwerf et al. (2013) adapted this model for goat herds, by changing herd size and livestock demography of goats. They found that the model structure for dairy cattle could not capture the dynamics of the abortion storms in Dutch dairy goat herds. Therefore, in the present study a Q fever within-herd transmission model was developed to describe the disease dynamics in goat herds with abortion storms, to evaluate the effect of control measures in problem herds.

In both Q fever models for goats, variability of abortion patterns among herds did not represent the (very) variable patterns as observed in the field. In the model by Hogerwerf et al. (2013) no abortion storms occurred unless infection parameters were altered (e.g. the abortion rate and infection rate). In the present model, herds displayed abortion storms, thus conclusions based on this model only apply to those herds with abortion storms and need to be interpreted as such. This is still relevant, considering the goal of the present model (to evaluate different control strategies) and because human health risks occur from these problem herds with epidemic (rather than endemic) transmission dynamics.

In the present model we used frequency-dependent transmission ($dI/dt = \beta SI/N$), so transmission rates do not change with population density. As in this model the total number of goats in the herd ($N \approx 600$) is fairly constant during the period of pregnancy and giving birth, the results of frequency-dependent and density-dependent ($dI/dt = \beta SI$) transmission will not differ much. In the model by (Courcoul et al., 2011), the number of animals in the herd was also fairly constant, and although the model was coded as density-dependent, frequency-dependency would have yielded similar results. In the model by Hogerwerf et al. (2013), frequency-dependent transmission was assumed.

The main difference between the Q fever models for goats therefore is that in the present model abortion storms were simulated and control strategies were evaluated. In the model of Hogerwerf et al. (2013) Q fever dynamics in goat herds was compared with that in cattle herds. An important difference in the structure of the models is that in the present model, persistent infection of animals can only occur if they are infected when pregnant. Due to the seasonal reproductive pattern this is an important assumption for *C. burnetii* transmission in goat herds. As stated earlier, new experiments by Roest et al. (in prep) support this model assumption.

5. Conclusions

The present model results indicate that only vaccination is capable of preventing and controlling Q fever outbreaks in dairy goat herds, regardless of herd management style. Van Asseldonk et al. (2013) calculated that the total cost including the incurred human health costs of the outbreak was approximately 307 Million Euro. Based on the output of the model presented here it is calculated that the cost for maintaining protection against human Q fever via a dairy goat vaccination programme is relatively low (Van Asseldonk et al., 2015). Vaccination should therefore be considered as an ongoing control strategy to keep herds Q fever free and prevent indirect human health risks. Culling after abortion storms does not lead to long-term disease elimination at the herd level, however it does reduce human health risks on the short run during the outbreak.

Acknowledgements

We would like to thank Aline de Koeijer (Central Veterinary Institute of Wageningen UR), Mirjam Nielen and Don Klinkenberg (Faculty of Veterinary Medicine, Utrecht University) for discussions and helping to construct the conceptual model of Q fever dynamics. Animal pathologist Lucien van Keulen (Central Veterinary Institute of Wageningen UR) provided feedback on the conceptual model. Piet Vellema, Saskia Luttikholt and René van den Brom (Animal Health Service, Deventer) provided data on goat demography and information on the Dutch Q fever outbreak. Erik Schuiling (Livestock Research of Wageningen UR) provided insight in goat housing in the Dutch dairy goat industry. Thomas Hagenaars is acknowledged for critically reading the manuscript. This work was part of BO-Project *Maatschappelijk aanvaardbare dierziektebestrijding* (BO-08-010-011) and was funded by the Netherlands Ministry of Economic Affairs (EZ).

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.prevetmed.2015.11.004.

Appendix 1.

Deterministic Q fever model

Equations of the deterministic model simulations

Based on the state variables in the flow chart presented in Fig. 1, we derived a system of Ordinary Differential Equations (ODEs) to calculate the deterministic spread of Q fever within a herd. This Appendix describes all equations of the deterministic model in detail. The total number of goats in the model is tracked by N_{tot}. For bookkeeping the ODE system includes variable A, the total number of abortions since infection and variable E_{cum}, the cumulative amount of *C. burnetii* emitted into the environment since disease introduction. The deterministic model does not contain control strategies.

ODE-system

There are four infectious stages for the acutely infected goats, namely I_{np1} till I_{np4}. This is done to approximate the infectious period of an acute Q fever infection with a Gamma-distribution with $n_i = 4$ stages. Together I_{np1} till I_{np4} form the total number of acutely infected individuals I_{np}.

$$I_{np}(t) = I_{np1}(t) + I_{np2}(t) + I_{np3}(t) + I_{np4}(t) \quad (3)$$

The total time-varying number of animals in the populations is $N_{tot(t)}$.

$$N_{tot(t)} = S_{np}(t) + S_p(t) + I_{np}(t) + I_p(t) + I_{p2}(t) + J_{np}(t) + J_p(t) + R_{np}(t) + R_p(t) \quad (4)$$

The flow chart in Fig. 1 shows an overview how animals can traverse from one state to another. These states are modelled with variables in an ODE-system. For readability the time dependent variables and functions in Eqs. (3)–(19) are written without (t). The variable S_{np} denotes non-pregnant susceptibles, S_p stands for pregnant susceptibles, I_{np} for non-pregnant infected, I_p for pregnant infected, I_{p2} for late pregnant infected, J_{np} for non-pregnant persistently infected, J_p for pregnant persistently infected, R_{np} for non-pregnant recovered animals and R_p denotes the pregnant recovered. Black arrows in flow chart represent state transitions for the goat, grey arrows depict *C. burnetii* excretion routes resulting from faeces ε_f and partus ε_p. The transmission rate of the bacteria from the stable environment E and dust D to susceptible goats is denoted by β. The parameter μ symbolizes goat removal (for slaughter), while μ_E and μ_D stands for decay of *C. burnetii* in each environmental compartment. The forcing functions φ_c, φ_p, φ_a and φ_{in} determine conception, partus, abortion and influx of young animals in the herd.

Susceptible non-pregnant animals S_{np} (Eq. (3))

The term $Y\varphi_{in}$ in $\frac{dS_{np}}{dt}$ denotes the influx of young as a function of the forcing function φ_{in} and the number of young kept for herd supplementation. The term $\left(S_{np} - \left(1-\phi\right)\left(S_{np}+S_p\right)\right)\varphi_c$ in $\frac{dS_{np}}{dt}$ denotes the flux of animals which conceive as a function of the mating period (forcing function φ_c, see Eq. (21)). ϕ is the fraction of animals which will conceive. The term $S_p\varphi_p$ denotes the flux of animals from S_p to S_{np} with a normal parturition as a function of forcing function φ_p (see Eq. (22)). The term $(1-p)\gamma I_{np4}$ in $\frac{dS_{np}}{dt}$ denotes clearance of the infection without acquiring immunity by acutely infected non-pregnant animals. The term μS_{np} in $\frac{dS_{np}}{dt}$ is the flux of non-pregnant animals being removed. The term in $\beta S_{np}(E+D)/N_{tot}$ is the flux of non-pregnant animals which becomes acutely infected due to transmission from the environments E and D with infection rate β.

Susceptible pregnant animals S_p (Eq. (4))

The term $\beta S_p(E+D)/N_{tot}$ in $\frac{dS_p}{dt}$ is the flux of pregnant animals which becomes infected due to transmission from the environments E and D with infection rate β. The total environmental bacterial load of E and D exposes N_{tot} number of goats, thus the experienced infection pressure from both 'environments' for a goat is proportional to $(E+D)/N_{tot}$. With a constant transmission rate β from environment E and D to the goat, the rate at which *one* susceptible becomes infected is $\beta(E+D)/N_{tot}$. The *per capita* rate of change in each group of susceptibles (S_{np} and S_p) is $\beta(E+D)/N_{tot}$, which is similar to frequency dependent mixing (Keeling and Rohani, 2008).

Infected non-pregnant animals I_{np} (Eq. (5)–(8))

The term γI_{npi} in $\frac{dI_{npi}}{dt}$ denotes the transition of individuals from infectious state I_{npi} to infectious state $I_{np(i+1)}$with rate recovery γ; where $i \in [1,2,3,4]$ representing I_{np1} till I_{np4}. However, from state I_{np4} recovered animals enter state R_{np} with probability p or enter state S_{np} with probability $1-p$. The term $\left(I_{npi} - (1-\varphi)\left(I_{npi} + I_p/4\right)\right)\varphi_c$ in $\frac{dI_{npi}}{dt}$ denotes the flux of acutely infected animals that becomes pregnant and enters state I_p, as a function of the forcing function φ_c.

Infected pregnant animals $\boldsymbol{I_p}$ (Eq. (9)) and late pregnant infected animals $\boldsymbol{I_{p2}}$ (Eq. (10))

The term $r_I I_p \varphi_a$ in $\frac{dI_p}{dt}$ denotes the flux of aborting pregnant goats to state J_{np} as function of the forcing function φ_a, where r_I is the rate of abortion for animals in state I_p. The term $I_p\varphi_p$ in $\frac{dI_p}{dt}$ represents the flux of kidding goats as a function of the forcing function φ_p (see Eq. (22)). The term $\varphi_4\beta S_p(E+D)/N_{tot}$ in $\frac{dI_p}{dt}$ stands for the pregnant susceptible animals (S_p) which became infected early in their gestation and thereby enter state I_p, as function of the forcing function φ_4 (see Eq. (24)). The term $(1-\varphi_4)\beta S_p(E+D)/N_{tot}$ in $\frac{dI_{p2}}{dt}$ stands for the pregnant susceptible animals (S_p) which became infected late in their gestation and thereby enter state I_{p2}, as function of the forcing function φ_4. The term $I_p\varphi_p$ in $\frac{dI_p}{dt}$ and term $I_{p2}\varphi_p$ in $\frac{dI_{p2}}{dt}$ stand for the fluxes of kidding goats as a function of the forcing function φ_p.

Persistently infected animals J_p and J_{np} (Eqs. (11) and (12)) and recovered animals R_p and R_{np} (Eqs. (13) and (14))

α is the fraction of goats that become persistently infected after aborting or kidding. I_p animals enter the J_{np} state with the flux $\alpha\left(\left(I_p+I_{p2}\right)\varphi_p + r_I I_p\varphi_a\right)$ in $\frac{dJ_{np}}{dt}$. $(1-\alpha)$ is the fraction of aborting or kidding goats which recover from the infection and become immune, these animals enter the state R_{np} with the flux $(1-\alpha)\left(\left(I_p+I_{p2}\right)\varphi_p - r_I I_p\varphi_a\right)$ in $\frac{dR_{np}}{dt}$. Animals in state J_p always recover and enter state R_{np} after giving birth or having an abortion via the respective terms $J_p\varphi_p$ and $r_j J_p\varphi_a$, where r_j is the rate of abortion for animals in state J_p. In $\frac{dR_{np}}{dt}$ recovered non-pregnant goats are removed with the term μR_{np}. In $\frac{dR_{np}}{dt}$ recovered non-pregnant animals (R_{np}) become pregnant recovered animals (R_p) via the term $\left(R_{np} - (1-\phi)\left(R_{np}+R_p\right)\right)\varphi_c$, as a function of the forcing function. Recovered pregnant animals (R_p) become non-pregnant recovered animals (R_{np}) with term $R_p\varphi_p$ as a function of the forcing function φ_p.

Bacterial shedding and environmental contamination (Eqs. (15), (16) and (18))

In $\frac{dE}{dt}$ and $\frac{dD}{dt}$ the animals in the states I_{np}, I_p, I_{p2}, J_{np} and J_p excrete *C. burnetii* in faeces leading to a faeces excretion flux with size $\varepsilon_f\left(I_{np}+I_p+I_{p2}+J_{np}+J_p\right)$, excretion resulting from parturi-

tion and abortion results in excretion fluxes $\varepsilon_p\left(I_p+J_p\right)\phi_p$ and $\varepsilon_p\left(r_I I_p+r_J J_p\right)\phi_a$. Fraction ρ of these excretion fluxes are targeted to dust (D) and fraction $1-\rho$ to manure (E). The *C. burnetii* load of E and D decays with rates μ_E and μ_D. For bookkeeping the overall cumulative excretion is tracked in E_{cum}.

Births and death of animals (Eq. (17))

The ODE for Y tracks how many animals are removed from the states S_{np}, I_{np}, $J_{np}$and R_{np} with removal rate μ. Forcing function ϕ_{in} (Eq. (23)) causes animals (Y) to be introduced after the end of the kidding period in to state S_{np}. To maintain a constant herd size of the years, the number of young introduced into the herd equals the total number of animals removed from the herd since the previous introduction. The removal rate μ is taken to be age independent i.e. animals reach on average an age of $1/\mu_t$ years (note $\mu \neq \mu_t$).

Abortions (Eq. (19))

The total number of abortions since the start of the simulations is tracked with $\frac{dA}{dt}$. Neither of the bookkeeping variables A and E_{cum} affect any of the other states in the system.

ODE-system (Eqs. (3)–(19))

The ODE-system was coded in Mathematica 8.0 (Wolfram Research Inc, 2012). Parameter values of the model can be found in Table 2, and their estimation is described in detail in Appendix 2 (parameter values) and in Chapter SI 1 of the Supplementary information(goat demography).

$$\frac{dS_{np}}{dt} = \mathrm{Y}\varphi_{in} - (S_{np} - (1-\phi)(S_{np}+S_p))\varphi_c + S_p\varphi_p + (1-p)\gamma I_{np4} - \mu S_{np} - \frac{\beta S_{np}(\mathrm{E}+\mathrm{D})}{N_{tot}} \quad (5)$$

$$\frac{dS_p}{dt} = (S_{np} - (1-\phi)(S_{np}+S_p))\varphi_c - S_p\varphi_p - \frac{\beta S_p(\mathrm{E}+\mathrm{D})}{N_{tot}} \quad (6)$$

$$\frac{dI_{np1}}{dt} = \frac{\beta S_{np}(\mathrm{E}+\mathrm{D})}{N_{tot}} - \gamma I_{np1} - \mu I_{np1} - (I_{np1} - (1-\phi)(I_{np1}+I_p/4))\varphi_c \quad (7)$$

$$\frac{dI_{np2}}{dt} = \gamma I_{np1} - \gamma I_{np2} - \mu I_{np2} - \left(I_{np2} - \left(1-\phi\right)\left(I_{np2}+I_p/4\right)\right)\varphi_c \quad (8)$$

$$\frac{dI_{np3}}{dt} = \gamma I_{np2} - \gamma I_{np3} - \mu I_{np3} - \left(I_{np3} - \left(1-\phi\right)\left(I_{np3}+I_p/4\right)\right)\varphi_c \quad (9)$$

$$\frac{dI_{np4}}{dt} = \gamma I_{np3} - \gamma I_{np4} - \mu I_{np4} - \left(I_{np4} - \left(1-\phi\right)\left(I_{np4}+I_p/4\right)\right)\varphi_c \quad (10)$$

$$\frac{dI_p}{dt} = \left(I_{np} - \left(1-\phi\right)\left(I_{np}+I_p\right)\right)\varphi_c - I_p\varphi_p - r_I I_p\varphi_a + \frac{\varphi_4\beta S_p(\mathrm{E}+\mathrm{D})}{N_{tot}} \quad (11)$$

$$\frac{dI_{p2}}{dt} = -I_{p2}\varphi_p + (1-\varphi_4)\frac{\beta S_p(\mathrm{E}+\mathrm{D})}{N_{tot}} \quad (12)$$

$$\frac{dJ_{np}}{dt} = -\left(J_{np} - \left(1-\phi\right)\left(J_p+J_{np}\right)\right)\varphi_c + \alpha\left(\left(I_p+I_{p2}\right)\varphi_p + r_I I_p\varphi_a\right) - \mu J_{np} \quad (13)$$

$$\frac{dJ_p}{dt} = \left(J_{np} - \left(1-\phi\right)\left(J_p+J_{np}\right)\right)\varphi_c - J_p\varphi_p - r_J J_p\varphi_a \quad (14)$$

$$\frac{dR_{np}}{dt} = p\gamma I_{np4} - \left(R_{np} - (1-\phi)\left(R_{np}+R_p\right)\right)\varphi_c + R_p\varphi_p - \mu R_{np} + (1-\alpha)\left(\left(I_p+I_{p2}\right)\varphi_p - r_I I_p\varphi_a\right) + J_p\varphi_p + r_J J_p\varphi_a \quad (15)$$

$$\frac{dR_p}{dt} = \left(R_{np} - \left(1-\phi\right)\left(R_{np}+R_p\right)\right)\varphi_c - R_p\varphi_p \quad (16)$$

$$\frac{dE}{dt} = (1-\rho)\left(\varepsilon_f\left(I_{np}+I_p+I_{p2}+J_{np}+J_p\right) + \varepsilon_p\left(\left(I_p+J_p\right)\varphi_p + \left(r_I I_p + r_J J_p\right)\varphi_a\right)\right) - \mu_E \mathrm{E} \quad (17)$$

$$\frac{dD}{dt} = \rho\left(\varepsilon_f\left(I_{np}+I_p+I_{p2}+J_{np}+J_p\right) + \varepsilon_p\left(\left(I_p+J_p\right)\varphi_p + \left(r_I I_p + r_J J_p\right)\varphi_a\right)\right) - \mu_D \mathrm{D} \quad (18)$$

$$\frac{dY}{dt} = \mu\left(S_{np}+I_{np}+J_{np}+R_{np}\right) - Y\varphi_{in} \quad (19)$$

$$\frac{dE_{cum}}{dt} = \varepsilon_f\left(I_{np}+I_p+I_{p2}+J_{np}+J_p\right) + \varepsilon_p\left(\left(I_p+J_p\right)\varphi_p + \left(r_I I_p + r_J J_p\right)\varphi_a\right) \quad (20)$$

$$\frac{dA}{dt} = +r_I I_p\varphi_a + r_J J_p\varphi_a \quad (21)$$

Forcing functions for seasonal events (Eqs. (20)–(24))

The forcing functions φ_c, φ_p, φ_a and φ_{in} determine conception, partus, abortion and influx of young. These functions are descriptive only, with φ_p being an approximate of the birth pattern based on herd data provided by the Animal Health Service (see Chapter SI 1 of the Supplementary Information). The forcing functions for conception φ_c is identical in shape to φ_p but shifted in time for the length of the gestation period. The forcing function for abortion φ_a produces by approximation an uniform distribution for the probability to abort over time. Forcing function φ_4 causes pregnant goats which are infected in the last four weeks of their gestation period to enter state I_{p2} instead of state I_p. The abbreviation CDF stands for Cumulative Density Function and Mod for modulus. The modulo used is 365 days.

$$\varphi_a(t) = \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_a, 1\right], \mathrm{Mod}\left[t, 365, t_a - 365/2\right]\right]\left(1 - \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_a + T_a, 1\right], \mathrm{Mod}\left[t, 365, t_a - 365/2\right]\right]\right) \quad (22)$$

$$\varphi_c(t) = \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_c - 2T_p, 1\right], \mathrm{Mod}\left[t, 365, t_c - 365/2\right]\right]\left(\frac{1 - \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_c + 2T_p, 1\right], \mathrm{Mod}\left[t, 365, t_c - 365/2\right]\right]}{\kappa_c\left(1 + e^{-\frac{\mathrm{Mod}\left[t, 365, t_c - 365/2\right] - t_c}{\kappa_c}}\right)}\right) \quad (23)$$

$$\varphi_p(t) = \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_p - 2T_p, 1\right], \mathrm{Mod}\left[t, 365, t_p - 365/2\right]\right]\left(\frac{1 - \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_p + 2T_p, 1\right], \mathrm{Mod}\left[t, 365, t_p - 365/2\right]\right]}{\kappa_p\left(1 + e^{-\frac{\mathrm{Mod}\left[t, 365, t_p - 365/2\right] - t_p}{\kappa_p}}\right)}\right) \quad (24)$$

$$\varphi_{in}(t) = \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_{in} - T_p, 1\right], \mathrm{Mod}\left[t, 365, t_{in} - 365/2\right]\right]\left(\frac{1 - \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_{in} + T_p, 1\right], \mathrm{Mod}\left[t, 365, t_{in} - 365/2\right]\right]}{\kappa_{in}\left(1 + e^{-\frac{\mathrm{Mod}\left[t, 365, t_{in} - 365/2\right] - t_i}{\kappa_{in}}}\right)}\right) \quad (25)$$

$$\varphi_4(t) = 1 - \mathrm{CDF}\left[\mathrm{LogisticDistribution}\left[t_l, 1\right], \mathrm{Mod}\left[t, 365, t_l - 365/2\right]\right] \text{ with} t_l = t_p - T_l + 365 \quad (26)$$

Appendix 2.

Choice of parameter values

Demography parameters

Average gestation time (T_g) and removal rate (μ). We set the average time of gestation to 1.5×10^2 days, which is almost 22 weeks (Souriau et al., 2003; Arricau-Bouvery et al., 2005). The fraction of goats that successfully conceives (ϕ) is set at 0.95. This value is a strategy choice of the farmer and can be altered. If he wishes that a goat has a parturition every other year for prolonged milking then ϕ could be set to 0.475. A goat attains an average age of 2.7 years (see Chapter SI 1 of the Supplementary information), thus the annual average birth rate (μ_t) is 1/2.7. Birth and death must be in balance, while pregnant goats are not culled. The equation for the removal rate of non-pregnant animals (μ) is given below.

$$\mu = \mu_t\left(1 + \phi\frac{T_g}{365 - T_g}\right) \quad (27)$$

Average day of parturition (t_p) and its standard deviation (T_p). An average goat has its day of parturition (t_p) on day 55 of the calendar year (Chapter SI 1 of the Supplementary information). The kidding season is centred at t_p, during a 92-day period 95% of all young are born: $T_p = 46$ (Chapter SI 1).

Average day of conception (t_c) and its standard deviation (T_c). The average day of conception (t_c) is T_g days before t_p. Thus an average goat conceives in the 39th week of the calendar year. The breeding season is centred at t_c, and the standard deviation of the moment of conceptions is the same as for the births ($T_c = T_p$).

Infection parameters

Fraction of infected pregnant animals to abort (f_I and f_J). Sanford et al., 1994 describe abortions that occurred in goat herds that were exposed to three goats from another herd that kidded prematurely during a winter fair. Twenty-one days after exposure abortions began and affected 20–46% of the pregnant animals in each herd. Palmer et al., 1983 found in one herd 91% of the goats aborted or had weak, nonviable kids, but in other herds, abortion rates of 5–20% occurred. The abortion fraction in affected Dutch dairy herds ranged from 10 to 60% (Van den Brom and Vellema, 2009) and from 7% to 80% (Roest et al., 2011b), with averages of respectively 20 and 23%. Because for these natural affected herds the fraction of infected pregnant goats is unknown, the abortion fraction of infected pregnant goats was estimated to be between 7 and 100%. Only under experimental conditions it is possible to estimate this more precisely, namely 8 abortions out of 12 infected pregnant goats (Arricau-Bouvery et al., 2005), 6 out of 6 (Arricau-Bouvery et al., 2003) and 3 out of 7 (Roest et al., 2012). We estimated $f_I = 0.75$ for the first partus and $f_J = 0.25$ for the second infected gestation.

Persistently infected fraction (α). Goats can be chronically infected and may shed *C. burnetii* for up to two pregnancies after being infected (Hatchette et al., 2001). In a fraction of the infected goats the next gestation will again lead to a (now fully) infected placenta (Berri et al., 2007). They described a Q fever outbreak in a French dairy goat herd over two kidding seasons. In the second kidding season 12 of 17 (0.7) goats were re-current emitters in milk. We assume that a fraction α of the infected pregnant goats will become persistently infected, with $\alpha = 0.7$.

Period in which infection does not lead to abortion (T_l). After non-experimental exposure it takes minimally 21 days to induce abortions (Sanford et al., 1994). Between 14 and 28 days post inoculation (dpi) the *C. burnetii* bacteria reach the trophoblast of the placenta where they start to multiply (Roest et al., 2012). If the partus occurs before 28 dpi the level of bacterial excretion is expected to be low and negligible, therefore we set the last period of pregnancy in which infection does not lead to abortion (T_l) to 28 days.

Average day of abortion (t_a). When twelve unvaccinated goats were challenged at day 84 of gestation, eight aborted between days 123 and 145 of gestation, reducing the average gestation period with 12 days (Arricau-Bouvery et al., 2005). When six unvaccinated goats were challenged at day 90 of gestation the first abortion occurred at day 102 of gestation, the other five between day 115 and 138 (Arricau-Bouvery et al., 2003). Of seven pregnant goats which were nasally exposed on day 76 of gestation, three had an abortion on gestation day 122, 136 and 139, one had weak live kids on day 142 and two had strong live kids on day 144 and 145. The control goats gave birth between day 150 and 154 of gestation (Roest et al., 2012). In the field, the Dutch Animal Health Service did not observe abortions in commercial dairy goats before day 100 of gestation during the Q fever epidemic (Vellema, pers.com.). Therefore, considering all the above, in this model 95% of aborting goats have their abortion between day 100 and the end of gestation (t_p) at day 150, with the average day of abortion (t_a) being on 25 days before t_p.

Infectious period of non-pregnant goats (T_i) and recovery rate (γ). Vaccination of naïve goats induces antibodies after three weeks (Rousset et al., 2009b). Due to lack of data on the effect of Q fever on non-vaccinated non-pregnant goats we take an infectious period of four weeks (28 days). We approximate the infectious period of an acute Q fever infection with a Gamma-distribution with n_i stages. Assuming 95% of the infection is cleared at day 28 and $n_i = 4$, we find an average infectious period (T_i) of 14 days and a recovery rate (γ) of n_i/T_i day^{-1} from stage tot stage. Goats born from infected mothers clear themselves in 28 days after birth (Roest et al., 2012), which is before they can acquire immunity via memory cells.

Probability to gain long-term immunity (p). Based on sheep data, inoculation of non-pregnant animals with a low dose of *C. burnetii* lead to low or no antibody immune response (Lennette et al., 1952). Inoculation with a high dose lead to a faster and stronger acquired immune response. We interpreted these observations as: if the innate immune system of the host can clear the infection, no long-term acquired immunity is gained. Therefore an individual in I_{np} that clears its infection has a probability of p to gain long-term immunity against future *C. burnetii* infections and traverses to R_{np}, a fraction of $1 - p$ transitions back to S_{np}. We assume a value of 0.5 for p.

Transmission rate of Q fever from the environment (β). Table A2-1 (this Appendix) shows the abortion percentages on 13 Q fever

affected commercial dairy goat farms for the years 2006 and 2007 (Animal Health Service, 2008). If we compare two subsequent kidding seasons, five farms show a high-low pattern, two farms show no differences and six farms show a low-high pattern. Information for the years 2005 and 2008 are absent, so it cannot be determined whether these two subsequent kidding seasons were the first and second year of infection, or the second and third year. We assumed that the low-high farms are in the first and second season of infection, and the high-low farms in the second and third season of infection. All combined, this yields a low-high-low abortion percentage pattern during three kidding seasons. We calibrated a value of 1.0 for β as that produces outbreak dynamics with low abortion numbers in the first season, a peak in the second and fewer abortions in the following seasons.

Infected material from abortion or parturition contains a bacterial load of about 10^{12} hamster-infective doses per kg (Welsh et al., 1951), the infected placenta itself weighing about 1 kg. Instead of choosing a transmission parameter β of $1/(1\times10^{12})$ per day per hamster-infective dose, we scaled the pathogen load to the contribution of infected material from one abortion or parturition, i.e. a β of 1 per day per scaled pathogen.

Shedding parameters

Shedding from faeces (ε_f) and partus products (ε_p) to manure and dust (ρ). The pathogen is present in large numbers in the foetal membranes and foetal fluids of infected animals (Sanchez et al., 2006). A placenta of a positive sheep can contain 10^1–10^9 hamster-infective doses per gram (Welsh et al., 1951). Not-vaccinated aborting goats and not-vaccinated goats with normal parturition have identical shedding patterns (Rousset et al., 2009a). We set the amount of bacteria released at partus or abortion (ε_p) to 1 infectious unit.

After partus goats can excrete *C. burnetii* in faeces up to twenty days (Arricau-Bouvery and Rodolakis, 2005). It is experimentally difficult to determine whether contaminated faeces result from direct excretion of the host or is a result from indirect contamination from a contaminated environment. In the best-case scenario excretion of *C. burnetii* via faeces does not occur and in the worst-case it is still much less than the excretion resulting from birth/partus. We take the worst-case scenario. Due to lack of data we assumed that all animals in any of the infectious states (I_{np}, I_p, I_{p2}, J_{np} and J_p) have identical excretion rates for *C. burnetii* in urine and faeces. Assuming 1 kg of faeces contains 10^6 times less bacteria compared to a placenta, which weighs approximately 1 kg, and combining this with a yearly manure production of 1000 kg, we derive a daily excretion rate in urine and faeces (ε_f) of 2.7×10^{-6} infectious units for an infected individual.

Excreted *C. burnetii* can aerosolize (Welsh et al., 1958; Tigertt et al., 1961; Marrie et al., 1996; Stein et al., 2005; EFSA, 2010; Jones et al., 2011; Hogerwerf et al., 2012) and settle as dust on horizontal surfaces (de Bruin et al., 2011). We assume that 1% of all excretion ends up in dust, thus $\rho = 0.01$.

Survival parameters for Coxiella burnetii *bacteria*

Survival in manure (μ_E) and dust (μ_D). No viable *C. burnetii* bacteria were found in manure sampled weeks after the last kidding in an infected herd in a Dutch deep litter stable, although DNA of dead bacteria was found (Roest et al., 2011a). Based on spiking experiments in dung heaps, a decay rate (μ_E) of 1/17.4 day^{-1} can be estimated (Roest et al., 2011a). In the model we take $\mu_E = 1/20$.

Depending on the matrix (dust, wool, soil, straw, contaminated buildings, fomites, tick faeces) *C. burnetii* bacteria can survive for periods of months to years (McCaul and Williams, 1981; McCaul, 1991; Drew, 2004; Brouqui et al., 2007). Unfortunately, it is unclear whether 99% or 1% of the bacteria survived during these periods, making it impossible to quantify a mortality rate for the bacterium in dust (μ_D). We take $\mu_D = \mu_E/10$, meaning that after 2 years 3% of the bacterial load in dust remains.

Table A2-1
Abortion percentage during 2006 and 2007 (Animal Health Service, 2008).

Farm	Abortion percentage in year		Year-to-year pattern
	2006[a]	2007[a]	
1	26	5	High–low
2	34	0	High–low
3	50	12	High–low
4	8	3	High–low
5	13	0	High–low
6	16	16	Equal
7	4	4	Equal
8	3	53	Low–high
9	1	35	Low–high
10	0	10	Low–high
11	0	55	Low–high
12	5	30	Low–high
13	0	8	Low–high

[a] Data for 2005 and 2008 are not available. Control measures were not yet obligated and were not implemented.

Vaccination parameters

Vaccination of naïve goats induces antibodies after 3 weeks (Rousset et al., 2009b). Vaccination does not prevent infection and does not clear the infection in infected goats (Rousset et al., 2009b). The bulk of pathogen emission is associated with the partus, thus infected pregnant animals should be prevented. When vaccinated before infection, most abortions are prevented (Arricau-Bouvery et al., 2005). The findings of Hogerwerf et al. (2011) suggest that vaccination is more protective in nulliparous animals than in parous animals. Vaccination induces an overall decrease in shedding levels and the highest reduction is found in nulliparous animals (de Cremoux et al., 2012). Thus before the very first pregnancy the susceptibles should be vaccinated. In practice this means that the young nulliparous animals should be vaccinated before they conceive. The manufacturer of the Coxevac vaccine recommends vaccination after 3 months of age (after the period needed to reach active immunity acquisition) and 3 weeks before mating (EMA, 2012).

Under field conditions unvaccinated young goats have a higher bacterial prevalence in the uterine fluid compared to vaccinated young goats (OR from 1 to 0.005) and when comparing unvaccinated old goats with vaccinated old goats the OR improves from 0.44 to 0.03 (Hogerwerf et al., 2011).

Under experimental conditions the vaccine-induced reduction of emission is roughly a million-fold (Arricau-Bouvery et al., 2005). Thus, the emission by a vaccinated animal is negligible compared to an unvaccinated animal. Therefore, in the model we assume that the emission of vaccinated animals is zero, effectively moving a vaccinated animal to the state R_{np}. Also, we assume that only animals in state S_{np} can benefit from vaccination and are moved to R_{np}.

Vaccine efficacy (v_e). Taking a conservative assumption for vaccine efficacy (v_e) of 90%, this means that nine of ten animals were correctly vaccinated and also developed an effective immune response.

References

Animal Health Service, 2008. Verslag Q-fever op 13 melkgeitenbedrijven van maart 29 pagina.s. In: Service, A.H. (Ed.). Netherlands Ministry for Economic Affairs, Agriculture and Innovation (EL&I), Deventer, p. 29.

Arricau-Bouvery, N., Rodolakis, A., 2005. Is Q Fever an emerging or re-emerging zoonosis? Vet. Res. 36, 327–349.

Arricau-Bouvery, N., Souriau, A., Bodier, C., Dufour, P., Rousset, E., Rodolakis, A., 2005. Effect of vaccination with phase I and phase II *Coxiella burnetii* vaccines in pregnant goats. Vaccine 23, 4392–4402.

Arricau-Bouvery, N., Souriau, A., Lechopier, P., Rodolakis, A., 2003. Experimental *Coxiella burnetii* infection in pregnant goats: excretion routes. Vet. Res. 34, 423–433.
Berri, M., Crochet, D., Santiago, S., Rodolakis, A., 2005. Spread of *Coxiella burnetii* infection in a flock of sheep after an episode of Q fever. Vet. Rec. 157, 737–740.
Berri, M., Rousset, E., Champion, J.L., Russo, P., Rodolakis, A., 2007. Goats may experience reproductive failures and shed *Coxiella burnetii* at two successive parturitions after a Q fever infection. Res. Vet. Sci. 83, 47–52.
Bildfell, R.J., Thomson, G.W., Haines, D.M., McEwen, B.J., Smart, N., 2000. *Coxiella burnetii* infection is associated with placentitis in cases of bovine abortion. J. Vet. Diagn. Invest. 12, 419–425.
Brooke, R.J., Kretzschmar, M.E., Mutters, N.T., Teunis, P.F., 2013. Human dose response relation for airborne exposure to *Coxiella burnetii*. BMC Infect. Dis. 13, 488.
Brouqui, P., Marrie, T., Raoult, D., 2007. Coxiella. In: Murray, E.S. (Ed.), Manual of Clinical Microbiology. ASM Press, Washington, D.C, pp. 1062–1069.
Burnet, F.M., Freeman, M., 1983. Classics in infectious-diseases-experimental studies on the Virus of Q-Fever (Reprinted). Rev. Infect. Dis. 5, 800–808.
Courcoul, A., Hogerwerf, L., Klinkenberg, D., Nielen, M., Vergu, E., Beaudeau, F., 2011. Modelling effectiveness of herd level vaccination against Q fever in dairy cattle. Vet. Res. 42, 68.
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. Proc. R. Soc. B 277, 2857–2865.
Cox, H.R., Tesar, W.C., Irons, J.V., 1947. Q-Fever in the United-States.4. Isolation and identification of Rickettsias in an outbreak among stock handlers and slaughterhouse workers. Jama-J. Am. Med. Assoc. 133, 820–821.
de Bruin, A., de Groot, A., de Heer, L., Bok, J., Wielinga, P.R., Hamans, M., van Rotterdam, B.J., Janse, I., 2011. Detection of *Coxiella burnetii* in complex matrices by using multiplex quantitative PCR during a major Q fever outbreak in The Netherlands. Appl. Environ. Microbiol. 77, 6516–6523.
de Cremoux, R., Rousset, E., Touratier, A., Audusseau, G., Nicollet, P., Ribaud, D., David, V., Le Pape, M., 2012. Assessment of vaccination by a phase I *Coxiella burnetii*-inactivated vaccine in goat herds in clinical Q fever situation. Fems Immunol. Med. Microbiol. 64, 104–106.
Drew, W.L., 2004. Rickettsia, Coxiella, Ehrlichia and Bartonella. In: Ryan, K.J., Ray, C.G. (Eds.), Sherris Medical Microbiology: An Introduction to Infectious Diseases. McGraw Hill, pp. 471–479.
EFSA, 2010. Scientific opinion on Q fever. EFSA J. 8, 1595.
EMA, 2012.Coxevac: EPAR - Product Information. In: Agency, E.M. (Ed.) European Medicine Agency, Coxevac - inactivated Coxiella burnetii vaccine product information.
Hatchette, T.F., Hudson, R.C., Schlech, W.F., Campbell, N.A., Hatchette, J.E., Ratnam, S., Raoult, D., Donovan, C., Marrie, T.J., 2001. Goat-associated Q fever: a new disease in Newfoundland. Emerg. Infect. Dis. 7, 413–419.
Hogerwerf, L., Borlee, F., Still, K., Heederik, D., van Rotterdam, B., de Bruin, A., Nielen, M., Wouters, I.M., 2012. Detection of *Coxiella burnetii* DNA in inhalable airborne dust samples from goat farms after mandatory culling. Appl. Environ. Microbiol. 78, 5410–5412.
Hogerwerf, L., Courcoul, A., Klinkenberg, D., Beaudeau, F., Vergu, E., Nielen, M., 2013. Dairy goat demography and Q fever infection dynamics. Vet. Res. 44, 28.
Hogerwerf, L., Koop, G., Klinkenberg, D., Roest, H.I., Vellema, P., Nielen, M., 2014. Test and cull of high risk *Coxiella burnetii* infected pregnant dairy goats is not feasible due to poor test performance. Vet. J. 200, 343–345.
Hogerwerf, L., van den Brom, R., Roest, H.I., Bouma, A., Vellema, P., Pieterse, M., Dercksen, D., Nielen, M., 2011. Reduction of *Coxiella burnetii* prevalence by vaccination of goats and sheep, the Netherlands. Emerg. Infect. Dis. 17, 379–386.
Jones, R.M., Hertwig, S., Pitman, J., Vipond, R., Aspan, A., Bolske, G., McCaughey, C., McKenna, J.P., van Rotterdam, B.J., de Bruin, A., Ruuls, R., Buijs, R., Roest, H.J., Sawyer, J., 2011. Interlaboratory comparison of real-time polymerase chain reaction methods to detect *Coxiella burnetii*, the causative agent of Q fever. J. Vet. Diagn. Invest. 23, 108–111.
Keeling, M.J., Rohani, P., 2008. Modeling Infectious Diseases in Humans and Animals. Princeton University Press Princeton.
Klaassen, C.H.W., Nabuurs-Franssen, M.H., Tilburg, J.J.H.C., Hamans, M.A.W.M., Horrevorts, A.M., 2009. Multigenotype Q fever outbreak, the Netherlands. Emerg. Infect. Dis. 15, 613–614.
Lennette, E.H., Holmes, M.A., Abinanti, F.R., 1952. Q-Fever studies.14: observations on the Pathogenesis of the experimental infection induced in sheep by the intravenous route. Am. J. Hyg. 55, 254–267.
Marrie, T.J., Stein, A., Janigan, D., Raoult, D., 1996. Route of infection determines the clinical manifestations of acute Q fever. J. Infect. Dis. 173, 484–487.
McCaul, T.F., 1991. The development cycle of *Coxiella burnetii*, Q fever. In: The Biology of *Coxiella burnetii*. CRC Press, Florida, pp. 223–258.
McCaul, T.F., Williams, J.C., 1981. Developmental cycle of *Coxiella burnetii*: structure and morphogenesis of vegetative and sporogenic differentiations. J. Bacteriol. 147, 1063–1076.
Palmer, N.C., Kierstead, M., Key, D.W., Williams, J.C., Peacock, M.G., Vellend, H., 1983. Placentitis and abortion in goats and sheep in Ontario caused by *Coxiella-Burnetii*. Can. Vet. J.-Revue Vet. Can. 24, 60–61.
RIVM, 2012. RijksinstituutvoorVolksgezondheiden Milieu (RIVM), the Dutch National Institute for Public Health and the Environment. http://rivm.nl/Onderwerpen/Q/Q_koorts (accessed: 11.12.).
Roest, H.I.J., 2013. *Coxiella burnetii* in Pregnant Goats. Faculty of Veterinary Medicine. Universiteit Utrecht, Utrecht, pp. 200.
Roest, H.I.J., Dinkla, A., van Rotterdam, B., de Bruin, A., Dercksen, D., Vellema, P., 2011. Overleving van Coxiella burnetii in geitenmest. WUR Report 11/CVI0212. Wageningen University and Research (WUR).
Roest, H.I.J., Ruuls, R.C., Tilburg, J.J.H.C., Nabuurs-Franssen, M.H., Klaassen, C.H.W., Vellema, P., van den Brom, R., Dercksen, D., Wouda, W., Spierenburg, M.A.H., van der Spek, A.N., Buijs, R., de Boer, A.G., Willemsen, P.T.J., van Zijderveld, F.G., 2011b. Molecular epidemiology of *Coxiella burnetii* from ruminants in Q fever outbreak, the Netherlands. Emerg. Infect. Dis. 17, 668–675.
Roest, H.I.J., Tilburg, J.J.H.C., Van der Hoek, W., Vellema, P., Van Zijderveld, F.G., Klaassen, C.H.W., Raoult, D., 2011c. The Q fever epidemic in The Netherlands: history, onset, response and reflection. Epidemiol. Infect. 139, 1–12.
Roest, H.J., van Gelderen, B., Dinkla, A., Frangoulidis, D., van Zijderveld, F., Rebel, A., van Keulen, L., 2012. Q fever in pregnant goats: pathogenesis and excretion of *Coxiella burnetii*. PLoS One 7, e48949.
Rousset, E., Berri, M., Durand, B., Dufour, P., Prigent, M., Delcroix, T., Touratier, A., Rodolakis, A., 2009a. *Coxiella burnetii* shedding Routes and antibody Response after outbreaks of Q fever-induced abortion in dairy goat herds. Appl. Environ. Microbiol. 75, 428–433.
Rousset, E., Durand, B., Champion, J.L., Prigent, M., Dufour, P., Forfait, C., Marois, M., Gasnier, T., Duquesne, V., Thiery, R., Aubert, M.F., 2009b. Efficiency of a phase 1 vaccine for the reduction of vaginal *Coxiella burnetii* shedding in a clinically affected goat herd. Clin. Microbiol. Infect. 15, 188–189.
Sanchez, J., Souriau, A., Buendia, A.J., Arricau-Bouvery, N., Martinez, C.M., Salinas, J., Rodolakis, A., Navarro, J.A., 2006. Experimental *Coxiella burnetii* infection in pregnant goats: a histopathological and immunohistochemical study. J. Comp. Pathol. 135, 108–115.
Sanford, S.E., Josephson, G.K.A., Macdonald, A., 1994. *Coxiella-Burnetti* (Q-Fever) abortion storms in goat herds after attendance at an annual fair. Can. Vet. J.-Revue Vet. Can. 35, 376–378.
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 Vet. Res., 7.
Schimmer, B., Ter Schegget, R., Wegdam, M., Zuchner, L., de Bruin, A., Schneeberger, P.M., Veenstra, T., Vellema, P., 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 Infect. Dis. 10.
Schuiling, H.J., 2007. Prolonged lactations in goats Wageningen UR Livestock Research Animal Sciences Group.
Souriau, A., Arricau-Bouvery, N., Bodier, C., Rodolakis, A., 2003. Comparison of the efficacy of Q fever vaccines against *Coxiella burnetii* experimental challenge in pregnant goats. Rickettsiology: Present Future Dir. 990, 521–523.
Stein, A., Louveau, C., Lepidi, H., Ricci, F., Baylac, P., Davoust, B., Raoult, D., 2005. Q fever pneumonia: virulence of *Coxiella burnetii* pathovars in a murine model of aerosol infection. Infect. Immun. 73, 2469–2477.
Tigertt, W.D., Benenson, A.S., Gochenour, W.S., 1961. Airborne Q fever. Bacteriol. Rev. 25, 285–2893.
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. Emerg. Infect. Dis. 18, 887–889.
Van Asseldonk, M.A., Prins, J., Bergevoet, R.H., 2013. Economic assessment of Q fever in the Netherlands. Prev. Vet. Med. 112, 27–34.
Van Asseldonk, M.A.P.M., Bontje, D.M., Backer, J.A., van Roermund, H.J.W., Bergevoet, R.H.M., 2015. Economic aspects of Q fever control in dairy goats. Prev. Vet. Med. 121, 7.
Van den Brom, R., Moll, L., van Schaik, G., Vellema, P., 2012a. Demography of Q fever seroprevalence in sheep and goats in The Netherlands in 2008. Prev. Vet. Med.
Van den Brom, R., van Engelen, E., Luttikholt, S., Moll, L., van Maanen, K., Vellema, P., 2012b. *Coxiella burnetii* in bulk tank milk samples from dairy goat and dairy sheep farms in The Netherlands in 2008. Vet. Rec. 170, 310.
Van den Brom, R., Vellema, P., 2009. Q fever outbreaks in small ruminants and people in the Netherlands. Small Rumin. Res. 86, 74–79.
Van der Hoek, W., Dijkstra, F., Wijers, N., Rietveld, A., Wijkmans, C.J., van Steenbergen, J.E., Notermans, D.W., Schneeberger, P.M., 2010. [Three years of Q fever in the Netherlands: faster diagnosis]. Ned Tijdschr Geneeskd 154, A1845.
Van Moll, P., Baumgartner, W., Eskens, U., Hanichen, T., 1993. Immunocytochemical demonstration of *Coxiella burnetii* antigen in the fetal placenta of naturally infected sheep and cattle. J. Comp. Pathol. 109, 295–301.
VWZ, 2010. Evaluatiecommissie Q-koorts: Rapport van verwerping tot verheffing. In: Ministerie van Volksgezondheid Welzijn en Sport (Ed.) Opmeer dukkerij, Den Haag, Den Haag, 133.
Welsh, H.H., Lennette, E.H., Abinanti, F.R., Winn, J.F., 1951. Q fever in California. IV. Occurrence of *Coxiella burnetii* in the placenta of naturally infected sheep. Public Health Rep. 66, 1473–1477.
Welsh, H.H., Lennette, E.H., Abinanti, F.R., Winn, J.F., 1958. Air-Borne Transmission of Q fever—the role of parturition in the generation of infective aerosols. Ann. N. Y. Acad. Sci. 70, 528–540.
Wolfram Research Inc, 2012. Mathematica. Champaign, Illinois, USA.